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Health effects of radiation (acute and late effects)

Hideo Tatsuzaki, M.D., Ph.D.

National Institute of Radiological Sciences (NIRS)

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- Classification of radiation effect (Stochastic effects and Deterministic Effects)
- Acute radiation syndrome
- Dose assessment
- Effect on organ systems
- Local radiation injury
- Late effects

Stochastic effect?

Specific Biological Effects
Dose – Response Models

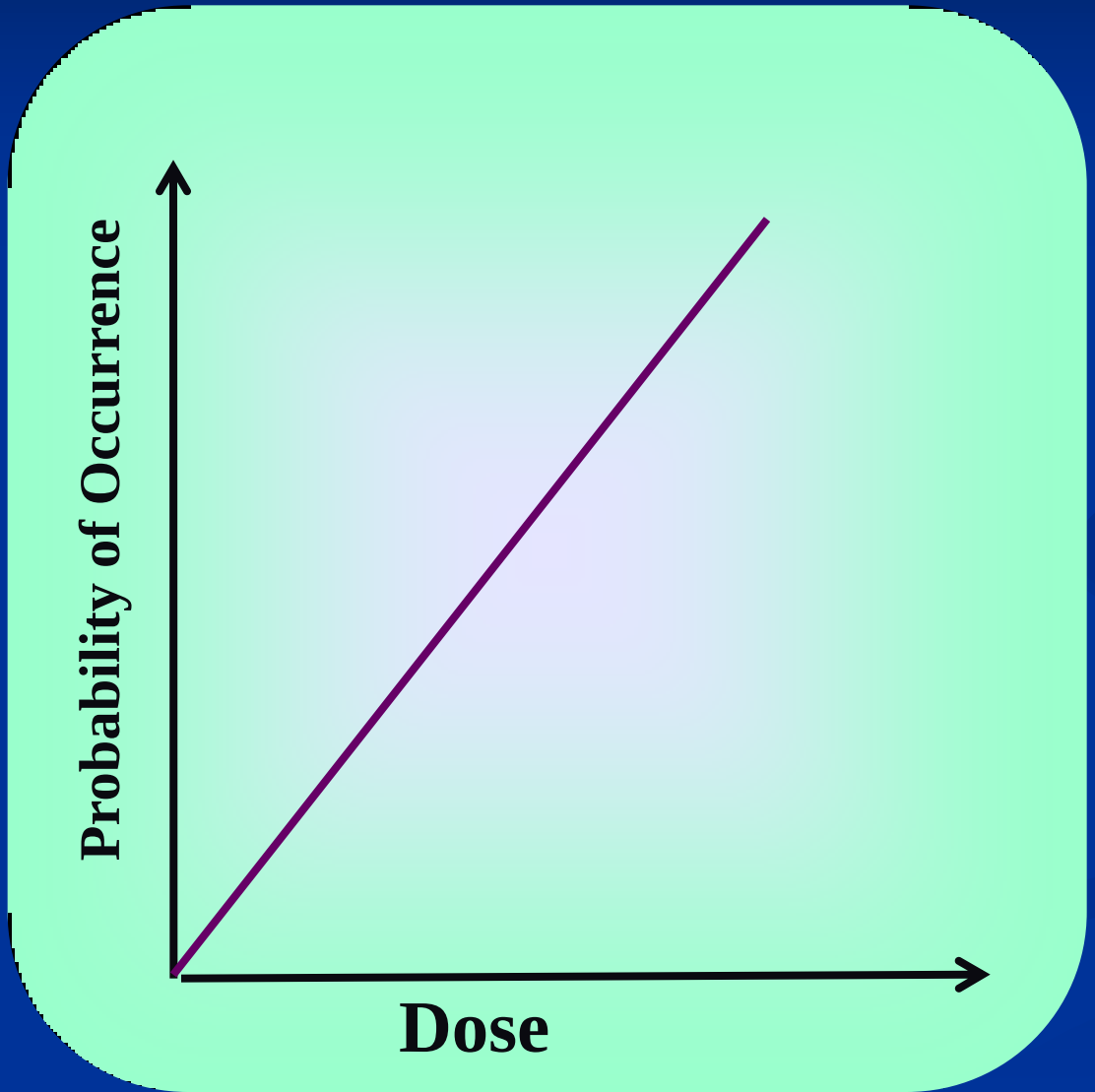
Stochastic Effects

- Severity independent of dose (both somatic and genetic)
- Examples: leukemia, malignant tumors

Deterministic Effects

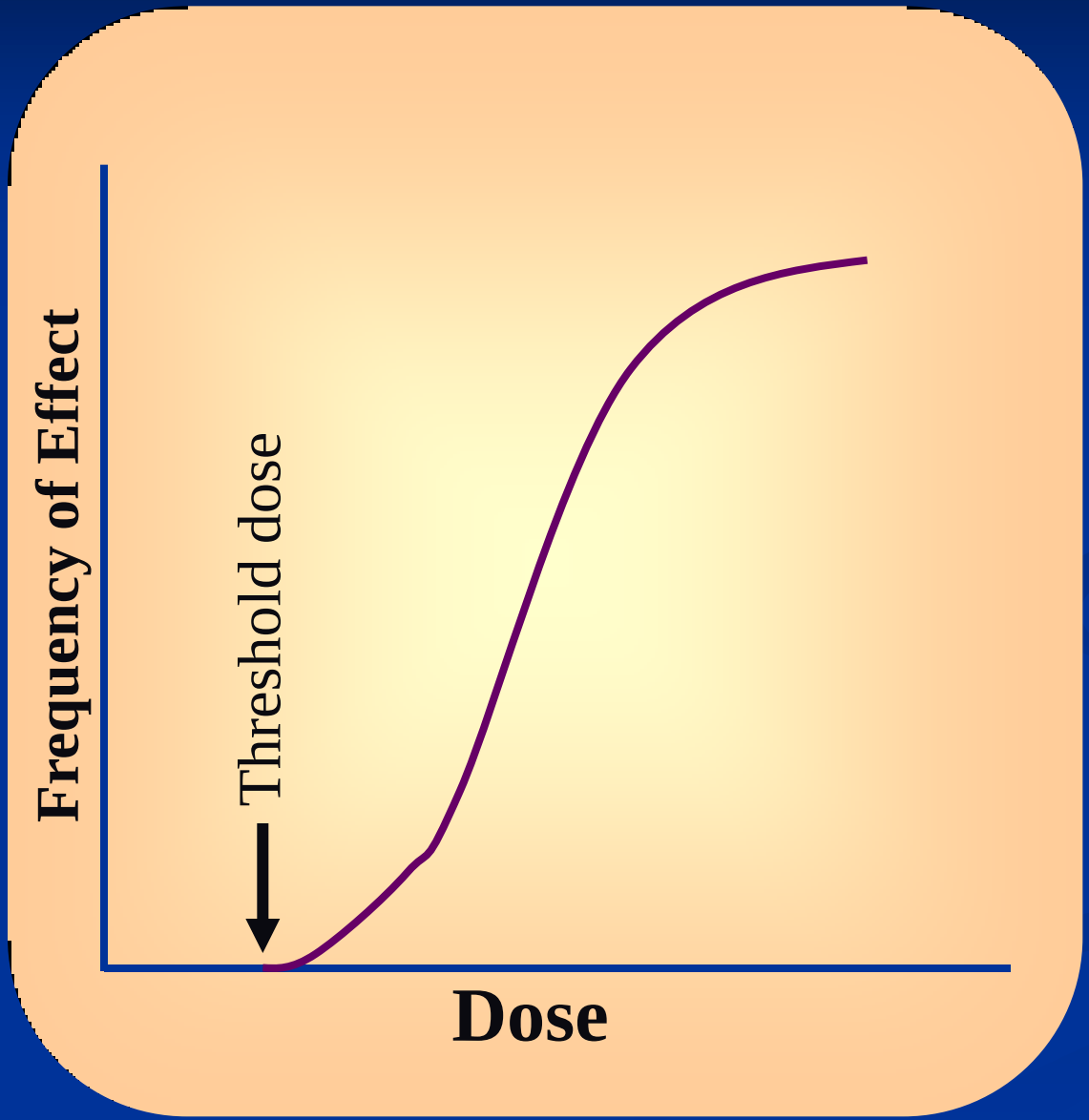
- Severity varies with magnitude of dose, above a threshold dose (somatic)
- Examples: cataracts, fertility impairment

