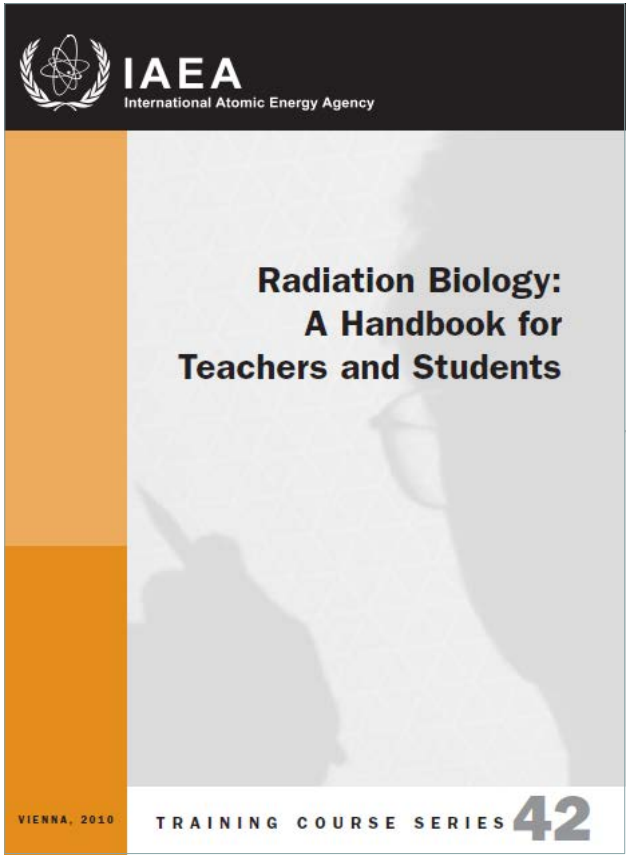
Radiation Biology: A Handbook for Teachers and Students



Slide Series prepared in 2011 by

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International Atomic Energy Agency

Minimum Essential Syllabus for Radiobiology (1)

Handbook page

Minimum Essential Syllabus for Radiobiology (2)

Handbook page

Extra Module for Radiation Oncologists (1)

Handbook page

Extra Module for Radiation Oncologists (2)

Handbook page

Extra Module for Radiation Protection Personnel

Handbook page

Section 2.

Sources of Additional Illustrative Material and Slides

- EJ Hall and A Giaccia. Radiobiology for the Radiologist: 6th edition. (2006). JB Lippincott, Philadelphia, USA. *Figures and Tables.*
- VAN DER KOGEL, A.J., JOINER, M.C., Editors, Basic Clinical Radiobiology: 4th edition. (2009). Hodder Arnold, London, UK. *Figures and Tables.*
- TANNOCK, I.F., HILL, R.P., BRISTOW, R.G., HARRINGTON, L., Editors, The Basic Science of Oncology, 4th edition. (2005). McGraw-Hill. *Figures and Tables.*
- http://www.iaea.org/Publications/Training/Aso/register.html IAEA slide series of Modules in Radiobiology.
- http://lowdose.energy.gov/radiobio_slideshow.aspx Slide sets on Low Dose effects.
- http://www.astro.org/arro/Certification/PhysicsRadBioCurriculum/documents/2011arrosg.pdf ASTRO questions and answers text (2011).

Section 3.

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- EJ Hall and A Giaccia. Radiobiology for the Radiologist: 6th edition. (2006). JB Lippincott, Philadelphia, USA. *Figures and Tables.*
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- http://www.iaea.org/Publications/Training/Aso/register.html IAEA slide series of Modules in Radiobiology.
- http://www.cancer.gov/search/results NCI slide series on Understanding Cancer.
- http://www.astro.org/arro/Certification/PhysicsRadBioCurriculum/documents/2011arrosg.pdf ASTRO questions and answers text (2011).

Section 4.

Sources of Additional Illustrative Material and Slides

- "Radiobiology for the Radiologist" 6th edition, 2006. EJ Hall and A Giaccia. JB Lippincott, Philadelphia, USA. Figures and Tables in Chapters 10-15.
- http://www.iaea.org/Publications/Training/Aso/register.html IAEA slide series of Modules in Radiobiology including Protection.
- http://rpop.iaea.org/RPOP/RPoP/Content/AdditionalResources/Training/1_TrainingMaterial/index.htm Slide sets on Medical Radiation Protection.
- http://lowdose.energy.gov/radiobio_slideshow.aspx Slide sets on Low Dose effects.

