Radiation tolerance of normal tissues

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Presentation Layout

- Why it is important to know normal tissue toxicity
- Factors influencing normal tissue toxicity
- Direct & indirect methods of measuring toxicities
- QUANTEC
- Toxicity assessment tools
- Individual sites

Is accurate estimation of radiation effects in normal tissue possible ?

- True dose to normal tissue - D_A

- Problems
  - Dynamic nature of patient
  - Mapping tumor regression over a course of rx
  - Planned dose ≠ delivered dose for any given #
  - Cell or fluid loss during treatment

How can we try to be accurate ?

- Documentation

- Time dependent patient anatomy over a course – **Imaging / contouring / auto segmentation / image guidance – laborious**

(Inter institution comparison difficult – ex: inner / outer wall rectum)

- Calculate dose at each time point
  - Algorithm plays an important role
  - Monte Carlo take care of RT calculation through all the components
    - treatment unit head
    - CT based patient geometry
    - Represents gold standard of dose calculation
- Inspite of these - Dose volume analysis is still poorly understood
- Tissue deformation and tracking tools are being tried

Dose tracking tools

- MOSFET detectors (metal oxide semiconductor field – effect transistor
- Optical point
- Volumetric methods
- MR based GEL technologies
- Carbon Nano tube approaches
- Deformation & dose validation phantoms

Biomarkers and surrogate endpoints for normal-tissue effects

- Patient to patient variation in response as well as toxicity exists
- It is currently hypothetical to say a hyper responsive phenotype exists
- Biomarker to know the above – infancy
- Predictive factors / response markers & surrogate endpoints

Predictive factors for toxicity

- TGF ß activation after first # of RT – breast ca
- IL-6, IL-1∝ elevation in patients developing pneumonia
- Genetic variations
  - Ataxia telangectasia – hyper radiosensitive
  - SNPs are studied to know genetic variations
  - Candidate gene studies & genome wide association

Response markers

- IL-1∝ and IL-6 weekly assessment – not useful
- TGF-ß1 level normalization at end of RT – 90% PPV for not developing radiation pneumonitis – may help for dose escalation from 73.6 to 80 Gy in NSCLC – however not useful

Surrogate end points

- Using low grade as indicator of high grade toxicity

What is QUANTEC

- Quantitative analysis of normal tissue effects
- Effort of various investigators contribution – QUANTEC steering committee
- 1991- Emami et al – published dose/volume / outcome data
- QUANTEC reviews various data generated 3D/IMRT/IGRT era
- Suggests shortcomings of current predictive models & highlights research areas

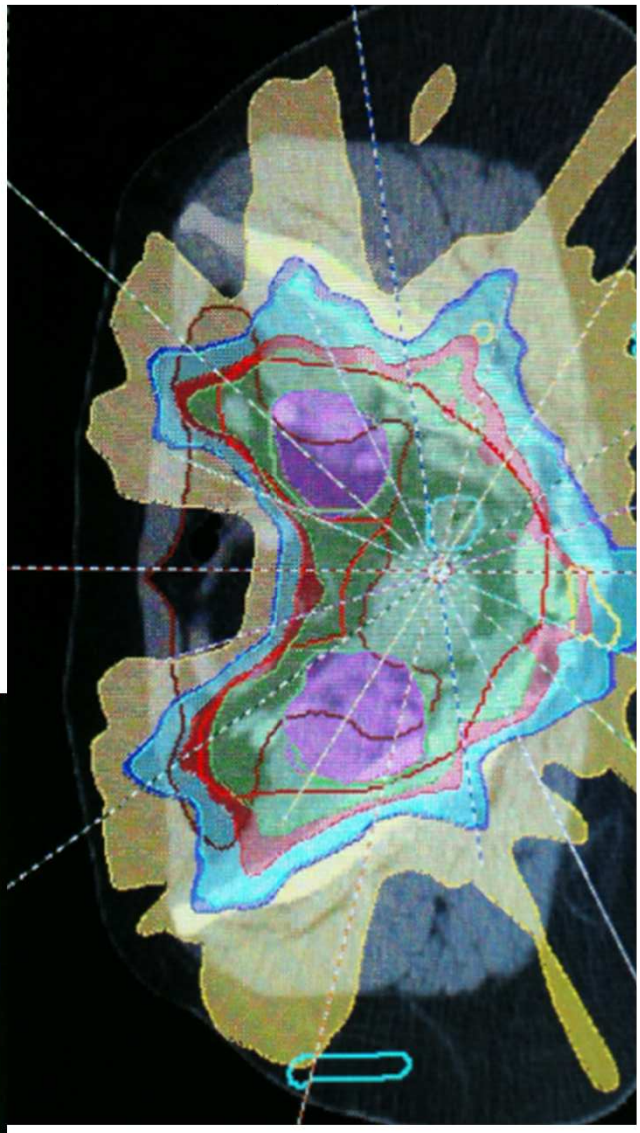
Aims of QUANTEC

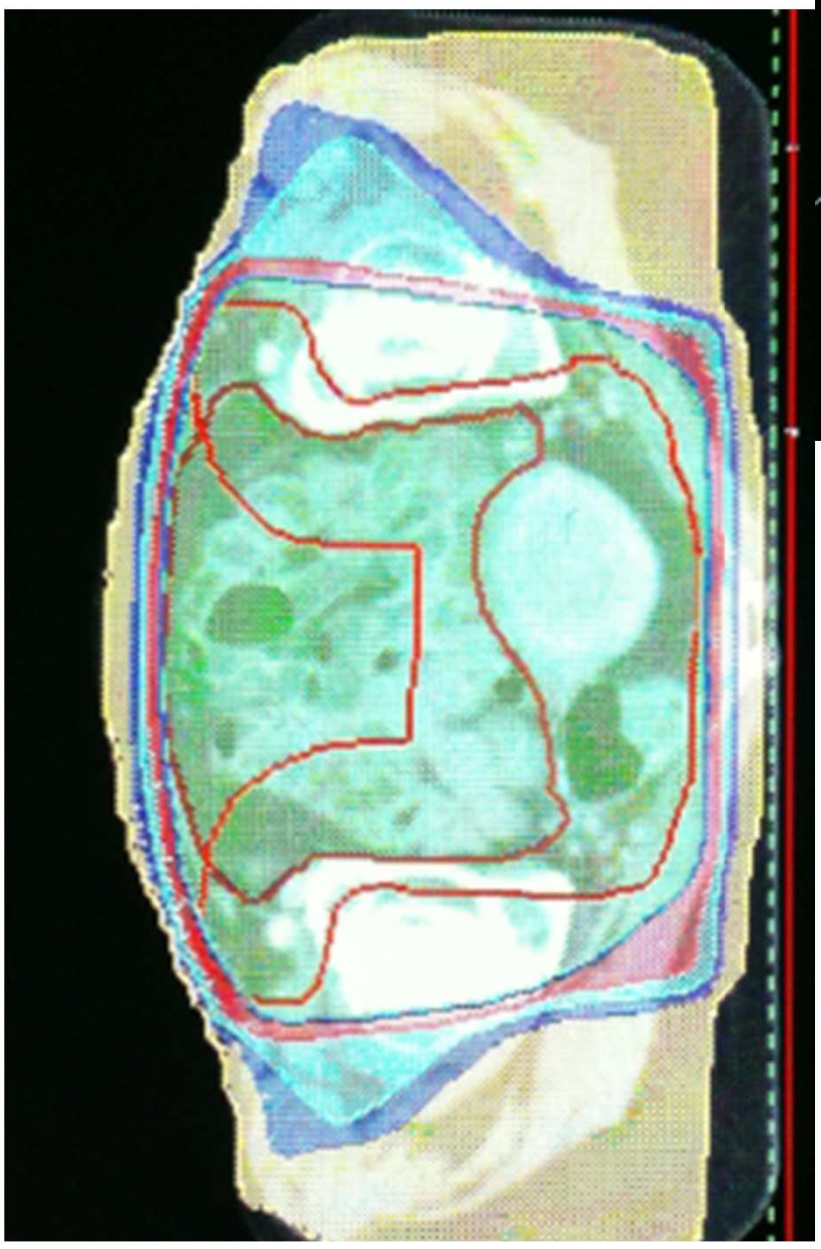
- critical overview of the current state of knowledge on quantitative dose–response and dose–volume relationships
- practical guidance
- future research avenues

- One of the goals of QUANTEC is to summarize the available 3D dose–volume/outcome data.

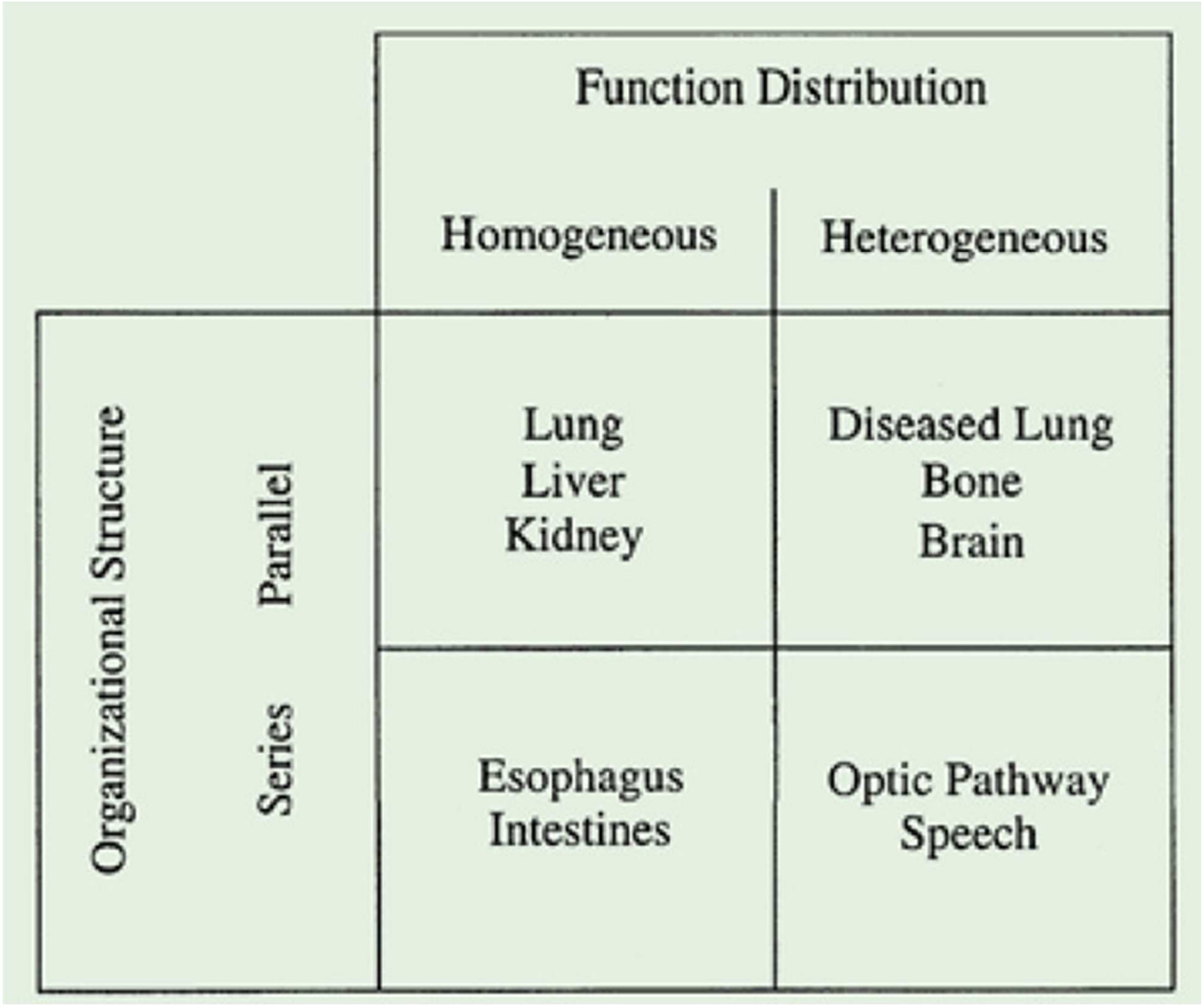
Why QUANTEC ?

- Transition from 2D – 3D – IMRT – SRS-SRT – Protons
- Earlier whole / partial organ tolerances
- Currently tissue volumes exposed is known by imaging
- Currently CTRT is standard in locally advanced stage.
- Cancer survivors are increasing





- Toxicity often underreported / unrecorded
- NTCP data are mostly retrospective from charts
- Schulthesiss & Withers-Serial / parallel
- EMAMI -1062 citations – 1/3 2/3 whole organ
- Kutchner – DVH
- Layman-Kutchner-Burman DVH reduction scheme – it is mathematical


Function Distribution
Homogeneous
Heterogeneous
Organizational Structure
Parallel
Series
Lung
Liver
Kidney
Diseased Lung
Bone
Brain
Esophagus
Intestines
Optic Pathway
Speech

Dose volume outcome may not be applicable in

- Hypo fractionation
- Rotational delivery

Dose volume relationship

1990

- Parallel Opposed fields
- RT as single modality
- Conventional # / hyperfrac trials
- Authors search for “Safe” dose – volume constraint
- Layman model widely used
- Analysis-mainly on group of patients
- Lack of consistency – Organ contouring

2009

- Conformal/IMRT
- CTRT widely used
- Conventional # / hypofractionation trials
- Risk – benefit tradeoff in individual patient
- Layman model still widely used – but new modeling being persued
- Analysis-individual patient level
- Lack of consistency – Organ contouring

1990

- Models applied with parameters from literature
- Lack of quantitative, evidence based dose-volume constraints
- Only partial organ tolerance from Emami et al

2009

- Adjustments for significant patient or treatment characteristics
- Toxicity is underscored and underreported inspite of CTC-AE definitions
- Lack of quantitative evidence based dose-volume constraints
- QUANTEC – has systematically reviewed literature

Problems of DVH

- DVH model assumes that the functioning of organ is uniform
- critical, radiosensitive structures are not homogeneously distributed within organs
- However lung base is more sensitive than apex

Grading of toxicities

- Grade 1—mild or asymptomatic
- Grade 2—moderate, not interfering with activities of daily living (ADLs)
- Grade 3—severe interference with ADLs, possible intervention
- Grade 4—life-threatening or disabling, intervention indicated; and
- Grade 5—Death

Scoring Late toxicities

- RTOG
- EORTC
- NCI consensus – SOMA (Subjective, objective, management criteria) with lab & imaging
- NCI – CTC AE 3
- LENT

Table 1 RTOG/EORTC Late Radiation Morbidity Scoring Schema[3]

Organ Tissue	Grade 1	Grade 2	Grade 3	Grade 4
Brain	Mild headache Slight lethargy	Moderate headache Great lethargy	Severe headaches Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis Coma
Spinal cord	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadriplegia
Salivary glands	Slight dryness of mouth Good response on stimulation	Moderate dryness of mouth Poor response on stimulation	Complete dryness of mouth No response on stimulation	Fibrosis
Lung	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency/ Continuous O_2/Assisted ventilation
Heart	Asymptomatic or mild symptoms Transient T wave inversion & ST changes Sinus tachycardia >110 (at rest)	Moderate angina on effort Mild pericarditis Normal heart size Persistent abnormal T wave and ST changes Low QRS	Severe angina Pericardial effusion Constrictive pericarditis Moderate heart failure Cardiac enlargement EKG abnormalities	Tamponade/severe heart failure/severe constrictive pericarditis
Esophagus	Mild fibrosis Slight difficulty in swallowing solids No pain on swallowing	Unable to take solid food normally Swallowing semi-solid food Dilatation may be indicated	Severe fibrosis Able to swallow only liquids May have pain on swallowing Dilation required	Necrosis/perforation Fistula

Small and large intestine	Mild diarrhea Mild cramping Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement >5 times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/perforation Fistula
Liver	Mild lassitude Nausea, dyspepsia Slightly abnormal liver function	Moderate symptoms Some abnormal liver function tests Serum albumin normal	Disabling hepatitic insufficiency Liver function tests grossly abnormal Low albumin Edema or ascites	Necrosis/hepatic coma or encephalopathy
Kidney	Transient albuminuria No hypertension Mild impairment of renal function Urea 25-35 mg% Creatinine 1.5-2.0 mg% Creatinine clearance >75%	Persistent moderate albuminuria (2+) Mild hypertension No related anemia Moderate impairment of renal function Urea>36-60 mg% Creatinine clearance (50-74%)	Severe albuminuria Severe hypertension Persistent anemia (<10g%) Severe renal failure Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance <50%	Malignant hypertension Uremic coma/urea >100%

LENT-SOMA form

1 0 9

AFFIX RTOG LABEL HERE

Trial number 3

Institution number..... 7

Patient's family name (first 5 letters) 10

Today's date (Day/Month/Year) 15

BRAIN	Grade 1	Grade 2	Grade 3	Grade 4	Score: 0 if normal else grade n°
SUBJECTIVE SIGNS Headache	Occasional, minimal	Intermittent, tolerable	Persistent, intense	Refractory and excruciating	
Somnolence	Occasional, able to work or perform normal activity	Intermittent, interferes with work or normal activity	Persistent, needs some assistance for self care	Refractory, prevents daily activity, coma	
Intellectual deficit	Minor loss of ability to reason and judge	Moderate loss of ability to reason and judge	Major loss of ability to reason and judge	Complete loss of reasoning and judgement	
Functional competence	Perform complex tasks with minor inconvenience	Cannot perform complex tasks	Cannot perform simple tasks	Incapable of selfcare/ supervision, coma	

Modulators of radiation effect

- Effect – function of tissue renewal property
- Depends on
  - Dose
  - Fraction size
  - Duration
  - Interval between #
  - Dose rate
  - Specific organs (organizational structure – serial/parellel & compensatory capacities – volume)
  - volume

Dose factors

- **Strandquist plot** – effect depends on dose
- **Ellis** – Different tissues-different slope
  - Tumor has different slope compared to normal
  - Effect depends on fraction size & time for acute

    But only on fraction size for late effects
- **1980 – LQ model** – Acute responding tissue & tumor- high ∝/ß & Late responding – low∝/ß. Simple mathematical formula to compare various dose & fractionation schemes. Clinically acceptable & safe
- All these formula are approximation (based on single cell survival curves) – hence clinical judgment imp

