Normal Tissue Tolerance

A. A Little Historical Perspective...

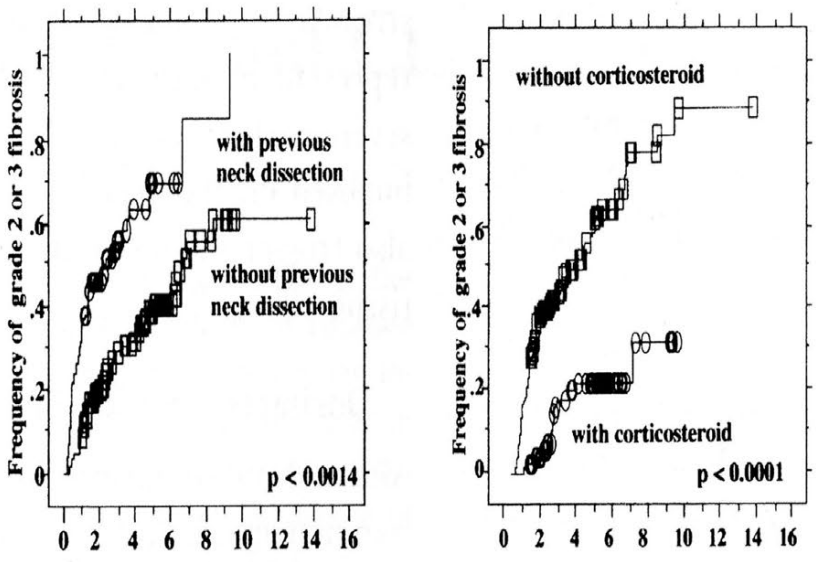
1] **most of our knowledge about the histopathology of early and late effects in normal tissues, and tissue "tolerances" comes from observations on humans**

2] **"tissue tolerance" in radiation therapy** - not exactly a black and white concept

a. *owing to the variability of individual reactions and to statistical fluctuations, you can only speak about "tolerance" in terms of probabilities* , i.e., the dose giving rise to an average tissue complication frequency of 5, 50 or 95% in a cohort of patients

1) the situation is made even more complicated because:

- *what is or isn't "tolerable" is a subjective decision* (the physician's and/or the patient's)
- *different types of complications are more serious than others* (for example, contrast a radiation-induced myelitis with telangiectasia of the skin)
- *age of the patient may also play an important role in what is or isn't tolerable*
- *patient confounding factors* (e.g., preexisting illness, prior surgery, etc.) *can also influence the risk and severity of radiotherapy complications*



O'Sullivan and Levin, Semin Radiat Oncol 13(3): 274-289, 2003

Years after (fairly standard) XRT for advanced H&N carcinoma

Patient "confounding factors" can influence the likelihood, timing and severity of late complications after radiation therapy.

- *the tolerance dose for a particular normal tissue complication varies with the fractionation pattern (determined by the tissue's α/β ratio)*

Individual patient genetics can also be an important confounding factor

Based on data from nearly 4,000 patients (mainly of European ancestry), this recent study from the international radiogenomics consortium assessed risk factors for the development of late complications after radiotherapy for prostate cancer. Not only were assorted clinical and dosimetric factors associated with late complications, so were select genes containing single nucleotide polymorphisms (SNPs).

Multivariable models including SNPs and clinical risk factors.

Model	HR (95% CI)	P
Rectal bleeding		
rs17055178 ◄	1.84 (1.49 to 2.24)	<.001
Rectum volume (cm^3) receiving 65 Gy	1.33 (1.08 to 1.63)	.007
Rectum volume (percent) receiving 70 Gy	1.44 (1.18 to 1.77)	<.001
Arthritis	2.06 (1.12 to 3.48)	.02
Inflammatory bowel diverticular disease	1.80 (1.07 to 2.83)	.03
Rectal dose standard deviation§	1.10 (1.03 to 1.18)	.008
Intestinal volume (percent) receiving 15 Gy	1.26 (1.03 to 1.52)	.03
Gleason score ≥7	1.25 (1.00 to 1.57)	.05
Cardiovascular disease	1.44 (1.01 to 2.02)	.05
Increased urinary frequency		
rs17599026 ◄	1.37 (1.08 to 1.71)	.01
Age at treatment >75	1.50 (1.16 to 1.92)	.002
Diabetes	1.53 (1.15 to 2.00)	.005
Cardiovascular disease	1.57 (1.04 to 2.31)	.04
Prior pelvic surgery	1.57 (1.06 to 2.24)	.02
Presence of hemorrhoids	1.56 (1.02 to 2.27)	.04
Decreased urinary stream		
rs10969913 ◄	2.23 (1.36 to 3.44)	.002
rs7720298 ◄	1.25 (1.05 to 1.48)	.01
Presence of hemorrhoids	2.06 (1.29 to 3.13)	.004
Prior TURP	1.67 (1.13 to 2.39)	.01
Bladder volume (cm^3) receiving 70 Gy	1.35 (1.09 to 1.87)	.002
Hematuria		
rs11122573 ◄	1.77 (1.39 to 2.23)	<.001
rs75991123 ◄	1.61 (1.22 to 2.09)	<.001
Prior TURP	2.33 (1.70 to 3.12)	<.001
Bladder volume (%) receiving 74 Gy	1.29 (1.09 to 1.51)	.003
Receipt of EBRT	1.92 (1.17 to 3.20)	.01
Age at treatment	2.80 (1.21 to 5.91)	.02

JNCI J Natl Cancer Inst (2020) 112(2): djz075

Note: It's not clear what these genes do normally, let alone what happens when they contain SNPs that are associated with clinical radiosensitivity

3] **Bergonié and Tribondeau** (1906) were the original gurus of tissue tolerance with their simple rules of thumb to predict tissue radioresponsiveness

Bergonié

☞ "Radiosensitivity" is greatest for cells that:

are **relatively undifferentiated** (stem cell-like)
have a **high mitotic rate** (rapidly proliferating)
have a **long mitotic future** (immortalized)

Tribondeau

b. **Rubin and Casarett** (late 1960's)

1) developed the "VIM, DIM, RPM, FPM" cellular sensitivity system based on Bergonié and Tribondeau's ideas

2) Rubin and Casarett's main claim to fame however was their exhaustive categorization of normal tissue complication types and frequencies, along with radiation tolerance doses

a} to this day (even though the data was collected during the 1960's), it is perfectly OK to refer their tables of data *provided you keep in mind that the tolerance doses quoted are based on fairly standard fractionation, e.g. 2 Gy per fraction delivered once per day over about 6 weeks*

b) using the Rubin and Casarett system, tissue were classified as "Class I - Class III"

A Compilation of Tissue and Organ Sensitivities

Class-I Organs: Fatal/Severe Morbidity[a]

Organ	Injury	$TD_{5/5}$	$TD_{50/5}$	Whole or Partial Organ (Field size or length)
Bone marrow	Aplasia, pancytopenia	250	450	Whole
		3000	4000	Segmental
Liver	Acute and chronic hepatitis	2500	4000	Whole
		1500	2000	Whole strip
Stomach	Performation, ulcer, hemorrhage	4500	5500	100 cm
Intestine	Ulcer, perforation,	4500	5500	400 cm
	hemorrhage	5000	6500	100 cm
Brain	Infarction, necrosis	5000	6000	Whole
Spinal cord	Infarction, necrosis	4500	5500	10 cm
Heart	Pericarditis and pancarditis	4500	5500	60%
		7000	8000	25%
Lung	Acute and chronic pneumonitis	3000	3500	100 cm
		1500	2500	Whole
Kidney	Acute and chronic	1500	2000	Whole (strip)
	nephrosclerosis	2000	2500	Whole
Fetus	Death	200	400	Whole

Class-II Organs: Moderate/Mild Morbidity[a]

Organ	Injury	$TD_{5/5}$	$TD_{50/5}$	Whole or Partial Organ (Field Size or Length)
Oral cavity and pharynx	Ulceration, mucositis	6000	7500	50 cm
Skin	Acute and Chronic dermatitis	5500	7000	100 cm
Esophagus	Esophagitis, ulceration	6000	7500	75 cm
Rectum	Ulcer, stricture	6000	8000	100 cm
Salivary glands	Xerostomia	5000	7000	50 cm
Bladder	Contracture	6000	8000	Whole
Ureters	Stricture	7500	10,000	5-10 cm
Testes	Sterilization	100	200	Whole
Ovary	Sterilization	200-300	625-1200	Whole
Growing cartilage, bone (child)	Growth arrest, dwarfting	1000	3000	Whole
		1000	3000	10 cm
Mature cartilage, bone (adult)	Necrosis, fracture, sclerosis	6000	10,000	Whole
		6000	10,000	10 cm
Eye				
retina		5500	7000	Whole
cornea		5000	>6000	Whole
lens		500	1200	Whole or part
Endocrine Glands				
thyroid	Hypothyroidism	4500	15,000	Whole
adrenal	Hypoadrenalism	>6000	–	Whole
pituitary	Hypopituitarism	4500	20,000-30,000	Whole
Peripheral nerves	Neuritis	6000	10,000	10 cm
Ear				
Middle	Serous otitis	5000	7000	Whole
Vestibular	Meniere's syndrome	6000	7000	Whole

Class-III Organs: Mild/No Morbidity[a]

Organ	Injury	$TD_{5/5}$	$TD_{50/50}$	Whole or Partial Organ (Field Size or Length)
Muscle (child)	Atrophy	2000-3000	4000-5000	Whole
Muscle (adult)	Fibrosis	6000	8000	Whole
Lymph nodes and Lymphatics	Atrophy, sclerosis	5000	>7000	Whole node
Large Arteries and viens	Sclerosis	>8000	>10,000	10 cm
Articular Cartilage	None	>50,000	>500,000	Joint surface (m.m.)
Uterus	Necrosis, Perforation	>10,000	>20,000	Whole
Vagina	Ulcer, Fistula	9000	>10,000	Whole
Breast (Child)	No Development	1000	1500	Whole
Breast (Adult)	Atrophy, Necrosis	>5000	>10,000	Whole

[a] Data from Rubin et al., 1975.

