SRO-Tutorial

Normal tissue tolerance, complications and protection against radiation

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In general

The aim of curative radiation therapy is to

• achieve local tumor control

• without producing major damage to surrounding normal tissue
Local tumor control

Tumorvernichtung

Toleranz überschritten

Heilung

Uncomplicated local tumor control

Erfahrungen über die Verträglichkeitsgrenze für Röntgenstrahlen und deren Nutzanwendung zur Verhütung von Schäden*).

Von
H. Holthusen, Hamburg.

57. Band
Mit 255 Bildern im Text

Urban & Schwarzenberg / Berlin / 1936

Severe normal tissue damage
In general

The tolerance doses is critically dependent on

- the total dose
- the fractionation schedule
- the volume of normal tissue irradiated

- $TD_{5/5} = 5\%$ probability of severe sequelae in 5 years
- $TD_{50/5} = 50\%$ probability of severe sequelae in 5 years

What are these tolerance doses?
Normal tissue tolerance

**Answer**

<table>
<thead>
<tr>
<th>Organ</th>
<th>TD 5/5 volume</th>
<th>TD 50/5 volume</th>
<th>Selected end point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/3</td>
<td>2/3</td>
<td>3/3</td>
</tr>
<tr>
<td>Kidney</td>
<td>50</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>Brain</td>
<td>60</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>Brain stem</td>
<td>60</td>
<td>53</td>
<td>50</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>5 cm: 50</td>
<td>10 cm: 50</td>
<td>20 cm: 47</td>
</tr>
<tr>
<td>Lung</td>
<td>45</td>
<td>30</td>
<td>17.5</td>
</tr>
<tr>
<td>Heart</td>
<td>60</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>Esophagus</td>
<td>60</td>
<td>58</td>
<td>55</td>
</tr>
<tr>
<td>Stomach</td>
<td>60</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>Small intestine</td>
<td>50</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Colon</td>
<td>55</td>
<td>45</td>
<td>65</td>
</tr>
<tr>
<td>Rectum</td>
<td>Volume 100 cm³</td>
<td>60</td>
<td>Volume 100 cm³</td>
</tr>
<tr>
<td>Liver</td>
<td>50</td>
<td>35</td>
<td>30</td>
</tr>
</tbody>
</table>

Normal tissue tolerance

Agenda

• What is the “pathology” of radiation damage
  • LQ-model
  • pathophysiology
  • mechanisms of repair

• How is radiation damage evaluated and categorized?
  • CTC, RTOG-EORTC, LENT-SOMA, CTCAE vs. 3.0

• Radiation damage of specific organs and structures

• Which factors might influence radiation damage?
**Normal tissue tolerance**

**Why does radiation damage cells?**

- **Tumor in the spinal cord**

<table>
<thead>
<tr>
<th>Damage to</th>
<th>Tumor</th>
<th>Spinal cord</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x 40Gy:</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>40 x 1Gy:</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20 x 2Gy:</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>10 x 3Gy:</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>15 x 2.5Gy:</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Why does radiation damage cells?

- *Dose is an important factor for radiosensitivity*
- *Fractionation is an important factor for radiosensitivity*
- *Different dose-fractionation schedules might be “isoeffective”*
Pathophysiology of radiation damage

Zellkern (DNA) ist das Haupttarget für die Zellinaktivierung

E. Dikomey Refresherkurs DEGRO 2005
Pathophysiology of radiation damage

DNA-Schäden

- Einzelstrangbrüche
- Basenschäden
- Doppelstrangbrüche
- Gehäufte Läsionen

Häufigkeit

- ~ 2000 pro Zelle pro Gy
- ~ 1000 pro Zelle pro Gy
- ~ 30 pro Zelle pro Gy

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Pathophysiology of radiation damage