TD 5/5 & TD 50/5

- Assumes uniform irradiation
- Whole organ
- Conventional 2Gy/# - 5#/wk
- Assumes normal organ function at base line
- No surgical manipulation / concurrent drugs
- Age range excludes children & elderly

Parameters of Therapy: Tolerance Doses (TD5/5–TD50/5)			
Single Dose (Gy)x		Fractionated Dose (Gy)	
Ovary	2 - 6	Testes	1 - 2
Bone marrow	2 - 10	Ovary	6 - 10
Testes	2 - 10	Eye (lens)	6 - 12
Eye (lens)	2 - 10	Kidney	20 - 30
Mucosa	5 - 20	Thyroid	20 - 40
Gastrointestinal	5 - 10	Lung	23 - 28
Lung	7 - 10	Skin	30 - 40
Colorectal	10 - 20	Liver	35 - 40
Kidney	10 - 20	Bone marrow	40 - 50
Vasculoconnective tissue	10 - 20	Heart	43 - 50
Liver	15 - 20	Gastrointestinal	50 - 55
Skin	15 - 20	Vasculoconnective tissue	50 - 60
Peripheral nerve	15 - 20	Spinal cord	50 - 60
Spinal cord	15 - 20	Brain	55 - 70
Brain	15 - 25	Peripheral nerve	65 - 77
Heart	18 - 20	Mucosa	65 - 77
Bone and cartilage	>30	Bone and cartilage	>70
Muscle	>70	Muscle	>70

Volume factors

	$TD_{5/5}$ Volume			$TD_{50/5}$ Volume			Selected End Point
Organ	1/3	2/3	3/3	1/3	2/3	3/3	
Kidney	50	30	23	-	40	28	Clinical nephritis
Brain	60	50	45	75	65	60	Necrosis, infarction
Brainstem	60	53	50	-	-	65	Necrosis, infarction
Spinal cord	5 cm: 50	10 cm: 50	20 cm: 47	5 cm: 70	10 cm: 70	20 cm: -	Myelitis, necrosis
Lung	45	30	17.5	65	40	24.5	Pneumonitis
Heart	60	45	40	70	55	50	Pericarditis
Esophagus	60	58	55	72	70	68	Clinical stricture/perforation
Stomach	60	55	50	70	67	65	Ulceration, perforation
Small intestine	50	-	40	60	-	55	Obstruction, perforation/fistula
Colon	55	-	45	65	-	55	Obstruction, perforation/ulceration/fistula
Rectum	Volume: 100 cm^3		60	Volume: 100 cm^3		80	Severe proctitis/necrosis/fistula
Liver	50	35	30	55	45	40	Liver failure

The LENT Paradigm

1. Clinical detection
2. Time course of events
3. Dose /time/volume
4. Chemical / biologic modifiers
5. Radiologic imaging
6. Lab tests
7. Differential diagnosis
8. Pathologic diagnosis
9. Management
10. Follow up

Individual sites

- Data are best estimates of available data
- High level evidence lacking
- constraints should be used with appropriate caution and interpreted within the clinical context

Brain

Subjective

- Headache,
- somnolence,
- intellectual deficits,
- functional
- neurologic losses
- Memory alterations

Objective

- neurologic deficit,
- loss of cognitive function,
- mood and personality changes
- focal to generalized seizures

- Late
  - Radiation necrosis & cognitive deterioration
  - To document –new symptom & imaging sufficient
  - Biopsy rarely done
- Surgery, Chemo, steroids, antiepileptics, opioids also impairs neurologic & cognitive fx, hence interpretation difficult
- Brain necrosis & gliosis – 6 to 12 months

Dose/ Time / Volume

- 50Gy well tolerated
- Children threshold 30-35Gy
- TD5/5 – 50Gy; TD50: 70 – 80
- Conformal RT – 50 – 110gy with ~ risk 5% to 20%
- Partial brain 50 – 60gy – minimal effect on memory & cognition
- Children – more sensitive
- Mtx, ß-interferon ↑ necrosis
- Valproate – low risk for necrosis

Brain- Radiation necrosis – Conventional RT α /ß = 3

- 5 to 10 % - 120 Gy to 150Gy BED (72 gy & 90 GY in 2 Gy/#)
- For twice daily #, complications at >80 Gy BED
- No evidence to say children are at more risk

Brain- Radiation necrosis - SRS

- Depends on – Dose, volume & region
- IN SRS
  - 31-40mm - maximum – 15 Gy
  - 21 – 30mm – max – 18Gy
  - <20mm – max- 24 Gy
- However >12 Gy single # correlates with incidence of necrosis

Neurocognitive functions in children

- Extensively studied in childhood ALL
- ALL 24 Gy to whole brain
  - 13 – point IQ ↓ at 5yrs after RT
  - Poorer academic achievement & self image
  - Greater psycologic distress
- 14 to 18 Gy – no / less toxicites
- Medulloblastoma – WBRT
  - IQ better by 10-15 points in 23.4Gy vs 36 Gy
- Supratentorial – RT induced cognitive decline

Neurocognitive functions in Adults

- Evidence is weak
- Improved cognitive effects after RT - probably due to decrease in tumor size
- ≤ 2 ys after WBRT – no difference in cogn.
- ≥ 5 ys after WBRT – condition improved
- >2Gy/# cognitive decline
- Limited evidence – 2 Gy / # causing cognitive decline

Factors affecting risk

- Dose, # size, volume
- Necrosis -Brain stem & callosum – more prone
- Chemo, short overall treatment time, old age, DM
- Young age – more neurocognitive Decline
- Female, NF-1 mutation, extent of surgery, hydrocephalus, MTX, location & volume

Special Situations

- Re- irradiation
  - 3-55 months – cumulative BED <100Gy- no necrosis
- Primary CNS lymphoma in > 60 yrs
  - > 40 gy WBRT - ↑ in cognitive decline
- Hippocampus – memory formation – limit the dose

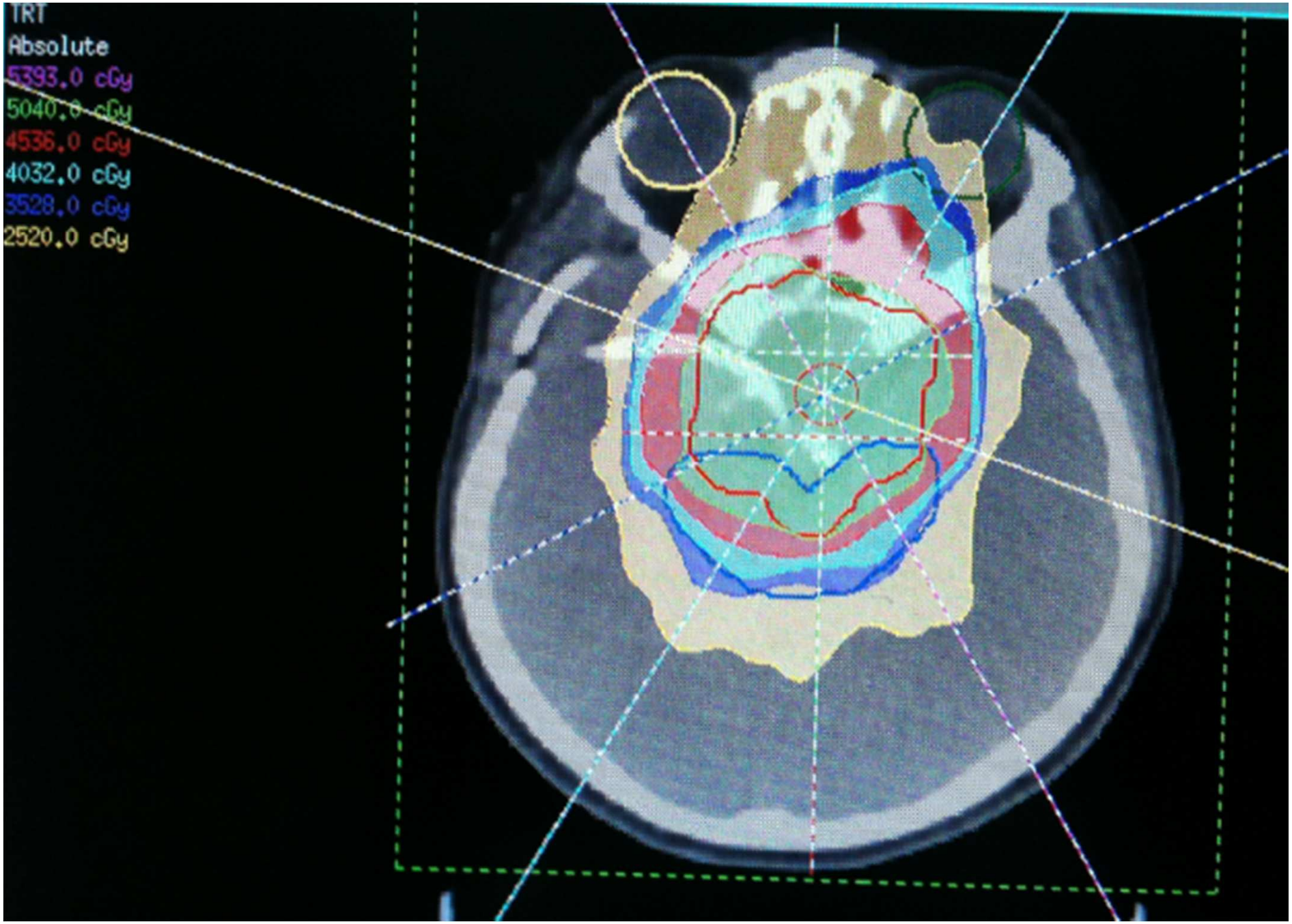
Recommended dose–volume limits

- 5 to 10 % necrosis risk – 120 gy BED – 2Gy/#
- Brain is sensitive to > 2Gy/# and twice daily #s
- 5% complication at 5 yrs for partial brain- 72gy – though Emami et al says 60gy
- Radiosurgery
  - Risk ↑ if >12 Gy to 5-10 cm^3
  - Volume receiving 12 Gy and region important
  - Brain stem & corpus callosum – more stringent limits

Brain Stem – α /ß = 2.1

- RT induced brain stem injury – manifests months – years

- Difficult to differentiate between disease progression / side effects


TRT
Absolute
5393.0 cGy
5040.0 cGy
4536.0 cGy
4032.0 cGy
3528.0 cGy
2520.0 cGy

- Includes midbrain, pons, medulla
- Midbrain inferior to 3rd ventricle and optic tracts
- Inferior extent upto foramen magnum
- Near cerebral and cerebellar peduncles borders are indistinct
- Coronal and sagittal planes - useful

Predictors of brain stem toxicity

- Dmax > 64 Gy
- V50 >5.9ml
- V55 > 2.7 ml
- V60) 0.9ml
- Two or more skull-base surgeries
- Diabetes

Brain stem toxicity data in SRS/SRT

- Before 1994 – 29% neuropathies
- After 1994 – 5% and 2% facial and trigeminal neuropathies
- Risk if Dmax > 12.5Gy & prior open resection, tumor dia > 8mm, volume > 1.7ml, length of cr. Nerve irradiated >16mm, planning without MRI

Brain stem – pediatric patients

- No toxicity in brain stem glioma patients – 54 – 60 Gy (2Gy/#)
- 75.26 at 1.26Gy twice daily, 78GY in 1Gy twice daily
- Pediatric tolerance same as adult

Brain stem- factors affecting risk

- Targets larger and close to brain stem
- Lack of MRI planning
- Number of surgeries
- Hydrocephalus
- Diabetes
- Hypertension

Recommended dose–volume limits

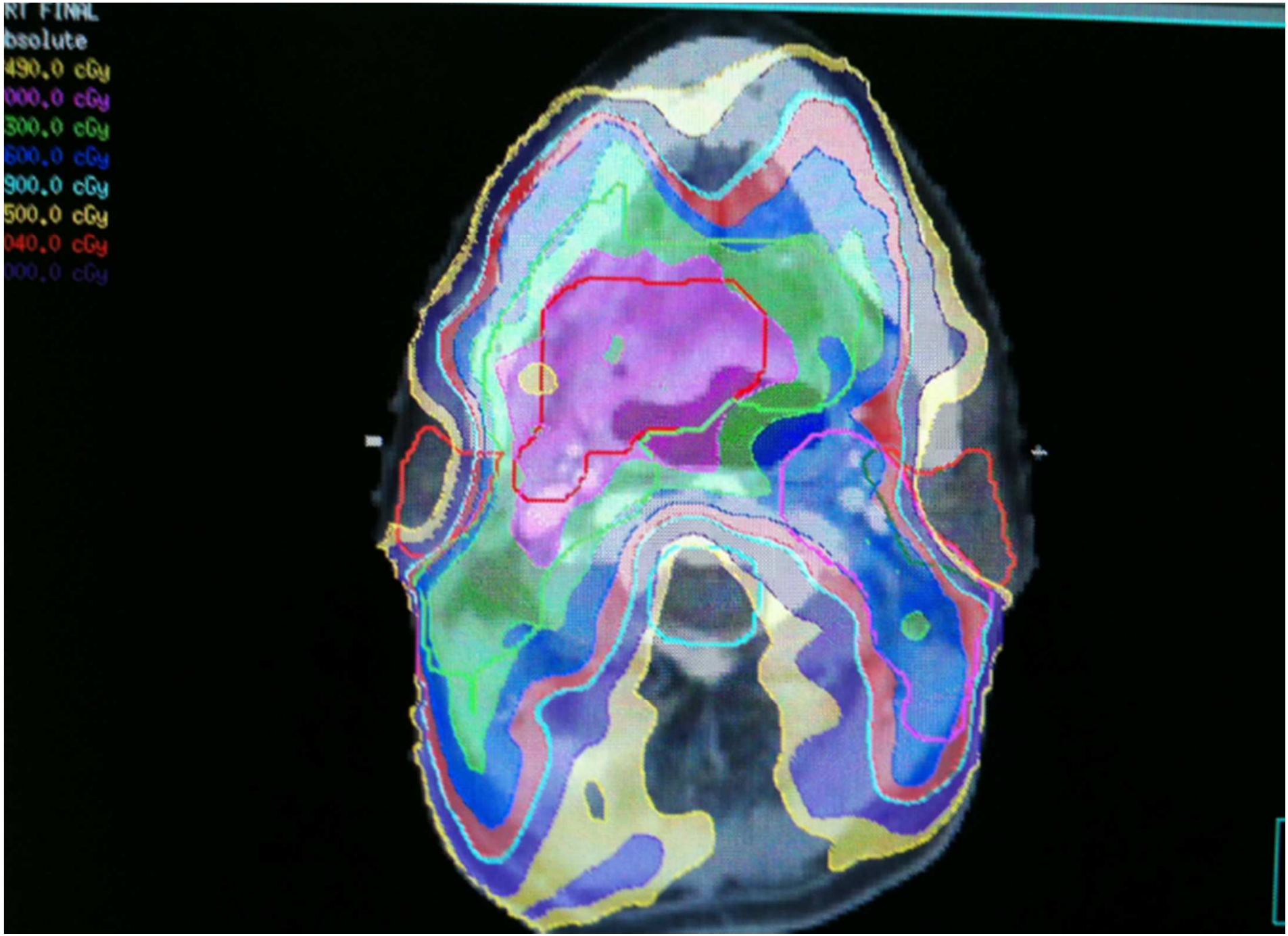
- Entire brain stem – 54 Gy
- 1-10cc – 59 Gy Max
- Risk markedly increases beyond 64Gy
- For SRS – Max 12.5Gy (<5% risk)
- 15 to 20 Gy used in poor prognosis patient

Toxicity scoring

- CTC AE is used
- Baseline history, PE, Neurologic examination, cranial nerve, motor, sensory & cerebellar function examination
- Heart rate & BP are critical in patients earlier operated for brainstem lesions
- Above examinations repeated at regular intervals
- If suspicion, MRI shows structural alterations

Spinal cord

- Paraesthesia (tingling sensation, shooting pain, and Lhermitte's syndrome) ,
- numbness,
- motor weakness,
- loss of sphincter control
- Brown-Séquard syndrome
- total paraparesis and paraplegia


RT FINAL
bsolute
490.0 cGy
000.0 cGy
300.0 cGy
600.0 cGy
900.0 cGy
500.0 cGy
040.0 cGy
000.0 cGy

Defining volume

- Entire circumference of cord, vertebral body and spinal nerve roots
- In radiosurgery Spinal cord+ 3 mm + thecal sac and contents
- Few slices superiorly and inferiorly

Time course of events

- Spinal cord- Lhermitte's – 2 to 4 months

- Paresis, numbness, altered sphincter control – 6 to 12 months

Dose/Time/Volume

- 45 Gy well tolerated (risk <0.2%)
- True TD 5/5 – 57 to 61 Gy
- TD 50 – 68 to 73Gy
- Hyperfractionation ↓ cord tolerance by 10 to 15%
- IT MTX/ IV Mtx, cisp, cytarabine ↑ risk

Dose-Volume data

- Cervical cord more sensitive
- Pathology – vascular / endothelial damage, glial cell injury or both
- Full thickness cord more damage,
- lateral part (white matter more sensitive than central point – grey matter-possibly because of vascular density)
- Rhesus monkey experiments suggest – 76 % recovery at 1 yr, 85% at 2 and 101% at 3 yrs

Re-irradiation of cord

- Dose, volume and time interval important
- No myelopathy for cumulative dose of ≤ 60 Gy