Please note that classifying an organ as Class 1-2-3 is NOT the same as calling it radiosensitive-intermediate-radioresistant. Rather *this grouping of tissues is based how bad the overall outcome would be of exceeding the stated tolerance dose.*

Adapted from Rubin P, Casarett GW: Clinical Radiation Pathology. Philadelphia, W.B. Saunders, 1968.

4] heirs to Rubin and Cassarett?

a. first, there was Emami *et al.* (IJROBP *21*: 109-122, 1991), who provided a 20 year update to Rubin and Cassarett's work, and at a time that corresponded with the dawn of the 3D treatment planning age

1} ***only then was it fully realized that there had been very little research on normal tissue tolerances/histopathology in the intervening two decades, least of all with respect to partial organ irradiation***

Tolerance doses of Emami et al. (1991) predicted tolerance doses

ORGAN	INJURY	ONE-THIRD	TWO-THIRDS	WHOLE ORGAN
Bladder	Contracture	--	8000	6500
Brain	Necrosis/infarction	6000	5000	4500
Brainstem	Necrosis/infarction	6000	5300	5000
Colon	Obstruction/ perforation	5500	--	4500
Ear mid/external	Acute serous otitis	3000	3000	3000*
Ear mid/external	Chronic serous otitis	5500	5500	5500*
Esophagus	Perforation, stricture	6000	58000	5500
Femoral head	Necrosis	--	--	5200
Heart	Pericarditis	6000	4500	4000
Kidney	Nephritis	5000	3000	2300
Larnyx	Necrosis	7900*	7000*	7000*
T-M joints mandible	Marked limitation of joint function	6500	6000	6000
Liver	Liver failure	5000	3500	3000
Lung	Pneumonitis	4500	3000	1750
Brachial plexus	Nerve damage	6200	6100	6000
Optic chiasma	Blindness	--	--	5000
Eye lens	Cataract	--	--	1000
Optic nerve	Blindness	--	--	5000
Retina	Blindness	--	--	4500
Rectum	Proctitis/necrosis/ fistula/stenosis	--	--	6000
Parotid gland	Xerostomia	--	3200*	3200*
Skin	Necrosis/ulceration	7000	6000	5500 100 cm^2
Small intestine	Obstruction/ perforation	5000	--	4000*
Spinal cord	Myelitis/necrosis	5000 5 cm^2	5000 10 cm^2	4700 20 cm^2
Stomach	Ulceration/ perforation	6000	5500	5000

Modified from Emami B, et al: Tolerance of normal tissue to therapeutic radiation, *Int J Radiat Oncol Biol Phys* 21:109-122, 1991
$TD_{5/5}$, Tissue dose associated with a 5% injury rate within 5 years.
*<50% of volume does not make a significant change

2} Emami's tolerance dose and irradiated volume combinations are still used by many today (his paper is one of, if not the, most cited papers in the history of the Red Journal, going back over 40 years!)

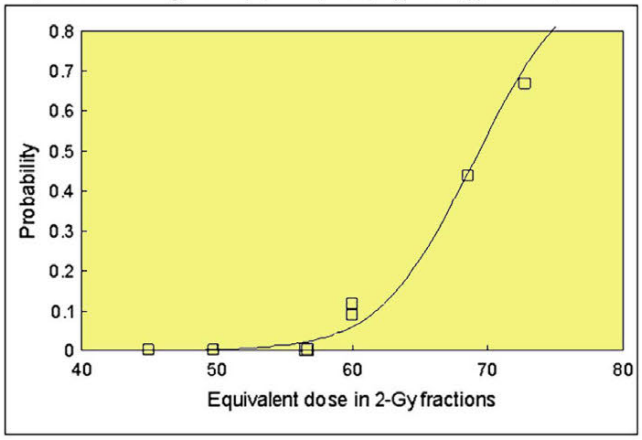
4] and then, another 20 years later, came: QUANTEC ("Quantitative Analyses of Normal Tissue Effects in the Clinic") - *see IJROBP Supplement, Volume 76, Number 3, March, 2010*

the QUANTEC data and guidelines promised to be much more modern in terms of taking into account factors such as altered fractionation, volume effects, 3-D conformal radiotherapy (note: *not* IMRT) or SRS/SBRT/SABR; concurrent chemotherapy; patient confounding factors, etc.

QUANTEC: Dose-Volume Metrics

Organ	Volume Segmented: Irradiation Type	Endpoint	Dose-Volume Parameters	Rate	Comments
Brain	Whole organ: 3DRT	Symptomatic necrosis	Dmax <60 Gy	<3%	Data at 72 and 90 Gy, extrapolated from BED models
	Whole organ: 3DRT	Symptomatic necrosis	Dmax <72 Gy	5%	
	Whole organ: 3DRT	Symptomatic necrosis	Dmax <90 Gy	10%	
Brainstem	Whole organ: whole brainstem	Permanent cranial neuropathy or necrosis	Dmax <54 Gy	<5%	
	Whole organ: 3DRT	Permanent cranial neuropathy or necrosis	D1-10 mL ≤59 Gy	<5%	
	Whole organ: 3DRT	Permanent cranial neuropathy or necrosis	Dmax <64 Gy	<5%	Point dose <1 mL
Optic nerve/ chiasm	Whole organ: 3DRT	Optic neuropathy	Dmax <55 Gy	<3%	Given the small size, 3DRT is often whole organ
	Whole organ: 3DRT	Optic neuropathy	Dmax 55-60 Gy	3%-7%	
	Whole organ: 3DRT	Optic neuropathy	Dmax >60 Gy	7%-20%	
Spinal cord	Partial organ: 3DRT	Myelopathy	Dmax 50 Gy	0.2%	Including full cord cross-section
	Partial organ: 3DRT	Myelopathy	Dmax 60 Gy	6%	
	Partial organ: 3DRT	Myelopathy	Dmax 69 Gy	50%	
Cochlea	Whole organ: 3DRT	Sensory neural hearing loss	Mean dose ≤45 Gy	<30%	Mean dose to cochlea, hearing at 4 kHz
Parotid	Bilateral whole parotids: 3DRT	Long-term parotid salivary function reduced to	Mean dose <25 Gy	<20%	For combined parotid glands

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S42–S49, 2010

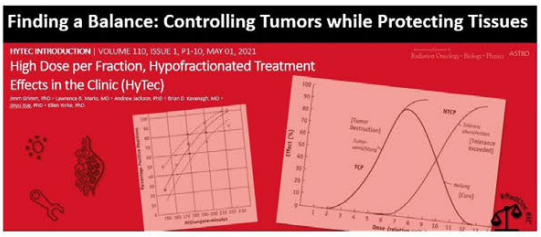


The dose–response function for the myelopathy of the cervical spinal cord

For some tissues, QUANTEC was also noteworthy in providing complete (or close to complete) dose response curves for normal tissue complication probabilities, data that is traditionally hard to come by.

NTCP data is useful for, among other things, biological modeling for treatment planning purposes.

5] and then, ~10 years after QUANTEC, came HyTEC ("High Dose per Fraction, **Hy**pofractionated **T**reatment **E**ffects in the **C**linic" - *see IJROBP, Volume 110, Number 1, April 2021*)

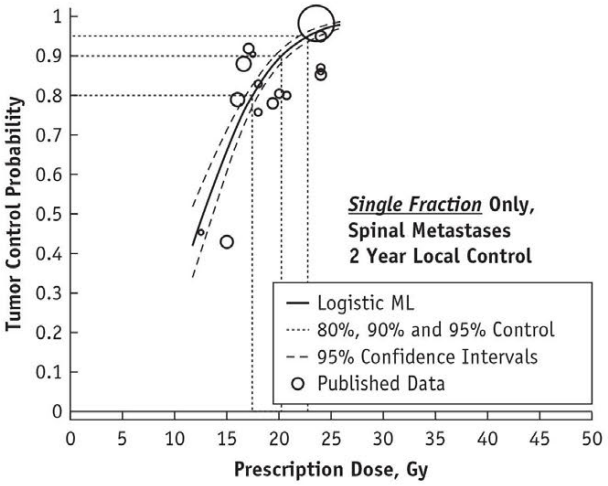


a. **HyTEC used a similar approach to QUANTEC vis-a-vis trying to further refine the time, dose fractionation and volume dependencies for normal tissue complications and accordingly, the estimation of dose constraints for treatment planning purposes, *however it now included treatments employing IMRT and SRS/SBRT as well***

b. **and to up the ante even further, HyTEC also assessed *tumor control probabilities*, i.e., it didn't limit itself to effects in normal tissues like QUANTEC did**

For example:

Int J Radiation Oncol Biol Phys, Vol. 110, No. 1, pp. 112-123, 2021

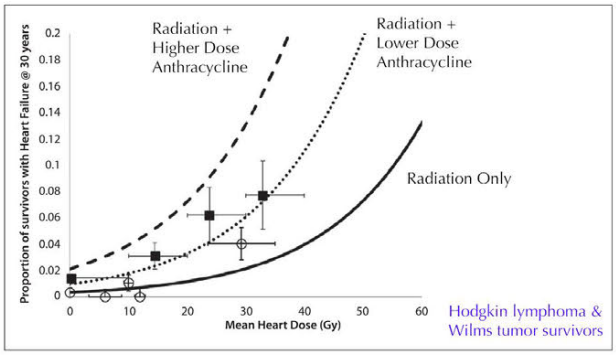


2 year tumor control probability as a function of prescription dose for spinal cord metastases treaed with single fraction SBRT.