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Number per cell per Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double strand breaks</td>
<td>40</td>
</tr>
<tr>
<td>Single strand breaks</td>
<td>1000</td>
</tr>
<tr>
<td>Base damages</td>
<td>&gt; 2000</td>
</tr>
<tr>
<td>Sugar damages</td>
<td>800 - 1000</td>
</tr>
<tr>
<td>DNA-DNA crosslinks</td>
<td>30</td>
</tr>
<tr>
<td>DNA-protein crosslinks</td>
<td>150</td>
</tr>
<tr>
<td>Alkali-labile sites</td>
<td>200-300</td>
</tr>
</tbody>
</table>

*Number of Clustered Lesions not yet quantified.*
Normal tissue tolerance

Pathophysiology of radiation damage

Erkennung und Reparatur von DNA-Schäden

- Basenschäden und Einzelstrangbrüche

Basenexzisionsreparatur (BER)

Erzeugung

Erkennung

Entfernung

Reparatur-
synthese

Ligation

Purschke et al. 2004 Int J Radiat Biol 80, 29-38

Reparaturinkubation bei 37°C (h)

Relative Anzahl der DNA-Schäden

HeLa
4 Gy → Reparatur bei 37°C

Reparatur ist nach 12 abgeschlossen
Nahezu 100% der Schäden werden repariert

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Normal tissue tolerance

Pathophysiology of radiation damage

Erkennung und Reparatur von DNA-Schäden

- Doppelstrangbrüche

Nicht homologe Endverknüpfung

- in Säugetierzellen dominant
  - in allen Zellzyklusphasen
  - fehlerhaft

Homologe Rekombination

- in Hefe dominant
  - nur in später S and G2-Phase
  - fehlerfrei

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Pathophysiology of radiation damage

Kinetik der Reparatur

- Doppelstrangbrüche

\[ f_{\text{fast}} = 60-70\% \]
\[ f_{\text{slow}} = 30-35\% \]
\[ \tau_1 = 2-5\text{min} \]
\[ \tau_2 = 100-150\text{min} \]

40 Gy → 37°C

Relative Anzahl der Doppelstrangbrüche

residuelle DSB

\[ \text{Dikomey and Brammer 2000 Int J Radiat Biol 76, 773-781} \]

- Es gibt schnell und langsam reparierende DSB
- Reparatur ist nach 12 abgeschlossen
- Reparaturkinetik ist unabhängig von der Dosis

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Pathophysiology of radiation damage

Kapazität der Reparatur

- Doppelstrangbrüche


- 95-98% der Schäden werden repariert
- Für Fibroblasten korrelieren die residuellen DSB mit der Strahlenempfindlichkeit

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Pathophysiology of radiation damage

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Pathophysiology of radiation damage

- Bildung von Mikrokernen (Micronuclei, MN)

- acentrisches Fragment wird über Mikrokern entfernt
- Verlust an DNA führt zu Verlust an essentiellen Proteinen
- Zellen stellen die Proliferation nach 2-4 Teilungen ein
- Reproduktiver Zelltod (früher als Mitotischer Zelltod bezeichnet)

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Pathophysiology of radiation damage

Zusammenfassung 1

Absorption der Strahlung
Ionisation der DNA
Bildung von DNA-Schäden
Falschreparatur
Bildung von letalen Chromosomenaberrationen
Bildung eines Microkerns
Reproduktiver Zelltod
Zellauflösung

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Pathophysiology of radiation damage

Zellinaktivierung durch ionisierende Strahlen

Bestrahlung
DNA-Schäden

p53
p21
G1-Arrest
Reproduktiver Zelltod
Apoptose
Zellinaktivierung

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Pathophysiology of radiation damage

Zusammenfassung 2

- Zellinaktivierung durch ionisierende Strahlen

bei einer Überlebensrate von 10%

Normal: 10% Chrom Aberr., 14% Apoptose, 76% G1-Arrest.

Fibroblasten: 44% Chrom Aberr., 53% Apoptose, 3% G1-Arrest.

Lymphozyten: 20% Chrom Aberr., 5% Apoptose, 75% G1-Arrest.