Linear No Threshold Response

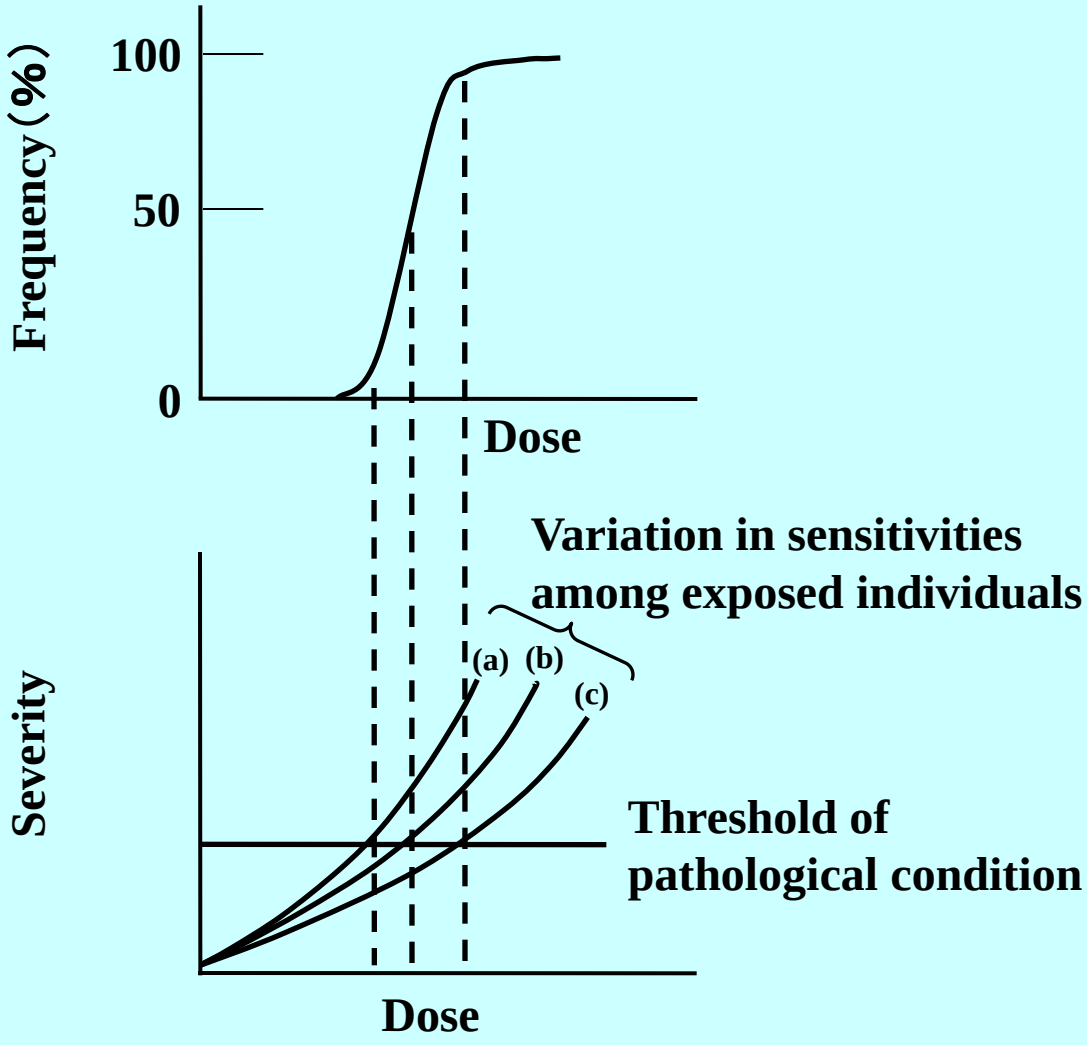


- Applies to stochastic effects
- Assumes that any amount of radiation has some detrimental effect

Nonlinear Threshold Response



- Applies to deterministic effects



Relationships between dose and the frequency and severity of tissue reactions (deterministic effects). Upper panel : expected sigmoidal increase in frequency in a population of individuals with varying sensitivities. Lower panel : expected dose-severity relationships for three individuals with different sensitivities. from ICRP (1991b).

Table 1: Thresholds for Tissue Reactions (radiation doses that cause a 1% reaction)

Projected threshold estimates of the acute absorbed doses for 1% incidences of morbidity and mortality involving adult human organs and tissues after whole body gamma ray exposures.

Effect	Organ/tissue	Time to develop effect	Absorbed dose (Gy)[e]
Morbidity:			1% Incidence
Temporary sterility	Testes	3–9 weeks	~0.1[a,b]
Permanent sterility	Testes	3 weeks	~6[a,b]
Permanent sterility	Ovaries	< 1 week	~3[a,b]
Depression of blood-forming process	Bone marrow	3–7 weeks	~0.5[a,b]
Main phase of skin reddening	Skin (large areas)	1–4 weeks	< 3~6[b]
Skin burns	Skin (large areas)	2–3 weeks	5~10[b]
Temporary hair loss	Skin	2–3 weeks	~4[b]
Cataracts (visual impairment)	Eyes	Several years	~1.5[a,c]
Mortality:			
Bone marrow syndrome:			
without medical care	Bone marrow	30–60 days	~1[b]
with good medical care	Bone marrow	30–60 days	2~3[b,d]
Gastro-intestinal syndrome:			
without medical care	Small intestine	6–9 days	~6[d]
with good medical care	Small intestine	6–9 days	> 6[b,c,d]
Pneumonitis	Lung	1–7 months	6[b,c,d]

a) ICRP (1984)
b) UNSCEAR (1988)
c) Edwards and Lloyd (1996)
d) Scott and Hahn (1989), Scott (1993)
e) Most values rounded to the nearest Gy; ranges indicate area dependence for skin and differing medical support for bone marrow.

(Source: ICRP Publication 103 (The 2007 Recommendations of the International Commission on Radiological Protection))

Deterministic effects from Glossary of ICRP103 (2007)