Day 1: Physics and Chemistry of Radiation Interaction with Matter

a) Interactions of electromagnetic radiations with matter, photoelectric effect, compton scatter, pair production, dependence on photon energy, dependence on Z (atomic number) of absorbing material, distribution of energy deposition (scale), half value layer

b) Interactions of particles with matter, electrons, energy dependence, alpha particles, neutrons

c) Linear energy transfer (LET)/Relative biologic effectiveness (RBE)

d) Definition of dose; gray (Gy)

e) Principles of dosimetry: Ionization chambers, Thermoluminescence (TLD)

f) Radiation Chemistry of water

g) Formation and reaction of free radicals with oxygen, scavengers:

- Direct/Indirect effects of radiation on macromolecules
- Concept of chemical restitution/competition

Day 2: Molecular Radiation Biology

a) Types of radiation lesions to DNA, and repair: base damage, single strand breaks (SSB), double strand breaks (DSB), mechanisms of repair, molecular role of e.g. p53, ataxia teleangiectasia mutated gene (ATM)

b) Effects on chromosomes – use in biodosimetry

c) Radiobiological definition of cell death and cell survival

d) Manifestations of radiation-induced cell death (apoptosis, necrosis, mitotic catastrophe, senescence)

e) Survival curves and models, clonogenicity (main criterion), limitations of determination of cell numbers at a fixed time

f) Cell cycle: sensitivities in different phases, and cell cycle checkpoints

g) RBE – cell survival – change in slope and shoulder of survival curve, dependence of RBE on dose

h) Cellular repair: sub lethal damage repair (SLDR)/potential lethal damage repair (PLDR) cell survival, half time of repair

i) Dose rate effects: dependence on repair and proliferation

j) Chemical modifiers Oxygen effect: radiation sensitizers/protectors

k) Other cellular targets, e.g. membranes, mitochondria

l) Bystander effects at low doses

Day 3: Tumour Radiobiology including Tumour Growth and Micro-environmental Effects

a) Tumour growth characteristics e.g. exponential growth

b) Dependence of tumour cure probability on dose, tumour size, fractionation, overall treatment time

c) Tumour stem cells/clonogenic tumour cell inactivation. Poisson statistics of tumour cure.

d) Time factor in radiotherapy

e) Palliative radiotherapy (tumour growth delay)

Day 4: Normal Tissue Effects

a) Concept of damage manifested early versus late: underlying mechanisms e.g. oxidative stress and cell kinetics

b) Early effects:

- Clinical manifestation
- Time course and dose response, latency
- Hypoplasia due to cell killing
- Interacting factors: inflammation, cytokines
- Dose/dose-rate/time/fractionation dependence

c) Late effects:

- Clinical manifestation
- Time course and dose response, latency
- Dependence on fraction size
- Chronic inflammatory responses
- Micro vascular injury fibrosis
- Consequential late effects

d) Whole body exposure: Radiation syndromes

Day 5: Radiation Carcinogenesis

a) A-bomb survivors: leukaemia, solid tumours, dose dependence, dependence on age at exposure, concept of relative versus absolute risk

b) Mechanisms of multistage carcinogenesis. In vitro transformation, animal models, radiation-induced mutations

c) Dose response relationship, dose-rate and latency in humans, organ dependence, estimation of radiation risk

d) Definition of sievert (Sv), organ weighting factors

Day 5: In Utero and Heritable Radiation Effects

Radiation Effects in Utero

a) Types of injury

b) Dependence on stage of pregnancy

c) Protection of the embryo

d) Dose response for mental retardation

Radiation Induced heritable damage

a) Mutations

b) Doubling dose

c) Risk estimation, single gene disorders and multi-factorial diseases

Practicals/Tutorials

a) Dosimetry with ionization chambers; shielding

b) Chromosome aberrations in lymphocytes (0-3 Gy): dicentrics and micronuclei

c) Data analysis for cell survival curves; scoring colonies

d) Data analysis of in vivo fractionation studies: skin, gastro-intestinal tract, kidney, spinal cord.

