Chapter 20 – Clinical Response of Normal Tissues – Lecture 2

11/21/2024

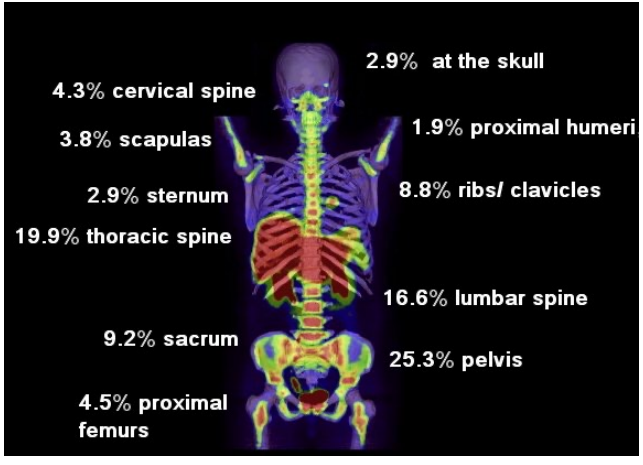
Outlines

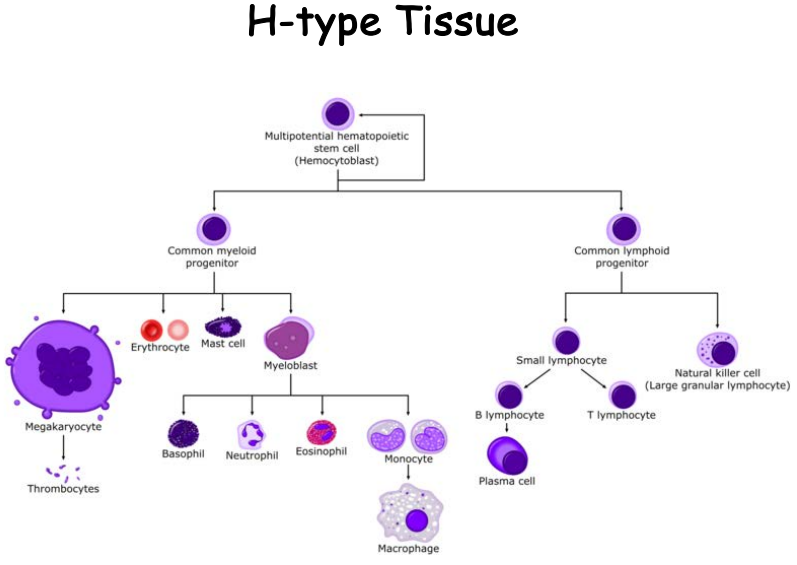
- Cells and Tissues
- Early (Acute) and Late Effects
- Functional Subunits in Normal Tissues
- The Volume Effect in Radiotherapy: Tissue Architecture
- Radiation Pathology of Tissues
  - Casarett's Classification
  - Michalowski's H- and F-Type Populations
- Growth Factors
- **Specific Tissues and Organs**
- Grading of Late Effects

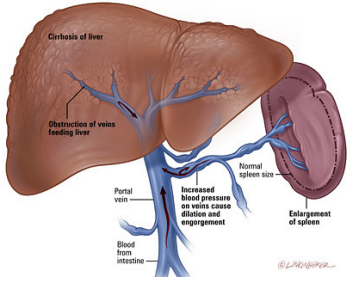
Mechanism

Organ by organ clinical observation

Hematopoietic System



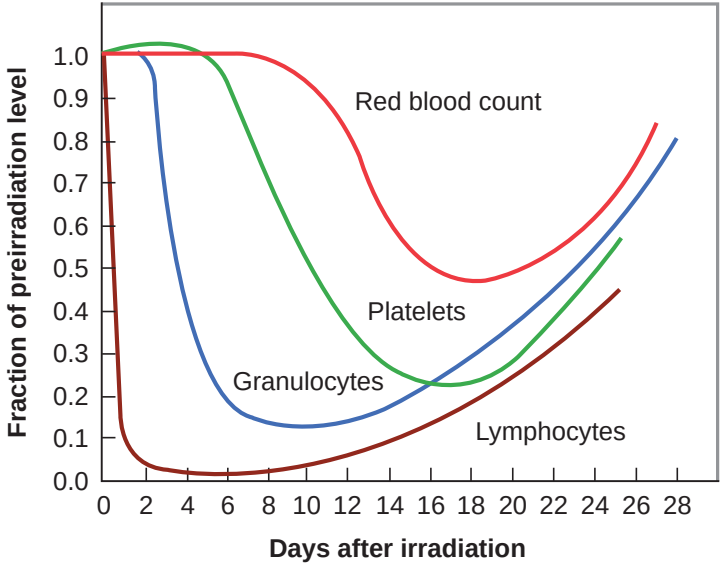




Hematopoietic tissues are located primarily in the bone marrow
Liver and spleen normally have no hematopoietic activity, but can become active in some circumstances

Hematopoietic Tissues

Pattern of depletion and recovery following 4-6 Gy of **TBI**



The stem cells of hematopoietic tissues are particularly radiosensitive with a D_0 < 1 Gy

Lymphocytopenia — Lymphocytes radiosensitive

↓

Granulocytopenia

↓

Thrombocytopenia

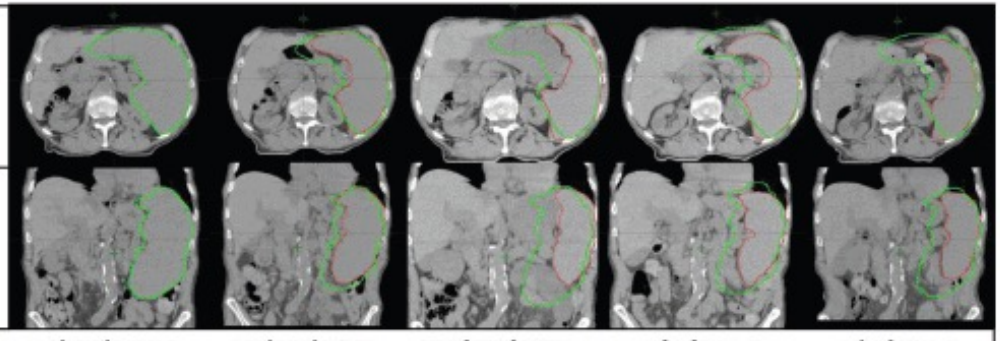
↓

Anemia

The time at which the nadir occurs is a combination of the radiosensitivity of the stem cells and the lifetime of the mature functional cells

Hematopoietic Tissues

Palliative spleen irradiation for splenomegaly

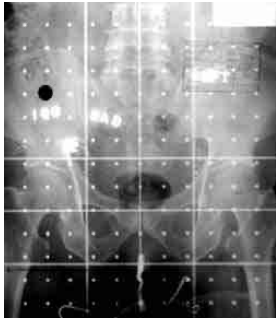


Date Time (weeks)	7/12/2017 0	18/12/2017 1	26/12/2017 2	4/1/2018 3	1/2/2018 8 (4 after the end of the treatment)
CumDose (Gy)	0	5	12,5	20	27,5
SVol. (cm^3)	1866	1576	1085	1177	1036
Vol.Ratio (%)	100	84	58	63	56

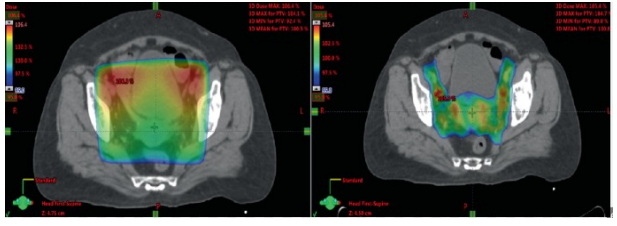
Green line: initial spleen volume; Red line: current spleen volume; CumDose: cumulative dose; SVol.: spleen volume; Vol.Ratio: volume ratio [(current spleen volume/initial spleen volume)x100].

https://doi.org/10.3332/ecancer.2018.887

Hematopoietic Tissues



Partial Body Irradiation



IMRT to spare bone marrow

Irradiated Volume

The effects of partial body radiation on BM are the same as those following total body irradiation
Fractionated dose > 30 Gy may cause permanent aplasia

Unirradiated Volume

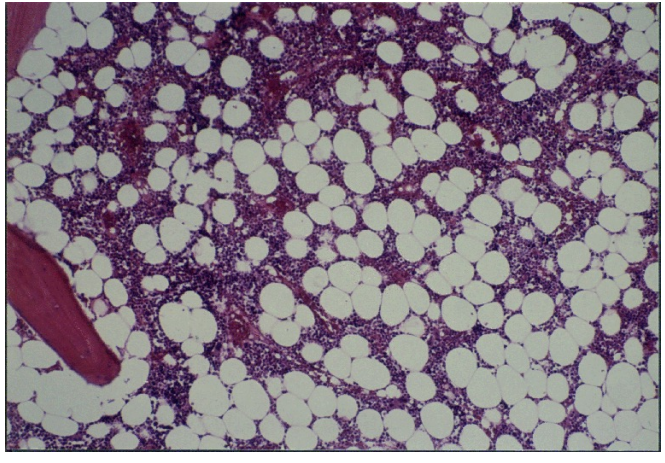
The stem cells start dividing within hours, and **a compensatory hyperplasia** attempts to maintain a total production of blood elements

Hematopoiesis may extend to long bones, liver, spleen

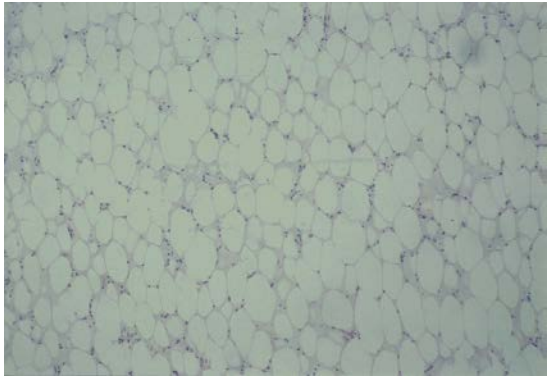
Pools of stem cells falls progressively as differentiation is accelerated

Patients remain sensitive to new insult for months or even years following irradiation

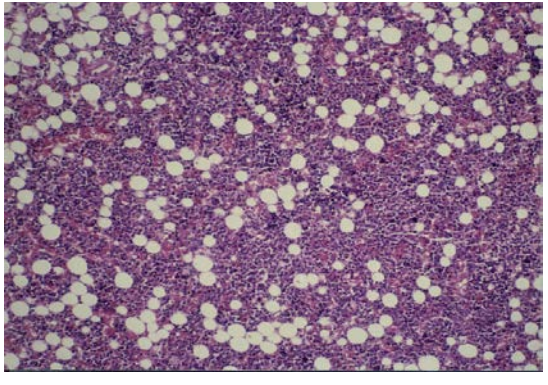
Hematopoietic Tissues



Normal marrow



Hypocellular marrow



Regenerating marrow

Hematopoietic System

Effect of Chemotherapy

Normally, only 10% of hematopoietic stem cells are cycling

Following irradiation, a greater proportion of stem cells divide actively to regenerate blood elements

Many chemotherapy agents specifically target cycling cells

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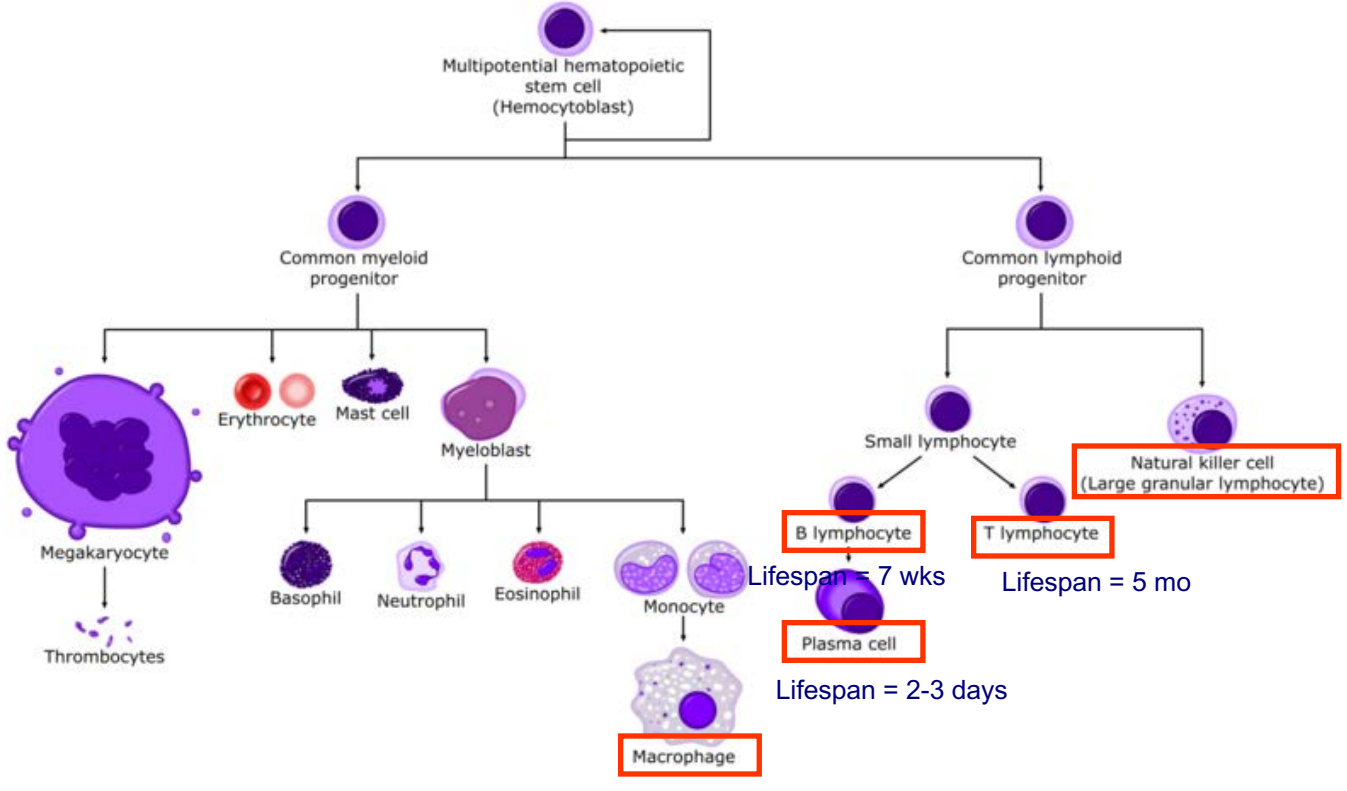
Marrow of patients irradiated to a larger volume are more sensitive to cytotoxic chemo drugs

Lymphoid Tissue and the Immune System



Lymphoid Tissue and the Immune System

RADIATION AND THE IMMUNE RESPONSE

CELL TYPE	RADIOSEN-SITIVITY	RADIORESI-STANCE	OTHER
Macrophage		Resistant up to 100Gy	Activated by radiation
B-cells	80-100cGy		For all lymphocytes, unprimed cells are eliminated quickly following radiation, primed cells remain.
Plasma cells		60-90Gy	
T-Helper	1-2Gy (unprimed)	>10Gy primed	
T-suppressor	1-5Gy (unprimed)	>10Gy (primed)	
T-cytotoxic	2-5Gy for subpopulation (minority)	>10Gy for majority subpopulation	
Granulocytes		Resistant to 50Gy	
NK cells		Resistant to 20Gy	
Hematopoietic precursors	<1Gy		
PMNs	0.9Gy		Short lifespan of PMNs causes loss of PMNs from circulation after irradadiation.

Cytokines—Production is enhanced by radiation; induction is at the level of mRNA.

TBI

Circulating lymphocytes – # rapidly fall

Lymphoid tissue (nodes, spleen) – rapidly depleted of cells

Lymphocytes are very radiosensitive largely because of apoptosis

B cells are more radiosensitive than T cells

Lymphoid Tissue and the Immune System

Effect of Irradiation on Immune Function

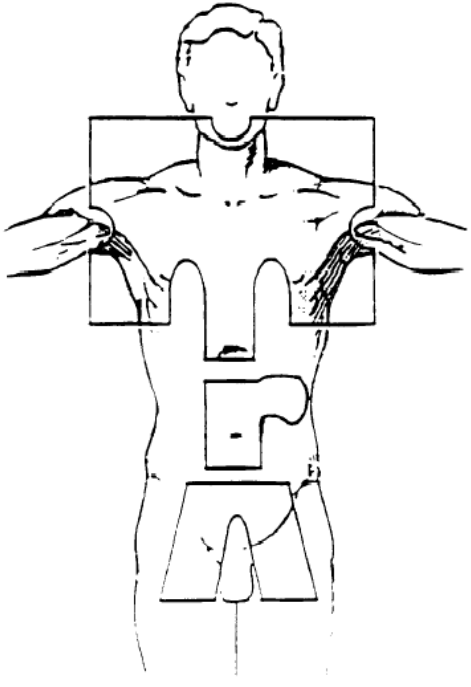
Radiation exposure often result in **increased susceptibility to infection**

The effect depends on the volume irradiated, the number of surviving cells, as well as their capacity to migrate and become lodged in the microenvironment

A total body dose of 3.5-4.5 Gy inhibits the immune response against a new antigen (unprimed T cells are very radiosensitive)

Partial body irradiation has a limited effect on the immune response

Lymphoid Tissue and the Immune System



TLI

Use of Radiation for Immune Ablation

Total lymphoid irradiation (TLI) is used to treat Hodgkin's disease, autoimmune disease, and to prepare patients for organ transplantation

TLI leads to long-lasting T cell lymphopenia

Radiation appears to promote tolerance, enhances the chances of allograft survival

Hematopoietic and Immune Systems

TABLE 20.2 A Compilation of Tissue and Organ Sensitivities

Injury		$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Class I organs			$LD_{50/60}$	
Bone marrow	Aplasia, pancytopenia	2.5	4.5	Whole segment
Lymph nodes and lymphatics	Atrophy, sclerosis	50	70	Whole node

Question 1

Which of the following is the correct temporal sequence for the appearance of the stated radiation effect on peripheral blood components?

A. lymphocytopenia, granulocytopenia, thrombocytopenia, anemia

B. anemia, lymphocytopenia, granulocytopenia, thrombocytopenia

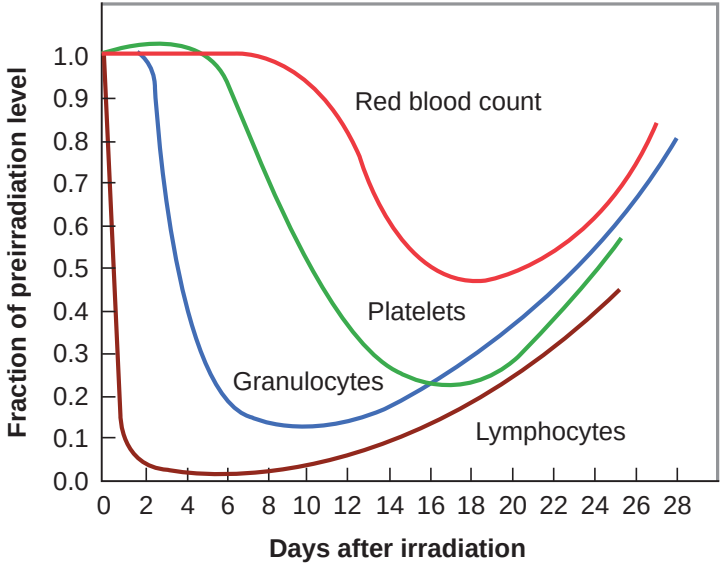
C. granulocytopenia, thromobocytopenia, anemia, lymphocytopenia

D. lymphocytopenia, anemia, granulocytopenia, thrombocytopenia

E. lymphocytopenia, thrombocytopenia, granulocytopenia, anemia

Hematopoietic Tissues

Pattern of depletion and recovery following 4-6 Gy of **TBI**



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Lymphocytopenia — Lymphocytes radiosensitive

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Granulocytopenia

↓

Thrombocytopenia

↓

Anemia

The time at which the nadir occurs is a combination of the radiosensitivity of the stem cells and the lifetime of the mature functional cells

Question 2

Which of the following statements is TRUE concerning radiation effects on the bone marrow?

