**Neoplasia**

**5 Lectures**

***OBJECTIVES AND KEY PRINCIPLES TO BE TAUGHT:***

Upon completion of these lectures, the student should:

1. Define a neoplasm. Contrast neoplastic growth with hyperplasia, metaplasia, and dysplasia.
2. Know the basic principles of the nomenclature of benign and malignant processes.
3. Define and use in the proper context:
   1. Adenoma.
   2. Papilloma.
   3. Polyp.
   4. Cystadenoma.
   5. Adenocarcinoma.
   6. Sarcoma.
4. Compare and contrast benign and malignant tumors with respect to:
   1. demarcation from surrounding tissue (capsule, local invasiveness.
   2. rate of growth
   3. degree of differentiation (Explain the meaning of differentiation).
   4. distant spread (metastases).
5. Describe the morphologic changes associated with poorly differentiated tumors; define and understand the usage of the terms anaplasia, pleomorphism, nuclear atypia, loss of polarity, abnormal mitoses, tumor giant cells.
6. Understand the clinical significance of invasiveness and metastasis.
7. Describe the anatomic pathways utilized by tumors in metastatic spread. Know which pathways are more commonly used by carcinomas versus sarcomas.
8. List some common sites of distant metastases. Know which organs are least commonly involved in metastases
9. Recognize the epidemiologic data of cancer distribution in regard to age, race, geographic factors, and genetic backgrounds.
10. List some inherited syndromes associated with a genetic predisposition to cancer.
11. Compare and contrast clinical features of cancer in patients with an inherited predisposition versus sporadic cancer, in terms of multiple primary tumors, age at onset, and genetic alterations.
12. Understand the concept that tumorigenesis is a multistep process involving the accumulation of genetic alterations.
13. Understand the concept of tumor clonality.
14. Describe the seven fundamental changes in cell physiology associated with the malignant phenotype: self-sufficiency in growth signals, insensitivity to growth inhibition, evasion of apoptosis, genomic instability, immortalization, sustained angiogenesis, and invasion and metastasis.
15. Understand the relationship between tumor progression and cellular heterogeneity within a tumor, and the implications in terms of treatment and metastatic potential.
16. Correlate the molecular and morphologic features of colon carcinoma as an example of tumor progression.
17. Understand the concepts of dominant oncogenes, protooncogenes and recessive tumor suppressor gene.
18. Review the principles of signal transduction in cells. Be familiar with the different classes of growth factors, growth factor receptors, signal-transducing molecules, and nuclear regulatory factors.
19. Describe the concept of DNA-damage checkpoints and the roles played by P53 and CKIs in the DNA damage response.
20. List the types of structural chromosome changes seen in tumors (deletions, translocations, double minute chromosomes) and the associated oncogenic mechanisms associated with each type (loss of tumor suppressor gene, oncogene activation, gene amplification).
21. Understand the normal functions of the RAS, ABL, ERB-B2, MYC, beta-catenin, and cyclin D1 gene products, the types of genetic alterations found in these genes, and the types of neoplasms that carry alterations in these genes.
22. List the various causes of neoplasm
23. Define tumor grade and clinical stage.
24. Define cachexia and its cause.
25. Define paraneoplastic syndrome, and know examples of tumors associated with endocrinopathies, osseous changes, and vascular and hematologic changes.
26. Be familiar with the general principles, value, procedures, and applications of biopsy, exfoliative and aspiration cytology, and frozen section.
27. List some examples of special markers used to diagnose cancer by immunohistochemistry and flowcytometry.
28. Discuss the use of molecular diagnostic testing in the setting of cancer diagnosis, prognosis, minimal residual disease evaluation, and diagnosis of hereditary predisposition.

