

Surgery/Medicine Oncology Lecture

Principles of Surgical Oncology/Introduction to oncology.

Medicine Objectives:

- •1- definition of cancer
- •2- etiology of cancer
- •3- staging of malignant diseases
- •4- principles of pathological classification of malignant
 - •5- general symptoms and signs of malignancy
 •6- principles of cancer management
 (curative Vs palliative concept)

Surgery objectives:

- •1- Types of tumors
- •2- Applied surgical pathology of tumors
- •3- Pathological basis of tumor staging
 - •4- Tumor staging
- •5- Principles of biopsy and cytology
- •6- Principles of surgery of tumors
 Overview of tumor markers

We recommend that you study this lecture before common solid tumors lecture it will be much easier you will finish 3 lectures in no time.

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References: Surgery and Medicine slides, doctors' notes, Pathoma

[Important | Medicine notes | Surgery notes | Extra | Editing file: Surgery / Medicine]

Definition: Normally, we have 3 types of cells:

Labile cells: cells that can proliferate and are in continuous division like skin, mucous membranes, and hematopoietic cells. they are subjected to wear and tear.

Stable cells: cells that proliferate on demand like hepatocytes and bone cells when subjected to fracture.

Permanent cells: cells that don't proliferate like cardiac cells, skeletal muscles, and neurons.

These cells' division is controlled and regulated.

Neoplasia: it's a new tissue growth that is unregulated, irreversible and monoclonal (Meaning that tumor cells have developed from one cell type). These



These cells:

- Have lost their functions. Patients with leukemia have high WBCs count but are non functional (so they are susceptible to infections), causing lymphadenopathy and hepatosplenomegaly.
- Have the ability to send distant metastasis.
- Have the ability to invade surrounding tissues.
- **Epigenetic defects**: The **defect** here is not in the DNA sequence like any other mutation, but it's in the expression of certain genes, like tumor suppressor genes or proto oncogene, which will cause tumorigenesis.

Metaplasia	Dysplasia premalignant (if undetected > cancer)
It's an adaptive and reversible process where one "well-differentiated" cell type is replaced by another "well-differentiated" cell type from the same germ layer. Ex, transitional cells turn into squamous cells due to chronic irritation to compensate. Another example is barrett's esophagus	Abnormal proliferation of cells with loss of size, shape, and orientation. (so the problem here that it's not totally mature or differentiated). Ex, Leukoplakia happens due to chronic irritation of the tongue which can turn into squamous cell carcinoma. They turn into squamous because it can handle the irritation better but the consequence of this is a change in the cells' DNA.

once we enter metaplasia or dysplasia the cells change their behavior and that's dangerous (unlike hypertrophy and hyperplasia)



Hallmarks of cancer: Important

- Six changes for cancer found in most, if not all:
 - 1. Self-sufficiency in growth signals. (they produce their own)
 - 2. Insensitivity to growth-inhibitory signals. (they escaped body control)
 - 3. Absence of apoptosis (immortal)

4. Limitless proliferative capacity.

Change in cell

size or number

Reversible

Hypertrophy

Atrophy

Normal cells

Reversible

type and structure

Irreversible

Irreversible

- 5. Sustained angiogenesis. (they make their own blood supply)²
- 6. Tissue invasion and metastasis.

¹ loss of contact phenomenon: just like if you have a cut wound in your hand, the skin eventually will stop growing as the two edges 'contact' and cover the wounded part, why? Because of contact phenomenon; malignant cell that they lose these signals leading to disorganized growth and arrangement.

² "new metabolic therapies target angiogenesis"

Etiology:

we all have mutated cells, but why don't we develop malignancy? because we have intact "checkpoints" cell growth regulators, DNA repair mechanisms, and immune system. When these mechanisms and systems are defective we will have higher risk of malignancy.

Cellular growth is controlled by <u>proto-oncogenes</u> (it's a normal "good" gene), tumor suppressor genes, and apoptosis regulators.

Pathoma Recall

- Mutation in a proto-oncogene > gain of function > oncogenes > higher risk for cancer.
 Oncogenes include:
 - o Growth factors: increased expression of growth factors will induce cellular growth.
 - o Growth factor receptors: increased expression of a growth factor receptor will induce cellular growth as well.
 - Signal transducers: normally signal transducer binds to GTP and converts it to GDP which will stop the signal when it's necessary. If a mutation happens it will not stop the signal and growth will continue and that what happens with RAS mutation.
 - Cell cycle regulators mediate progression through the cell cycle.
- Mutation in a tumor suppressor gene > loss of function (the ability of cancer 'suppression' decreases) > higher risk for cancer.
- Mutation in an apoptosis regulator > increased apoptosis inhibition (which leads to abnormal growth) > cancer.