Extra Module for Radiation Oncologists
Day 1: Physics

a) Dosimetry in radiotherapy

b) Depth doses for photons, electrons, protons and heavy particles (concept of Bragg peak), particle therapy

c) Isodose curves (fraction doses adding up, contrast with isoeffect curves, not linear), dose volume histograms

d) Boron Neutron Capture Therapy (BNCT), requirement for preferential boron uptake in tumour, concern re-vascular uptake, poor characteristics of penetration of thermal neutron beams

e) Physics of radioimmunotherapy, use of different isotopes, problems of tissue distribution, dose calculations

Day 1: Molecular and Cellular Biology

a) Principles of some common techniques e.g. immunoblotting, microarrays, proteomics (2-D gels)

b) Techniques to modify gene expression

c) DNA/Chromatin structure and function; (De)-methylation, (De)-acetylation

e) Regulation of transcription, translation and post-translational modification, e.g. glycosylation, meristylation

f) Cell signalling – signalling cascades, receptor/ligand interactions, phosphorylation/dephosphorylation reactions

g) Oncogenes and Tumour suppressor genes

h) Mechanisms of action of some signal-transduction therapeutic agents e.g. Epidermal growth factor receptor (EGFR) inhibitors, Ras inhibitors, Farnesyltransferase inhibitors (FTI).

i) Radiation effects on cell signalling, e.g. EGFR pathway

Day 1: The Cell Cycle (and Signal Transduction Pathways)

a) Cell cycle description

b) Methods to determine cell cycle parameters, e.g. flow cytometry – DNA staining and bromo deoxyuridine (BrdU)

c) Control of cell cycle: cyclins, cyclin dependent kinases (CDKs), cyclin dependent kinase inhibitors (CDKIs), role of p53

d) Radiation-induced cell cycle checkpoints

Day 2: Cell Death Mechanisms

a) Radiobiological definition of cell death (loss of reproductive ability-reproductive death), abortive cell divisions after irradiation

b) Apoptosis – Developmental and stress induced, morphological and biochemical features, molecular pathways

c) Necrosis – Morphological, pathological, and biochemical features

d) Mitotic catastrophe – Morphology

e) Cell senescence and radiation-induced differentiation

Day 2: DNA Damage and Repair

a) Types of lesions and frequency per cell per Gy

b) Multiple damaged sites (clustered damage)

c) Types and Molecular mechanisms of DNA repair:

- Base damage
- Single strand breaks
- Double-strand breaks: homologous recombination repair (HR), non-homologous end-joining (NHEJ)
- Repair of cross-links
- Mutations affecting repair (ATM etc)
- Molecular responses to DNA damage (p53, ATM, etc)

d) Principles of assay techniques – elution, electrophoresis including comets, repair foci, plasmid-based assays

Other molecular targets:

a) Membranes (Oxidative damage, lipid peroxidation, sphingomyelinase activation in endothelial cells).

b) Activation of stress response genes, radiation induced signal transduction

Day 2: Cell Survival Curves

a) Colony formation assays versus cell viability assays

b) Dose-survival relationships

c) Linear-quadratic model; two component exponential model, definition of survival curve parameters

d) Sub-lethal and potentially lethal damage repair, half time of repair and incomplete repair, effect of unequal fraction size on repair

e) Dose rate and fractionation effects

f) Oxygen effect – level, time scale, mechanisms

g) LET versus OER and RBE; Radio-sensitizers, protectors

h) Low dose hypersensitivity, induced radio-resistance, mechanisms

i) Bystander effects, mechanisms

Day 3: Tumour Biology and Host/tumour Interactions

a) Growth kinetics of experimental tumours and cancer in patients, impact of tumour pathology, tumour progression, metastatic spread

b) Vasculature, angiogenesis and tumour microenvironment

c) Hypoxia – Oxygen measurements, radiobiological-hypoxic fractions, acute/transient (perfusion-limited) versus chronic (diffusion-limited) hypoxia

d) Mechanism of reoxygenation, hypoxic cell radiosensitisers, bioreductive agents

e) Methods of correction of hypoxia-associated radioresistance in tumours: high LET radiotherapy, hypoxic cell radiosensitizers, increased oxygen concentration in breathing air, correction of anaemia

f) Tumour response assays – tumour cure 50 (TCD50), threshold dose (TD50), in vivo/in vitro colonies, tumour regrowth delay, (TGD), in vitro tumour models (e.g. spheroids), human tumour xenografts and isogeneic/ transgenic mouse tumours

g) Differences between tumour types

h) Virally-associated cancers: molecular and biological basis to induction and radiation response of virally-associated cancers

