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 $\neq$ 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 β activation after first # of RT – breast ca
- IL-6, IL-1α 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$\alpha$ and IL-6 weekly assessment – not useful
- TGF-β1 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
<table>
<thead>
<tr>
<th>Function Distribution</th>
<th>Heterogeneous</th>
<th>Diseased Lung</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogeneous</td>
<td></td>
<td>Liver</td>
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<tr>
<td></td>
<td></td>
<td>Kidney</td>
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<td></td>
<td>Esophagus</td>
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<tr>
<td></td>
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<td></td>
<td>Intestines</td>
</tr>
</tbody>
</table>

Organizational Structure

Series Parallel
Dose volume outcome may not be applicable in

• Hypo fractionation

• Rotational delivery
## Dose volume relationship

<table>
<thead>
<tr>
<th>1990</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Parallel Opposed fields</td>
<td>- Conformal/IMRT</td>
</tr>
<tr>
<td>- RT as single modality</td>
<td>- CTRT widely used</td>
</tr>
<tr>
<td>- Conventional # / hyperfrac trials</td>
<td>- Conventional # / hypofractionation trials</td>
</tr>
<tr>
<td>- Authors search for “Safe” dose – volume constraint</td>
<td>- Risk – benefit tradeoff in individual patient</td>
</tr>
<tr>
<td>- Layman model widely used</td>
<td>- Layman model still widely used – but new modeling being persued</td>
</tr>
<tr>
<td>- Analysis-mainly on group of patients</td>
<td>- Analysis-individual patient level</td>
</tr>
<tr>
<td>- Lack of consistency – Organ contouring</td>
<td>- Lack of consistency – Organ contouring</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Organ Tissue</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Mild headache</td>
<td>Moderate headache</td>
<td>Severe headaches</td>
<td>Seizures or paralysis</td>
</tr>
<tr>
<td></td>
<td>Slight lethargy</td>
<td>Great lethargy</td>
<td>Severe CNS dysfunction</td>
<td>Coma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(partial loss of power or dyskinesia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Mild L’Hermitte’s syndrome</td>
<td>Severe L’Hermitte’s syndrome</td>
<td>Objective neurological findings at or below</td>
<td>Mono, para quadriplegia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cord level treated</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Slight dryness of mouth</td>
<td>Moderate dryness of mouth</td>
<td>Complete dryness of mouth</td>
<td>Fibrosis</td>
</tr>
<tr>
<td></td>
<td>Good response on stimulation</td>
<td>Poor response on stimulation</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Asymptomatic or mild symptoms (dry cough)</td>
<td>Moderate symptomatic fibrosis or pneumonitis</td>
<td>Severe symptomatic fibrosis or pneumonitis</td>
<td>Severe respiratory insufficiency/</td>
</tr>
<tr>
<td></td>
<td>Slight radiographic appearances</td>
<td>(severe cough)</td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low grade fever</td>
<td></td>
<td>O2/Assisted ventilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patchy radiographic appearances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>Asymptomatic or mild symptoms</td>
<td>Moderate angina on effort</td>
<td>Severe angina</td>
<td>Tamponade/severe heart failure/severe</td>
</tr>
<tr>
<td></td>
<td>Transient T wave inversion &amp; ST changes</td>
<td>Mild pericarditis</td>
<td>Pericardial effusion</td>
<td>constrictive pericarditis</td>
</tr>
<tr>
<td></td>
<td>Sinus tachycardia &gt;110 (at rest)</td>
<td>Normal heart size</td>
<td>Constrictive pericarditis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Persistent abnormal T wave and ST changes</td>
<td>Moderate heart failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low QRS</td>
<td>Cardiac enlargement</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>Mild fibrosis</td>
<td>Unable to take solid food normally</td>
<td>Severe fibrosis</td>
<td>Necrosis/perforation</td>
</tr>
<tr>
<td></td>
<td>Slight difficulty in swallowing solids</td>
<td>Swallowing semi-solid food</td>
<td>Able to swallow only liquids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No pain on swallowing</td>
<td>Dilatation may be indicated</td>
<td>May have pain on swallowing</td>
<td>Fistula</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dilatation required</td>
<td></td>
</tr>
<tr>
<td>Small and large intestine</td>
<td>Mild diarrhea</td>
<td>Moderate diarrhea and colic</td>
<td>Obstruction or bleeding requiring surgery</td>
<td>Necrosis/perforation Fistula</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>----------------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td></td>
<td>Mild cramping</td>
<td>Bowel movement &gt;5 times daily</td>
<td>Excessive rectal mucus or intermittent bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bowel movement 5 times daily</td>
<td>Excessive rectal mucus or intermittent bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Slight rectal discharge or bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Mild lassitude</td>
<td>Moderate symptoms</td>
<td>Disabling hepatic insufficiency</td>
<td>Necrosis/hepatic coma or encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Nausea, dyspepsia</td>
<td>Some abnormal liver function tests</td>
<td>Liver function tests grossly abnormal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Slightly abnormal liver function</td>
<td>Serum albumin normal</td>
<td>Low albumin Edema or ascites</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>Transient albuminuria</td>
<td>Persistent moderate albuminuria (2+)</td>
<td>Severe albuminuria</td>
<td>Malignant hypertension</td>
</tr>
<tr>
<td></td>
<td>No hypertension</td>
<td>Mild hypertension No related anemia</td>
<td>Severe hypertension Persistent anemia (&lt;10g%)</td>
<td>Uremic coma/urea</td>
</tr>
<tr>
<td></td>
<td>Mild impairment of renal function</td>
<td>Moderate impairment of renal function</td>
<td>Severe renal failure</td>
<td>Urea &gt;100%</td>
</tr>
<tr>
<td></td>
<td>Urea 25-35 mg%</td>
<td>Urea &gt;36-60 mg%</td>
<td>Urea &gt;60 mg%</td>
<td>Urea &gt;100%</td>
</tr>
<tr>
<td></td>
<td>Creatinine 1.5-2.0 mg%</td>
<td>Creatinine &gt;4.0 mg%</td>
<td>Creatinine &gt;4.0 mg%</td>
<td>Creatinine clearance &lt;50%</td>
</tr>
<tr>
<td></td>
<td>Creatinine clearance &gt;75%</td>
<td>Creatinine clearance (50-74%)</td>
<td>Creatinine clearance &lt;50%</td>
<td></td>
</tr>
</tbody>
</table>
## LENT-SOMA form