***TAKE HOME MESSAGES:***

1. A neoplasm is "an abnormal mass of tissue the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after the cessation of the stimuli which evoked the change."
2. Benign and malignant tumors can be distinguished on the basis of the degree of differentiation, rate of growth, local invasiveness, and distant spread.
3. Anaplastic neoplasm are highly malignant, poorly differentiated tumors; associated with marked pleomorphism, nuclear atypia, loss of polarity, abnormal mitoses, tumor giant cells.
4. Benign tumors remain localized to the site of origin, whereas malignant tumors are locally invasive and they metastasize to distant sites.
5. The incidence of cancer varies with age, race, geographic factors, and genetic backgrounds. Cancers are most common at the two extremes of age. The geographic variation results mostly from different environmental exposures. Most cancers are sporadic, but some are familial. Predisposition to hereditary cancers may be autosomal dominant or autosomal recessive.
6. A tumor mass results from the clonal expansion of a single progenitor cell that has incurred genetic damage. Such genetic damage (or mutation) may be acquired by the action of environmental agents, such as chemicals, radiation, or viruses, or it may be inherited in the germ line.
7. Carcinogenesis is a multistep process at both the phenotypic and the genetic levels, resulting from the accumulation of multiple mutations.
8. The seven fundamental changes in cell physiology associated with the malignant phenotype are: self-sufficiency in growth signals, insensitivity to growth inhibition, evasion of apoptosis, genomic instability, immortalization, sustained angiogenesis, and invasion and metastasis.
9. During tumor progression, cellular heterogeneity occur within a tumor. This affects the response to treatment and metastatic potential.
10. Oncogenes can promote uncontrolled cell proliferation by several mechanisms:
    1. Stimulus-independent expression of growth factor and its receptor, setting up an autocrine loop of cell proliferation.
    2. Mutations in genes encoding growth factor receptors, leading to overexpression or constitutive signaling by the receptor (e.g., EGF receptors) in breast, lung, and other tumors
    3. Mutations in genes encoding signaling molecules, e.g. RAS is commonly mutated in human cancers. Fusion of ABL tyrosine kinase with BCR protein in certain leukemias generates a hybrid protein with constitutive kinase activity
    4. Overproduction or unregulated activity of transcription factors, e.g. Translocation of MYC in some lymphomas leads to overexpression and unregulated expression of its target genes controlling cell cycling and survival
    5. Mutations that activate cyclin genes or inactivate normal regulators of cyclins and cyclin-dependent kinases, e.g. complexes of cyclins with cyclin-dependent kinases (CDKs) drive the cell cycle by phosphorylating various substrates; CDKs are controlled by inhibitors; mutations in genes encoding cyclins, CDKs, and CDK inhibitors result in uncontrolled cell cycle progression. Such mutations are found in wide variety of cancers including melanomas, brain, lung, and pancreatic cancer.
11. Tumor suppressor genes encode proteins that inhibit cellular proliferation by regulating the cell cycle. Unlike oncogenes, both copies of the gene must be lost for tumor development, leading to loss of heterozygosity at the gene locus. In cases with familial predisposition to develop tumors, the affected individuals inherit one defective (nonfunctional) copy of a tumor suppressor gene and lose the second one through somatic mutation. In sporadic cases both copies are lost through somatic mutations. E.g. p53 and Rb gene.
12. Apoptosis can be initiated through the extrinsic or intrinsic pathways. Both pathways result in the activation of a proteolytic cascade of caspases that destroys the cell. In 85% of follicular B-cell lymphomas the anti-apoptotic gene BCL2 is activated by the t(8;14) translocation.
13. Tumor cells reactivate telomerase, thus continue to divid.
14. Vascularization of tumors is essential for their growth and is controlled by the balance between angiogenic and anti-angiogenic factors that are produced by tumor and stromal cells.
15. Ability to invade tissues, a hallmark of malignancy, occurs in four steps: loosening of cell-cell contacts, degradation of ECM, attachment to novel ECM components, and migration of tumor cells.
16. The metastatic site of many tumors can be predicted by the location of the primary tumor. Many tumors arrest in the first capillary bed they encounter (lung and liver, most commonly).Some tumors show organ tropism, probably due to expression of adhesion or chemokine receptors whose ligands are expressed by the metastatic site.
