Refresher Course

The Medical Diagnosis and Treatment of Radiation Overexposed People

Jean Marc BERTHO, Nina M. GRIFFITHS and Patrick GOURMELON

Institute for Protection and Nuclear Safety
Radiation Accidents = Rare Events
1950 - 2001

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
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<tbody>
<tr>
<td>Number of Accidents</td>
<td>~ 500</td>
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<tr>
<td>Number of Victims:</td>
<td>~ 2,000</td>
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<tr>
<td>Number of Reported Deaths:</td>
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<td>Reactors</td>
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<td>Chernobyl + Navy</td>
<td>40</td>
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<td>Sources</td>
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<td>Medicine</td>
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<tr>
<td>Industry</td>
<td>30</td>
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</table>

(4 accidents) (15 accidents)
Past Doctrine

- Risk Areas are perfectly identified
  - Accidental exposure to medical, industrial, or military source
  - Breach in nuclear reactor core (Chernobyl)

- Issue of orphan sealed source

- Unintended accident scenario

- Accidents involving a small number of people requiring treatment
Terrorism Threat in the Present Situation

- Willingness to inflict mass casualties
- Spread of the suicidal attitude of the terrorists
- Use of sophisticated technologies
- Extension of the nuclear terrorist threat to the chemical and biological fields
New Doctrine NRBC

- Situation of « Major » Accident
- Unpredictable Event Site
- “All-Hazards” Approach

NRBC Doctrine
- N ➔ Nuclear
- R ➔ Radiological
- B ➔ Biological
- C ➔ Chemical

Any event must be considered and handled as NRBC a priori until properly classified

New strategies, including medical ones, are needed to respond to new specific risks
Potential Intentional Radiation Scenarios

- Dispersion of radioactivity without explosives
- Concealment of unshielded Sources
- Radiation Dispersal Devices (RDD) “Dirty Bombs”
- Attack of Nuclear Reactors
- Hijacking of Nuclear Weapons or Improvised Nuclear Devices (IND)
The Scenarios in Terms of Health Consequences

**EVENT SCENARIO**
- Immediate victims localized in space
  - Foreseeable Mass Casualties
    - Immediate Psycho-social impact
      - Radiation Dispersal Devices « Dirty Bomb »
      - Wounds, Burns, Contaminations
      - Immediate Vital Risk
        - Long Term Risk: cancer
  - Unshielded Source Concealment
    - High activity
      - Whole Body Irradiation
      - Immediate Vital Risk
        - Acute Radiation Syndrome

**INSIDIOUS SCENARIO**
- Victims distributed in time and scattered in space
  - Mass Casualties?
    - Delayed Psycho-social impact
      - Radionuclide Dispersion
      - Strict Contamination
      - Long Term Risk: cancer
  - Unshielded Source Concealment
    - Medium activity
      - Localized Irradiation
      - Cutaneous Radiation Injuries
        - without Vital Risk
Scenario 1: Medical Management Doctrine for Radiation Dispersal Device « Dirty Bomb »

- Pyrotechnic Risk + Radiological Risk
- Burns, Blasts, Wounds associated with:
  - External Contamination
  - Internal Contamination by inhalation and/or by wounds

Immediate Vital Risk

Application of the usual principles of the conventional Resuscitation

Golden Rule

The Medical and Surgical Emergencies prevail over the Radiological Emergency

Medicochirurgical Triage

- Absolute Emergency
- Relative Emergency
External Decontamination
(Undressing, Showering, Washing)

◆ The External Contamination has to be taken into account as soon as Possible
  ● « Radiological Burn Syndrome »
  ● Factor of Dispersion of Radionucleides
  ● Secondary Internal Contamination

Superficial Beta Radiation Burns

Tchernobyl 30 Days
BASIC SCHEME OF MEDICAL AND RADIOLOGICAL TRIAGE ON SCENE OF THE ACCIDENT OR THE ATTACK

EXCLUSION ZONE

VICTIM ASSEMBLY POINT
2nd TRIAGE*

CONTROLED ZONE

DECONTAMINATION CHAINS

ADVANCED MEDICAL POST

LIFE-THREATENING PERSON EVACUATION POINT

SUPPORT ZONE
Clean Area

CLOSEST HOSPITAL

BURN TREATMENT CENTER

SPECIALIZED HOSPITAL

RECEPTION FACILITY

STAFF ENTRANCE AIRLOCK

STAFF EXIT AIRLOCK

MARKING AREA

PICKING NORIA
1st TRIAGE*

NON LIFE-THREATENING PERSON DECONTAMINATION

DECONTAMINATION CHAINS

EVACUATION NORIA

STAFF EXIT AIRLOCK

STAFF ENTRANCE AIRLOCK

MARKING AREA
The Scenarios in Terms of Health Consequences

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    - Localized Irradiation
    - Cutaneous Radiation Injuries
    - without Vital Risk
# Sealed Source in Subway

