RADIATION INDUCED TOXICITY OF ABDOMINAL ORGANS

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DEPT. OF RADIATION ONCOLOGY

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LEARNING OBJECTIVES

- WHAT??? ;- TOXICITY
- HOW???:- MECHANISM
- WHO??? :- ORGANS AFFECTED
- WHEN??? :- FACTORS GOVERNS
- WHERE???:-ORGAN CONCERNED
- STRATEGIES TO PREVENT???

10 Bollywood Stars Who Hate Alcohol

WHAT ?

...ATE RADIATION TO ACHIEVE BETTER THERAPEUTIC RATIO

Signature

NORMAL TISSUE

REVIEW SERIES: HYPOXIA AND INFLAMMATION — The Journal of Clinical Investigation

Reducing radiation-induced gastrointestinal toxicity — the role of the PHD/HIF axis

Monica M. Olcina and Amato J. Giaccia

Prof. Dr. S N Senapati

5/16/2024

HOW?

APOPTOSIS

NECROPTOSIS

SENESCENCE

ROPTOSIS

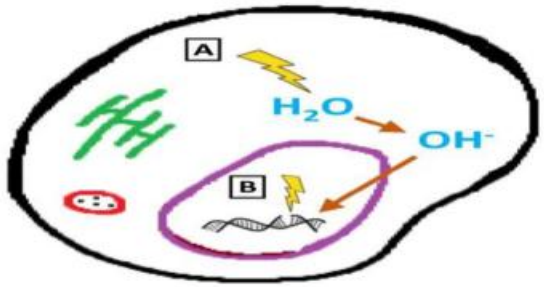
MMUNOGENIC CELL DEATH

FERROPTOSIS

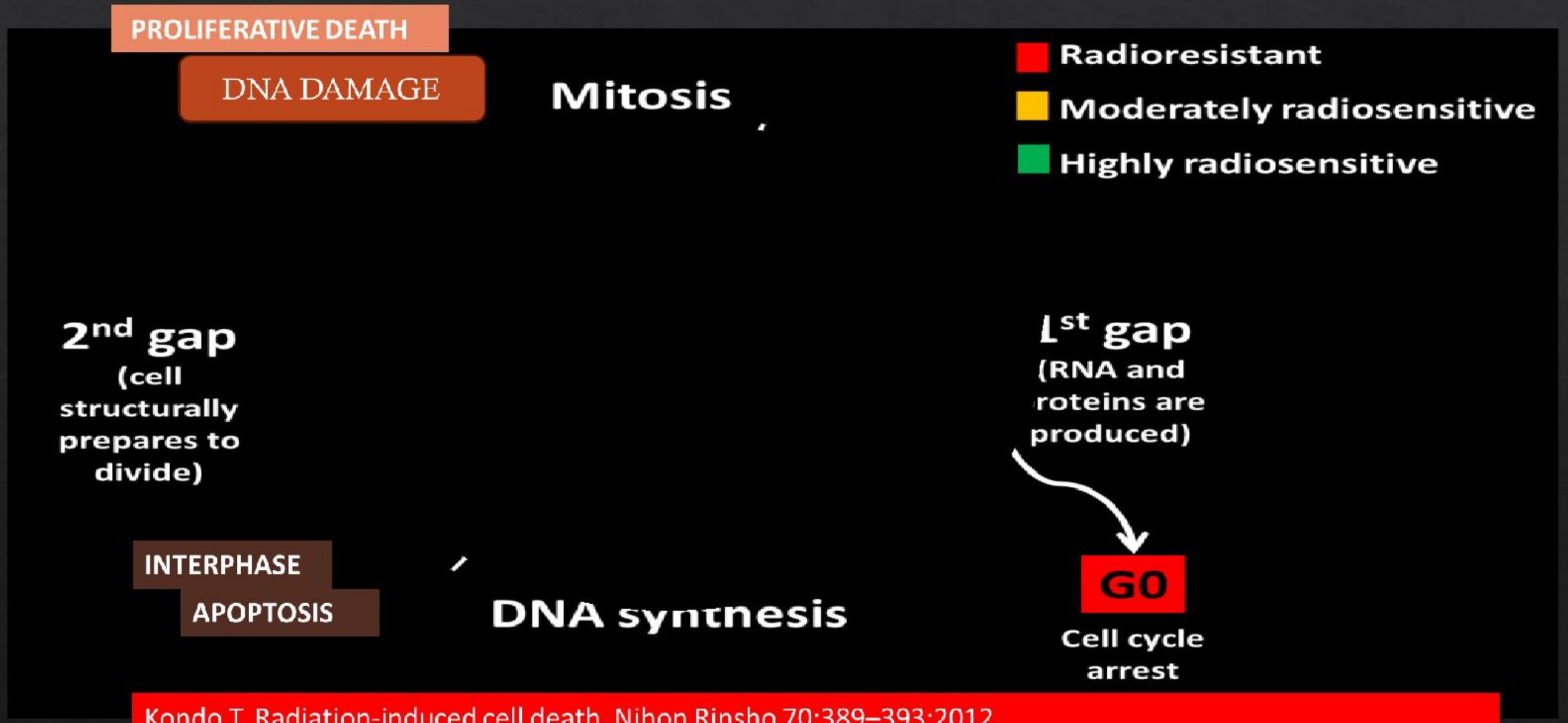
LOW DOSES TEND TO INDUCE APOPTOSIS, WHILE HIGH DOSES ARE MORE INCLINED TO INDUCE CELL NECROSIS. EXPERIMENTAL RESULTS SHOW THAT ACTIVE CASPASE-8 INDUCES CELL APOPTOSIS UNDER LOW-DOSE RADIATION AND INHIBITS NECROSIS BY CLEAVING RIP. HOWEVER, DECREASED CASPASE-8 ACTIVITY PROMPTS THE FORMATION OF INTRACELLULAR RIP1/RIP3 COMPLEX TO MEDIATE NECROPTOSIS IN TUMOR CELLS (Zhou et al. 2021). (Przybyszewski et al. 2008).

EFFECT OF RADIATION

Radiation damages DNA and cellular components in tumor and bystander cells, indirectly via free radicals generated from water molecules (A, 70%) or from direct ionization (B, 30%)

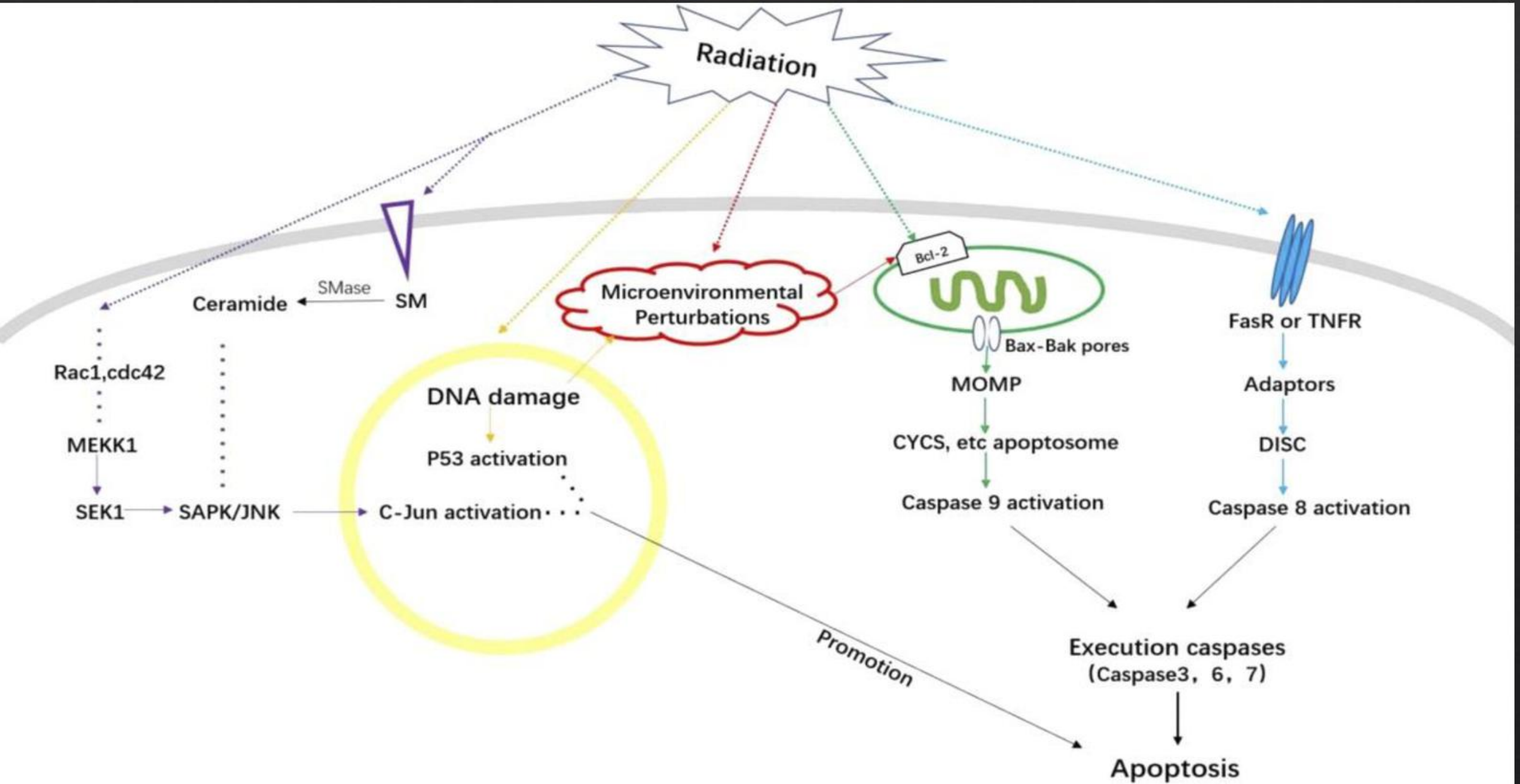


MITOTIC CELL DEATH

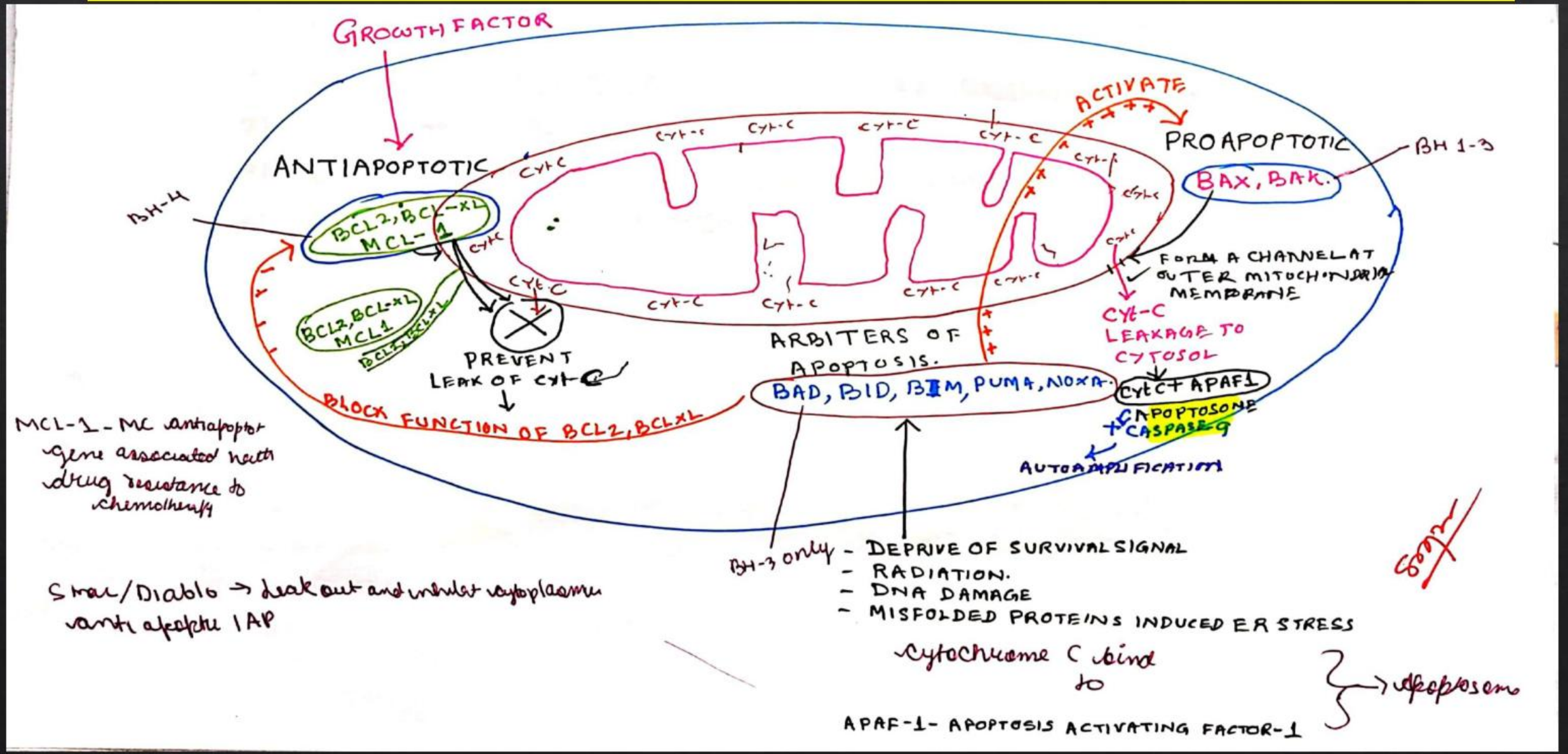


Kondo T. Radiation-induced cell death. Nihon Rinsho 70:389–393;2012.

APOPTOSIS


Radiation
SMase
Ceramide
SM
Microenvironmental Perturbations
Bcl-2
Bax-Bak pores
MOMP
CYCS, etc apoptosome
Caspase 9 activation
FasR or TNFR
Adaptors
DISC
Caspase 8 activation
Rac1,cdc42
MEKK1
SEK1
SAPK/JNK
DNA damage
P53 activation
C-Jun activation
Promotion
Execution caspases
(Caspase3, 6, 7)
Apoptosis