- Deterministic effect

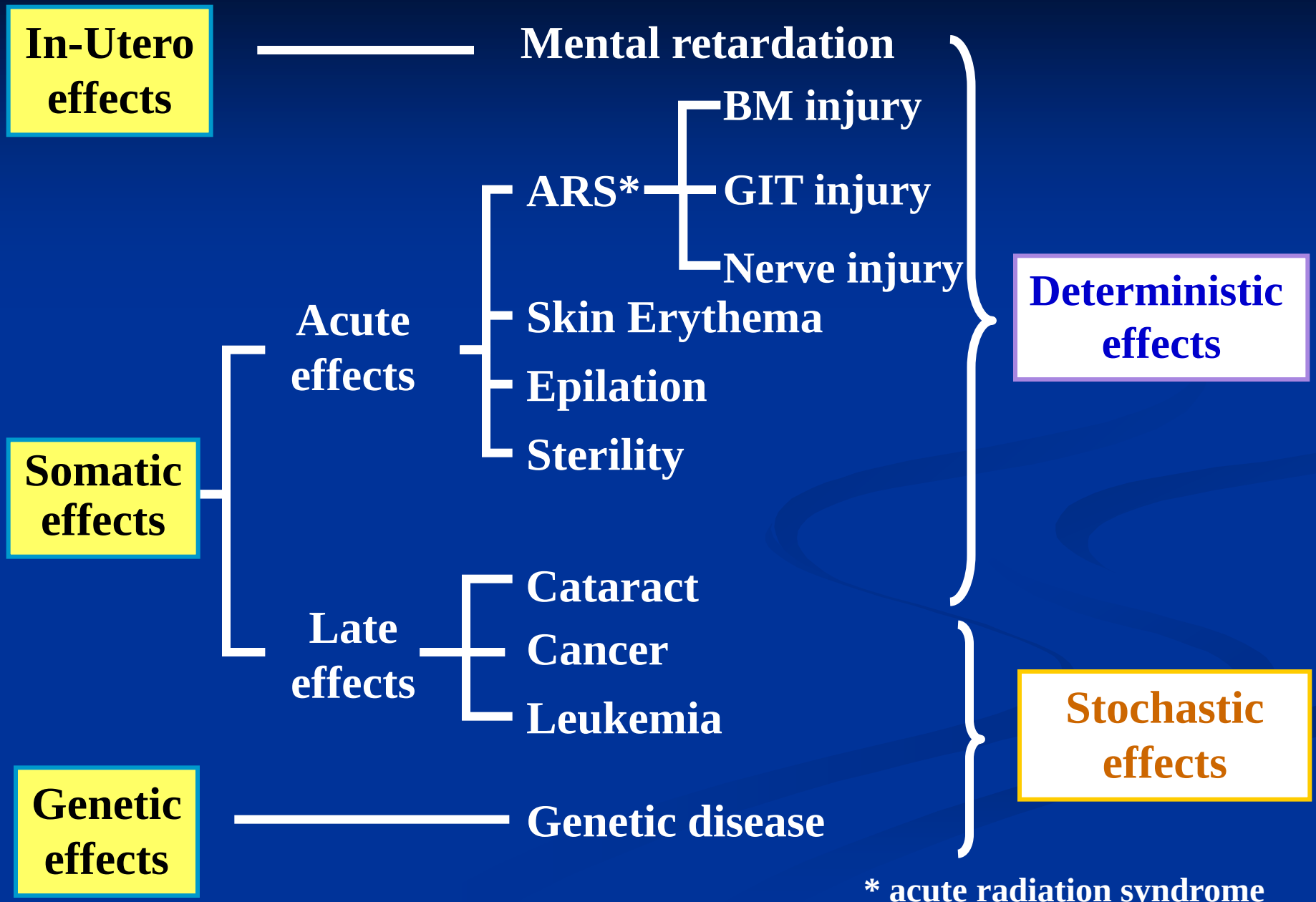
- Injury in populations of cells, characterised by a threshold dose and an increase in the severity of the reaction as the dose is increased further. Also termed tissue reaction. In some cases, deterministic effects are modifiable by post-irradiation procedures including biological response modifiers.

Stochastic effects from Glossary of ICRP103 (2007)

- Stochastic effects of radiation

- Malignant disease and heritable effects for which the probability of an effect occurring, but not its severity, is regarded as a function of dose without threshold.

Human Effects of Radiation



* acute radiation syndrome

What happen after high dose whole body exposure?

Acute radiation syndrome (ARS)

Concept and prodromal syndrome

Acute Radiation Syndrome

DEFINITION

A combination of clinical syndromes occurring in stages during a period of minutes / hours to weeks after exposure, as injury to various tissues and organs is expressed. ARS is caused by brief exposure of a major part of the body to more than approximately 1 Sv.

Acute Radiation Syndrome

- A Large Gamma Radiation Dose in a Short Duration

  $LD_{50/30} = 4.50$ Gy

  - Lethal dose to 50% of population in 30 days without treatment

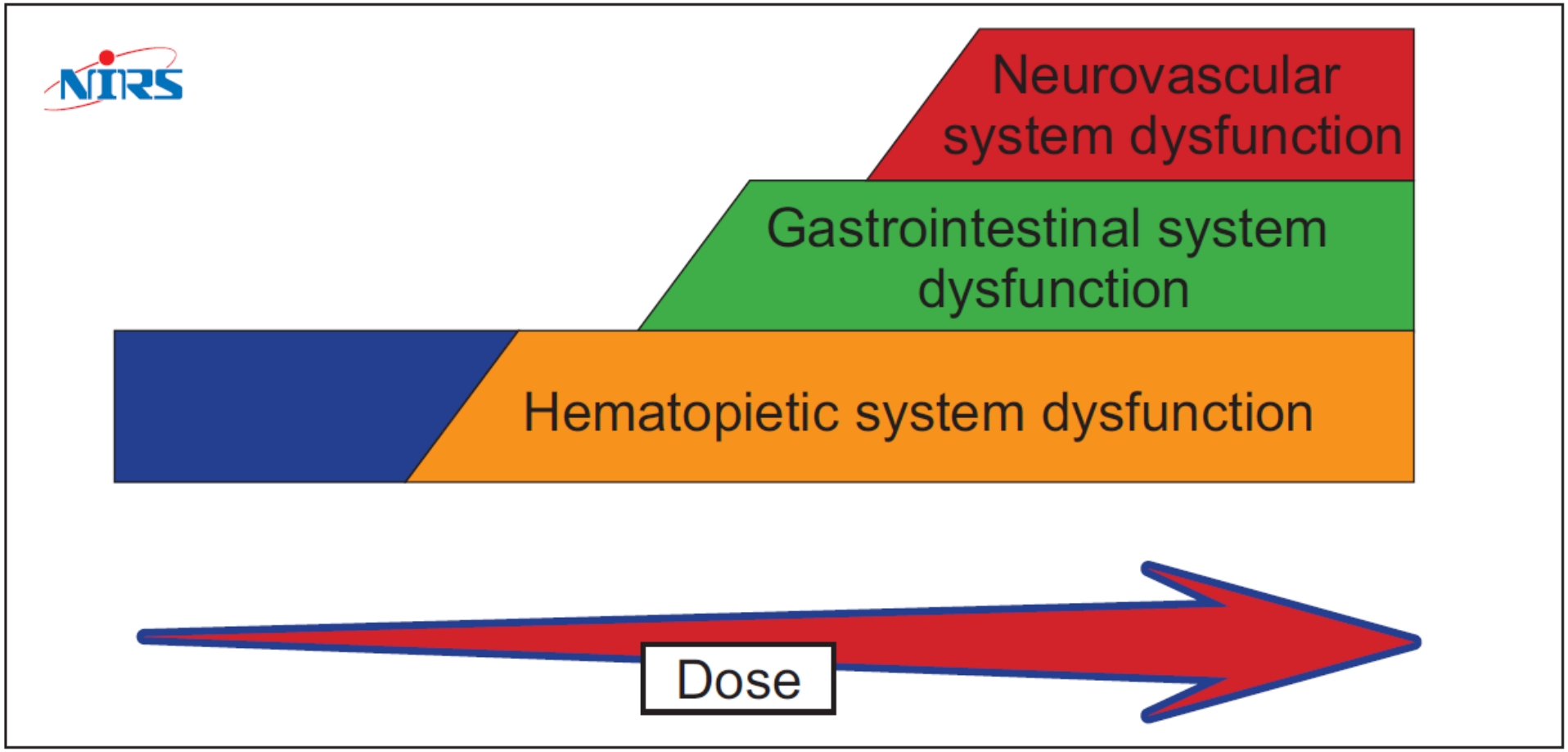
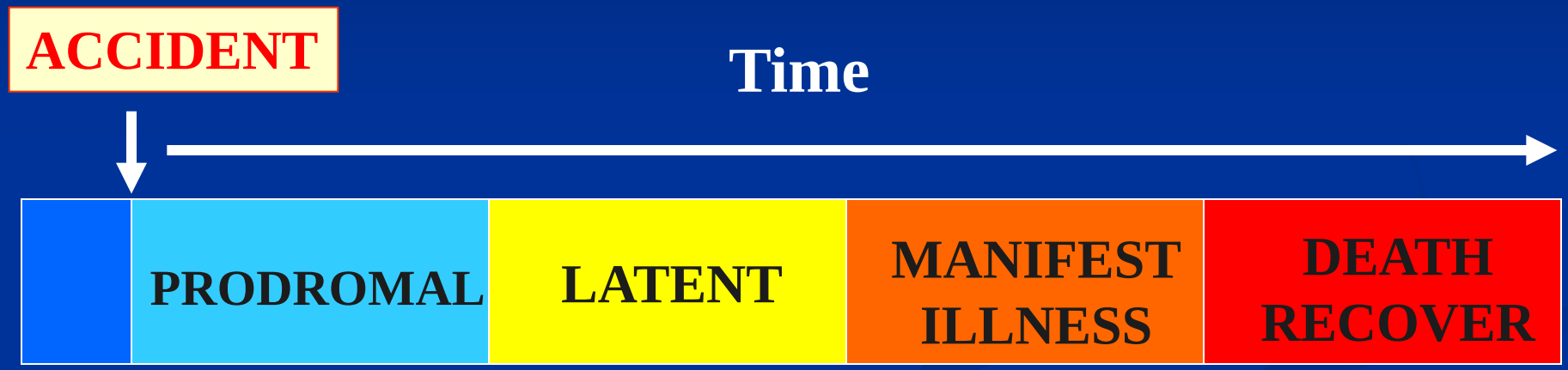