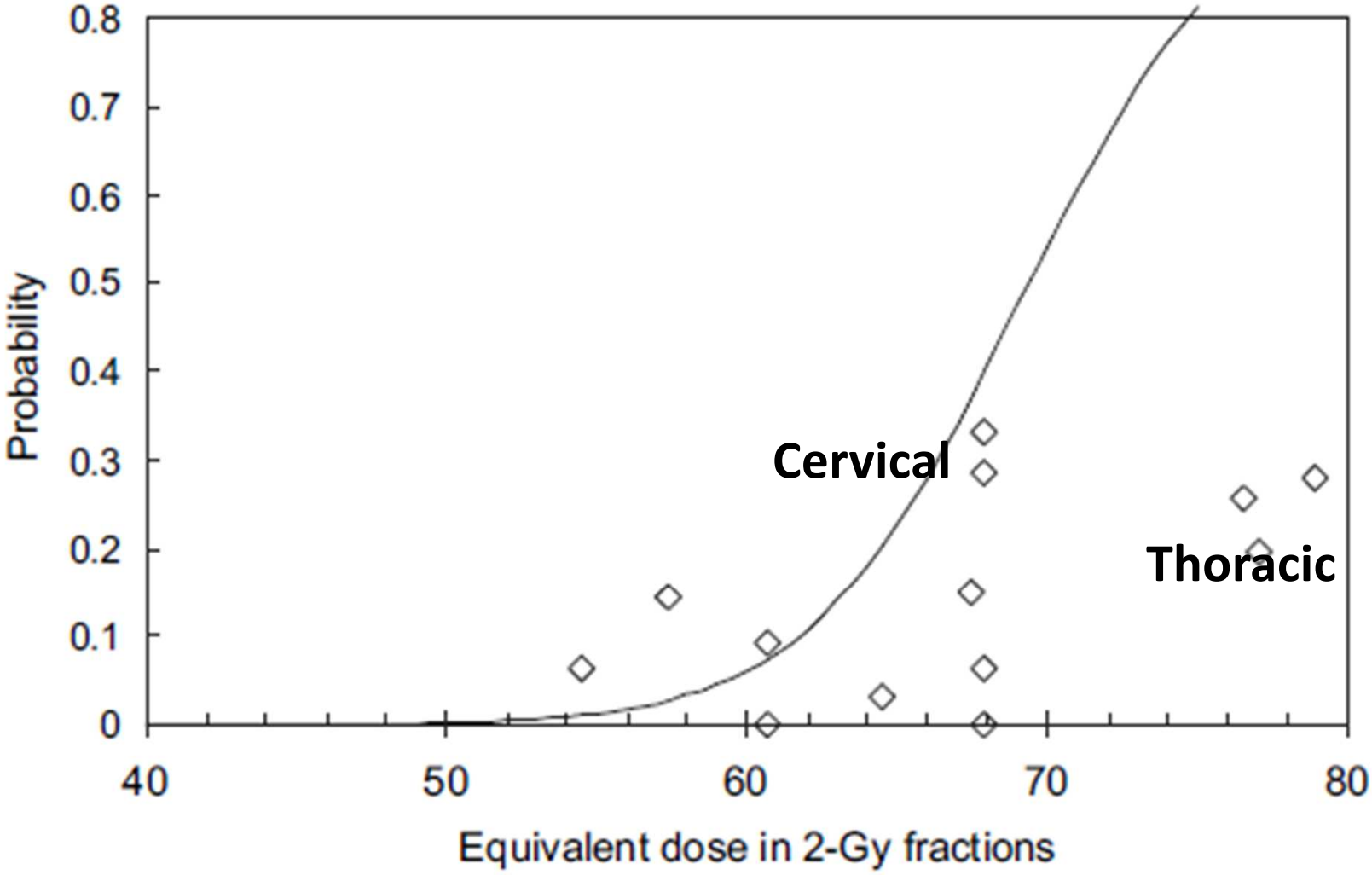
Factors affecting risk

- Pediatric age – more risk
- Intrathecal ARA-C, MTX, intraperitonal fludarabine immideately before radiation
- Any concurrent chemo - caution

Recommended dose–volume limits

- 50 gy – 0.2 %
- 60Gy – 6 %
- 69gy – 50% incidence of myelopathy
- SRS – 13 Gy max
- SRT – 20Gy in 3 # - <1% risk

Difference between Cervical & thoracic tolerance



Optic Nerves & Chiasma

- Radiation induced optic neuropathy – uncommon but disabling
- Painless rapid visual loss

- Pathology – Vascular injury
- Interval between RT and symptom - ≤ 3 yrs
- Optic nerve – monocular vision loss
- Hemianopia/ Quadrant loss

- Chiasma – bilateral vision loss
- Pitutary adenoma – inferior central chiasma – upper outer quadrant visual loss
- Optic tract injury- small vision loss

Defining volume

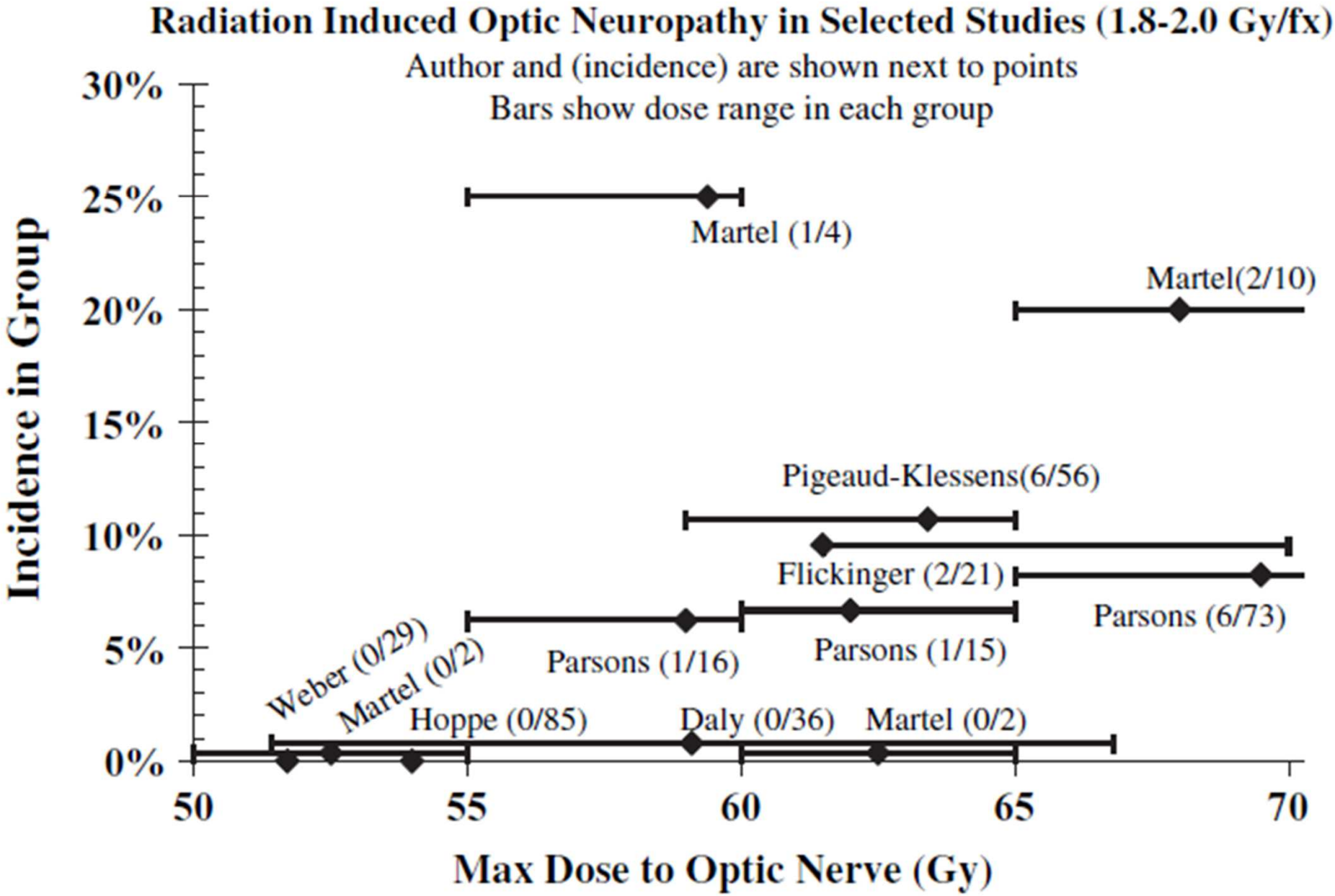
- Posterior aspect of the center of globe
- Bracketed by rectus muscle
- Angle up through optic canals – medial to anterior clenoid process
- Thin-2-5mm thick
- Medial fibers – cross to opposite side in optic chiasma, lateral fibers cross opp. Side
- Superior to sella turcica
- OC is bracketed by carotid arteries laterally

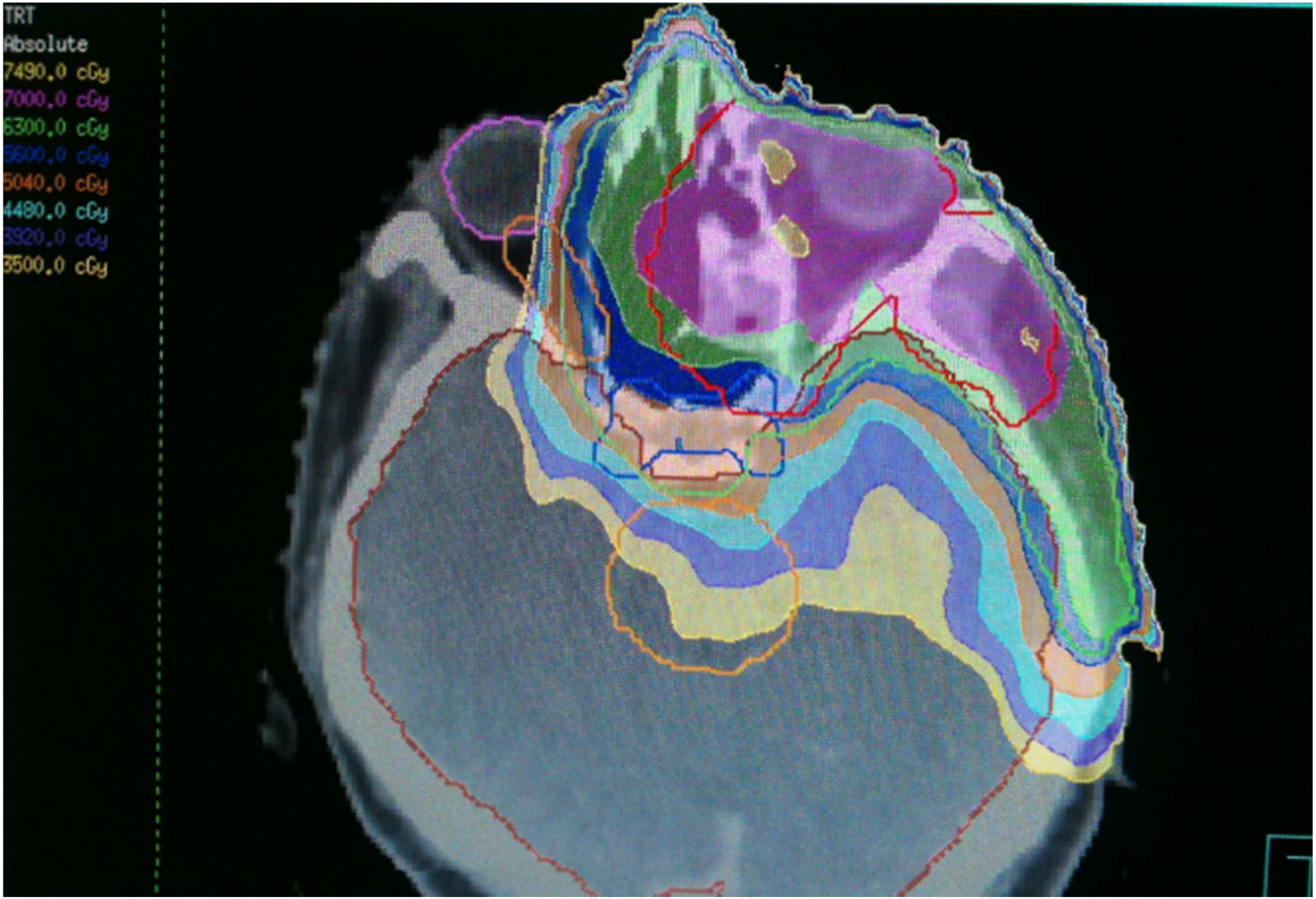
Tolerance at conventional fractionation

- Emami et al- whole organ
  - 5 % complications at 50 Gy
  - 50 % complications at 65 Gy
- Steep increase in complications > 60 Gy
- Tolerance low in pituitary tumors (constraints – 45 Gy)
- <1.9Gy/# ON tolerance is better

Tolerance at single fraction

- Constraint < 8 Gy
- 0% risk at doses <10 Gy, 27% at 10 to <15 Gy
- Elderly at more risk >60 yrs (26% for 50 yrs vs 56% for 70 yrs at >60 Gy)
- Chemo, DM, HTN – may be risk factor
- Reirradiation – data are lacking
- Care while using hypofractionation
- ? Bevacizumab may help in RION


Radiation Induced Optic Neuropathy in Selected Studies (1.8-2.0 Gy/fx)
Author and (incidence) are shown next to points
Bars show dose range in each group
Incidence in Group
30%
25%
20%
15%
10%
5%
0%
50
55
60
65
70
Max Dose to Optic Nerve (Gy)
Martel (1/4)
Martel(2/10)
Pigeaud-Klessens(6/56)
Flickinger (2/21)
Parsons (6/73)
Parsons (1/16)
Parsons (1/15)
Weber (0/29)
Martel (0/2)
Hoppe (0/85)
Daly (0/36)
Martel (0/2)

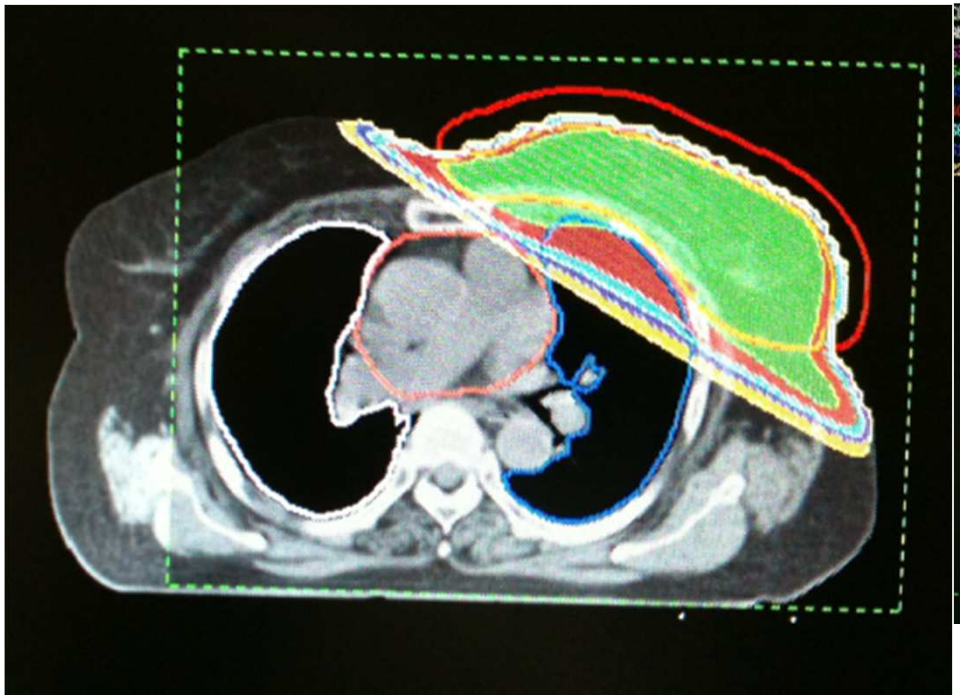

TRT
Absolute
7490.0 cGy
7000.0 cGy
6300.0 cGy
5600.0 cGy
5040.0 cGy
4480.0 cGy
3920.0 cGy
3500.0 cGy