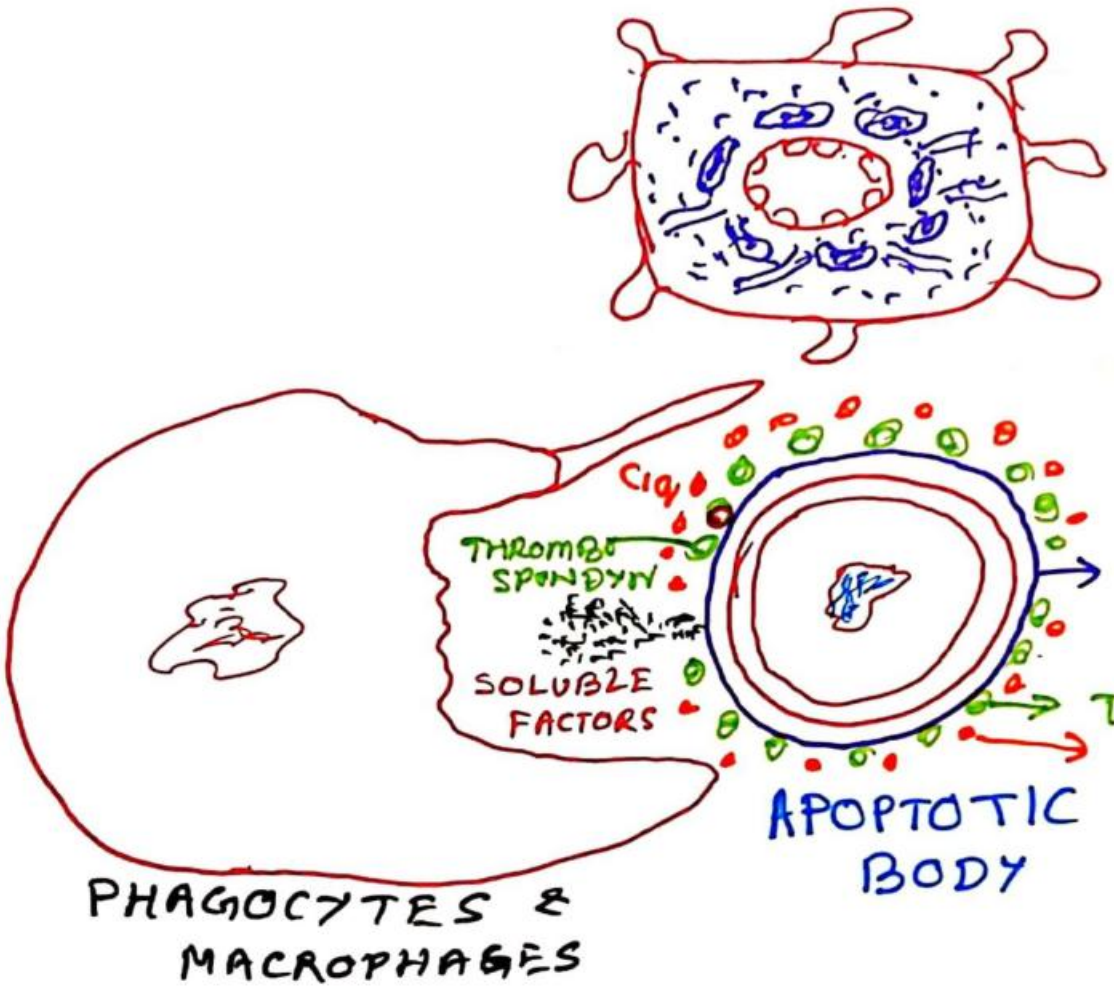
INTRINSIC PATHWAY OF APOPTOSIS
MITOCHONDRIA/ENDOPLASMIC RETICULUM

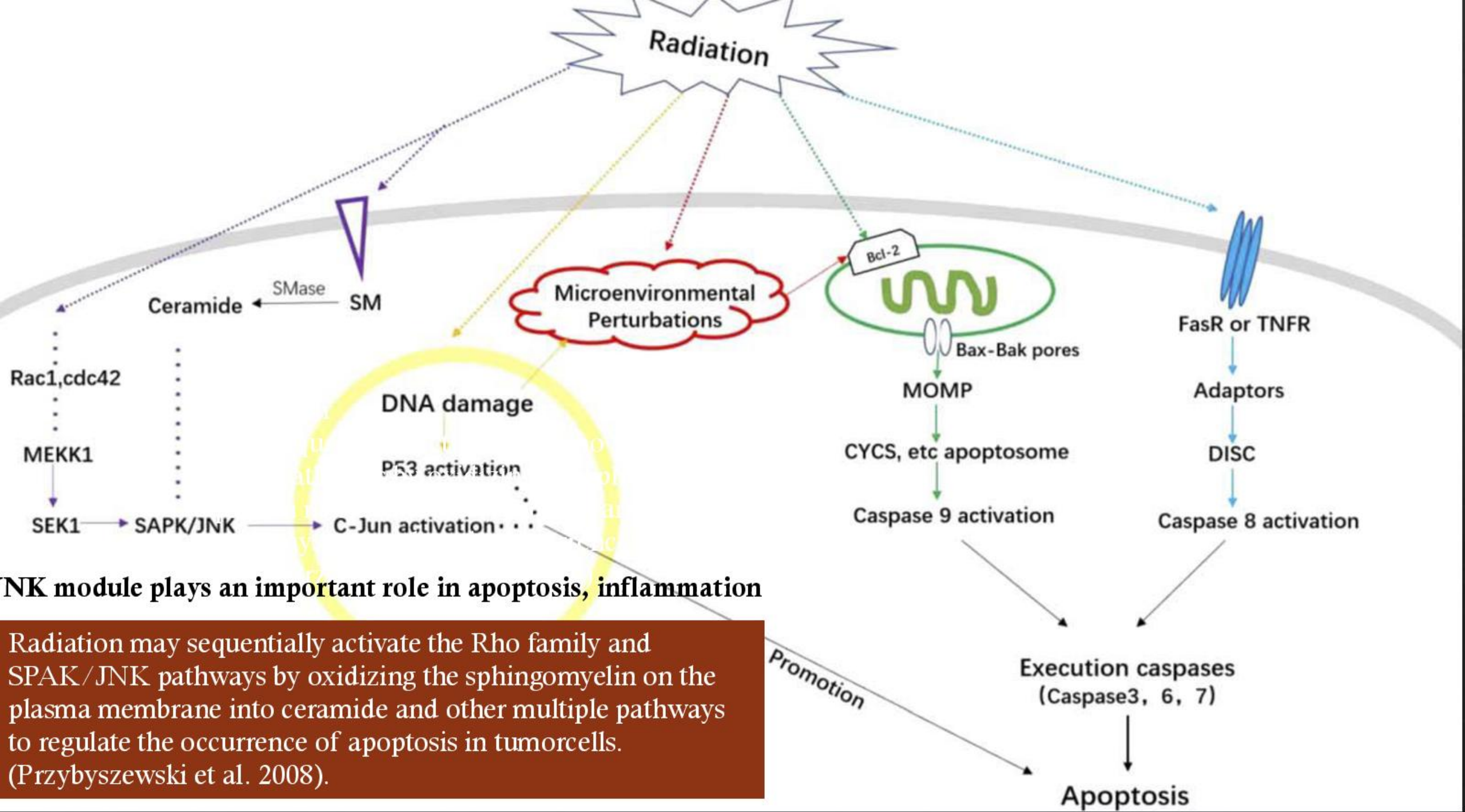


APOPTOTIC PATHWAY

MORPHOLOGY OF APOPTOSIS

IN APOPTOSIS



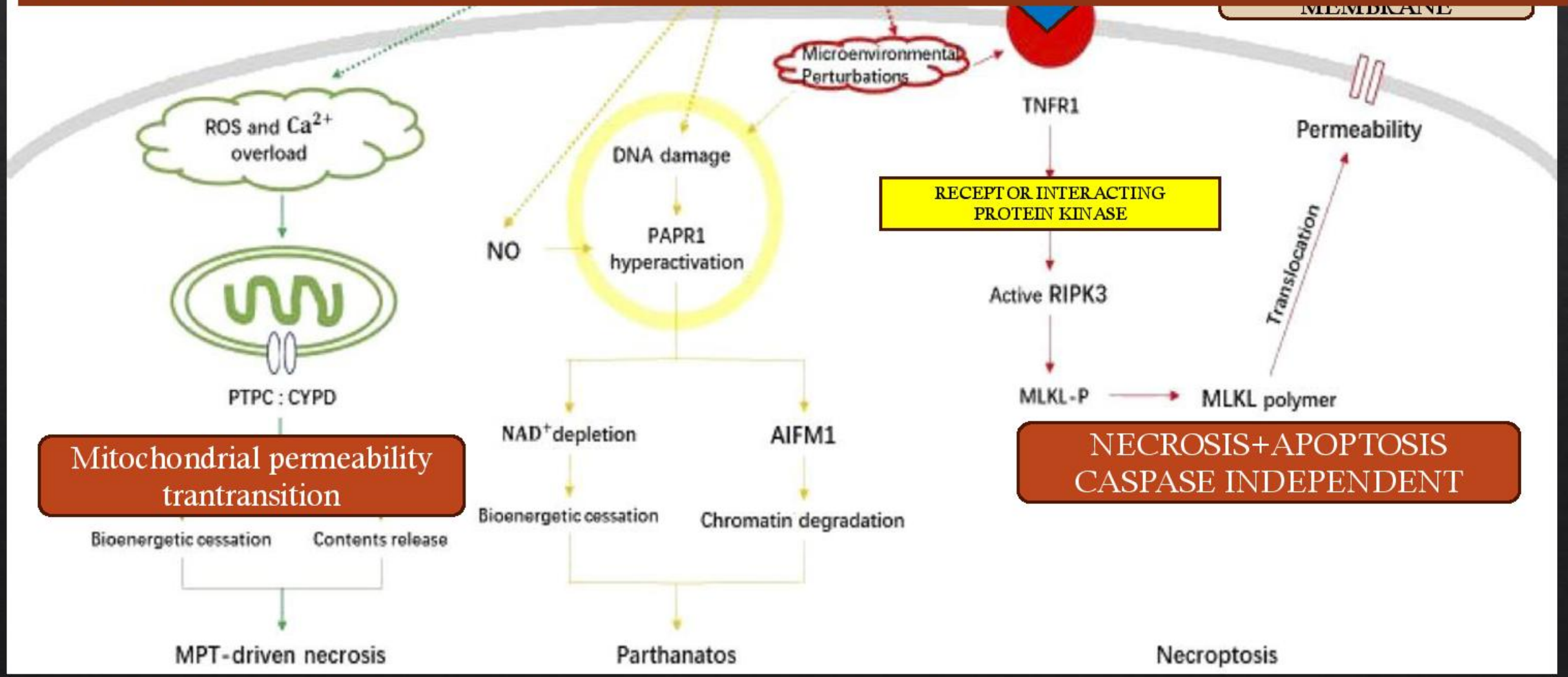


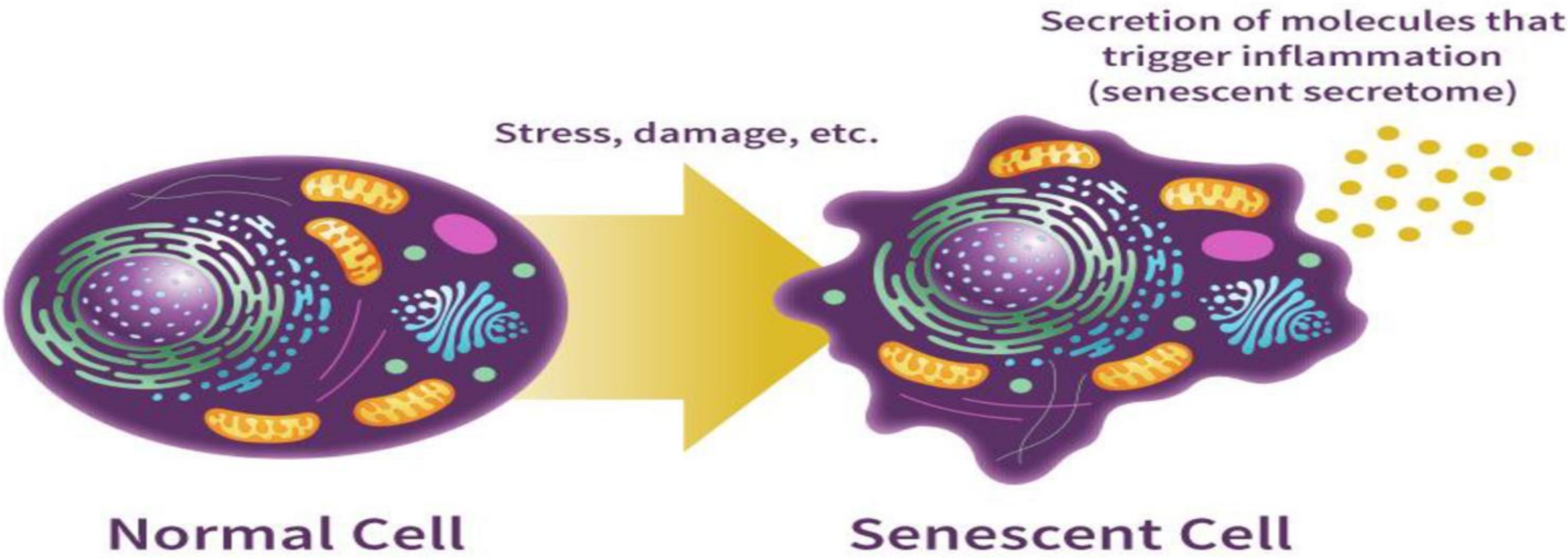
NK module plays an important role in apoptosis, inflammation

Radiation may sequentially activate the Rho family and SPAK/JNK pathways by oxidizing the sphingomyelin on the plasma membrane into ceramide and other multiple pathways to regulate the occurrence of apoptosis in tumorcells. (Przybyszewski et al. 2008).

RADIATION TRIGGER OXIDATIVE STRESS, PEROXIDATION OF INTRACELLULAR MACROMOLECULES, OVERPRODUCTION OF ROS AND THE CONCENTRATION OF CALCIUM IONS INCREASES WHICH ACTIVATE AND PROMOTE THE MPT-DRIVEN NECROSIS (GALLUZZI ET AL. 2014). Parthanatos occurs with hyperactivation of PAPR1 when radiation inflicts excessive DNA damage or provokes intracellular production of iNOS and NO in tumor cells (Zhou et al. 2021).

MPT (MITOCHONDRIALPERMEABILITY TRANSITION
PERMEABLE TRANSITION PORE COMPLEX" (PTPC

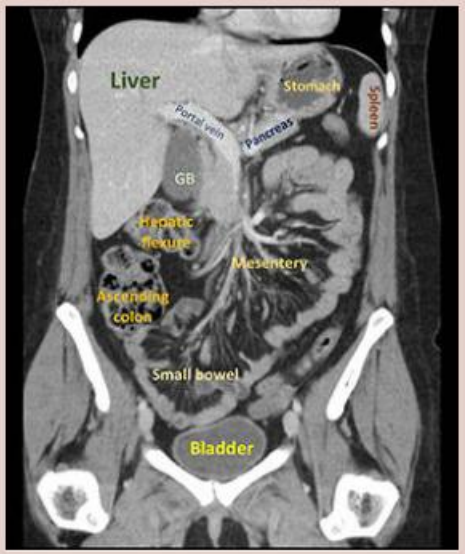




AT THE ONSET OF SENESCENCE, ALTHOUGH METABOLISM IS STILL ONGOING, CELLS WILL PERMANENTLY LOSE THEIR ABILITY TO PROLIFERATE,BE IRREVERSIBLY BLOCKED IN THE STATE OF G1 PHASE, AND EVENTUALLY DIE (REGULSKI 2017). IS A FORM OF PROLIFERATION CELL DEATH TRIGGERED BY RADIATION. ACTIVATION OF P53 FACILITATES CELL SURVIVAL THROUGH GROWTH ARREST AND DNA DAMAGE REPAIR. ACCORDING TO THE EXTENT AND TYPE OF DAMAGE, HOWEVER, P53 PROMOTES THE SENESCENCE OF TUMOR CELLS AFTER RADIOTHERAPY, OFTEN ACCOMPANIED BY P21 EXPRESSION.WHEN P53 SIGNALING IS IMPAIRED,RADIATION-INDUCED SENESCENCE SEEMS TO BE DIMINISHED.

WHO?

Site of Cancer	Organs of concern
CA GEJ/ CA Stomach	
CA Pancrease	
Paraaortic irradiation (Cervix/ Lymphoma/ Testicular Tumours)	
CA Gallbladder	
HCC/ Cholangiocarcinoma	
Retroperitoneal Sarcoma	
RCC/ Wilm's Tumour	



ACUTE:-I,II,III,IV
LATE:-TELANGIECTASIA,OEDEMA,FIBROSIS

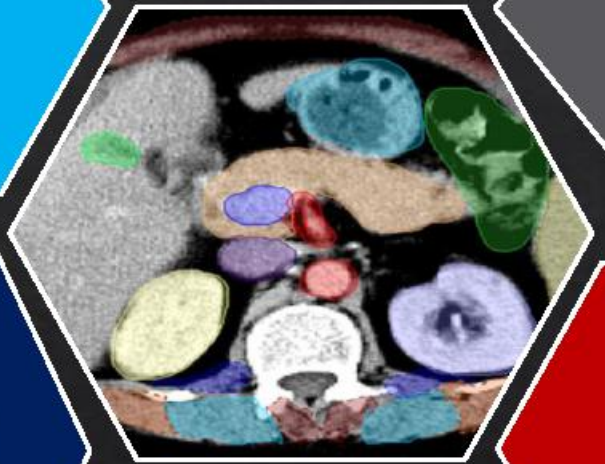
SKIN

LIVER

- VENO OCCLUSIVE DISEASES
- DECLINE IN HEPATIC FUNCTION
- WORSENING CHILD-PUGH SCORE
- INCREASING ASCITES
- HEPATITIS,CIRRHOSIS

PANCREAS

DIABETES, LIPASE & AMYLASE DEF.



STOMACH

GASTRITIS,ULCERATION,CHRONIC ATROPHIC GASTRITIS,INTESTINAL METAPLASIA

KIDNEY

NEPHRITIS,RENAL FAILURE

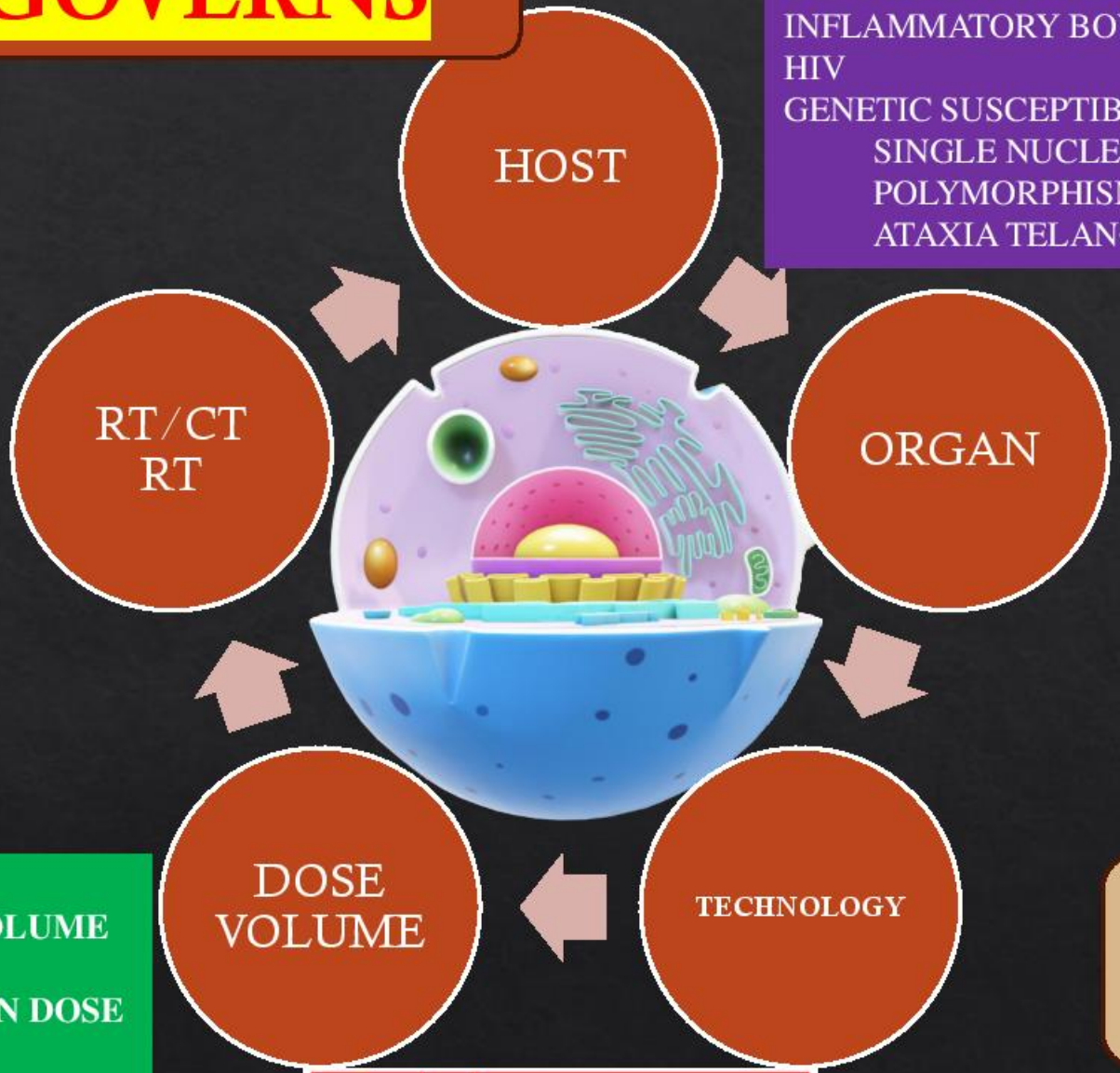
BOWEL

RADIATION ENTERITIS
INT OBSTRUCTION

ORGAN OF CONCERN

ORGAN (MOSTLY MIXED TYPE- PARALLEL & SERIAL, ACCORDING TO FSUS)	ACUTE SYMPTOMS	CHRONIC SYMPTOMS

FACTORS GOVERNS



MEDICAL COMORBIDITIES
VASCULAR DISEASES
CONNECTIVE TISSUE DISEASE
INFLAMMATORY BOWEL DISEASE
HIV
GENETIC SUSCEPTIBILITY
- SINGLE NUCLEOTIDE POLYMORPHISM
- ATAXIA TELANGECTASIA

COMBINED MODALITY THERAPIES
SURGERY (PRIOR TO RT)
CHEMOTHERAPY, PARTICULARLY CONCURRENT (EG-5-FU)

- ACUTE Vs LATE REACTING TISSUE
- SERIAL Vs PARALLEL
- TOLERANCE

- **TREATMENT VOLUME**
- **TOTAL DOSE**
- **FRACTIONATION DOSE**
- **SCHEDULE**

IMRT
IGRT
VMAT

World Journal of Gastroenterology

CASARETTS CLASSIFICATION OF RADIOSENSITIVITY

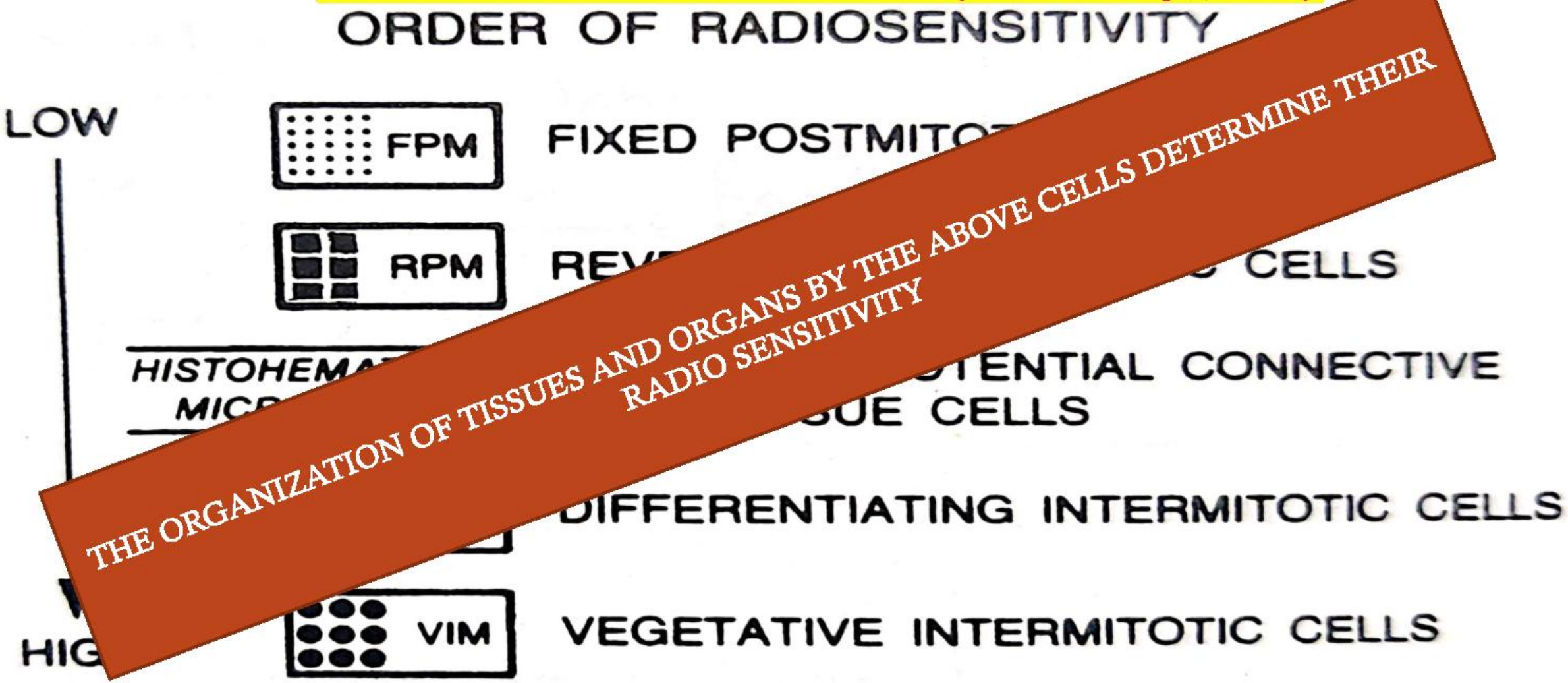
Cell Type	Properties	Examples	Sensitivity[a]

THE TIME INTERVAL BETWEEN THE IRRADIATION AND THE CRISIS DEPENDS ON
LIFE SPAN OF VEGETATIVE INTERMITOTIC CELL
PERCENTAGE OF SURVIVING FUNCTIONAL CELLS