Day 4: Radiobiology of Normal Tissue Damage

a) Early normal tissue damage:

• Pathogenesis in critical normal tissues (skin, G-I tract mucosa, bladder, bone marrow), kinetics/latency cell turnover and stem cell function, role of inflammation, cytokines, reactive oxygen species

• Dose response.

b) Late normal tissue damage:

Pathogenesis in critical tissues (Lung, heart, central nervous system (CNS), skin, kidney, liver, G-I tract, bladder, salivary gland) kinetics/latency cell turnover

• Role of inflammation, cytokines, reactive oxygen species

• Microvascular damage, fibrosis, ischaemia and atrophy

• Functional vs. structural damage

• Growth factors and stimulated regeneration (including stem cells)

• Concept of normal tissue tolerance

• Over-reacting patients - radiosensitivity syndromes

• Concept of functional subunits – parallel and serial organisation

c) Second cancers in radiotherapy patients

d) Conditioning for bone marrow transplantation

Day 4: Time-Dose Fractionation

a) The 5 Rs of fractionated radiotherapy (Repair, Repopulation, Radiosensitivity, Redistribution, Reoxygenation)

b) Isoeffect curves

c) Linear-quadratic (LQ) parameters, biological effective dose (BED), linear-quadratic equivalent dose (LQED)

d) Residual injury and re-treatment

e) Accelerated repopulation in tumours and normal tissues, time factor in radiotherapy

f) Therapeutic ratio

g) Concept of tumour control probability (TCP) and normal tissue complication probability (NTCP) models

h) Modified Fractionation (Hyper-, Hypo-, Accelerated, Concomitant boost)

i) Radiobiology of resource-sparing protocols, e.g. for palliative treatments

Day 4: Brachytherapy and Volume Effects

Brachytherapy

a) Radiobiological principles

b) Half time of repair

c) Dose distribution

d) Volume specification

Volume Effects

a) Isoeffect versus iso-tolerance

b) Radiobiological interpretation of dose-volume histograms

c) Volume considerations of functional versus structural damage

d) Conformal and intensity modulated radiation therapy (IMRT) techniques

Day 5: Principles of Combined Radiation and Drug Treatments

a) Spatial cooperation versus interactive effects

b) Different toxicities in tumour and normal tissues

c) Possible mechanisms of interaction

d) Principles of clinical use including concurrent and sequential treatments, role of chemotherapy in consequential late radiation toxicity, late cardiac effects

e) Tumour micro-environmental effects in chemotherapy

Day 5: Biological and Novel Therapies

a) Biological therapies and their mechanism of action

b) Novel targets for anti-cancer drugs including vasculature and cell signal control and oncogene products

c) Bioreductive drugs, antibody-directed enzyme prodrug therapy (ADEPT)

d) Photodynamic therapy

e) Gene therapy, gene-directed enzyme prodrug therapy (GDEPT), radiation-induced gene expression including molecular switching techniques

f) Radioimmunotherapy and targeted radiotherapy

Day 6: Predictive Assays

a) Rationale for normal tissues and tumours – intrinsic radiosensitivity, surviving fraction at 2Gy (SF2), cell kinetics, and hypoxia

b) Molecular, subcellular, cellular and non-invasive tests

c) Results to date

d) Future possibilities, e.g. gene expression profiling

Day 6: Clinical Radiobiology of Common Cancers

a) Radiobiological issues in the treatment of the common cancers such as cervix, head and neck, lung, breast, prostate

b) Resistance mechanisms and clinical radiobiology

c) Cervix cancer, SF2, Hypoxia, Repopulation, Brachytherapy and external beam treatments, BED, LQED calculations

d) Head and neck cancer, optimum fractionation schedules, volume effects –Morbidity scoring scales, salivary gland sparing, role of brachytherapy

e) Lung cancer e.g. biological imaging of target volume using positron emission tomography (PET), accelerated radiotherapy. Radiochemotherapy schedules

f) Breast cancer e.g. role of hypofractionation and brachytherapy, cardiac effects, antiestrogens and radiation toxicity

g) Prostate cancer e.g. role of hypofractionation and brachytherapy, dose escalation, biochemical relapse