Tumorzellen: 15% Chrom Aberr., 6% Apoptose, 79% G1-Arrest.

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Pathophysiology of radiation damage

Radiation-Induced Apoptosis

**INITIATORS**
- DNA Damage
- ATM
- JNK
- p38 mapk

**EFFECTORS**
- p53
- Bax
- Cytochrome c
- Apaf-1
- Apoptosome Complex

**TERMINAL PHASE**
- Caspase 3, 6, 7
- Caspase 8
- Caspase 9
- Pro-caspase 9
- Cytochrome c

Members of TNFR family With Death Domains (TNFRI, Fas, TRAIL)

FADD

Autoactivation of procaspase 8

Sphingomyelin

Ceramide

Mitochondria

JNK - jun kinase
ATM - mutated in ataxia telangiectasia
FADD - Fas activated death domain
Apaf - apoptosis activating factor
Pathophysiology of radiation damage

... but things can be simplified:

Outcomes of DNA repair:

- **Accurate repair:** cell survives without mutations
- **Misrepair:** cell survives but at the cost of genetic changes
- **Inadequate repair:** cell inactivation or death due to
  - mitotic death
  - apoptosis
  - permanent arrest

S. Powell Refresherkurs ASTRO 2005
Normal tissue tolerance

Pathophysiology of radiation damage

Summary of Key Points

- IR creates a heterogeneous spectrum of DNA lesions
- DSBs constitute the most dangerous type of damage
- IR sensitivity correlates best with DSBs
- Multiple pathways of DNA repair exist, including BER, NER, HR, NHR, MMR
- Inadequate DSB repair can either lead to
  - cell death/ inactivation
    (due to chromosome aberrations or apoptosis), or to
  - carcinogenesis (due to chromosome aberrations or an increased rate of small mutations)
Pathophysiology of radiation damage

- **half-time of repair**
- **long** (1 – several hours)
  - skin, kidney, spinal cord
- **intermediate** (30-60 min)
  - colon, lung
- **shortest** (< 30 min)
  - jejunal mucosa

- **interfraction interval**: > 6 hours to avoid late toxicity due to incomplete repair

Acc. to H. Thames Refresherkurs ASTRO 2004
Summary

• we have radiation damage to cells
  • SSB, DSB and other DNA lesions

• we have multiple repair-mechanisms
  • fast, intermediate, slow

• we have different kinds of cell-death
  • reproductive (mitotic), apoptotic, G₁-arrest

• How can we use this knowledge to predict radiosensitivity?
The probability of survival ($S$) for a cell in dependence of a radiation dose ($D$) can be described by the function

$$S = e^{-(\alpha D + \beta D^2)}$$

“The Linear-Quadratic model”
Normal tissue tolerance

**Linear Quadratic model**

\[ S = e^{-(\alpha D + \beta D^2)} \]

**Figure 2.11.** The frequency of chromosomal aberrations (dicentrics and rings) is a linear-quadratic function of dose because the aberrations are the consequence of the interaction of two separate breaks. At low doses, both breaks may be caused by the same electron; the probability of an exchange aberration is proportional to dose (D). At higher doses, the two breaks are more likely to be caused by separate electrons. The probability of an exchange aberration is proportional to the square of the dose (D^2).

E. Hall: Radiobiology for the Radiologist 2000
Normal tissue tolerance

**Linear Quadratic model**

**single-hit injury** \((e^{-\alpha D})\)

= exponential curve
  (linear in half-log cell surv. curve)

**multi-hit (cumulative)**

**injury** \((e^{-\beta D^2})\)

= continuously bending curve
  related by a coefficient “\(\beta\)” to the square of the dose

**\(\alpha / \beta\)** = dose, at which single and multi-hit mechanisms contribute equally to cell killing

\[
S = e^{-(\alpha D + \beta D^2)}
\]
Linear Quadratic model

What does the \( \alpha/\beta \)-ratio tell?