A. In general, B cells are more radiosensitive than T cells.
B. Following total body irradiation, thrombocytopenia is typically observed before neutropenia.
C. Lymphocyte counts do not drop until several weeks after total-body irradiation.
D. Individuals suffering from the bone marrow syndrome usually die of severe anemia.

Lymphoid Tissue and the Immune System

RADIATION AND THE IMMUNE RESPONSE

CELL TYPE	RADIOSEN-SITIVITY	RADIORESI-STANCE	OTHER
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TBI

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Lymphocytes are very radiosensitive largely because of apoptosis

B cells are more radiosensitive than T cells

Question 3

Which of the following types of blood cells is most radioresistant?

A. Granuocyte/monocyte colony forming cells (GM-CFC)
B. Spleen-colony forming units (CFU-S)
C. Macrophages
D. Unprimed T-helper cells
E. B-cells

Question 4

Which of the following statements is TRUE concerning radiation effects on the bone marrow?

A. The absolute lymphocyte count rate of decrease over 2 days may estimate the severity of total body irradiation induced injury

B. Following total body irradiation, thrombocytopenia is typically observed before neutropenia

C. Lymphocyte counts do not decrease until several weeks after total body irradiation

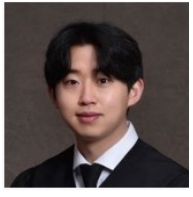
D. Individuals suffering from bone marrow syndrome usually die of severe anenmia

E. There is no late effect pathology associated with bone marrow irradiation

Take My Money

Having all that money would be stressful!

I would probably donate most because I know that many lottery winners end up with less money than they had originally.

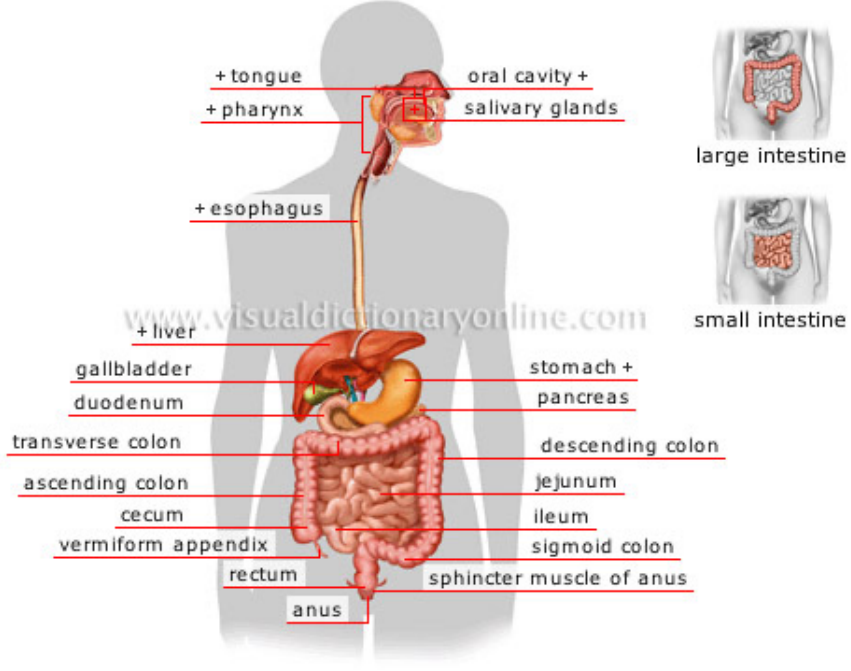
A. 

B. 

C. 

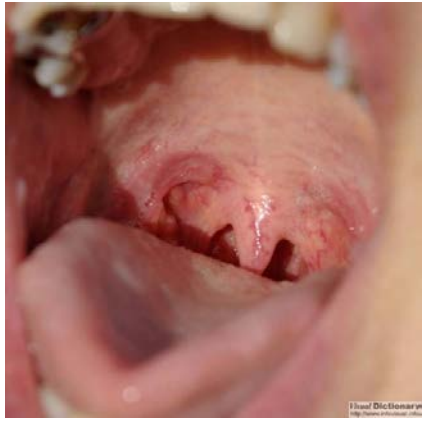
D. 

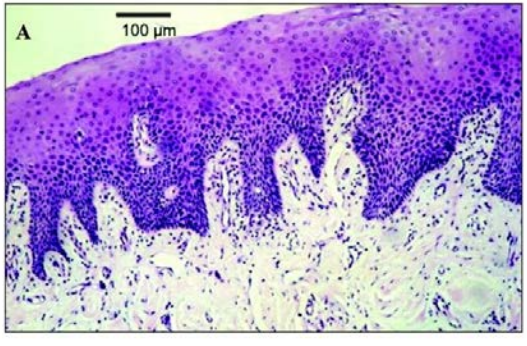
The Digestive Tract



The digestive tract is made up of several organs like the **oral cavity**, **pharynx**, **esophagus**, **stomach**, **small intestine**, **large intestine**, **rectum** and the **anus**

The Digestive Tract – Oral Cavity





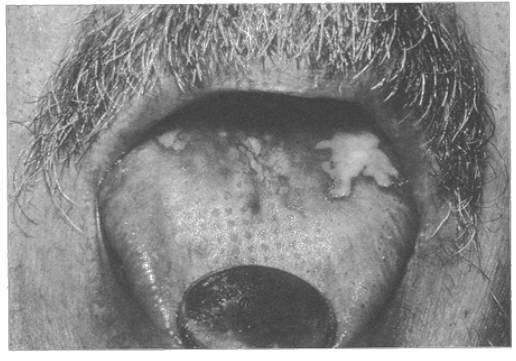
H-Type Tissue

The cellular organization of the oral mucosa is similar to that of the skin

The lifespan of the differentiated cells is much shorter than in epidermis → more rapid reaction to radiation

Mucositis is a major dose limiting factor in the treatment of head & neck cancer

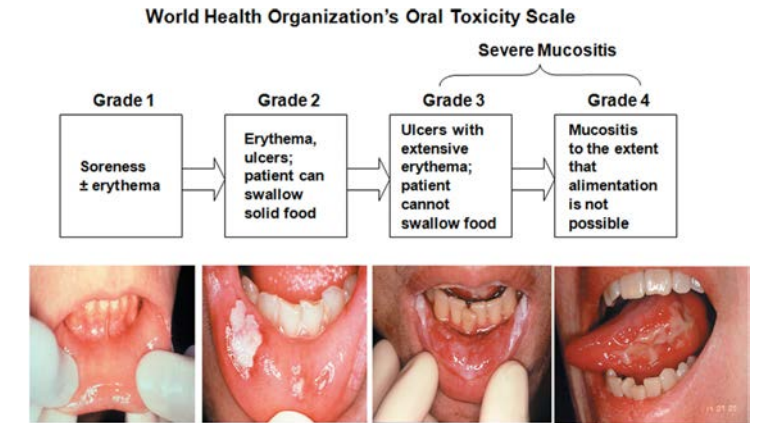
The Digestive Tract – Oral Cavity



Confluent mucositis

Desquamation of the oral cavity occurs by about day 12

Desquamation occurs first in the soft palate, followed by the hypopharynx, vallecula, floor of mouth, cheeks, epiglottis, base of tongue, vocal cords, and dorsum of tongue

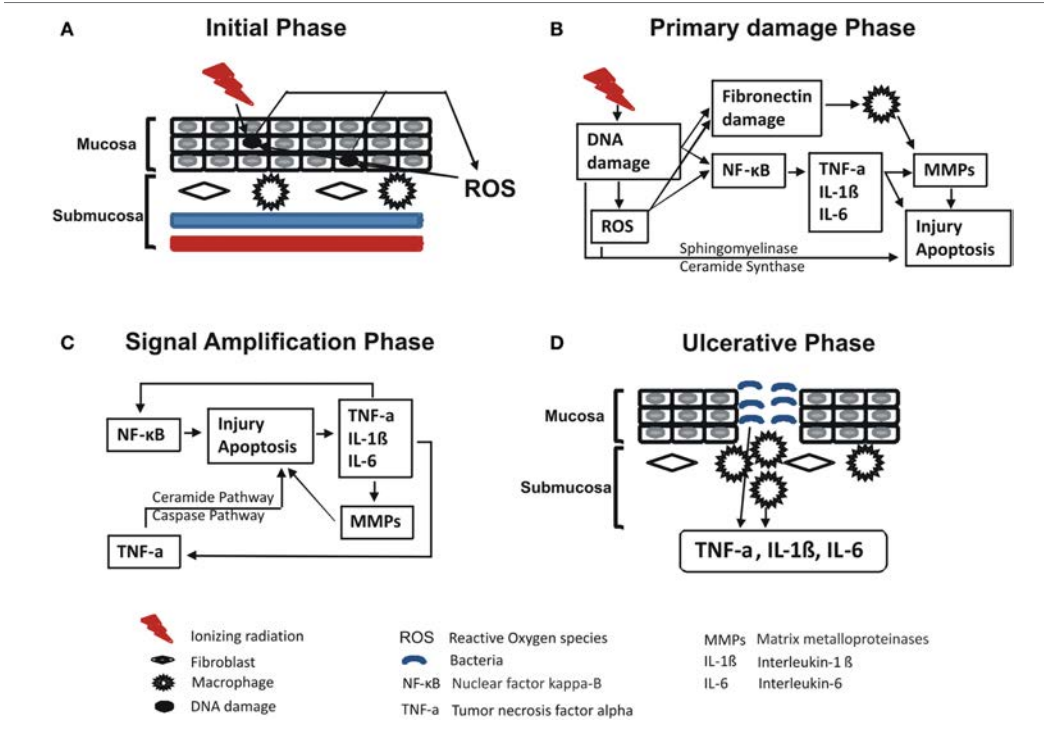


The Digestive Tract – Oral Cavity

The pathophysiology of radiation-induced oral mucositis (RIOM) is not fully understood

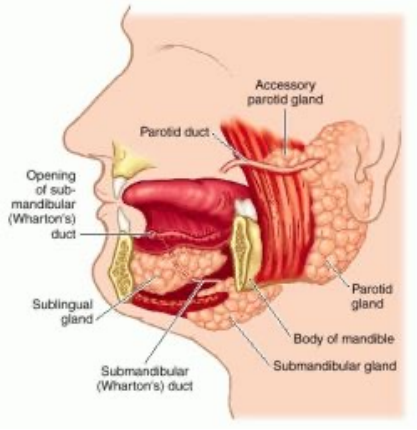
Recent studies proposed that the pathogenesis of RIOM involves release of various **pro-inflammatory cytokines** from epithelial, vascular, and connective tissue cells at the site of tissue injury

Secondary infection with bacteria or yeast may also occur



Maria 2017; Frontiers in Oncology 7: 89

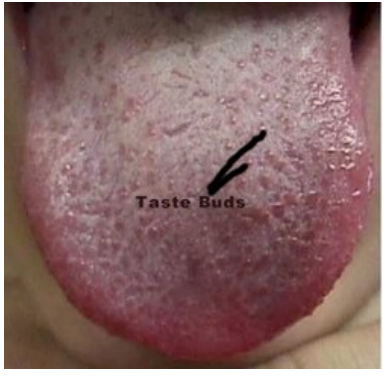
The Digestive Tract – Oral Cavity



Salivary Gland

The serous acinar cells of the salivary glands die by **apoptosis**

Xerostomia (dry mouth) appears during and after radiation and is the main clinical effect that can interfere with nutrition, deteriorate oral hygiene, and predispose to dental problems



Taste Buds

Impairment of taste acuity occurs during the 3rd week

The Digestive Tract – Oral Cavity

Sequence of Events During Treatment of H&N Cancer

Week 1

Asymptomatic to slight focal hyperemia and edema caused by dilatation of capillaries in sensitive patients

Week 2

Increasing pain and loss of desire to eat
Sense of taste is altered
Erythema and edema increase
Early patchy desquamative mucositis occurs

The Digestive Tract – Oral Cavity

Week 3

Mucositis and swelling with depletion of gland secretions leading to difficulty in swallowing
Mucositis plaques are confluent

Week 4

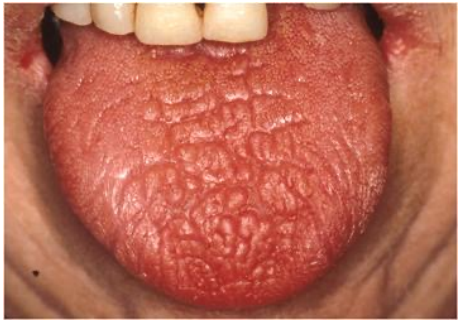
Confluent mucositis sloughs, resulting in denuded lamina propria
Mucosa becomes covered by fibrin and neutrophils

Week 5

Maximum radiation damage apparent
Extreme sensitivity to touch, temperature, and grainy food
Recovery of epithelial layer may begin during therapy

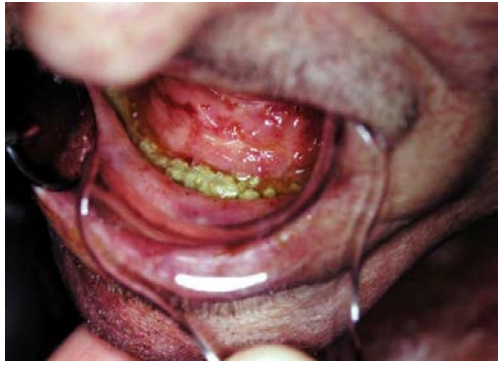
The Digestive Tract – Oral Cavity

Late Effects



Oral Tongue

Tongue consists of muscle bundles which undergo mild progressive **fibrosis** and **fiber atrophy** after irradiation
Picture also showing severe xerostomia



Osteoradionecrosis (ORN)

ORN can be spontaneous, but it most commonly results from tissue injury. Even apparently innocuous forms of trauma such as denture-related injury, ulcers, or tooth extraction can overwhelm the reparative capacity of the radiation-injured bone. **Pentoxifylline** may be helpful for the treatment of radiation fibrosis and osteoradionecrosis.

The Digestive Tract – Oral Cavity

	Injury	$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Oral cavity and pharynx	Ulceration, mucositis	60	75	50 cm^2
Salivary glands	Xerostomia	32	46	1/3 or 1/2

QUANTEC

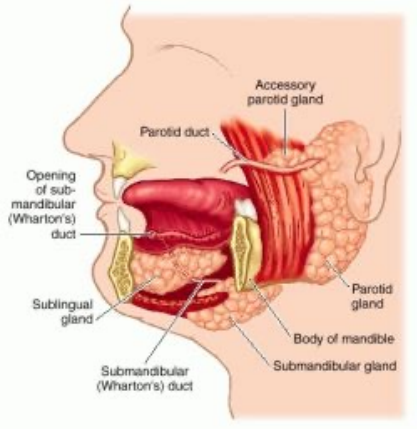
Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Pharynx	Pharyngeal constrictors	Whole organ	Symptomatic dysphagia and aspiration	Mean dose <50	<20	Based on Section B4 in paper
Parotid	Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <25	<20	For combined parotid glands¶
	Unilateral whole parotid gland	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <20	<20	For single parotid gland. At least one parotid gland spared to <20 Gy¶
	Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <39	<50	For combined parotid glands (per Fig. 3 in paper) ¶

Question 1

Which of the following statements is TRUE concerning irradiation of the salivary glands?

A. Serous acinar cells die only by mitotic catastrophe after irradiation.
B. The serous acinar cells of the parotid and submaxillary glands are considered the target cells for radiation-induced salivary gland damage.
C. Salivary dysfunction is a late radiation effect rarely observed earlier than six months following treatment.
D. Mucous cells are more radiosensitive than serous cells.
E. Dose fractionation results in significant sparing of serous cells.

The Digestive Tract – Oral Cavity



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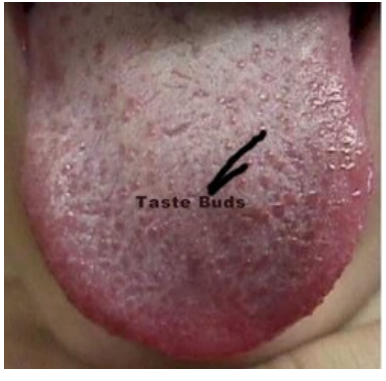


Taste Buds

Impairment of taste acuity occurs during the 3rd week

Question 2

Medical residents only

The tolerance dose for xerostomia resulting from treatment of a head and neck tumor with 3 Gy fractions compared to 2 Gy fractions would be expected to:

A. Increase substantially
B. Increase slightly
C. Decrease substantially
D. Remain about the same
E. Either increase or decrease depending upon the particular patient

Serous cells die by apoptosis, hence tolerance not influenced by fraction size

Question 3

Medical residents only

One type of radiation-induced bone injury is mandibular radionecrosis (MORN). Which of the following is NOT a risk factor for MORN?

A. Presence of teeth
B. Pre-existing dental disease
C. Use of fluorinated water
D. Tooth extraction after radiotherapy
E. Use of large doses per fraction during treatment

Medical residents only

Question 4

The oral mucosa and skin present with many similar pathological features during their progression toward radiation toxicity. Which of the following statements regarding the overlapping pathologies observed in these tissues is FALSE?

A. Oral mucositis is a result of the death and consequent desquamation of the epithelial layers, and is therefore an analogous event to the radiodermatitis (dry/moist desquamation) seen as an early response in irradiated skin

B. Erythema secondary to vasodilation is observed in skin following doses greater than about 2 Gy, similar to the case for mucositis

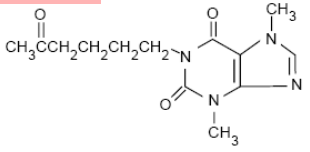
C. Radiation effects in both oral mucosa and skin are dependent on total dose, fraction size, and volume irradiated

D. Possible late effects in both skin and oral mucosa include ulceration and fibrosis

E. The development of dental caries following oral radiotherapy is similar mechanistically to the infections that accompany radiation-induced dermal ulcers; both result from ischemic necrosis due to the loss of small blood vessels (dental caries are results of xerostomia rather than infection)

Question 5

Medical residents only

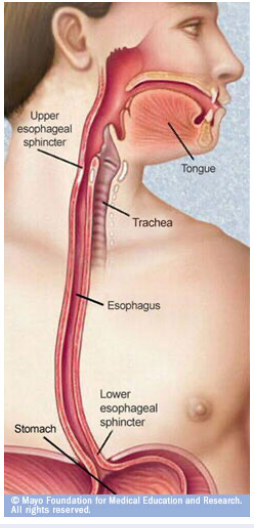


A drug used to treat fibrosis and osteoradionecrosis is:

A. Amifostine
B. Tirapazamine
C. Nicotinamide
D. Pentoxifylline
E. Misonidazole

- Pentoxifylline is a commonly used medication for muscle pain associated with peripheral artery disease. It improves peripheral blood flow, flexibility of red blood cell membranes, microcirculation, and tissue oxygenation and reduces viscosity of blood.
- Tocopherol (vitamin E) impairs tissue fibrosis and is a potent oxygen radical scavenger that may reduce damage caused by free radicals impacting necrosis.