[a]Sensitivity decreases for each successive group

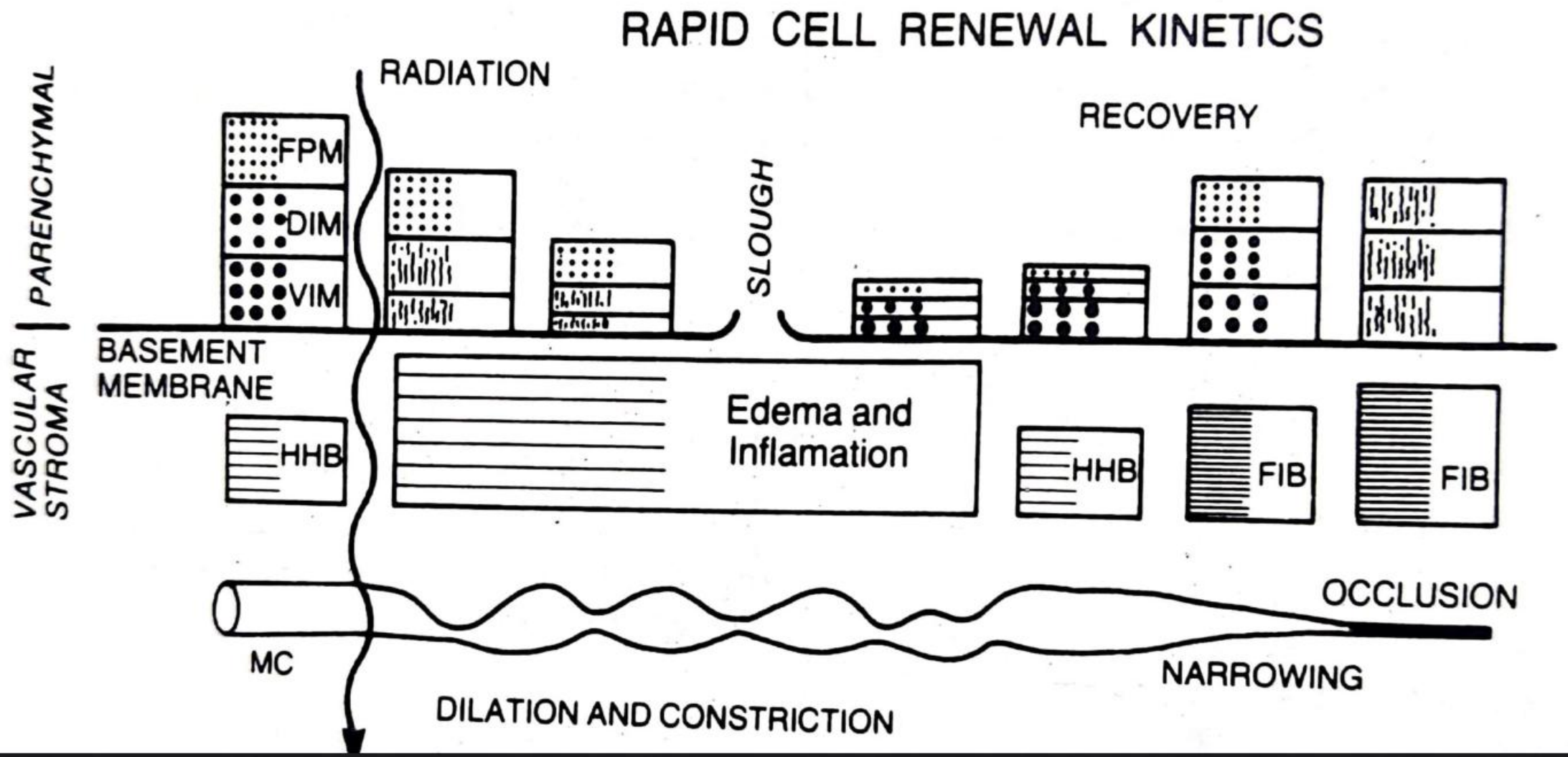
[b]Intermediate in sensitivity between groups II and III

PHILOSOPHY BEHIND THE COMPLICATIONS IN RELATION TO CELL RADIOSENSITIVITY(cowdery etal)

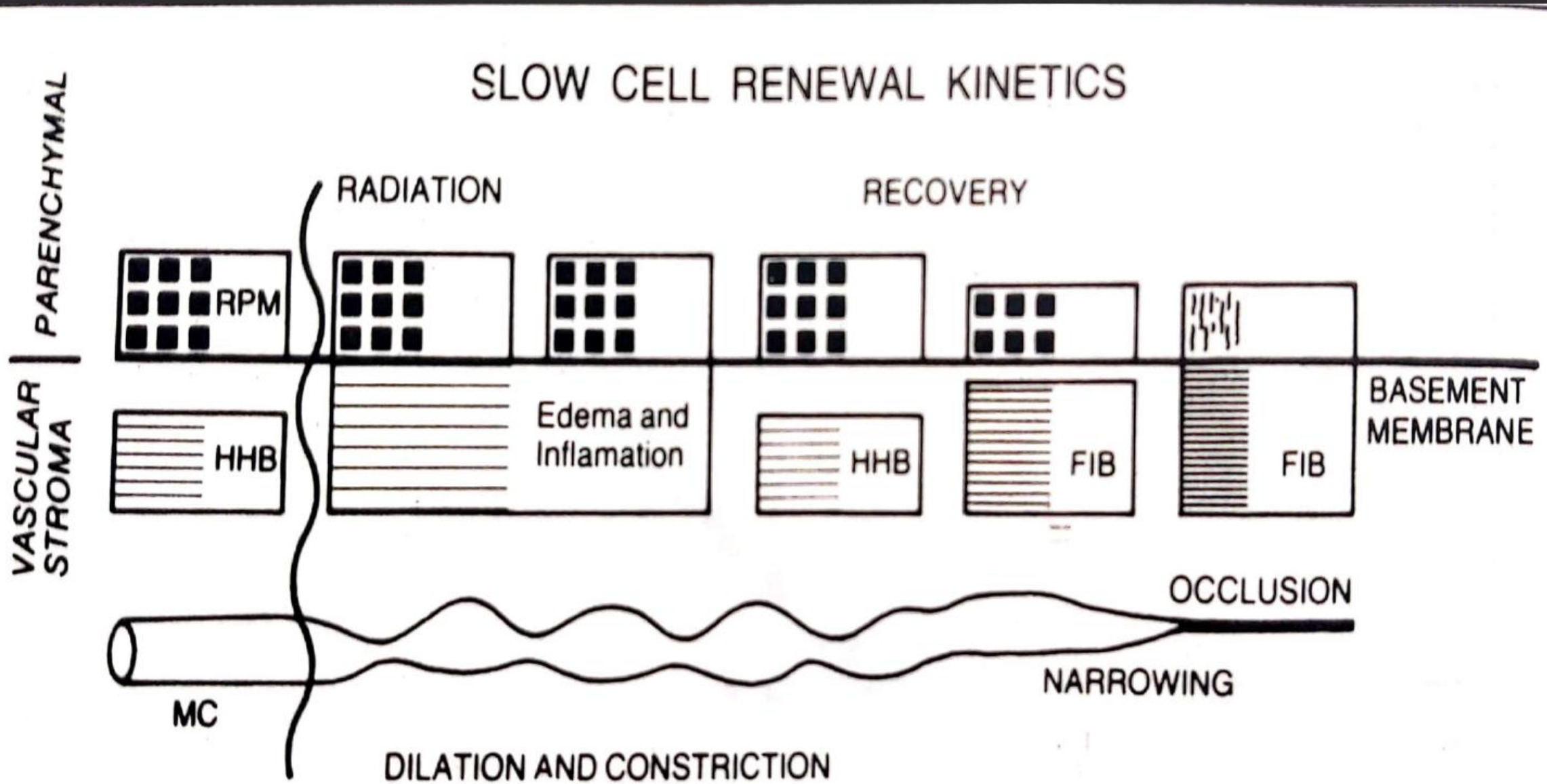


THE ORGANIZATION OF TISSUES AND ORGANS BY THE ABOVE CELLS DETERMINE THEIR RADIO SENSITIVITY

RAPIDLY PROLIFERATING TISSUE,ACUTE TOXICITY

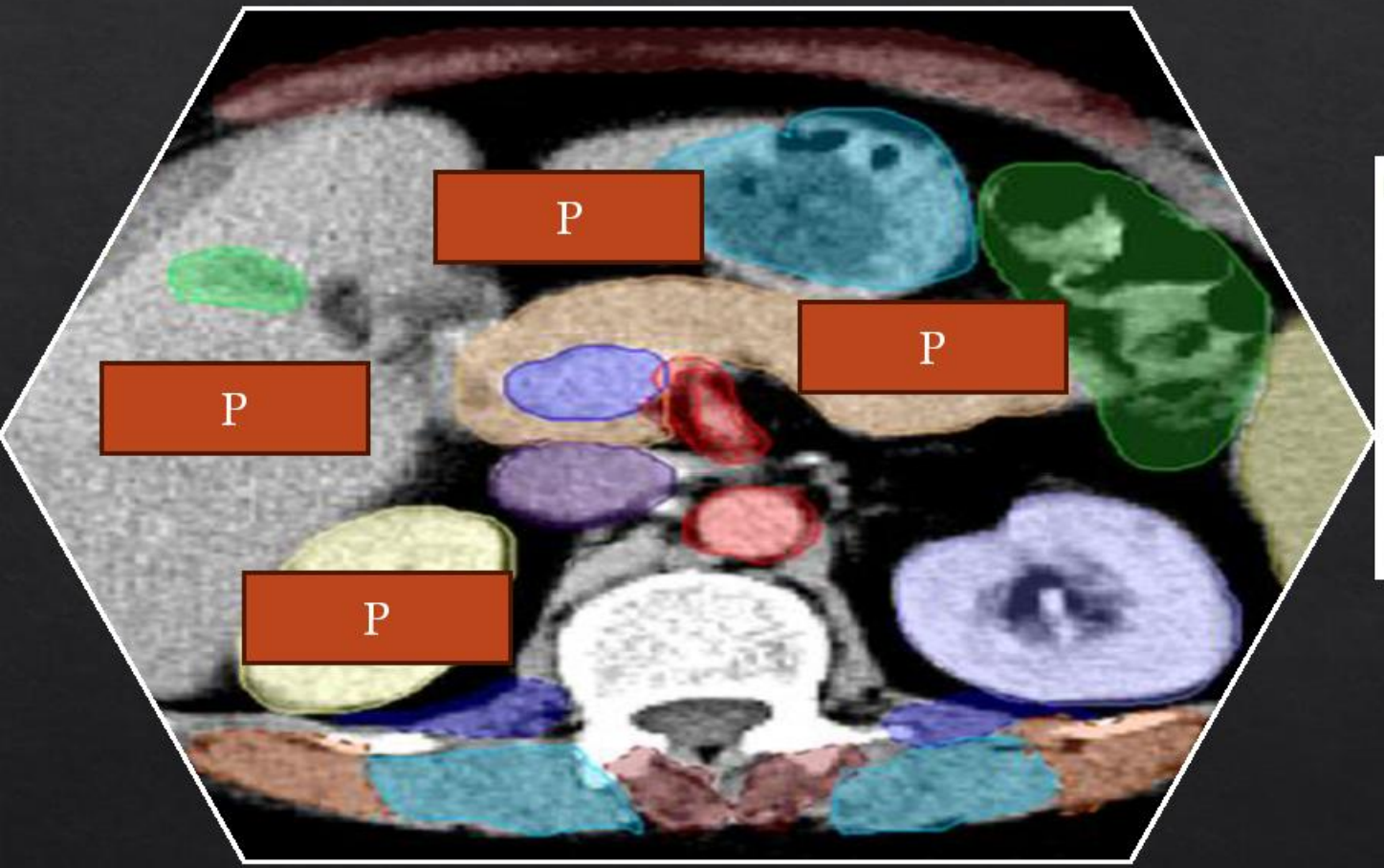


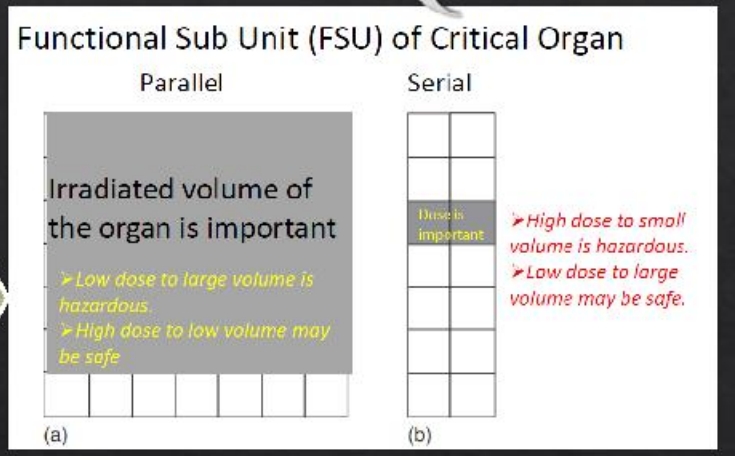
SLOW RENEWAL KINETICS,LATE TOXICITY

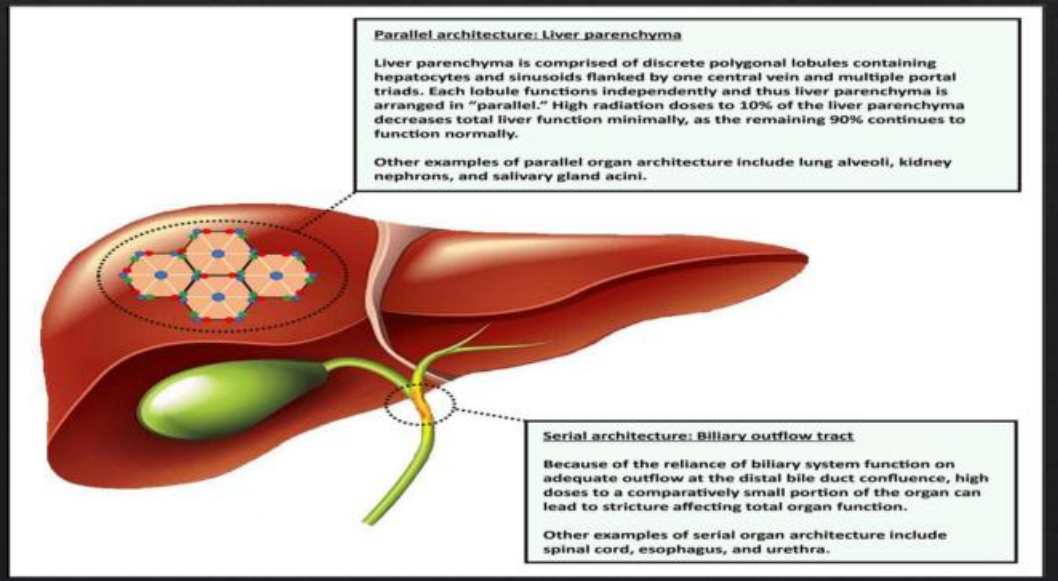


SERIAL Vs PARALLEL

- Emami et al
- Quantec







- **(TD5/5 AND TD50/5) = 50 Gy & 65 Gy**

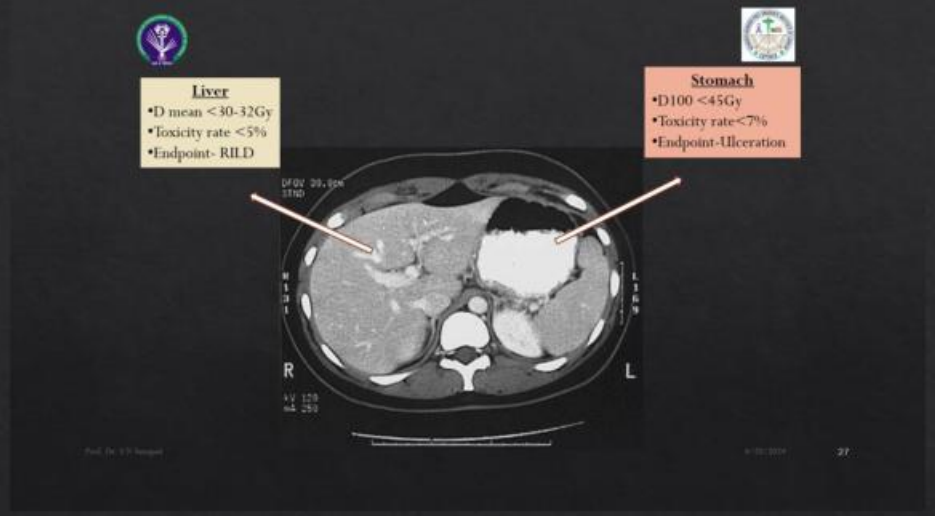
5% AND 50% OF PATIENTS RISK OF DELAYED GASTRIC TOXICITY IN 5 YEARS HAVE BEEN ESTIMATED AT 50 GY AND 65 GY RESPECTIVELY FOR GASTRIC ULCERATION OR PERFORATION.

(V28 < 20%) ONLY < 5%

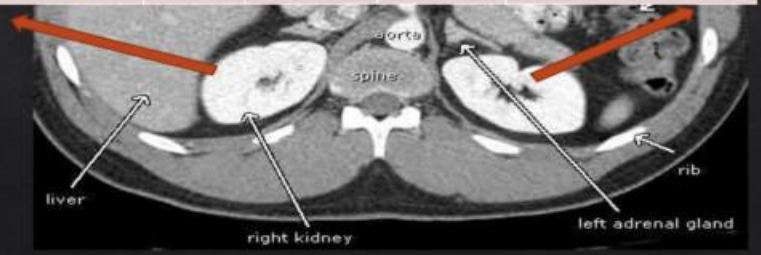
IF LESS THAN 20% OF THE KIDNEY VOLUME ARE EXPOSED TO 28 GY (V28 < 20%) ONLY < 5% OF PATIENTS WILL DEVELOP A CLINICALLY RELEVANT KIDNEY DYSFUNCTION

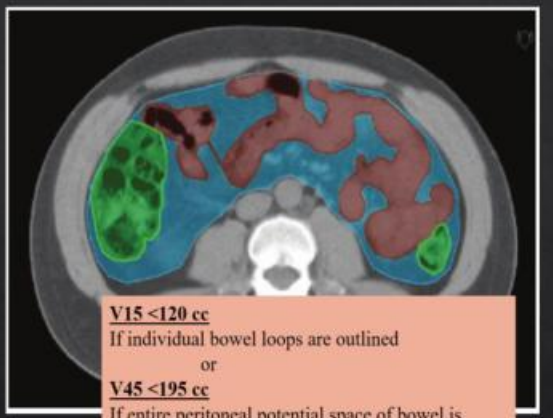
DOSE LIMITATIONS OF OAR IN RADIATION THERAPY FOR UPPER ABDOMINAL MALIGNANCIES

OAR	Dose limitation	End point	Rate (%)
Spinal cord	• Dmax = 50 • Dmax = 60 • Dmax = 69	Myelopathy	• 0.2 • 6 • 50
Whole liver	• Mean dose 30–32 • Mean dose <42	Classical RILD	• <5 • <50
Small intestine	• V45 < 195 cc (Entire potential space within peritoneal cavity)	Grade ≥ 3 acute toxicity	• <10
Heart	• Mean dose <26 (Pericardium) • V30 < 46% (pericardium) • V25 < 10% (whole heart)	Pericarditis Long-term cardiac mortality	• <15% • <15% • <1
Bilateral whole kidneys	• Mean dose <15–18 • Mean dose <28	Clinically relevant renal dysfunction	• <5 • <50



Kidney, Bilateral	Mean	<15-18Gy	Toxicity Rate <5%	Toxicity Endpoint Clinical Dysfunction
Kidney, Bilateral	Mean	<28Gy	<5%	Clinical Dysfunction
Kidney, Bilateral	V12	<55%	<50%	Clinical Dysfunction
Kidney, Bilateral	V20	<32%	<5%	Clinical Dysfunction
Kidney, Bilateral	V23	<30%	<5%	Clinical Dysfunction
Kidney, Bilateral	V28	<20%	<5%	Clinical Dysfunction





V15 <120 cc
If individual bowel loops are outlined
or
V45 <195 cc
If entire peritoneal potential space of bowel is outlined

Toxicity Rate <10%
Endpoint – Grade 3+ Toxicity

AVAILABLE DOSE CONSTRAINTS & PROBABLE EFFECTS OF DOSES ON CONCERNED ORGANS

QUANTEC

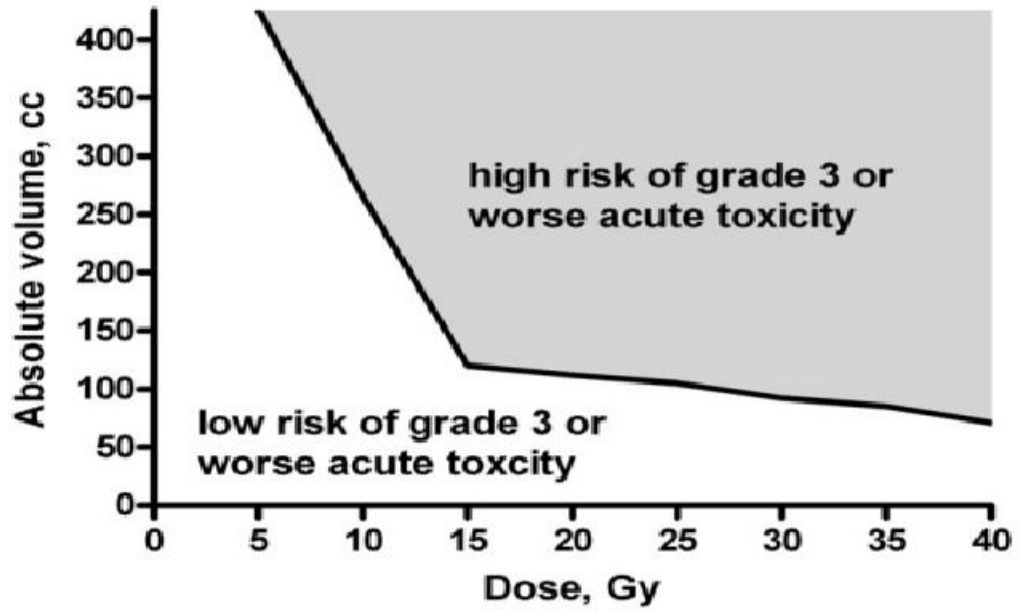


Fig. 1. Graphic representation of the Baglan–Robertson threshold model for risk of acute small bowel toxicity. Here, "low risk" implies ~10% and "high risk" ~40%. Note that the y-axis represents the absolute volume of individual bowel loops and not the peritoneal space.