- "\( \alpha \)"
  - linear component
  - no or little repair
  - less sensitive to fractionation

- "\( \beta \)"
  - exponential component
  - potential for repair
  - more sensitive to fractionation

- "\( \alpha/\beta \)"
  - high: less potential for repair = less sensitive to fractionation
  - low: more potential for repair = more sensitive to fractionation
Linear Quadratic model

What damages can be “repaired”? 

- **sublethal damage**
  - DNA single strand breaks (SSB)
  - can be repaired
  - if not repaired, can be damaged lethally if hit again (multi-hit)

- **lethal damage**
  - DNA double strand break (DSB)
  - low/no potential for repair

- **potential lethal damage (PLD)**
  - potential repair in non-proliferating cells
Linear Quadratic model

Effect of fractionation

• fractionation
  • sublethal damage repair

• single dose/hypofractionation
  • no or minor repair

• Repair
  • “fast”: 10-20 min
  • “slow”: > 2 h
  • intercellular repair: hours – days
  • “half-time” of repair: 2 hours
Normal tissue tolerance

Linear Quadratic model

What are the $\alpha/\beta$-values?

<table>
<thead>
<tr>
<th>Early responding</th>
<th>$\alpha/\beta$(Gy)</th>
<th>Late responding</th>
<th>$\alpha/\beta$(Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jejunal mucosa</td>
<td>13</td>
<td>Spinal cord</td>
<td>1.6 - 5</td>
</tr>
<tr>
<td>Colonic mucosa</td>
<td>7</td>
<td>Kidney</td>
<td>0.5 - 5</td>
</tr>
<tr>
<td>Skin epithelium</td>
<td>10</td>
<td>Liver</td>
<td>1.4 - 3.5</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>9</td>
<td>Lung</td>
<td>2.5 - 6.3</td>
</tr>
<tr>
<td>Spermatogenic cells</td>
<td>13</td>
<td>Skin</td>
<td>2.5 - 4.5</td>
</tr>
<tr>
<td>Human tumors</td>
<td>6-25</td>
<td>Thyroid gland</td>
<td>2.5 - 4.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cartilage</td>
<td>1.0 – 4.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone</td>
<td>1.8 – 2.5</td>
</tr>
</tbody>
</table>
Normal tissue tolerance
Linear Quadratic model

Which factors influence cell survival after radiation?

• **intrinsic cell sensitivity**
• **radiosensitivity in different phases of the cell cycle**
• **dose-fractionation**
• **protraction (dose rate)**
• **oxygenation**
• **linear energy transfer**
Normal tissue tolerance

Linear Quadratic model

Intrinsic cell sensitivity
Normal tissue tolerance

**Linear Quadratic model**

Radiosensitivity dependent on the phase of cell cycle
Normal tissue tolerance

Linear Quadratic model

Protraction of radiation (dose rate)
Linear Quadratic model

Oxygen-effect and LET

- hypoxic cells are less radiosensitive (up to factor 3) = oxygen enhancement ratio (OER)
- re-oxygenation is one of the advantages of fractionation
- LET low: oxygen effect high
- LET high: oxygen effect low
Normal tissue tolerance

Linear Quadratic model

What do we have?
- an $\alpha/\beta$- value for different tissues

What do we want?
- calculate an isoeffective dose-fractionation schedule
- predict normal tissue tolerance probability (NTCP)

What do we need?
- the „endpoint“ (=side effect)
Linear Quadratic model

Calculation of isoeffective dose-fractionation schedules

• “Withers-Formula” (to compare 2 treatment regimes)

\[ Total\ D_{new} = Total\ D_{old} \times \frac{(\alpha/\beta + \text{fraction dose}_{old})}{(\alpha/\beta + \text{fraction dose}_{new})} \]

e.g. „what is the equivalent dose to 40Gy/2Gy fractions for the spinal cord, if I want to give 3Gy fraction doses?“

\[ D_{new} = 40\text{Gy} \times \frac{(3 + 2)}{(3 + 3)} = 40\text{Gy} \times \frac{5}{6} = \frac{200}{6} = 33.3\text{Gy} \]
Normal tissue tolerance

