



Radiation Oncology

Initial Certification Qualifying (Computer-based) Exam: Study Guide for Radiation and Cancer Biology

This exam tests your knowledge of the principles of radiation and cancer biology underlying the practice of radiation oncology. Included are questions on the general domains listed below. Exam performance will be reported to you based on an overall pass/fail grade, with specific information provided regarding quintile performance in the 10 individual domains. Because of the nature of scientific knowledge and subcategories, there may be some overlap of items across domains. Each exam will include items from every domain, but individual subtopics may not be included in every exam and the number of items per domain depends on the domain.

I.	Interaction of radiation with matter	1% to 4%
II.	Molecular and cellular damage and repair	13% to 17%
III.	Cellular response to radiation	7% to 10%
IV.	Linear energy transfer (LET) and oxygen effect	3% to 5%
V.	Tumor biology and microenvironment	3% to 5%
VI.	Cancer biology	19% to 23%
VII.	Radiobiology of normal tissues	9% to 12%
VIII.	Dose delivery	11% to 15%
IX.	Combined modality therapy	11% to 15%
X.	Late effects and radiation protection	6% to 9%

The ranges above are those generally in effect for the exam to be administered in 2020 and are intended only for guidance in candidate preparation. They do not necessarily represent a precise number of scorable items.

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- I. Interaction of radiation with matter**
 - a. Definition of ionizing radiation, free radicals, and radical damage
 - b. Direct and indirect action of radiation, numbers and types of DNA lesions
 - c. Consequences of unrepaired DNA DSB

 - II. Molecular and cellular damage and repair**
 - a. Molecular mechanisms of DNA damage
 - i. Assays for measuring DNA damage and repair
 - ii. Single lethal hits, accumulated damage, and multiple damaged sites
 - b. Molecular mechanisms of DNA repair
 - i. Repair of base damage, single-strand and double-strand breaks

- ii. DSB repair: Homologous recombination and non-homologous end joining
- iii. Molecular mechanisms of DNA DSB damage recognition and damage signaling to initiate repair
- c. Cellular recovery
 - i. Repair at the cellular level
 - ii. Sublethal damage repair
 - iii. Dose-rate effects and repair
 - iv. Dose-fractionation effects and repair
- d. Chromosome and chromatid damage
 - i. Assays for measuring chromosome damage – Giemsa to FISH
 - ii. Dose-response relationships
 - iii. Use of peripheral blood lymphocytes in *in vivo* dosimetry
 - iv. Human genetic diseases that affect DNA repair, fragility, and radiosensitivity
 - v. Stable and unstable chromatid and chromosome aberrations

III. Cellular responses to radiation

- a. Mechanisms of cell death
 - i. Mechanisms and major characteristics of pathways of radiation-induced apoptosis, necrosis, autophagy, and senescence
 - ii. Mitotic-linked cell death and chromosome aberrations
 - iii. Cell division post-radiation and time to clonogen death
- b. Cell and tissue survival assays: measurement of response
 - i. In vitro clonogenic assays - effects of dose and dose rate
 - ii. In vivo clonogenic assays - bone marrow stem cell assays, jejunal crypt stem cell assay, skin clones, and kidney tubules
- c. Models of cell survival
 - i. Random nature of cell killing and Poisson statistics
 - ii. Single hit, multitarget models of cell survival – survival curve descriptors
 - iii. Linear-quadratic models: definition of α/β ratio
 - iv. Calculations of cell survival with dose and dose rate
 - v. Shapes of the dose-response curves for early and late responding tissues
 - vi. Isoeffect curves and impact of changing fraction size and number on survival and LQ parameters

IV. Linear energy transfer (LET) and oxygen effect

- a. Linear energy transfer
 - i. Definition of LET and quality of radiation
 - ii. RBE defined
 - iii. RBE as a function of LET in cells and tissues
 - iv. Effect on RBE on change in fractionation
- b. Oxygen Effect
 - i. Definition of OER
 - ii. Dose or dose per fraction effects
 - iii. OER vs LET
 - iv. Impact of O₂ concentration
 - v. Mechanisms of oxygen effect