<table>
<thead>
<tr>
<th>BRAIN</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>6SUBJECTIVE SIGNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>Occasional, minimal</td>
<td>Intermittent, tolerable</td>
<td>Persistent, intense</td>
<td>Refractory and excruciating</td>
</tr>
<tr>
<td>Somnolence</td>
<td>Occasional, able to work or perform normal activity</td>
<td>Intermittent, interferes with work or normal activity</td>
<td>Persistent, needs some assistance for self care</td>
<td>Refractory, prevents daily activity, coma</td>
</tr>
<tr>
<td>Intellectual deficit</td>
<td>Minor loss of ability to reason and judge</td>
<td>Moderate loss of ability to reason and judge</td>
<td>Major loss of ability to reason and judge</td>
<td>Complete loss of reasoning and judgement</td>
</tr>
<tr>
<td>Functional competence</td>
<td>Perform complex tasks with minor inconvenience</td>
<td>Cannot perform complex tasks</td>
<td>Cannot perform simple tasks</td>
<td>Incapable of self-care/supervision, coma</td>
</tr>
</tbody>
</table>

Score: 109
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/parallel & 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 $\alpha/\beta$ & Late responding – low$\alpha/\beta$. 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
<table>
<thead>
<tr>
<th>Parameters of Therapy: Tolerance Doses (TD5/5–TD50/5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single Dose (Gy)</strong></td>
</tr>
<tr>
<td>Ovary</td>
</tr>
<tr>
<td>Bone marrow</td>
</tr>
<tr>
<td>Testes</td>
</tr>
<tr>
<td>Eye (lens)</td>
</tr>
<tr>
<td>Mucosa</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Colorectal</td>
</tr>
<tr>
<td>Kidney</td>
</tr>
<tr>
<td>Vasculoconnective tissue</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Skin</td>
</tr>
<tr>
<td>Peripheral nerve</td>
</tr>
<tr>
<td>Spinal cord</td>
</tr>
<tr>
<td>Brain</td>
</tr>
<tr>
<td>Heart</td>
</tr>
<tr>
<td>Bone and cartilage</td>
</tr>
<tr>
<td>Muscle</td>
</tr>
<tr>
<td>Organ</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Kidney</td>
</tr>
<tr>
<td>Brain</td>
</tr>
<tr>
<td>Brainstem</td>
</tr>
<tr>
<td>Spinal cord</td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Heart</td>
</tr>
<tr>
<td>Esophagus</td>
</tr>
<tr>
<td>Stomach</td>
</tr>
<tr>
<td>Small intestine</td>
</tr>
<tr>
<td>Colon</td>
</tr>
<tr>
<td>Rectum</td>
</tr>
<tr>
<td>Liver</td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>Subjective</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Headache,</td>
<td>• neurologic deficit,</td>
</tr>
<tr>
<td>• somnolence,</td>
<td>• loss of cognitive function,</td>
</tr>
<tr>
<td>• intellectual deficits,</td>
<td>• mood and personality changes</td>
</tr>
<tr>
<td>• functional</td>
<td>• focal to generalized seizures</td>
</tr>
<tr>
<td>• neurologic losses</td>
<td></td>
</tr>
<tr>
<td>• Memory alterations</td>
<td></td>
</tr>
</tbody>
</table>
• 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, β-interferon ↑ necrosis
- Valproate – low risk for necrosis
Brain- Radiation necrosis –
Conventional RT $\alpha /\beta = 3$