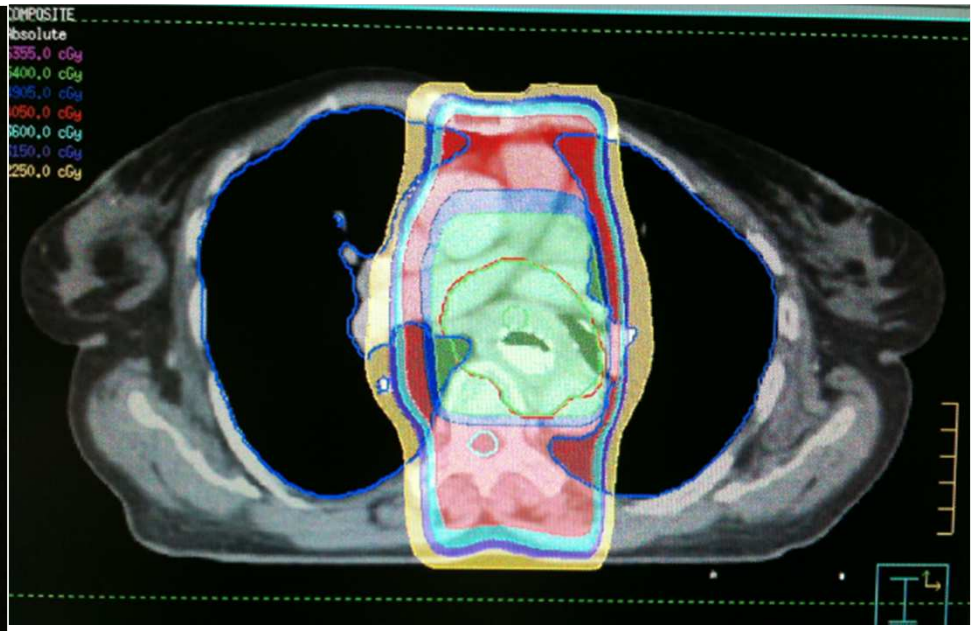
Eye

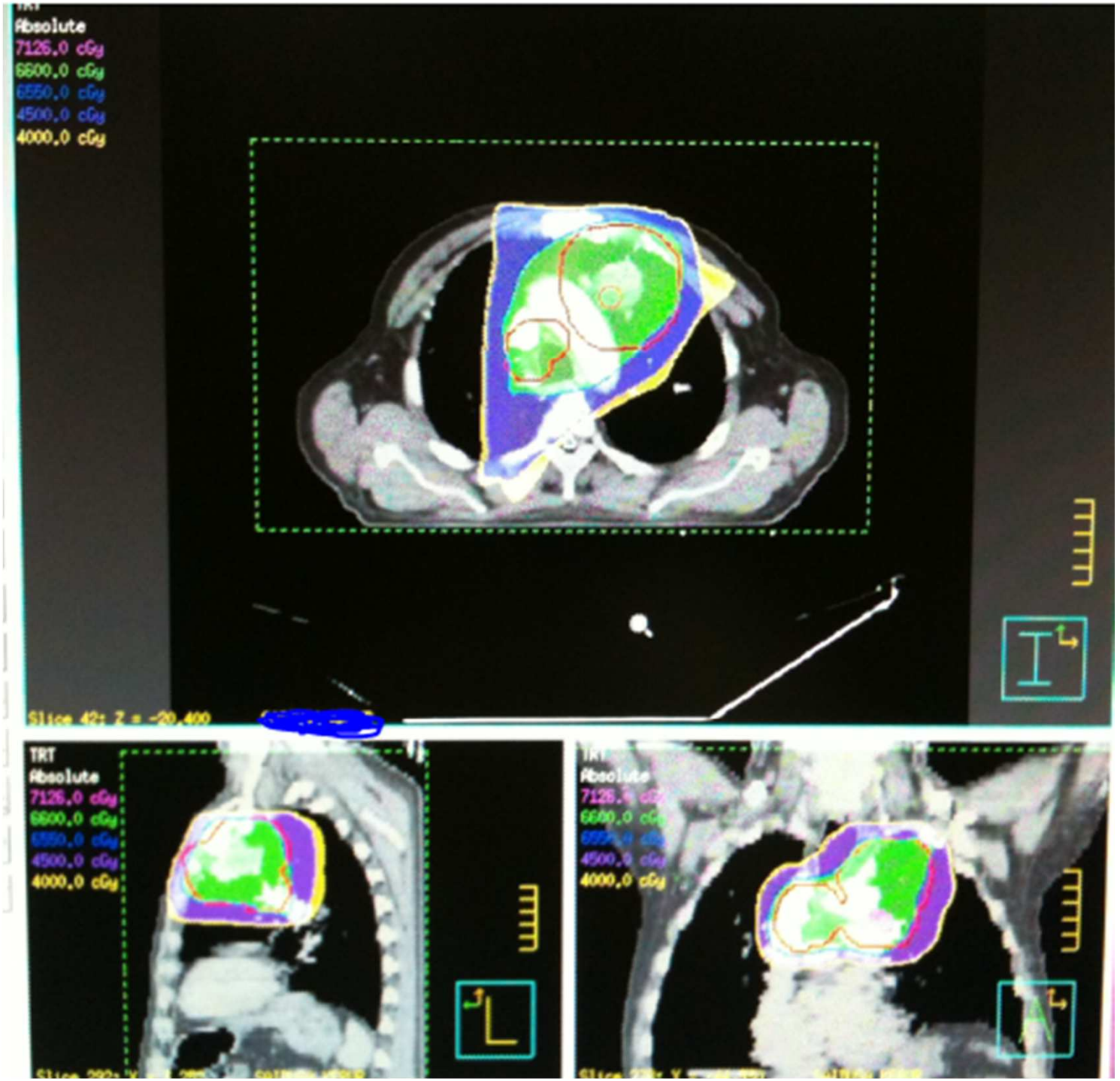
- Retina, lens, conjunctiva, lacrimal apparatus, optic nerve, & lid can get affected
- Survivors of rhabdomyosarcoma - dry eye/ cataract, orbital hypoplasia, ptosis, retinopathy, keratoconjunctivitis, optic neuropathy, lid epithilioma, impairment of vision – 30 to 65 Gy
- Corticosteroids and GVHD ↑risk of catract
- High dose/# increases risk of toxicity

Lung

- Radiation pneumonitis occurs in (within 10 mths)
  - 5 – 50% of lung cancer
  - 5 – 10% of mediastinal lymphatics RT
  - 1 – 5 % of Breast cancer patients
- Large no. of pts experience Subclinical RT-induced injury
  - ↓ in PFT
  - Radiologic changes

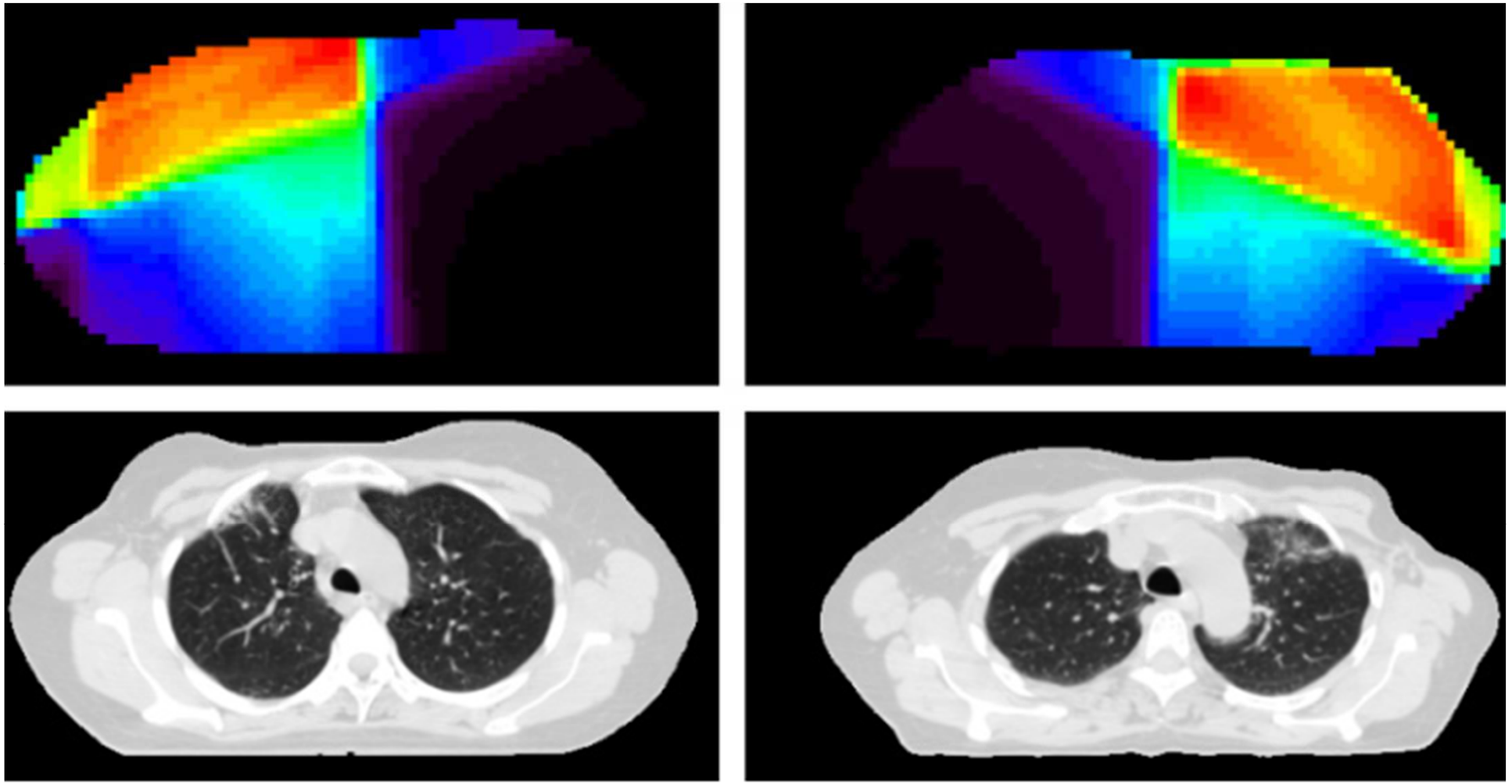


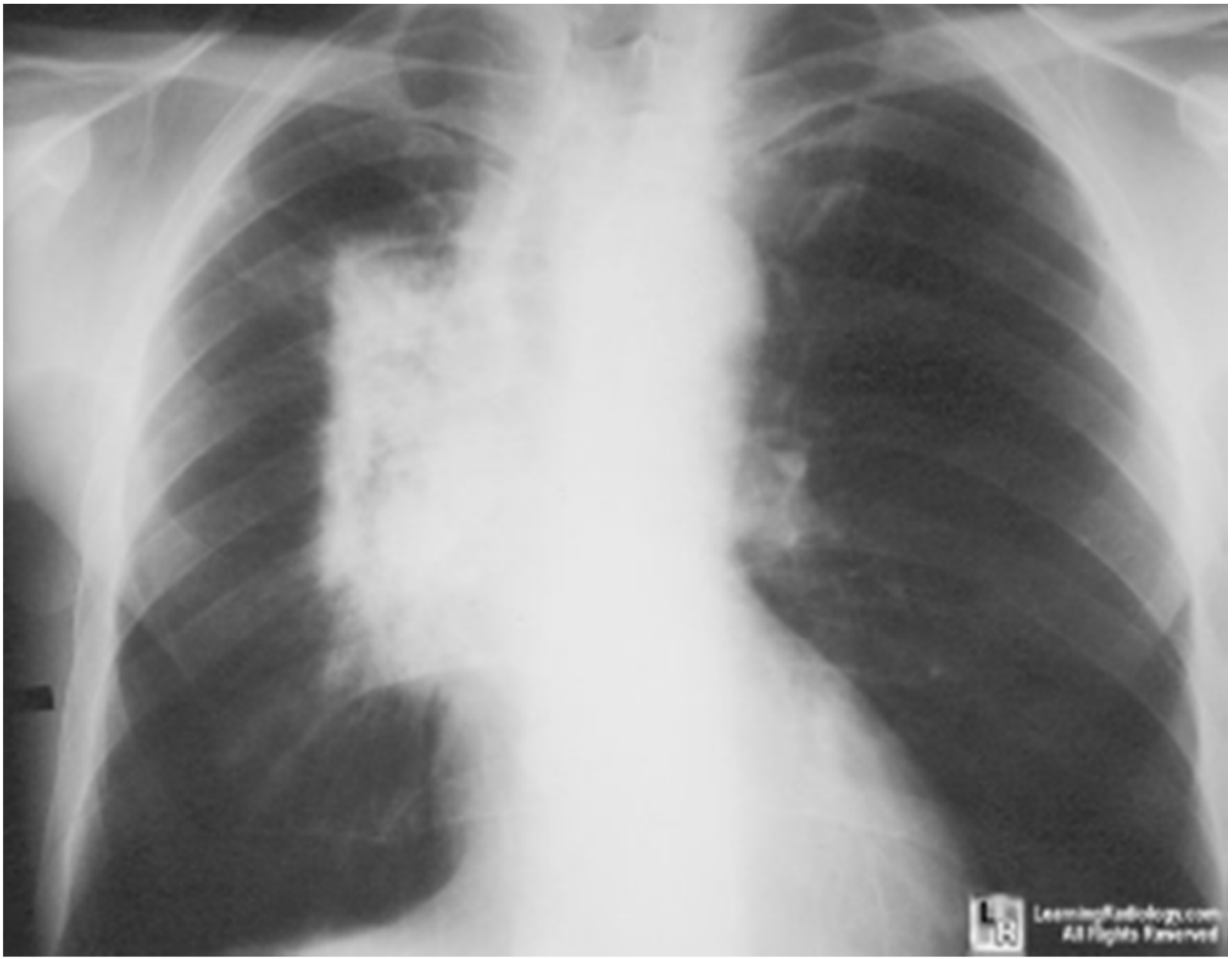

COMPOSITE
Absolute
355.0 cGy
400.0 cGy
805.0 cGy
050.0 cGy
600.0 cGy
150.0 cGy
250.0 cGy


Absolute
7126,0 cGy
6600,0 cGy
6550,0 cGy
4500,0 cGy
4000,0 cGy
Slice 42: Z = -20,400
TRT
Absolute
7126,0 cGy
6600,0 cGy
6550,0 cGy
4500,0 cGy
4000,0 cGy
TRT
Absolute
7126,0 cGy
6600,0 cGy
4500,0 cGy
4000,0 cGy

- Mean lung dose & Vx – both are important
- Mean – 10-20Gy; V13 >40%, V20 >25%, V30 >10%
- Actinomycin D (recall phenomenon), Doxo, Bleo, Busulphan, Cyclophos, BCNU & interferons ↑ risk
- Radiology – pneumonitic patch well defined outline
- Lab – perfusion ↓; PFT impaired
- IL-6, serum surfactant apoprotein, TGF-ß are on testing as predictive markers
- Differential diagnosis – Recurrence/ persistant disease / mets / lymphangitc carcinomatosis / infections

Increased density on CT

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- Patho – only if recurrence suspected
- Management – Steroids – Prednislone 30-60mg/day or dex – 16 to 20mg/day; symptoms clears in 24-48 hrs. Pentoxyphylline & tocopherol are tried

Dose tolerance of lung

- Single high dose - pneumonitis
  - 8.5Gy – 5%
  - 9.3Gy – 50%
  - 11 Gy – 80%
- V20 <22% -> 0% pneumonitis (Graham et al)
- V20 >40% - > 36% pneumonitis
- V13 > 40 % ipsilateral lung – 5% complications
- V13 -36% to lower lung, 42% of total lung or 62% of ipsilateral lung – 20% late complication risk
- Both Mean Lung dose & Vx is important

Dose volume threshold

- Lower lobe tumors more toxicity than upper
- Radiation pneumonitis is predicted on
  - Mean lung dose
  - High dose regions

Factors affecting risk

- Elderly at more risk to RP
- Smokers – less risk for RP
- No difference in left vs right lung
- Chemotherapy
  - Docetaxel, gemcitabine
  - No risk with Cisp/pacli/etoposide/carbop
- Higher fraction size – more risk

Heart

- Acute – Pericarditis – 20% progress to chronic
- Late – CHF, ischemia, CAD, MI – months to years
- Relative risk of cardiac events– 1.2 to 3.5 (Early breast cancer trial)
- IMN irradiation increases risk & Left side RT
- Modern RT has reduced cardiac mortality risks
- Subclinical abnormalities – upto 50%
- HL patient – RR of lethal MI 2.5%

Factors affecting risk

- Age, Female, DM, smoking, HTN, total cholesterol, high sensitive CRP, parental H/O MI in <60yrs
- Chemotherapy
  - Anthracycline

Dose volume limits

- Breast cancer – minimize to as less as possible
- V_{25Gy} <10% - <1% probability of cardiac mortality ≈ 15 yrs. after RT
- HL no chemo – whole heart tolerates 30gy
- HL patients receiving Chemo – whole heart tolerance - 15Gy
- Pericarditis – if pericardial dose > 26Gy and V30 > 46%
- Left ventricle RT - ↓ perfusion

Liver

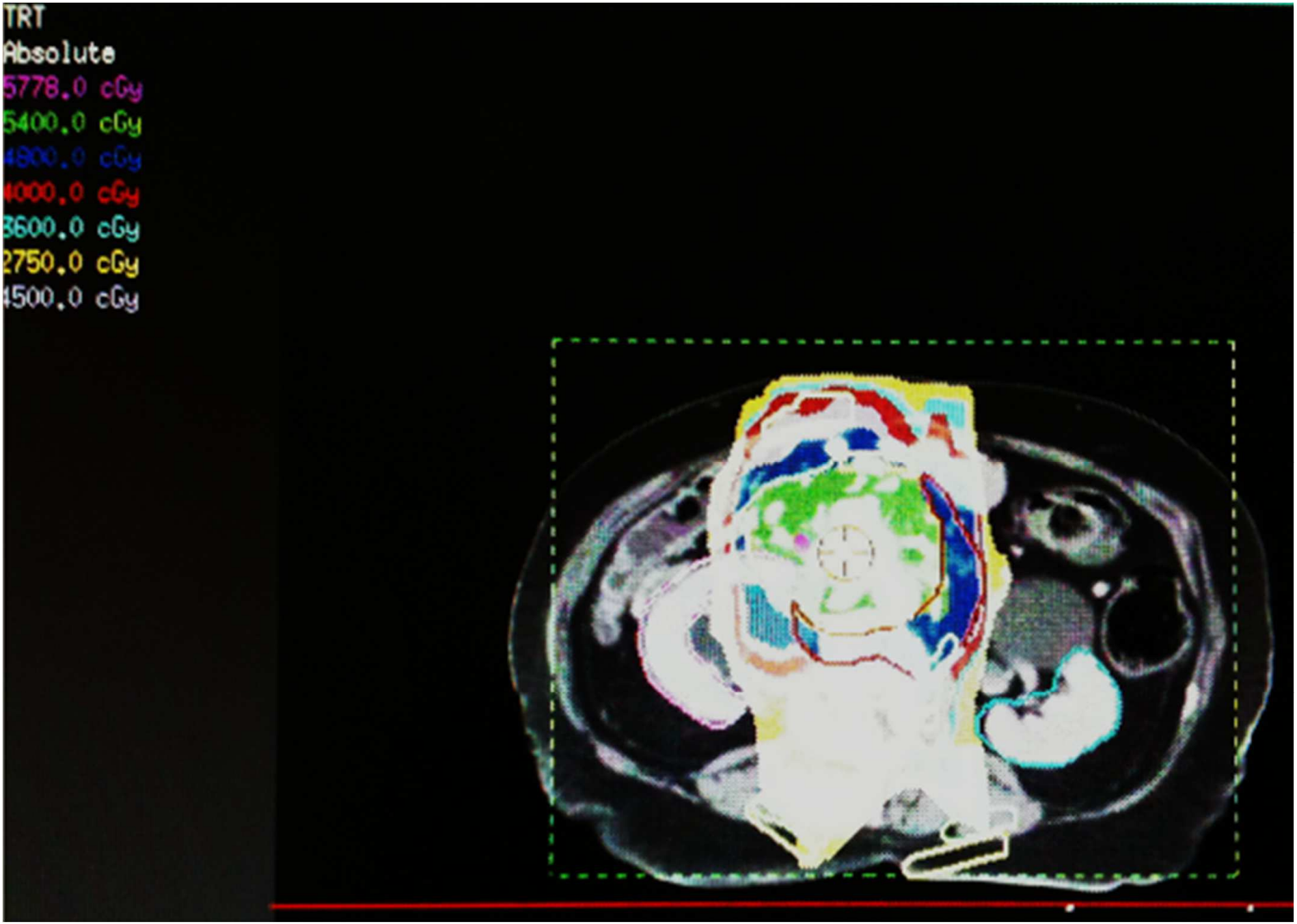
- Upper abdominal pain - Abdominal swelling – hepatomegaly & ascites – weigh gain
- Anicteric ascites 2 – 4 months after RT; CTRT (1 to 4 weeks-BMT setting)
- Whole liver – 20 to 30Gy – Upper 33 to 35 Gy
- Radiation hepatomegaly > 35 Gy; 1/3rd to ½ can receive >40Gy
- BCNU, Mtx, CHOP,, Pro-Mace-MOPP ↑ risk

- Liver movement with respiration – minimized by:
  - Abdominal compression
  - Shallow breathing
  - Breath holding
  - Deformation modeling
  - Gated treatment
  - Real time tracking