V15 = 120 cc
If individual bowel loops are outlined

or

V45 = 195 cc
If entire peritoneal potential space of bowel is outlined

patients without Grade 3 toxicity, the mean V15 was 127 cc, whereas for patients who had Grade 3 toxicity the mean V15 was 319 c

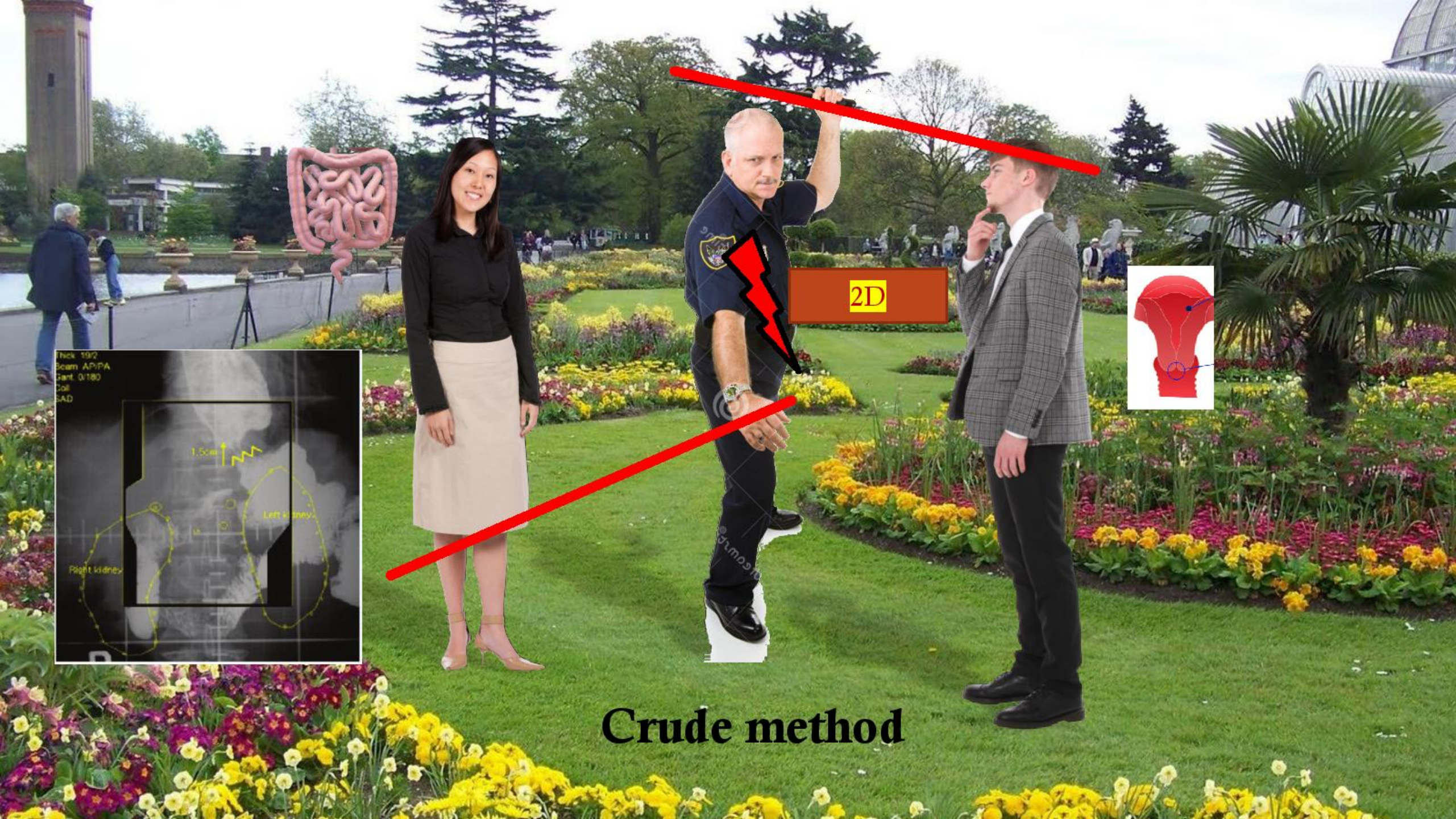
ELSEVIER
Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S101–S107, 2010

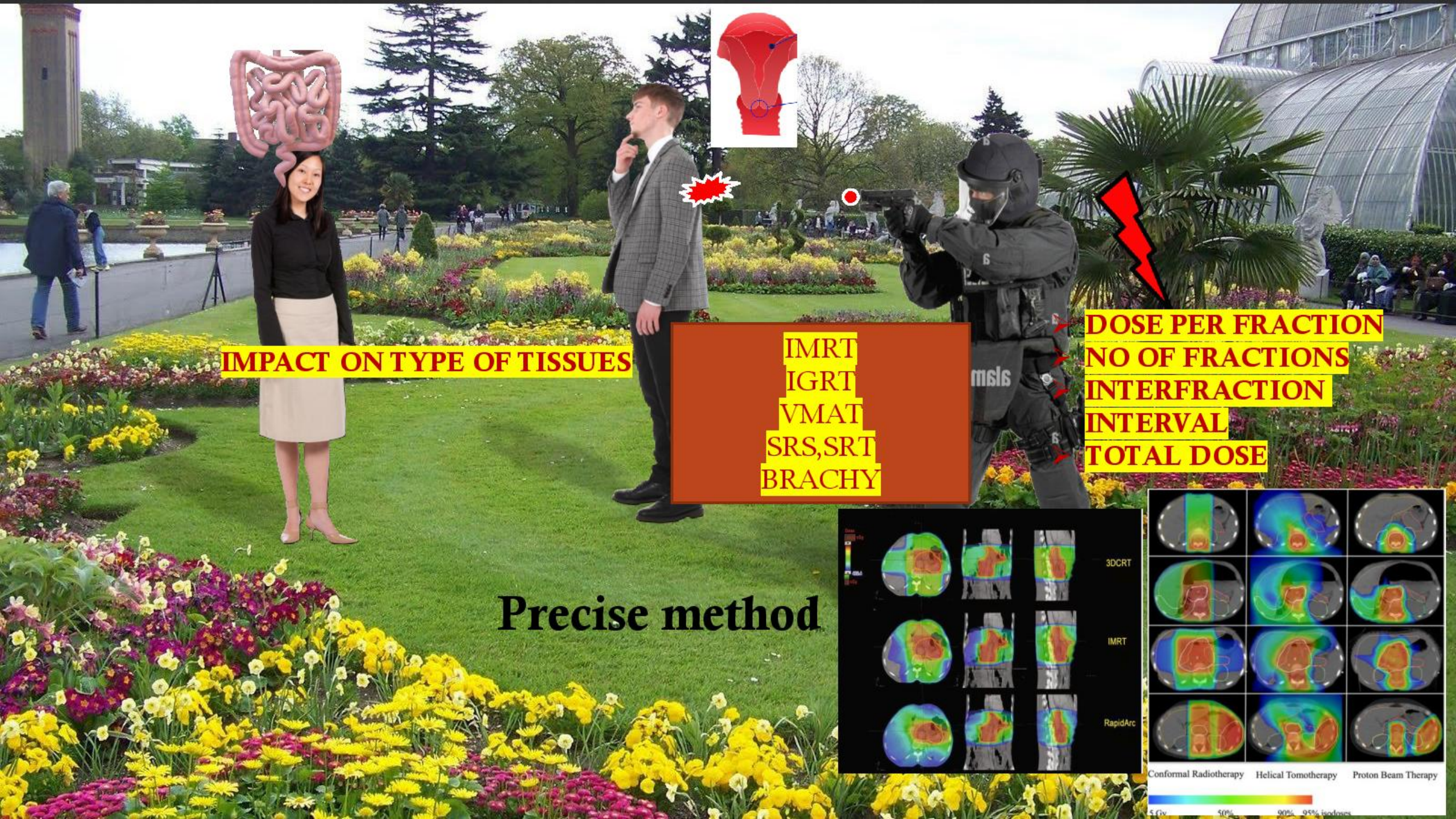
0360-3016/10/$–see front matter
doi:10.1016/j.ijrobp.2009.05.071

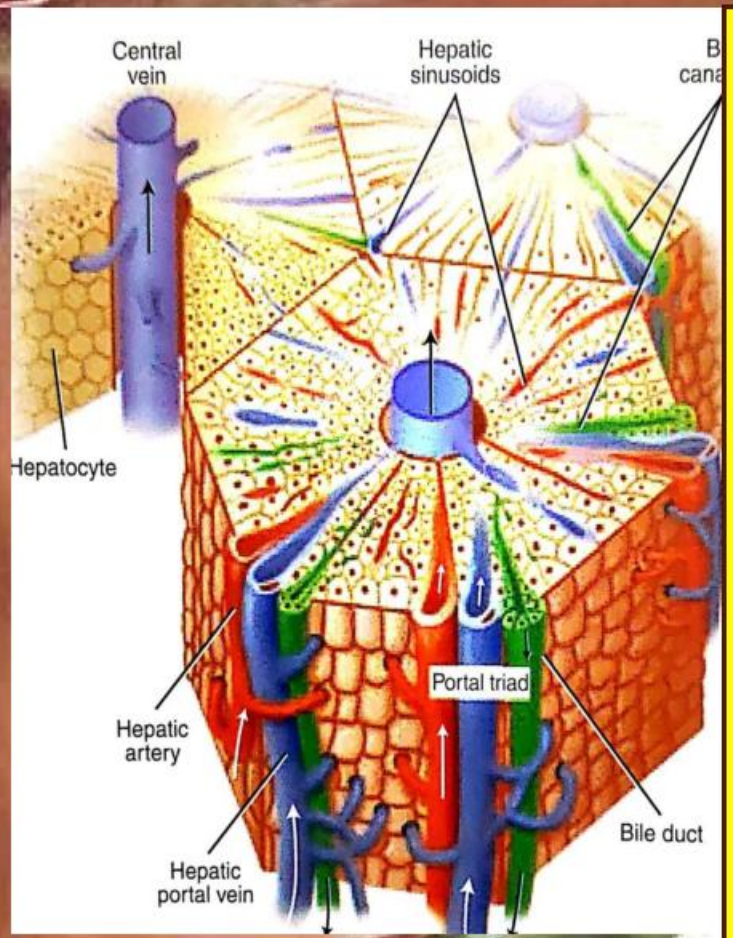
QUANTEC: ORGAN SPECIFIC PAPER Abdomen: Stomach/Small Bowel

RADIATION DOSE–VOLUME EFFECTS IN THE STOMACH AND SMALL BOWEL

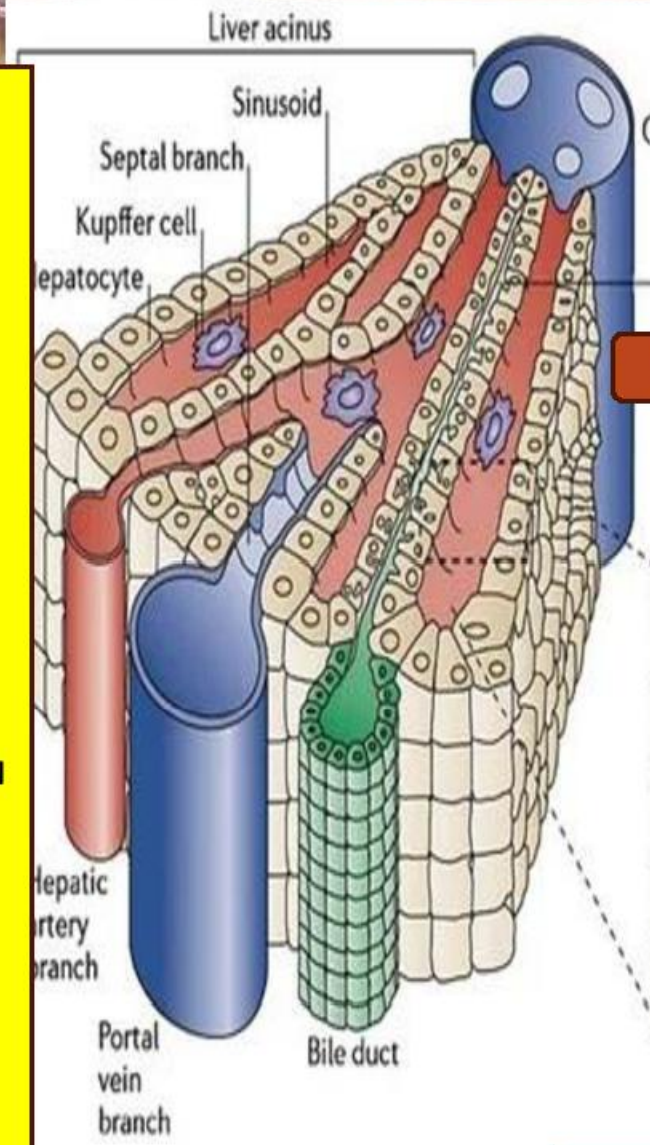
Brian D. Kavanagh, M.D., M.P.H.,* Charlie C. Pan, M.D.,† Laura A. Dawson, M.D.,‡ Shiva K. Das, Ph.D.,§ X. Allen Li, Ph.D.,¶ Randall K. Ten Haken, Ph.D.,* and Moyed Miften, Ph.D.*


2D
Right kidney
Crude method

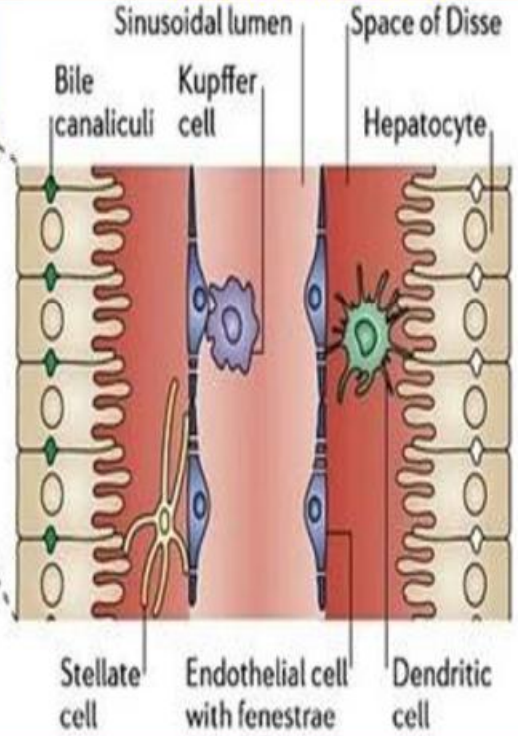

IMPACT ON TYPE OF TISSUES
IMRT
IGRT
VMAT
SRS,SRT
BRACHY
DOSE PER FRACTION
NO OF FRACTIONS
INTERFRACTION
INTERVAL
TOTAL DOSE
Precise method
3DCRT
IMRT
RapidArc
Conformal Radiotherapy
Helical Tomotherapy
Proton Beam Therapy



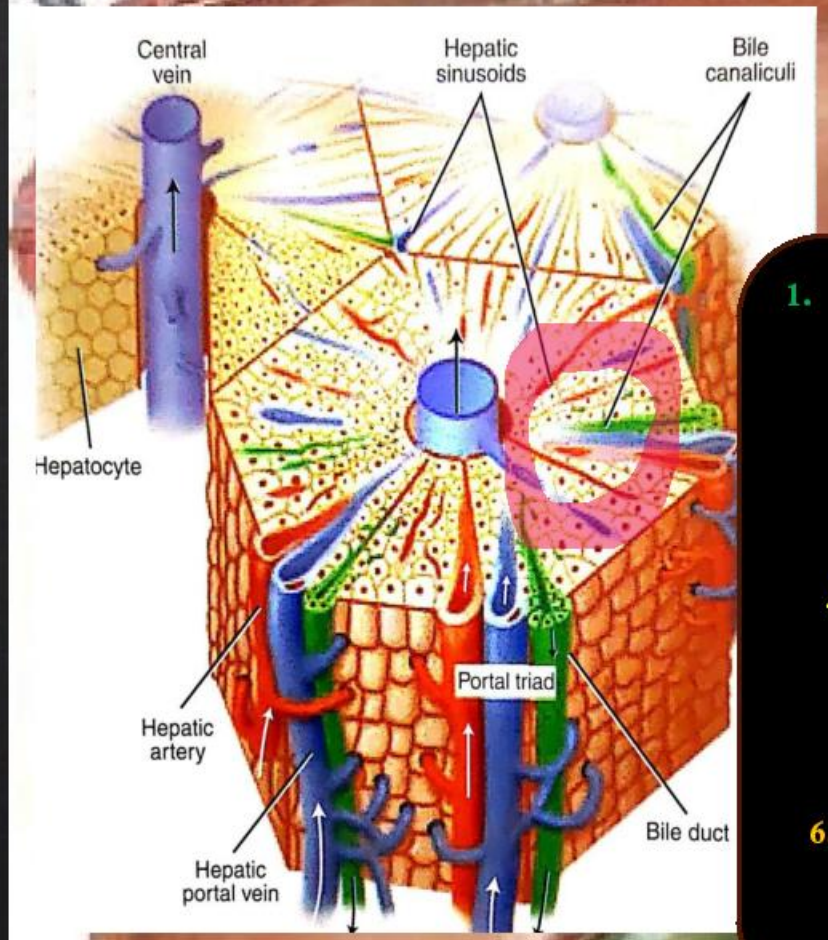
1. **BILE PRODUCTION**
2. **LIPID METABOLISM,**
3. **GLYCOMETABOLISM**
4. **ELIMINATION OF VARIOUS WASTE PRODUCTS**
5. **IMMUNITY**
6. **AND PLASMA PROTEIN SYNTHESIS**



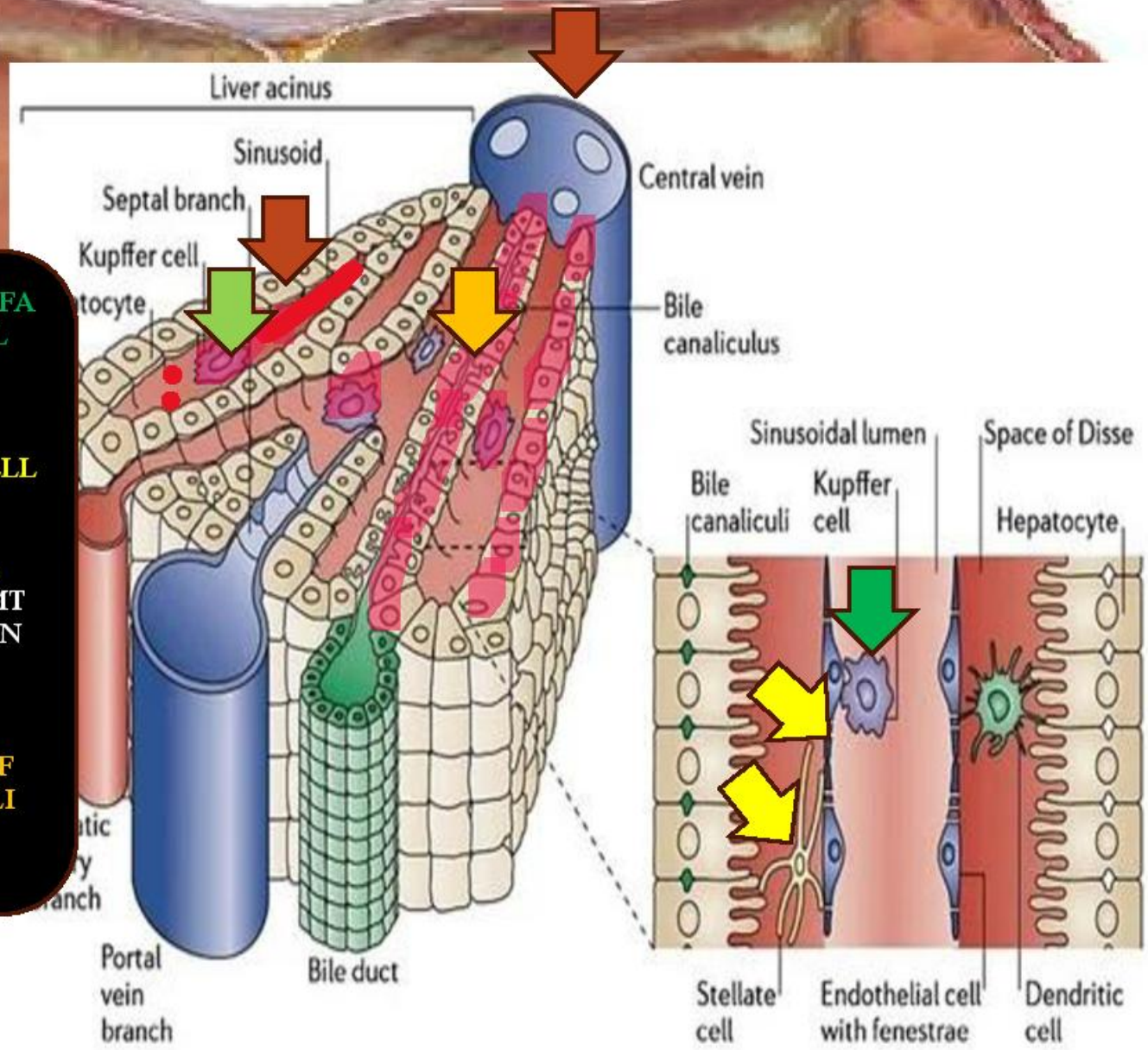
CANAL OF HERING:-CONTAINS OVAL CELL;-STEM CELL



