Clinical Radiobiology

Syllabus

Radiation Biology is a diverse subject encompassing a broad spectrum of basic and clinical sciences. It is developing rapidly, particularly in areas of clinical relevance. It is recognised that it is important to develop a broad knowledge in basic Radiobiology before the clinical applications become apparent. Candidates are encouraged to develop and maintain an attitude of scholarly interest in the subject, particularly in the relationship between basic Radiobiology and clinical practice. Such an attitude is essential for the further development of the candidate in Part II and beyond.

The subject should be seen as necessary background for all aspects of training in the specialty of Radiation Oncology and as critical for quality practice beyond Part II. Because of the applied nature of the subject, the Candidate studying for Clinical Radiobiology Part I will invariably have a greater depth of perspective and enhanced applicability of the subject if study is undertaken in the context of clinical employment in a Department of Radiation Oncology (eg. scoring reactions, viewing dosimetry results, putting fields on patients, checking set-ups etc). Part I Candidates will not be expected to have a detailed technical knowledge of the specialty or give exhaustive details of experimental techniques or radiotherapy trial results.

Candidates studying for Part II will be expected to maintain and update their Clinical Radiobiology knowledge with special emphasis placed on the immediate clinical application of laboratory radiobiology, experimental radiotherapy and clinical radiotherapy trial results. The Part II Candidate will be expected to be able to critically discuss clinical and technical nuances of various treatment approaches in a radiobiological context. Critical discussion of trial results in a radiobiological context will also be expected from the Part II Candidate. Written or oral questions in the Part II Exam with a primary radiobiological basis as part of their answer should be expected. (See Competencies Section).

The object of the course is therefore to provide the Candidate with sufficient knowledge of the biological effects of ionising radiation for an understanding of the rationale of clinical practice and for an appraisal of the validity of changes to standard practice. It is expected that the Candidate will have a working knowledge of experimental techniques used in Radiation Biology, but emphasis will be placed on clinically applied aspects of the subject. A knowledge of the biological aspects of radiation protection is also within the scope of the course.

Candidates should be aware of the particular need to develop an understanding of the many factors determining the tolerance of normal tissues to irradiation. Such special emphasis is desirable in view of the rapid developments occurring in this area, and the importance of normal tissue tolerance in optimising radiotherapeutic treatments.

A new molecular biology section has been included, recognising the explosion in molecular biology and the increasing utilisation of such technology in medicine and biology, including radiobiology. The emphasis is that the candidate develops a working understanding of the principles of common molecular techniques and a familiarity with the key molecules involved in radiation responses in mammalian cells and tissues. In some cases, a number of genes are known to function in a common pathway (eg, the Ras signal transduction cascade; the G1 cell cycle checkpoint). In such cases, a simple overview of the pathway itself, in addition to its key components, is desirable.
The main aim of this section is to facilitate critical reading and understanding of the oncological literature, which is permeated by molecular-based investigations, and which will increasingly report molecular-based strategies for cancer detection, diagnosis and therapy.

Because of the diversity and rapidity of changes in Radiobiology, no single textbook is adequate. A list of TOPICS FOR USE AS A FRAMEWORK FOR STUDY has been prepared as a guideline to the syllabus. This list of topics is not intended to be comprehensive and Candidates must maintain a familiarity firstly with the relevant literature and current trends in the field as well as a thorough appraisal of past examination papers.

To minimise the problem of trying to assimilate information from too many sources, a reading list has been prepared consisting of one recommended text book for detailed study, additional books for reference and several specifically recommended journal references (marked with *). It is essential that the current journal literature be regularly perused for information on relevant evolving areas of research and salient review articles. A list of representative articles is provided, purely for guidance and demonstration as to the nature and type of articles, which may be useful (this is not a comprehensive or required list).

REQUIRED COMPETENCIES

Laboratory Radiobiology
Candidates will have a basic understanding of the principles and practicalities of common experimental radiation assay systems (cell culture, animal models etc). Candidates will have a basic understanding of the principles and practice of common molecular biology techniques.
Clinical Radiobiology

Candidates will have a detailed understanding of historical and contemporary studies on radiation endpoints in humans and their application to the practice of radiotherapy.