• 5 to 10% - 120 Gy to 150 Gy 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
- $\leq 2$ ys after WBRT – no difference in cogn.
- $\geq 5$ ys after WBRT – condition improved
- $>2$Gy/# 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 cm³
  – Volume receiving 12 Gy and region important
  – Brain stem & corpus callosum – more stringent limits
Brain Stem – $\alpha / \beta = 2.1$

- RT induced brain stem injury – manifests months – years

- Difficult to differentiate between disease progression / side effects
• Includes midbrain, pons, medulla
• Midbrain inferior to 3\textsuperscript{rd} 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
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 $\leq 60$ Gy
Factors affecting risk

• Pediatric age – more risk
• Intrathecal ARA-C, MTX, intraperitoneal fludarabine immediately 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 clonoid 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
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 epithelioma, impairment of vision – 30 to 65 Gy
- Corticosteroids and GVHD ↑risk of cataract
- 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
• 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-β are on testing as predictive markers
• Differential diagnosis – Recurrence/ persiant disease / mets / lymphangitic carcinomatosis / infections
Increased density on CT
• 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/pacl/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
- $V_{25\text{Gy}} < 10\%$ - <1\% probability of cardiac mortality
  $\approx 15$ yrs. after RT
- HL no chemo – whole heart tolerates 30gy
- HL patients receiving Chemo – whole heart tolerance - 15Gy
- Pericarditis – if pericardial dose $> 26\text{Gy}$ and $V_{30} > 46\%$
- Left ventricle RT - $\downarrow$ 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; 1/3 rd 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 to 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
• 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 insufficiency
- 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%

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bilateral kidney irradiation</th>
<th>Partial kidney irradiation</th>
<th>Bilateral kidneys</th>
<th>Bilateral kidneys</th>
<th>Bilateral kidneys</th>
<th>Bilateral kidneys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-volume metric</td>
<td>Mean kidney dose &lt; 10 Gy</td>
<td>Mean kidney dose &lt; 18 Gy</td>
<td>V&lt;sub&gt;29&lt;/sub&gt;Gy &lt; 20%</td>
<td>V&lt;sub&gt;25&lt;/sub&gt;Gy &lt; 30%</td>
<td>V&lt;sub&gt;20&lt;/sub&gt;Gy &lt; 32%</td>
<td>V&lt;sub&gt;12&lt;/sub&gt;Gy &lt; 55%</td>
</tr>
<tr>
<td>Investigator</td>
<td>Cheng et al. (8)</td>
<td>Cassady (10)</td>
<td>Nevinny-Stickel et al. (34)</td>
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<td>Jansen et al. (15)</td>
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<td></td>
<td>Welz et al. (13)*</td>
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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 function ↓ - <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
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 esophagastis 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
• Esophagitis 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
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%
Skin & Soft tissue

• Acute – Erythema (2\textsuperscript{nd} -3\textsuperscript{rd} wk), hypersenstivity, edema, alopecia (3\textsuperscript{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
• 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 epithelial cells, ↑mitotic index, inflammation, vascular dilatation
  – Microvascular destruction, epidermal atrophy, dense dermal fibrosis, loss of pilosaceous 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
• Pathophysiology
  – 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 weakness skin 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

• Hyperprolactinemia, 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

- Spermatogenesis – 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 cyclophosphamidine & age
- Amenorrhea & premature ovarian failure in adult women than adolescents
Bone

- Scoliosis/ kyphosis/lordosis/limb asymmetry
- 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
- Fractionation – 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 after 2 to 5 years
TBI

• With conditioning chemotherapy for BMT
• Space travel – accidental exposure
• Potential terrorist threat / accidents
• 1.5 to 7.5 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)