1] This was in recognition of the fact that the "philosophy" behind extreme hypofractionation is that killing the tumor takes priority, whereas the philosophy behind more conventional radiotherapy was always that sparing normal tissues took priority.

6] And today, another initiative is ongoing, namely **PENTEC** ("**Pe**diatric **N**ormal **T**issue **E**ffects in the **C**linic")

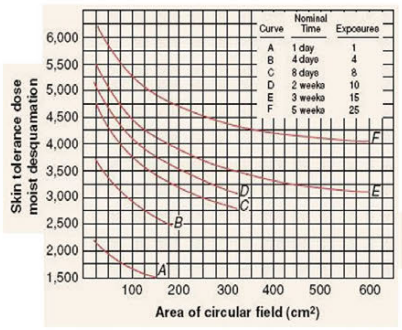
a. *"...the PENTEC collaboration aims to provide a comprehensive overview of the published literature on long-term side-effects of radiation therapy for cancer in children and adolescents and to derive guidance for current and future clinical practice on the dose–volume–risk relationship for several organs at risk."* (From: LS Constine et al., Clinical Oncology *31*:199-207, 2019)



Dose-response curves for long-term risk of heart failure in survivors of childhood cancer

C. Volume Effects in Irradiated Normal Tissues

1) it has LONG (at least since the 1930's) been known that the tolerance dose for normal tissue complications decreases with increasing irradiation volume...but why?



From Paterson R. *The treatment of malignant disease by radium and x-rays*. Baltimore: Williams & Wilkins, 1949:39.

2) Withers and colleagues have attempted to address tissue organization issues by proposing the **Functional Subunit Model (FSU)**

a. in this model, *the volume dependence of late-responding tissue radiation tolerance is viewed as a function of the extent to which the tissue is organized into discrete functional units, and how these units are arranged*

What is the definition of a functional subunit? Technically, there are two:

Anatomical/physiological definition:

The minimum structural entity within a tissue that can, by itself, carry out the function of the tissue as a whole

Radiobiological definition:

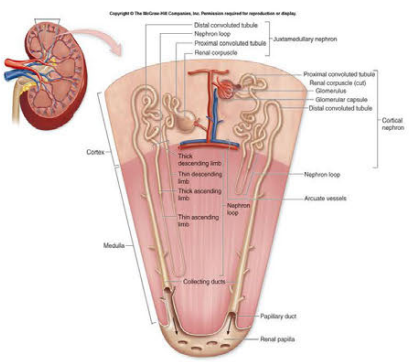
The minimum clonogenic entity required to regenerate – on a micro scale – the tissue's structure and/or function (e.g., epilation usually occurs at a lower dose than desquamation because hair FSUs contain fewer clonogens than skin FSUs)

1] for example, the functional subunit of the kidney is probably the nephron, that of the liver is probably the hepatic lobule, for the lung, maybe an alveolar sack, and that of the spinal cord **possibly** a nerve fiber or bundle; for other tissues however, exactly what a functional subunit is in an anatomical sense is still unclear

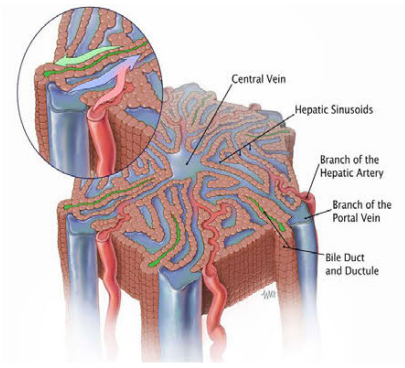
2] for the FSU's that do have an anatomical/structural definition, it is further assumed that, when damaged, that they *cannot* be resupplied with surviving cells from surrounding FSU's, whereas, for FSU's without a clear structural demarcation, repopulation from outside the damaged area *would be* possible

a) *this would therefore represent a theoretical recovery advantage for tissues with anatomically-undefined FSU's*

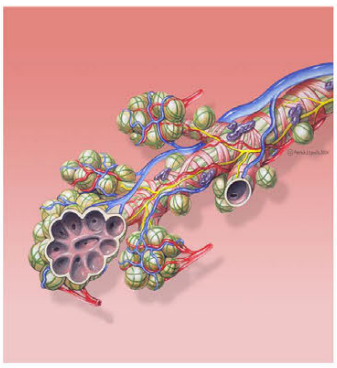
For some tissues, FSUs have clear anatomical counterparts, but for many others, what actually constitutes an FSU remains unclear



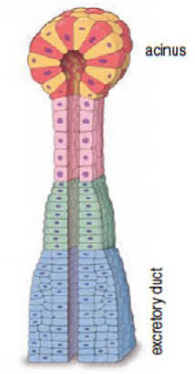
Nephron of the kidney



Lobule of the liver

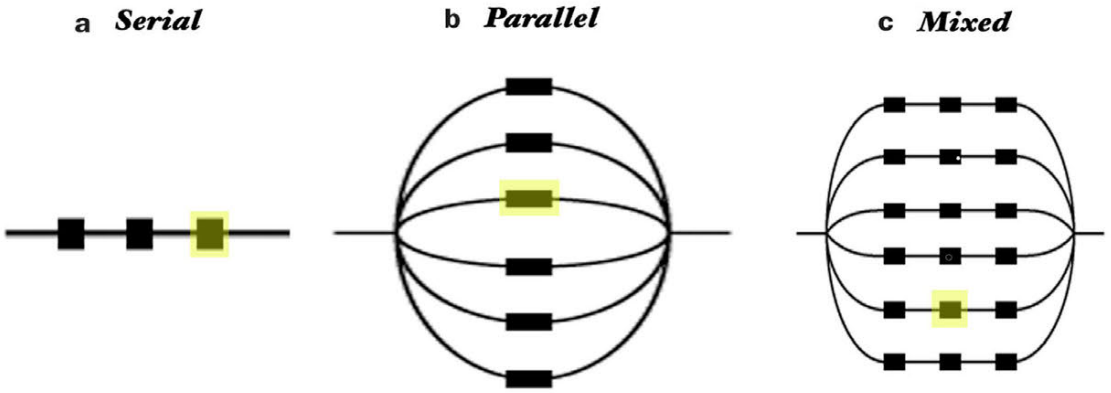


Alveolar sacs of the lung



Salvion

c. some tissues have functional subunits that are arranged in series (**serial organization**) and others that are arranged in parallel (**parallel organization**); still other tissues have either unknown or "hybrid" types of functional organization



Valdagni, R. & Rancati, T. *Nat. Rev. Urol.* advance online publication 14 May 2013

| Schematic representation of tissue architectures.

a | In serial organs, functional subunits (a cell or a group of organized cells) are organized in chains. Damage to one subunit results in toxicity that affects the whole tissue.

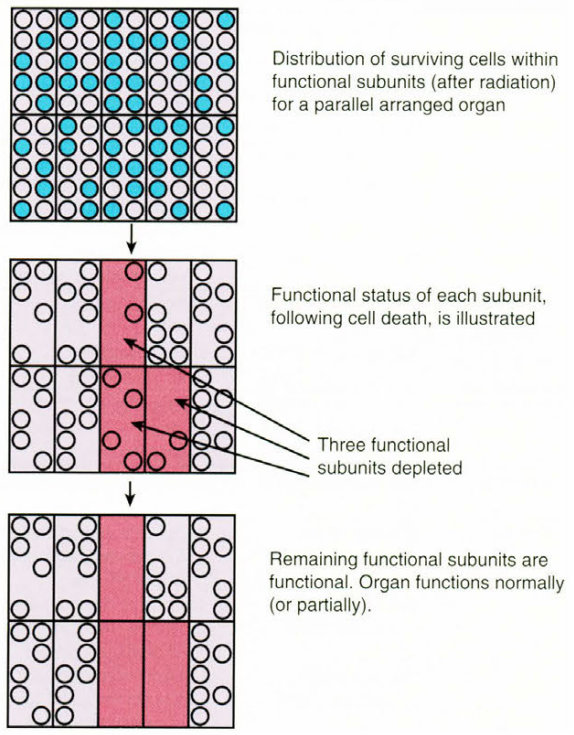
b | By contrast, parallel organs are those in which the functional subunits are organized in parallel strings so that tissue toxicity is caused by damage to a substantial number of chains.