## Acute Radiation Syndrome

### Co-60 Source 1000 Ci

<table>
<thead>
<tr>
<th>Distance (m)</th>
<th>Dose Rate (Gy/h)</th>
<th>Dose in 30 mn (Gy)</th>
<th>Number of victims Each 30 mn of exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>50</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>12.5</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>1.5</td>
<td>16</td>
</tr>
</tbody>
</table>

- About 30 Acute Radiation Sickness each 30 mn of exposure and for 1000 Curies

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Radiothérapie
The Acute Radiation Syndrome (ARS)

Initial phase

Acute phase

Severity

Dose (Gy)

Time after exposure

minutes hours days weeks

0.5 1.5 2 10 25

Latency period

Severity

Dose (Gy)

Time after exposure

minutes hours days weeks

0.5 1.5 2 10 25

Latency period

The diagram illustrates the progression of the Acute Radiation Syndrome (ARS) over time after exposure. The severity of the syndrome is shown along the y-axis, with dose (Gy) on the x-axis. The time after exposure is divided into minutes, hours, days, and weeks, allowing for the visualization of different latency periods and acute phases of the syndrome.
### The Prodromal Phase of the ARS (24 Hours)

- Asthenia, Fatigue syndrome
- Anorexia
- Nausea
- Emesis
- Diarrhea

- Headache
- Hyperthermia
- Hypotension
- Cognitive deficits « Transient Incapacitation Syndrome »
  « Permanant Incapacitation Syndrome »

- Erythema
The Prodromal Phase of the ARS
Anorexia, Nausea, Emesis
Prodromal Phase of Tokai Mura Accident

The Criticality

Time

O’clock

10:35

Workers

- A: loss of consciousness, vomiting, diarrhea
- B: vomiting, nausea
- C: nausea

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The Prodromal Phase of the ARS
Decrease of the Lymphocyte Count

(Adapted from Andrews, 1980)
The Acute Radiation Syndrome (ARS)

Time after exposure:
- Initial phase:
  - Latency period: 5 days
  - Acute phase:
    - 0.5, 1.5, 5 gy levels

Severity:
- Dose (Gy):
  - 0.5, 1.5, 5, 10, 25 gy levels

Graph:
- X-axis: minutes, hours, days, weeks
- Y-axis: dose (Gy)
- Z-axis: severity

Graph shows the time after exposure and the severity of ARS at different levels of dose and time periods.
Mean Survival Time without Treatment as a Function of Dose after Homogenous Whole-body Irradiation


- Hematopoietic Syndrome
- Gastro-Intestinal Syndrome
- Cerebrovascular Syndrome
The Acute Radiation Syndrome
Whole-body Irradiation

- **Bone Marrow**
  - 12 Gy

- **Gastrointestinal**
  - 30 Gy

- **Cerebrovascular**

- **Subclinical**
  - 1 Gy

**Increasing Dose**

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The Hematopoietic Syndrome
The Compartmentalisation of Hematopoiesis

Normal Physiological situation

- Resting Stem Cells
- Proliferating compartment: Stem Cell and Progenitors
- Differentiating compartment: Precursors
- Mature Cells

Block of Proliferation, Cell Death

Activation → Proliferation, Differentiation

Depletion by lack of Renewal

Blood Aplasia

BLOOD

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Survival Curve for CFU-S

( Hall E.J. Radiobiology for the Radiologist, 2000 )
Peripheral Blood Aplasia

![Graphs showing changes in platelets, lymphocytes, and neutrophils over time after exposure.](image-url)
The Concept of Residual Hematopoiesis

◆ Some Hematopoietic Stem Cells can survive to Irradiation:
  ● They are radioresistant due to their resting state
  ● Accidental Irradiation are heterogeneous, leading to the protection of some bone marrow territories

◆ This is the concept of Residual Hematopoiesis.

◆ Then, an endogeneous reconstitution of the hematopoiesis can be observed, with sub-lethal or lethal doses of irradiation
Accidental Heterogenous Irradiation
Mol, Belgium, 1965.