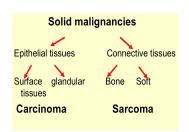
Causes of cancer:

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DNA mutation (when you have DNA defect you will start to have cancer "DNA controls everything")	Genetic predisposition	Infections (they increase cells proliferation)
- Carcinogenic agents (they damage the DNA): Radiation or chemicals (Tobacco, alcohol, asbestos (causes mesothelioma and lung cancer), arsenic, chemotherapy, etc) -Random Somatic mutation -Inherited germline mutations. (bad copy of the gene inherited from the parents).	Rb (it's a tumor suppressor gene that regulates progression of cell cycle from phase G1 to S). P53 (same action as Rb but with different pathways). APC. CDKN2A. BRCA1. BRCA2.	Viral: (they can cause cancer by inducing cells proliferation 'viruses replicates by making the human cells replicate. Another mechanism is by decreasing the immunity like HIV) HPV-cervical cancer HBV, HCV-hepatocellular carcinoma, EBV-lymphoma Bacterial: H.pylori-stomach cancer Fungi: "aflatoxin found in aspergillus can cause HCC" Parasites: schistosoma

*Anything that induces cells proliferation can cause cancer. Smoking increases the risk of cancer (chronic irritation > proliferation > chance of mutation increases > higher risk of cancer). But why don't all smokers develop cancer? Because **the cause of cancer formation is multifactorial.** So the cause of lung cancer is not smoking "it is only a risk factor"; there are other things that would lead to cancer development in that particular smoker like genetic predisposition, bad lifestyle, etc.. "The unknown factors are much more than the known factors".

Types of Tumors:

• Based on composition: 1-solid (further classified into epithelial and connective tissue tumors 'see the picture') 2-liquid tumors "blood neoplasms"

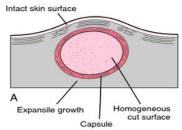


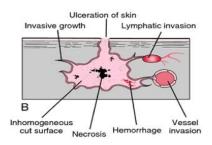
• Based on their parent cell: (lineage of differentiation)

Epithelium (solid)	Benign	Glandular: Adenoma Surface: ex, papilloma
	Malignant	Glandular: Adeno <u>carcinoma</u> (more aggressive than sarcomas) Surface: Ex, Papillary <u>carcinoma</u> , squamous cell <u>carcinoma</u> , and transitional cell <u>carcinoma</u> . carcinomas arise from the epithelium.
Mesenchyme	Benign	E.g. Lipoma
(solid) ³	Malignant	E.g. Lipo <u>sarcoma</u> . sarcomas are those originating from connective tissue.
Melanocyte	Benign	Nevus
(solid)	Malignant	Melanoma
Lymphocytes	Benign	Do not exist
(Liquid)	Malignant	Myeloproliferative disorders = leukemia Lymphoproliferative disorders= lymphoma (could be solid or liquid)

Teratoma (solid)	Hamartoma (solid)	Blastoma (solid or liquid)
-Is a tumor made up of several different types of tissue, such as hair, muscle, or bone. -They are usually found in germ	Is a mostly benign, focal malformation that resembles a neoplasm in the tissue of its origin. It is composed of tissue elements normally found at that site, but they	Cancer cells derived from immature (precursor) cells or embryonic tissue. Most commonly in children.
cell areas (testes and ovaries)	are growing in a disorganized manner.	-Ex. Hepatoblastoma and
-They arise from totipotential cells (they can differentiate into many types of cells; that's why we see different types of tissues in the tumor) -Ex. Dermoid cyst	Ex. Angiomyolipoma of the kidney. It's made up of blood vessels, smooth muscle cells and fat.	myeloblastoma. Blastoma as a suffix, with the Latin or Greek word for the organ or tissue of origin as the root.

Benign vs Malignant:





 $^{^{3}}$ (connective tissue) It can arise from bones, cartilage, fat, nerves, etc

Normal	Cancer	
9		Large, variably shaped nuclei
49.4	000000	Many dividing cells;
0	-	Disorganized arrangement
6		Variation in size and shape
		Loss of normal features

FUN FACT: Prostate and breast tissue are similar Under the microscope.

Benign	Malignant
 Regulated growth Low nuclear to cytoplasmic ratio Minimal mitotic activity Encapsulated No invasion No metastasis Treated with local excision. 	 Unregulated growth Nuclear pleomorphism and hyperchromasia High mitotic activity and atypical mitosis Non-encapsulated Invasive Metastasizes Radical excision with or without chemotherapy or radiotherapy or both.

benign polyps are simply removed by colonoscopy, follow up for recurrence. malignant polyps are treated by radical surgery (in this case, right hemicolectomy) Radical surgery: you remove the tumor + the adjacent tissue + the draining lymph nodes.