Fig. 3 Radiation Doses and Symptoms of Acute Radiation Syndrome

Time Course of Acute Radiation Syndrome



- Asymptomatic

- Anorexia
- Nausea
- Vomiting
- Diarrhea

- Return of Prodromata
- Infection
- Hemorrhage

Dose assessment

Required for estimation of prognosis and selection of treatment options

How do we estimate exposed dose?

Dose assessment

- Biological methods
  - Clinical symptoms
  - Lymphocyte count
  - Chromosome analysis
- Physical methods
  - Reconstruction
  - ESR
    - others

Dose assessment

	findings	Time course	dose(Gy)
Clinical symptoms	Nausea, vomiting	48 h	～1
	erythema	5 h～ several days	～3
	Hair loss	2～3 w	～3
CBC	Lymphocyte <1000/mm^3	24～72 h	～0.5
Chromosome analysis	Abnormal chromosomes (dicentrics, etc.)	Several hours (several days for result)	～0.2

（IAEA/WHO Safety Report Series No.2 Diagnosis and Treatment of Radiation Injury 1988より改変）

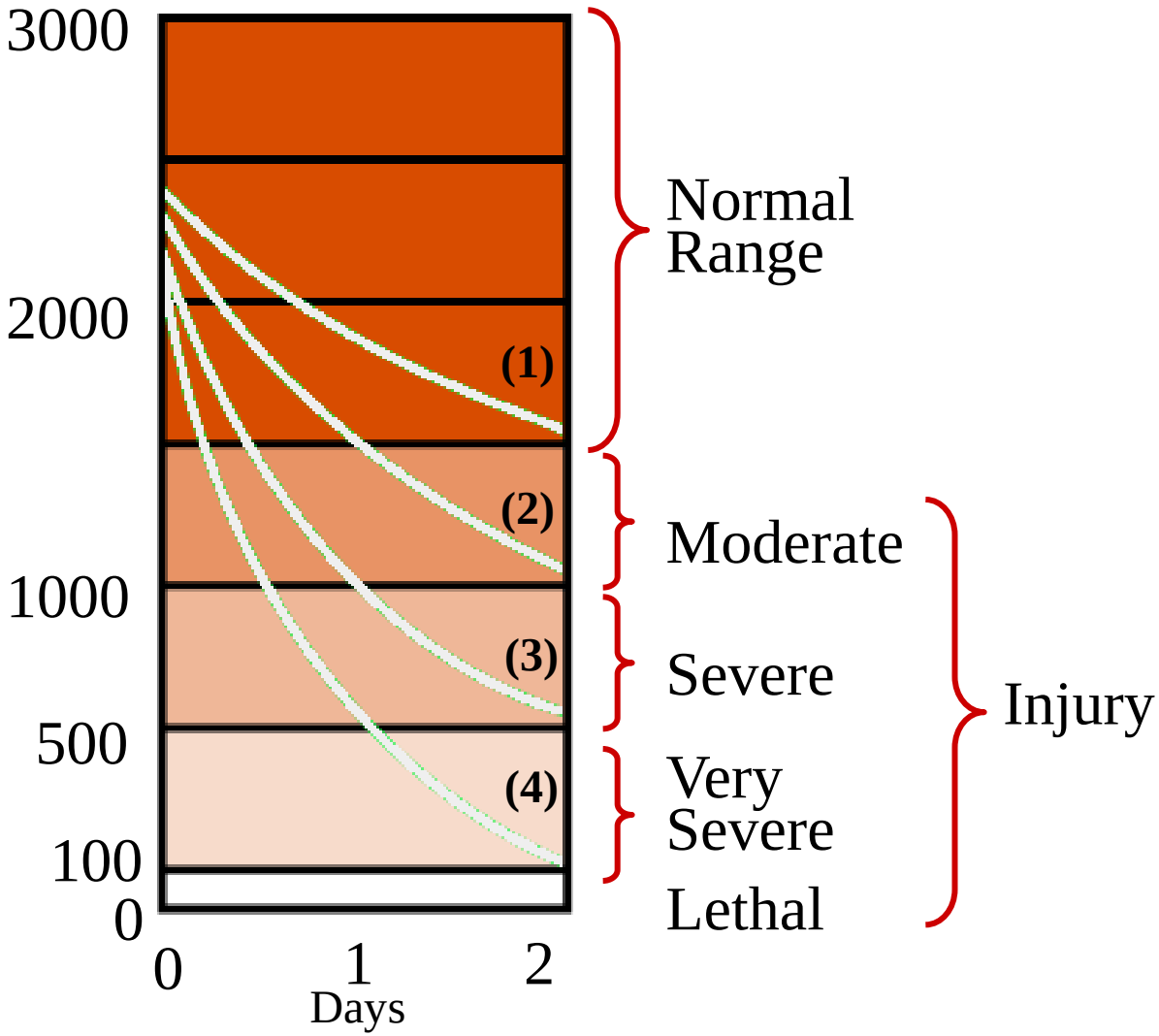
Dose estimation from symptoms

TABLE III. GUIDE FOR THE MANAGEMENT OF RADIATION INJURIES BASED ON EARLY SYMPTOMS

Clinical signs		Corresponding dose (Gy)		Decision
WBE	LE	WBE	LE	
No vomiting	No early erythema	<1	<10	Outpatient with five week surveillance period (blood, skin)
Vomiting 2–3 h after exposure	Early erythema or abnormal sensation 12–24 h after exposure	1–2	8–15	Surveillance in a general hospital (or outpatient for 3 weeks followed by hospitalization if necessary)
Vomiting 1–2 h after exposure	Early erythema or abnormal sensation 8–15 h after exposure	2–4	15–30	Hospitalization in a haematological or surgical (burns) department
Vomiting earlier than 1 h after exposure and/or other severe symptoms, e.g. hypotension	Early erythema, within the first 3–6 h (or less) after exposure, of skin and/or mucosa with oedema	>4	>30	Hospitalization in a well equipped haematological or surgical department with transfer to a specialized centre for radiopathology

(from IAEA Safety Report Series 2, 1998)

Patterns of Early Lymphocyte Response in Relation to Dose



Curve 1-3.1 Gy; curve 2-4.4 Gy; curve 3-5.6 Gy; curve 4-7.1 Gy.

From Health Physics 72(4): 1997

Effect on organ systems

BM, GI, lung, etc.