- Estimated mean dose to bone marrow: 5 Gy.
- But 16% of bone marrow received less than 1 Gy.
Chimerism after Cord Blood Transplantation
Tokaï Mura Accident
Treatment of the Hematopoietic Syndrome

◆ REVERSIBLE DAMAGE TO THE BONE MARROW
  ● Substitution And /Or Supportive Therapy
  ● STIMULATION THERAPY (Cytokine, G-CSF, GM –CSF, TPO, EPO )

◆ IRREVERSIBLE DAMAGE TO THE BONE MARROW
  ● Substitution And Supportive And Stimulation Therapy
  ● Additionally to Stem Cell Transplantation Therapy

◆ ASSOCIATED WITH IRREVERSIBLE DAMAGE OF OTHERS ORGANS (Gut, CNS)
  ➔ Palliative Therapy
Stem Cell Therapy

- Accidental Radiation Overdose
- 29 Patients with Hematopoietic Stem Cell Transplantation
- No Permanant Engraftment
- 24% of patients Graft-versus-host Disease (GVHD)

- Case Selection:
  - Autologous or syngenic Hematopoietic SCT
  - Narrow Dose Therapeutic Window:
    Lethal Marrow Injury without Lethal Injury to other organs (<10 Gy)

→ It is difficult to be optimistic about the contribution of hematopoietic SCT to treat patients of radiation overdose.
The Gastro-intestinal Syndrome

Control

16 Gy Day 5

Fluid and Electrolyte Loss

Disrupt Crypts

Denudation of villi

Endotoxemia, Bacteremia

DEATH
The Cerebrovascular Syndrome

- > 50 Gy
- Permanent Incapacitation Syndrome
- Disorientation
- Confusion
- Prostration
- Ataxia
- Seizures
- Absence Deep tendon and Corneal Reflexes
- Hyperthermia
- Respiratory Distress
- Cardiovascular Shock
- Death within 2 days
THE DOGMA OF THE ARS

Single Organ Failure

BM

GUT

CNS
Manifestations of the ARS

Dose (in Gy) | Morphological manifestations (lesions)
---|---
1 | hematopoietic
5 | gastrointestinal
10 | Cerebro-vasc.
20 | 
50 | 

Functional manifestations

| System | 
|---|---|
| hematopoietic | 
| gastrointestinal | 
| cerebro-vasc. | 
Multiple Organ Dysfunction Syndrome (MODS)
Tokaï-Mura Accident

Haematopoietic syndrome

Gastrointestinal disease

Cutaneous syndrome

Lung disease

Kidney dysfunction

Liver dysfunction

IRRADIATION

Time after irradiation (weeks)

1 2 3 4 5 6 7 8 9 10 11 death

Haematopoietic syndrome

Gastrointestinal disease

Cutaneous syndrome

Lung disease

Kidney dysfunction

Liver dysfunction

PBSCT

Aplasia

Hemophagocytosis

Diarrhoea

GI bleeding

Erythema, Blister

Massive exudate

Lung oedema
The New Concept:
Multiple Organ Dysfunction Syndrome (MODS)
Multiple Organ Failure (MOF)
Possible Mechanisms for MOF in Radiation

(From Dr Makoto Akashi)
MULTIPLE ORGAN DYSFUNCTION SYNDROME (MODS)

DOSE

TYPE OF PARTICLE
Neutron, Gamma, X

IRRADIATED VOLUME
Heterogeneity of the Dose

HOST RESPONSE TO THE INSULT
Biological Dosimetry Versus Biological Indicators

- Dose assessment is not well adapted for the medical management of overexposed victims

- Absolute necessity to identify biological indicators of damages and if possible prognosis indicators

- The assessment of the heterogeneity of the irradiation and the spatial distribution of the dose is a high priority for the diagnosis and the therapeutic strategy (Bone marrow transplantation decision)
MEDICAL MANAGEMENT OF RADIATION ACCIDENTS

Edited by T M Fledner, I Friessecke and K Beyrer

MANUAL ON THE ACUTE RADIATION SYNDROME

BIR Published by The British Institute of Radiology

METREPOL
## Overall Prognostic Aspects of the ARS on the Basis of the Organ Specific Grading and Manifestations

### Organ System
- **N**: neurovascular system
- **H**: haematopoietic system
- **C**: cutaneous system
- **G**: gastrointestinal system

### Manifestations of the Acute Radiation Syndrome

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Degree 1</th>
<th>Degree 2</th>
<th>Degree 3</th>
<th>Degree 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Serious/fatal</td>
</tr>
<tr>
<td></td>
<td>Damage</td>
<td>Damage</td>
<td>Damage</td>
<td>Damage</td>
</tr>
</tbody>
</table>