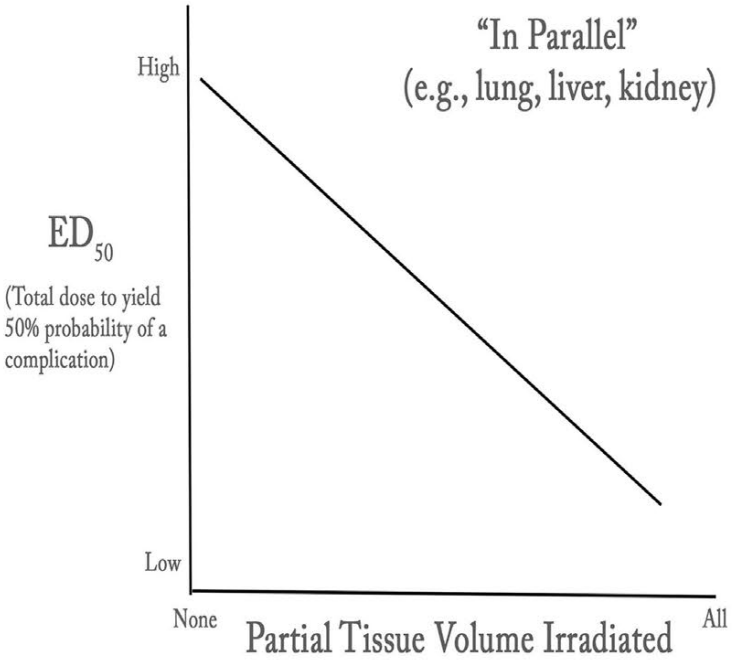
c | Mixed organs have combined features of serial and parallel tissues.

c. **Tissues with functional subunits in parallel include the lung, kidney and liver**

1. *for these tissues, irradiation of a small volume to high or even very high doses is well-tolerated, but irradiation of large volumes is not*

Radiation-killed cells in teal

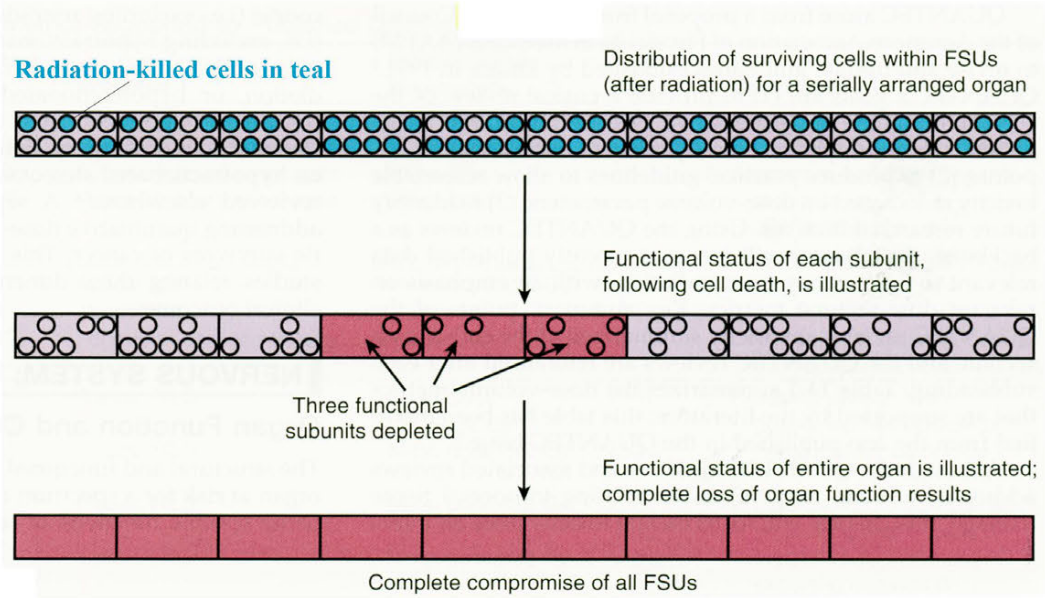


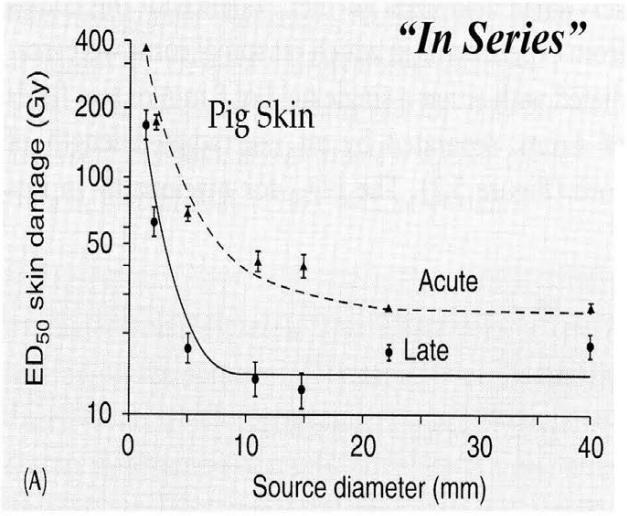


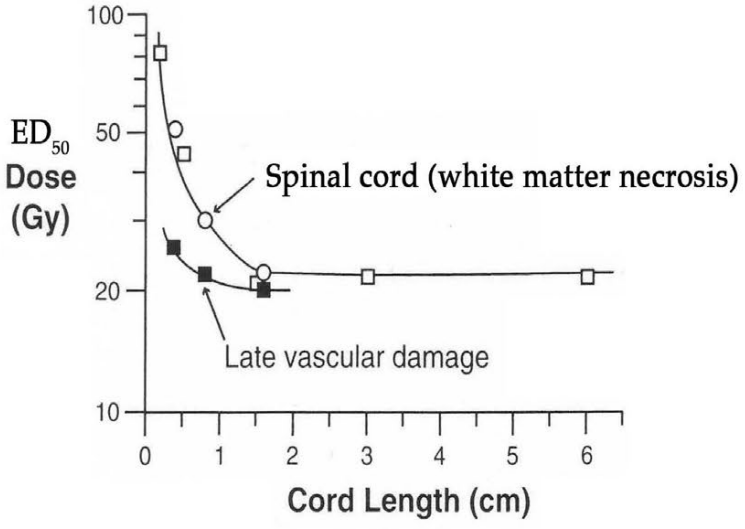
d. **Tissues with functional subunits in series include the spinal cord and peripheral nerves skin, gut and many other hollow or tubular structures (i.e., esophagus, urethra, bladder, rectum)**

1. *for these tissues, the inactivation of a single FSU could cause the function of the entire organ to be lost; in this case, there is a very steep dose response for small volumes, but once the damage is done, the dose response is then flat for larger volumes*

a} clinical implication: presence of a dosimetric hot spot can be disastrous for serial tissues (yet have little consequence for parallel tissues)!

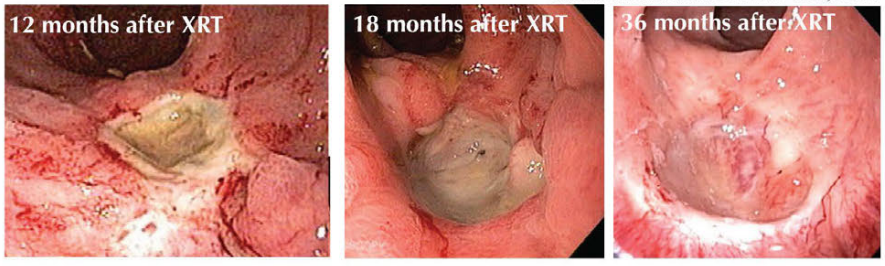






Semin Radiat Oncol 27:378-392, 2017

Example: A hot spot in the anterior rectal wall during prostate SABR produced a non-healing wound ultimately requiring surgical bypass.



Retreatment Tolerance of Previously Irradiated Tissues

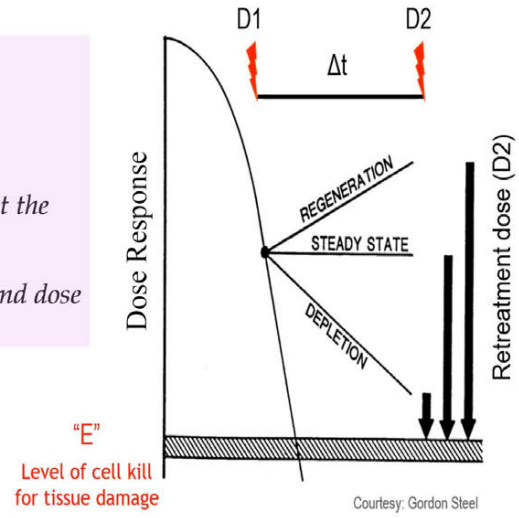
1] Background - while almost every clinician at one time or another wants to know what the re-treatment tolerance of previously irradiated normal tissues is, almost nobody knows:

a. *what the important factors are governing re-treatment tolerance; (repair rates, proliferation rates, volume effects, inherent radiosensitivity, etc.)*

b. *what influence the timing between the first and repeat treatment has;*

c. *to what extent there is "residual damage" remaining from the first treatment at the time of the second treatment;*

d. *to what extent re-treatment tolerance changes as a function of the total dose (and dose per fraction?) for the first treatment relative to the second treatment*



3] a survey of particular tissues assessed for their retreatment tolerance:

a. **Skin**:

1) looking at acute reactions *in the epidermis only* (i.e., without considering the inter-relationship between the epidermis and dermis), **as long as at least 2 months have passed since the initial treatment, 90-100% of the full radiation tolerance can be delivered a second time**

