ABR | American Board of Radiology

Radiation Oncology

Initial Certification Qualifying (Computer-based) Examination: 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.

Primary Domains:

- **I. Interaction of radiation with matter**
- **II. Molecular and cellular damage and repair**
- **III. Cellular responses to radiation**
- **IV. Linear energy transfer (LET) and oxygen effect**
- **V. Tumor biology and microenvironment**
- **VI. Cancer biology**
- **VII. Radiobiology of normal tissues**
- **VIII. Dose delivery**
- **IX. Combined modality therapy**
- **X. Late effects and radiation protection**

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 O_2 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. Radiobiologyof 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
d. Radiobiological aspects of different radiation modalities
  i. Protons, high LET sources
  ii. Stereotactic radiosurgery/radiotherapy, IMRT, IORT
  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 hereditable 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 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:

- Hall, EJ.; Giaccia, AJ., Radiobiology for the Radiologist, 8th Ed., 2018, Lippincott Williams & Wilkins, Phila., Pa
- Joiner, MC and van der Kogel, AJ, Basic Clinical Radiobiology, 5th Edition, 2018, CRC Press
- Weinberg, RA., The Biology of Cancer, 2nd Edition, 2013, Garland Science, New York, NY

Secondary References:

- Eriksson, D. and T. Stigbrand, Radiation-induced cell death mechanisms. Tumour Biol, 2010. 31(4):

p. 363-72.
- Good, J.S. and K.J. Harrington, The hallmarks of cancer and the radiation oncologist: updating the 5Rs of radiobiology. Clin Oncol (R Coll Radiol), 2013. 25(10): p. 569-77.
- Barker, H.E., et al., The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. Nat Rev Cancer, 2015. 15(7): p. 409-25.
- Bristow, R.G. and R.P. Hill, Hypoxia and metabolism. Hypoxia, DNA repair and genetic instability. Nat Rev Cancer. 2008 Mar;8 (3):180-92.
- Hanahan, D. and R.A. Weinberg, Hallmarks of cancer: the next generation. Cell, 2011. 144(5): p. 646-74.
- Whitfield, M. L., L. K. George, G. D. Grant and C. M. Perou (2006). "Common markers of proliferation." Nat Rev Cancer 6(2): 99-106.
- Schaue, D. and W. H. McBride (2015). "Opportunities and challenges of radiotherapy for treating cancer." Nat Rev Clin Oncol 12(9): 527-540.
- Pajonk, F., E. Vlashi and W. H. McBride (2010). "Radiation resistance of cancer stem cells: the 4 R's of radiobiology revisited." Stem Cells 28(4): 639-648.
- Otto, T. and P. Sicinski (2017). "Cell cycle proteins as promising targets in cancer therapy." Nat Rev Cancer 17(2): 93-115.
- Huang, M., A. Shen, J. Ding and M. Geng (2014). "Molecularly targeted cancer therapy: some lessons from the past decade." Trends Pharmacol Sci 35(1): 41-50.
- Demaria, S., E.B. Golden, and S.C. Formenti, Role of Local Radiation Therapy in Cancer Immunotherapy. JAMA Oncol, 2015. 1(9): p. 1325-32.

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