The Digestive Tract – Esophagus



Rapid proliferating squamous cell epithelium

Acute

Esophagitis appear at about 10 - 12 days
Symptoms include dysphagia, odynophagia (pain with swallowing) or acid reflux
Can be potentiated by hyperfractionation; concurrent chemotherapy

Late

Late effects are related to **muscle layer**; they include necrosis and a thickening of the epithelium
Symptoms include difficulty on swallowing and ulceration after high doses

	Injury	$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Esophagus	Esophagitis, ulceration	55 60	50 70	Whole 1/3

Esophagus	Whole organ	3D-CRT	Grade ≥3 acute esophagitis	Mean dose <34	5–20	Based on RTOG and several studies
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V35 <50%	<30	A variety of alternate threshold doses have been implicated. Appears to be a dose/volume response
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V50 <40%	<30	
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V70 <20%	<30	

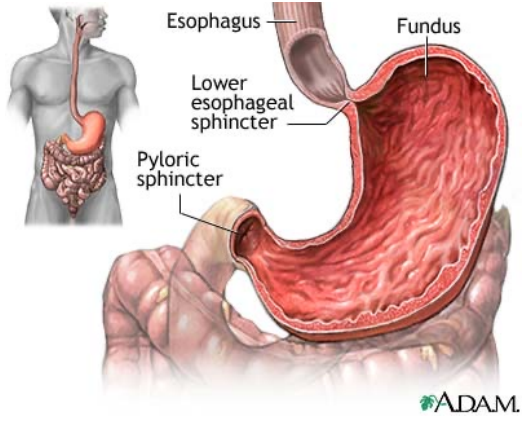
Question 1

Medical residents only

Acute radiation esophagitis presents as dysphagia or a substernal burning sensation as early as 2 weeks after the start of conventionally fractionated radiation therapy. Medical management most often involves:

A. Angiotensin converting enzyme inhibitors
B. Gene therapy with manganese superoxide dismutase
C. Non-steroidal anti-inflammatory drugs
D. Pentoxifylline
E. Vitamin E

The Digestive Tract – Stomach



Precursor cells of gastric glands give rise to mucin-secreting surface columnar cells with short lifespan (~ 3 or 4 days) and to acid-secreting parietal and pepsinogen-secreting chief cells that have long lifespan (hundreds of days)

Early

Irradiation causes nausea, vomiting
Delayed gastric emptying and **epithelial denudement** are the two main early radiation effects

Acute ulceration may occur shortly after the completion of treatment (> 40 Gy) but rarely leads to perforation

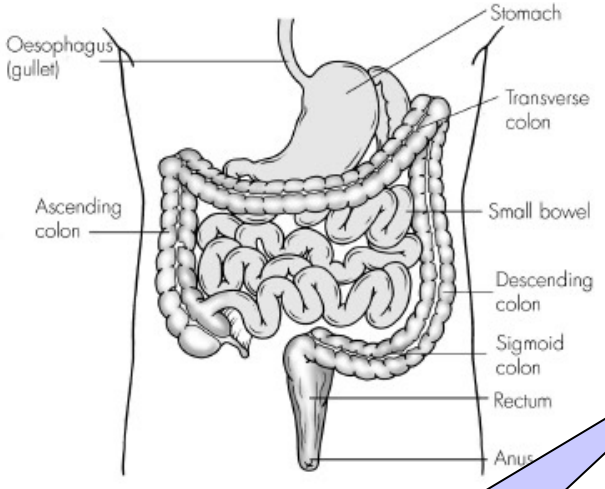
Late

Dyspepsia (6 months to 4 yrs) and **gastritis** (1 to 12 months)
Late ulceration **and** **submucosal fibrosis** leading to antral fibrosis

	Injury	$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Stomach	Perforation, ulcer, hemorrhage	50 60	65 70	Whole 1/3

Stomach	Whole organ	Whole organ	Ulceration	D100‖ <45	<7	

The Digestive Tract – Small and Large Intestine



Should be viewed as persistent unchecked inflammatory response

Early

Acute mucositis due to epithelial denudation
Symptoms manifest as **diarrhea**
Regenerative response appears rapidly
Acute symptoms are seldom dose-limiting – interruption of treatment for a few days usually alleviate symptoms

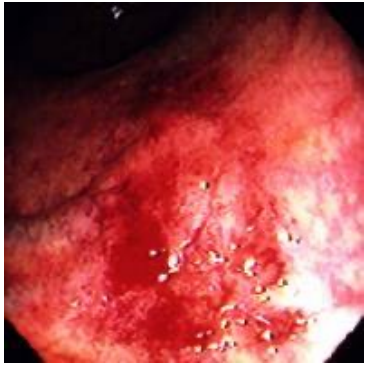
Late

Fibrosis and **ischemia** are typical late effects
Late effects involve **all tissue layers** and are caused by atrophy of the mucosa (due to vascular injury)
Subsequent breakdown results from mechanical irritation and bacterial infection

Overgrowth of the fibromuscular tissue with **stenosis** and serosal breakdown and **adhesion** formation may also occur

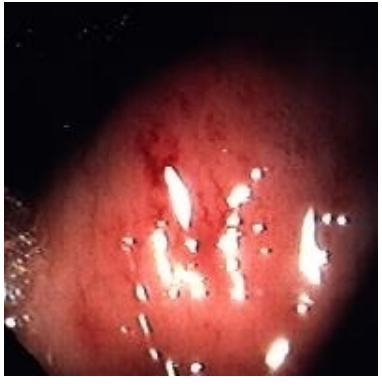
The Digestive Tract – Small and Large Intestine

Small bowel



Friability and oozing of blood from atrophic-appearing mucosa due to radiation

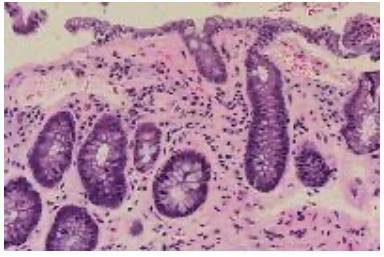
Large bowel



Characteristic mucosal changes observed in radiation proctitis with multiple telangiectasias

Sucralfate enemas constitute first-line treatment of hemorrhagic radiation proctitis.
Laser photocoagulation, **argon beam coagulation**, and **local formalin therapy** are also efficacious and may be considered as second-line therapy in such patients.

The Digestive Tract – Small and Large Intestine

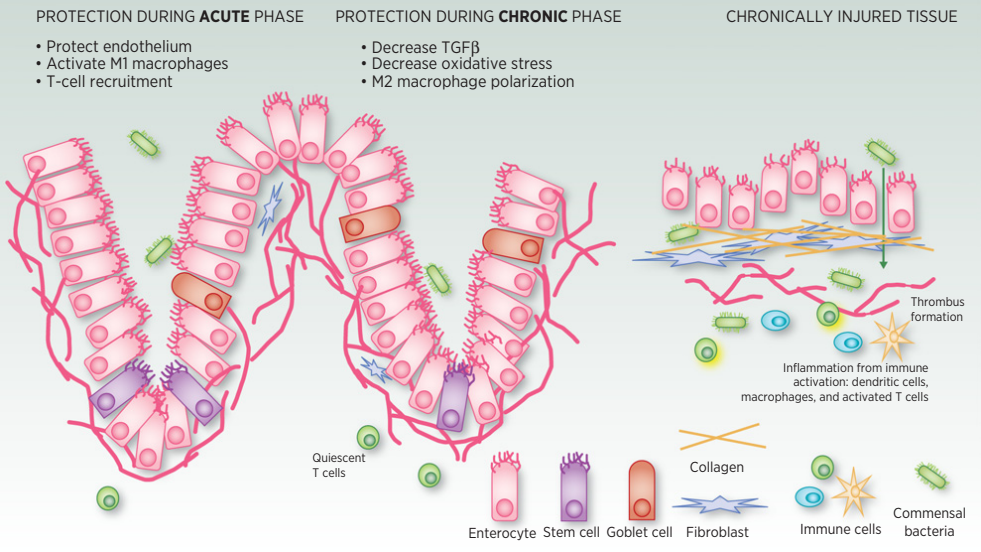


This slide illustrates disorderly crypts, fibrosis of lamina propria, and vascular dilatation, all of which are characteristic of colonic injury due to radiation

	Injury	$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Intestine	Obstruction, perforation, fistula	40 50	55 65	Whole 1/3 or 1/2
Rectum	Ulcer, stenosis, fistula	60	80	No volume effect

Small bowel	Individual small bowel loops	3D-CRT	Grade ≥ 3 acute toxicity[§]	V15 <120 cc	<10	Volume based on segmentation of the individual loops of bowel, not the entire potential peritoneal space
	Entire potential space within peritoneal cavity	3D-CRT	Grade ≥ 3 acute toxicity[§]	V45 <195 cc	<10	Volume based on the entire potential space within the peritoneal cavity
Rectum	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V50 <50%	<15 <10	Prostate cancer treatment
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V60 <35%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V65 <25%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V70 <20%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V75 <15%	<15 <10	

Therapeutic Opportunities with Pharmacologic Mitigators



Key Features

- Flattening of villi
- Relative depletion of stem cells
- Increase in goblet cells
- Fibrosis
- Microvascular rarefaction
- Chronic inflammation

1. Directly protect against or mitigate the O_2 free radical injury
2. Target downstream tissue responses after radiation exposure

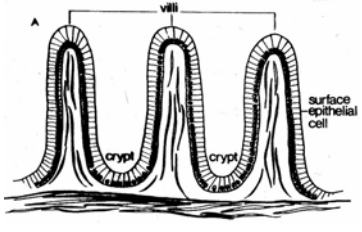
Huh 2020 – Clinical Cancer Research; 26: 3079-90

Question 1

Which of the following effects is typically observed within a week following irradiation of the small intestine?

A. hypertrophic villi
B. lymphocyte infiltration
C. atrophic villi
D. mucosal atrophy
E. bowel stenosis

Think about this picture:



Question 2

Concerning irradiation of the small and large intestine, which of the following statements is FALSE?

A. Chronic radiation injury is attributable primarily to fibrosis and vascular insufficiency (chronic ischemia)

B. The most common portions of the intestinal tract that display radiation damage include the cecum, terminal ileum, rectum, and distal sigmoid

C. Acute radiation injury is most prominent in the mucosa, whereas late effects tend to manifest themselves in the submucosa

D. Compared to hierachical tissues, the gastrointestinal mucosal is a slowly renewing system

E. Killing of the stem cells in the gut crypts and the resulting failure to replace mature cells causes the gastrointestinal syndrome following acute radiation exposure

Even if you are not sure of all the statements, focus on what you do know

Question 3

Which of the following statements concerning complications arising from pelvic irradiation is FALSE?

A. Diarrhea is the most common manifestation of radiation injury to the bowel

B. Diarrhea usually does not appear until at least 6 months following the completion of radiotherapy

C. Late bowel reactions include mucosal atrophy, stenosis, ulceration, obstruction, adhesions and perforation.

D. Bowel stenosis can develop in the absence of severe mucosal atrophy or ulceration

E. Adhesions following irradiation contribute to late bowel injury and usually develop 2-7 months after irradiation

Diarrhea is an early response that occurs during the course of radiation therapy

Question 4

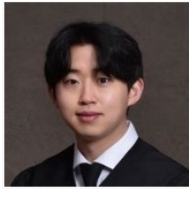
What portion of the gastrointestinal tract generally exhibits the greatest **acute** radiation-induced injury for a given dose?

A. Stomach
B. Oropharynx
C. Small intestine
D. Large intestine
E. Esophagus

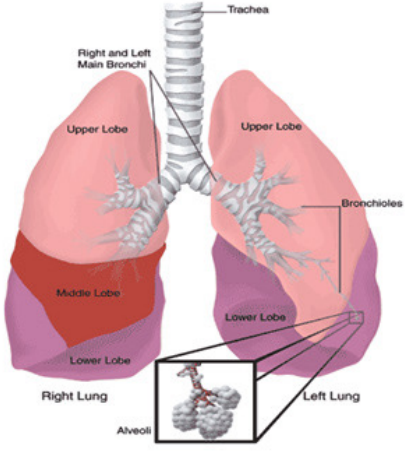
Think about GI syndrome in the context of total body irradiation

Entrepreneur & Philanthropy

With that much money, I would try to open a radiation center in a low resource area of the world and work in it. After opening and running the clinic, I would retire early and focus on raising a good family



Lungs



Structurally defined FSU in parallel
Late-responding tissue with α/β ratio of 3 Gy
Tolerance depends on dose, volume, and fraction size

Radiation target cells – pulmonary endothelial cells & type II pneumocytes

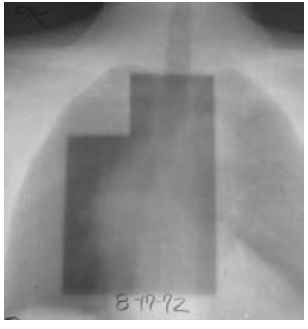
Subacute

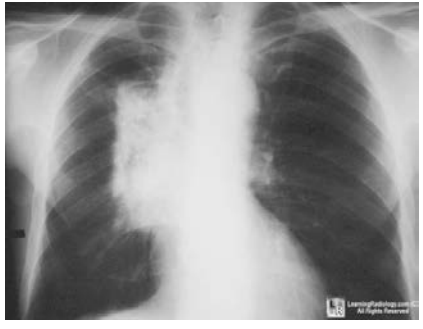
Acute (subacute) pneumonitis
Latency – 2- 6 months
Symptoms – cough, dyspnea, may be asymptomatic
Imaging – opacity on chest x-ray

Late

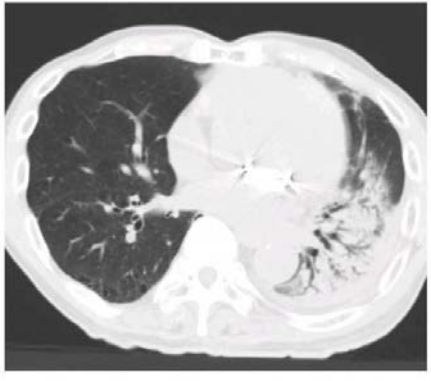
Pulmonary fibrosis
Latency – more than a year
Symptoms – difficulty with breathing
TGF-β plays an important role in lung fibrosis

Lungs





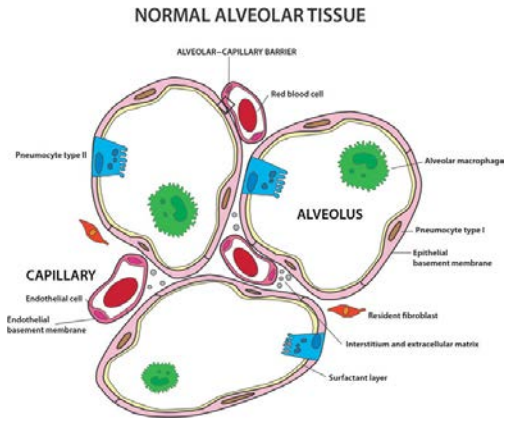
Radiation pneumonitis



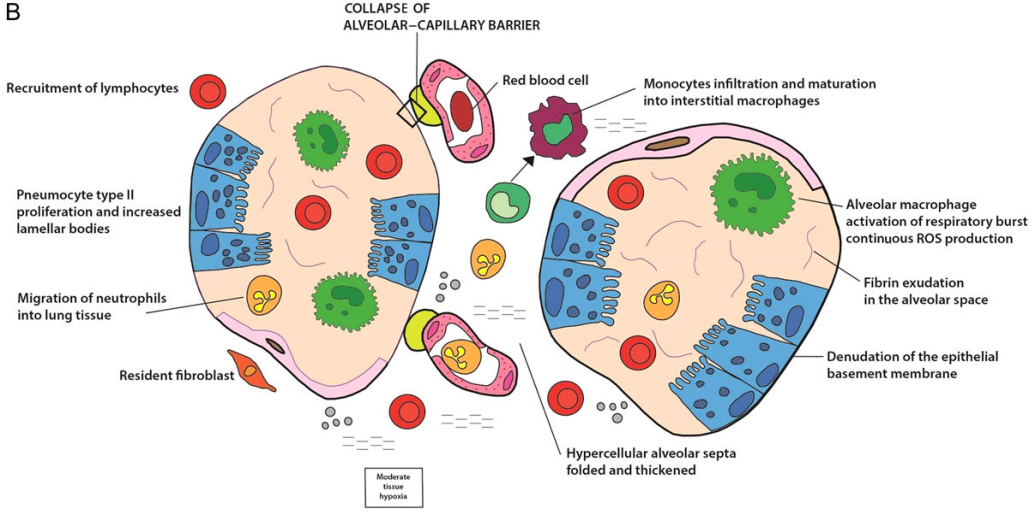
Regions of pneumonitis can extend outside of the treatment field, known as *abscopal* effects.

Chemo agents such as bleomycin, cyclophosphamide, mustines can also cause lung damage → concurrent use of radiation and these drugs will reduce lung tolerance

Cytokines and Radiation-Induced Lung Injuries



Acute Phase of Radiation Pneumonitis

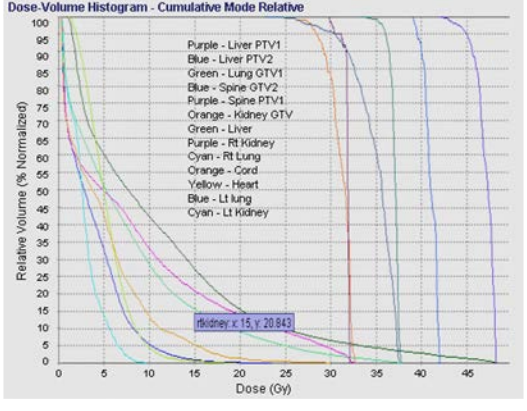


Classical paradigm of the target cell kill hypothesis has shifted to a theory of **orchestrated response**, starting with *ROS generation*, followed by various activation of *signal transduction pathways* inducing processes leading to replacement of damaged cells, influx of inflammatory cells from peripheral blood and **cytokine production**, and development of radiation complications.