Experimental Radiotherapy
Candidates will have a basic understanding of all common experimental radiotherapy modalities and other cytotoxic agents. Understanding of the results and implications of these studies is also required.

Basic Biological Mechanisms
Candidates will have a basic understanding of cellular and sub-cellular events associated with radiation, tumour and non-tumour cellular events and kinetics.

Protection
Candidates will have a thorough understanding of stochastic and non-stochastic radiation endpoints and a broad understanding of protection issues, definitions and typical dose thresholds.

The above competencies will change in emphasis in relation to Part I and Part II Candidates. For example, Part II Candidates will be expected to give a detailed critique of clinical trials and radiation techniques whereas Part I Candidates will only be expected to provide summary understanding of clinical and technical issues at the level of a Biologist or other Scientist outside the specialty of Radiation Oncology.

RECOMMENDED TEXT FOR DETAILED STUDY
Steel G.G., Basic Clinical Radiobiology, 3rd Edition, (2002), Arnold

Recommended Reading List

1. Awwad HK. Early reacting tissue: skin. In: Radiation Oncology: Radiobiological and Physiological Perspectives. London: Kluwer Academic Publishers, 1990:189-221.
2. Hall EJ. Radiobiology for the Radiologist. 5th Ed. Philadelphia: JB Lippincott, 2000.
3. Perez CA, Brady LW. Principles and Practice of Radiation Oncology. 3rd Ed. Philadelphia: Lippincott, 1992.
4. Nias AHW. An Introduction to Radiobiology. 2nd Ed. John Wiley & Sons, 1998
5. Potten CS. Radiation of the Skin. London: Taylor and Francis, 1985.
6. Scherer E, Streffer C, Trott K-R. Radiobiology of Organs and Tissues. Springer-Verlag, 1991.
7. Tannock IF, Hill RP. Basic Science of Oncology. 3rd Ed. McGraw Hill, 1998.
8. Thames HD, Hendry JH. Fractionation in Radiotherapy. London: Taylor & Francis, 1987.
9. Tubiana M, Dutreix J, Wambersie A. Introduction to Radiobiology. London: Taylor and Francis, 1990.
10. Effects of the A-bomb on the human body. Harwood Academic Publishers, 1995.
11. Code of Practice for the Disposal of Radioactive Waste by the User. Australian Government Publishing Service, 1985. www.arpansa.gov.au
12. The Biological Basis Recommendations of the International Commission on Radiobiological Protection (IRCP). Publication 60 Ed. Permagon Press, 1997. http://www.icrp.org
13. for Dose Limitation in the Skin, Annals of the ICRP. Publication 59 Ed. Permagon Press, 1991. http://www.icrp.org
14. Risks Associated with Ionising Radiations of the ICRP. Permagon Press, 1991. http://www.icrp.org
15. Developmental Effects of Irradiation On The Brain of the Embryo and Foetus, Annals of the ICRP. Publication 49 ed. Permagon Press, 1986. http://www.icrp.org
16. Non Stochastic Effects of Ionising Radiation, Annals of the IRCP. Publication 41 ed. Permagon Press, 1984. http://www.icrp.org
17. Beir V. Health Effects of Exposure to Low Levels of ionising Radiation. Washington: National Academy Press, 1990.
18. Steele GG. The Radiobiology of Human Cells and Tissues. London: Taylor & Francis, 1990.
19. DeVita VT. Cancer - Principles and Practice of Oncology. 6th Ed. Lippincott-Raven, 2001.
20. Potten CS, Henry JH. Radiation and Gut. Elsevier, 1995.