Kidney -Dose volume data

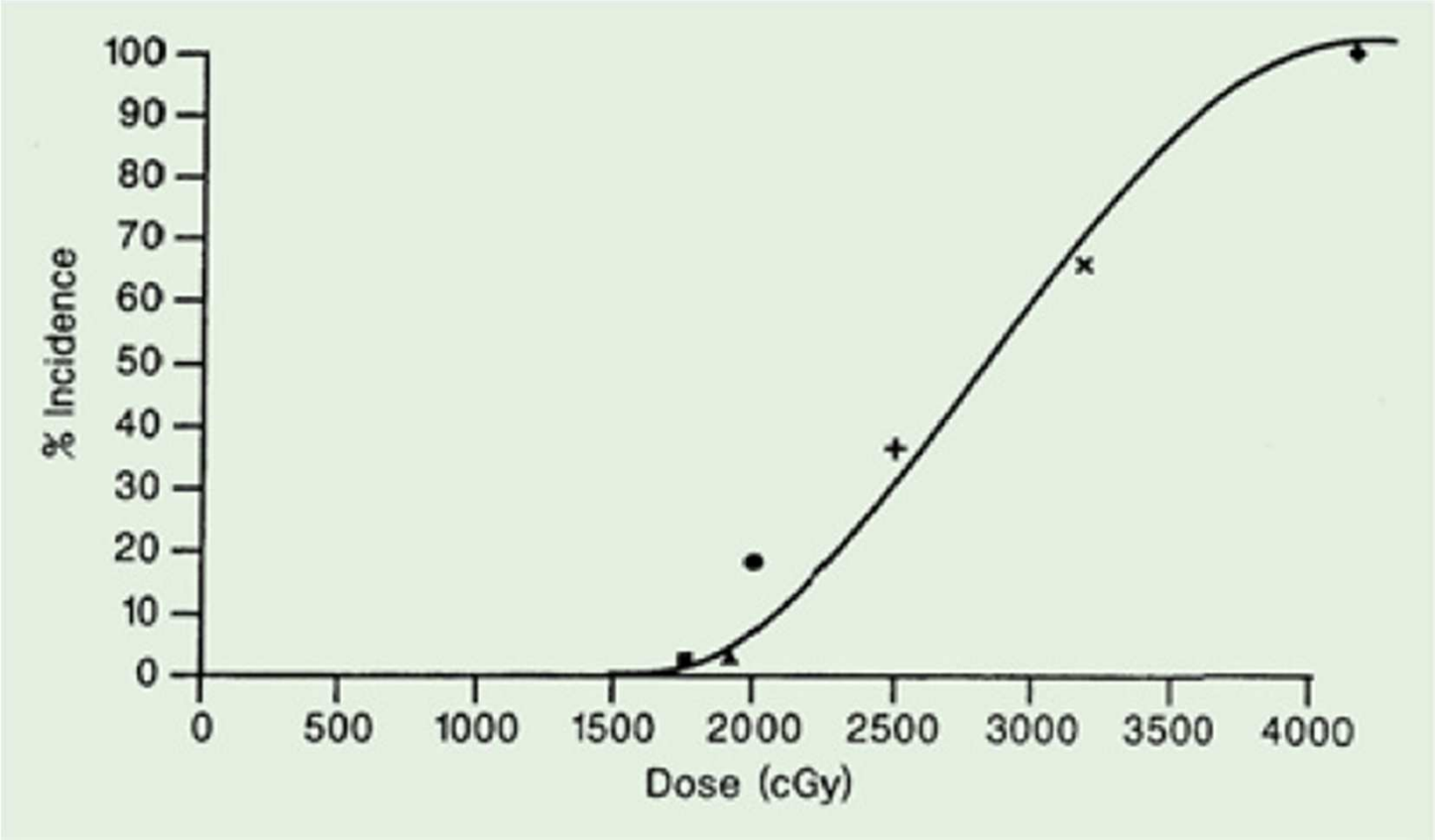
- Toxicity - depends on whole volume / partial volume t one / both kidneys
- Whole kidney (Bilateral as in TBI)
  - 5% toxicity – 9.8Gy (Median 12Gy)

- Non TBI patients
  - 5% toxicity – 18-23 Gy; 50% with 28Gy
  - ↑ creat clearance observed after 10 to 20gy to both kidneys


TRT
Absolute
5778.0 cGy
5400.0 cGy
4800.0 cGy
4000.0 cGy
3600.0 cGy
2750.0 cGy
4500.0 cGy

- Threshold 15 Gy (Children 12 to 14 Gy)
- TD 5/5 – 20Gy for both kidneys
- TBI setting – If BED >16Gy ↑ risk
- Dose volume tolerance reports lacking – clinicians are cautious
- Cisp. BCNU, Retinoic acid, Act-D - ↑ risk
- ^{99m}TC renogram – early diagnosis of damage
- BUN, Creat, CC – changes rare before 6 months
- Microscopic hematuria, proteinuria, urinary casts
- GFR – Initial ↑ by 15% to 20% after >20Gy & then ↓ by 20 to 25% of baseline

- After TBI – arteriolonephrosclerosis
- TD 5/5 – 20Gy for both kidney



Factors affecting renal damage

- Renal insuffiency
- DM
- HTN
- Liver diseases
- Heart diseases
- Smoking
- Dexa/ Ace inhibitor/ acetyl salicylic acid – prevent RT injury

Table 5. Suggested dose–volume constraints for estimated risk of <5%

Variable	Dose–volume metric	Investigator
Bilateral kidney irradiation		
TBI	Mean kidney dose <10 Gy	Cheng *et al.* (8)
Non-TBI	Mean kidney dose <18 Gy	Cassady (10)
Partial kidney irradiation		
Bilateral kidneys	Mean kidney dose <18 Gy	Nevinny-Stickel *et al.* (34)
Bilateral kidneys	$V_{28Gy} < 20\%$	Nevinny-Stickel *et al.* (34)
Bilateral kidneys	$V_{23Gy} < 30\%$	Nevinny-Stickel *et al.* (34)
Bilateral kidneys	$V_{20Gy} < 32\%$	Jansen *et al.* (15)
Bilateral kidneys	$V_{12Gy} < 55\%$	Welz *et al.* (13)*
If mean kidney dose to 1 kidney >18 Gy	V_{6Gy} (remaining kidney) <30%	

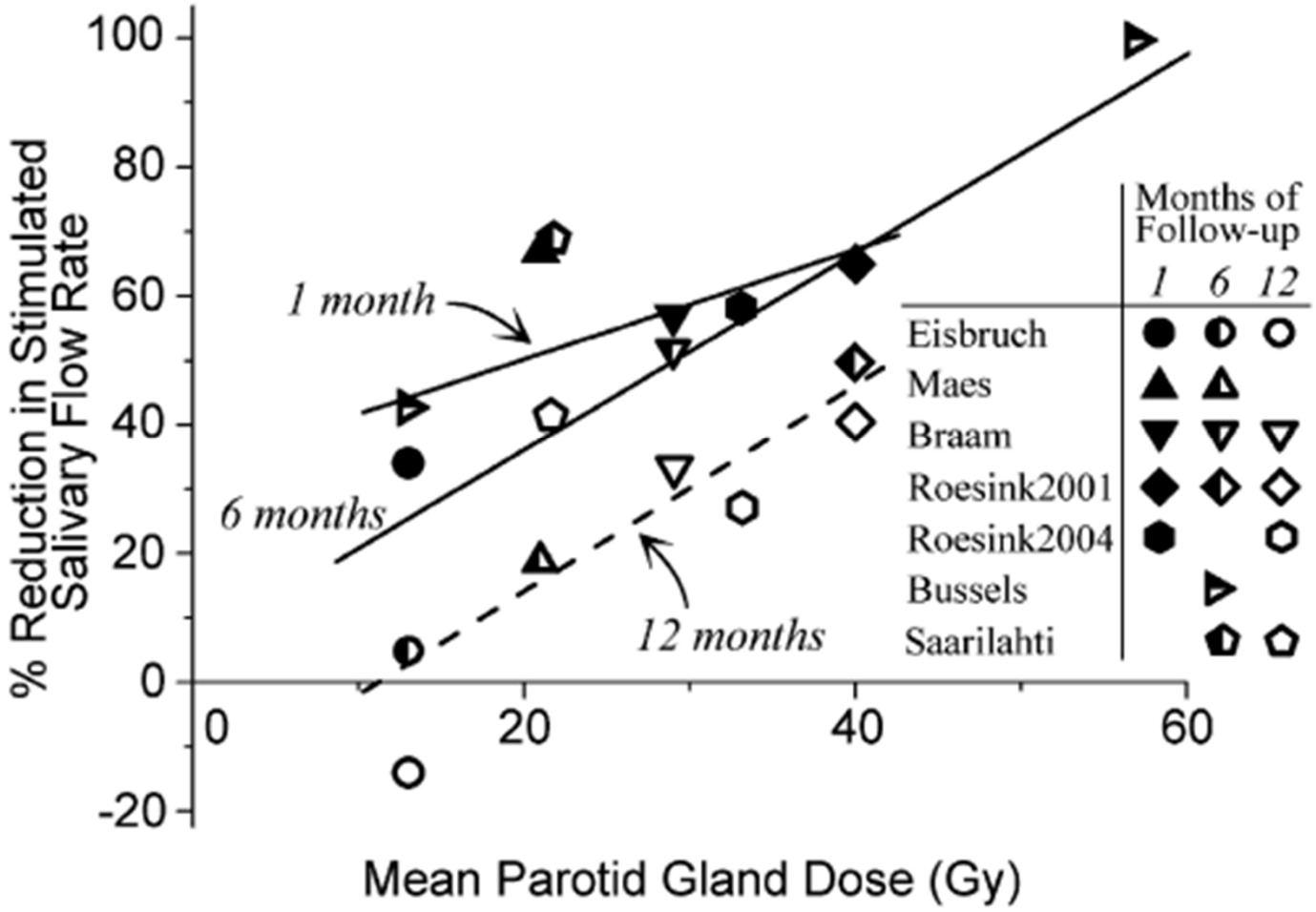
Salivary Gland

- Poor orodental hygine / oral infections / sleep disorders / oral pain / difficulty in chewing & swallowing
- Stimulated salivary production – 60 to 70% by parotid
- Resting (unstimulated) – primarily from submandibular/sublingual gland

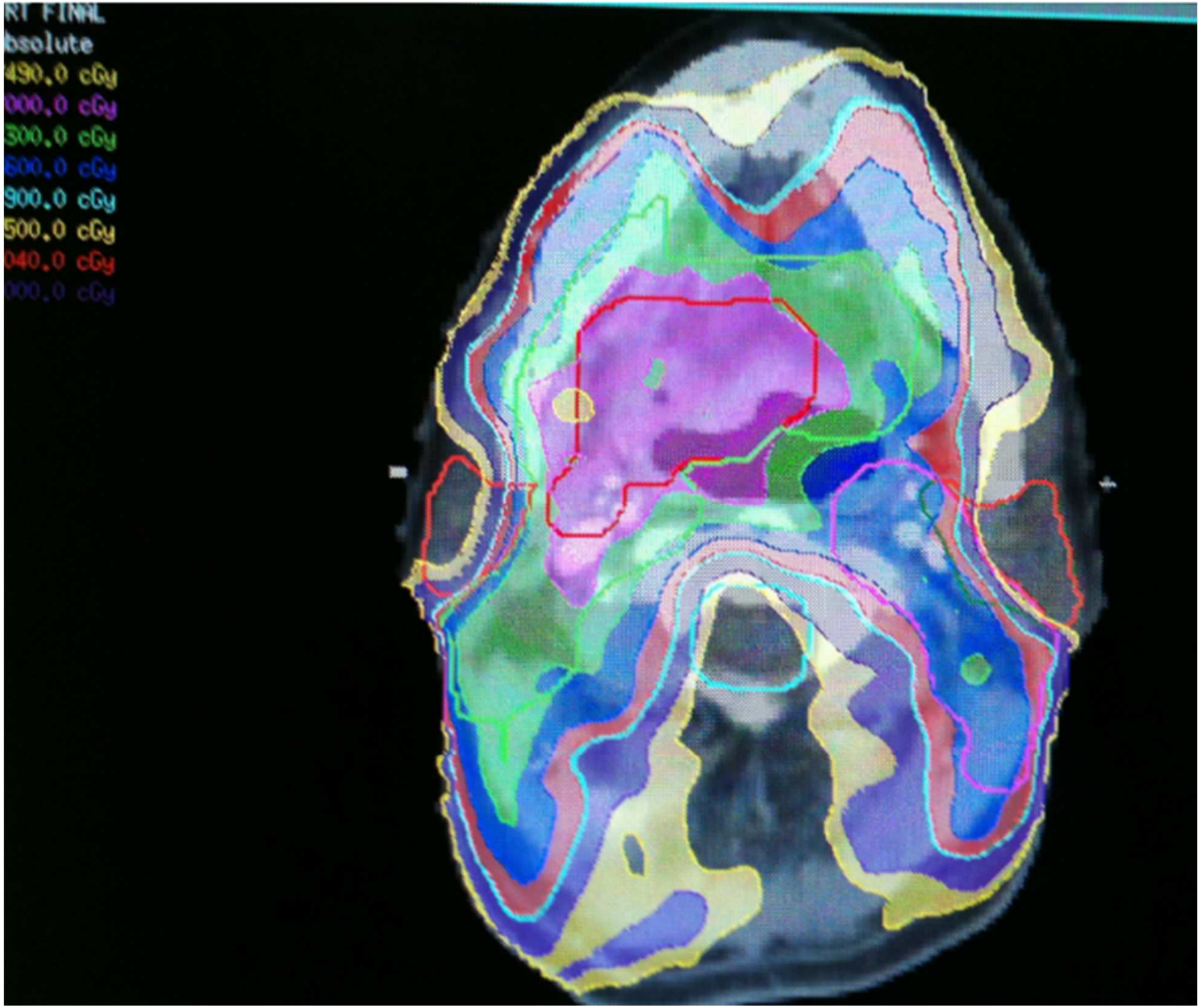
- Measurements – objective criteria, measured salivary production – rest / simulation, Imaging – scintigraphy of parotid ejection #, dynamic MRI sialography of ductal flow.
- ↓ in salivary function – within 1 week if starting RT & persists
- Recovery ≈ 2 yrs after RT

- Mean parotid gland dose – correlated with whole mouth / individual salivary gland production.
- Minimal finction ↓ - <10-15Gy mean dose
- Gradually ↓ between 20 – 40 Gy; >75% reduction (Gr 4) at doses above 40Gy.
- Risk ↓ if at least one parotid / even one SMG spared

Mean percentage of reduction in stimulated salivary flow rate vs. mean parotid gland dose for different follow-up durations



- Submandibular sparing - ↓both stimulated & unstimulated xerostomia
- Amifostine – reduces xerostomia rates
- Sparing one parotid / submandibular gland – eliminates xerostomia
- At least one parotid - < 20 Gy or if both mean dose < 25gy
- Lower the mean dose – better the function
- Submandibular sparing to <35Gy – when possible - ↓ xerostomia

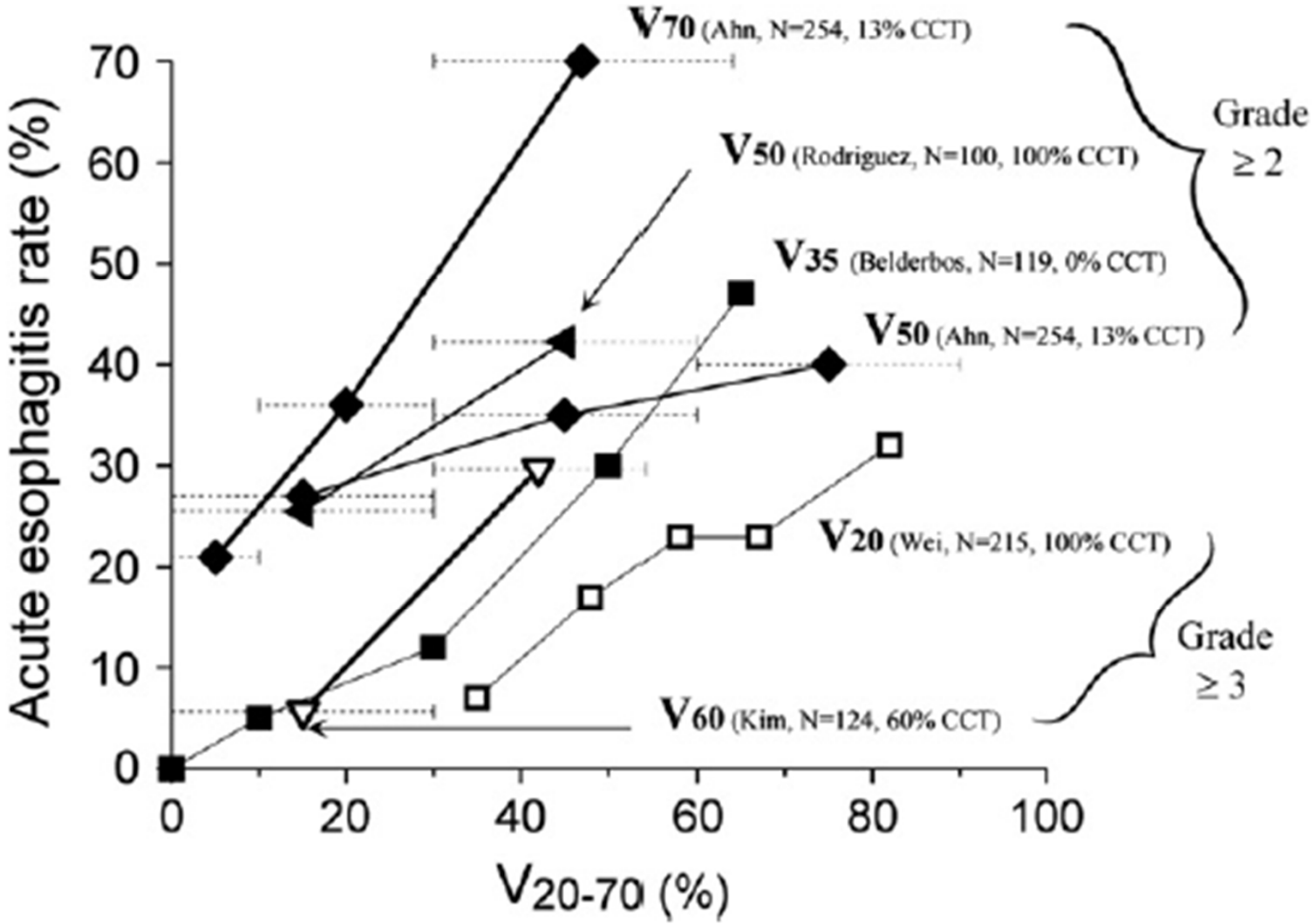

RT FINAL
bsolute
490.0 cGy
000.0 cGy
300.0 cGy
600.0 cGy
900.0 cGy
500.0 cGy
040.0 cGy
800.0 cGy