Oncology consultation:

- When to suspect cancer?
 - Ex. if there is a liver mass > we either classify it as high suspicion for malignancy or low suspicion for malignancy.
- How to diagnose cancer?
 - determining the easiest, fastest, and safest way to make the diagnosis. Ex, if there is a peripheral lung mass, there is no point in inserting a bronchoscope. Or if it is vascular, an invasive procedure may cause bleeding. Or to determine the situations where a biopsy must be taken to make the diagnosis.
- What the essential work up for staging? each type of tumor requires a specific set of work up, and we determine that.
- How to treat cancer?
 - to plan the management. Ex: a surgery must be done before chemotherapy for a certain types of malignancies and visa versa.
- What is the prognosis of your patient?

Staging and Grading: a lot of people mix up between stage and grade. There is some differences in grading and staging systems among the different types of tumors, but here is the general principles that we should know..

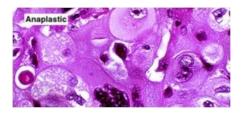
1. Grading: "ماله علاقة هو صارله ميتاستيسيس و لا لا هو بس همه الهستولوجي

it's a microscopic assessment of differentiation (يعني ابغى اعرف الى اي حد الخلايا هذي تشبه الخلية الام).

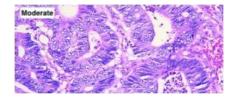
Grading is a way of classifying cancer cells. The pathologist gives the cancer a grade based on how different they look from normal cells (differentiation synonymous with grading), how quickly they are growing and dividing, and how likely they are to spread. (How aggressive is the cancer?)

Grading	Differentiation
GX (grade cannot be assessed)	
G1 'low grade'	well differentiated
G2 'intermediate grade'	Moderately differentiated
G3 'high grade'	Poorly differentiated
G4 'high grade'	Undifferentiated

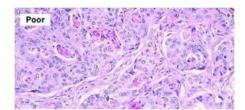
- Anaplastic: cancer cells divide rapidly with little or no resemblance to normal parent cell.
- ما "no differentiation at all." أخلاص كل المعالم راحت تماما



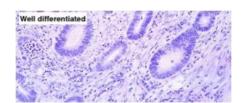
- Moderately differentiated
- You still can see that it's glandular



- Poorly differentiated → does not resemble parent tissue
- poorly differentiated "if i didn't tell that it was taken from the colon you probably wouldn't know



- Well differentiated → resembles normal parent tissue
- You still can see that it's glandular



- The idea here is that with every division of cells, mutations increase and get worse, that's why poorly differentiated cells indicate poor prognosis.

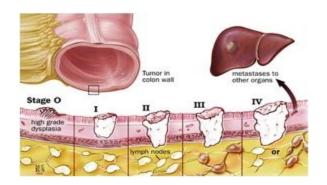
2. Staging: stage the tumor immediately after diagnosing the patient.

 a. It's an assessment of size and spread of cancer. classifies the tumor itself (Vs grading which classifies 'tumor cells')

b. Staging is done to:

- i. Decide and plan the treatment.
- ii. Asses the prognosis.

Whenever you deal with malignant tumor, always remember that there is primary tumor & there may be secondaries.



• Classical staging system:

Stage I,II	Stage III	Stage IV
Confined to the organ	Direct invasion	Metastasis

TNM staging system:

Clinical, Radiological, Pathological TNM or surgical staging

NM Classification (American Joint Commission on Cancer)		Dukes' Classification		
Stages	T-	N	M	Stages
Stage 0	Tis	NO -	MO	
Stage I	T1	N0	MO	A
otage i	T2	N0	MO	B1
Stage II	T3	N0	MO	B2
otage ii	T4	N0	MO	B2
Stage III	T1, T2	N1 or N2	M0	C1
otage III	T3, T4	N1 or N2	MO	C2
Stage IV	Any T	Any N	MT	D

T (Tis,Ta,Tb,T1,2,3,4) \rightarrow tumor (size and/or depth of invasion) depth is usually used with tubular structures such as breast and intestines. "For primary tumor only"

Tx	то	Tis ⁴	T1,2,3,4*
Tumor cannot be assessed.	No evidence of tumor.	Carcinoma in situ.	Depending on the size and/or extension from primary tumor.

*It depends on the primary tumor, for example, in bladder cancer T1 means it invaded the subepithelial connective tissue, T2 means it invaded muscularis propria and so on. Each can be divided to provide further details such as T3a or T3b.