17. Individuals with inherited mutations of genes involved in DNA repair systems are at a greatly increased risk of developing cancer. E.g. Patients with HNPCC syndrome have defects in the mismatch repair system and develop carcinomas of the colon.  Another e.g. Patients with xeroderma pigmentosum have a defect in the nucleotide excision repair pathway and are at increased risk for the development of cancers of the skin exposed to UV light, because of an inability to repair pyrimidine dimers.
18. Structural chromosome changes seen in tumors are deletions, translocations and gene amplification. Point mutation can be detected in some tumors as well.
19. Chemical carcinogens have highly reactive eletrophile groups that directly damage DNA, leading to mutations and eventually cancer. Examples of human carcinogens include direct-acting (e.g., alkylating agents used for chemotherapy), indirect-acting (e.g., benzopyrene, azo dyes, and aflatoxin), and promoters/agents that cause pathologic hyperplasias of liver, endometrium.
20. Ionizing radiation causes chromosome breakage, translocations, and, less frequently, point mutations, leading to genetic damage and carcinogenesis.UV rays induce the formation of pyrimidine dimers within DNA, leading to mutations.
21. HPV has been associated with benign warts, as well as cervical cancer. The oncogenic ability of HPV is related to the expression of two viral oncoproteins, E6 and E7; they bind to RB and p53, respectively, neutralizing their function.
22. EBV has been implicated in the pathogenesis of Burkitt lymphomas, lymphomas in immunosuppressed individuals with HIV infection or organ transplantation, some forms of Hodgkin lymphoma, and nasopharyngeal carcinoma.
23. Between 70% and 85% of hepatocellular carcinomas worldwide are due to infection with HBV or HCV.
24. Cachexia, defined by progressive loss of body fat and lean body mass, accompanied by profound weakness, anorexia, and anemia, is caused by release of cytokines by the tumor or host.
25. Paraneoplastic syndromes, defined by systemic symptoms that cannot be explained by tumor spread or by hormones appropriate to the tissue, are caused by the ectopic production and secretion of bioactive substances, such as ACTH, PTHrP, or TGF-α.
26. Grading of tumors is determined by cytologic appearance and is based on the idea that behavior and differentiation are related, with poorly differentiated tumors having more aggressive behavior.
27. Staging, determined by surgical exploration or imaging, is based on size, local and regional lymph node spread, and distant metastases. Staging has greater clinical value than grading.
28. Several sampling approaches exist for the diagnosis of tumors, including excision, biopsy, fine-needle aspiration, and cytologic smears.
29. Immunohistochemistry and flow cytometry help in the diagnosis and classification of tumors, because distinct protein expression patterns define different entities.
30. Proteins released by tumors into the serum, such as PSA, can be used to screen populations for cancer and to monitor recurrence following treatment.
31. Molecular analyses are used to determine diagnosis, prognosis, the detection of minimal residual disease, and the diagnosis of hereditary predisposition to cancer. Molecular profiling of tumors by cDNA arrays can determine expression of large segments of the genome at once and can be useful in molecular stratification of otherwise identical tumors for the purpose of treatment and prognostication.

***FURTHER READING:***

* Kumar, Cotran and Robbins: Basic pathology, 8th edition.

**Keywords:**

Papilloma, Polyp, Cystadenoma, Adenocarcinoma, Sarcoma, benign, malignant degree of differentiation, anaplasia, pleomorphism, nuclear atypia, loss of polarity, abnormal mitoses, tumor giant cells, invasion, metastasis, epidemiologic data of cancer distribution, genetic predisposition to cancer ( inherited predisposition), sporadic cancer, tumorigenesis, genetic alterations, tumor clonality, self-sufficiency in growth signals, insensitivity to growth inhibition, evasion of apoptosis, genomic instability, immortalization, sustained angiogenesis, cellular heterogeneity oncogenes, protooncogenes, tumor suppressor gene growth factors, growth factor receptors, signal-transducing molecules, and nuclear regulatory factors, P53, Rb, apoptosis, deletions, translocations, double minute chromosomes, gene amplification, initiation, promotion, tumor grade, clinical stage, cachexia, paraneoplastic syndrome, biopsy, exfoliative and aspiration cytology, immunohistochemistry, flowcytometry, tumor biochemical markers, molecular diagnostic testing, minimal residual disease evaluation, diagnosis of hereditary predisposition.