Recommended Text as Primary Reference for Molecular Biology Section

1. Alberts B et al. Molecular Biology of the Cell, 4th Ed, Garland Publishing. NY, 2002. *(Note: this comprehensive text covers most areas in the molecular biology section well. In particular, there are many good diagrams, which should be studied closely. However, it should be borne in mind that the vast majority of the book is not required reading, ie. Is outside the scope of the course (follow the 'Topics to be used as a Framework for Study' as a guide).*

Supplementary Texts for Molecular Biology Section

2. Trent RJ. Molecular Medicine. An Introductory Text for Students, Churchill Livingstone, 1993
3. Cooper GM. The Cell. A Molecular Approach. 3rd Ed. Sinaur Associates 2004
4. Franks LM and Teich NM. An Introduction to the Cellular and Molecular Biology of Cancer. 3rd Ed, Oxford University Press, 1997
5. Lewin B. Genes VIII. Oxford University and Cell Press, 2003

Journals

Due to the rapid expansion of knowledge of Radiation Biology, it is essential that the general literature be perused. As a minimum requirement, the following journals should be reviewed on a regular basis:

1. International Journal of Radiation Oncology, Biology and Physics
2. Clinical Oncology
3. Radiotherapy and Oncology (Estro)

Illustrative Articles

1. Gordon AT, McMillan TJ. A Role for Molecular Radiobiology in Radiotherapy? Clin.Oncol. 1987; 9:70-78.
2. Itanik. Treatment of Cancer with Radiobiology and Drugs. Clin.Oncol. 1996; 14:2156 2171.
3. Barth A, et al. Boron Neutron Capture Therapy in Brain Tumours, Past History, Current Status. Cancer - Investigation 1996; 14:534-550.
4. Akiyama M. Late Effects of Radiation on the Human Immune System: An Overview of Immune Response Among the Atomic Bomb Survivors. Int.J.Radiat.Biol. 1995; 68:497-508.
5. Raju MR. Proton Radiobiology, Surgery in Radiotherapy. Int.J.Radiat.Biol. 1995; 67:237-259.
6. Brenner DJ. Radiation Biology in Brachytherapy. J.Surg.Oncol. 1997; 65:66-70.
7. Denekamp J. The Broad Spectrum of Pre-Clinical Radiobiology: British Contributions. Int.J.Radiat.Biol.Phys. 1996; 36:497-509.
8. Little JB. Cellular-Molecular and Carcinogenic Effects of Radiation. Haematology Oncology Clinics of Nth America 1997; 7:337-352.
9. Bentzen SM. Quantitative Clinical Radiobiology. Acta Oncol. 1993; 32:259-275.*
10. Horwich A. Cancer Research Campaign Review of Radiobiology Research. Brit.Journal of Cancer 1993; 67:198-201.
11. Arrand JE, Michael BD. Recent Advances in the Study of Ionising Radiation Damage and Repair. Int.J.Radiat.Biol. 1992; 61:717-720.
12. Leibel SA, et al. The Biological Basis for Conformal 3D Radiation Therapy. Int.J.Radiat.Oncol.Biol.Phys. 1991; 21:805-811.
13. Fu KK, Philips TL. The Biologic Rationale of Combined Radiotherapy and Chemotherapy. Haematology Oncology Clinics of Nth America 1991; 5:737-751.*
14. Guichard M, Lartigau E. The Oxygen Effect: An Account of Knowledge and Practical Applications. Bulletins of Cancer Radiotherapy 1991; 78:441-453.
15. Bowie C. Radon & Health. The Lancet 1991; 337:409-413.
16. Coleman CN. Clinical Applications of Molecular Biology and Radiation Oncology. Seminars of Radiation Oncology 1996; 6:245-249.