Lungs

	Injury	$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Lung	Acute and chronic pneumonitis	17.5 45	24.5 65	Whole 1/3

Because of the parallel arrangement of FSU, small volume can tolerate high dose

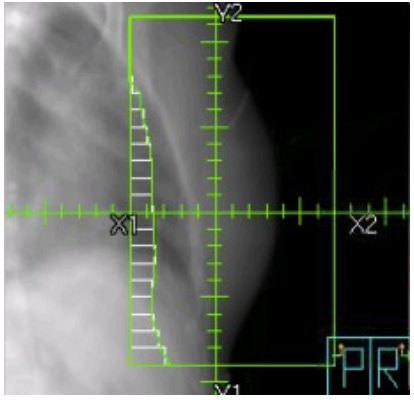


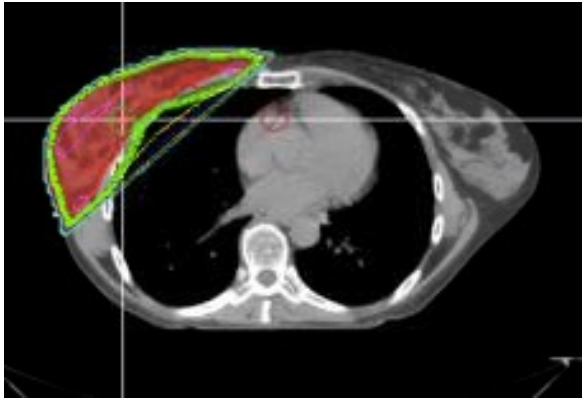
Dose Volume Histogram

In practice, many radiation oncologists are using the V20, V30 (i.e., the volume of lung receiving 20 Gy, 30 Gy) or mean lung dose as a defining limiting factor

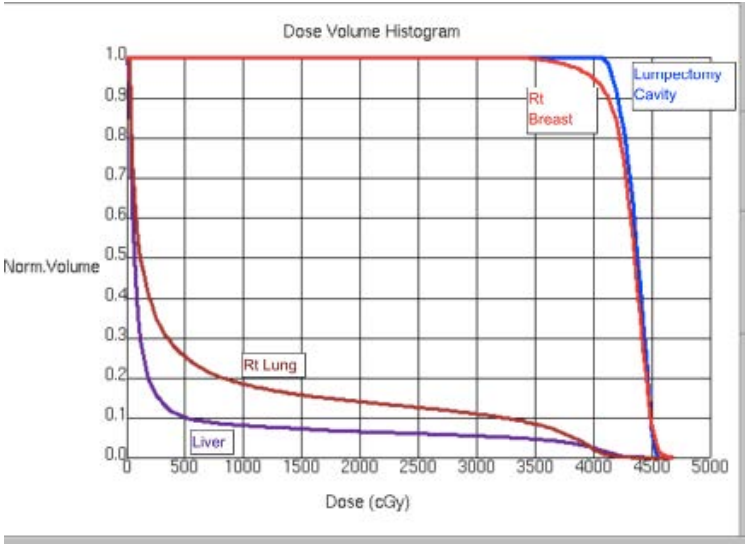
Lung	Whole organ	3D-CRT	Symptomatic pneumonitis	V20 ≤ 30%	<20	For combined lung. Gradual dose response
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 7	5	Excludes purposeful whole lung irradiation
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 13	10	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 20	20	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 24	30	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 27	40	

Lungs – Case Study

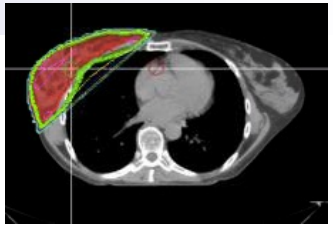




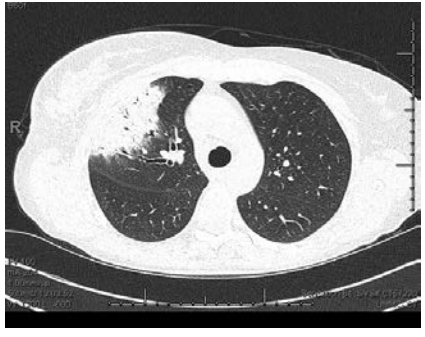
- 4240 cGy / 16 fx + 1000 cGy / 4 fx boost
- Completed July, 2013

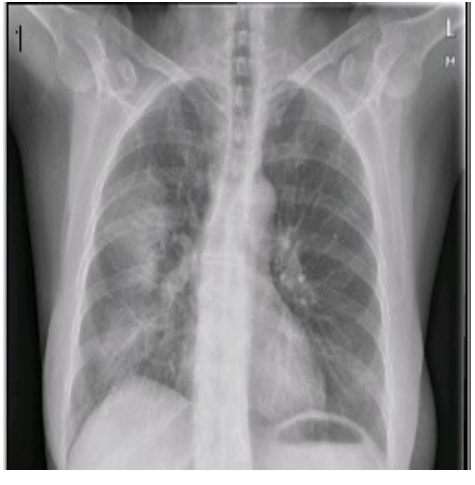


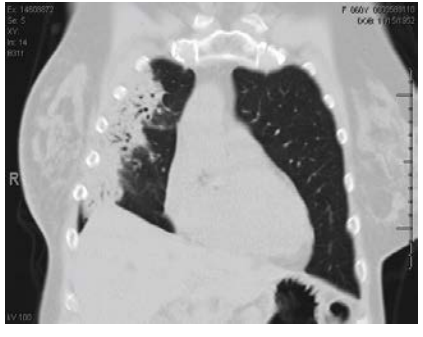
Oct 2013 (3 mo s/p XRT)



- Dry cough, fever 100.8° F, chest tightness
- Sx not improved with Abx







Her symptoms resolved with prolonged steroids

Question 1

Which of the following statements regarding the development of radiation-induced lung damage is TRUE?

A. The volume of lung irradiated has relatively little effect on the tolerance dose. Parallel FSU, strong volume effect.

B. Radiation-induced pneumonitis is delineated by the treatment field. Abscopal effect. See slide.

C. The majority of patients who develop radiation pneumonitis go on to develop pulmonary fibrosis.

D. The $TD_{5/5}$ for whole lung irradiation with a single dose is approximately 17.5 Gy. See Emami Table

E. Fractionation has little or no effect on lung tolerance.

Question 2

The tolerance dose 5% in 5 yrs (TD5/5) and 50% in 5 yrs (TD50/5) for lung pneumonitis is best represented by which of the following doses?

A. 8Gy and 15Gy respectively
B. 17Gy and 24Gy respectively
C. 22Gy and 30Gy respectively
D. 32Gy and 39Gy respectively

	Injury	$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Lung	Acute and chronic pneumonitis	17.5 45	24.5 65	Whole 1/3

Fractionated dose

Question 3

Medical residents only

With respect to radiation-induced toxicity in the lung, which of the following statements is FALSE?

A. The likelihood of the injury is dependent on the volume irradiated

B. Radiation pneumonitis is a characteristic late effect of lung radiotherapy that occurs 6-12 months after treatment completion. Latency = 2-6 mo

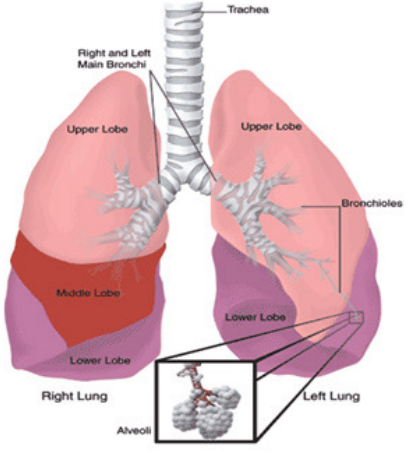
C. The dose response curve for lung injury following whole lung irradiation is steep regardless of the dose per fraction used

D. Lung toxicity is enhanced when radiation is combined with carboplatin-paclitaxel.

E. Several cell types are involved in the development of pulmonary late effects, including the type II pneumocyte, the alveolar macrophage and vascular endothelial cells

See slide

Lungs



Structurally defined FSU in parallel
Late-responding tissue with α/β ratio of 3 Gy
Tolerance depends on dose, volume, and fraction size

Radiation target cells – pulmonary endothelial cells & type II pneumocytes

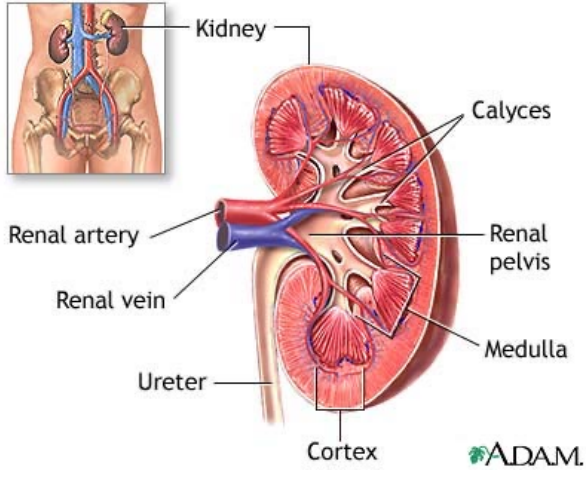
Subacute

Acute (subacute) pneumonitis
Latency – 2- 6 months
Symptoms – cough, dyspnea, may be asymptomatic
Imaging – opacity on chest x-ray

Late

Pulmonary fibrosis
Latency – more than a year
Symptoms – difficulty with breathing
TGF-β plays an important role in lung fibrosis

Kidneys



Kidney is a late-responding tissue

Renal irradiation can lead to the development of **radiation nephropathy**, which is characterized by proteinuria, anemia, hypertension and a chronic, progressive decrease in renal function

The morphologic changes include glomerulosclerosis, tubulointerstitial fibrosis

Recent data from both the laboratory and clinic suggest that this late effect can be modulated by drugs that drugs that block the **renin-angiotensin system**

Kidneys

FSU = nephron (each containing ~ 1,000 stem cells)

Tolerance dose – because of the small size of each FSU, kidney has a relatively low tolerance dose

Volume effect – because of the parallel FSU arrangement, part of the kidney may tolerate much higher doses

	Injury	$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Kidney	Acute and chronic nephrosclerosis	23	28	Whole
		50	45	1/3 or 1/2

Kidney	Bilateral whole kidney‡	Bilateral whole organ or 3D-CRT	Clinically relevant renal dysfunction	Mean dose <15–18	<5	
	Bilateral whole kidney‡	Bilateral whole organ	Clinically relevant renal dysfunction	Mean dose <28	<50	
	Bilateral whole kidney‡	3D-CRT	Clinically relevant renal dysfuntction	V12 <55% V20 <32% V23 <30% V28 <20%	<5	For combined kidney

Question 1

Which of the following statements is TRUE concerning the response of the kidney to radiation? The kidney:

A. is considered a relatively radiosensitive organ because of the marked sensitivity of cells that comprise the nephron
B. exhibits little sparing with increasing dose fractionation
C. has a relatively low tolerance dose because of the limited number of cells that comprise each functional subunit
D. displays substantial re-treatment tolerance
E. manifests symptoms of radiation nephropathy generally within 3 months following the completion of radiotherapy

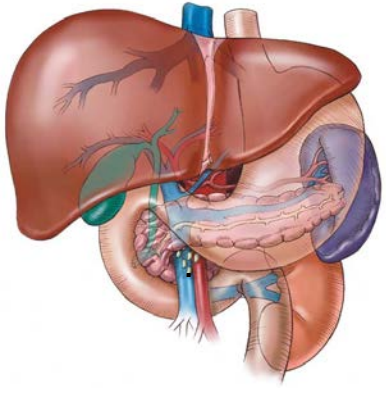
Question 2

Medical residents only

Renal irradiation can lead to the development of radiation nephropathy, which is characterized by proteinuria, anemia, hypertension and a chronic, progressive decrease in renal function. The decline in kidney function characteristic of radiation nephropathy can be:

A. Treated with anti-hypertensive agents such as beta blockers
B. Prevented using anti-inflammatory agents
C. Reversed using calcium channel blockers
D. Mitigated using drugs that block the renin-angiotensin system
E. Accelerated at lower radiation doses

Liver



Radiation-Induced Liver Disease (RILD)

(Historically called "radiation hepatitis“)

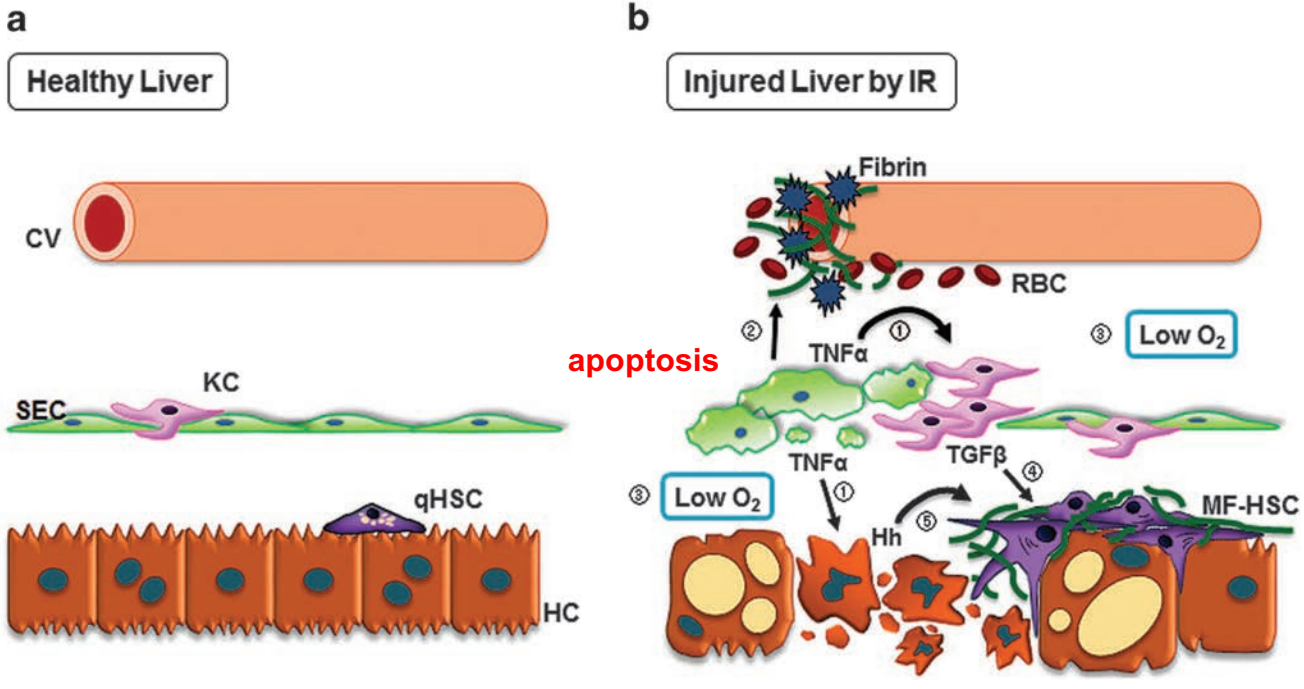
Usually develops 1-2 months after RT (range 2 weeks - 8 months)

Clinical syndrome – fatigue, ascites, anicteric hepatomegaly, elevated liver function tests (esp. alkaline phosphatase)

Pathologic changes – veno-occlusive disease (VOD), marked central venous congestion, sparing of large veins, entrapment of erythrocytes, atrophy of adjacent hepatocytes

Pathogenesis – since the principal observed injury in the liver is vascular in nature, the radiobiological target has been hypothesized as the **endothelial cell**

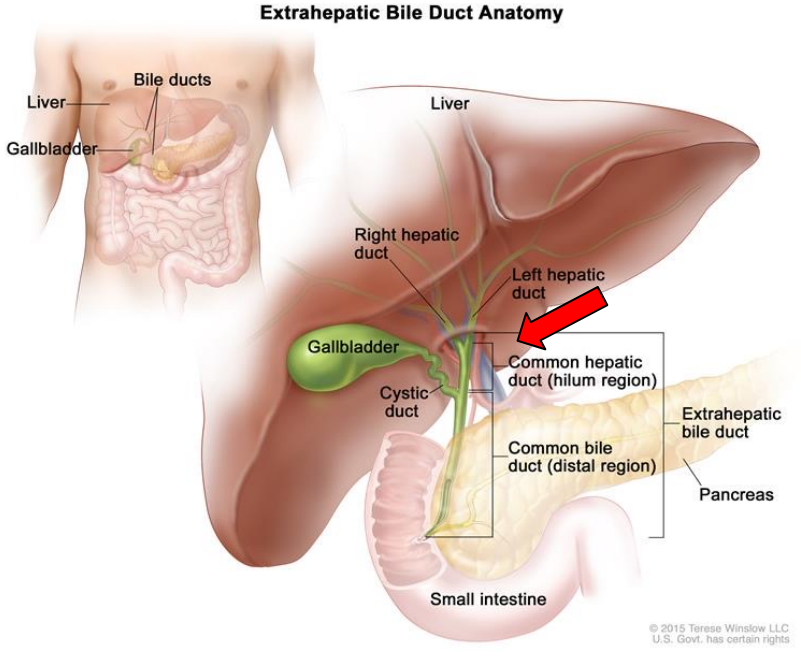
Liver



RILD pathogenesis includes complex and multicellular responses associated with vascular changes, increased collagen synthesis and sequential activation of key growth factors and cytokines, such as **TNF-α**, **TGF-β** and **hedgehog** (Hh), which are important regulators in repair responses to liver damage.

Kim & Jung 2017 – Experimental & Molecular Medicine 49: e359

Liver



- Liver **hilum** (where bile duct, hepatic artery, and portal veins are centrally located) functions as a **serial** FSU tissue
- Damage to the bile duct will lead to dysfunctionality

Liver

Tolerance – in terms of radiosensitivity, liver ranks immediately below the kidney and lung

Volume effect – FSU arranged in parallel, therefore much larger doses are tolerated if only part of the organ is exposed; on the other hand, fatal hepatitis may result from a fractionated protocol of only 35 Gy if the whole liver irradiated (life span of hepatocyte is ~ 1 year)

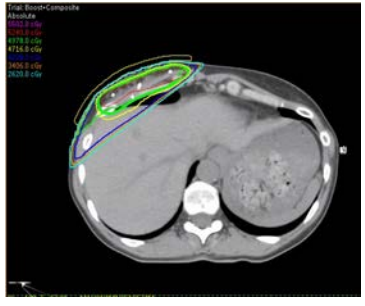
	Injury	$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Liver	Acute and chronic hepatitis	30 50	40 55	Whole 1/3

Liver

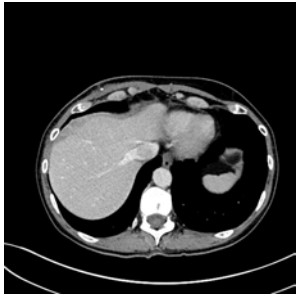
Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)[†]	Endpoint	Dose (Gy), or dose/volume parameters[†]	Rate (%)	Notes on dose/volume parameters
Liver	Whole liver – GTV	3D-CRT or Whole organ	Classic RILD[††]	Mean dose <30-32	<5	Excluding patients with pre-existing liver disease or hepatocellular carcinoma, as tolerance doses are lower in these patients
	Whole liver – GTV	3D-CRT	Classic RILD	Mean dose <42	<50	
	Whole liver – GTV	3D-CRT or Whole organ	Classic RILD	Mean dose <28	<5	In patients with Child-Pugh A preexisting liver disease or hepatocellular carcinoma, excluding hepatitis B reactivation as an endpoint
	Whole liver – GTV	3D-CRT	Classic RILD	Mean dose <36	<50	
	Whole liver –GTV	SBRT (hypofraction)	Classic RILD	Mean dose <13	<5	3 fractions, for primary liver cancer
				<18	<5	6 fractions, for primary liver cancer
	Whole liver – GTV	SBRT (hypofraction)	Classic RILD	Mean dose <15	<5	3 fractions, for liver metastases
				<20	<5	6 fractions, for liver metastases
	>700 cc of normal liver	SBRT (hypofraction)	Classic RILD	D_{max} <15	<5	Critical volume based, in 3–5 fractions

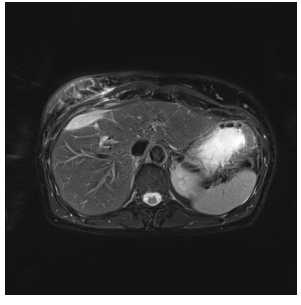
Liver – Case Study

R breast cancer, s/p lumpectomy and RT

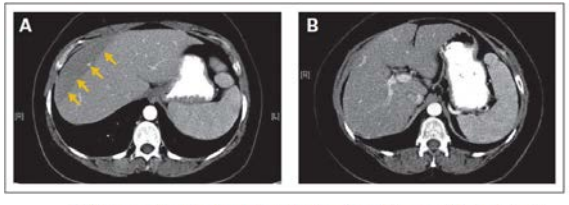


1 mo after RT, presented with right upper abdominal pain, nausea, vomiting
MRI showed masslike infiltrative process





Case Report



RILD, previously termed *radiation hepatitis*, manifests 4 to 8 weeks after radiation exposure.[2-5] Significant RILD develops in 6% to 66% of patients exposed to an excess of 30 to 35 Gy of radiation, depending on irradiated liver volume and hepatic functional reserve.[3,5] Patients may present with a triad of ascites, hepatomegaly, and elevated liver enzymes.[2] The majority of patients recover completely in 3 to 5 months, while a minority progress towards a chronic stage, with worsening liver fibrosis and failure, only rarely developing fulminant hepatic failure.[3,5] The term "radiation hepatitis" is a misnomer, since pathologic evaluation fails to reveal inflammation, instead showing nonspecific veno-occlusive disease.[3-5] Radiation-induced endothelial damage exposes the subendothelial basement membrane, leading to platelet activation and aggregation, and stimulation of dormant hepatic stellate cells. Fibrin thrombus causes venous occlusion, panlobular congestion, diffuse hemorrhagic and necrotic foci, and distention of hepatic sinusoids.[3-5] Prolonged obstruction and activation of hepatic stellate cells results in hepatocyte loss and fibrosis mediated by transforming growth factor-β1 release.[3-5] Radiologically, RILD presents with a "straight-border" sign, which is defined as any hepatic attenuation difference bordered by straight lines.[1] Fatty infiltration, fibrosis, and vascular abnormalities can all present similarly.[1] RILD presents as demarcated areas of hypo- or hyperattenuation in a nonanatomic distribution, contrasting with vascular lesions.[1] Our patient developed RILD following hepatic radiation exposure during irradiation of right chest wall/axilla 6 weeks earlier. Subsequent tests after 4 months and later imaging showed complete normalization of liver enzymes and hepatic appearance (Fig 1B). As of May 2008, our patient was free of recurrent disease.