ITO CELL-STELLATE CELL-FIBROSIS

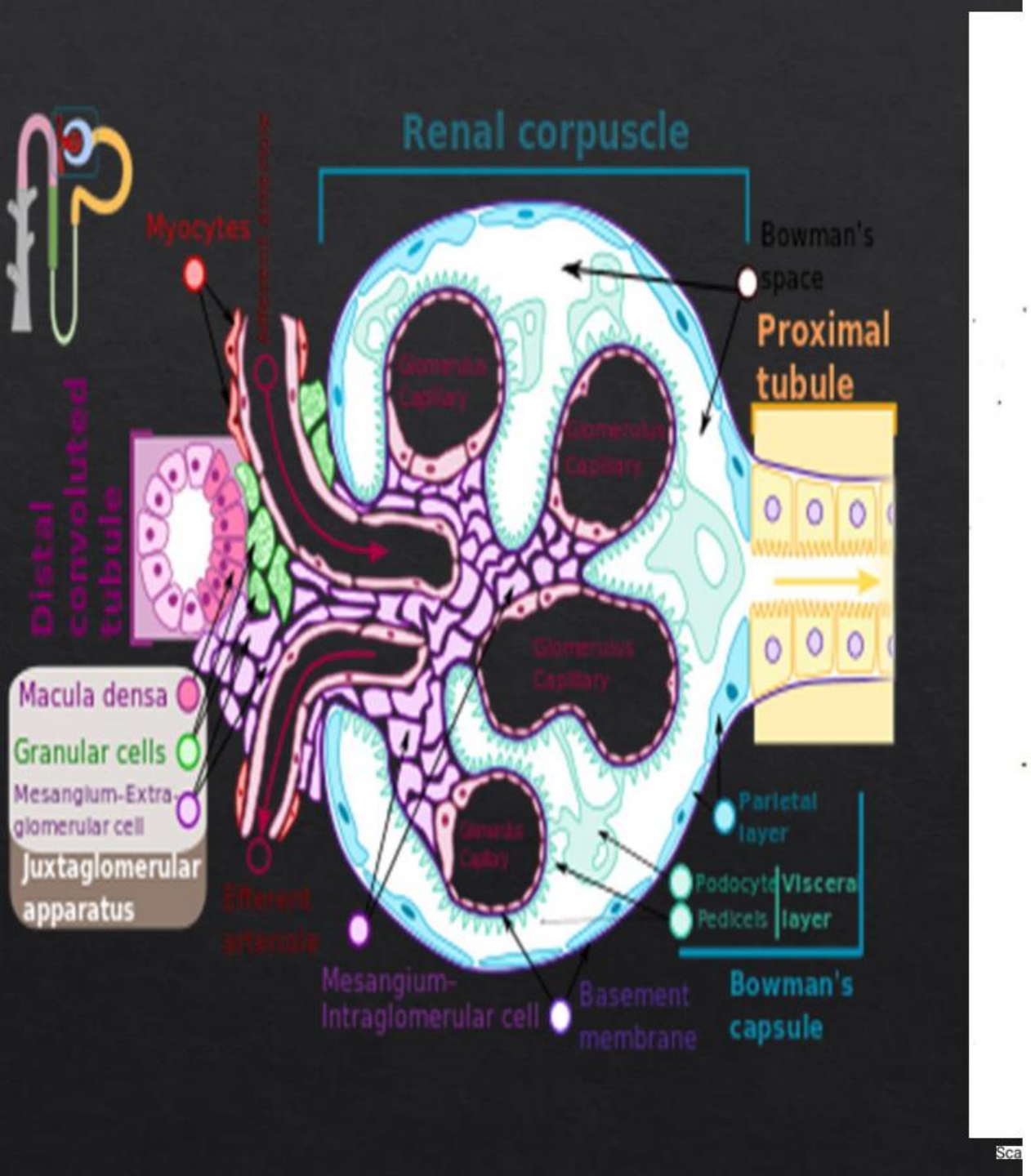


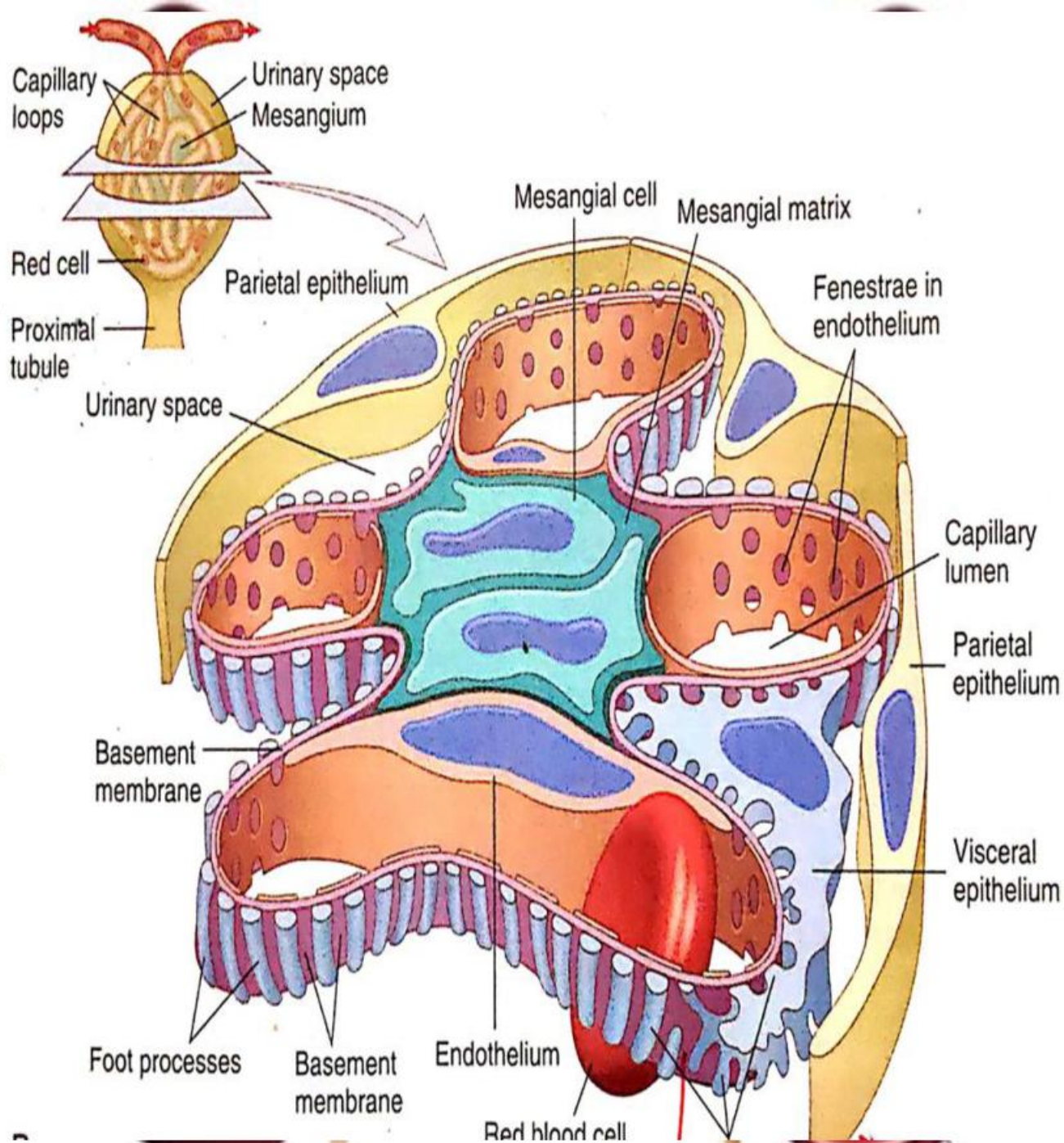
1. PRODN OF TNF ALFA BY KUFFER CELL
2. HEPATOCYTE:- SENESENSE
3. SINUSOIDAL ENDOTHELIAL CELL ACTIVATION & APOPTOSIS
4. STELLATE CELL ACTIVATION & EMT AND PRODUCTION OF TGF BETA.
5. PERIVENULAR FIBROSIS
6. OBSTRUCTION OF BILE CANALICULI
7. SINUSOIDAL OBSTRUCTION

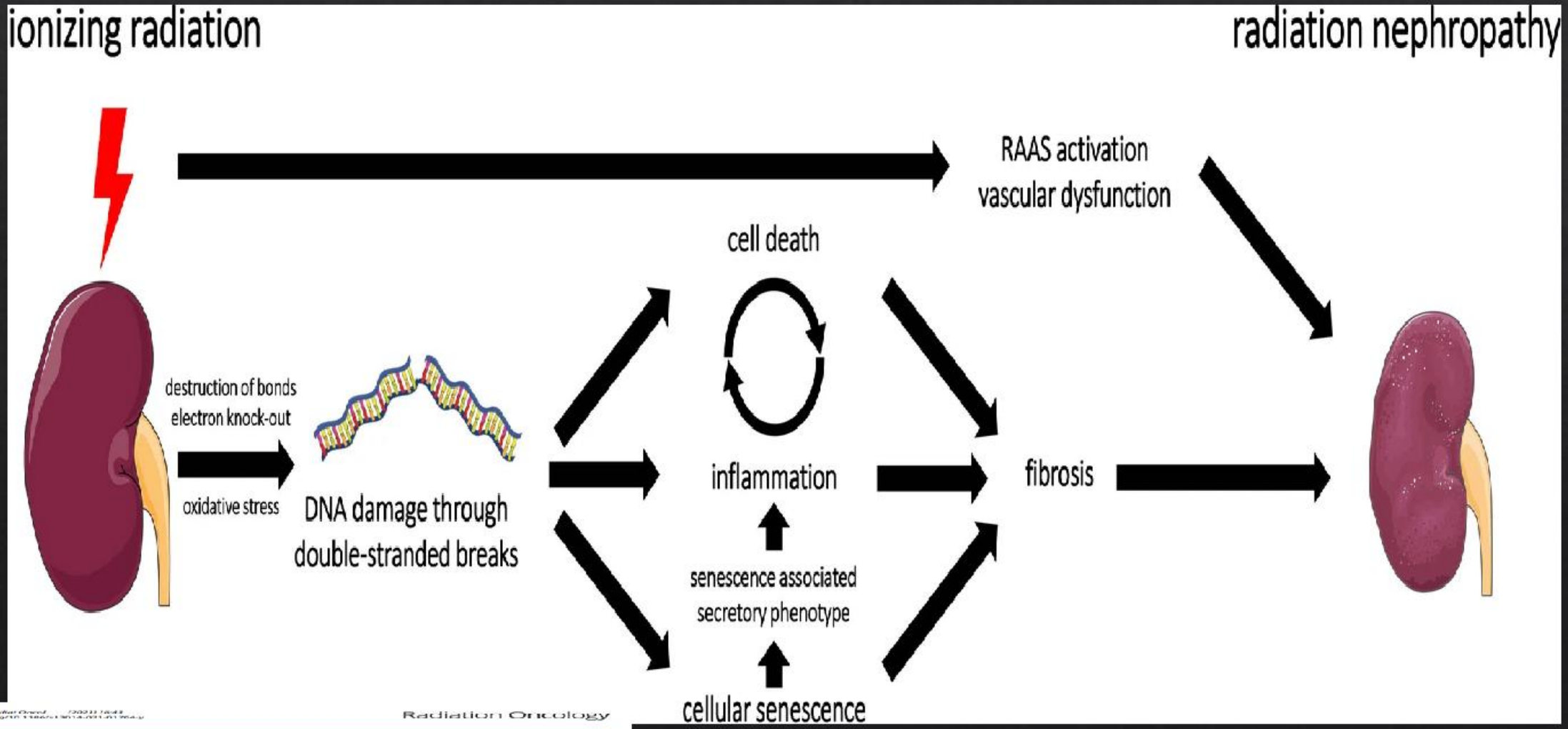


CLASSIC		NON CLASSIC
➢ FATIGUE,ABDOMINAL PAIN, INCREASED ABDOMINAL GIRTH, HEPATOMEGALY ➢ ANICTERIC ➢ ASCITES 1–3MONTHS AFTER LIVER RT.	CLINICAL FEATURE	➢ MORE DYSREGULATED HEPATIC FUNCTIONS WITH JAUNDICE
➢ ALKALINE PHOSPHATASE (ALP) TRANSAMINASE AND BILIRUBIN :- N	BIOCHEMICAL	➢ TRANSAMINASES:- FIVEFOLD INCREASE
➢ OBLITERATION OF THE CENTRAL VEIN ➢ DEATH OF CENTRILOBULAR HEPATOCYTES ➢ HSC ACTIVATION CONTRIBUTING TO HEPATIC FIBROSIS	PATHOLOGY	➢ HEPATOCELLULAR LOSS, HEPATIC DYSFUNCTION, HEPATIC SINUSOIDAL ENDOTHELIAL DEATH ➢ HSC ACTIVATION

AMONG THE PATIENTS RECEIVING HEPATIC RADIATION OF 30–35 GY, ~6–66% OF PATIENTS PRESENT SIGNIFICANT RILD.9, 4–8 WEEKS AFTER TERMINATION OF RT, IT HAS BEEN REPORTED TO APPEAR AS EARLY AS 2 WEEKS OR AS LATE AS 7 MONTHS AFTER RT.


Renal corpuscle
Myocytes
Bowman's space
Proximal tubule
Distal convoluted tubule
Macula densa
Granular cells
Mesangium-Extra-glomerular cell
Juxtaglomerular apparatus
Efferent arteriole
Parietal layer
Podocyte Pedicels
Visceral layer
Mesangium-Intraglomerular cell
Basement membrane
Bowman's capsule


Capillary loops
Urinary space
Mesangium
Red cell
Proximal tubule
Parietal epithelium
Mesangial cell
Mesangial matrix
Fenestrae in endothelium
Urinary space
Capillary lumen
Parietal epithelium
Basement membrane
Visceral epithelium
Foot processes
Basement membrane
Endothelium
Red blood cell