Practicals / Tutorials

- DNA Laboratory techniques: practical demonstrations of some of the techniques from the above lectures e.g. comet assay, micronuclei, flow cytometry (DNA analysis), gel electrophoresis
- Survival curves in practice: practical session on the shapes of survival curves, and their importance in various clinical scenarios
- Analysis of scoring of normal tissue damage: LENT/SOMA versus RTOG/EORTC scoring systems, head and neck squamous cell carcinoma (HNSCC), Cervix Ca
- LQ model: BED, LQED, α/β ratio values:
    a) Fractionation calculations in practice
    b) Physical dose distribution and biological response distribution
    c) Combined brachy/teletherapy treatments; compensations for interruptions in treatment
    d) Importance of treating all fields per day
    e) Influence of radiation source decay with respect to repair half-time and dose effectiveness
    f) Clinical impact of errors in dose delivery
- Critical reading of relevant literature

Extra Module for Radiation Protection Personnel

Day 1: Environmental radiation exposure and radiation accidents:

Dose estimation:

a) Retrospective dose estimation for past exposures: e.g. for A–bomb survivors, populations exposed by the Chernobyl accident, the Techa River pollution, the Semipalatinsk test site.

b) Radioecology: atmospheric dispersion, deposition (wet and dry), uptake in food chain, dose commitment from internal and external exposure. Relevant radioisotopes (Cs, I, Sr)

c) Biological dosimetry in accidental exposures: Stable and unstable chromosome aberrations (lymphocytes, haemoglobin and glycophorin-A (GPA) mutations)

Day 1: Diagnosis and Medical Management of Radiation Syndromes

a) Lethal dose-50 (LD-50): laboratory experiments and human estimates

b) Radiation syndromes (Neurovascular, Haematopoietic, Cutaneous and G-I tract syndromes)

c) Diagnosis and medical management of radiation accidents: Radiobiological rationale for therapeutic strategies such as barrier nursing, bone marrow stem cell transplantation, cytokine treatment

d) Methods of triage for treatment after a radiation accident:

- Acute symptoms (vomiting, diarrhoea, hair loss, nausea)
- Laboratory tests (lymphocyte count and granulocyte count)

Day 2: Molecular Mechanisms of Multistage Carcinogenesis

- Initiation, promotion, progression
- Activation of oncogenes (i.e. genetic rearrangements)
- Inactivation of suppressor genes (e.g. p53), loss of heterozygosity (LOH), polymorphisms
- Genomic instability, mini and microsatellites
- Genetic susceptibility to radiation-induced cancer (e.g. Retinoblastoma (Rb) gene)

Day 2: Epidemiological Evidence for Radiation Carcinogenesis:

- Epidemiological methods, cohort studies and case control studies
- Bomb survivor life-span studies: mortality and cancer incidence – design of study, results, dose response, latency, absolute vs. relative risk
- Patients treated for benign diseases such as ankylosing spondylitis, mastitis, tinea capitis
- Tuberculosis patients undergoing multiple fluoroscopy
- Radon exposure of hard-rock miners or in homes, interaction with smoking
- The influence of age at exposure and gender on incidence and latency
- Dose-response relationships for radiation-induced leukaemia and cancers, particularly at low doses. Limitations of epidemiological studies
- The influence of dose rate; absolute vs. relative risk models
- Life time risk extrapolations

Day 2: Heritable Effects

a) Methods to determine radiation-induced rates of single gene mutations

b) Doubling dose at low dose, low dose rate irradiation

c) Critical germ cell stages for heritable radiation damage

d) Factors affecting the risk of heritable radiation damage: mutational component, potential recoverability correction factor (PRCF)

e) Risk estimation for single gene disorders and multifactorial diseases

Day 2: Effects on the Developing Embryo

a) Intrauterine death, congenital malformations, and neonatal death, microcephaly, severe mental retardation, growth retardation

b) Dependence on gestational age of radiation effects on the embryo or foetus

c) Dose dependence of risk of severe mental retardation after exposure in weeks 8-15 and weeks 16-25, evidence for thresholds

d) Protection of the embryo in diagnostic radiology and from occupational exposure

Radiation Protection

a) Effective and committed dose, definition of sievert (Sv), organ weighting factors, linear no-threshold (LNT) model

b) Dose limits for occupational and public exposures and their justification.

c) Dose limits for stochastic and deterministic effects

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