V. Tumor biology and microenvironment

- a. Solid tumor assay systems
 - i. Concept of xenograft and syngeneic tumor models

- ii. Assay of tumor response to treatment– growth delay
- iii. TCD50 tumor control assay
- b. Tumor microenvironment
 - i. Characteristics of tumor vasculature and microenvironment; effect of radiation on them
 - ii. How tumor microenvironment can regulate tumor growth and vasculature
 - iii. Angiogenesis and neovasculogenesis
 - iv. Clinical consequence and relevance of hypoxia in tumors and tumor progressions
 - v. Reoxygenation after irradiation
 - vi. Cellular and molecular responses to hypoxia and hypoxia-induced signal transduction
 - vii. Cellular composition of tumors
 - viii. Immune microenvironment and role of inflammation

VI. Cancer biology

- a. Cell and tissue kinetics
 - i. Methods to assess cell cycle kinetics
 - ii. Proteins involved in cell cycle control and checkpoint initiation (e.g., CDKs, cyclins, CDK inhibitors)
 - iii. Phases of cell cycle and radiation sensitivity
 - iv. Cell cycle arrest and redistribution after irradiation
- b. Molecular signaling
 - i. Main signaling pathways and critical proteins involved (e.g., PI3K/AKT, RAS/ERK, TGF- β , Wnt, Notch, NFkB)
 - a) Receptors/ligand (e.g., EGFR, VEGFR, c-MET, HER2, FGFR, ALK)
 - b) Kinases
 - 1). Definition of kinases (e.g., STKs, TKs/RTKs, DSKs)
 - 2). Common kinases in cancer (e.g., ATM, ATR, Chk1, Chk2, PI3K, MAPK) and corresponding phosphatases (e.g., PTEN)
 - ii. Molecular signaling pathways activated by IR
 - iii. Transcription factors involved in cancer regulation (e.g., MYC, TP53 and associated proteins)
 - iv. Cell death pathways and main associated players
 - a). Intrinsic vs extrinsic apoptosis (caspases)
 - b). *BCL-2* family member proteins (pro- vs anti-apoptotic)
- c. Mechanisms of cancer development
 - i. Hallmarks of cancer and how they could affect 4/5 Rs of radiobiology
 - ii. Common oncogenes (e.g., *HER2/neu*, *Ras*, *Myc*) & tumor suppressors (*Rb*, *p16*, *p53*, *BRCA1/BRCA2*, *APC*, *NF1*)
 - iii. Telomeres and pathways in cancer to overcome telomere shortening (e.g., TERT promoter mutations and alternative lengthening of telomeres [ALT])
 - iv. Signaling abnormalities and association with treatment response
 - iv. Cancer as a genetic disease
 - v. Multistep nature of carcinogenesis
 - vi. Signaling abnormalities in carcinogenesis
 - vii. Prognostic and therapeutic significance of tumor characteristics
- d. Cancer genetics/genomics
 - i. Types of epigenetic regulation (e.g., DNA methylation (DNMTs/TETs), histone modifications (e.g. HDACs/HATs), chromatin remodelers)
 - ii. Main epigenetic alterations (e.g., CpG island methylator phenotype [CIMP]) in cancer
 - a). *IDH1/2* mutations in glioma and AML
 - b). *TET2* mutations in AML

- iii. Epigenetic targets in cancer (DNMTi, HDACi, IDHi, EZH2i)
- iv. Omics approaches in cancer (next-gen sequencing/arrays) and newer methods (ctDNA)
- v. Biomarkers in cancer (e.g., BCR-ABL, EGFR, ALK)
- vi. Molecular profiling of cancer

VII. Radiobiology of normal tissues

- a. Clinically relevant normal tissue responses to radiation
 - i. Responses in early versus late responding tissues
 - ii. Reirradiation
- b. Mechanisms of normal tissue radiation responses
 - i. Molecular and cellular responses in slowly and rapidly proliferating tissues
 - ii. Mechanisms underlying clinical symptoms
 - iii. Tissue kinetics
- c. Total body irradiation
 - i. Prodromal radiation syndrome
 - ii. Acute radiation syndromes
 - iii. Mean lethal dose and dose/time responses
 - iv. Immunological effects
 - v. Assessment and treatment of radiation accidents
 - vi. Bone marrow transplantation