Esophagus

- CCRT / hypofractionation – 15-25% Gr 3 esophagitis (acute - < 90 days)
- TOF – occurs in 0.4 to 1%
- Acute esophagitis – occurs between 4 – 8 wks
- Late – stricture - ~ 3 – 8 months
- Differentiating esophagistis from candidiasis important
- Reflux may worsen RT induced esophagitis

- Contoured from cricoid – GE junction
- Esophagus can move 5-9mm in AP / CC directions
- Mean dose 34 Gy recommended as per RTOG 0617 –NSCLC study
- Esophagistis increases with CCRT (49% with Gemcitabine)
- Older patients have more esophagitis than young

Incidence of acute esophagitis according to Vx



- Hypofractionation – risk of esophagitis to be kept in mind
- RTOG 0167 recommends – mean dose to esophagus < 34 Gy & V60 to be calculated for each patient
- Doses of 74 Gy to a segment of esophagus with CT appears safe

Stomach & small bowel

- Nausea & Vomiting can occur within hrs
- Stomach - Days to weeks – dyspepsia - > ulceration -> life threatening
- Small bowel – cramping / diarrhea / interference in nutrient absorption – starts 1 to 2 weeks after RT
- Weight loss – secondary
- Intestinal obstruction – weeks to months
- Bowel adhesions requiring surgery

- Late toxicity
  - Stomach- dyspepsia , ulceration
  - Small bowel – persistent diarrhea, ulceration, fistula , perforation & bleeding (majority within 3 yrs, but risk period is indefinite)

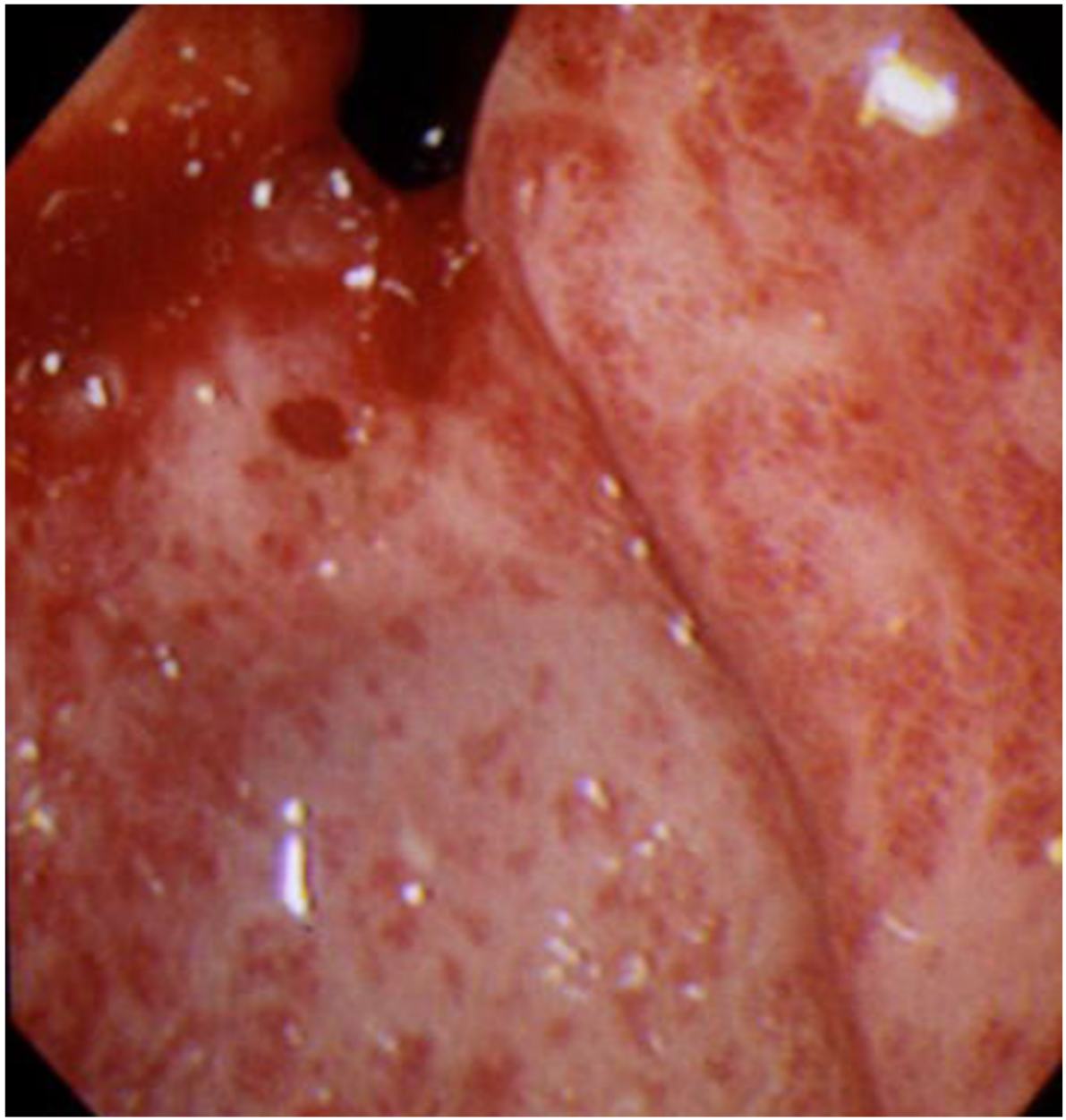
Defining volume - Stomach

- Oral contrast – useful in defining
- Position varies based on content
- Avoid large meal / carbonated drinks before sim / treatment

Defining volume – Small bowel

- Sometimes difficult to differentiate small bowel from nodes / large bowel
- Contrast helps but affects dose calculation
- Calculate without heterogeneity correction - if contrast is used
- Prone position significantly ↓ volume of small bowel receiving 80 to 100% prescribed dose

Radiation induced gastritis+telangectasia



Early effects

- Early effect – Nausea – 4% if dose ≤ 40Gy
  – 36% if dose ≤ 60Gy
- 5FU increases nausea
- 8Gy single # in hemi body RT – 66% moderate – severe nausea – relieved (6%) by Ondensetrone 2 hrs prior RT & 8mg bd

Late radiation effects - Stomach

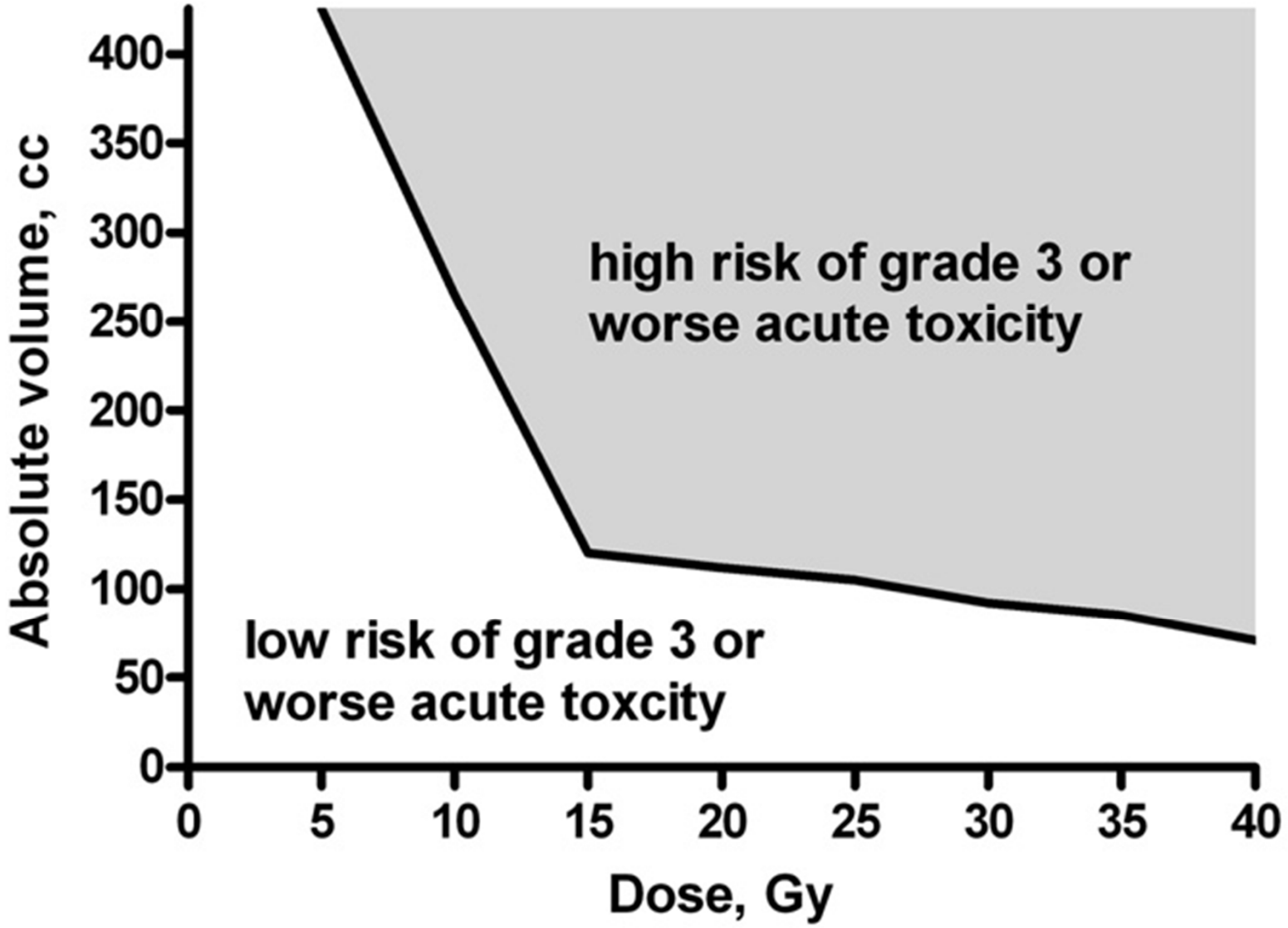
- Higher fraction size – more complications
- Chemo (Gemcitabine / 5 FU) increases chances of ulceration
- 50Gy – 2% to 6% risk of clinical severe late injury
- Effect of volume – not well characterized for stomach

Late radiation effects – small bowel

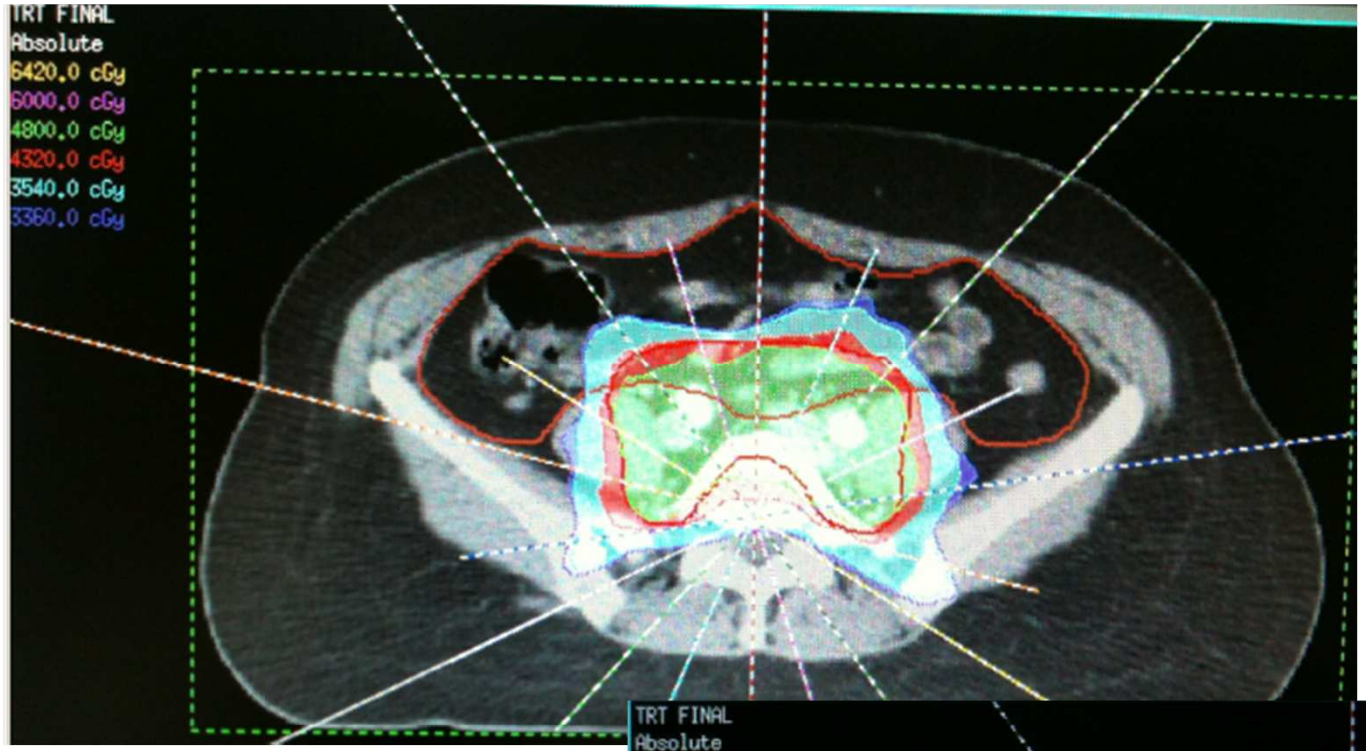
- Diarrhea/ obstruction / constriction / fistula / perforation / ulcer
- CCRT ↑ risk
- RT alone – 5% Gr III GI toxicity ; CTRT – 14 %(Cisp 40mg/m2)
- 5FU regimens – more toxic with RT
- Extended field RT – more toxicity compared to pelvic only

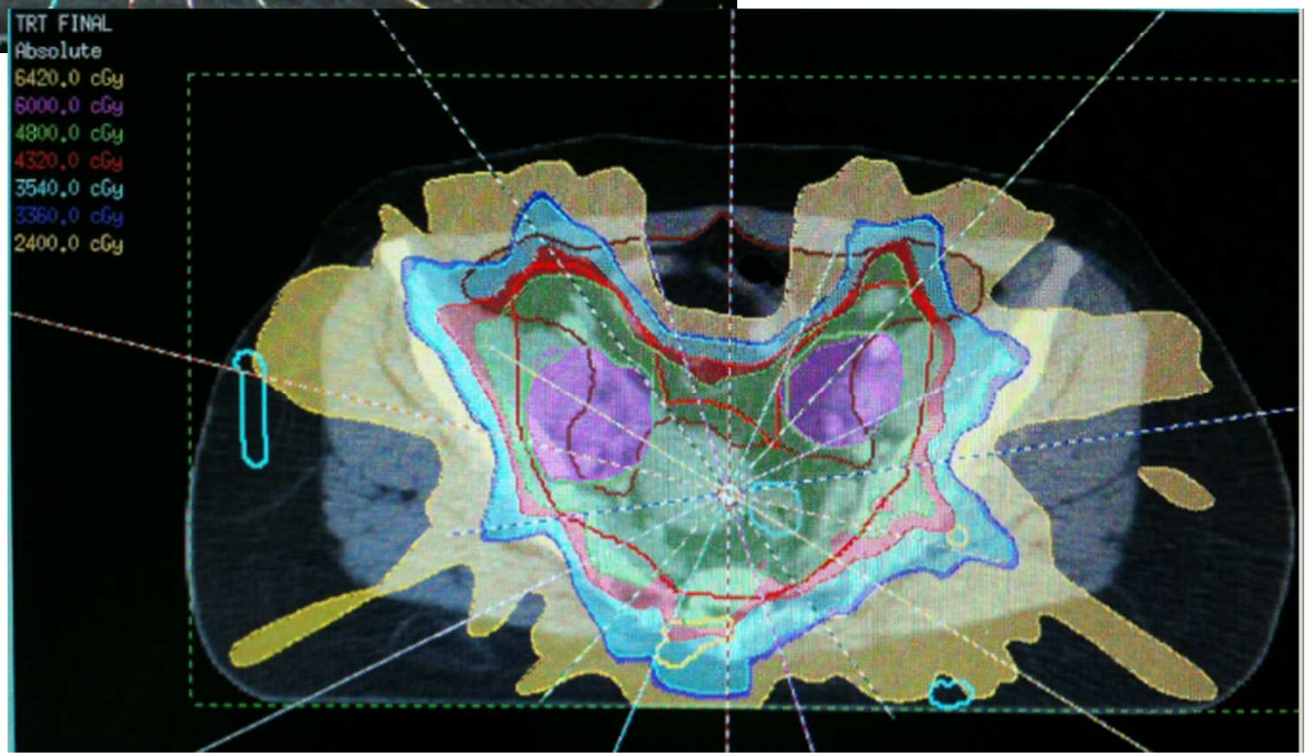
- Post OP – adhesions – small bowel toxicity is more
- Preoperative CTRT in rectal cancer –less small bowel toxicity (9%) compared to post operative CTRT (15%) – German rectal cancer study
- 50 gy – obstruction / perforation – 2 to 9%
- 25Gy/5# - similar risk

Baglan–Robertson threshold model for risk of acute small bowel toxicity



- Peritoneal cavity is surrogate to small bowel
- 45-50Gy should be < 195cc
- Special situation
  - SRT - <4% stomach can receive >22.5Gy
    - <5% intestine receive >22.5Gy
    - <50% > 12.5 Gy & 50% isodose line not reaching opposite luminal wall
- Single # Brachy in liver – D1ml 11gy


TRT FINAL
Absolute
6420.0 cGy
6000.0 cGy
4800.0 cGy
4320.0 cGy
3540.0 cGy
3360.0 cGy


TRT FINAL
Absolute
6420.0 cGy
6000.0 cGy
4800.0 cGy
4320.0 cGy
3540.0 cGy
3360.0 cGy
2400.0 cGy