Question 1

Which of the following statements is true regarding radiation-induced liver disease (RILD)?

A. Hepatocytes are the principal radiobiological target. Endothelial cells
B. Liver is a flexible type tissue, so volume does not affect tolerance. Parallel organ; volume effect
C. High plasma levels of TGF-β predict for a decreased probability of developing RILD.
D. Fraction size is not a factor in tolerance to RILD.
E. In the bone marrow transplant setting, symptoms of RILD are observable within 3 months after treatment completion.

Question 2

With respect to the morphologic changes associated with radiation-induced liver disease, notably veno-occlusive disease (VOD), all of the following may be observed, EXCEPT:

A. Heavy congestion in the sinusoids
B. Atrophy of the liver plates
C. Fiber-filled lumen of the sublobular veins
D. Apoptotic Kupffer cells filled with hematoxylin
E. Subacute morphological changes

Medical physics students are not required to know the details of VOD

Question 3

Concerning radiation induced liver disease (RILD), all of the following statements are true, EXCEPT:

A. RILD is a clinical syndrome of ascites, elevated liver enzymes, and hepatomegaly in the absence of jaundice

B. RILD is rarely observed earlier than 6 months following completion of radiotherapy 1-2 mo after RT

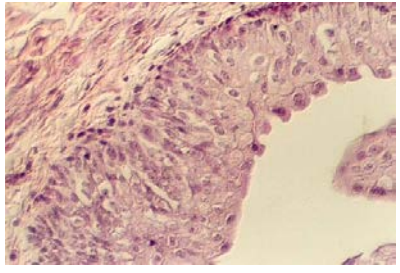
C. Suprahepatic vein obstruction and veno-occlusive liver disease are seen in RILD

D. Pathologic changes in RILD include marked venous congestion in the central portion of each lobule-with sparing of the larger veins – and atrophy of hepatocytes adjacent to the congested veins

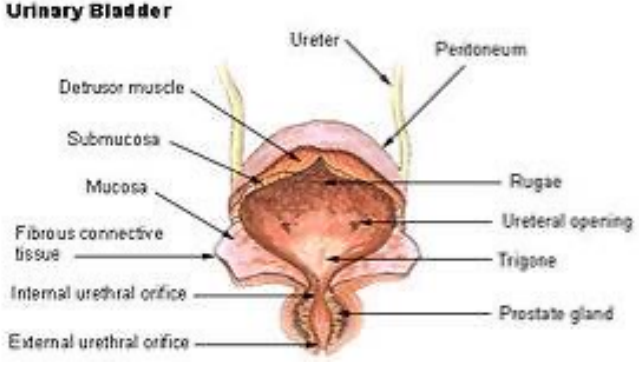
E. Killing of vascular endothelial cells appears to be of greater importance than hepatocyte lethality in the pathologic changes observed in RILD See slide

Focus on what's discussed in the slides

Bladder Epithelium



The bladder epithelium consists of a basal layer formed of small diploid cells, covered by several layers of larger transitional cells and at the surface by a very large polyploid cells



	Injury	$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Bladder	Contracture	65	80	2/3
		80	85	1/3

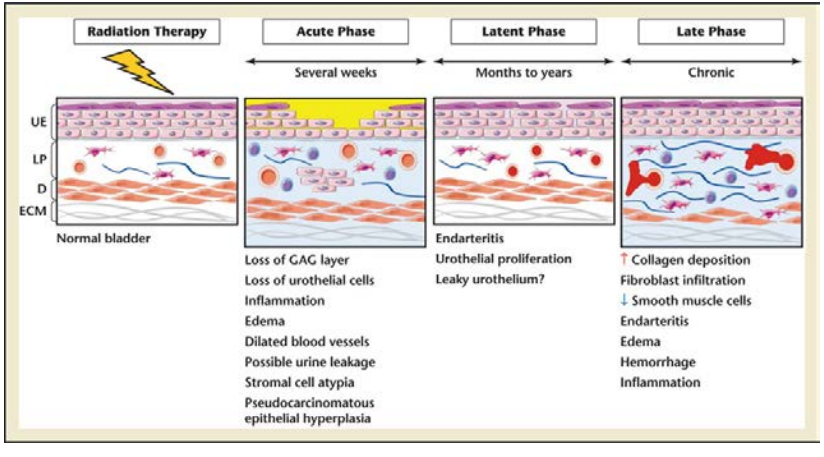
Cell renewal rate is low – the superficial cells have a lifespan of several months

Urinary frequency is due to loss of the surface cells and irritation of the deeper cellular layers by urine, leading to stimulation of cellular proliferation

Subsequent late effects are related to fibrosis and reduction in bladder capacity

Bladder – QUANTEC

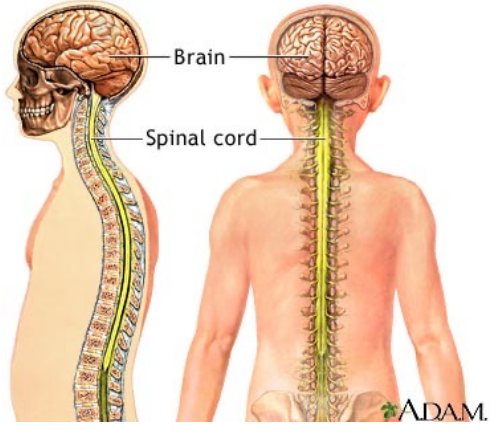
Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)[†]	Endpoint	Dose (Gy), or dose/volume parameters[†]	Rate (%)	Notes on dose/volume parameters
Bladder	Whole organ	3D-CRT	Grade ≥ 3 late RTOG	Dmax <65	<6	Bladder cancer treatment. Variations in bladder size/shape/ location during RT hamper ability to generate accurate data
	Whole organ	3D-CRT	Grade ≥3 late RTOG	V65 ≤50 % V70 ≤35 % V75 ≤25 % V80 ≤15 %		Prostate cancer treatment Based on current RTOG 0415 recommendation



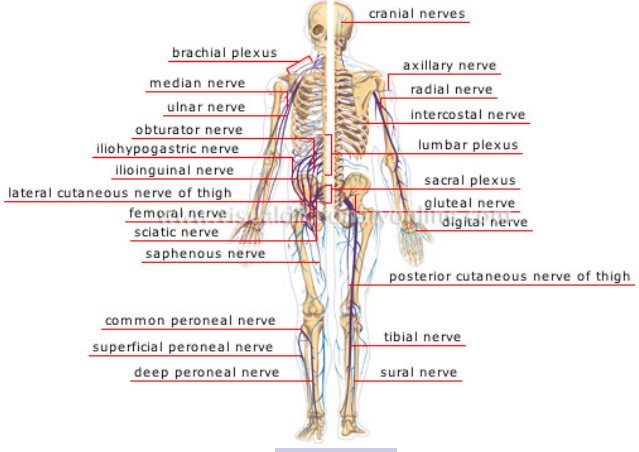
- Acute inflammatory phase
- Latent symptom free phase
- Late chronic inflammatory phase

Zwaans 2016 – Rev Urol. *2016;18(2):57-65*

Central and Peripheral Nervous System



CNS



PNS

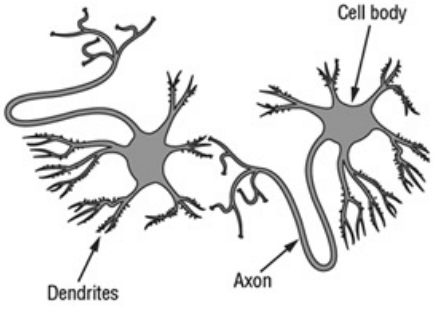
The nervous system is less sensitive to radiation than other late-responding organs and tissues such as the kidney or lung

However, we try not to push to the $TD_{5/5}$ and we use wide margins of safety in dose because damage to these tissues results in severe consequence, including paralysis

Brain

Target Cells

Neurons

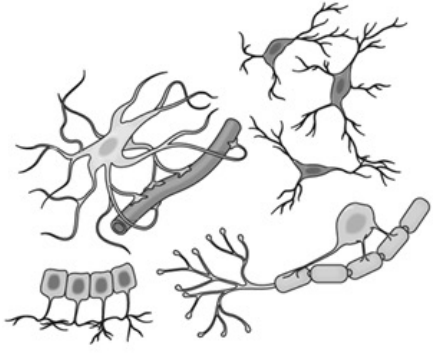


Typical neurons

Neurons receive stimulation from their branches, known as dendrites. They communicate with other neurons, creating a network with millions of other by firing a nerve impulse along an axon.

Non-proliferating end cells

Glial cells

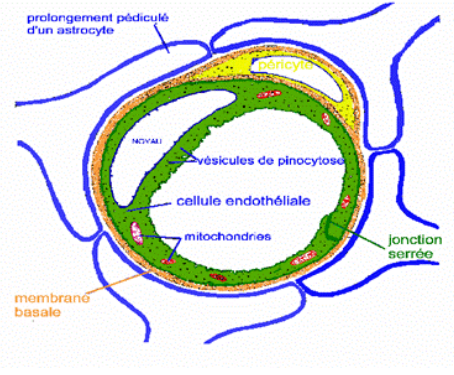


Various types of glial cells

Glia carry nutrients, speed repair, provide myelin for axons, support the blood–brain barrier, and may form their own communication network. They are also involved in neurogenesis.

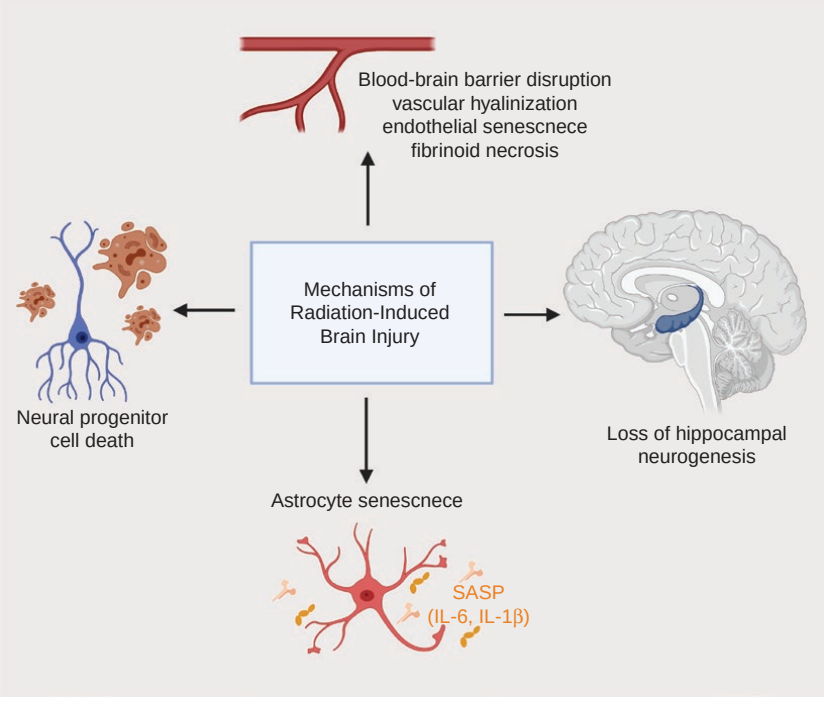
Slow turnover
Only 1% are stem cells

Vascular endothelial cells



Slow turnover
Can proliferate rapidly after injury

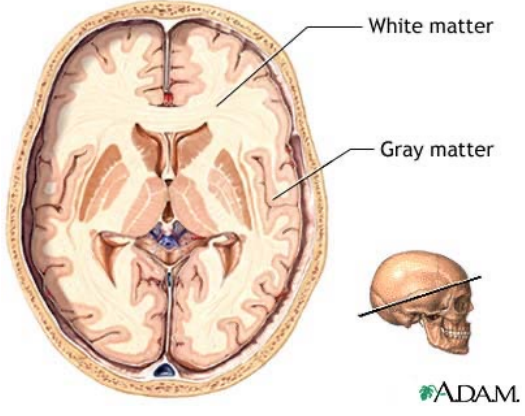
Mechanism of Radiation-Induced Brain Injury



The cellular response to radiation injury in the brain involves multiple cell types including astrocytes, microglia, oligodendrocytes, endothelial cells, and neurons that initiate and respond to inflammatory cascades and contribute to progressive neurological damage.

Turnquist 2020; Neuro-Oncology Advances 2(1): 1-10

Brain



Acute

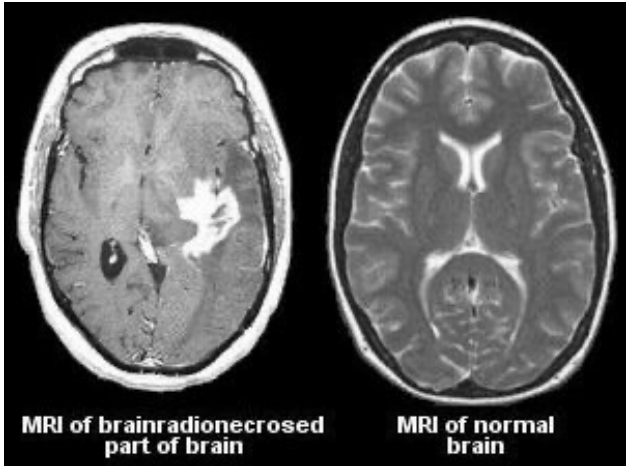
The acute lesions include an **increase in blood brain barrier permeability and edema**, due in part to a rapid burst of apoptotic cell death, which is seen in a variety of normal brain cells, including endothelial cells.

First 6 months (Early-Delayed)

Somnolence syndrome – due to transient demyelination
Leukoencephalopathy – destruction of the myelin sheaths

Pathology usually involves white matter

Brain



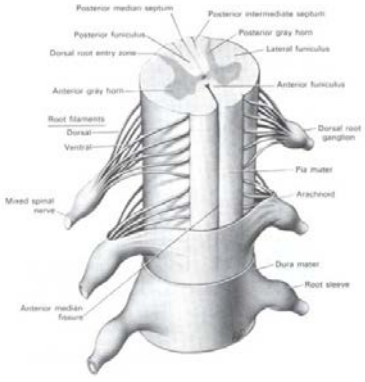
Beyond 6 months to a year

Brain radionecrosis

Pathology – primarily limited to white matter, additionally gray matter also show changes along with vascular lesions such as telangiectasia and focal hemorrhages

Symptoms – cognitive defects, seizure, difficulty with speech, balance problems

Spinal Cord



Lhermitte's sign is an electrical sensation that runs down the back and into the limbs, and is produced by bending the neck forward.