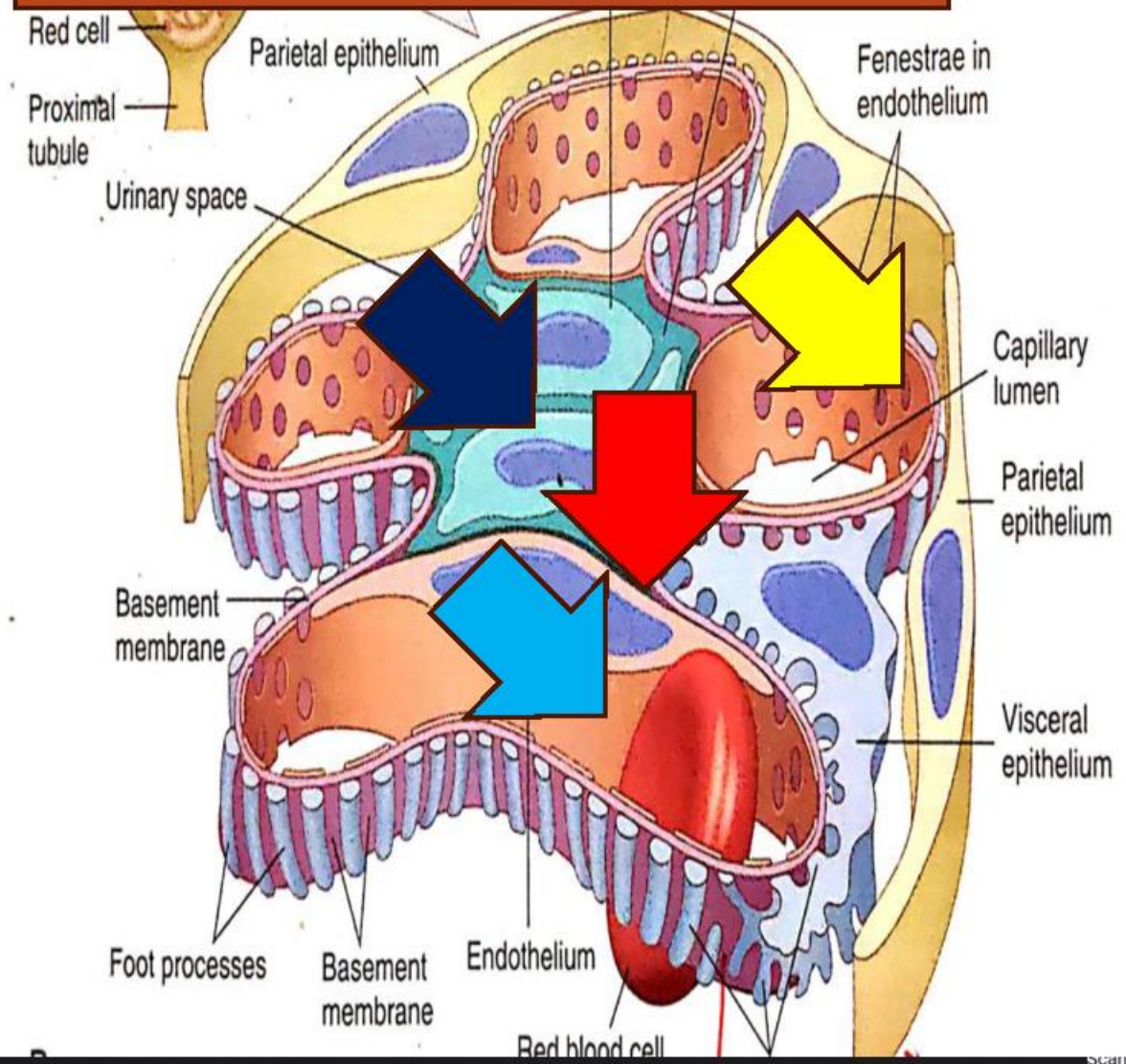
Radiation Oncology

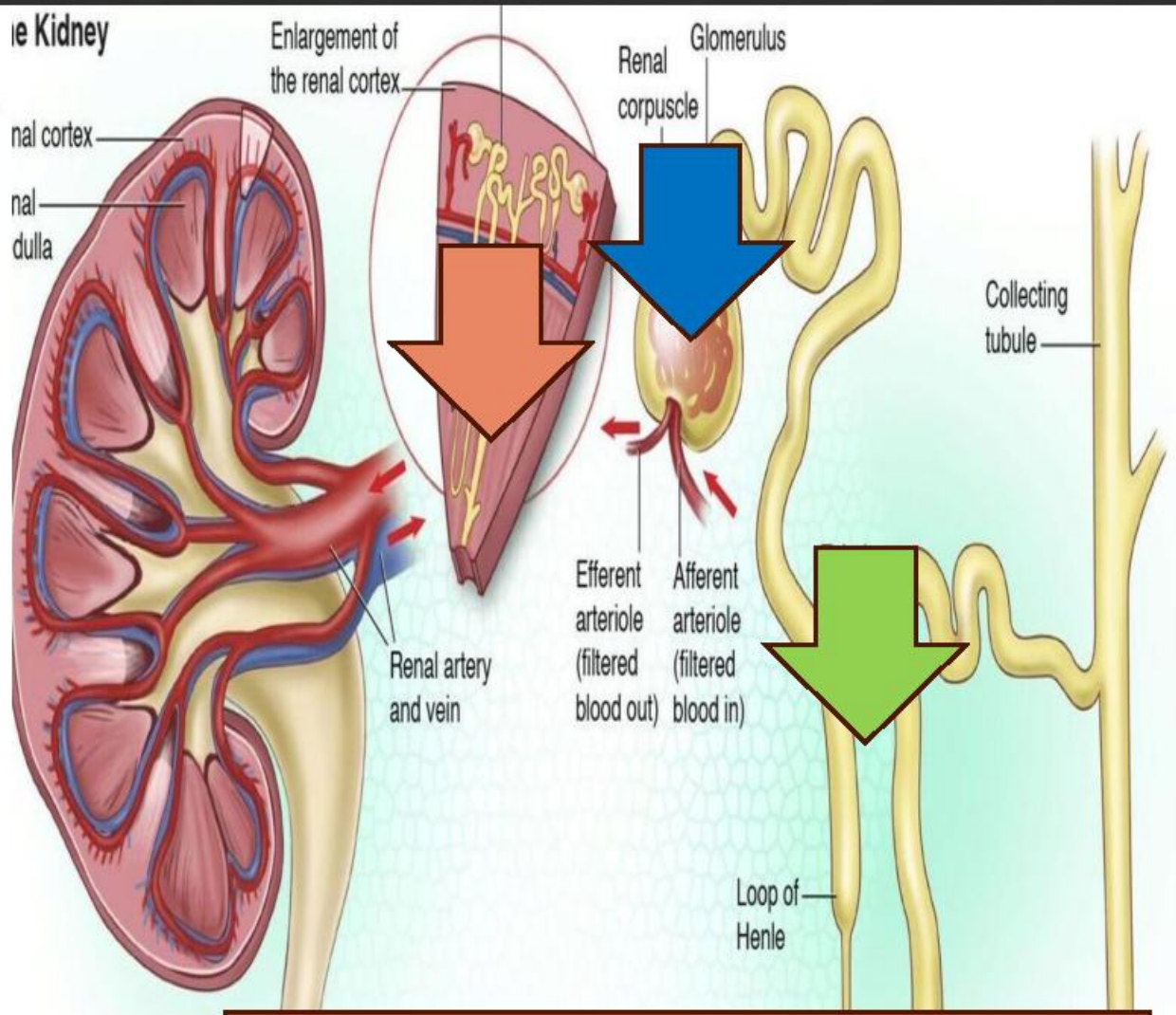
REVIEW Open Access

Radiation-induced kidney toxicity: molecular and cellular pathogenesis

Richard Klaus, Maximillian Niyazi and Birgit Lange-Sperandio

1. LOSS OF ENDOTHELIAL CELLS
2. SUB ENDOTHELIAL EXPANSION
3. OCCLUDED CAPILLARY LOOP
4. MESANGIOLYSIS



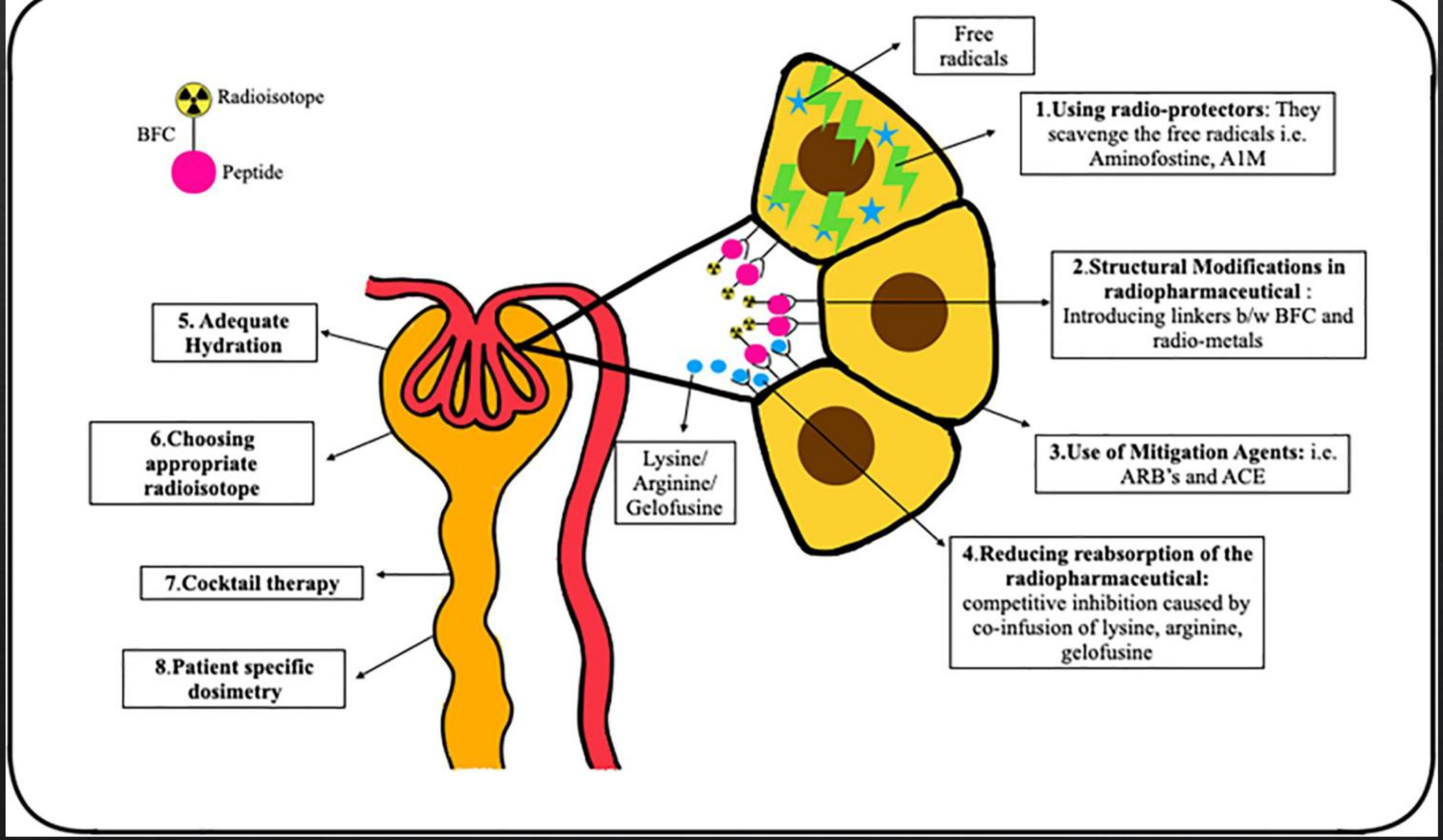


1. GLOMERULOSCLEROSIS
2. RENAL INTERSTITIAL FIBROSIS
3. TUBULAR ATROPHY

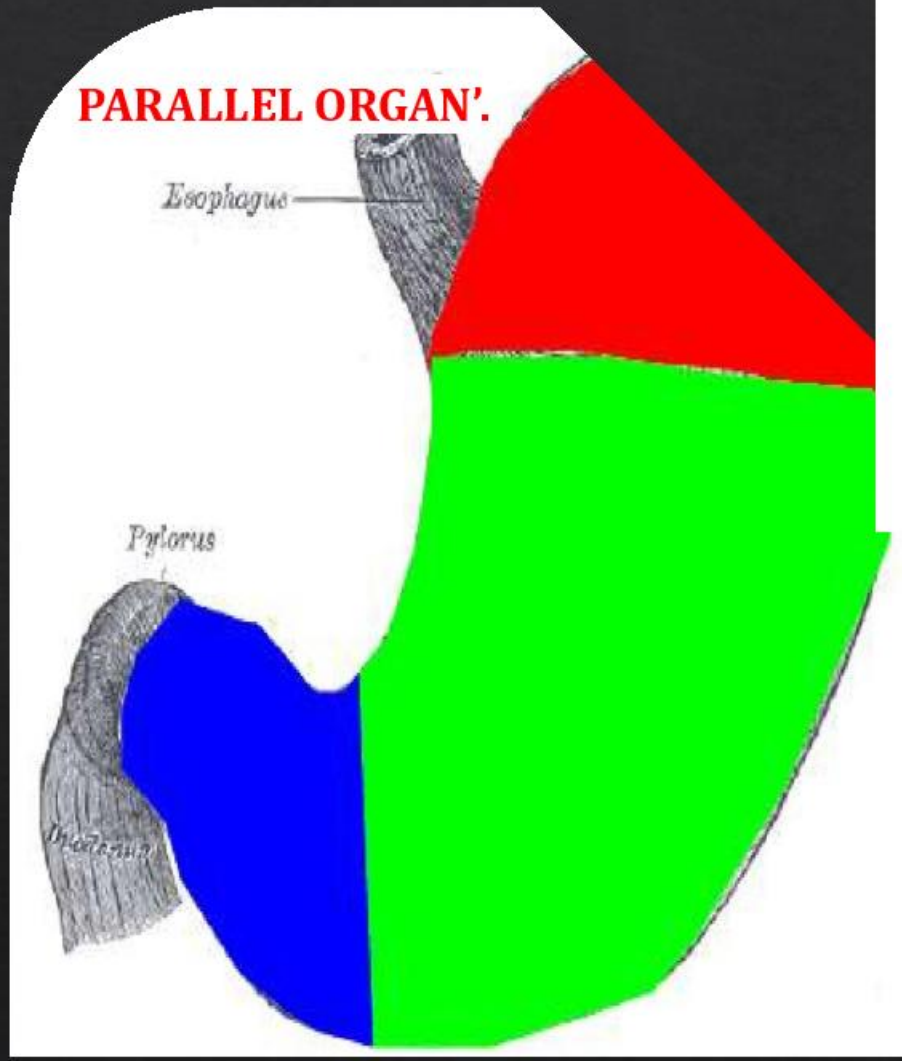
CLINICAL STAGES OF RADIATION NEPHROPATHY

TYPE	TIME AFTER RADIOTHERAPY	TYPE SYMPTOMS

PATHOLOGY	MECHANISM	DRUG	MECHANISM


Radioisotope
BFC
Peptide
Free radicals
1.Using radio-protectors: They scavenge the free radicals i.e. Aminofostine, A1M
2.Structural Modifications in radiopharmaceutical : Introducing linkers b/w BFC and radio-metals
3.Use of Mitigation Agents: i.e. ARB's and ACE
4.Reducing reabsorption of the radiopharmaceutical: competitive inhibition caused by co-infusion of lysine, arginine, gelofusine
Lysine/ Arginine/ Gelofusine
5. Adequate Hydration
6.Choosing appropriate radioisotope
7.Cocktail therapy
8.Patient specific dosimetry

RADIATION-INDUCED GASTRIC INJURY



Radiation risk factors

Total gastric dose, >45 Gy

% Total gastric volume receiving ≥50 Gy (V50), > 16%

% Total gastric volume receiving ≥25 Gy (V25), >6.3%

Irradiation of gastric antrum

Combined chemotherapy

Host risk factors

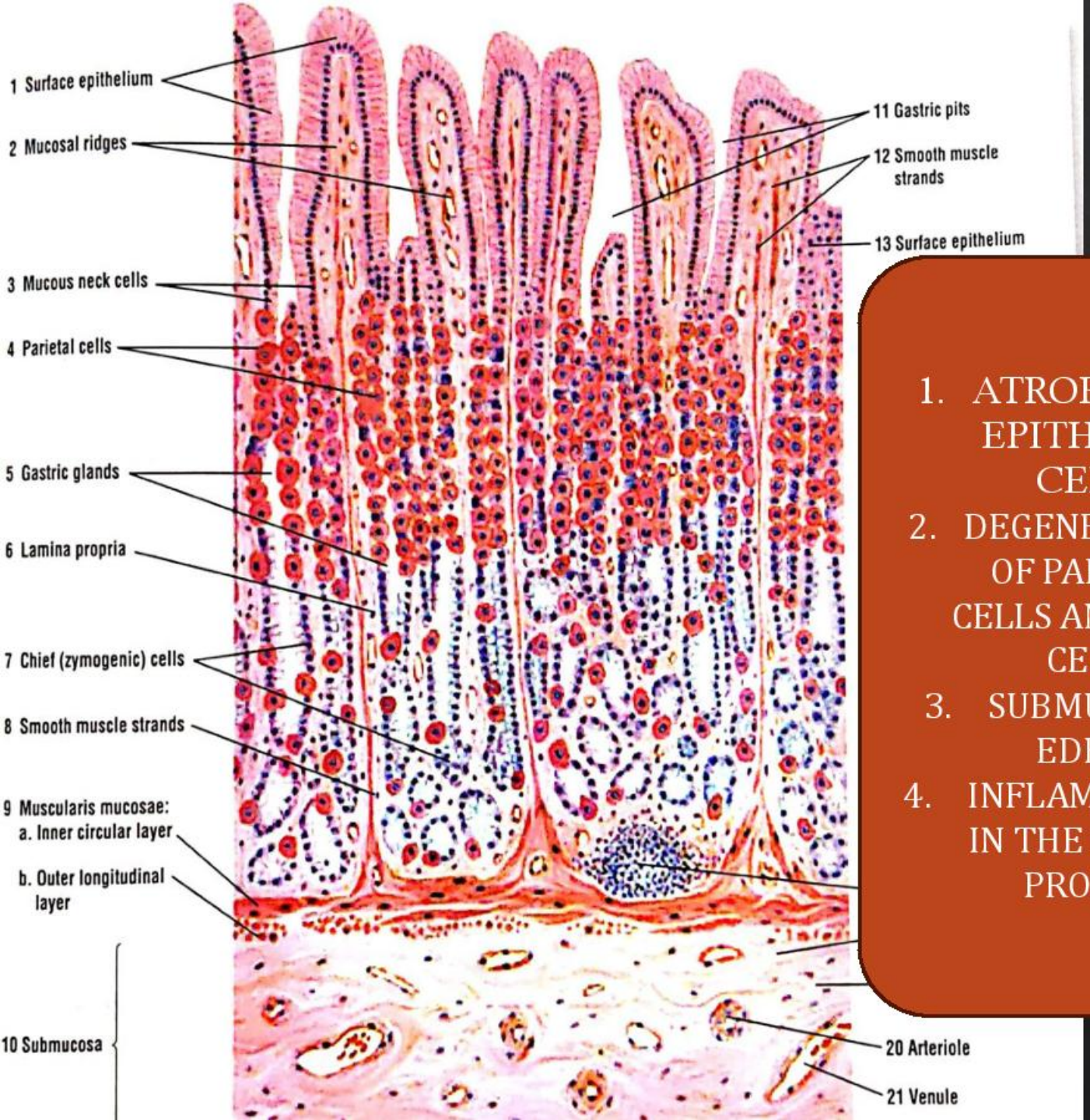
Main portal vein tumor thrombosis

Cirrhosis and portal hypertension

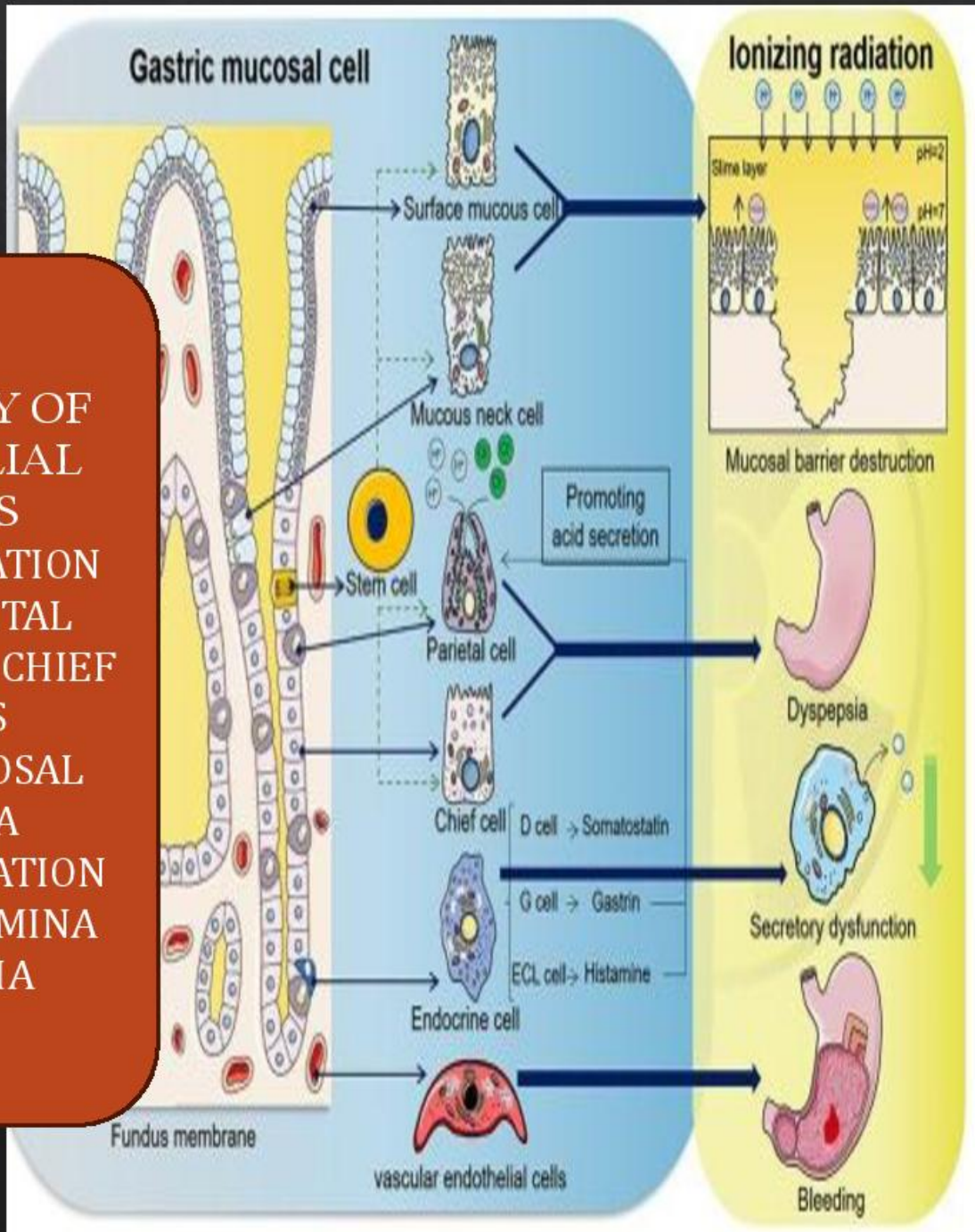
History of upper gastrointestinal bleeding

NO SYMPTOMS/ABDOMINAL PAIN,
ABDOMINAL DISTENSION
HEMATEMESIS

- GASTROSCOPY,:- IRRADIATED AREA SHOWS PUNCTATE ULCER. FUSION OF RED PLAQUES, FLATTENING OF FOLDS, ANNULAR ULCERS AND TELANGIECTASIA
- BARIUM MEAL
- CT SCAN:- THICKENING OF THE GASTRIC WALL AND NARROWING OF THE GASTRIC CAVITY
- SERUM GASTRITIS MARKERS (GASTRIN 17, PEPSINOGEN I AND II.



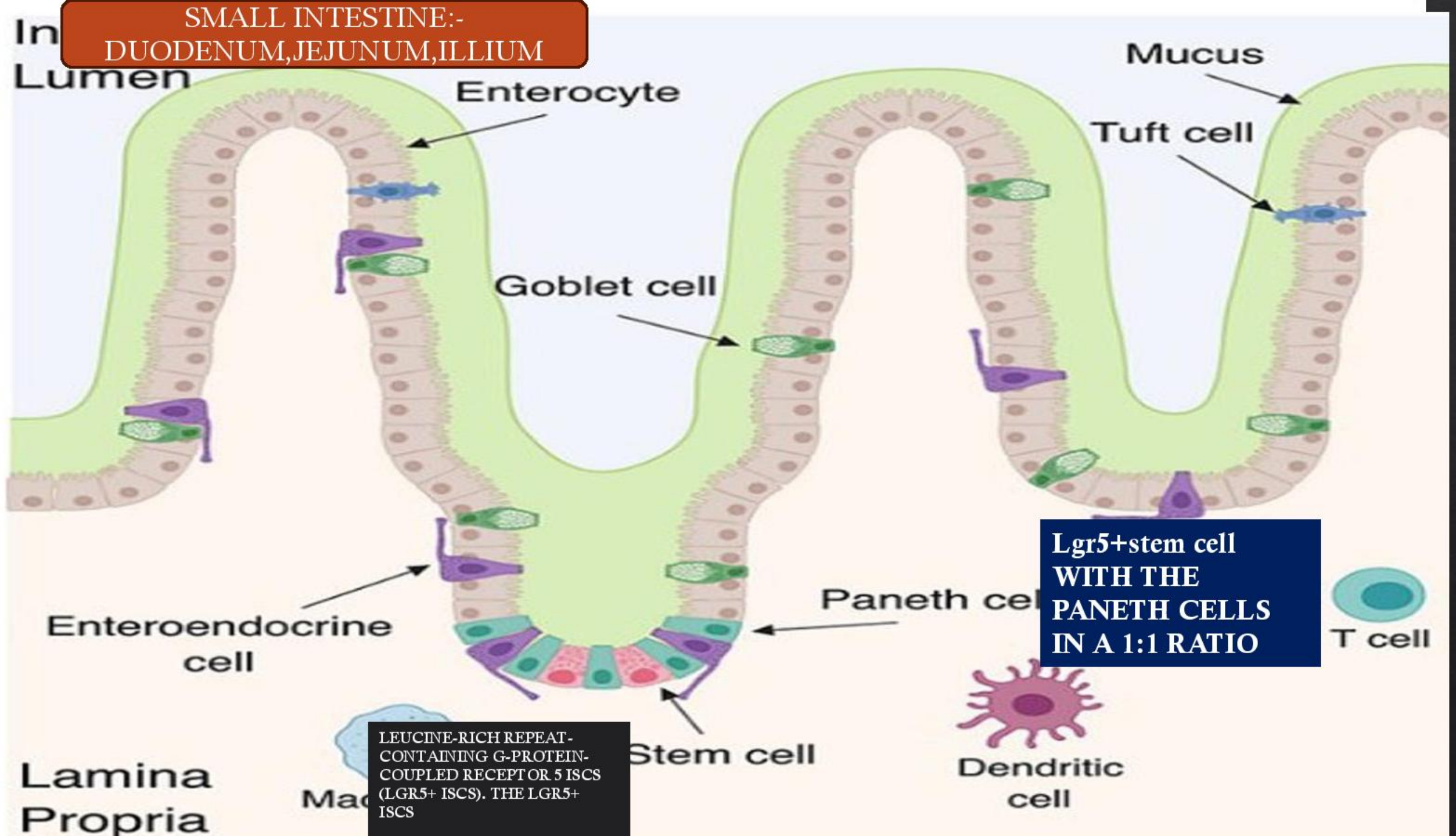
1. ATROPHY OF EPITHELIAL CELLS
2. DEGENERATION OF PARIETAL CELLS AND CHIEF CELLS
3. SUBMUCOSAL EDEMA
4. INFLAMMATION IN THE LAMINA PROPRIA