VIII. Dose delivery

- a. Therapeutic ratio
 - i. Tumor control probability (TCP) curves
 - ii. Normal tissue complication probability (NTCP) curves
 - iii. Causes of treatment failure
- b. Time, dose, and fractionation
 - i. The four R's of fractionation
 - ii. Radiobiological rationale behind dose fractionation
 - iii. Effect of tissue/tumor type on the response to dose fractionation (α/β ratios)
 - iv. Quantitation of multifraction survival curves
 - v. BED and isoeffect dose calculations
 - vi. Hypofractionation
- c. Brachytherapy
 - i. Dose-rate effects (HDR and LDR)
 - ii. Choice of isotopes
 - iii. Radiolabeled antibodies and other ligands
- d. Radiobiological aspects of different radiation modalities
 - i. Protons, high LET sources
 - ii. Stereotactic radiosurgery/radiotherapy, IMRT, IORT, and systemic radionuclides
 - iii. Dose distributions and dose heterogeneity

IX. Combined modality therapy

- a. Chemotherapeutic agents and radiation therapy
 - i. Classes of chemotherapy agents
 - ii. Mechanisms of action
 - iii. Oxygen effect on radiation therapy and chemotherapy
 - iv. Main drug resistance mechanisms (e.g., MDR genes)
 - v. Interactions/synergism of chemotherapy with radiation therapy
 - vi. Targeted therapeutic agents

- b. Radiosensitizers, bioreductive drugs, and radioprotectors
 - i. Definition of therapeutic window
 - ii. Tumor radiosensitizers (e.g., oxygen) and mimics (e.g., nitromidazole)
 - iii. Normal tissue radioprotectors (e.g., amifostine)
 - iv. Biological response modifiers (e.g., IL-2 and IFN)
 - v. DNA repair inhibitors (e.g., PARPi, ATMi, ATRi, Chk1/2i)
- c. Immune therapeutics
 - i. Types of immunotherapy treatments in oncology
 - a) Monoclonal antibodies (MABs)
 - b) Checkpoint inhibitors
 - c) Cytokines
 - d) Vaccines
 - e) Adoptive cell transfer types (chimeric antigen receptors [CARs], tumor infiltrating lymphocytes [TILs], and T cell receptors [TCRs])
 - ii. Combination of immune therapies and radiation
 - a) Recently published trials (e.g., PACIFIC, KEYNOTE)
 - b) Known predictors of response/biomarkers
- d. Hyperthermia

X. Late effects and radiation protection

- a. Radiation carcinogenesis
 - i. Dose response for radiation-induced cancers
 - ii. Importance of age at exposure, time since exposure, sex, and tissue
 - iii. Second tumors in radiation therapy patients
 - iv. Risk estimates in humans
- b. Heritable effects of radiation
 - i. Relative vs absolute mutation risk
 - ii. Doubling dose
 - iii. Heritable effects in humans
 - iv. Risk estimates for hereditary effects
- c. Radiation effects in the developing embryo
 - i. Dependence of abnormalities and death on dose and gestational stage
 - ii. Microcephaly, intellectual disabilities
- d. Radiation protection
 - i. Stochastic effects and tissue reactions
 - ii. Tissue and radiation weighting factors
 - iii. Equivalent dose, effective dose, committed dose
 - iv. Dose limits for occupational and public exposure

References: References are intended as a resource for exam takers and will form the sources for the majority of individual items in the exam. Individual items may be sourced from references not cited in this study guide. Primary references are intended to be the source of the majority of exam items.

Secondary references are for individual smaller categories of items.

Primary References:

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- Joiner, M.C. and van der Kogel, A.J., *Basic Clinical Radiobiology*, 5th Edition, 2018, CRC Press

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NOTE: This study guide is subject to future revision as feedback is received on both content and clarity.