Linear Quadratic model

Calculation of isoeffective dose-fractionation schedules

• “Withers-Formula”

E.g. „what is the equivalent dose to 40Gy/2Gy fractions for the spinal cord, if I want to give 3Gy fraction doses?“

\[ D_{\text{new}} = 40 \text{Gy} \times \left( \frac{3 + 2}{3 + 3} \right) = 40 \text{Gy} \times \frac{5}{6} = \frac{200}{6} = 33.3 \text{Gy} \]

and the tumor?

\[ = 40 \text{Gy} \times \left( \frac{10 + 2}{10 + 3} \right) = 40 \text{Gy} \times \frac{12}{13} = \frac{480}{13} = 36.9 \text{Gy} \]
Normal tissue tolerance

Linear Quadratic model

Take home message

33.3 Gy = 40 Gy x \( \frac{3 + 2}{3 + 3} \)

36.9 Gy = 40 Gy x \( \frac{10 + 2}{10 + 3} \)

Tissues with low \( \alpha/\beta \)-ratio are more sensitive to fractionation or clinically

Increasing fraction-size is more important for normal tissue with low \( \alpha/\beta \)-ratio than for most tumors
Linear Quadratic model

Calculation of Biological Equivalent Dose (BED)

• for comparison of very different dose-fraction-regimes

\[
\text{BED} = \text{Total D} \times (1 + \frac{\text{fraction dose}}{\alpha/\beta})
\]

e.g. “what is the BED of stereotactic irradiation of a lung tumor with 3x10Gy?“

\[
\text{BED} = 30\text{Gy} \times (1 + \frac{10}{10}) = 30\text{Gy} \times (1 + 1) = 60\text{Gy}
\]
Linear Quadratic model

Summary

• “Withers formula”
  for calculation of isoeffective fraction- or total doses

\[ \text{Total } D_{\text{new}} = \text{Total } D_{\text{old}} \times \frac{\alpha/\beta + \text{fraction dose}_{\text{old}}}{\alpha/\beta + \text{fraction dose}_{\text{new}}} \]

• “BED-formula”
  • for comparison of different dose-fractionation schedules in term of its biological effect

\[ \text{BED} = \text{Total } D \times \left( 1 + \frac{\text{fraction dose}}{\alpha/\beta} \right) \]
Normal tissue tolerance
Normal tissue reaction

Normal Tissue Radiation Toxicity
The Textbook Classification

- **Acute**
  - Clonogenic cell death
  - Apoptosis
  - Inflammation

- **Delayed (chronic, late)**
  - **Primary:** clonogenic/apoptotic death of slowly proliferating cells, vascular sclerosis
  - **Consequential:** chronic injury secondary to severe acute injury
Pathophysiology of radiation damage

Radiation Effects in Normal Tissues
The Pathobiology-Based Classification

- Cytocidal effects
  (clonogenic cell death, apoptosis)

- Functional effects – intracellular, plasma membrane, extracellular (transcription factor activation, protein modification, redox activation/inactivation, etc.)

- Secondary effects
  (inflammation, cytokines, etc.)

All 3 types of effects interact and contribute to organ dysfunction

“The New Formalism” (IJROBP 2001)
Normal tissue tolerance

Pathophysiology of radiation damage

Normal Tissue Radiation Toxicity
Examples of Secondary Effects

- Hypercoagulability
- Cytokine production
- ROS generation

Inflammation

- Leukocyte adhesion
- Leukocyte chemotaxis
- Cytokine production
- ROS generation

Endothelial dysfunction

- Oxidative imbalance
- Hypercoagulability
- Cytokine production
- Leukocyte chemotaxis

Organ dysfunction

M. Hauer-Jensen Refresherkurs ASTRO 2005
In general

“Most organ system are composed of many cell subpopulations - 20-40 or more – each performing an important activity”