2) for late reactions *in the dermis only* (fibrosis), **there is some recovery of tolerance with time between the first and second course of treatment**, however not as much as for the acute reactions in the epidermis

a] **somewhere between 40% and 60% tolerance can be recovered for fibrosis** endpoints (in the skin and elsewhere), but this varies with the time between the two treatment courses - longer is better - and how "hot" the initial treatment was compared to the retreatment, i.e., a more severe inital treatment course means less receovery potential for the second treatment than if the inital treatment was milder

b. **Kidney**: problematic

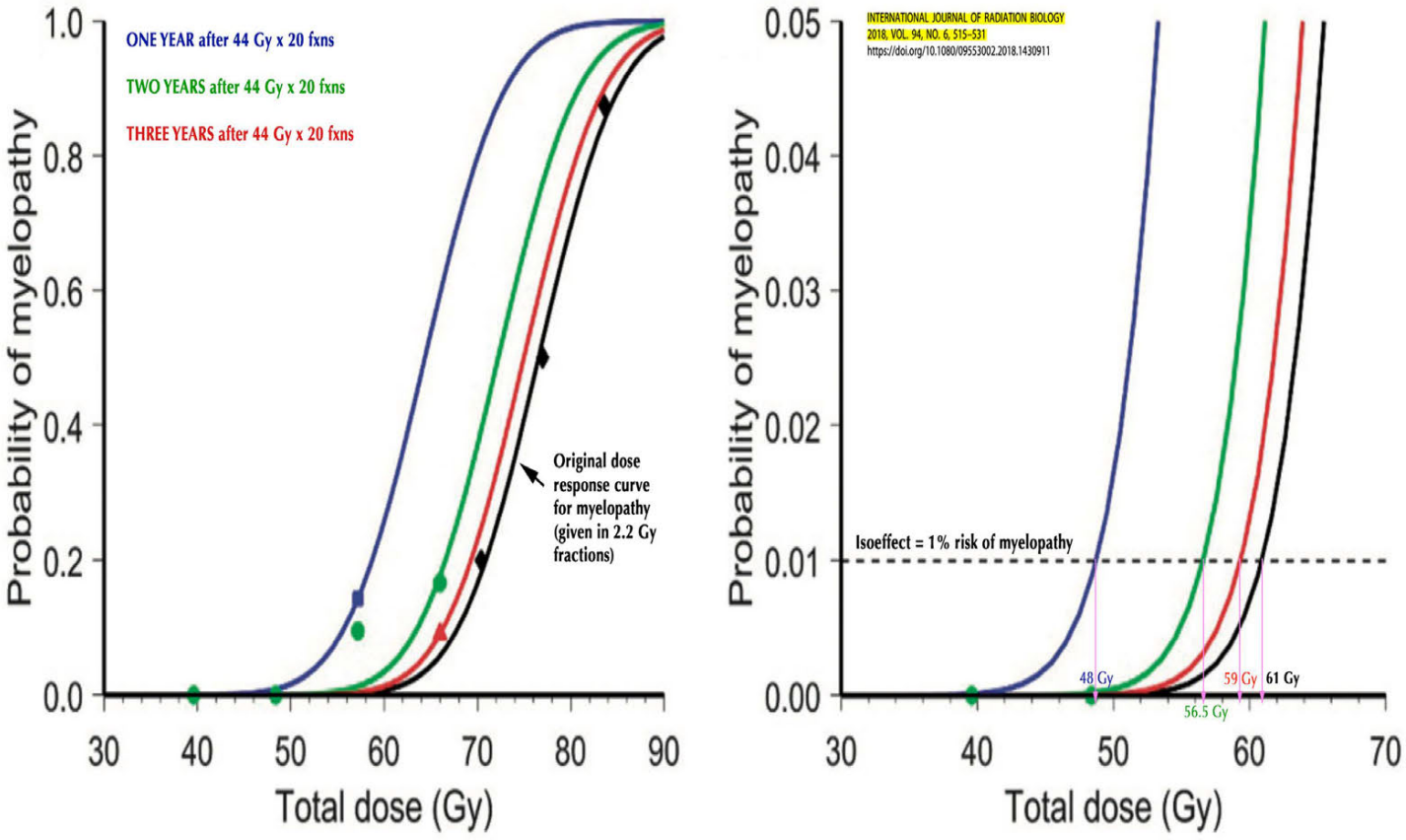
1) the kidney shows a progressive, dose-dependent development of functional damage with time after a first course of treatment; as a result, *retreatment tolerance actually goes down the longer the interval between the first and second course!*

2) this being the case, it's probably better to not retreat kidneys at all..or, if absolutely necessary, ***use the smallest volume, the lowest total dose and the smallest dose per fraction as practical***

c. **Spinal Cord**: *the tissue we're probably most worried about, and the one that nobody thinks can tolerate **any** retreatment!*

1) ***Contrary to popular belief, the retreatment tolerance of the spinal cord does increase, starting within a few weeks after the initial course of treatment and continuing for 9 months or more***

2) In fact, careful experiments using rhesus monkeys showed that, **with 1-2 years between the first and second course of treatment, ~50% retreatment tolerance was observed (and even higher for 3 years between treatments)**. Still, for human purposes, many would assume 25% recovery just to be extra, extra safe



Interesting to note that in the rhesus monkey, the $TD_{5/5}$ for myelopathy (with no prior irradiation) is in the vicinity of 65 Gy... up to 10 Gy higher than what is typically quoted for humans. (The monkeys probably are a little more radioresistant than humans overall, but not by *that* much.)

Is this more evidence of "downward dose creep" when it comes to spinal cord irradiation?

Human Experience with Retreatment Tolerance – quite a few small studies have been conducted, mostly with head and neck cancer patients, and although many different treatment techniques were used, a couple of things seem apparent:

1. **complication rates after retreatment can be highly variable**
2. **these complication rates are higher than would typically be considered acceptable, not to mention that local control of the tumors isn't very good either**

Advances in Radiation Oncology: April–June 2016

Comparison of prior studies of rectal cancer reirradiation

Study	N	MRD (Gy)	MCD (Gy)	Acute toxicity		Late toxicity		Median OS (mo)
				G3 (%)	G4 (%)	G3 (%)	G4 (%)	
Das et al	50	39	89	4	0	24	2	26
Lingareddy et al	52	30.6	84.4	31	0	23	10	12
Mohiuddien et al	103	34.8	85.8	22	6	17	4	26
Ng et al	56	39.6	87.3	13	0	2	0	19
Valentini et al	59	40.8	90.8	5.1	0	12	0	42
Youssef et al	31	39	77	3	0	3	0	22

MCD, median cumulative dose; MRD, median retreatment dose.

3. another interesting finding (not shown in table) is that **complications that occurred after the second treatment took significantly less time to develop than those that occurred in patients who only received a single course of treatment**

bottom line: re-irradiation can be administered in select cases (to up to 50-60 Gy) for effective palliation and/or reasonably good local control...bearing in mind that the risk of complications will be higher than after a single course of treatment

Summary of pertinent findings on retreatment tolerance

• ***For rapidly-growing normal tissues replenished by stem cells – such as skin, gut or bone marrow – as long as at least 3 months have passed since the first treatment, these tissues can be retreated to nearly the same total dose as given the first time*** (Why? Because within 3 months, nearly all of the cells in these tissues have been replaced, so the cells present at the time of the second treatment never experienced the first one)

• ***Some** slowly-growing normal tissues can recover partially from damage caused by the first treatment, and can tolerate moderate retreatment (i.e., can give up to 50% of the original dose), and the longer the time between treatments, the higher the dose the tissue can tolerate the second time around (The CNS is like this, and the lung too.)*

• ***Other slowly-growing tissues seem to harbor permanent, residual damage, so can never tolerate more than about 30% of the original dose when given as a retreatment, regardless of how much time has elapsed between the treatments (The bladder is like this.)***

• ***Finally, the exception to every other rule is the kidney, whose tolerance of retreatment decreases as the time between the first and second treatment increases*** (Why? Because there is evidence that both the development of kidney injury, and recovery from it, takes so long that the last thing you'd want to happen is for your second treatment to take place right when the initial injury is manifesting.) ***Because of this weirdness, the general rule is not to retreat kidneys at all.***

6] some remaining "unknown quantities"

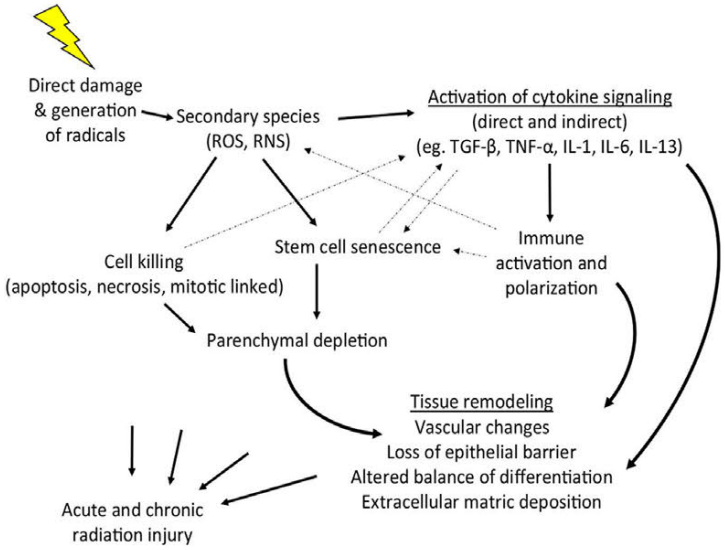
a. **volume dependencies for retreatment tolerance**

1) **the influence of how much overlap there is in treatment volumes between the original and subsequent retreatment fields**

b. **how retreatment tolerance varies with the time-dose-fractionation parameters of the first versus second treatment**

1) A recent Phase III trial out of China (You *et al*., Lancet *401*:P917-927, March 18, 2023) retreated ~140 patients with recurrent nasopharyngeal carcinoma with hyperfractionation (65 Gy in 54 fractions, given twice daily using IMRT) and found retreatment to be much better tolerated. **Looking at Grade 3 or higher late complications only, there were about 34% in the hyperfractionation group versus 57% in the conventional fractionation group.** Overall survival at 3 years was also better in the hyperfractionation group.