Radiation-induced changes in the spinal cord are similar to those seen in the brain w.r.t. latency, tolerance dose, and histology

Early-Delayed

Lhermittes sign
May occur at doses as low as 35 Gy
Usually reversible and does not predict permanent myelopathy
Pathology – transient demyelination from inhibition of oligodendrocyte proliferation

6-18 months

Demyelination and necrosis of the white matter

1-2 years

Vasculopathy

Spinal Cord

Effect of fractionation

Spinal cord is a late-responding tissue with a small α/β ratio, hence tolerance depends on dose per fraction

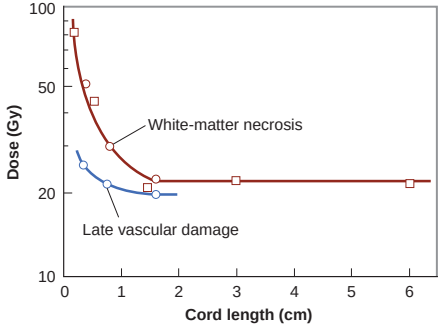
Lower dose per fraction reduce the risk of late effects

Sublethal Damage Repair

There is evidence of two components of repair – one with a $t_{1/2}$ less than 1 hour and one with $t_{1/2}$ close to 4 hours

If 2 fractions are given per day, the time b/w fractions must be at least 6 hours

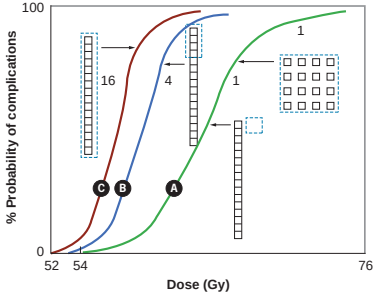
Spinal Cord



Volume Effect

Spinal cord is the clearest example of a tissue in which FSUs are arranged **in series**

The probability of myelopathy depends on the length irradiated

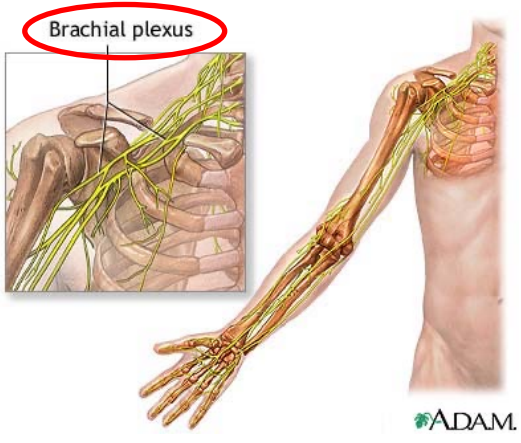


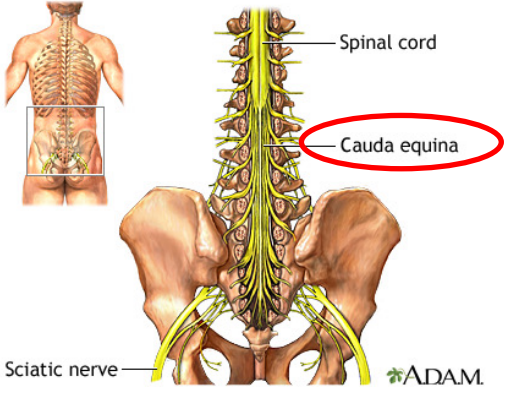
Chemo Effect

Chemo agents such as methotrexate, cisplatin, vinblastine, AraC are neurotoxic

Concurrent or sequential use of chemo reduces the spinal cord (and brain) tolerance

Peripheral Nerves





Radiation injury of peripheral nerves probably is more common than effects on spinal cord

It is thought to be more radioresistant than spinal cord or brain, but there are few data to support this

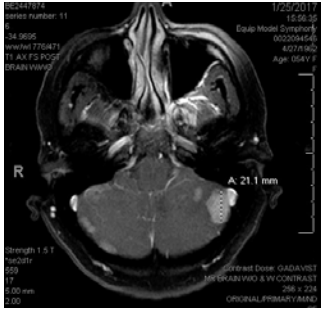
$TD_{5/5}$ is 60 Gy/2 Gy fx, and probability of injury rises steeply with increasing dose

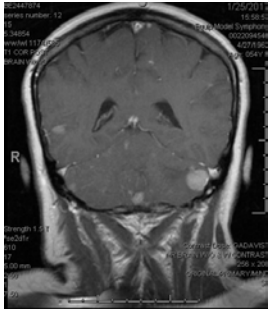
CNS and PNS

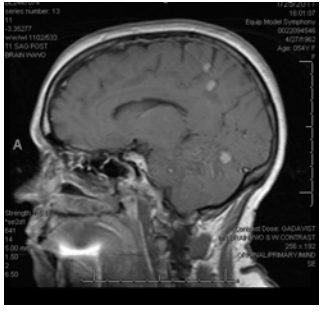
Injury		$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Brain	Infarction, necrosis	45 60	60 75	Whole 1/3
Spinal cord	Infarction, necrosis	47 50	— 70	20 cm 5 or 10 cm
Peripheral nerves	Neuritis	60	100	—

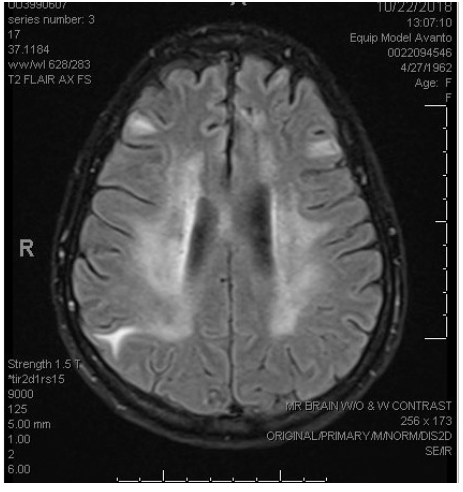
Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)[†]	Endpoint	Dose (Gy), or dose/volume parameters[†]	Rate (%)	Notes on dose/volume parameters
Brain	Whole organ	3D-CRT	Symptomatic necrosis	Dmax <60	<3	Data at 72 and 90 Gy, extrapolated from BED models
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 72	5	
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 90	10	
	Whole organ	SRS (single fraction)	Symptomatic necrosis	V12 <5–10 cc	<20	Rapid rise when V12 > 5–10 cc
Brain stem	Whole organ	Whole organ	Permanent cranial neuropathy or necrosis	Dmax <54	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	D1–10 cc[‖] ≤59	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	Dmax <64	<5	Point dose <<1 cc
	Whole organ	SRS (single fraction)	Permanent cranial neuropathy or necrosis	Dmax <12.5	<5	For patients with acoustic tumors
Optic nerve / chiasm	Whole organ	3D-CRT	Optic neuropathy	Dmax <55	<3	Given the small size, 3D CRT is often whole organ[‡‡]
	Whole organ	3D-CRT	Optic neuropathy	Dmax 55–60	3–7	
	Whole organ	3D-CRT	Optic neuropathy	Dmax >60	>7-20	
	Whole organ	SRS (single fraction)	Optic neuropathy	Dmax <12	<10	

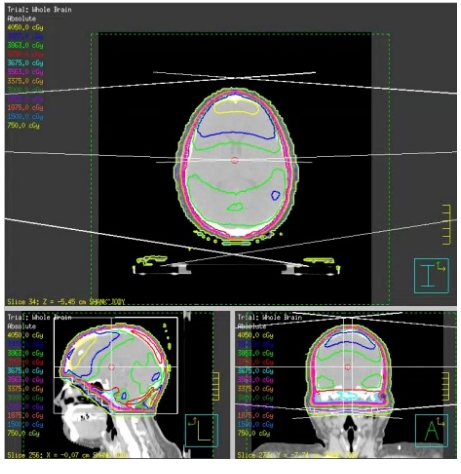
CNS & PNS – Case Study











Metastatic breast cancer

3750 cGy/15 fractions

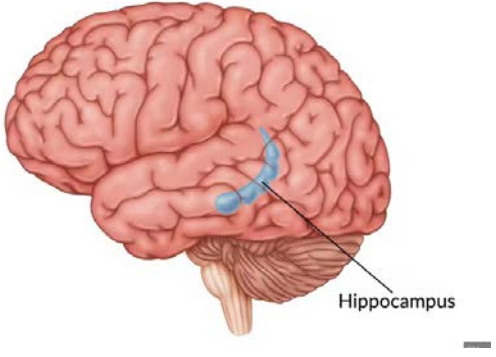
Jan 2017

Oct 2018

Significant Cognitive Decline

Hippocampal Avoidance Whole Brain Radiotherapy

Hippocampus is a small part of the brain that plays a key role in learning, memory and spatial awareness



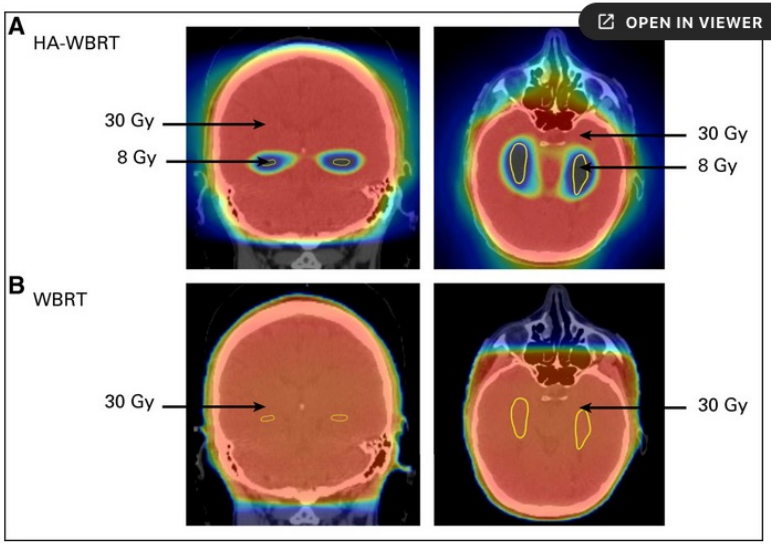
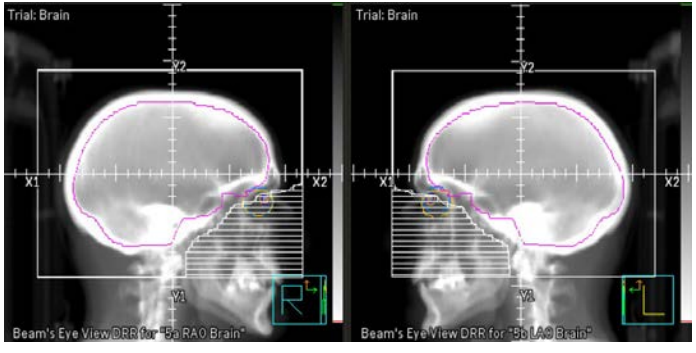


Fig 1. Several-fold reduction in radiation dose to hippocampi (yellow) using (A) hippocampal avoidant whole-brain radiotherapy (HA-WBRT) *v* (B) conventional WBRT.

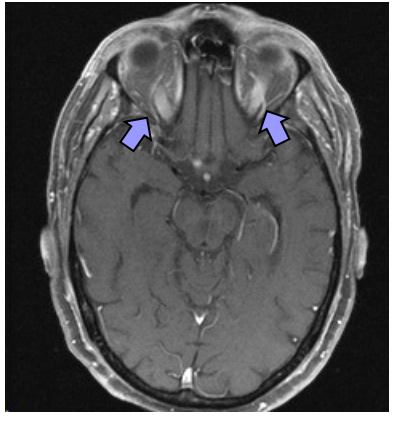
HA-WBRT better preserves cognitive function

CNS & PNS – Case Study

Lung cancer with brain metastases
3000 cGy in 10 fractions
Completed 05/2020



~ 1.5 years later, he lost vision in R eye; subsequently he became blind also in the left eye



MRI showed enhancement of the optic nerves

Optic Neuritis

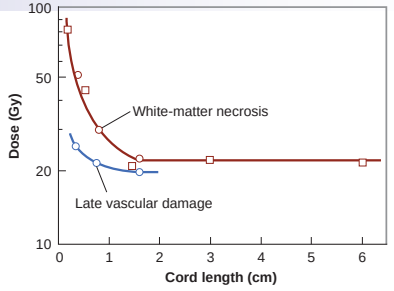
Treated with Avastin, Pentoxifylline and Vitamin E with no improvement

Question 1

Radiation effects in the nervous system typically arise as a consequence of damage to:

A. Axons
B. Neurons
C. Oligodendrocytes and glial cells
D. The perikaryon
E. Dendrites

Question 2



The TD_5 as a function of length of spinal cord irradiated:

A. decreases as a linear function of increasing cord length.

B. initially decreases with increasing cord length, and then remains relatively constant for higher total doses.

C. increases steeply for lengths greater than approximately 10 cm.

D. decreases with decreasing cord length.

E. increases with cord length before reaching a plateau.

Question 3

The tolerance dose 5% in 5 yrs (TD5/5) and 50% in 5 yrs (TD50/5) necrosis of brain tissue is best represented by which of the following doses?

A. 24Gy and 36Gy respectively
B. 36Gy and 45Gy respectively
C. 45Gy and 60Gy respectively
D. 57Gy and 68Gy respectively

Doses not specifically mentioned in the slides are not going to be on the exam

Question 4

Medical residents only

Which of the following statements concerning irradiation of the CNS is FALSE?

A. Selective damage to gray matter would preclude radiation as the cause of injury
B. Demyelination and white matter necrosis are common manifestations of radiation-induced injury to the CNS
C. Oligodendrocytes and vascular endothelial cells are considered to be the principal target cells for radiation-induced damage to the CNS
D. Most forms of radiation injury to the CNS are characterized by distinct pathognomonic characteristics specific to radiation-induced damage
E. Cognitive deficits are a late effect seen in both children and adults

Question 5

Medical residents only

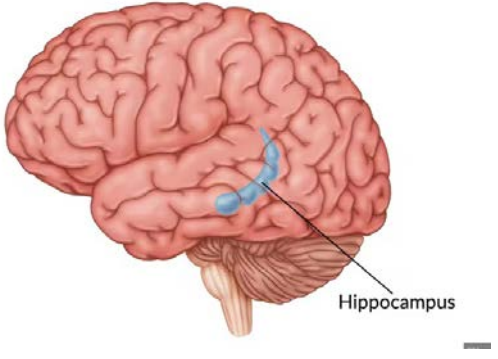
Which of the following statements concerning the late radiation effects of the brain is FALSE?

A. The classical late radiation effect in the brain is localized necrosis generally limited to the involved white matter, with focal coagulative necrosis and demyelination as dominant features
B. Symptoms of late radiation effects include motor, sensory and/or speech/receptive deficits, seizures and symptoms of increased intracranial pressure
C. The “somnolence syndrome” is observed 1-6 months post-radiation
D. During the 3-6 month period following completion of RT, a general neurologic deterioration may occur that results from transient, diffuse demyelination
E. Arterial cerebrovasculopathy is commonly observed

Question 6

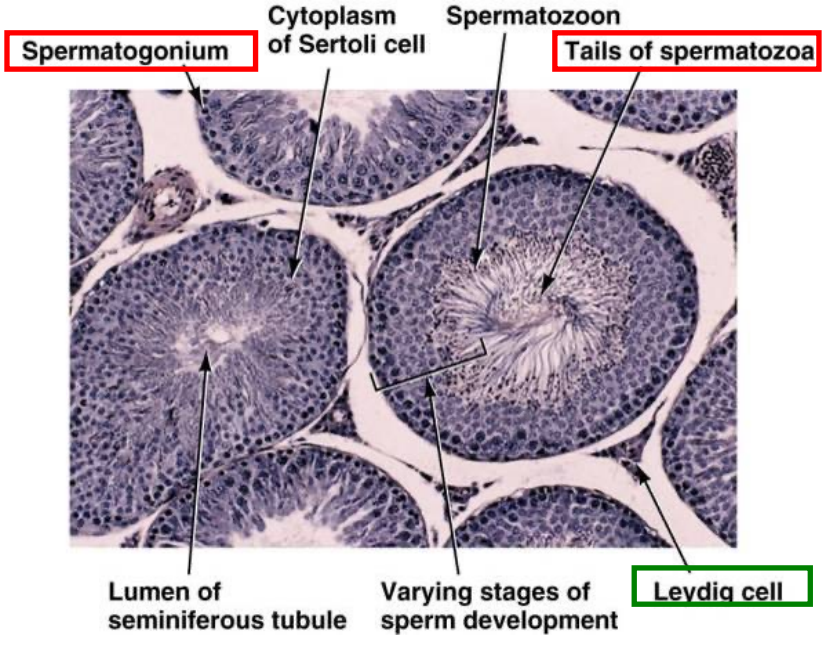
The cells thought to be responsible for radiation-induced cognitive dysfunction reside in:

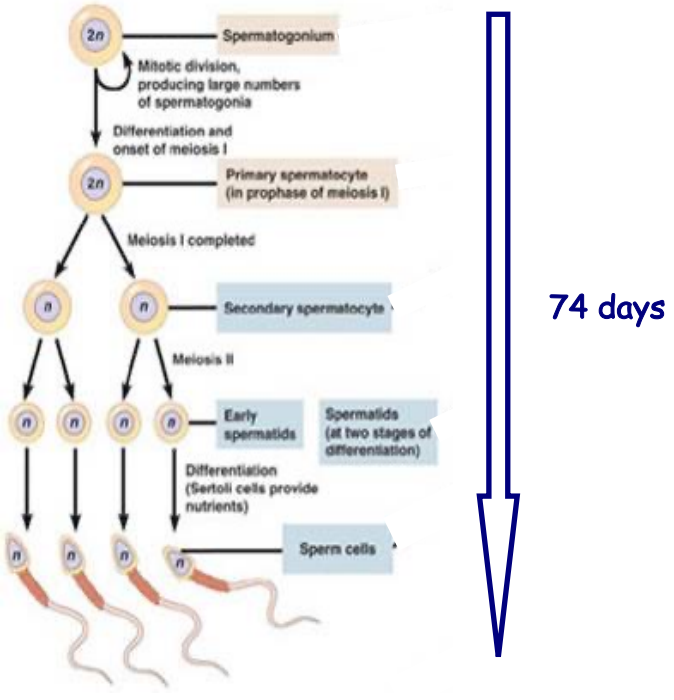
A. Medulla oblongata
B. Cerebral cortex
C. Substantia nigra
D. Hippocampus
E. Hypothalamus



Cute Honey

Testes


Spermatogonium
Cytoplasm of Sertoli cell
Spermatozoon
Tails of spermatozoa
Lumen of seminiferous tubule
Varying stages of sperm development
Leydig cell


2n
Spermatogonium
Mitotic division, producing large numbers of spermatogonia
Differentiation and onset of meiosis I
2n
Primary spermatocyte (in prophase of meiosis I)
Meiosis I completed
n
n
Secondary spermatocyte
Meiosis II
n
n
n
n
Early spermatids
Spermatids (at two stages of differentiation)
Differentiation (Sertoli cells provide nutrients)
n
n
n
n
Sperm cells
74 days

Testes

Self-renewal system: spermatogonia → spermatocytes → spermatids → spermatozoa

Latent period b/w irradiation and sterility

Oligospermia and reduced fertility: **0.1- 0.15 Gy**

Azoospermia and temporary sterility: **0.5 Gy**

Recovery is dose dependent

Permanent sterility

6 Gy – *single dose*
2.5-3 Gy, *fractionated*, 2-4 wks

} Chapter 11

Induction of sterility does not affect hormone balance, libido, or physical capability (because Leydig cells are radioresistant)

Clamshell

Note that fractionated dose or continuous LDR irradiation is more effective than a single acute exposure

Testes

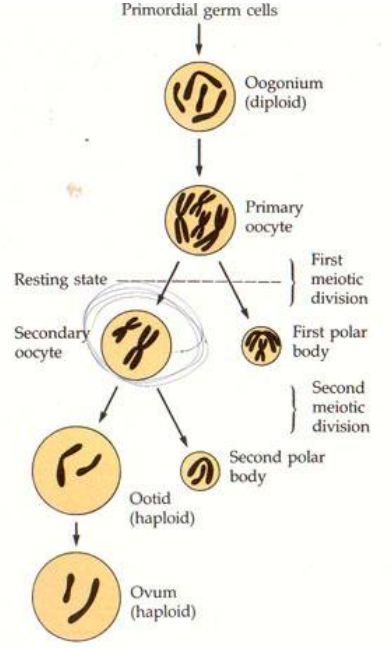
Chemotherapy and Sterility

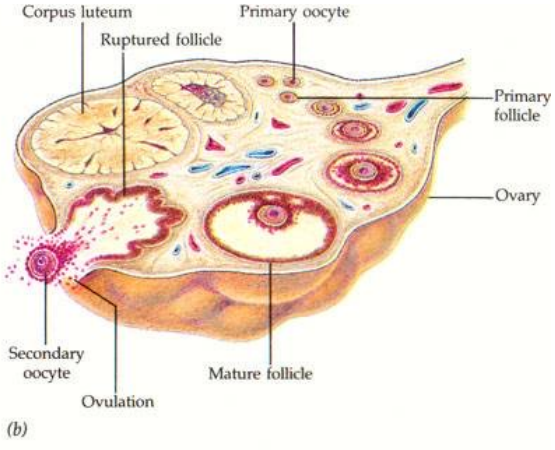
A number of cytotoxic drugs have substantial effects on spermatogenesis

The **alkylating agents** included in the MOPP regimen used for Hodgkin's disease in the past led to sterility in almost all patients

The drugs were given over the course of several months, therefore, simulated LDR radiation, killing stem cells as they came into cycle

Ovaries





After the fetal stage, oocytes no longer divide
D_0 of oocyte ~ 0.12 Gy

Hormonal secretion is associated with follicular maturation

Ovaries

By 3 days after birth, all cells progressed to primary oocyte stage; no further cell division