Recommended dose/volume limits

- 45 gy to whole stomach – ulceration 5 to 7 %
- SBRT – volume receiving >22.5 should be <4%/ 5cc & Maximum point dose < 30Gy/3#, Avoid circumferential margin
- If bowel loops are contoured – absolute volume receiving ≥15 Gy should be <120Gy
- Entire peritoneal cavity – V45 < 195cc

Rectum – volume delineation

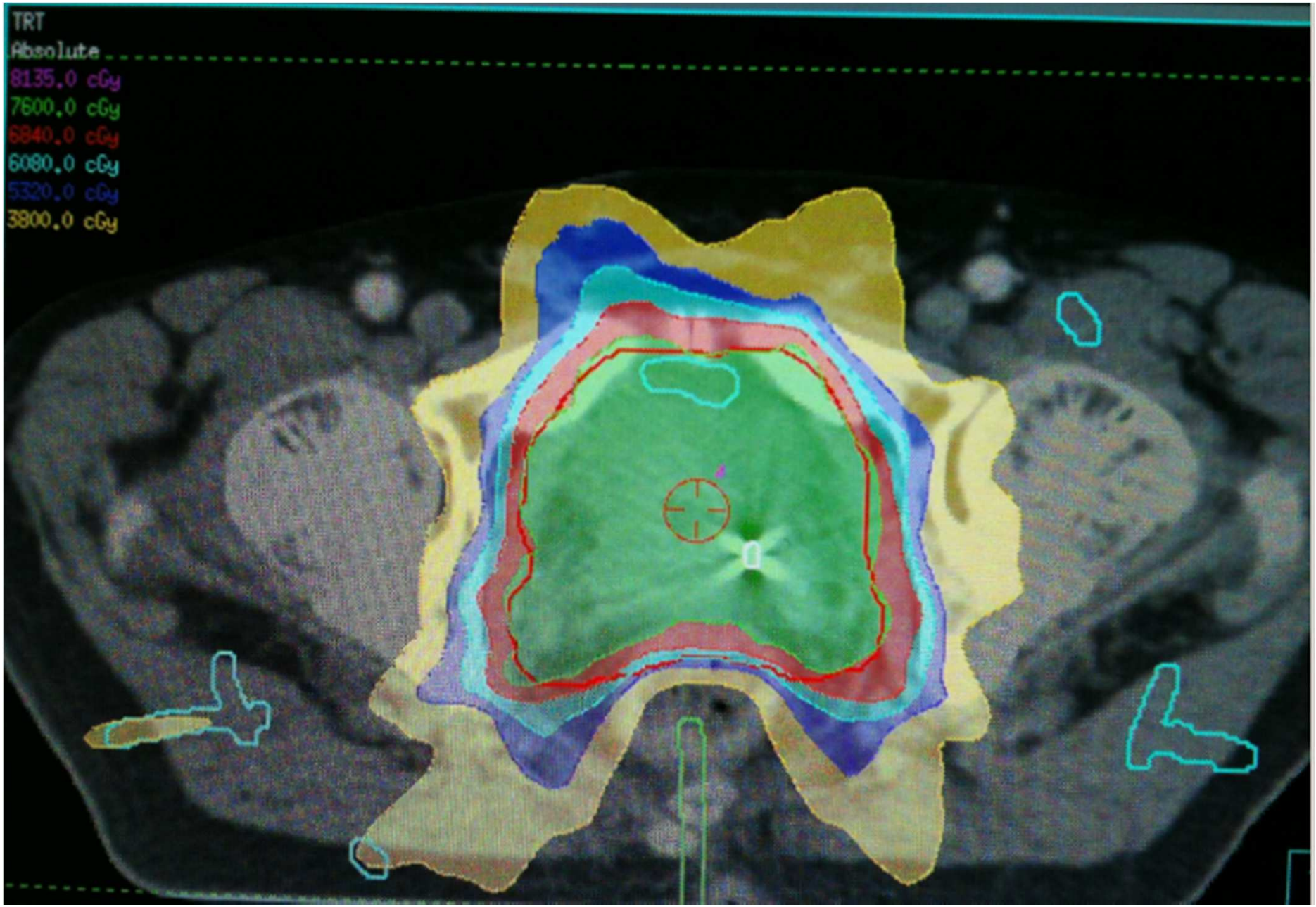
- Superior – rectosigmoid flexure
- Inferior – Anal canal
- Contoured as a solid though it is hollow
- Uncertainties of rectal filling variations are not considered in dose tolerance analysis

Factors affecting risk

- Diabetes / hemorrhoids / Inflammatory bowel disease / advanced age / ADT / rectum size/ prior abdominal surgery & severe acute rectal toxicity
- ↓ acute toxicity ↓late toxicity
- Image guidance - ↓ risk of toxicity

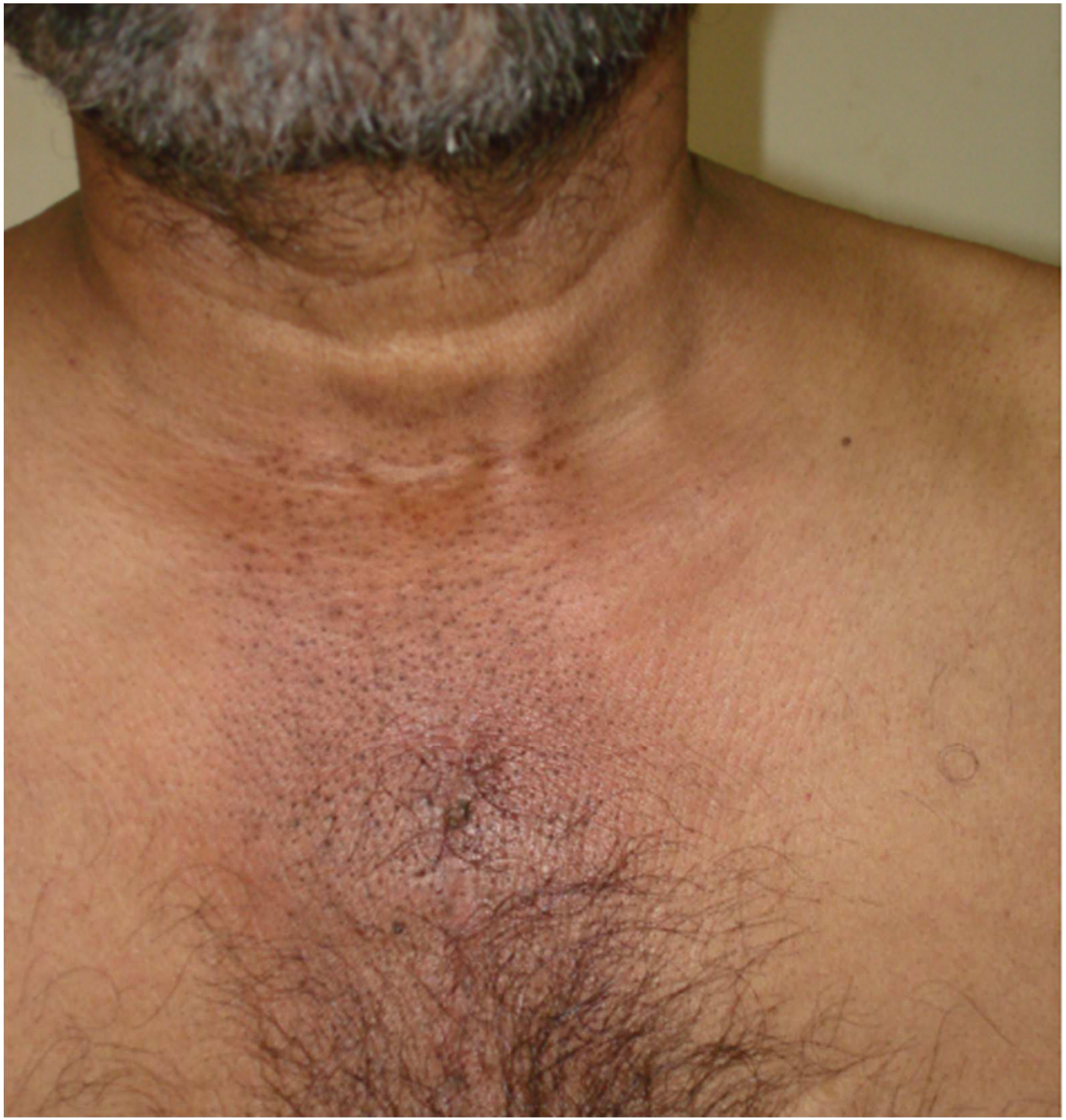
Recommended dose/volume limits

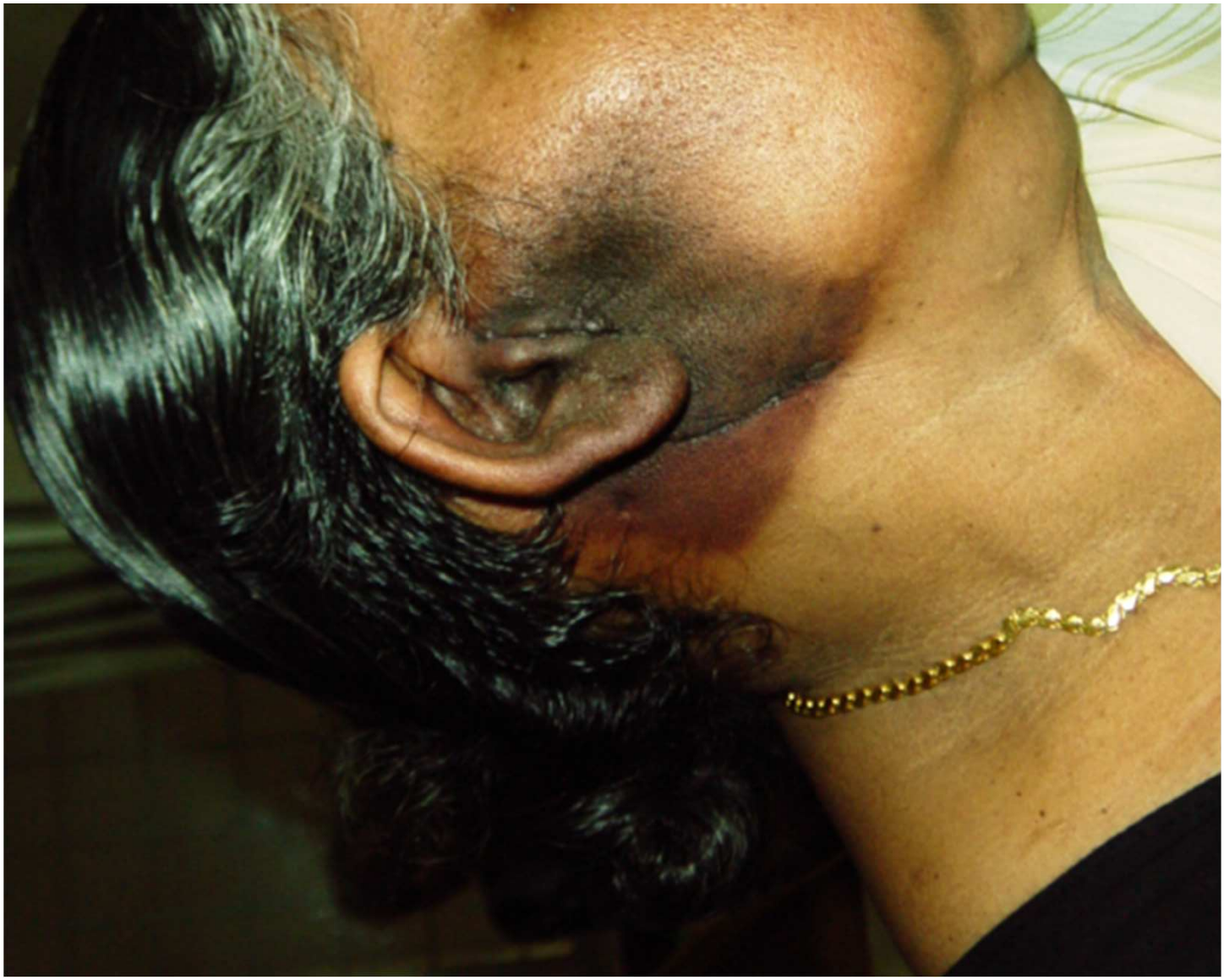
- In prostate cancer – empty rectum at simulation advised – to avoid systematic error
- Image guided RT – avoids day today variations
- V50 < 50%
- V60 < 35%
- V65 <25%
- V70 < 20%
- V75 <15%

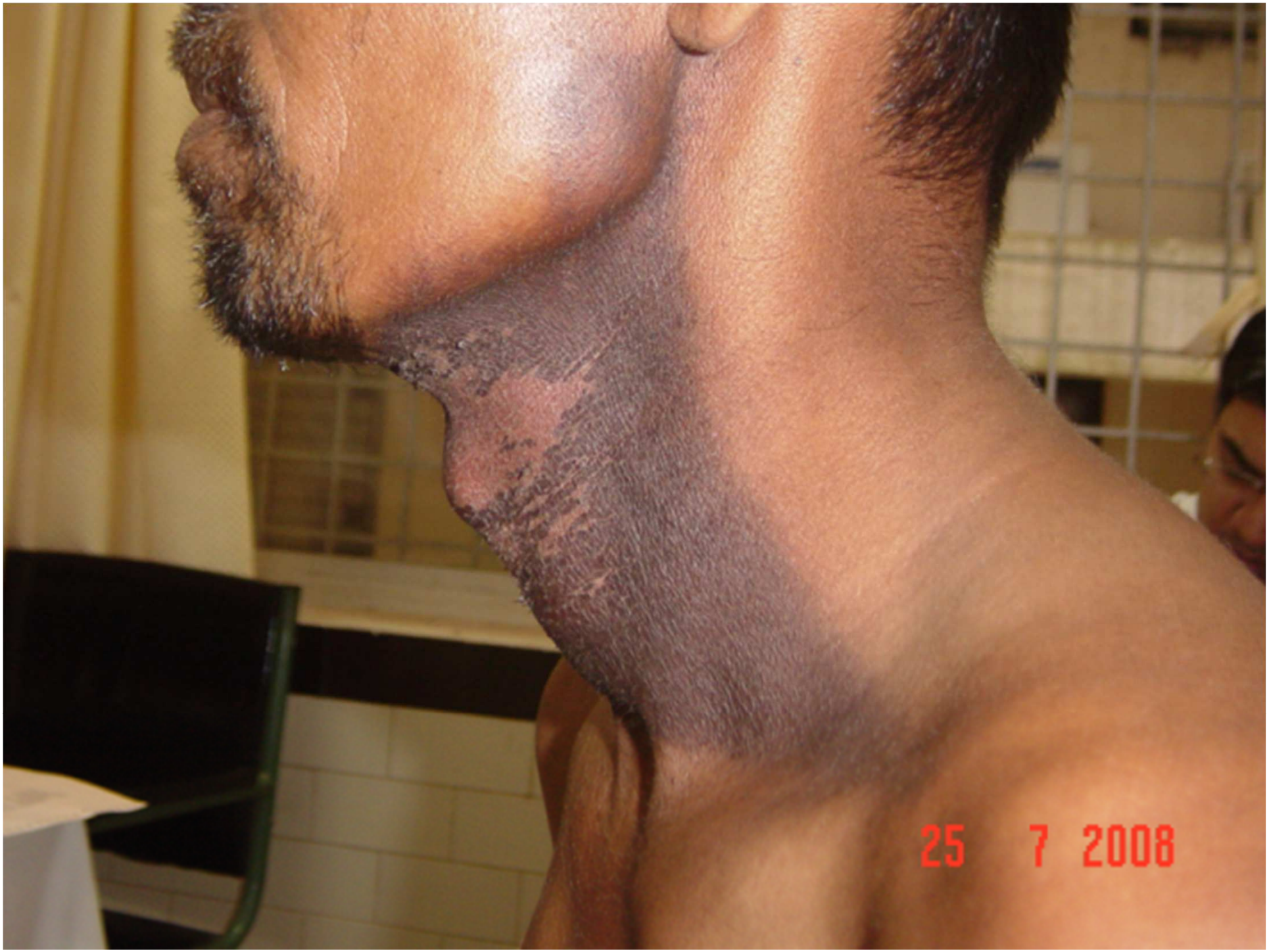

TRT
Absolute
8135.0 cGy
7600.0 cGy
6840.0 cGy
6080.0 cGy
5320.0 cGy
3800.0 cGy

Skin & Soft tissue

- Acute – Erythema (2^{nd} -3^{rd} wk), hypersenstivity, edema, alopecia (3^{rd} wk onwards; regeneration – 9wks), hyperpigmentation, desquamation
- Late – telangectasia (5 yrs) , dermal fibrosis (3 yrs), sebaceous gland atrophy, loss of hair follicle, altered melanin deposition, skin ulceration
- ↑ dose /#; ↑ volume -> ↑ late toxicity risk
- Hair follicle D50 of 43 gy – permanent alopecia