- Degree 1: Mild Damage
- Degree 2: Moderate Damage
- Degree 3: Severe Damage
- Degree 4: Serious/fatal Damage
Organ Specific Grading System for the Gastrointestinal System (G)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Degree 1 Mild</th>
<th>Degree 2 Moderate</th>
<th>Degree 3 Severe</th>
<th>Degree 4 Serious/fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency, stools/day</td>
<td>2-3</td>
<td>4-6</td>
<td>7-9</td>
<td>&gt; 10</td>
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<tr>
<td>Consistency</td>
<td>Bulky</td>
<td>Loose</td>
<td>Loose</td>
<td>Watery</td>
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<tr>
<td>Bleeding</td>
<td>Occult</td>
<td>Intermittent</td>
<td>Persistent</td>
<td>Persistent with large amount</td>
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<tr>
<td>Abdominal cramps or pain</td>
<td>Minimal</td>
<td>Moderate</td>
<td>Intense</td>
<td>Excruciating</td>
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</table>
### Organ Specific Grading System for the Hematopoietic System (H)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Degree 1 Mild</th>
<th>Degree 2 Moderate</th>
<th>Degree 3 Severe</th>
<th>Degree 4 Serious fatal</th>
<th>Reference values</th>
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<tr>
<td><strong>Lymphocyte changes</strong></td>
<td>&gt; 1.5 x 10⁹ cells/L</td>
<td>1-1.5 x 10⁹ cells/L</td>
<td>0.5-1 x 10⁹ cells/L</td>
<td>&lt; 0.5 x 10⁹ cells/L</td>
<td>1.4-3.5 x 10⁹ cells/L</td>
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<tr>
<td><strong>Granulocyte changes</strong></td>
<td>&gt; 2 x 10⁹ cells/L</td>
<td>1-2 x 10⁹ cells/L</td>
<td>0.5-1 x 10⁹ cells/L</td>
<td>&lt; 0.5 x 10⁹ cells/L</td>
<td>4-9 x 10⁹ cells/L</td>
</tr>
<tr>
<td><strong>Thrombocyte changes</strong></td>
<td>&gt; 100 x 10⁹ cells/L</td>
<td>50-100x10⁹ cells/L</td>
<td>20-50x 10⁹ cells/L</td>
<td>&lt; 20 x 10⁹ cells/L</td>
<td>140-400x10⁹ cells/L³</td>
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<td><strong>Blood loss</strong></td>
<td>Petechiae, easy bruising, normal hemoglobin level</td>
<td>Mild blood loss with &lt;10% decrease in hemoglobin level</td>
<td>Gross blood loss with 10%-20% decrease in Hemoglobin level</td>
<td>Spontaneous bleeding or blood loss with &gt;20% decrease in hemoglobin level</td>
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</table>
General Approach to Triage and Therapy of the ARS

GRADING CODE: Nᵢ Hᵢ Cᵢ Gᵢ

1. Ambulatory Monitoring
2. Blood Component Transfusion
3. Hospitalization
   - Blood Component Transfusion
   - Growth Factor Therapy
4. ICUs
   - Blood Component Transfusion
   - Growth Factor Therapy
   - Stem Cell Transplantation Therapy

Adapted from N. Dainiak (2003)
<table>
<thead>
<tr>
<th>Degree of damage</th>
<th>RC 1</th>
<th>RC 2</th>
<th>RC 3</th>
<th>RC 4</th>
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<tbody>
<tr>
<td>Mild</td>
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<td>Serious/Fatal</td>
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<tr>
<td>Prognosis</td>
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<tr>
<td>Spontaneous</td>
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<tr>
<td>Recovery</td>
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<td>Certain</td>
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<td>Likely</td>
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<td>Possible</td>
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<td>Most unlikely</td>
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<tr>
<td>Hospitalisation</td>
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<tr>
<td>Not necessary</td>
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<td>Outpatient care</td>
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<tr>
<td>Observation</td>
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<td>1 week, then</td>
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<td>Outpatient care</td>
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<td>Necessary</td>
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<td>Emergency,</td>
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<tr>
<td>Intensive care</td>
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<td>Necessary</td>
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<tr>
<td>Therapy</td>
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<tr>
<td>Not necessary</td>
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<td>Bridging therapy</td>
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<td>Intensive</td>
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<td>Therapeutic</td>
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<td>Approaches</td>
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<tr>
<td>Invasive therapy</td>
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<tr>
<td>Necessary</td>
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</table>
Conclusion of the ARS

◆ In accidents, the exposure parameters are generally completely or partially unknown.
◆ The accidental situation is almost always heterogeneous.
◆ There is a residual hematopoiesis.
◆ There is a combined syndrome involving hematopoietic, gastrointestinal and nervous systems and skin leading to MODS and MOF.
◆ The pathology is complex, and difficult to treat.
◆ The outcome will depend on two factors
  • Physical parameters of irradiation: dose, dose rate
  • Heterogeneity of the irradiation
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  - Cutaneous Radiation Injuries
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The Cutaneous Radiation Syndrome