Bone marrow injury (blood)

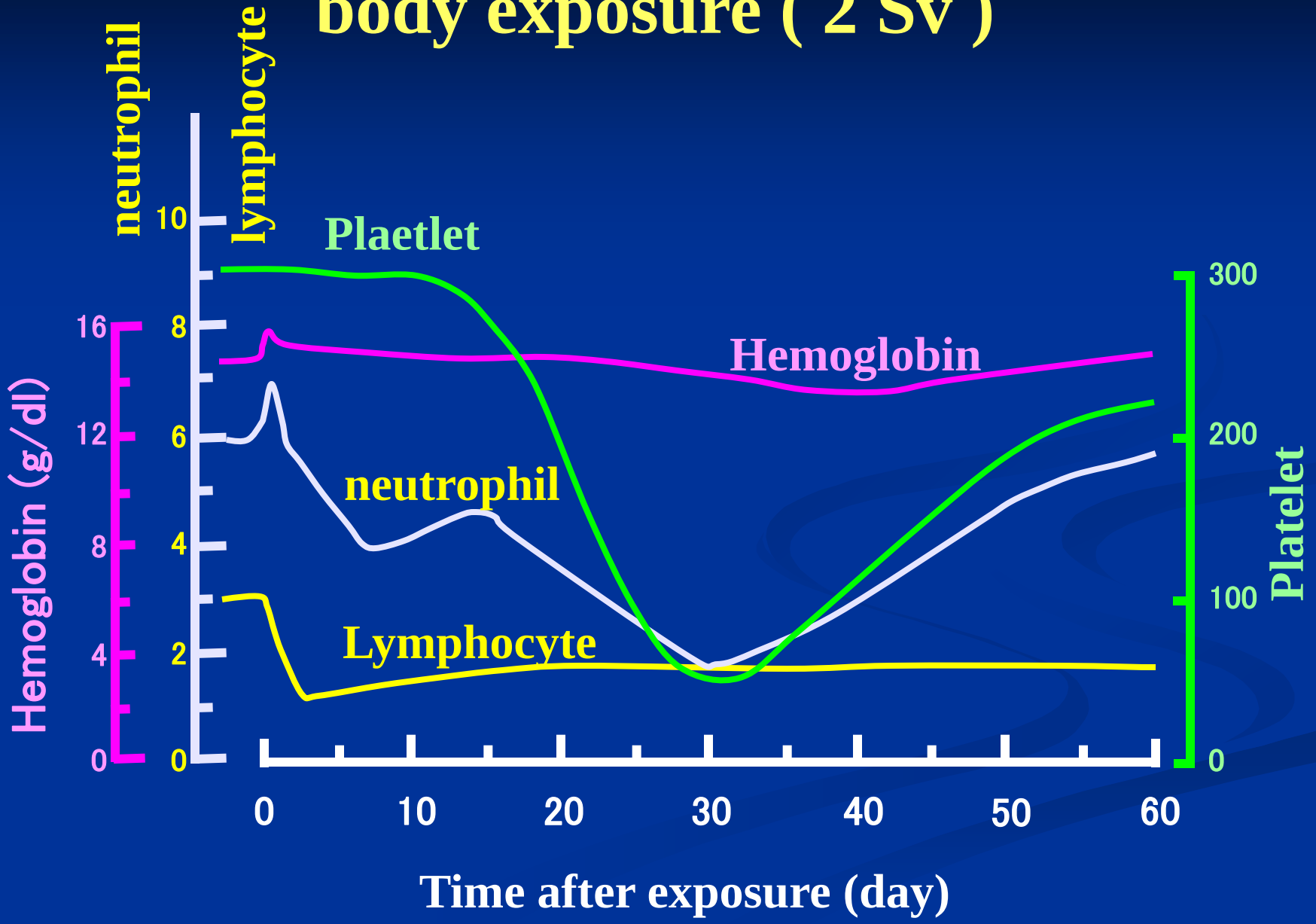
Leukopenia

- Immunodeficiency
- Infection

Thrombocytepenia

- Bleeding tendency
- Anemia

Change in peripheral blood count after whole body exposure (2 Sv)



GI injury

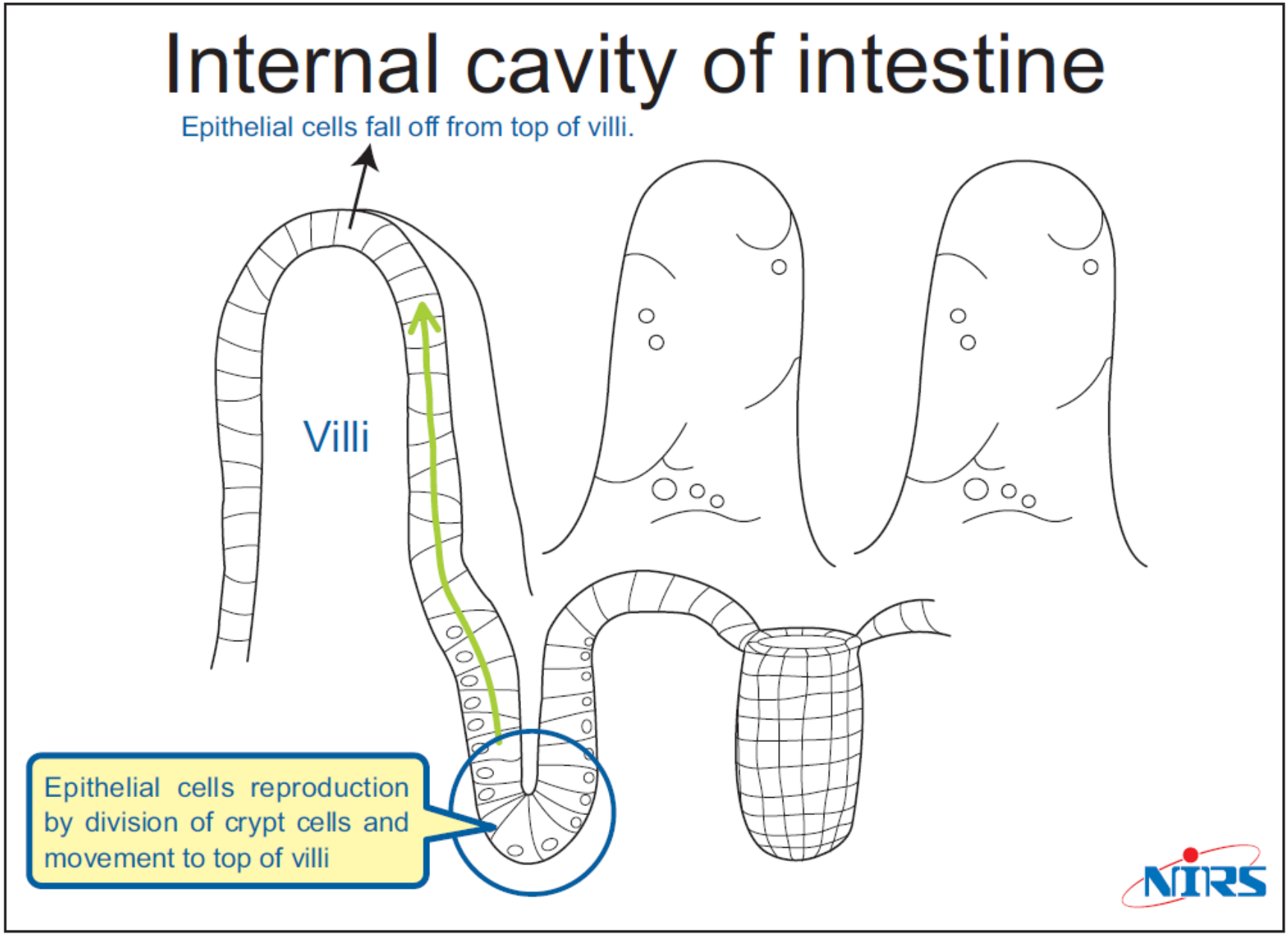


Fig. 5: Structure of inner surface of small intestine
(adopted from UNSCEAR 1988)

GI tract injury

1. Insufficiency in Regeneration of mucosal epithelial cells
   - Ileus, mal-absorption, anorexia, nausea, vomiting, diarrhea, uncontrollable GI bleeding (after progression in falling of mucosa) , loss of body fluids.