17. Yarnold J. Molecular Aspects of Cellular Responses to Radiotherapy. Radiother.Oncol. 1997; 44:1-9.*
18. Beck-Bornholdt H-P, et al. Hyperfraction - Where Do We Stand? Radiother.Oncol. 1997; 43:1-22.*
19. Nine Decades of Radiobiology: Is Radiation Therapy Any Better For It? Hall, E.J. *Cancer* 1993: 71; 753-766*
20. Radiological Oncologists: The Unfolding of the Medical Specialty. del Regato J.A. Radiology Centennial Inc. 1993*
21. International Journal of Radiation Oncology, Biology & Physics Vol 31: 1093-1319 (1995). Special Issue on the late effect in normal tissues.*
22. Fractionation in Radiation Therapy: A series of 18 review articles in Seminars in Radiation Oncology, Vol 1: No 1, January 1992*
23. Michalowski A. On radiation damage to normal tissues and its treatment: 1. Growth factors. Acta Oncol. 1990; 29:1017-1023.*
24. Michalowski AS. On radiation damage to normal tissues and its treatment: II Anti-inflammatory drugs. Acta Oncol. 1994; 33:139-157.*
25. Thames HD, Bentzen SM, Turesson I, Overgaard M, Van den Bogaert W. Time-dose factors in radiotherapy: a review of the human data. Radiother.Oncol. 1990; 19:219-235.
26. Thames HD. On the origin of dose fractionation regimens in radiotherapy. Semin.Radiat.Oncol. 1992; 2:3-9.*
27. Withers HR, Peters LJ. Textbook of radiotherapy. 3rd ed. Philadelphia: Lea and Febiger, 1980.
28. Withers HR, Taylor JM, Maciejewski B. Treatment volume and tissue tolerance. Int.J.Radiat.Oncol.Biol.Phys. 1988; 14:751-759.*
29. Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumor clonogene repopulation during radiotherapy. Acta Oncol. 1988; 27:131-146.*
30. Begg AC, Russell NS, Knaken H, Lebesque JV. Lack of correlation of human fibroblast radiosensitivity in vitro with early skin reactions in patients undergoing radiotherapy. Int.J.Radiat.Biol. 1993; 64:393-405.
31. Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. Int.J.Radiat.Oncol.Biol.Phys. 1982; 8:1981-1997.*
32. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. Int.J.Radiat.Oncol.Biol.Phys. 1991; 21:109-122.*
33. Fowler JF. Dose-rate effects in normal tissues. In: Anonymous Brachytherapy. Leersum: Nucletron International BV, 1989:26-40.
34. Fowler JF. Brief summary of radiobiological principles in fractionated radiotherapy. Semin.Radiat.Oncol. 1992; 2:16-21.*

Topics to be used as a framework for study

1. Radiation Interactions with Matter

Radiation chemistry: direct and indirect effects, free radicals, oxygen effect and radical scavengers (glutathione, radioprotectors)

LET & RBE, target theory, dual action theory, spatial and temporal distribution of radiation interaction processes, intracellular repair, general knowledge of repair models, microdosimetry, microbeam techniques.

Types of radiation, excitation and ionisation.

2. Introduction to Factors Influencing Radiation Response

Physical factors: dose, quality, dose rate, temperature.

Chemical factors: 0_2, radiosensitizers, radioprotectors

Biological factors: type of organism, cell type and stage, cell density and configuration, age, sex, host factors, partial or whole body exposure

Abscopal effect

3. Relevance of Radiation Biology to Radiotherapy

Experimental techniques in radiation biology: in vitro cell systems, in vivo animal tumours, relevance to solid human tumours
(see also Molecular Biology Section)

Biological endpoints of radiation biology.

Historical example, future implications.

4. Effects of Ionising Radiation on Mammalian Cells

The cell: relative radiosensitivity of nucleus and cytoplasm

Somatic and gametic: significance of radiation damage

Mechanisms of cell killing by radiation: apoptosis (interphase death), mitotic death, role of chromosome breakage, micronucleus induction

Survival curves: experimental technique in vitro and in vivo parameters, types, significance. Steepness of dose response curves.