Rubin 1968

“Organ tolerance is determined by the radiosensitivity of relevant stem cell subpopulations, which are not always proliferating or dividing”

Hall 1993

“And the most radiosensitive vital cell population determines organ tolerance and failure”
Functional subunit (FSU) concept

• Tolerance dose for a tissue depends not only on the “radiosensitivity” of the target cell, but also of the number or target cells in a FSU

• e.g. skin: Epilation requires less dose than moist desquamation
  • not because the cells in the hair follicle are more radiosensitive compared to basal epithelium
  • but because there is a smaller number of cells in the FSU that produces hair than in that in the sheet of cells from which the skin can regenerate

Vegesna, Withers et al Radiat Research 1987
Normal tissue tolerance

In general

“Serial” organs

e.g.

esophagus
stomach
small bowel
large bowel
urinary bladder
trachea
bronchi

defect > not compensated > side effect
In general

“Parallel” organs

e.g.
- lung
- liver
- kidney
- prostate
- skin
- glands

defect > organ function compensated > no side effect
Normal tissue reaction

Williams et al. Sem Rad Oncol 2003
Classification of adverse effects

In general: 4-6 grades

(0 no adverse effect)

1 Minor symptoms that do not require treatment
2 Moderate symptoms, requiring (passager) conservative treatment
3 Severe symptoms, negative impact on daily activities, require more aggressive treatment
4 Irreversible functional damage, requires major therapeutic intervention
(5 Death)
Classification of adverse effects

Intensity and frequency of symptoms

- **Occasional** (\(= <\) weekly) = monthly
- **Intermittent** = weekly
- **Persistent** = daily
- **Refractory** = constant
Normal tissue tolerance

Classification of Toxicity

Table 1. The Evolution of Toxicity Grading Systems (1979-1998)

<table>
<thead>
<tr>
<th>System</th>
<th>No. of Criteria</th>
<th>No. of Organs</th>
<th>Modality</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO (1979)</td>
<td>28</td>
<td>9</td>
<td>Chemo</td>
<td>Acute</td>
</tr>
<tr>
<td>CTC (1983)</td>
<td>18</td>
<td>13</td>
<td>Chemo</td>
<td>Acute</td>
</tr>
<tr>
<td>RTOG/EORTC-Acute (1984)</td>
<td>14</td>
<td>13</td>
<td>RT Acute</td>
<td>Acute</td>
</tr>
<tr>
<td>RTOG/EORTC-Late (1984)</td>
<td>16</td>
<td>13</td>
<td>RT Late</td>
<td>Late</td>
</tr>
<tr>
<td>LENT (1995)</td>
<td>152</td>
<td>22</td>
<td>RT Late</td>
<td>Late</td>
</tr>
<tr>
<td>CTC v 2.0 (1998)</td>
<td>260</td>
<td>22</td>
<td>All*</td>
<td>Acute</td>
</tr>
</tbody>
</table>

Abbreviation: WHO, World Health Organization.
*Limited pediatric and surgical criteria.


Trotti et al. Sem Rad Oncol 2003
## Normal tissue tolerance

### Classification of Toxicity

<table>
<thead>
<tr>
<th>System</th>
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<tr>
<td>CTC (1983)</td>
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<td>13</td>
<td>Chemo</td>
<td>Acute</td>
</tr>
<tr>
<td>CTC v2.0 (1998)</td>
<td>260</td>
<td>22</td>
<td>All*</td>
<td>Acute</td>
</tr>
<tr>
<td>CTCAE v3.0 (2003)</td>
<td>370</td>
<td>All</td>
<td>All</td>
<td>Acute and late</td>
</tr>
</tbody>
</table>

*Limited pediatric and surgical criteria.