Molecular Pathogenesis of Radiation Injury in Normal Tissues - we now know that radiation damage to normal tissues *starts* with the deaths of specific, critical cells, but then progresses by way of very complicated and self-perpetuating molecular processes



Pathways of radiation injury. Radiation induces direct damage in normal tissues but also can generate free radicals, which can themselves cause injury or give rise to secondary species that may also cause injury. As a consequence, normal tissue cells are killed through a variety of mechanisms. Normal tissue stem cells may enter a state of senescence, which when combined with the initial cell killing, may result in parenchymal depletion and resulting tissue dysfunction. Simultaneously, ROS can initiate cytokine signaling, as can cell death and senescence. Collectively, these effects lead to immune activation and alterations in immune cell polarization that can lead to chronic inflammation and further oxidative stress.

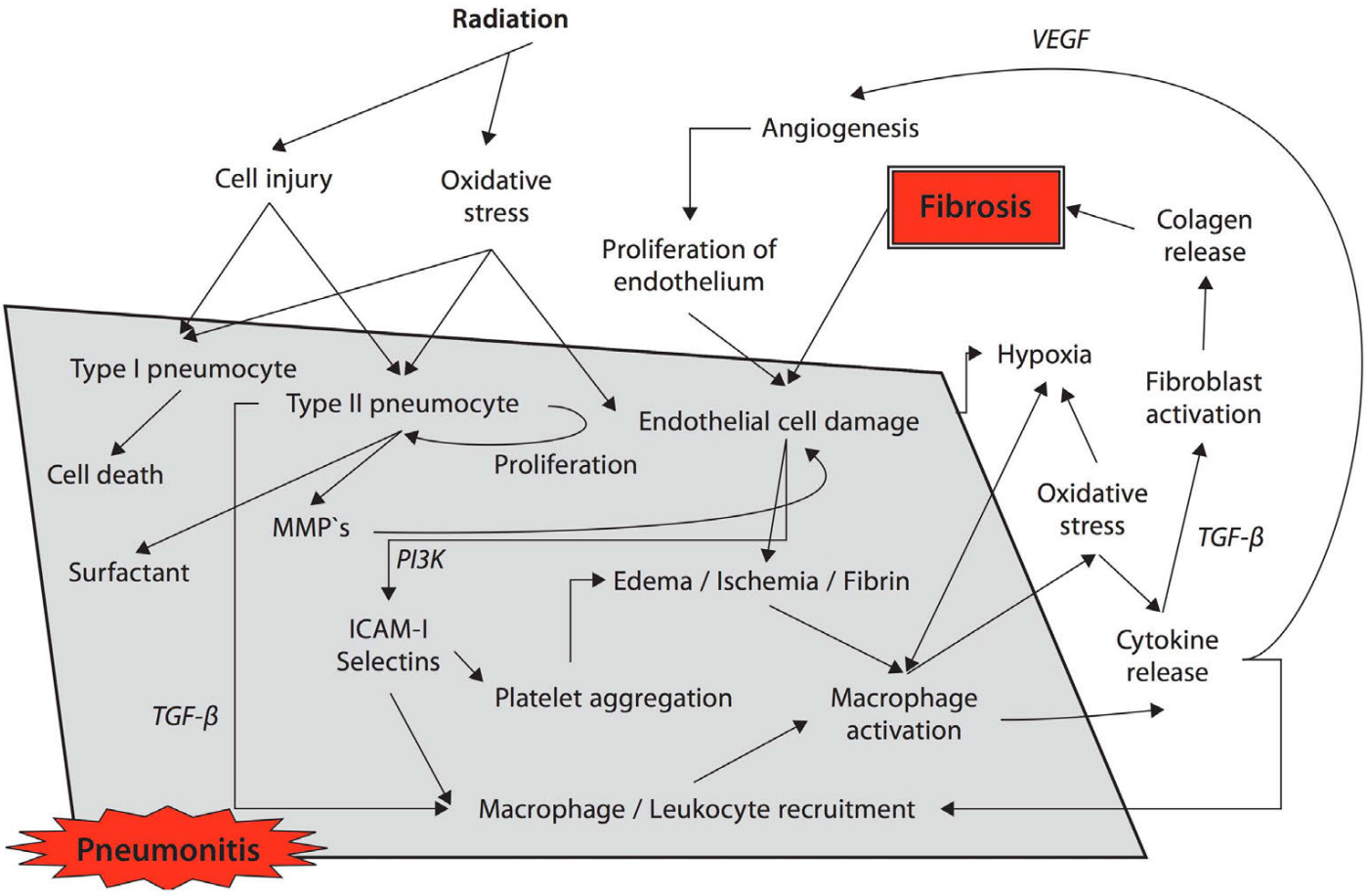
http://dx.doi.org/10.1016/j.semradonc.2017.04.001

1. two recurring "players" in this process are:

   a) **reactive oxygen species (ROS)**: free radicals that are initially generated by radiation-induced ionization of biological molecules, but that continue to be produced in a cyclic manner and create chronic oxidative stress in the tissue

   b) **cytokines**: a broad class of proteins that play multiple roles in the maintenance of tissue homeostasis under both normal and pathological conditions, and in particular, play important roles in wound healing, angiogenesis, inflammation and cell proliferation

2. however, each type of tissue injury has its own "schema", often involving different critical target cells, ROS and cytokines, for example, early and late radiation effects in lung:



3. cytokines are also thought to be the culprits in other types of radiation side effects, including:

- nausea/vomiting
- erythema
- edema
- somnolence
- fatigue

...likewise, ***cytokines also orchestrate certain immune responses in tissues after irradiation***

Select cytokines of interest:

- **Inflammatory Cytokines**
  - Tumor Necrosis Factor (TNF-a), Interleukin-1 (IL-1)
- **Angiogenesis**
  - Vascular Endothelial Growth Factor (VEGF), Basic Fibroblast Growth Factor (bFGF), TNF-α
- **Immune Cytokines**
  - IL-2 and IL-4
- **Fibrotic Cytokines**
  - Transforming Growth Factor beta (TGF-β), bFGF, IL-6
- **Growth Factors**
  - Colony Stimulating Factors - G-CSF, GM-CSF, IL-3, EPO, SCF
  - Epidermal Growth Factor (EGF), TGF-α, bFGF

1. cytokines can be tricky to study because:

a) they can play different roles in different contexts, and this can vary on a tissue-by-tissue basis

b) in terms of radiation response of both normal tissues and tumors, some act as radioprotectors, some as radiosensitizers and some as enhancers of repopulation

Radioprotection and Radiosensitization of Mice by Cytokines

	Bone Marrow			Intestine	
	Protection	**Restoration**	**Sensitization**	**Protection**	**Sensitization**
TNF-α	√				√
IL-1	√	√			√
IL-3, IL-4		√			
IL-6		√	√		
IL-11		√			
IL-12	√				√
SCF	√			√	
bFGF	√	√			
TGF-β			√		
IFN-α or -β			√		
IFN-γ					√
LIF, G-CSF, GM-CSF		√			

Note: Mice were exposed to acute effects of whole body radiation on the hematopoietic and gastrointestinal systems. The endpoints were $LD_{100/6}$ (GI death) and $LD_{100/30}$ (hematopoietic death). Restoration describes the effect of cytokines that increase survival when injected after a mid-lethal dose.

SCF, stem cell factor; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte macrophage colony stimulating factor.

Biomolecular Action of Ionizing Radiation; Editor:Shirley Lehnert, 2007

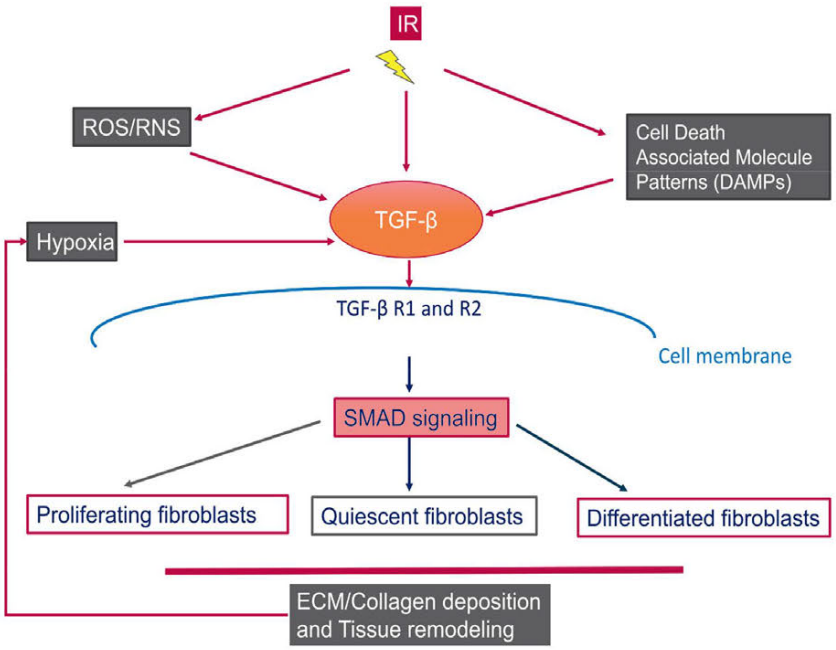
2. Why do radiation oncologists care about cytokines?

a. Reason #1 - ***to find out whether we can intervene in the development of tissue complications (late effects in particular) by manipulating cytokines whose activities are known to either mitigate or exacerbate normal tissue reactions***

b. Reason #2 - ***to see whether early changes in cytokine levels during or soon after the completion of radiation therapy might serve as biomarkers for the development of complications months or years later***

3. **by far, the cytokine we know the most about is TGF-β vis-a-vis its role in the etiology** of radiation pneumonitis and fibrosis