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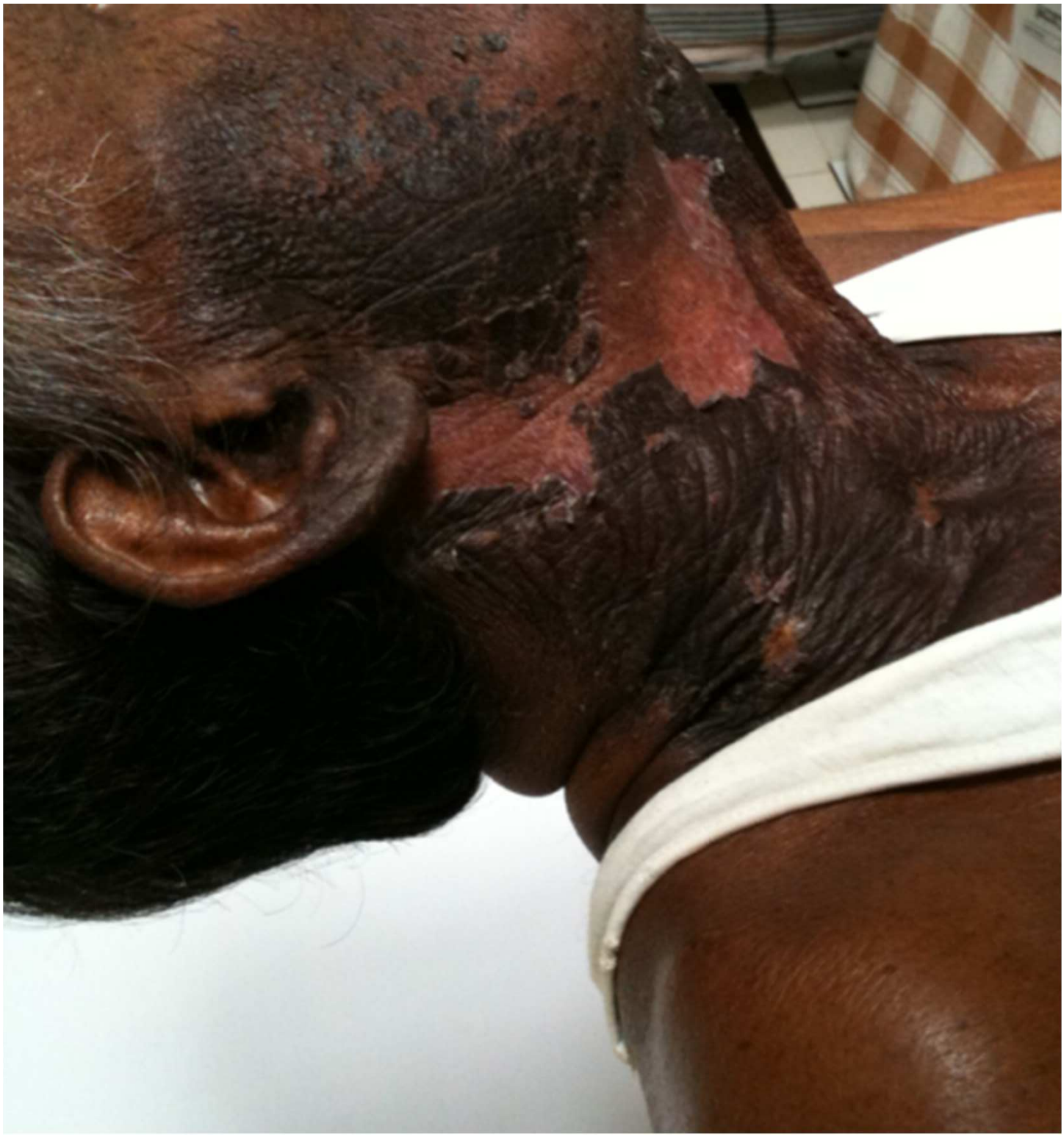
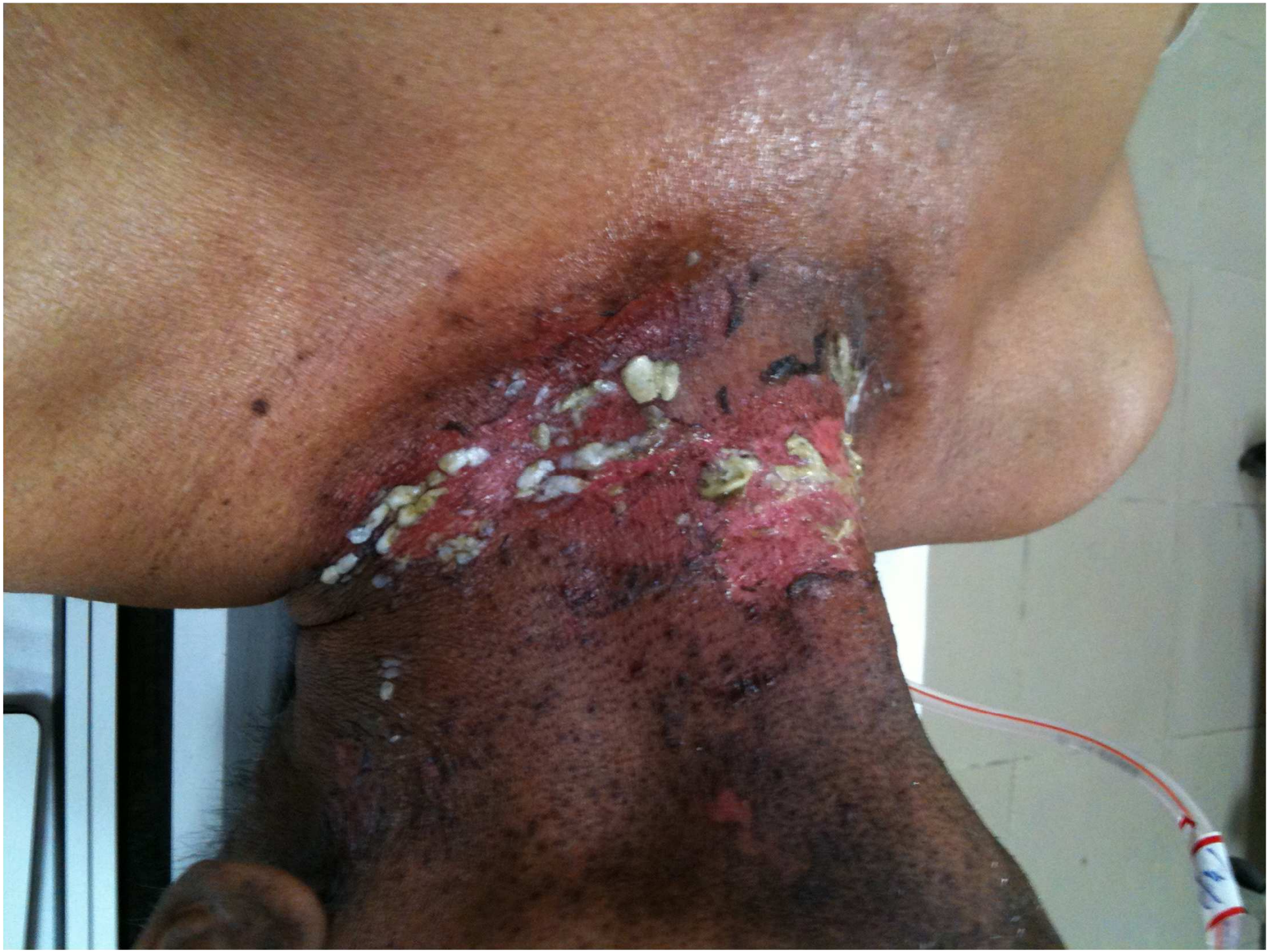




- Mtx, Act-D, Doxo - ↑ skin toxicity
- Radiologic finding – subcutaneous ↑ density
- Lab –↑ Plasma TGF-ß may indicate RT fibrosis
- DD – Breast – recurrence; systemic sclerosis, SLE, Lupus, Lichen sclerosus, stasis dermatitis
- Patho:
  - Acute-↓ basal epithilial cells, ↑mitotic index, inflammation, vascular dilatation
  - Microvascular destruction, epidermal atrophy, dense dermal fibrosis, loss of pilosabeceous units, atrophic sweat glands, arterial & venous lesions

- Management:
  - Acute –Symptomatic & care – self limiting
  - Prevent infection
  - Vit E & Pentoxiphylline - ? Useful in RT fibrosis
  - Hyperbaric oxygen – for ulcer healing
  - Skin graft – in non healing ulcers
- Pathophisiology
  - Injury to basal epithelial cells – erythema
  - ↓ in endothelial cell & vascular lumen – moist desq / necrosis
  - Telangectasis – destroyed capillary fusion below atrophied epidermis
  - Basal cell loss – 20 to 25 gy (2Gy/#);
- Mitoxantrone, Act-D, Pacli - ↑ skin toxicity

- ≥ 20 gy – epilation
- >45Gy – dry desquamation & hyperpigmentation
- Moist desquamation can occur in doses >45 Gy
- Moist desquamation prevents healing if RT continued
- 6 Months- 10 yrs – telangiectasia, fibrosis
- Second malignancy of skin

Thank You

Neuroendocrine

- GH – more sensitive to RT than ACTH
- GH ↓- ↓growth velocity / inadequate pubertal spurt; In adults asymptomatic/ ↓ muscle mass
- ACTH ↓ - muscle weaknessskin hyperpigmentation, hypotension, dehydration, anorexia.
- TRH ↓ - hypothyroidism – weight gain, cold intolerance, dry skin, brittle hair, menstrual irreg, hypotension, bradycardia, poor linear growth

- GNRH ↓ - ↓ sex hormone production – delayed puberty; precocious puberty can also occur – cause unclear – probably hypothalamic deregulation affects girls more than boys
- Hyperprolatinemia, infertility, ↓ libido, menstrual irregularities, galactorrhea, hot flushes & osteopenia
- **Time course -** highly variable, depends on dose, age during RT, patient age at assessment

- GH deficiency & precocious puberty > 18 to 20 GY to HP axis (ALL – prophylactic CRT)
- TRH, ACTH deficiency and hyperprolactenemia - > 40 to 50Gy (nasopharynx & paranasal tumors)
- Busulphan & cyclophosphamide ↑ risk
- Diagnosis – lab investigations, growth – X-ray of joints to assess normal age
- DD: idiopathic / congenital hormonal deficiency

- Management :
  - GH replacement in prepubescent children
  - GnRH agonist – block puberty
  - ACTH deficiency – hydrocortisone
  - TRH deficiency – thyroxin
  - Dopamine agonist (bromocriptine) – to treat hyperprolactinemia
  - Sex hormone replacement
- Children – biannual F/U

Thyroid

- Hyperthyroidism / hypothyroidism can develop
- Hyperthyroidism – heat intolerance, weight loss, insomnia, ↑ appetite, diarrhea, moist skin, tachycardia, nervousness, tremors, exophthalmous, goiter, thyroid enlargement
- Time course – 3 to 5 years hypo/hyper; nodules ≥ 10 yrs
- Dose > 20Gy to neck/ cervical spine or >7.5Gy TBI

- Chemo does not ↑ risk of hypothyroidism
- Assessment – USG / I125 scan– thyroid nodules
- Free T4 & TSH to monitor thyroid function
- DD: Graves/ Hashimoto's/ Idiopathic
- Patho – FNAC of thyroid nodule/ biopsy if ca suspected
- Management – Thyroid shielding if possible;
- Hypo - thyroxin replacement,
- Hyper - propylthiouracil, propranalol, I-131, thyroidectomy
- NCI recommends assessment upto 10 yrs post RT

Reproductive endocrine

- Ovary RT – infertility/ oligomenorrhea/amenorrhea, hot flushes, atrophic vulvitis & vaginitis, changes in fat distribution, breast changes, bone demineralization & ↓ libido
- Testis germ cell – oligospermia, azospermia, testicular atrophy
- Testis leydig cells – ↓ testosterone - ↓ libido, impaired sexual performance
- Delayed puberty in male & female children

- Oligospermia- in months, recover after low doses
- Amenorrhea can also recover after low doses – months /years later
- Ovary / testis – threshold for temporary 1 Gy; permanent > 3 to 4 Gy
- Alkylating agents impair testis & ovarian functions along with RT (HD data)

- Bone densitometry/ FSH/LH/testosterone/ estradiol estimation are useful investigations
- Semen analysis – oligospermia
- DD: Cranial RT patients can also have the above problems. To rule out other causes of infertility
- Management:
  - Testicular shield/ovarian transposition & shield (10hvl), sperm banking & oocyte harvest
  - Hormonal replacement

- Follow up – testicular size assessment in males
- Girls – FSH, LH & estradiol estimation at 12 years age.
- Boys – LH & testosterone level at 13 yrs age
- Consult endocrinologist for delayed puberty & endocrine fertility specialist for infertility

Male gonadal function

- Spermatogenisis – highly sensitive to - cyclophosphamide, procarbazine, and nitrogen mustard - used in HD
- Even without RT – 86% azoospermia with chemo
- <4G cyclophasphamide without RT retain fertility; cumulative >9g/m2 – unlikely fertility preserved
- RT – male – germinal epithelium > 1 Gy & Leidig cells 20 to 30Gy; <30Gy puberty in males unaffected
- Permanent azoospermia > 3 to 4 Gy

Female gonadal function

- menstrual irregularity, ovarian failure, and infertility - ↑ with cyclophosphamide & age
- Amenorrhea & premature ovarian failure in adult women than adolescents

Bone

- Scoliosis/ kyphosis/lordosis/limb assymetry
- Time – Occurs progressively till normal bone growth has ceased
- Avoid growth plate - ↓ late growth defects
- Partial irradiation of growth plate – more severe growth abnorms
- Management – mild scoliosis – physio; moderate – brace; severe – surgery
- Epiphyseal spillage – surgical pinning / osteotomy / osteoplasty

- Prevent scoliosis- by including entire vertebra instead of half
- Avascular necrosis of femoral head – 2 to 3 years after 30 to 60 Gy; corticosteroids ↑ risk

Bone marrow

- Toxicity depends on volume, **marrow reserve,** chemo history; exception – BMT patients receiving conditioning regimen
- ANC <500 ↑ risk of infection
- Platelet <20000 ↑ risk of bleeding
- Anemia- hypoxiemia, fatigue
- Single fraction as I TBI - latent period 1 to 2 weeks
- Fractioation – weeks to months

- Permanent suppression of limited marrow – 30 to 40Gy
- Chemo has additive effect
- Diagnosis – bone marrow ^{99m}Tc-sulfur colloid imaging. MRI is alternative inv.
- Lab – Bone marrow evaluation & PS
- DD: Metastatic marrow infiltration
- Management : Growth factors/ BMT

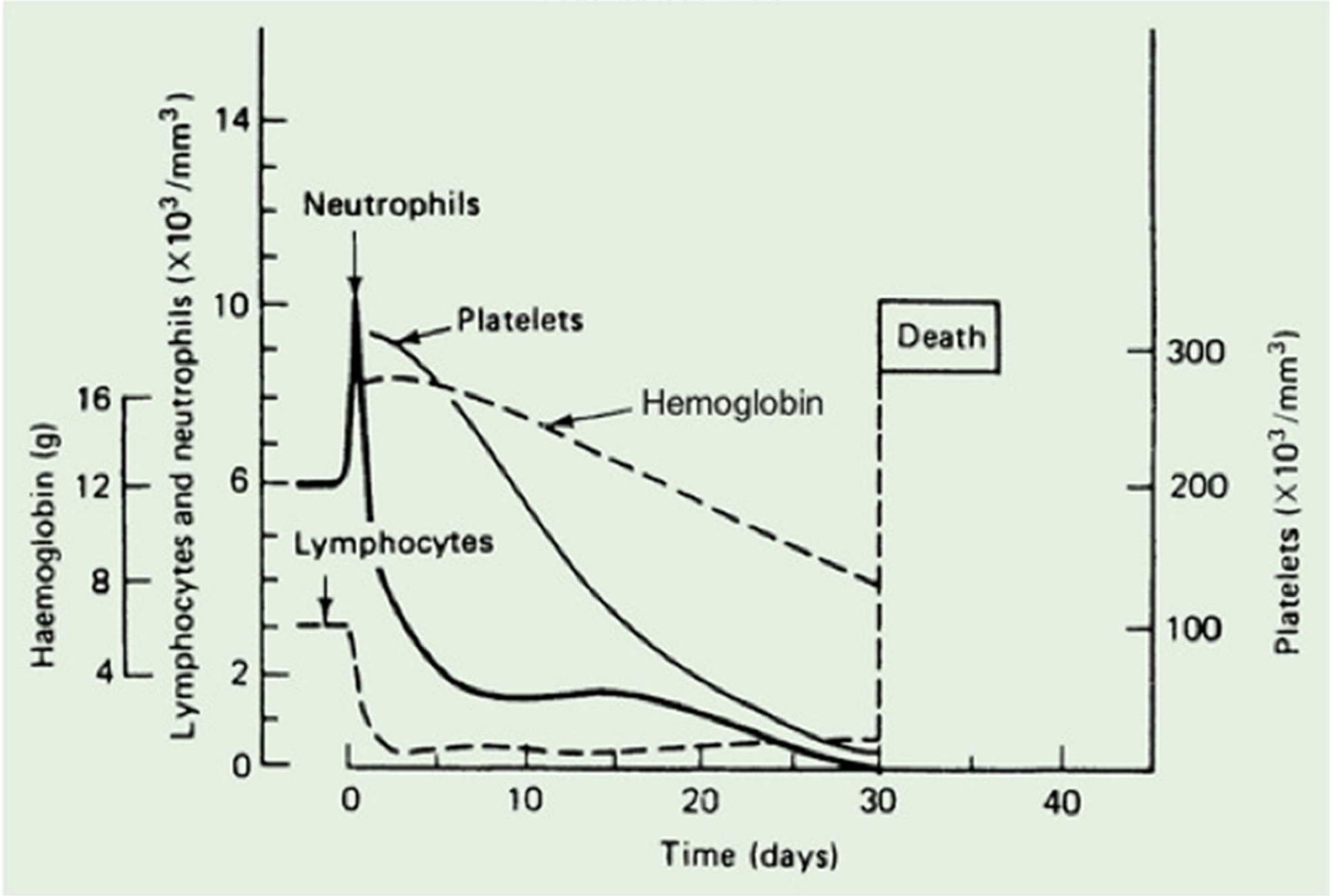
- <10 to 15% marrow RT – Permanent ablation in fractionated dose after 30Gy and 20Gy single #
- Remaining marrow compensates but irradiated marrow doesn’t recover
- If large area of marrow irradiated – in – field regeneration after2 to 5 years

TBI

- With conditioning chemotherapy for BMT
- Space travel – accidental exposure
- Potential terrorist threat / accidents
- 1.5 to7.5 Gy whole body exposure:
  - Rapid depletion of stem cells within 1 week
  - Without hemopoietic stem cell rescue – death due to granulocytopenia & thrombocytopenia-infection, hemorrhage
  - With stem cell rescue 7.5 to 10.5 Gy well tolerated

- Fractionated RT – for leukemia, myeloma & lymphoma
- Neutropenia in first week , 2 -3 weeks later – thrombocytopenia, 2 to 3 months anemia.

Hematologic response after 4.5Gy single



Second malignant neoplasm

- Hodgkin's Survivors ↑ risk
- Leukemia risk – related to alkylating agents & topoisomerase II inhibitors – risk plateau by 10 to 15 years
- RT induced secnd malignancy risk increases with time – sarcoma, melanoma, nreast, lung, thyroid & GI tract
- BMT patients at risk for – myelodisplasia, leukemia, lymphoma, liver, oral cavity, brain, bone, connective tissue, genitourinary & skin
- RT responsible for solid malignancy (breast cancer)