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Trotti et al. Sem Rad Oncol 2003
Classification of adverse effects

The LENT-SOMA scale (1995)

LENT = late effects in normal tissue
SOMA = subjective – objective – management - analytic
Normal tissue tolerance

### SPINAL CORD

#### Subjective

<table>
<thead>
<tr>
<th></th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesia (tingling sensation, shooting pain, Lhermitte's syndrome)</td>
<td>Occasional &amp; minimal</td>
<td>Intermittent &amp; tolerable</td>
<td>Persistent &amp; intense</td>
<td>Refractory &amp; excruciating</td>
</tr>
<tr>
<td>Sensory (numbness)</td>
<td>Minimal change</td>
<td>Mild unilateral sensory loss; works with some difficulties</td>
<td>Partial unilateral sensory loss; needs assistance for self care</td>
<td>Total loss of sensation, danger of self-injury</td>
</tr>
<tr>
<td>Motor (weakness)</td>
<td>Minor loss of strength</td>
<td>Weakness interfering with normal activities</td>
<td>Persistent weakness preventing basic activities</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Sphincter control</td>
<td>Occasional loss</td>
<td>Intermittent loss</td>
<td>Incomplete control</td>
<td>Complete incontinence</td>
</tr>
</tbody>
</table>

#### Objective

<table>
<thead>
<tr>
<th></th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
<th>SCORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic evaluation</td>
<td>Barely detectable decrease in sensation or motor weakness on one side, no effect on function</td>
<td>Easily detectable decrease in sensation or motor weakness on one side, disturbs but does not prevent function</td>
<td>Full Brown-Sequard syndrome, loss of sphincter function, prevents function</td>
<td>Complete transaction, disabling, requiring continuous care</td>
<td></td>
</tr>
</tbody>
</table>

#### Management

<table>
<thead>
<tr>
<th></th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
<th>SCORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Occasional non-narcotic medication</td>
<td>Persistent non-narcotic medication, intermittent low dose steroids</td>
<td>Intermittent high dose steroids</td>
<td>Persistent high dose steroids</td>
<td>LENT Score:</td>
</tr>
<tr>
<td>Neurologic function</td>
<td>Needs minor adaptation to continue working</td>
<td>Regular physiotherapy</td>
<td>Intensive physiotherapy plus regular supervision</td>
<td>Intensive nursing and/or life support</td>
<td></td>
</tr>
<tr>
<td>Incontinence</td>
<td>Occasional use of incontinence pads</td>
<td>Intermittent use of incontinence pads</td>
<td>Regular use of incontinence pads or self-catheterization</td>
<td>Permanent use of pads or self-catheterization</td>
<td></td>
</tr>
</tbody>
</table>

#### Analytic

<table>
<thead>
<tr>
<th></th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
<th>SCORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>Assessment of swelling, edema, atrophy</td>
<td>Extensive demyelination</td>
<td>Necrosis</td>
<td>Y/N Date:</td>
<td></td>
</tr>
<tr>
<td>MRS</td>
<td>Assessment of chemical spectra</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>Assessment of metabolic activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>Assessment of myelin basic protein levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>Assessment of total protein and myelin basic protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LENT-SOMA scales for all anatomic sites IJROBP 31(5): 1049-91;1995
**Normal tissue tolerance**

**LENT-SOMA scales for all anatomic sites**

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LENT-SOMA scales for all anatomic sites IJROBP 31(5): 1049-91;1995
Classification of adverse effects

CTCAE vs. 3.0  Common Terminology Criteria of Adverse Effects

• abandons the “90-day-rule”
• no differentiation between “acute” and “late” effects
• not specified on radiation toxicity, but integration of all potential noxes as surgery, chemotherapy, hormonal therapy or combinations
• 28 organ systems with >1000 sites and organ specific terms

“The first comprehensive multimodality grading system for reporting both acute and late effects in oncology”
Normal tissue tolerance

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)
Publish Date: August 9, 2006

Quick Reference
The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization
CATEGORY
A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grades).

Adverse Event Terms
An AE is any unsolicited and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analysis. Each AE term is mapped to a MedDRA term and code AEs are listed alphabetically within CATEGORIES.

Short AE Name
The ‘SHORT NAME’ column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms
A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word ‘related’ and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK
A ‘REMARK’ is a clarification of an AE.