TREATMENT

- OMEPRAZOLE, PANTOPRAZOLE, ESOMEPRAZOLE, LANSOPRAZOLE AND RABEPRAZOLE :-
  - INHIBITION OF GASTRIC ACID.
  - REDUCING NEUTROPHIL AGGREGATION
  - PERMEABILITY OF MAST CELL
  - REDUCING INFLAMMATORY CYTOKINE RELEASE
  - REGULATING OXIDATIVE STRESS BY SCAVENGING ROS AND FREE RADICALS
- VITAMIN A, VITAMIN C AND VITAMIN E ARE NATURAL ANTIOXIDANTS
- ARGON PLASMA COAGULATION (APC) IS A ROUTINE METHOD FOR ENDOSCOPIC TREATMENT OF HEMORRHAGIC GASTRITIS
- MESENCHYMAL STEM CELLS (MSCS) THERAPY
  - POTENTIAL TO DIFFERENTIATE INTO A VARIETY OF CELLS, BUT ALSO HAVE THE ABILITY TO SECRETE CYTOKINES AND MIGRATE TO DAMAGED TISSUES

SMALL INTESTINE:- DUODENUM,JEJUNUM,ILLIUM



Lgr5+stem cell WITH THE PANETH CELLS IN A 1:1 RATIO

LEUCINE-RICH REPEAT-CONTAINING G-PROTEIN-COUPLED RECEPTOR 5 ISCS (LGR5+ ISCS). THE LGR5+ ISCS

Cell Type	Category	Estimated Percentage of Population of IECs	Functions	Life Span
Enterocytes [9,15,17,40,46,58,63]	Non-secretory	±80%	Sampling of nutrients. Digestion of nutrients. Absorption of nutrients. Maintenance of structural integrity. Surveillance and control gut microbiota. Replacement of damaged Lgr5$^+$ ISCs.	3–5 days
Goblet cells [8,15,17,22,40,41,68,69]	Secretory	±10%	Sampling of gut microbiota. Sampling of nutrients. Secretion of mucus. Pooling of antimicrobial peptides. Secretion of trefoil factor. Regeneration and repair of epithelium. Replacement of damaged Lgr5$^+$ ISCs.	3–5 days
Paneth cells [2,14,17,29,30,40,54,75,76,77,78,79,80]	Secretory	±5%	Control of gut microbiota. Sampling of nutrients. Protection of Lgr5$^+$ ISCs. Nourishment of Lgr5$^+$ ISCs. Regulation of proliferation and differentiation of Lgr5$^+$ ISCs. Replacement of damaged Lgr5$^+$ ISCs.	3–7 weeks
Enteroendocrine cell [40,48]	Secretory	±1%	Sampling of nutrients. Secretion of gut hormones.	3–5 days
Tuft cells [64]	Non-secretory	<1%	Sampling of nutrients. Sampling of gut microbiota. Regulation of gut microbiota. Production of cytokines.	3–5 days

Digestion and absorption

Enterocytes

Tuft cell

IMMUNOREGULATORY CELLS PRODUCES IL-25, ACh, TSLP, β-endorphins, PGE_2, PGD_2 and LTC_4 ,

SECRETS MUC2,MUC3 AND FORMS A CARPET ALLOW NUTRIENTS NOT BACTERIA

Goblet cell

crine cell

leucine-rich repeat-containing G-protein-coupled receptor 5 ISCs (Lgr5+ ISCs). The Lgr5+ ISCs in a normal small intestine are found intermingled with the Paneth cells in a 1:1 ratio

Lgr5⁺ ISCs

Symmetric division :-clonal expansion

asymmetrical division leads

enterocytes, goblet cells,

enteroendocrine cells,

Crypt

Endothelial cell

Lgr5 ISC

Dendritic cell

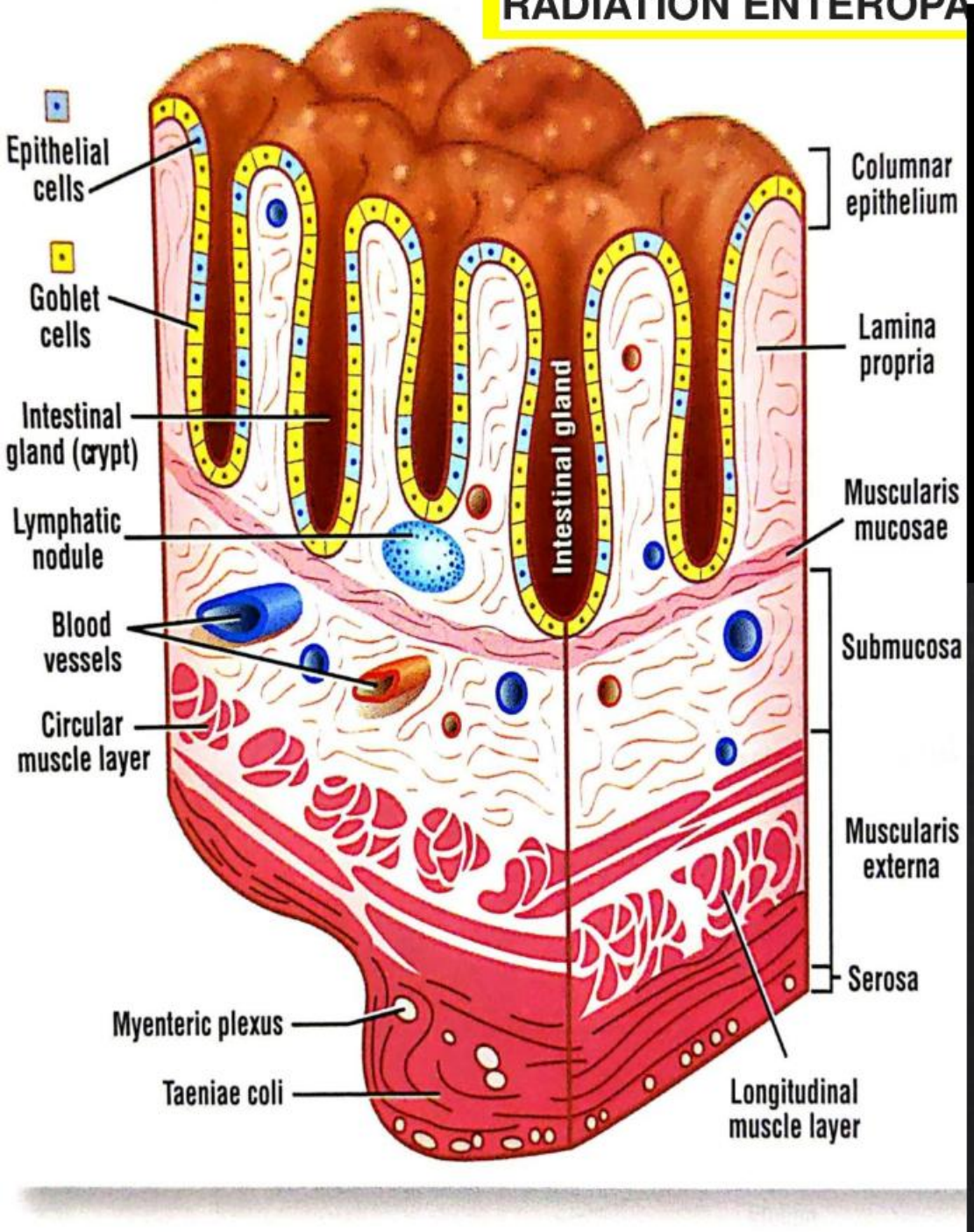
Highly sensitive to radiation

Can De Differentiate

Muscle cell

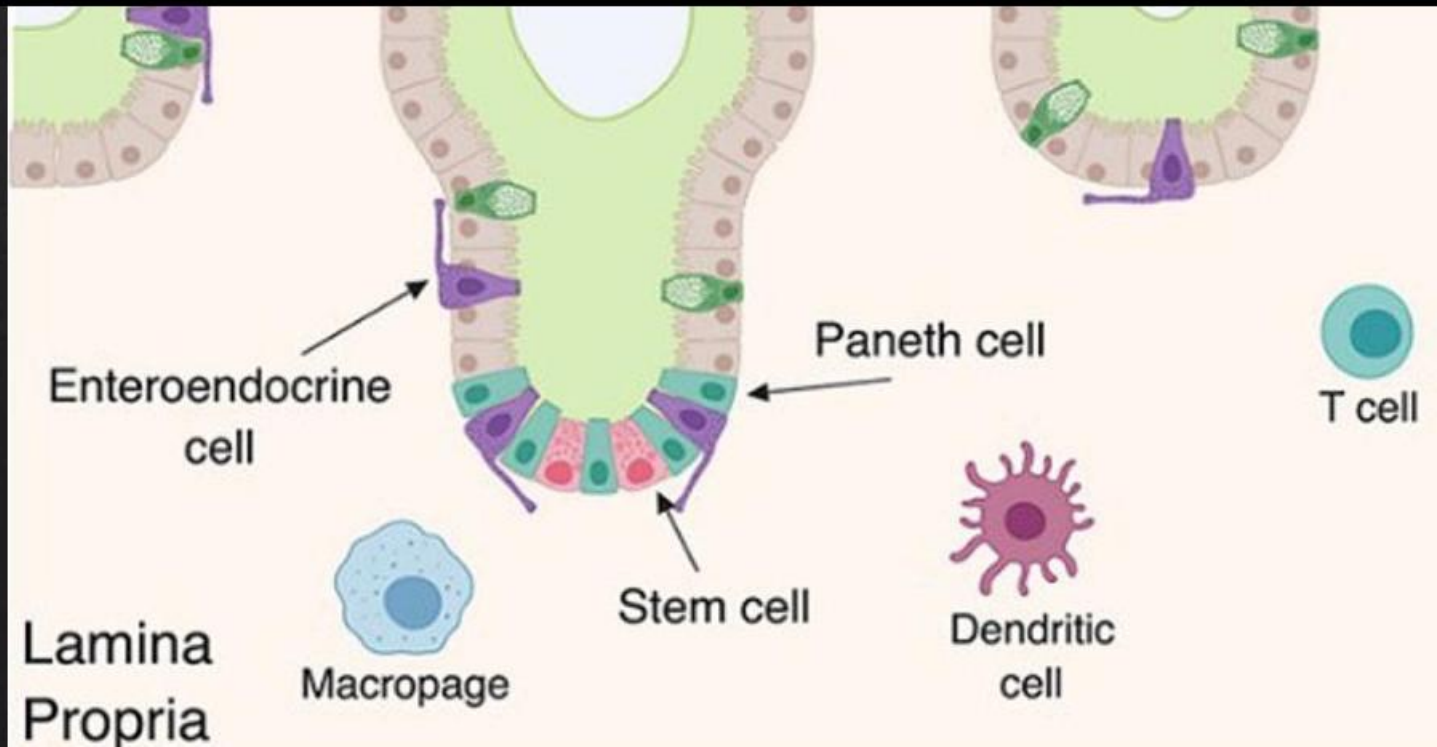
base of the intestinal crypts , in direct contact with the Lgr5+ ISCs . influence the proliferation and differentiation of the Lgr5+ ISC.Paneth cells contain an abundance of antimicrobial peptides and immunomodulating proteins that

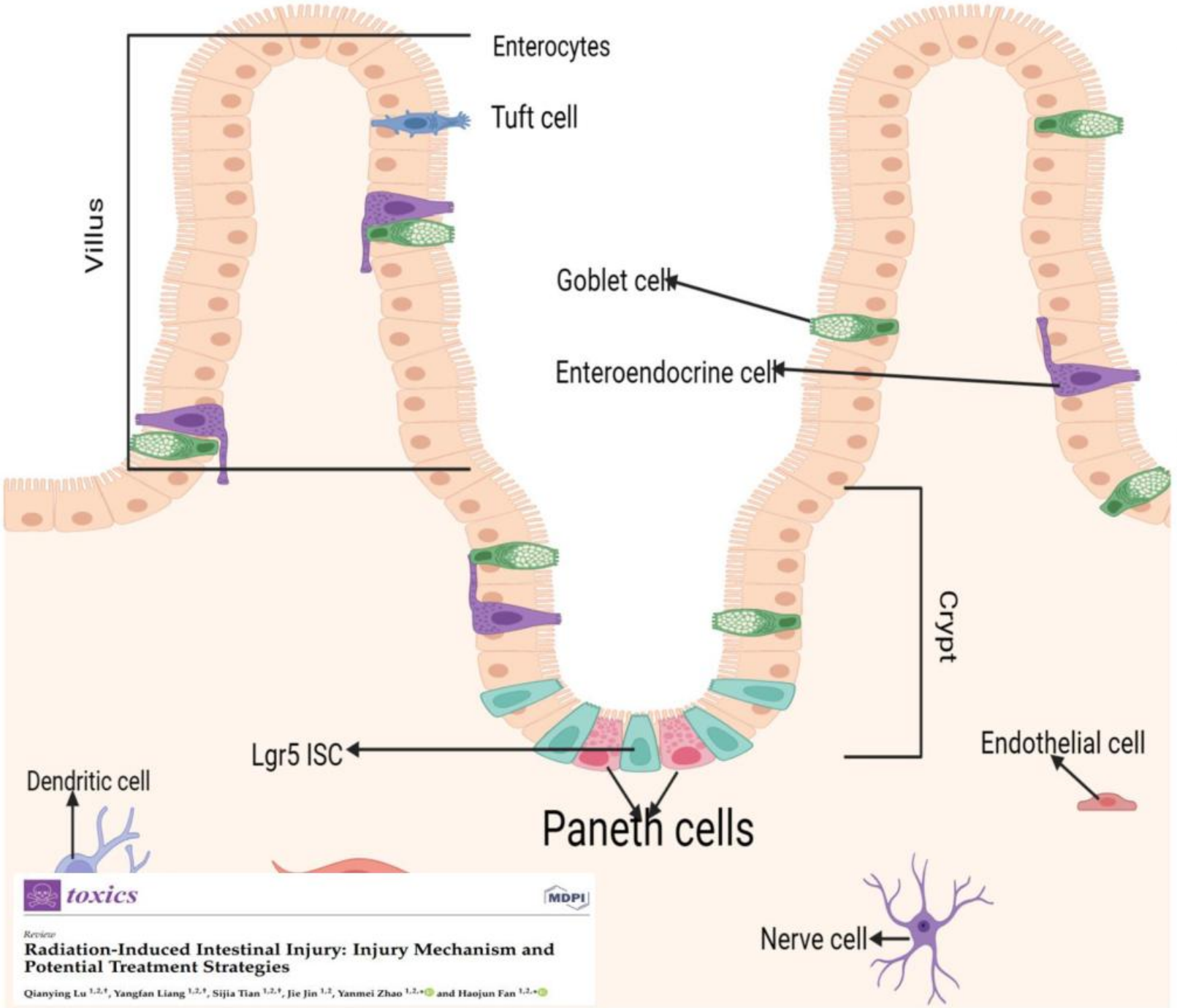
RADIATION ENTEROPATHY/RADIATION ENTERITIS



RISK FACTORS OF RE INCLUDE

1. AGE ABOVE 60 YEARS
2. SMOKING
3. DIABETES MELLITUS
4. HYPERTENSION
5. CONNECTIVE TISSUE DISORDERS
6. HIV STATUS,
7. PREVIOUS ABDOMINAL SURGERY, HYPO-ALBUMINEMIA
8. CONCURRENT ADMINISTRATION OF CHEMOTHERAPY WITH RADIOTHERAPY





toxics

MDPI

Review

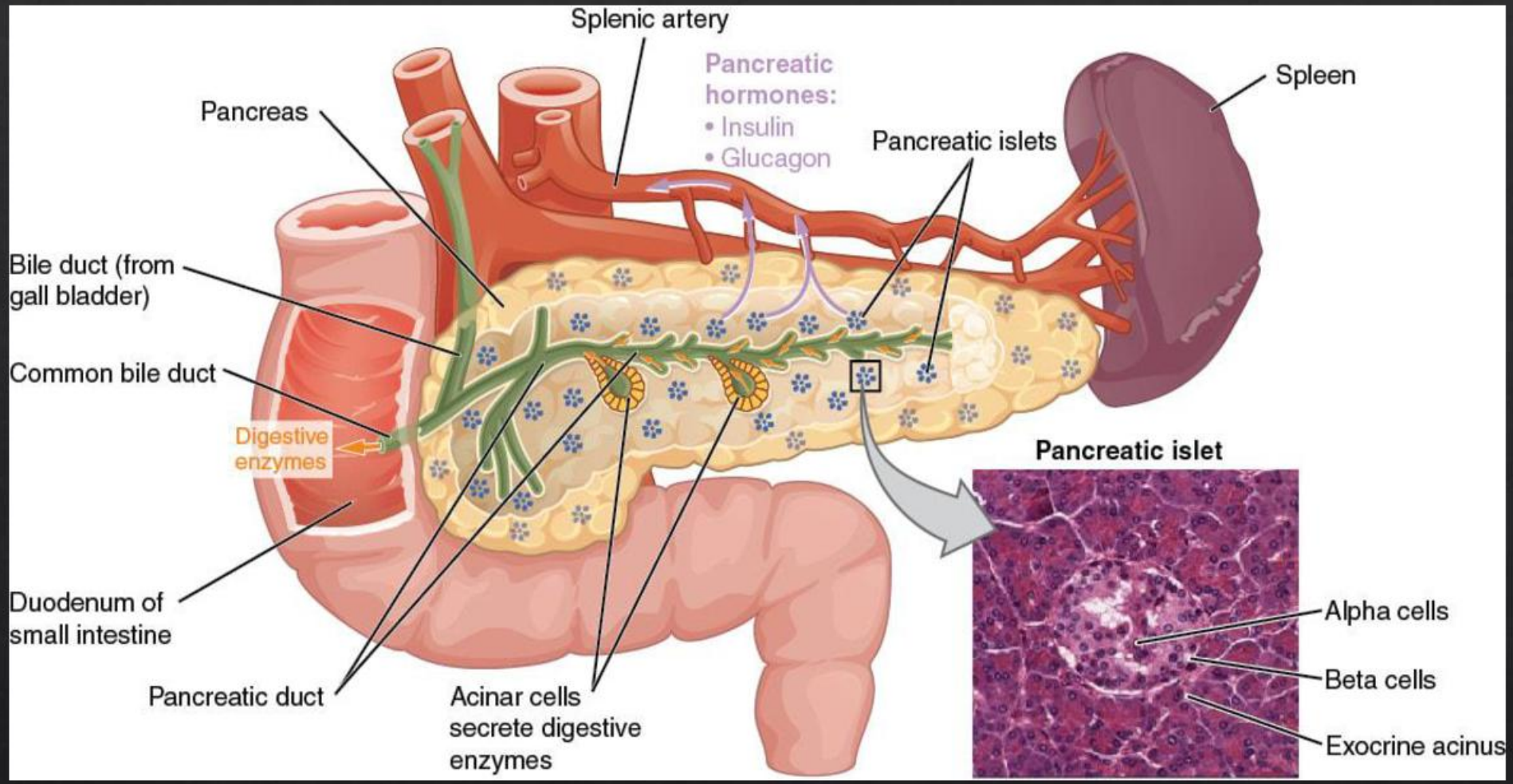
Radiation-Induced Intestinal Injury: Injury Mechanism and Potential Treatment Strategies

Qianying Lu [1,2,†], Yangfan Liang [1,2,†], Sijia Tian [1,2,†], Jie Jin [1,2], Yanmei Zhao [1,2,*] and Haojun Fan [1,2,*]

1. IONIZING RADIATION MOSTLY AFFECT THE LABILE CELLS SUCH AS THE LGR5+
2. HIGHER DOSE CAN AFFECT STABLE AND PERMANENT CELLS SUCH AS NERVE CELLS, VASCULAR ENDOTHELIAL CELLS AND MUSCLE CELLS
3. SLOUGHING-OFF OF THE EPITHELIAL CELLS AND/OR THEIR VILLI
4. BLEEDING AND PERFORATION
5. DAMAGE TO THE EPITHELIUM OF THE SMALL INTESTINE MAY ALSO LEAD TO DYSBIOSIS
6. LATE COMPLICATION:- STEATORRHEA,SHORT BOWEL SYNDROME,MALABSORPTION SYNDROME,BOWEL OBSTRUCTION,INTERNAL AND EXTERNAL FISTULAE,HEPATIC DYSFUNCTION, SECONDARY MALIGNANCIES