Cellular radiation damage: SLD, PLD, poly (ADP-ribose), slow repair, significance in radiotherapy practice. Repair capacity, repair kinetics

Oxygen effect: mechanism, hypoxia, OER, reoxygenation in tumours, significance in radiotherapy

Dose rate: Brachytherapy sources including ^{252}Cf: radiobiology of low, conventional, high dose rates and pulsed brachytherapy; hyperfractionation, significance in radiotherapy

Radiation effects on DNA: chromosomes, cellular macromolecules, cell membranes, effects of low LET and high LET radiations on cell

5. Mammalian Cell Radiosensitivity

Cells: variations in radiosensitivity, therapeutic implications for radiotherapy and chemotherapy. inherent radiosensitivity, radioresponsiveness

Cell populations: characteristics of normal and malignant cells, oncogenic transformation, types of cell populations

Biological factors influencing radiation response

6. Tissue and Organ Radiosensitivity and Radioresponsiveness

Radiosensitivity and Radioresponsiveness: Parenchymal and connective tissue cell populations, including vascular systems

Regeneration of normal tissues. Tumour and normal tissue repopulation.

Flexible and hierarchical kinetic models

7. Acute Effects

Endpoints, scoring.

Pathophysiology, mediators

Time and Fractionation Effects: Analysis and modelling

Radiation syndromes: BM, GI, CNS, cutaneous (MLD)

Suppression of immune system: mechanism, consequences

Biological dosimetry: blood counts, BM mitotic index, chromosome aberrations in peripheral blood lymphocytes, micronucleus assay, comet assay. In vivo versus in vitro radiation response.

Radiation accidents: typical examples

Total Body Irradiation for bone marrow transplantation etc.

8. Late Effects

Radiation pathology

Pathophysiology and mediators

Endpoints, scoring

Fractionation and Late Effects analysis and modelling

Latent Time consequential damage

9. Late Effects of Radiation (Somatic)

Carcinogenesis: mechanism in vitro and in vivo, oncogenes and anti-oncogenes.

Radiation-induced cancer of occupational, medical or military origin, recent controversial results for low level exposure, risk estimates. Radiation on hormesis.

Sterility, cataracts and cancer.

10. Late Effects of Radiation (Genetic)

Mutations: definition, types, potential hazards, mouse data, relevance to man.

Low level radiation: sources, potential hazards, linear and curvilinear dose response relationships, stochastic and deterministic (non-stochastic) effects, high background areas and cancer.

11. Effects of Radiation on Human Embryo & Foetus

Lethality, congenital abnormalities and late effects (leukaemia and childhood cancers), severe mental retardation. Doses involved.

12. Biology and Radiation Response of Tumours

Tumour growth: kinetics of tumour response. Growth fraction, cell loss factor, TAF, tumour bed effect. Flow cytometry.

Radiocurability: definition, factors involved, tumour control probability curves.

Causes of failure to control tumours by Radiation: tumour related, host related, technical/mechanical errors.

Relationship between clonogen numbers and tumour control probability. Local tumour control and impact on survival.

Volume doubling times, potential volume doubling times, repopulation, accelerated repopulation.

Factors determining tumour regression rates.

13. Applied Radiobiology

Fractionation: rationale, factors involved (5 R's)

Time, dose and fractionation relationships: isoeffect curves, isoeffect relationships, eg. NSD, CRE formalism's and their limitations. Partial tolerance, means of summating partial tolerance, steepness of dose response curves.

Introduction to new techniques to optimise radio-curability: combination therapy (adjuvant surgery or chemotherapy), hyperthermia, hypoxic cell radio-sensitisers, high LET radiation. Photodynamic therapy, BNCT, protons, pi mesons, heavy nuclei

The volume effect: general principles and current hypotheses (TRU, functional sub-units).

Shrinking field technique.

Multi-target, two component and linear quadratic models: α/β ratios for acute and late effects and means of deriving these values. Flexure dose. Isoeffect formulae. Clinical applications of the LQ model.

hyperfractionation, accelerated fractionation, hypofractionation, CHART. Split dose treatments.

Brachytherapy: low dose rate, high dose rate and pulsed treatments.

14. Hypoxia and Radiotherapy

Methods to overcome: fractionation (reoxygenation), HBO, hypoxic cell radiosensitizers, hyperthermia, high LET.