CITRIN *ET AL.* RADIATION RESEARCH 188, 1–20 (2017)

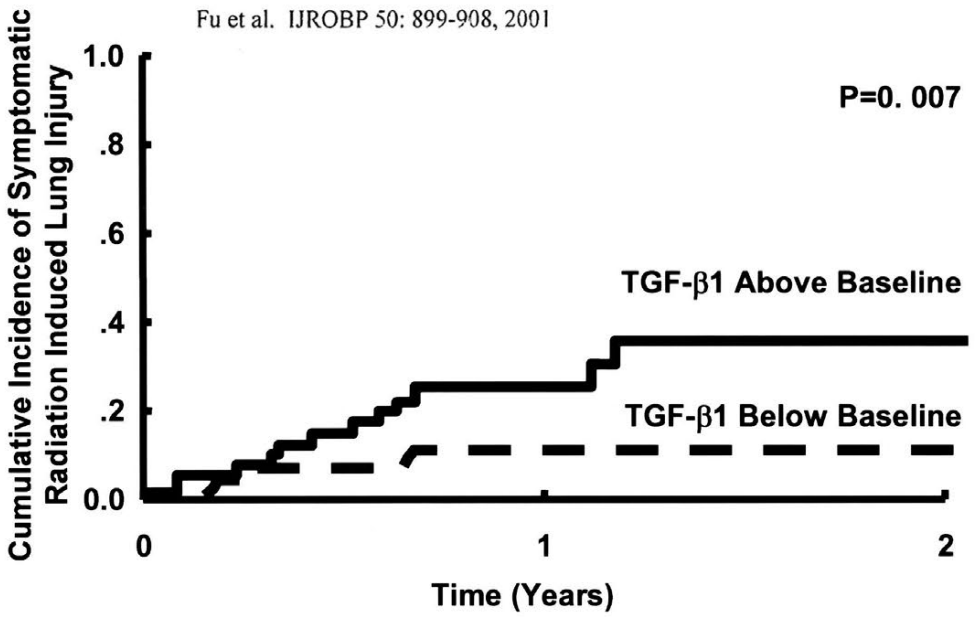


The central role of TGF-β in radiation fibrosis. TGF-β activation after irradiation can occur via reactive oxygen species or other indirect mechanisms. Once activated, TGF-β signaling results in activation of SMAD signaling pathways, with can stimulate fibroblast proliferation and extracellular matrix (ECM) deposition. These changes can contribute to hypoxia, which further contributes to the progression of fibrosis.

a. TGF-β plays a major role in fibroblast differentiation, death and collagen production

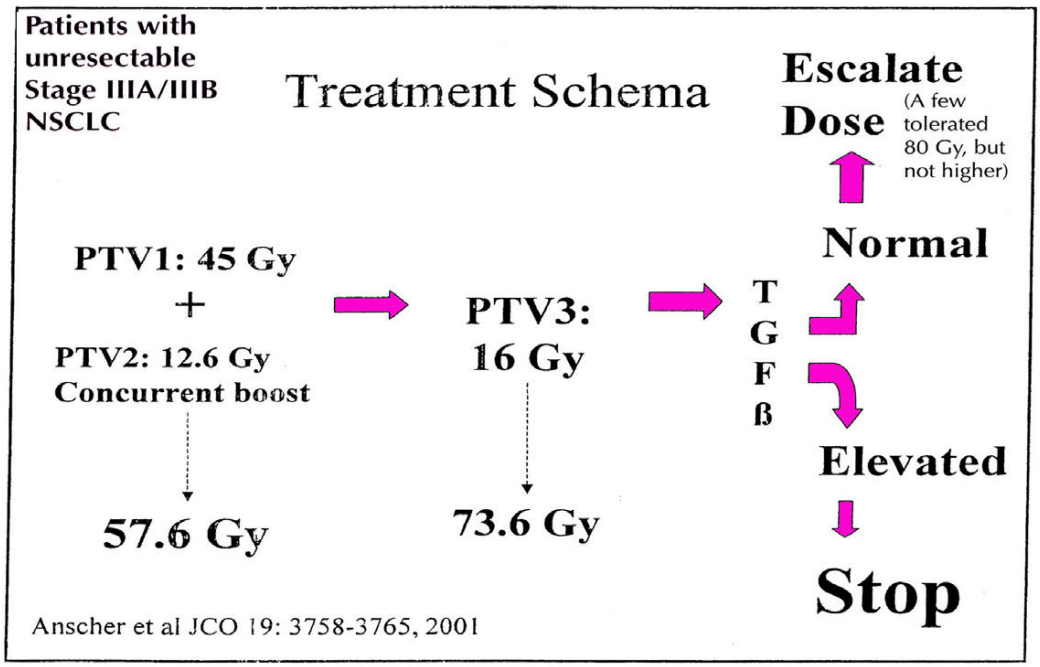
b. some of the earliest clinical studies – from the early 2000's – of TGF-β focused on lung injury

Fu *et al.* (2001) – showed a correlation between elevated TGF-β levels postirradiation and the later development of radiation pneumonitis



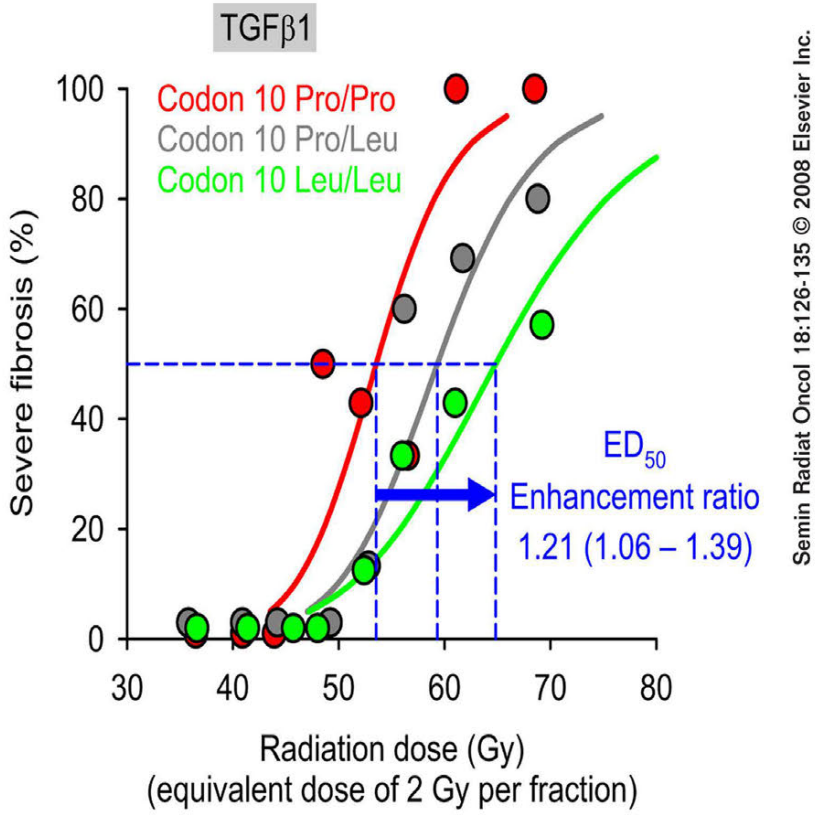
Comparison of the cumulative incidence of symptomatic radiation-induced lung injury in the entire group of 103 patients, depending upon whether the plasma TGFβ level at the end of radiotherapy was below the pre-RT baseline.

Anscher *et al.* (2001, 2003) - dose escalation study of patients with advanced NSCLC, using TGF-β as a marker for likelihood of developing radiation pneumonitis



a. as a proof of concept, this biomarker study was ahead of its time, however confounding factors muddied the waters, **so the study was ultimately discontinued**

Alsner *et al*. (2008) – one of the earliest genomics studies involving SNPs in the TGF-β gene and how these related to the likelihood of developing fibrosis after radiation therapy



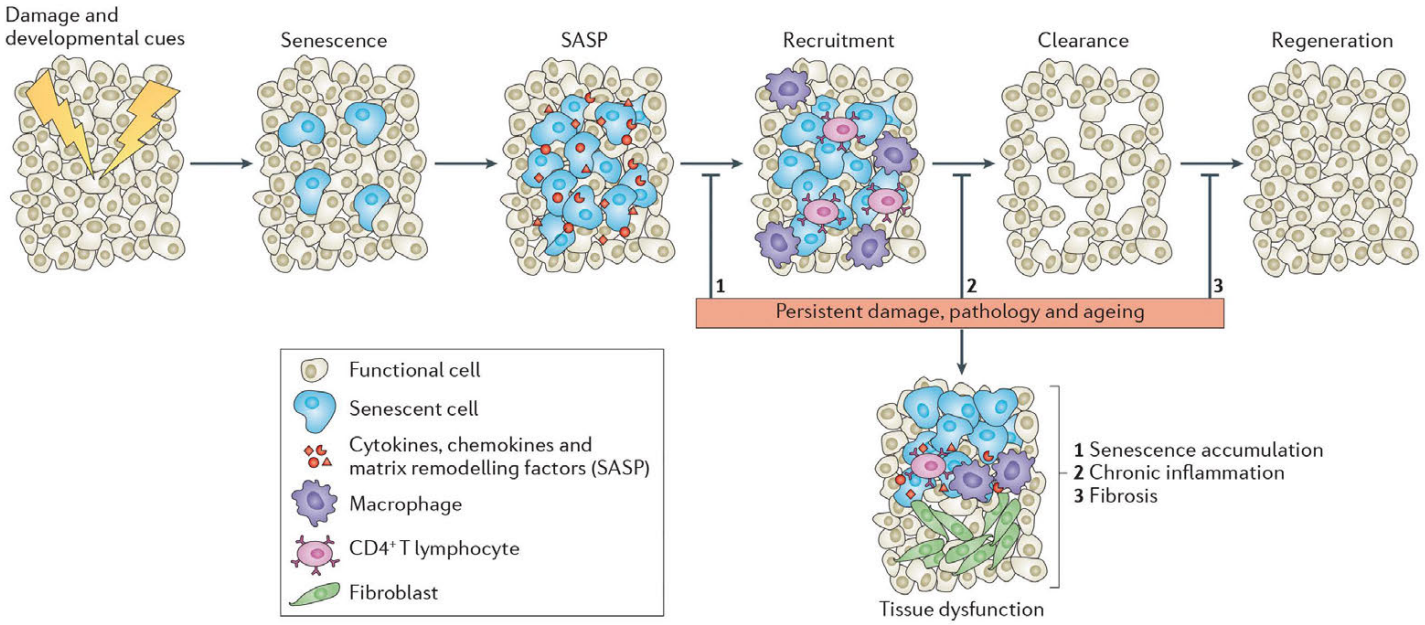
Dose-response curves for subcutaneous fibrosis in 41 breast cancer patients treated with postmastectomy radiotherapy using a 3-field technique stratified by the their TGF-β1 codon 10 genotype. The enhancement ratio (blue) between patients with Pro/Pro and Leu/Leu is the ratio between ED_{50} values (defined as the radiation dose, which, on average, is expected to cause moderate or severe fibrosis in 50% of the treatment fields) with 95% confidence intervals.