TREATMENT OF SMALL BOWEL COMPLICATIONS

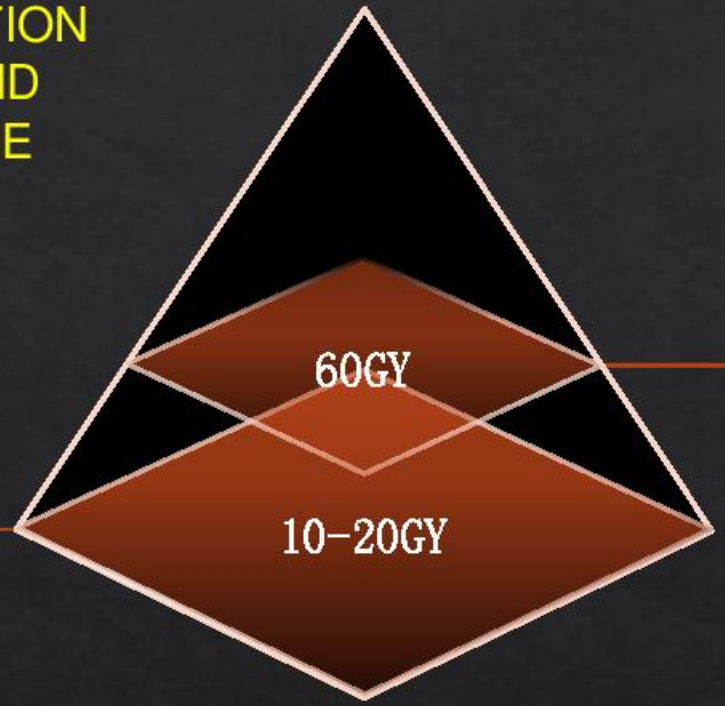
- ANALGESICS
- DIETARY MODIFICATION AND ANTI-DIARRHEAL DRUGS
- TOTAL PARENTERAL NUTRITION
- BLEEDING AND SMALL BOWEL OBSTRUCTION (STRICTURES, ADHESIONS, OR RECURRENT TUMOR):-RESECTION AND ANASTOMOSIS
- CREATION OF BYPASS OR BRINGING OUT OF STOMA
- BLEEDING :-TREATED CONSERVATIVELY, ENDOSCOPICALLY :- ARGON BEAM PLASMA COAGULATION AND RADIOFREQUENCY ABLATION, OR SURGICALLY
- STEROIDS, GLUTAMINE, ARGININE, STATINS, ANGIOTENSIN CONVERTING ENZYME INHIBITORS, ANTIOXIDANTS, HYPERBARIC OXYGEN, AND HERBAL MEDICATIONS REMAIN EXPERIMENTAL
- MESENCHYMAL STEM CELLS AND RECOMBINANT NICHE FACTORS FOR THE LGR5+ ISCS


Splenic artery
Pancreatic hormones:
• Insulin
• Glucagon
Pancreas
Spleen
Pancreatic islets
Bile duct (from gall bladder)
Common bile duct
Digestive enzymes
Pancreatic islet
Duodenum of small intestine
Alpha cells
Beta cells
Exocrine acinus
Pancreatic duct
Acinar cells secrete digestive enzymes

PANCREAS

- PANCREATIC ACINAR CELLS ARE KNOWN TO BE RADIORESISTANT.
- WITH LARGER DOSES OF RADIATION AND TECHNIQUES LIKE IMRT TEND TO SPARE A SIGNIFICANT VOLUME OF THIS CRITICAL ORGAN.

The latency periods:- early within one year for exocrine function, and very late for endocrine funtion



ACINAR INJURY

INFLAMMATORY CELLS ARE ABUNDANT AND THE NUMBER OF SECRETORY GRANULES IS REDUCED AND THE CYTOPLASM IS VACULOATED

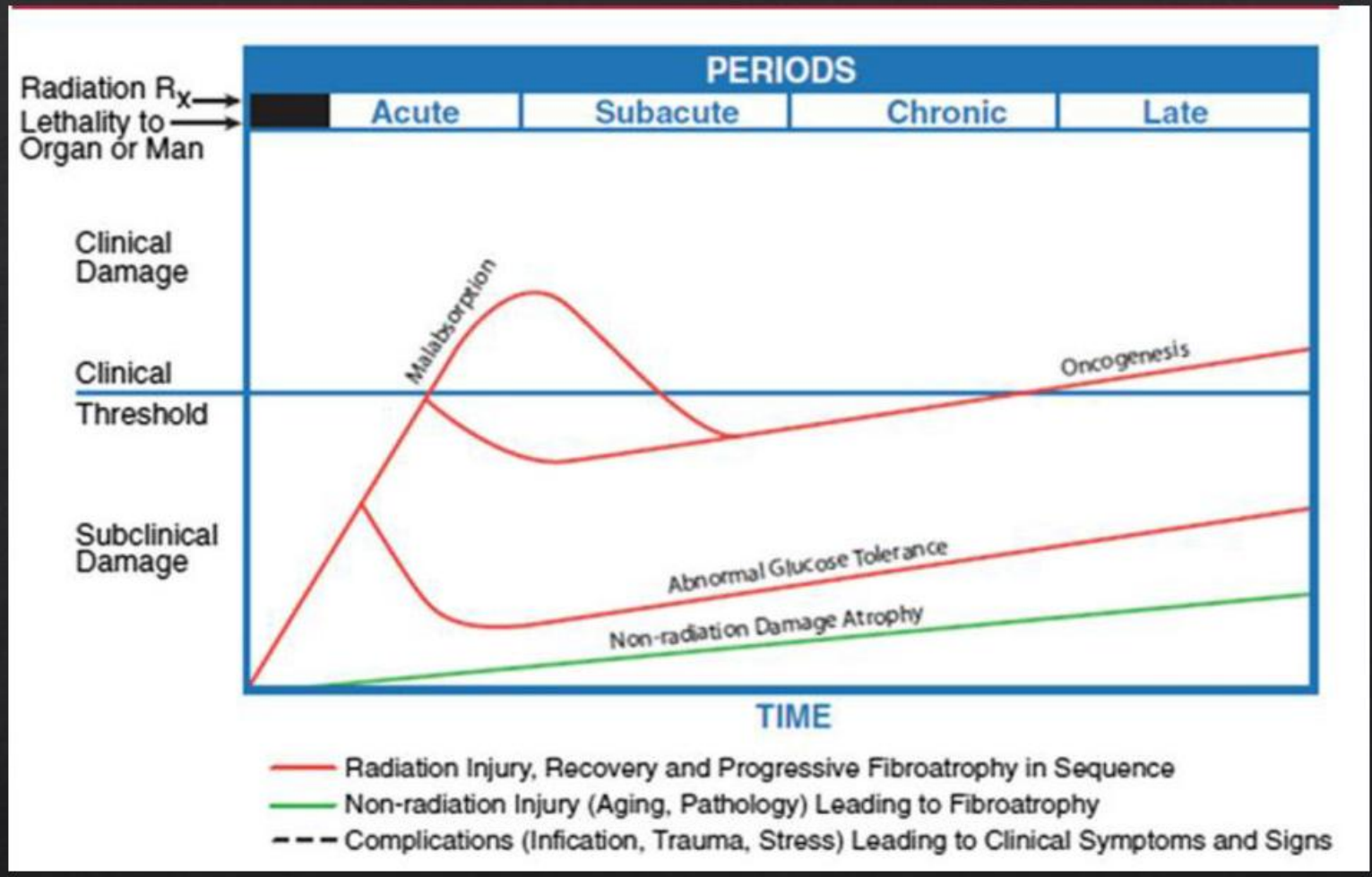
ZONAL NECROSIS AND DUCTULE DEGENERATION

LARGE DUCT MILD CELL CHANGES SMALL DUCTS DISTENDED LUMEN AND PLUGGING BY CELLULAR DEBRIS, ACUTE INJURY TO ARTERIOLES AND VENULES

	Focal	Global
Subclinical	Regional imaging abnormalities; e.g., calcifications on planar images, hyperenhancement on CT, or biliary duct abnormalities on retrograde cholangiopancreatography	Latent diabetes mellitus, glucose intolerance, malabsorption of proteins and fats, reduced levels of pancreatic enzymes in small intestine, or abnormalities in urinary bentiromide
Clinical	Cancer induction	Diabetes mellitus, steatorrhea

PANCREAS:

- RISK OF DIABETEES DUE TO LOSS OF INSULIN, C-PEPTIDE I.E ENDOCRINE AND EXOCRINE LIPASE AND ALPHA AMYLASE DEFICIENCY.
- A STUDY BY JERZY WYDMANSKI EVALUATED RADIATION INDUCED INJURY OF THE EXOCRINE PANCREAS AMONG 127 GASTRIC CANCER PATIENTS WITH TOTAL DOSE OF 45GY IN 25 FRACTIONS SHOWED LIPASE AND ALPHA AMYLASE DEFICIENCIES IN 48.2% AND 19.7% PATIENTS RESPECTIVELY.



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Radiotherapy and Oncology

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Gastric cancer

Risk of endocrine pancreatic insufficiency in patients receiving adjuvant chemoradiation for resected gastric cancer ☆

Cengiz Gemici [a,*], Mehmet Sa[illegible] [b], Resat Dabak [b], Mihriban Koca

[a] Department of Oncology; [b] Department of Endoc[illegible]
Meliepe University Medical Faculty, Turkey

Conclusion

Abdominal radiotherapy leads to a decrease in beta cell function which may lead to possible diabetogenic effect years later. Radiation-induced pancreatic injury and late effects of radiation on normal pancreatic tissue are unknown and not investigated extensively. Late radiation related pancreatic toxicity is a new concept and should be considered in radiation treatment and radiation toxicity reports.

THE STUDY
DECLINE IN
ADJUVANT

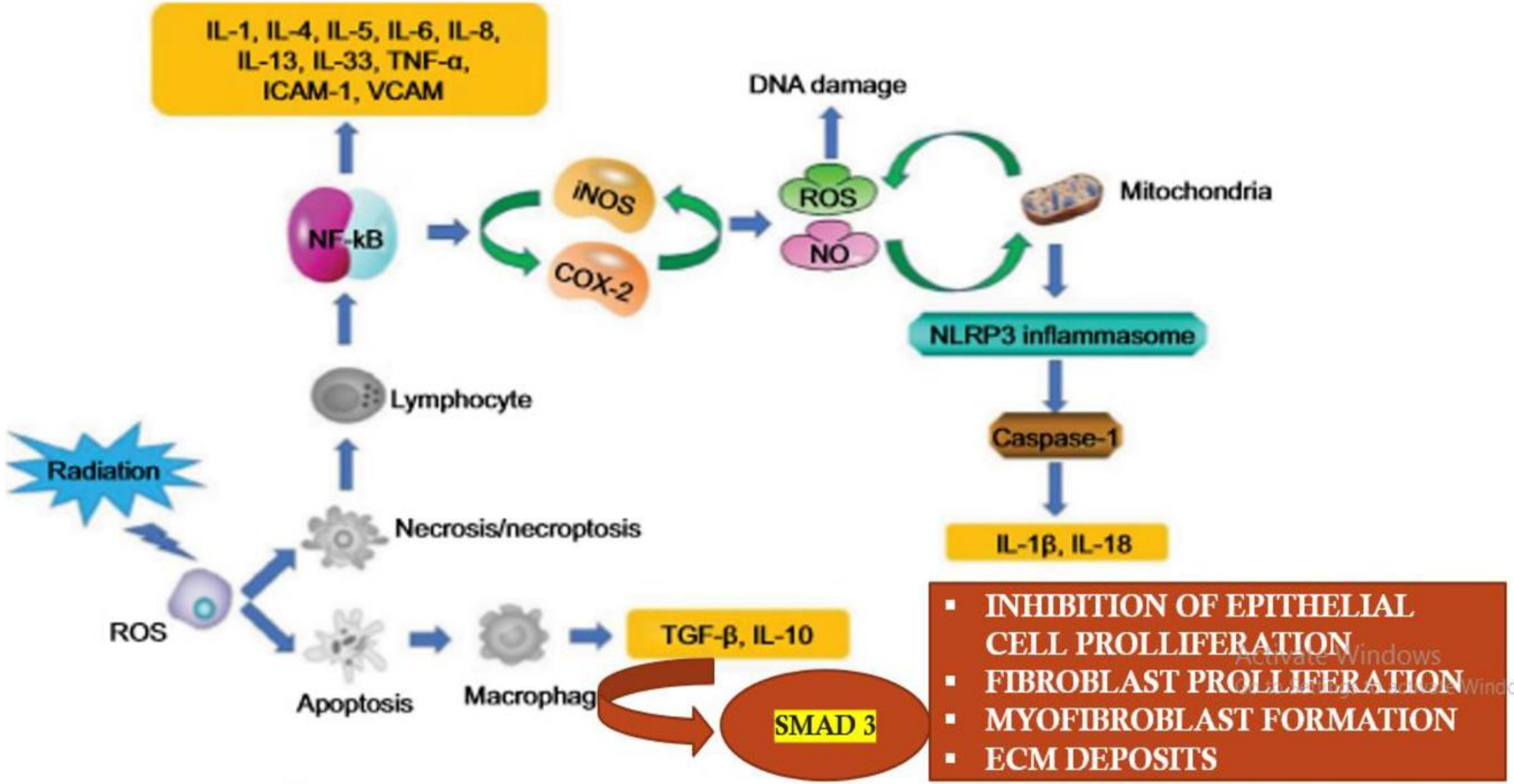
Comparison of the study group (radiotherapy +) and control group (radiotherapy −) according to endocrine functions of the pancreas at initial, 6 and 12 months of the study.

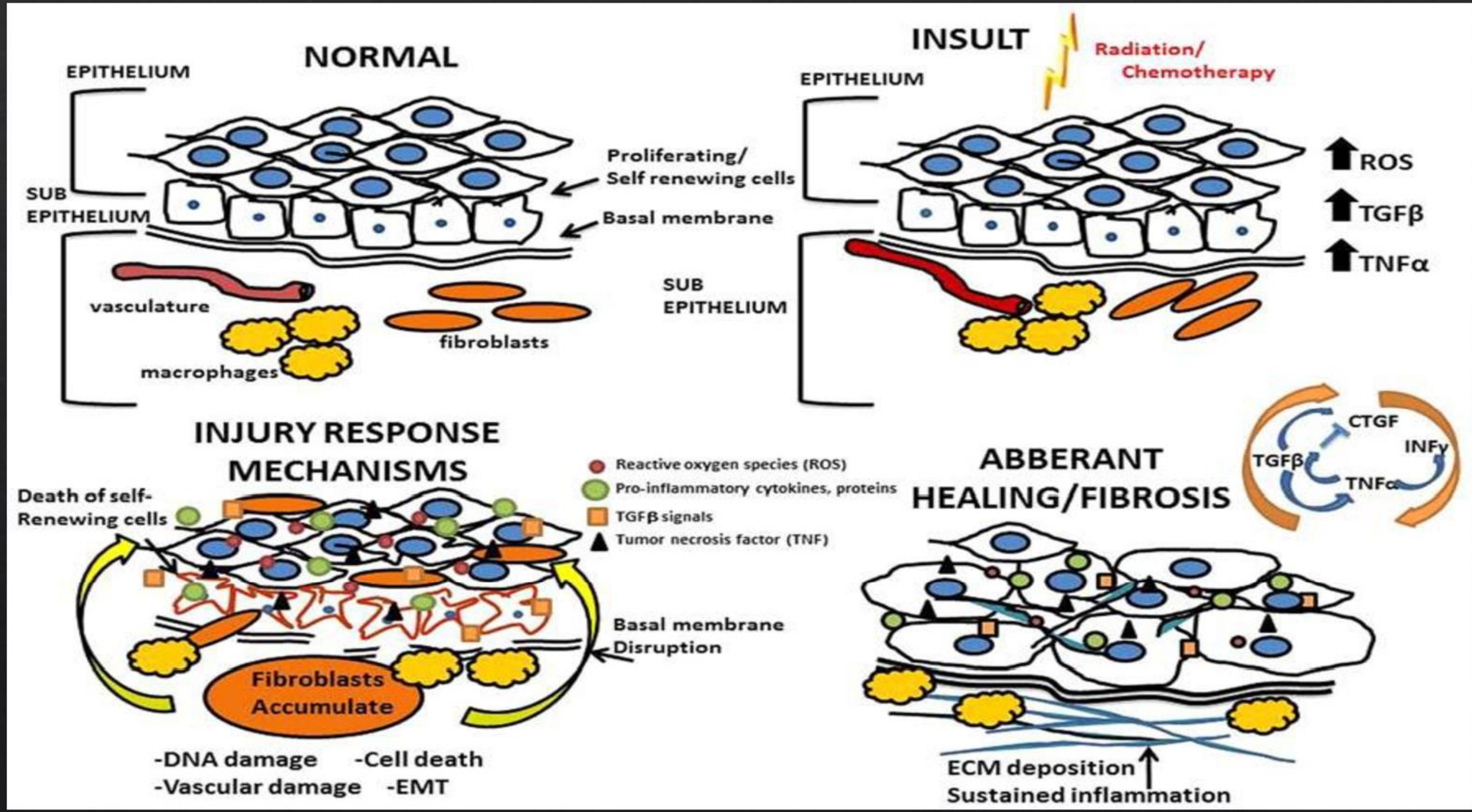
	Study group Radiotherapy (+)	Control group Radiotherapy (−)	p
FBG (mg/dl)			
Initial	92.54 ± 12.2	95.12 ± 22.3	NS
6 months	90.62 ± 12.4	95.19 ± 11.3	NS
12 months	88.46 ± 10.5	90.56 ± 18.0	NS
p	NS	NS	
		.89 ± 0.7	NS
		.89 ± 0.7	NS
		.15 ± 0.5	NS
		.25 ± 5.8	NS
		.51 ± 6.0	0.05
		.47 ± 12.0	0.001
		.65 ± 1.2	NS
		.40 ± 1.5	0.05
		.62 ± 1.9	0.007
HOMA-B			
Initial	85.73 ± 38.4	84.90 ± 32.1	NS
6 months	73.26 ± 28.5	82.49 ± 41.5	0.005
12 months	71.37 ± 24.3	81.49 ± 61.3	0.002
p	0.02	NS	

PRESERVATION OF ENDOCRINE FUNCTION :- MEAN RADIATION DOSE SHOULD BE BE KEPT BELOW 25 GY.

EARLY ENZYME SUBSTITUTION FOR EXOCRINE PANCREATIC INSUFFICIENCY, AND DIET AND LIFE STYLE CHANGES FOR PREVENTION OF FUTURE DIABETES RISK.

MECHANISM OF SKIN FIBROSIS




NORMAL
EPITHELIUM
SUB EPITHELIUM
Proliferating/ Self renewing cells
Basal membrane
vasculature
fibroblasts
macrophages
INSULT
Radiation/ Chemotherapy
EPITHELIUM
SUB EPITHELIUM
ROS
TGFβ
TNFα
INJURY RESPONSE MECHANISMS
Death of self-Renewing cells
Reactive oxygen species (ROS)
Pro-inflammatory cytokines, proteins
TGFβ signals
Tumor necrosis factor (TNF)
Basal membrane Disruption
Fibroblasts Accumulate
-DNA damage -Cell death
-Vascular damage -EMT
ABBERANT HEALING/FIBROSIS
CTGF
INFγ
TGFβ
TNFα
ECM deposition
Sustained inflammation

THERAPEUTIC STRATEGY TO INHIBIT RADIATION TOXICITY

CAUSATIVE FACTORS	MECHANISM	DRUGS
INFLAMMATORY MEDIATORS	INFLAMMATION VASCULAR MEDIATED INFLAMMATION INTESTINAL CRYPT CELL	CELOCOXIB PENTOXYPHYLLIN VITAMIN E
TGF-BETA TGF –BETA RECEPTOR	FIBROSIS	HALOFUGINONE LY-364947
TNF-ALFA	MACROPHASE	ETANERCEPT
ROS CLEARANCE		ALFA TOCOFEROL,ASCORBIC ACID
ENDOTHELIAL INJURY		STATIN
ANGIOTENSIN II	PRO INFLAMMATORY PRO FIBROGENIC	CAPTOPRIL
STEM CELL MOBILIZER	PROGENITOR CELL DAMAGE	G-CSF PLERIXAFOR

TAKE HOME MESSAGE
PREVENTION IS BETTER THAN CURE

- **Proper selection of cases**
- **Understanding the radiobiology of organ concerned**
- **Proper dose fractionation schedule**
- OAR Constraints
- **Stringent Plan evaluation**
- **Strict IGRT Matching to be ensured**
- **Proper dosimetry**
- **Understanding the toxicity and its proper management**

PRINCIPLES

- EFFICACY α DOSE TO THE TUMOR
- ----------
- DOSE TO NORMAL STRUCTURES

- DOSE= DAMAGE TO SERIAL ORGAN > PARALLEL ORGAN
- PROLLIFERATING CELL MORE AFFECTED THAN PARENCHYMAL CELL
- TOXICITY INVERSELY RELATED TO FUNCTIONAL UNIT


Thank you