2. Barrier insufficiency
   - Bacterial transmission from mucosa to blood stream
   - Sepsis

Lung injury

Lung injury by radiation (>8Gy)

Onset: 1～7 months (peak: 2-4 months)

Onset: mucosal edema (increase permiability)
→secretion accumulation in alveoli →thickening of alveoli wall

Radiation pneumonitis: 3～12weeks, loss of cells, stenosis of capillaries, hyaline membrane formation (fibrin, plasma protein)

Lung fibrosis: 6month～、accumulation of collagen

Lung ingury

Symptoms： dry cough, dyspnea, feaver.
hypoxia, respiratory failure in severe case

Diagnosis: non-specific, exclusion diagnosis. BAL
（CMV, herpes, bacteria, fungus）ARDS.
Combined lung infection

Problem after overcoming of bone marrow
suppression after 4 Gy and GI injury after 6 Gy,
due to advancement of technology

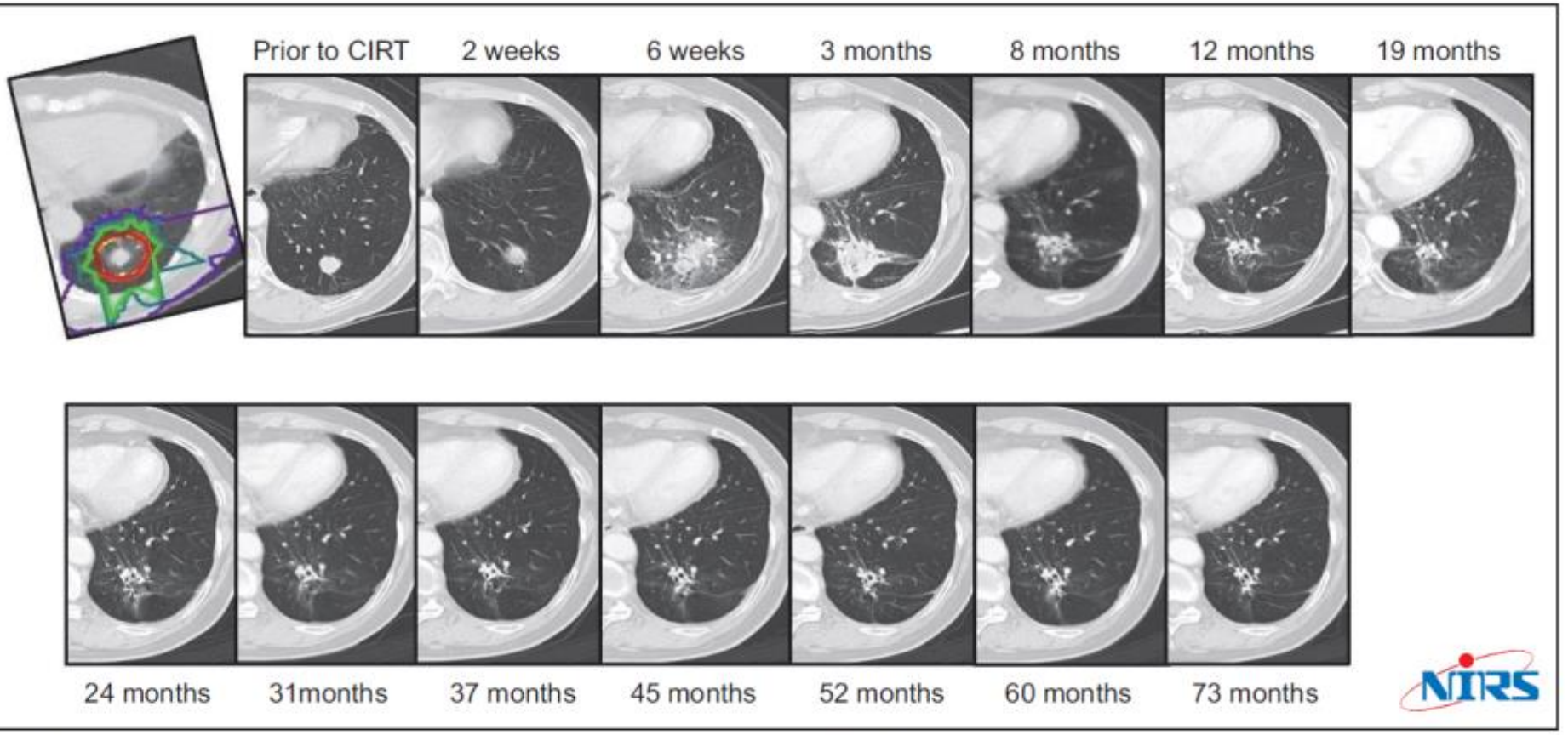


Fig. 4 Radiation pneumonitis associated with the treatment of lung cancer

Radiation pneumonitis occurred six weeks after irradiation, but the tumor disappeared 2 years later and five years later, only fibrosis in the lung was left.

Neurovascular syndrome（＞20Gy）

- Prodromal syndrome: Vomiting or diarrhea etc in several minutes after exposure
- CNS symptoms: confusion, disorientation
- Edema due to vascular permeability, lung edema, pleural effusion, ascites, hypotension, shock, high fever
  - Cause: (possibly) increased permeability in brain→severe edema, vascular damage, encephalitis, etc.
- Die in 1–2 days without treatment

Principal Therapeutic Measures for Acute Radiation Syndrome According to Degree

Whole body dose (Gy)	1-2	2-4	4-6	6-8	>8
Degree of severity of ARS	Mild	Moderate	Severe	Very severe	Lethal
Medical management and treatment	Oupatient observation for maximum of one month	Hospitalization			
		Isolation, as early as possible			
		Cytokines			
		Blood components transfusion: platelets, erythrocytes (when necessary)			
			Complete parenteral nutrition (first week) Metabolism correction, detoxication (when necessary)		
			Plasmapheresis (second or third week) Prophylaxis of disseminated intravascular		
				Stem cell Transplantation Conservative	

Adjusted and modified IAEA/ Diagnosis and Treatment of Radiation Injuries, Safety Reports Series No.2 IAEA, Vienna (1998)

Local radiation injury

Radiation skin injury: Big factor influencing prognosis if combined with whole body exposure

Burn by heat vs. radiation

	Heat burn	Radiation burn
symptoms	Sudden pain Severe inflammation Cell death at the wound, Destruction of tissue	No pain at the beginning Onset of symptoms differ with radiation dose
mechanism	Injury with heat Coagulation of protein, injury of cell metabolism, local circulation failure	DNA damage by radiation (sensitivity is depending on cell type)
Energy (2nd deg burn)	Large (4Cal/cm^2)	Small (0.0126Cal/cm^2):30Gy

Necrosis (>25Gy, >21 days)

- Large necrotic lesion covering 1/3 of right thigh (High dose exposure by Ir-192, Yanango, Peru, 1999)

Debridment of deep necrosis and surgical intervention such as skin transplantation are required.

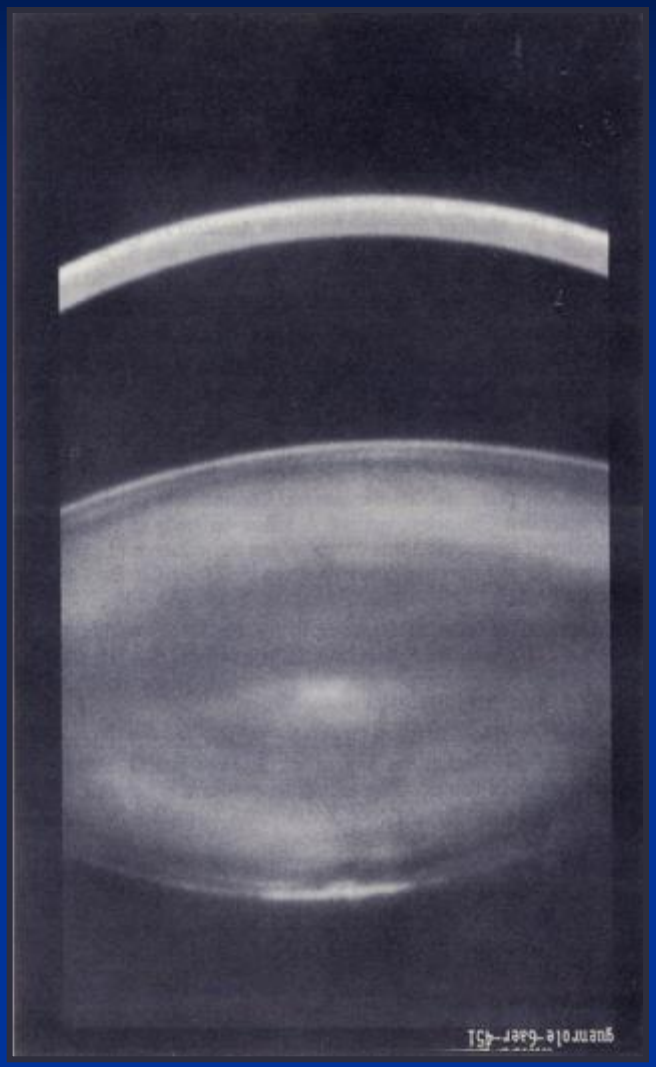
(modified from IAEA The radiological accident in Yanango 2000)

Late effect

Chronic skin injury (after 6 months)

- Chronic radiation dermatitis
  - Eczema like lesion
  - Ulcer formation
- Scarring, deformity, limitation of range of movement.
- Combined with fibrosis, sclerosis, bone atrophy.
- Malignant change. (mostly basal cell carcinoma. Most of them are curable.)