Emerging Science!

A. **Cellular Senescence and Late Complications**: cellular senescence – regardless of whether it's a natural result of aging or a pathological response to cell/tissue damage – is increasingly implicated in the etiology of late effects in normal tissues (particularly fibrosis)

1) because of this, there is much interest in the development of agents that either destroy senescent cells ("senolytics") or else preserve or modulate them ("senomorphics") depending on the exact therapeutic context

2) the theory as to the role of senescence (and radiation) in late fibrosis goes something like this:



a] irradiating a tissue will cause some cells to die via senescence, with the resulting development of the *senescence-associated secretory phenotype* (SASP)

1. cytokines and chemokines released as part of the SASP attract immune cells to the site of the injury, which *normally* would go on and clear out the senescent cells, making room (if possible, depending on the tissue) for unaffected cells of the tissue to regenerate and mitigate the injury

2. however, if the radiation damage is too severe, the patient has a pre-existing condition or comorbidity and/or that the patient is old (i.e., that their immune system and tissue-regenerating capacity is less robust), then the senescent cells will be retained and the SASP will continue, leading to chronic inflammation and eventually, fibrosis

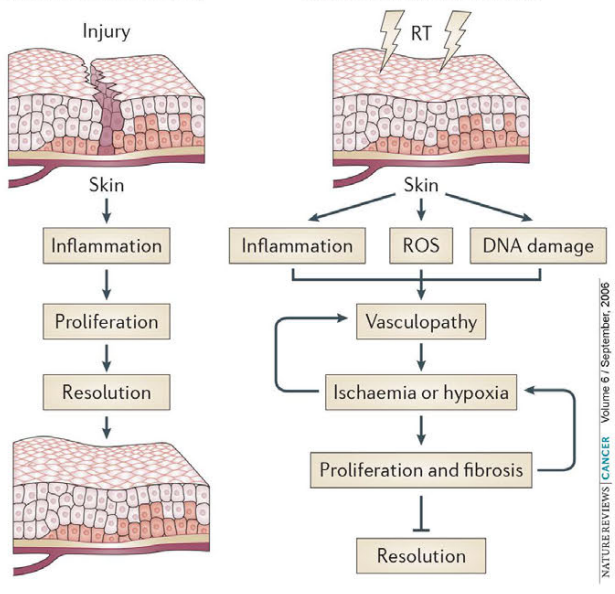
And finally, another interesting thing about radiation-induced normal tissue injury:

Wound-healing following radiotherapy – which often culminates in fibrosis – and "normal" wound healing are similar in some ways, but not in others.

(Along these same lines, tumors are sometimes described as being akin to "wounds that will not heal".)

Normal wound healing versus radiation fibrosis

The normal phases of wound healing progress from the injurious stimulus to inflammation, proliferation and finally resolution. By contrast, radiation generates reactive oxygen species (ROS), DNA damage and inflammation as the early stimuli that mediate the activation of a dysregulated proliferative phase. Unlike wound healing, radiation exerts a field effect on the vascular compartment. Endothelial dysfunction leads to a progressive vasculopathy that is characterized by impaired gaseous exchange and the development of tissue hypoxia, which drive an uncontrolled proliferative stage that replaces the normal proliferative phase of wound healing. This may represent a poorly coordinated haemostatic response that aims to preserve tissue oxygenation. The progressive and perpetuating proliferative phase prevents tissue resolution and results in the development of late adverse effects (see the figure; arrows represent positive feedback loops). RT, radiotherapy.



E. Proper Documentation of Normal Tissue Complications: A Pesky Problem

1] the fear/threat of causing unacceptable late complications in normal tissues has hounded radiation oncology since its earliest days

2] **so, you might <u>think</u> that everybody who publishes a clinical paper citing normal tissue complication rates for different fractionation schedules would use a uniform late effects scoring scale that would allow inter-comparison between different investigators, institutions, cooperative groups, etc...**

... BUT NOOOOOOOOO!

3] because of this problem, an international committee consisting of members of the (then) RTOG and EORTC was convened to develop a uniform scale for the recording and scoring of late normal tissue complications

a. their proposed scoring system was called the **SOMA Scale**, that contained four domains: *Subjective, Objective, Management and Analytic*

b. how the SOMA Scale worked: for each irraidiated tissue at risk for the development of a late complication, the radiation oncologist was expected to make a 4-pronged assessment of the patient during each followup visit (using a numerical scale from 1-4)

- <u>Subjective Scale</u>: asking **the patient** "On a scale of 1 to 4, how badly is this complication affecting your quality of life, e.g. how bad a cosmetic outcome, how much discomfort or pain, immobility, etc."
- <u>Objective Scale</u>: same as above, but the physician's assessment
- <u>Management Scale</u>: the physician would assign a value of 1 to 4 based on how much medical management the complication requires, e.g., pain meds, physical therapy, etc.
- <u>Analytic Scale</u>: an attempt to *quantitatively assess* the severity of the complication for comparative purposes, e.g., photographs, CT or MRI, functional assays, etc.

4] **so...30 years after the fact, is the SOMA system in routine clinical use (anywhere)?**

<u>ANSWER</u>: not really (but if at all, it would be in Europe, not the US)

<u>WHY NOT?</u>:

- time and labor-intensive to collect and store all this kind of information
- an "unfunded mandate"
- no rules/regulations/agencies to monitor and ensure compliance

5] SOMA does live on however, because similar scoring systems *are* in clinical use and they incorporate scoring domains similar to those first proposed in SOMA, for example, the **CTCAE** and the **PRO-CTCAE**

The Evolution of Toxicity Grading Systems (1979–1998)

System	Number of criteria	Number of organs	Modality	Phase
WHO (1979)	28	9	Chemo	Acute
CTC (1983)	18	13	Chemo	Acute
RTOG/EORTC-Acute (1984)	14	13	RT	Acute
RTOG/EORTC-Late (1984)	68	17	RT	Late
LENT/SOMA (1995)	140	13	RT	Late
CTC v2.0 (1998)	152	22	RT	Late
CTCAE v3.0 (2003)	260	22	All[a]	Acute
	370	All	All	Acute and late

WHO, World Health Organization; Chemo, chemotherapy; *RT*, radiation therapy [a] Limited pediatric and surgical criteria

	Mild grade 1+	Moderate grade 2+	Severe grade 3+	Life threatening grade 4+
S	Asymptomatic	Symptomatic usually	Persistent symptoms	Refractory symptoms
	Minimal symptoms	Marked symptoms	Intensive symptoms	Symptoms unresponsive to medication
O	Transient signs	Intermittent signs	Symptoms apparent	Advanced persistent signs
	Functionally intact	Function altered	Function impaired	Function collapsed
M	No interventions	Non-invasive intervention	Interventional radiology	Rad life saving surg
	Occasional medication	Continuous medication	Surgical correction	Intensive care unit
	Occasional non-narcotic	Regular non-narcotic	Occasional narcotic	Parenteral narcotic
A	Normal laboratory values	Abnormal laboratory	Very abnormal lab	Pailing lab values
	Borderline low,	Values,	Lab values not	Potentially lethal
	Correctable	Correctable	Correctable	BM <75 %
	BM cellularity <25 % decrease	B.M. cellularity >25–50 %	BM cellularity >50 %, <75 %	
ADL QOL	ADL regular	ADL Altered	ADL impaired	ADL extremely poor
	KPS 80–100	KP 60–75	KP 30–50	KP 10–25
	Fully ambulatory	Symptomatic, in bed <50 % day	Symptomatic, in bed >50 %	100 % bedridden

6] although some investigators are more conscientious than others in reporting complications *in general*, there is still a long way to go in terms of publishing the specifics, such as:

- better standardization of scoring systems for morbidities, including the milder ones
- better collection of *patient-reported* moribities and their impacts on quality of life
- accounting for baseline morbidities
- reporting on the severity grade of morbidities *in individuals*, instead of using group averages
- reporting on when morbidities occur relative to the end of treatment, their durations, and whether they're recurrent or not