ALSO CONSIDER
An ‘ALSO CONSIDER’ indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE
A ‘NAVIGATION NOTE’ indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the NAVIGATION NOTE states differently.

Grades
Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:
Grade 1 Mild AE
Grade 2 Moderate AE
Grade 3 Severe AE
Grade 4 Life-threatening or disabling AE
Grade 5 Death related to AE

A Semi-colon indicates ‘or’ within the description of the grade.
An ‘Em dash’ (—) indicates a grade not available.
Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5
Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.
The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: ‘Death not associated with CTCAE term – Select’ with 4 AE options: Death NOS, Disease progression NOS, Multi-organ failure, Sudden death.

Important:
• Grade 5 is the only appropriate Grade
• This AE is to be used in the situation where a death

1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
2. cannot be reported within a CTCAE CATEGORY as ‘Other (Specify)’

# Normal tissue tolerance

## Classification of adverse effects  
**CTCAE vs. 3.0**

<table>
<thead>
<tr>
<th>NEUROLOGY</th>
<th>Grade</th>
<th>Page 5 of 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>Short Name</td>
<td>1</td>
</tr>
<tr>
<td>Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)</td>
<td>Pyramidal tract dysfunction</td>
<td>Asymptomatic, abnormality on exam or testing only</td>
</tr>
<tr>
<td>Seizure</td>
<td>Seizure</td>
<td>—</td>
</tr>
<tr>
<td>Somnolence/depressed level of consciousness</td>
<td>Somnolence</td>
<td>—</td>
</tr>
<tr>
<td>Speech impairment (e.g., dysphasia or aphasia)</td>
<td>Speech impairment</td>
<td>—</td>
</tr>
</tbody>
</table>

**Remark:** Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction.

**Also consider:** Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).

## Normal tissue tolerance

### Classification of adverse effects CTCAE vs. 3.0

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental: periodontal disease</td>
<td>Periodontal</td>
<td>Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss</td>
<td>Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss</td>
<td>Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Remark:** Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.

| Dental: teeth | Teeth | Surface stains; dental caries; restorable, without extractions | Less than full mouth extractions; tooth fracture or crown amputation or repair indicated | Full mouth extractions indicated | — | — |

| Dental: teeth development | Teeth development | Hypoplasia of tooth or enamel not interfering with function | Functional impairment correctable with oral surgery | Maldevelopment with functional impairment not surgically correctable | — | — |

| Diarrhea | Diarrhea | Increase of ~4 stools per day over baseline; mild increase in ostomy output compared to baseline | Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL | Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL | Life-threatening consequences (e.g., hemodynamic collapse) | Death |

**Remark:** Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea.

**Also Consider:** Dehydration; Hypotension.

| Distension/bloating, abdominal | Distension | Asymptomatic | Symptomatic, but not interfering with GI function | Symptomatic, interfering with GI function | — | — |

**Also Consider:** Ascites (non-malignant); ileus, GI (functional obstruction of bowel, i.e., neccessitiation); Obstruction, GI – Select.

### Normal tissue tolerance

#### Classification of adverse effects  CTCAE vs. 3.0

<table>
<thead>
<tr>
<th>PULMONARY/UPPER RESPIRATORY</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Name</td>
<td>1</td>
</tr>
<tr>
<td>Nasal cavity/paranasal sinus reactions</td>
<td>Nasal/paranasal reactions</td>
</tr>
<tr>
<td>Obstruction/stenosis of airway</td>
<td>Airway obstruction</td>
</tr>
<tr>
<td>Pleural effusion (non-malignant)</td>
<td>Pleural effusion</td>
</tr>
</tbody>
</table>

**Also Consider:** Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – Select; Infection with normal ANC or Grade 1 or 2 neutrophils – Select; Infection with unknown ANC – Select.

**Also Consider:** Atelectasis, Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).

**Navigation Note:** Pleuritic pain is graded as Pain – Select in the PAIN CATEGORY.