Cataract by radiation



- Single irradiation: over 0.5 (~2) Gy leads to opacification of lens (latency period: 6 months to 35 years)
- Equivalent dose limit for lens at present Japanese Low
  - 150mSv/y (occupational)
  - 15mSv/y (public)
  - ICRP proposed 20 mSv/y (average over 5y) as occupational dose limit recently (ICRP: Statement on tissue reactions, 2011-Apr)

(body, extremities, whole body dose = 4.5 Gy)

Modified from Radiation. Research. 155, 409-416(2001)

Atomic bomb explosion

- During the World War II
  - 1945-07-16: 1st atomic bomb explosion experiment (U.S.A.)
- 1945-08-06: in Hiroshima
- 1945-08-09: in Nagasaki.

- Those explosions caused

  (in addition to radiation exposures)
  - explosive winds with destruction of houses,
  - burns from heat,
  - fires

Population for epidemiological studies on atomic bomb survivors

Population	Number of people
Subject of investigation	120,321
Exposed population	91,228
Dose evaluated (DS86)	~76,000

(BEIR V, 1990)

Excess Relative Risk of Solid Cancer

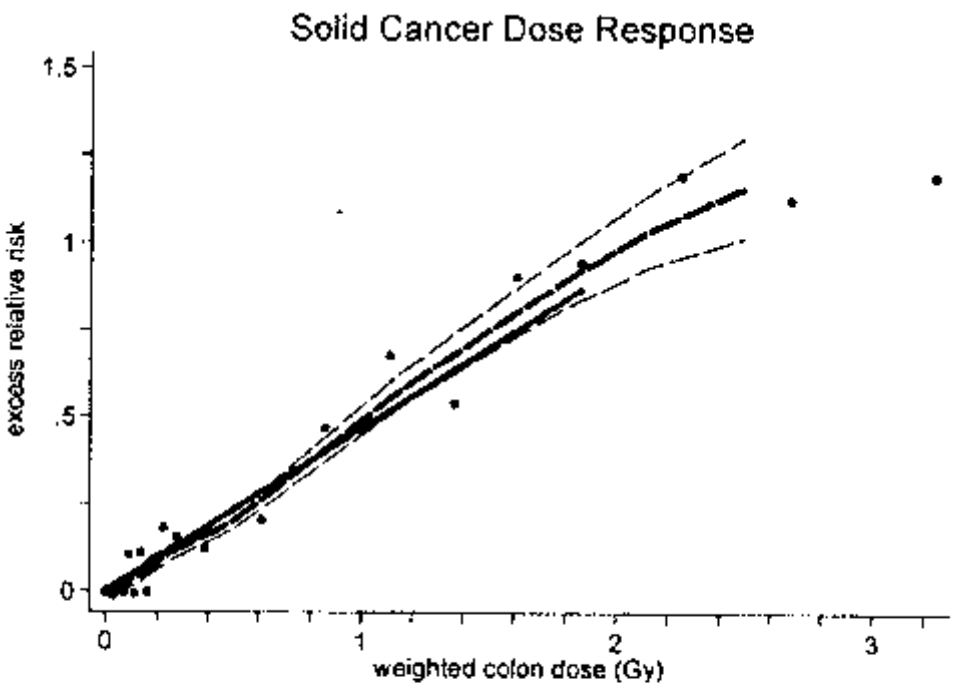


FIG. 3. Solid cancer dose–response function. The thick solid line is the fitted linear gender-averaged excess relative risk (ERR) dose response at age 70 after exposure at age 30 based on data in the 0- to 2-Gy dose range. The points are non-parametric estimates of the ERR in dose categories. The thick dashed line is a nonparametric smooth of the category-specific estimates and the thin dashed lines are one standard error above and below this smooth.

Preston DL,

2007

(Rad. Res. 168)

Site Specific Solid Cancer ERR

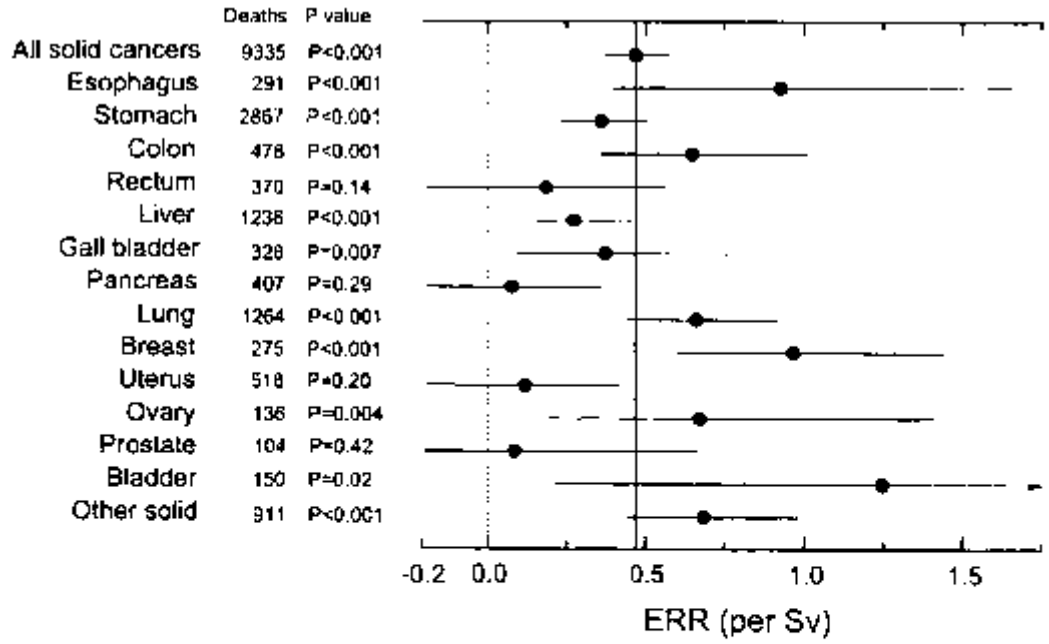
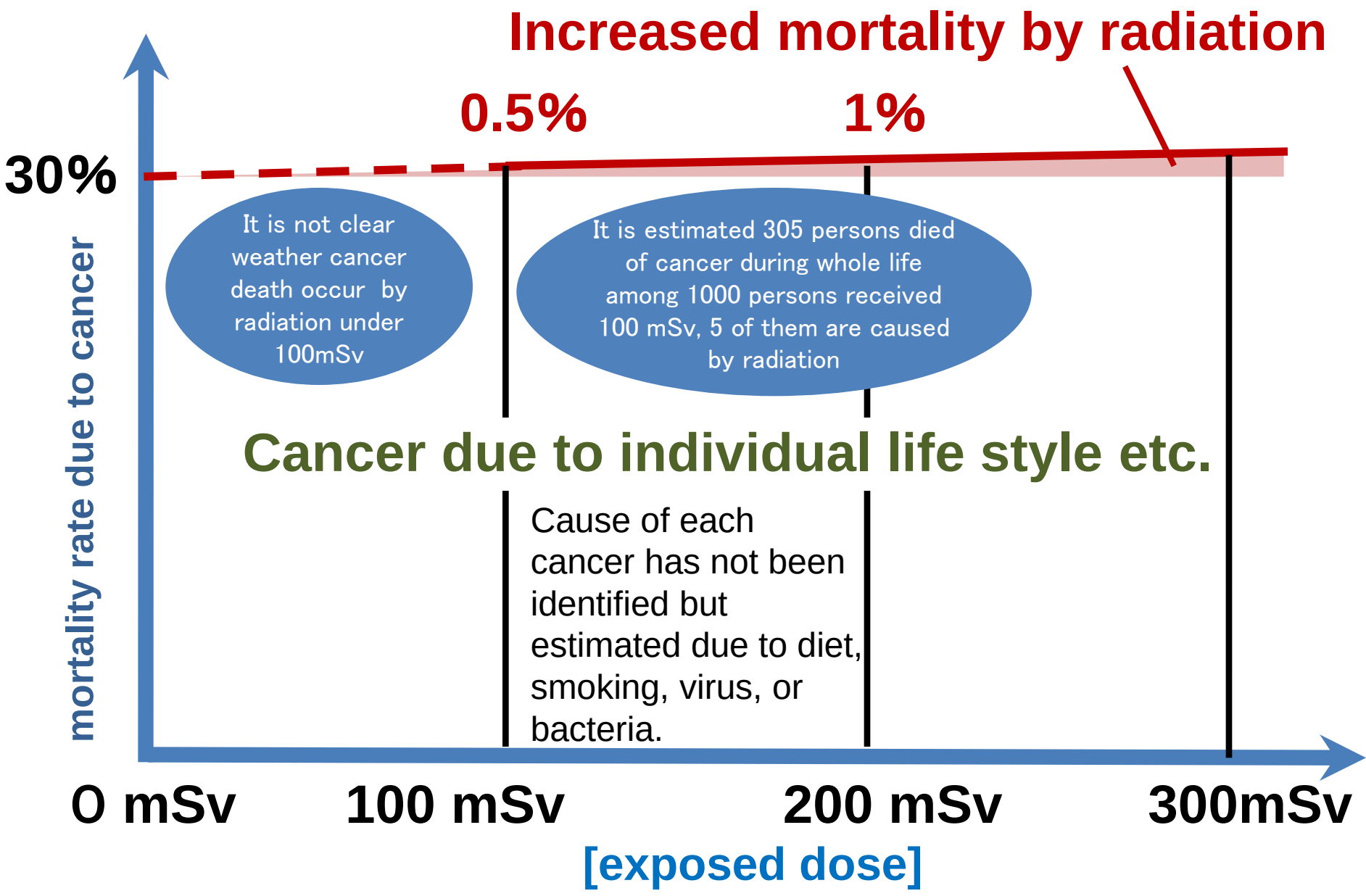