Neither latent period nor temporary sterility in females

Radiation can induce permanent ovarian failure; marked **age dependence**

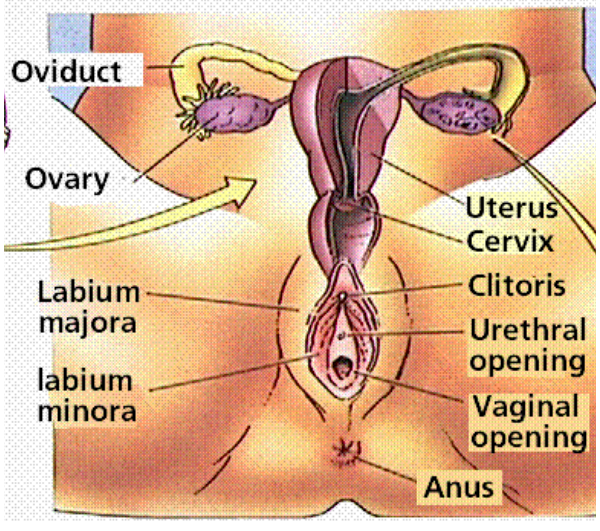
Permanent sterility

12 Gy – *prepuberty*

2 Gy, *premenopausal*

Radiation sterility produces hormonal changes like those seen in natural menopause

Female Genitalia



Vulva

The skin of vulva reacts like skin elsewhere, but clinical tolerance is lower because of friction and moisture

Vagina

Acute – erythema, moist desquamation, confluent mucositis

Late – atrophic mucosa, necrosis, ulceration (90 Gy), fistula (100 Gy)

Cervix & Uterus

Dose may reach 200 Gy with intracavitary treatments

Late effects include atrophy of the endometrial glands and stoma, ulceration

Testes, Ovaries Female Genitalia

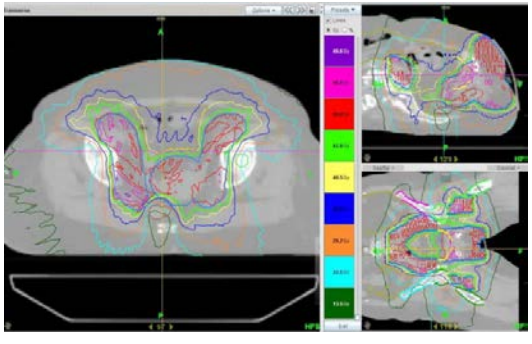
TABLE 19.2. *A Compilation of Tissue and Organ Sensitivities*

	Injury	$TD_{5/5}$, Gy	$TD_{50/5}$ Gy	Field Size
Testes	Sterilization	1	2	Whole
Ovaries	Sterilization	2–3	6–12	Whole (age dep.)
Uterus	Necrosis, perforation	100	200	Whole
Vagina	Ulcer, fistula	90	100	Whole

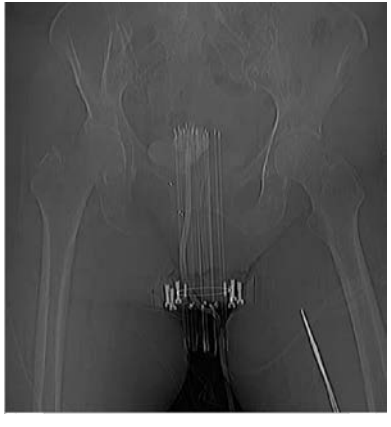
				V80 ≥15 %	
Penile bulb	Whole organ	3D-CRT	Severe erectile dysfunction	Mean dose to 95% of gland <50	<35
	Whole organ	3D-CRT	Severe erectile dysfunction	D90[‖] <50	<35
	Whole organ	3D-CRT	Severe erectile dysfunction	D60-70 <70	<55

Female Genitalia – Case Study

Locally advanced vulva cancer with vaginal involvement



4500 cGy/ 25 fx



2250 cGy/5 fx BID

Completed treatment 9/2012

9/2018 Follow Up

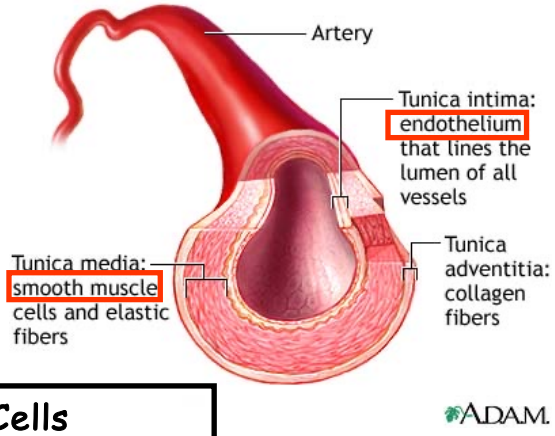
- Pain from the radiation damage to her vulva.
- Still smoking 1 pack per day
- Diffusely indurated and mildly erythematous with lymphedema changes, woody throughout
- Vagina narrowed to ~1 cm with woody induration and irregularly contoured
- Extensive radiation changes throughout vulva and groin area
- Superior aspect of gluteal fold with some skin breakdown

Question

Which of the following statements is CORRECT concerning the effects of radiation on the gonads?

A. Older women are more sensitive to radiation-induced sterility than younger women.
B. An acute dose of 3 Gy can both destroy the gametogenic epithelium and eliminate the production of sex hormones in adult men.
C. Spermatids and spermatozoa are quite radiosensitive whereas spermatogonia are relatively radioresistant.
D. A minimum waiting period of 5 years is recommended for both men and women before attempting procreation following radiotherapy, in order to reduce the risk of radiation-induced genetic effects.
E. If sterility in the male is not produced within the first month after the start of radiotherapy, it is unlikely to ever occur.

Blood Vessels and the Vascular Systems



Endothelium

Low proliferation under normal circumstance

Regions of constriction appear because of the abnormal proliferation of surviving cells

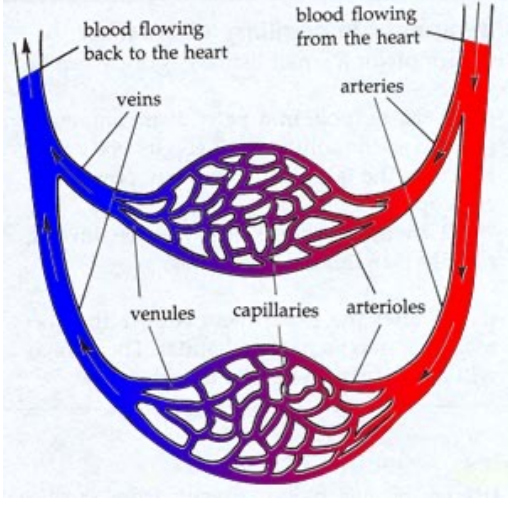
Denudation of the endothelium leads to the formation of thrombosis and capillary necrosis

Smooth Muscle Cells

Low proliferation → takes several years for the number of cells to diminish significantly following radiation

Muscle cells are replaced by collagen fibers → vessel walls lose their elasticity and blood flow is diminished

Blood Vessels and the Vascular System



Artery – damage may occur after 50-70 Gy
Veins – in general are less sensitive to radiation than arteries
Capillaries – damaged by 40 Gy

Injury		$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Large arteries and veins	Sclerosis	80	100	10 cm^2

Effects of radiation on blood vessels are important because late effects of many organs have a vascular component

Question

Medical residents only

Which of the following statements concerning radiation-induced damage to the microvasculature is INCORRECT?

A. Classic pathologic features of radiation damage to blood vessels include telangiectasia, “sausaging” and blebbing.

B. Historically, vascular endothelial cells are considered the target cells for vascular injury, however, damage to adventitial fibroblasts and medial smooth muscle cells may also play significant roles.

C. The order of sensitivity of blood vessel is: capillaries; arterioles; small-medium arteries; large arteries.

D. Due to the slow turnover kinetics of vascular endothelial cells, subcellular changes in these cells are generally not seen until approximately 6-12 months after irradiation.

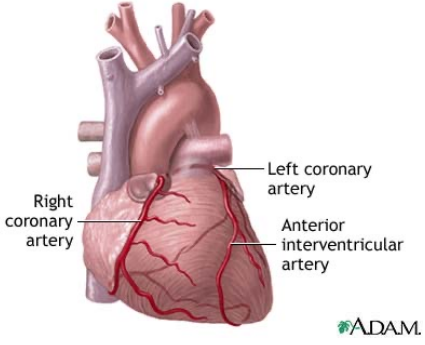
E. Bone marrow transplantation can result in pulmonary and hepatic veno-occlusive disease.

Answer

- Despite having cell turnover times that can be as long as months, changes in vascular endothelial cells, including alterations in the basement membrane and rough endoplasmic reticulum, have been seen within hours of irradiation.

Heart

Heart is a late-responding organ with α/β ratio of 1 Gy $\rightarrow$ fractionation leads to substantial sparing



The most radiosensitive cells of the heart are the **endothelial cells** lining the cardiovascular capillaries, while the most resistant cells are the **cardiac myocytes**

The adult cardiomyocytes has ~ 0.5% yearly turnover after 40 years of age, but the majority of lost or damaged cardiomyocytes will not be replenished after injury.

Radiation tolerance – heart is intermediate b/w the kidney and lung and the CNS

Late Effects

Pericarditis

Symptoms – chest pain, shortness of breath, low-grade fever

Tolerance dose & volume effect – 20 Gy if more than 50% of the heart irradiated; higher for partial exposure

Cardiomyopathy

Results from dense and diffuse fibrosis

Tolerance dose & volume effect – 30 Gy to most of the heart may reduce cardiac function; protection of part of the heart greatly reduces the incidence

Heart

Table Radiation-Induced Cardiac Toxicities

Disease Spectrum	Manifestation and Symptoms
Autonomic dysfunction	Circadian rhythm loss, heart rate variability, and loss of angina pain perception
Cardiomyopathy	Fibrosis, reduced ejection fraction, diastolic or systolic dysfunction or both, and pulmonary hypertension
Conduction system	Bundle-branch block, complete heart block, ventricular ectopic activity, and arrhythmias
Coronary artery	Accelerated atherosclerosis and risk of ischemia
Pericarditis	Effusions, constrictive pericarditis, and cardiac tamponade
Valvular	Regurgitation and stenosis
Vascular	Pulmonary artery stenosis and hypoplasia, aortic fibrosis

Pericarditis can occur within days to weeks of beginning radiation therapy
Late pericardial disease manifests at a median of 5-7 months after radiation

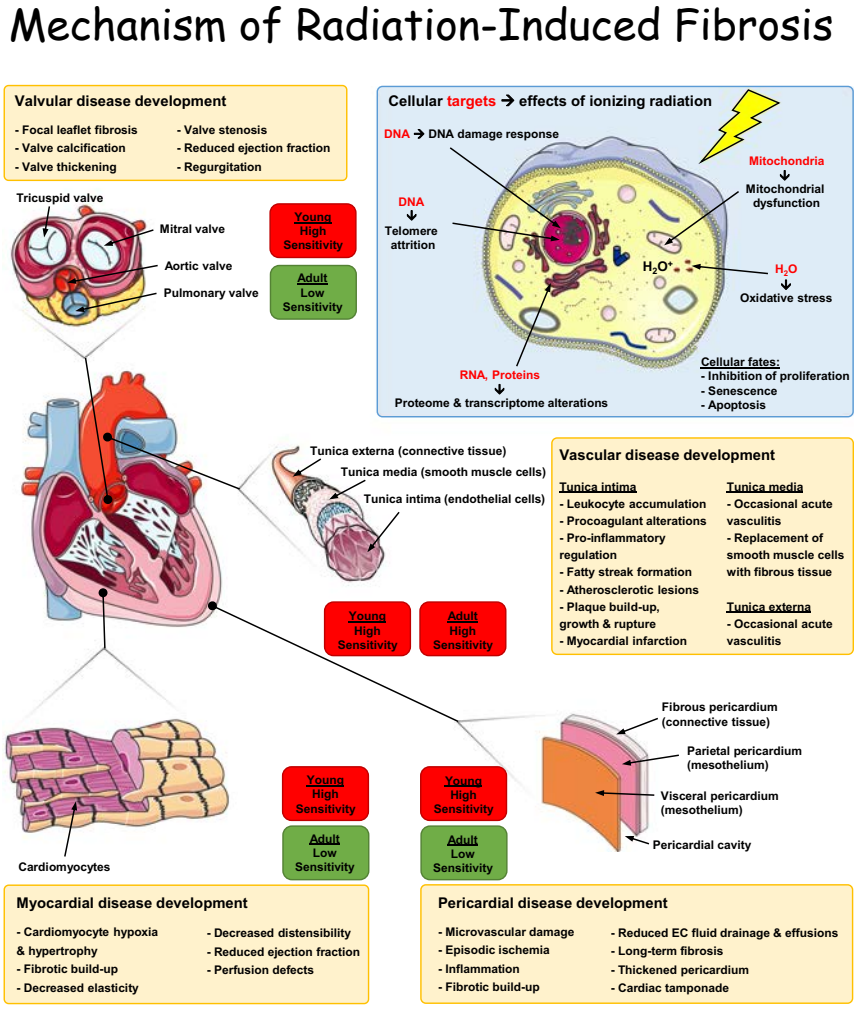
Major coronary events increases linearly with mean heart dose, with no apparent threshold

Simone 2017; Semin Radiat Oncol 27: 370-377

Heart

Mechanisms

- Inflammatory pathways
- DNA damage response
- Chronic oxidative stress
- Chronic hypoxia
- Epigenetic regulation
- Telomere extension



Spetz 2018; Curr Treat Options Cardio Med 20: 31

Heart

Effect of Chemotherapy

Adriamycin increases the severity of radiation-induced cardiac complications

In addition, adriamycin may reveal latent radiation damage many years after radiation therapy (this is known as **"radiation recall"**)

	Injury	$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Heart	Pericarditis and pancarditis	40 60	50 70	Whole 1/3

Heart	Pericardium Pericardium	3D-CRT 3D-CRT	Pericarditis Pericarditis	Mean dose <26 V30 <46%	<15 <15	Based on single study
	Whole organ	3D-CRT	Long-term cardiac mortality	V25 <10%	<1	Overly safe risk estimate based on model predictions

Question 1

Which one of the following statements regarding radiation-induced heart disease (RIHD) is FALSE?

1 Gy

A. The α/β ratio for pericarditis is approximately 8 Gy.
B. The most radiosensitive cells of the heart are the endothelial cells lining the cardiovascular capillaries, while the most resistant cells are the cardiac myocytes.
C. Fraction size, total dose and volume are all factors that can affect the tolerance dose for RIHD.
D. A number of studies have shown that patients <20 years and >60 years of age have an increased risk of developing RIHD.
E. Anthracyclines combined with radiation enhance cardiotoxicity compared to radiation alone.

Question 2

Which of the following conditions is NOT an expected manifestation of radiation-induced heart disease?

A. Accelerated coronary atherosclerosis
B. Hypertrophic cardiomyopathy
C. Cardiac fibrosis
D. Pericarditis
E. Cardiac myocyte degeneration

Question 3

Which of the following statements concerning the effects of radiation on the heart is TRUE?

A. Radiation associated valvular disease is rare in patients receiving ≥ 35 Gy to the heart.

B. In the absence of concurrent chemotherapy, cardiomyopathy is observed during or shortly after the completion of radiotherapy

C. An increased incidence of cardiovascular disease among Hodgkin's disease survivors who received mediastinal radiotherapy has not been observed

D. The critical structure associated with the pathogenesis of radiation-induced heart disease appears to be the endothelial lining of blood vessels

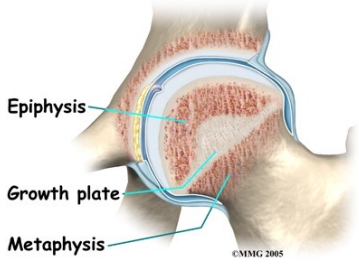
E. An excess relative risk for myocardial infarction has been detected in the Japanese atomic bomb survivors, but only among those who received doses greater than 10 Gy

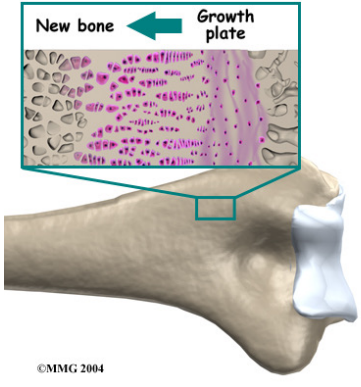
Question 4

With respect to radiation-induced heart disease (RIHD), which one of the following statements is FALSE?

A. Individuals 20-65 years of age have a lower risk for the development of radiation-induced coronary artery disease compared with other age groups
B. The parietal pericardium may be damaged by radiation therapy, with the injury typically presenting as an increased thickness of the fibrous layer
C. The risk of pericarditis increases with increasing dose per fraction
D. The majority of cardiac complications observed are consistent with the hypothesis that the most radiosensitive cells are the cardiomyocytes
E. Cardiac effects are described as “delayed”, and typically appear months to years after radiotherapy

Bone and Cartilage



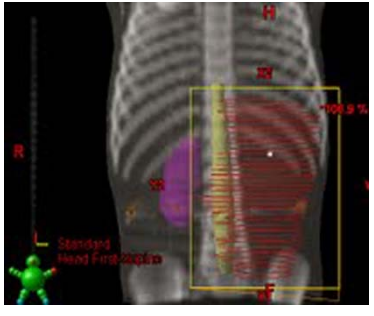


Children

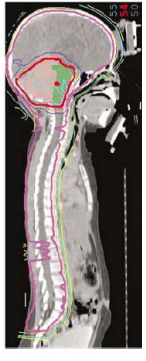
Doses as low as 10 Gy can slow growth

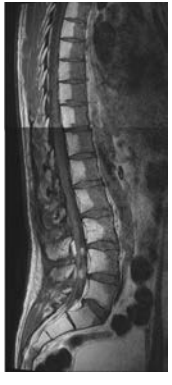
Doses above **20 Gy** can **close growth plate**

Sequelae are particularly serious in children younger than 2 years of age, and radiation can affect stature adversely up to the time of the puberty



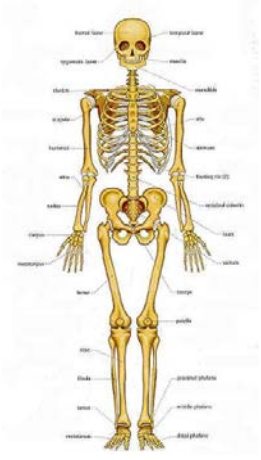
Include entire vertebral body in treatment field

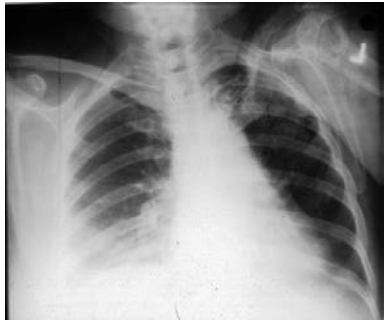




Craniospinal Irradiation w/ proton therapy

Bone and Cartilage





Adults

Osteoradionecrosis (discussed earlier)

Fracture – femoral and humeral heads
Irradiating bone leads to loss of osteoblasts and osteoclasts responsible for bone maintenance and remodeling, causing the bone to become brittle and prone to injury
$TD_{5/5}$ – 52 Gy
$TD_{50/5}$ – 65 Gy

⇦ fracture of the fibs and clavicles are sometimes seen in patients receiving RT for breast cancer