◆ Three Layers:
  - Epidermis (Hierarchical Tissue)
  - Dermis (Flexible)
  - Hypodermis (Flexible)

◆ The Skin Can Present Early And Late Post-radiation Reactions

◆ Early reactions essentially involve epidermis while late reactions involve the 3 skin layers.
The Cutaneous Radiation Syndrome

Acute Phases

Subacute Phase

Chronic Phase

Late Phase

4 H 24 H 48 H 4 Days 40 Days 1 year 10 Years
# The Cutaneous Radiation Syndrome

## Early Effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dose Range</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>6 - 12 Gy</td>
<td>Hours - 30 days - 10 weeks</td>
</tr>
<tr>
<td>Dry Desquamation</td>
<td>12 - 15 Gy</td>
<td>5 days – 8 weeks</td>
</tr>
<tr>
<td>Moist Desquamation</td>
<td>15 - 20 Gy</td>
<td>5 days - &gt;12 weeks</td>
</tr>
<tr>
<td>Ulcer/ Necrosis</td>
<td>25 - 30 Gy</td>
<td>2 - 8 weeks</td>
</tr>
<tr>
<td>Hair Loss</td>
<td>4 - 5 Gy</td>
<td></td>
</tr>
</tbody>
</table>

## Late Effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperpigmentation or Depigmentation</td>
<td>&gt; 12 Weeks</td>
</tr>
<tr>
<td>Keratosis</td>
<td>&gt; 12 Week</td>
</tr>
<tr>
<td>Atrophy</td>
<td>&gt; 12 Weeks</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>&gt; 12 Weeks</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>&gt; 12 weeks</td>
</tr>
</tbody>
</table>
Classical Surgical Treatment of the Cutaneous Radiation Syndrome

- Conservative treatment for superficial lesions of distal extremities
- Surgery for painful deep ulcerations and necrosis
  - Ulcerectomy
  - Necrectomy
  - Wound closure by rotation flap
  - Amputation
- In cases of profound and large necrosis, the lesion should be excised and the wound bed should be covered with a good quality, full-thickness skin graft
Artificial Skin Description  INTEGRA®
Bilayer Membrane Skin Replacement System

Dermal Replacement Layer + silicone layer

Integra  Neoderma Formation

2 Weeks
Neoderma Formation

50 Skin Autograft
Meshed
Silicone Layer
Removal
First Georgian Source Accident
Lilo 1997

Artificial Skin Graft

Unmeshed Autograft

Final Aspect
Second Georgian Accident Lia 2002 Day 88 P.I.

Day 140

Intergra Day 110

2nd Autograft Day 40

1st Autograft Day 110

Exeresis Day 180
Conclusion of the Cutaneous Radiation Syndrome

- The lesion is dynamic versus time: occurrence of sequence of waves
- The lesions can occur very late
- The radiological lesions lasting for more than one month have to be grafted.
- In any case the wound must left open.
- Wide and deep excision must be performed beyond of the necrotic tissues
- The necrosis is deep and can grow after each exeresis
- Final covering of the lesion by autograft of the lesion must be performed when the lack of the evolution of the wound bed is evident
- Pain is a prognosis indicator of recurrence
- The cicatrization is long, fragile and unpredictable
Psychosocial Issues: Major Health Impact

- **Acute Stress Reactions**
  - Exposed and Unexposed Persons
  - Some of these reactions could mimic radiation overexposure (Nausea, Vomiting, Rashes)
  - Anxiety attack, Hysterical attack, Headlong Flight, Stupor

- **Chronic Reactions**
  - Social withdrawal, Impaired Concentration, Insomnia, Chronic Anxiety
  - Deterioration in Quality of Life
  - Post Traumatic Stress Disorder

- **Social Stigma**
  - Social Discrimination (Goiania Accident)

- Early Psychological Care of Victims

- Post-accidental Epidemiology
  - Issue of the census of exposed and implicated population
Cytokine-based treatment for radiation-induced myelo- and/or immune suppression

Available now:
Granulocyte colony-stimulating factor (G-CSF)
Granulocyte-macrophage colony-stimulating factor (GM-CSF)
Pegylated G-CSF (Peg-G-CSF)

Future?
Single cytokine treatment
Interleukin-7 (IL-7)
Keratinocyte growth factor (KGF)
flt-3 (FL)
Thrombopoietin (TPO)