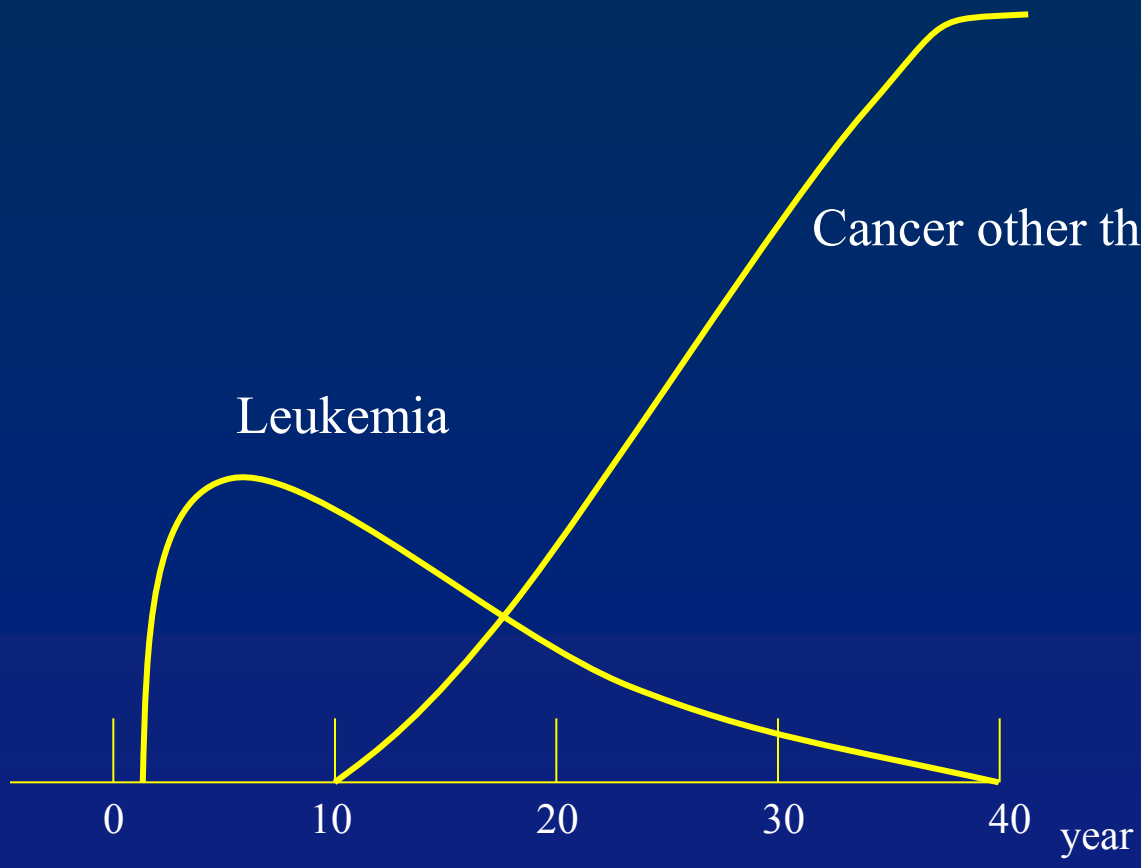
FIG. 4. Estimates of the site-specific solid cancer ERR with 90% confidence intervals and one-sided *P* values for testing the hypothesis of no dose response. Except for sex-specific cancers (breast, ovary, uterus and prostate), the estimates are averaged over sex. All estimates and *P* values are based on a model in which the age-at-exposure and attained-age effects were fixed at the estimates for all solid cancers as a group. The light dotted vertical line at 0 corresponds to no excess risk, while the dark solid vertical line indicates the sex-averaged risk for all solid cancers.

Preston DL, 2003
(Rad. Res. 160)

Increase of cancer & leukemia due to radiation



Time course of cancer induction by radiation after atomic bomb



Non-cancer disease incidence among Atomic bomb survivors

- Statistically significant positive linear dose-response relationship:
  - Thyroid disease ($P < 0.0001$)
  - Chronic liver disease and liver cirosis ($P = 0.001$)
  - Uterine myoma ($P < 0.00001$)
- New results:
  - Cataract ($P = 0.026$) : significant positive dose-response
  - Glaucoma ($P = 0.025$) : negative linear dose response （？？）
  - Hypertention ($P = 0.028$) : significant quadratic dose-response
  - Myocardial infarction (exposed under 40 yo) ($P = 0.049$) : significant quadratic dose-response
  - Kidney or ureter stone: significant only in male (sex difference verification $P = 0.007$)

    - Above results did not change after adjustment for smoking or alcohol drinking

Adult Health Study Report 8.

Yamada M, et al., 2004, Radiat Res 161:622

Genetic effects

- No evidence of clinical or subclinical genetic effects has yet been seen in children of A-bomb survivors.:

- Genetic studies: stillbirth, malformation, weight, sex ratio, chromosome aberrations, protein electrophoresis, mortality, DNA studies.

Massage to take home

- Human body has protective mechanism for repairing and recovering from radiation damage
- 2 types of effects: Deterministic effects and Stochastic effects. From time scale: acute effects and late effects
- (Radiation effects depend on quality of radiation or dose rate)