Bone and Cartilage

	Injury	$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Growing cartilage, child bone	Growth arrest, dwarfing	10	30	Whole
Mature cartilage, adult bone	Necrosis, fracture, sclerosis	60 60	100 100	Whole 10 cm^2

Question

All of the following normal tissue complications are of concern after high-dose irradiation of a short segment of bone, EXCEPT:

A. osteoradionecrosis
B. stress fractures
C. growth retardation after irradiation of epiphyseal in children
D. radiation-induced bone sarcomas
E. bone marrow failure

Compilation of Tissue and Organ Tolerance

TABLE 20.2 A Compilation of Tissue and Organ Sensitivities

	Injury	$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Class I organs				
Bone marrow	Aplasia, pancytopenia	2.5	4.5	Whole segment
Liver	Acute and chronic hepatitis	30 50	40 55	Whole 1/3
Intestine	Obstruction, perforation, fistula	40 50	55 65	Whole 1/3 or 1/2
Stomach	Perforation, ulcer, hemorrhage	50 60	65 70	Whole 1/3
Brain	Infarction, necrosis	45 60	60 75	Whole 1/3
Spinal cord	Infarction, necrosis	47 50	— 70	20 cm 5 or 10 cm
Heart	Pericarditis and pancarditis	40 60	50 70	Whole 1/3
Lung	Acute and chronic pneumonitis	17.5 45	24.5 65	Whole 1/3
Kidney	Acute and chronic nephrosclerosis	23 50	28 45	Whole 1/3 or 1/2
Class II organs				
Oral cavity and pharynx	Ulceration, mucositis	60	75	50 cm^2
Skin	Acute and chronic dermatitis, telangiectasia	55	65	100 cm^2
Esophagus	Esophagitis, ulceration	55 60	50 70	Whole 1/3
Rectum	Ulcer, stenosis, fistula	60	80	No volume effect
Salivary glands	Xerostomia	32	46	1/3 or 1/2
Bladder	Contracture	65 80	80 85	2/3 1/3
Ureters	Stricture	70	100	5–10 cm length
Testes	Sterilization	1	2	Whole
Ovaries	Sterilization	2–3	6–12	Whole (age dependent)

TABLE 20.2 A Compilation of Tissue and Organ Sensitivities *(Continued)*

	Injury	$TD_{5/5}$, Gy	$TD_{50/5}$, Gy	Field Size
Growing cartilage, child bone	Growth arrest, dwarfing	10	30	Whole
Mature cartilage, adult bone	Necrosis, fracture, sclerosis	60 60	100 100	Whole 10 cm^2
Eye				
Retina	Blindness	45	65	Whole
Cornea		50	6	Whole
Lens	Cataract	10	18	Whole
Endocrine				
Thyroid	Hypothyroidism	45	150	Whole
Adrenal	Hypoadrenalism	60	—	Whole
Pituitary	Hypopituitarism	45	200	Whole
Peripheral nerves	Neuritis	60	100	—
Ear				
Middle	Serous otitis	30	40	No volume effect
Vestibular	Meniere syndrome	60	70	—
Class III organs				
Muscle				
Child	Atrophy	20	40	Whole
Adult	Fibrosis	60	80	Whole
Lymph nodes and lymphatics	Atrophy, sclerosis	50	70	Whole node
Large arteries and veins	Sclerosis	80	100	10 cm^2
Uterus	Necrosis, perforation	100	200	Whole
Vagina	Ulcer, fistula	90	100	Whole
Breast				
Child	No development	10	15	Whole
Adult	Atrophy, necrosis	50	100	Whole

Tolerance Dose – Simplified Table

Organ	Injury	TD5%/5yr	TD50%/5yr
Bone marrow	aplasia	2.5	4.5
Intestine	perforation	40	55
Liver	hepatitis	30	40
Brain	necrosis	45	60
Lung	pneumonitis	17	24
Kidney	nephrosclerosis	23	28
Skin	dermatitis	55	65
Rectum	ulcer, fistula	60	80
Saliv. glands	xerostomia	32	46
Testes	sterilization	1	2
Ovaries	sterilization	2-3	6-12
Bone (child)	growth arrest	10	30
Bone (adult)	necrosis	60	100
P. nerves	neuritis	60	100
Muscle	fibrosis	60	80
Breast	atrophy	50	100

QUANTEC – IJROBP 2010

INTRODUCTORY PAPER

USE OF NORMAL TISSUE COMPLICATION PROBABILITY MODELS IN THE CLINIC

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The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) review summarizes the currently available three-dimensional dose/volume/outcome data to update and refine the normal tissue dose/volume tolerance guidelines provided by the classic Emami *et al.* paper published in 1991. A "clinician's view" on using the QUANTEC information in a responsible manner is presented along with a description of the most commonly used normal tissue complication probability (NTCP) models. A summary of organ-specific dose/volume/outcome data, based on the QUANTEC reviews, is included.

QUANTEC Summary Table

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)*

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Brain	Whole organ	3D-CRT	Symptomatic necrosis	Dmax <60	<3	Data at 72 and 90 Gy, extrapolated from BED models
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 72	5	
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 90	10	
	Whole organ	SRS (single fraction)	Symptomatic necrosis	V12 <5–10 cc	<20	Rapid rise when V12 > 5–10 cc
Brain stem	Whole organ	Whole organ	Permanent cranial neuropathy or necrosis	Dmax <54	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	D1–10 cc‖ ≤59	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	Dmax <64	<5	Point dose <<1 cc
	Whole organ	SRS (single fraction)	Permanent cranial neuropathy or necrosis	Dmax <12.5	<5	For patients with acoustic tumors
Optic nerve / chiasm	Whole organ	3D-CRT	Optic neuropathy	Dmax <55	<3	Given the small size, 3D CRT is often whole organ‡‡
	Whole organ	3D-CRT	Optic neuropathy	Dmax 55–60	3–7	
	Whole organ	3D-CRT	Optic neuropathy	Dmax >60	>7-20	
	Whole organ	SRS (single fraction)	Optic neuropathy	Dmax <12	<10	
Spinal cord	Partial organ	3D-CRT	Myelopathy	Dmax = 50	0.2	Including full cord cross-section
	Partial organ	3D-CRT	Myelopathy	Dmax = 60	6	
	Partial organ	3D-CRT	Myelopathy	Dmax = 69	50	
	Partial organ	SRS (single fraction)	Myelopathy	Dmax = 13	1	Partial cord cross-section irradiated
	Partial organ	SRS (hypofraction)	Myelopathy	Dmax = 20	1	3 fractions, partial cord cross-section irradiated

See full publication in Red Journal

QUANTEC Summary Table

	Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <39	<50	For combined parotid glands (per Fig. 3 in paper) ¶
Pharynx	Pharyngeal constrictors	Whole organ	Symptomatic dysphagia and aspiration	Mean dose <50	<20	Based on Section B4 in paper
Larynx	Whole organ	3D-CRT	Vocal dysfunction	Dmax <66	<20	With chemotherapy, based on single study (see Section A4.2 in paper)
	Whole organ	3D-CRT	Aspiration	Mean dose <50	<30	With chemotherapy, based on single study (see Fig. 1 in paper)
	Whole organ	3D-CRT	Edema	Mean dose <44	<20	Without chemotherapy, based on single study in patients without larynx cancer**
	Whole organ	3D-CRT	Edema	V50 <27%	<20	
Lung	Whole organ	3D-CRT	Symptomatic pneumonitis	V20 ≤ 30%	<20	For combined lung. Gradual dose response
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 7	5	Excludes purposeful whole lung irradiation
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 13	10	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 20	20	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 24	30	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 27	40	
Esophagus	Whole organ	3D-CRT	Grade ≥3 acute esophagitis	Mean dose <34	5–20	Based on RTOG and several studies
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V35 <50%	<30	A variety of alternate threshold doses have been implicated. Appears to be a dose/volume response
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V50 <40%	<30	
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V70 <20%	<30	
Heart	Pericardium	3D-CRT	Pericarditis	Mean dose <26	<15	Based on single study
	Pericardium	3D-CRT	Pericarditis	V30 <46%	<15	
	Whole organ	3D-CRT	Long-term cardiac mortality	V25 <10%	<1	Overly safe risk estimate based on model predictions

QUANTEC Summary Table

						irradiated
Cochlea	Whole organ	3D-CRT	Sensory neural hearing loss	Mean dose ≤45	<30	Mean dose to cochlear, hearing at 4 kHz
	Whole organ	SRS (single fraction)	Sensory neural hearing loss	Prescription dose ≤14	<25	Serviceable hearing
Parotid	Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <25	<20	For combined parotid glands[¶]
	Unilateral whole parotid gland	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <20	<20	For single parotid gland. At least one parotid gland spared to <20 Gy[¶]
Rectum	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V50 <50%	<15 <10	Prostate cancer treatment
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V60 <35%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V65 <25%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V70 <20%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V75 <15%	<15 <10	
Bladder	Whole organ	3D-CRT	Grade ≥ 3 late RTOG	Dmax <65	<6	Bladder cancer treatment. Variations in bladder size/shape/ location during RT hamper ability to generate accurate data
	Whole organ	3D-CRT	Grade ≥3 late RTOG	V65 ≤50 % V70 ≤35 % V75 ≤25 % V80 ≤15 %		Prostate cancer treatment Based on current RTOG 0415 recommendation
Penile bulb	Whole organ	3D-CRT	Severe erectile dysfunction	Mean dose to 95% of gland <50	<35	
	Whole organ	3D-CRT	Severe erectile dysfunction	D90[‖] <50	<35	
	Whole organ	3D-CRT	Severe erectile dysfunction	D60-70 <70	<55	

Outlines

- Cells and Tissues
- Early (Acute) and Late Effects
- Functional Subunits in Normal Tissues
- The Volume Effect in Radiotherapy: Tissue Architecture
- Radiation Pathology of Tissues
  - Casarett's Classification
  - Michalowski's H- and F-Type Populations
- Growth Factors
- Specific Tissues and Organs
- **Grading of Late Effects**

Mechanism

Organ by organ clinical observation

LENT and SOMA

EORTC and **RTOG** held the **Late Effects of Normal Tissue** (**LENT**) Conference in 1992, and introduced **SOMA** classification for late toxicity

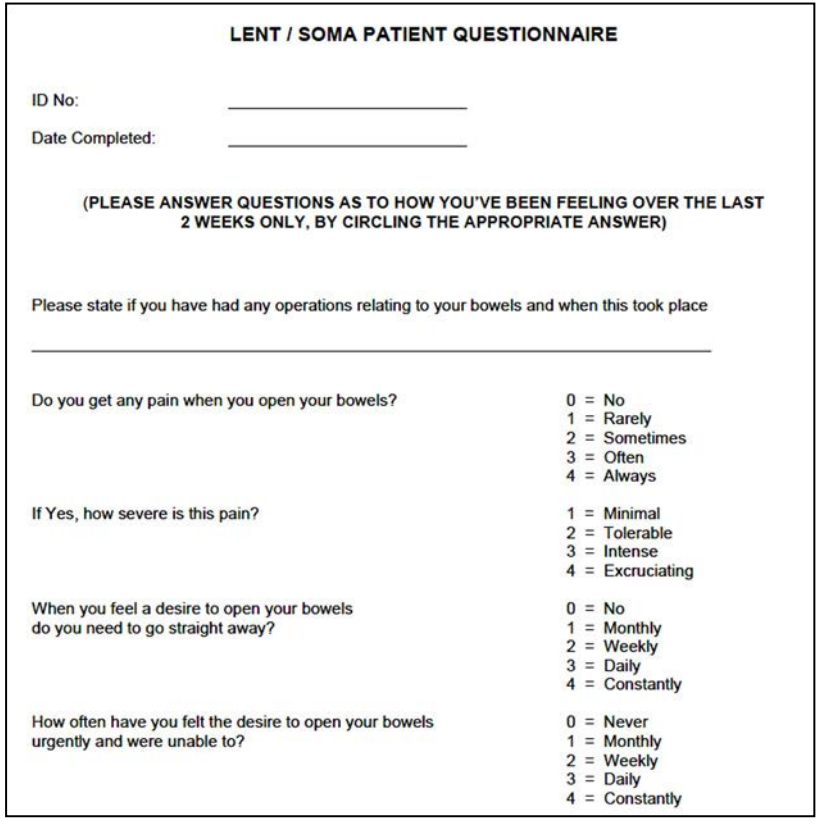
SOMA = **S**ubjective, **O**bjective, **M**anagement criteria with **A**nalytic laboratory and imaging procedures

Subjective	Symptoms perceived by the patient
Objective	Signs that can be assessed by clinician
Management	Active steps taken to ameliorate symptoms
Analytic	Findings that are quantifiable

These scales, specific for each organ, form a scaffold for understanding the expression of later injury

LENT and SOMA

Prostate Radiation



LENT / SOMA PATIENT QUESTIONNAIRE

ID No: _____

Date Completed: _____

(PLEASE ANSWER QUESTIONS AS TO HOW YOU'VE BEEN FEELING OVER THE LAST 2 WEEKS ONLY, BY CIRCLING THE APPROPRIATE ANSWER)

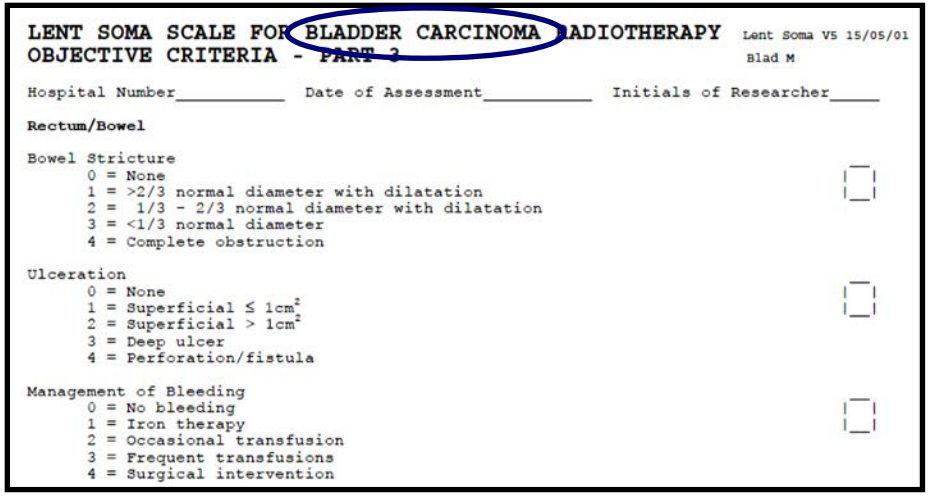
Please state if you have had any operations relating to your bowels and when this took place

_____

Do you get any pain when you open your bowels?	0 = No 1 = Rarely 2 = Sometimes 3 = Often 4 = Always
If Yes, how severe is this pain?	1 = Minimal 2 = Tolerable 3 = Intense 4 = Excruciating
When you feel a desire to open your bowels do you need to go straight away?	0 = No 1 = Monthly 2 = Weekly 3 = Daily 4 = Constantly
How often have you felt the desire to open your bowels urgently and were unable to?	0 = Never 1 = Monthly 2 = Weekly 3 = Daily 4 = Constantly

Subjective

LENT and SOMA



LENT SOMA SCALE FOR BLADDER CARCINOMA RADIOTHERAPY Lent Soma V5 15/05/01
OBJECTIVE CRITERIA - PART 2 Blad M

Hospital Number_____ Date of Assessment_____ Initials of Researcher____

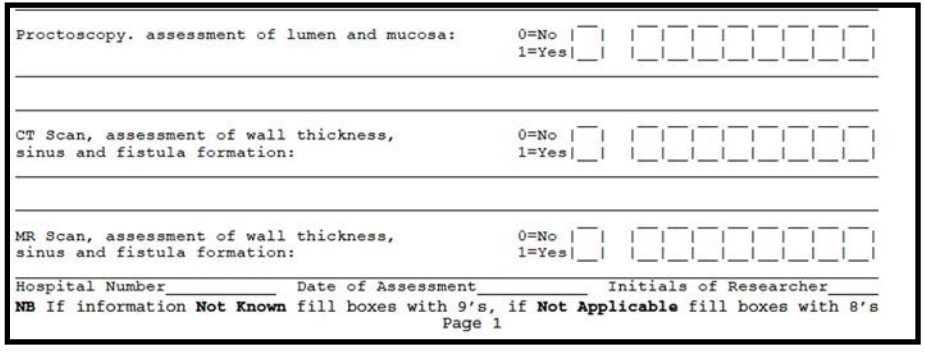
Rectum/Bowel

Bowel Stricture
0 = None
1 = >2/3 normal diameter with dilatation
2 = 1/3 - 2/3 normal diameter with dilatation
3 = <1/3 normal diameter
4 = Complete obstruction

Ulceration
0 = None
1 = Superficial ≤ 1cm²
2 = Superficial > 1cm²
3 = Deep ulcer
4 = Perforation/fistula

Management of Bleeding
0 = No bleeding
1 = Iron therapy
2 = Occasional transfusion
3 = Frequent transfusions
4 = Surgical intervention

Objective



Proctoscopy. assessment of lumen and mucosa: 0=No 1=Yes

CT Scan, assessment of wall thickness, sinus and fistula formation: 0=No 1=Yes

MR Scan, assessment of wall thickness, sinus and fistula formation: 0=No 1=Yes

Hospital Number_____ Date of Assessment_____ Initials of Researcher_____

NB If information **Not Known** fill boxes with 9's, if **Not Applicable** fill boxes with 8's

Page 1

Management

Analytic

LENT and SOMA – Anatomic Sites

Central Nervous System
- Brain
- Spinal cord
- Male hypothalamic/pituitary/gonadal axis
- Female hypothalamic/pituitary/gonadal axis

Head and Neck
- Eye
- Ear
- Mucosa
- Mandible
- Teeth
- Larynx
- Thyroid and hypothalamic/pituitary/thyroid axis

Gastrointestinal system
- Esophagus
- Stomach
- Small intestine/colon
- Rectum

Heart
- Blood vessels

Lung

Genitourinary system
- Kidney
- Ureter
- Bladder/urethera
- Testes
- Male sexual dysfunction

Bone, muscle, and skin
- Muscle/soft tissue
- Peripheral nerves
- Growing bones
- Mature bone (excluding mandible)
- Bone marrow
- Skin/subcutaenous tissue

Gynecologic system
- Vulvar
- Vagina
- Uterus/reproductive organs
- Female sexual dysfunction

Major digestive glands
- Liver

Breast

LENT and SOMA

Central Nervous System SOMA

Subjective	Objective	Management	Analytic
Headache	Neurologic deficit	Anticonvulsives	MRI
Somnolence	Cognitive function	Steroids	CT
Intellectual deficit	Mood and personality changes	Sedation	MRS
Functional competence	Seizures		PET
Memory			Magnetic mapping
			Serum
			Cerebrospinal Fluid

LENT and SOMA

Example of LENT and SOMA Scoring System and Grading Categories

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective (e.g., pain)	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Objective (e.g., neurologic deficit)	Barely detectable	Easily detectable	Focal motor signs, vision disturbances, etc	Hemiplegia, hemisensory deficit, etc
Management (e.g., pain)	Occasional nonnarcotic	Regular nonnarcotic	Regular narcotic	Surgical intervention
Analytic (e.g., CT and MRI, labs)				

Common Terminology Criteria for Adverse Events (CTCAE)

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

Published: November 27, 2017

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

Grade 1	Mild
Grade 2	Moderate
Grade 3	Severe
Grade 4	Life-threatening or disabling
Grade 5	Death