Basis of problem, experimental proof, reoxygenation.

Clinical and trial results using hypoxic sensitisers.

15. Combination Radiation-Surgery

Pre, post and intra-operative radiation.

Rationale, radiobiologic factors, current clinical results.

Irradiation of sub-clinical disease, debulking surgery, importance of clonogen numbers.

16. Combination Radiation-Chemotherapy

Radiosensitizers: types, mechanism

Classifications of drugs: types, survival curves, phase-specific and cell-cycle specific, mechanism of action, drug resistance, pharmaco-kinetics, kinetic and clinical exploitation.

Combination radiation and chemotherapy: rationale, acute and chronic effects including induction of cancer, examples.

Definitions of radiosensitizer, synergism, potentiation, antagonism.

Experimental systems in chemotherapy.

Potential hazards, especially effects on dose limiting normal tissue. Potential therapeutic gain. Dose-effect factor (DEF).

17. Hyperthermia

Use in radiotherapy: optimum sequencing of combined modalities with radiation.

Current limitations to the clinical use of hyperthermia.

18. Methods in Molecular Biology

Recombinant DNA technology: restriction endonucleases; generation of recombinant DNA molecules (including vector types, eg. plasmid, cosmid, phage)

DNA sequencing: dideoxy method only

Expression of cloned genes: including DNA transfection

Polymerase chain reaction

Detection of nucleic acids: Southern and Northern blot analysis
fluorescence *in situ* hybridisation (FISH) and ISH of mRNA on tissue sections

DNA libraries: cDNA, genomic libraries and screening thereof

Antisense oligonucleotide therapy

Immunohistochemistry, immunocytochemistry

Generation of poly- and mono-clonal antibodies

SDS-PAGE and Western blot analysis

Immunoprecipitation

Transgenic and Knockout mice

19. Miscellaneous Molecular Biology Topics

Sensing and response to ionising radiation-induced damage: eg. ATM, p53, DNA-dependent protein kinase

Apoptosis: eg, Bcl-2, p53-dependent and independent pathways, ceramide

Cell cycle: molecular control; checkpoints (especially G1), pRB, p53, cyclins, cyclin-dependent kinases

Signal transduction: eg, Ras pathway

Cytokines involved in post-radiation normal tissue damage

20. DNA Structure and Function

Structure of an eukaryotic gene eg, open reading frame, untranslated regions, introns, exons, regulatory elements

DNA replication; RNA transcription; translation

Oncogenes and tumour suppressor genes (TSGs): Knudson's 2-hit hypothesis

Radiation-activated gene therapy

Examination

Part One
One three hour written paper, with six equally weighted questions. The last of these questions is a multiple-choice format.

Exam Technique
Candidates are strongly advised to study multiple previous examination essay topics and extensively practice both technique and content. Essay answers are not required to be exhaustive or incredibly factually detailed. Often, a well set out 2-page answer with a comprehensively and accurately labelled graphic will be marked higher than a 3-4 page rambling text. The critical factors for demonstrating good knowledge of a subject relate to clear and accurate initial definitions, thorough and logical organisation of the coverage of the subject and appropriate perspective on the subject.

All questions should be answered with some clinical emphasis, unless they are purely laboratory-related questions. Extensive description of clinical findings and symptomatology is ***not*** required. Answers should be aimed at a general high level biological type audience. Recurring difficulties of candidates reflect non-adherence to definite instructions, eg., when a question specifically asks for a list, the candidate will commonly enter into a discursive discussion of that or a related subject. eg., a question may call for a discussion of the ***clinical*** aspects of fractionation and candidates will commonly spend the entire question discussing the 5R's and theory of fractionation.

Part Two
In the Radiotherapy papers, candidates will be expected to provide relevant radiobiological content in their answers, where appropriate. No specific Radiobiology exam questions will be set. Brief radiobiological comment may also be expected in the oral exam. Familiarity with basic BED calculations and their application will be expected.