⁴ cancer in situ, is it malignant or premalignant lesion? □IT IS MALIGNANT وهذا خطأ شائع مو کثیر یعرفونه Once it invades it becomes an aggressive tumor.

N (N0,1,2,3) \rightarrow Spread to regional lymph node.

Nx	N0	N1,2,3
Cancer is nearby lymph nodes cannot be measured.	There's no cancer nearby lymph nodes.	Refers to the number and location of lymph nodes that contain cancer.
		Higher number→ more lymph nodes

M (M0,1) \rightarrow Metastasis.

M0→ no distant metastasis.

M1→ metastasis to distant organs (beyond regional lymph nodes).



Modes of Spread:

Local invasion	Metastasis
- Continuity of primary tumor Within the organ To adjacent tissues e.g. bladder cancer invading the rectum	 Discontinuity of primary tumor. "حتى لو كان قريب" Hematogenous. Lymphatics (regional and distant lymph nodes). Trancolemic (peritoneal or pleural cavity. Implantation e.g. needle tracks, wounds. Common sites of metastasis: Bone, Brain, Lung, and Liver. "BBLL" e.g. cells of the bladder going to the lymphatic. Prostate cancer metastasizes to pelvis, long bones and vertebrae more than the liver

Clinical Presentation:

There are no specific symptoms for cancer patients, they come with different presentations and it depends on many factors.

- They can be asymptomatic.
- Main features of presentation: Important
 - Persistent. The symptoms may improve, but they do not disappear.
 - o Progressive.
 - o Disabling.
 - o Changes according to the site of origin.
- Symptoms related directly tumor.
 - o If it lies on the body surface (lump, bleeding or discharge, pigmentation).
 - Obstruction of a hollow structure. (bronchus→ lung collapse, in a segment of the bowel→ intestinal obstruction/ constipation, tumor at the head of pancreas→ obstructive jaundice).

- Tumor within a closed area. (it can increase the pressure in that area e.g. brain tumors would increase ICP).
- o Pressure on vital organ.
- o Invasion of an organ. (causing tissue destruction and organ failure).
- Symptoms of local invasion. (blood vessels > bleeding; nerves > pain). when a lung tumor invades the blood vessels > hemoptysis; gastric tumor > hematemesis.
- Secretory tumors. (depending on the origin of tumor Ex. adrenal cortex adenoma would cause Cushing's syndrome/or they can be ectopic secretions Ex. Lung cancer that secretes PTHrP or ACTH)
- Symptoms related indirectly to the tumor. <u>PICTURE</u> (summary of metastasized tumors' symptoms)
 - For example patients with bone metastasis would have pathological fractures.
- **Incidental finding** whenever you are take a history, diagnose, investigating or treat a tumor think of the possibility of the presence of secondary tumor.
- Cachexia.
 - It's a late presentation of most malignancies except for GI tumors (by affecting digestion)
 and Lung cancer (unknown cause of weight loss, but might be related to hormonal secretion) cause it affects absorption.
- Don't forget constitutional symptoms!!

Fatigue	Sweeting
Fever	Weight loss

Investigations:

Initially we start with simple blood test (Ex. tumor markers) until we reach complex imaging and investigations.

Remember cancer diagnosis is a pathological and tissue diagnosis "tissue is the issue".

Not clinical, radiological or serological. These help you to reach a diagnosis, but not to confirm it. But there is some **exceptions**:

1-70 year-old man with high PSA > you can diagnose him with prostatic cancer

2-patient with liver lesion, high AFP, and his CT shows liver mass > HCC

3-postpartum female patient with persistent increase in hCG > choriocarcinoma

Primary tumors	Metastatic tumors
-Represent de novo tumors in their initial site -Depends on the site, histology.	-These are cell colonies that has been sent by the primary tumor. Look for metastasized tumorsMost commonly to the liver, lung and bonesOnly few tumors can cross BBB such as squamous cell carcinoma and breast cancerMost GI tumors metastasize to the liver because of the portal circulation. Brain cancer rarely metastasize.



Cytology Individual cells	Biopsy ⁵ A piece of tissue
It gives the morphology of individual cells.	It preserves the histological tissue characteristics.
Types:	-Fine needle aspiration biopsy "FNAB"
-Exfoliative "(Ex.urine ⁶ , sputum)Fluid aspiration (Ex.ascitic fluid, pleural fluid).	-Core needle biopsy. <u>Trucut needle biopsy</u> can be guided by CT or US.
-Fine needle aspiration cytology "FNAC" (from a solid tumor)	-Incisional biopsy (by taking a piece of the organ) using forceps, needles (removes a small accessible piece of the lesion) Cup biopsy: captures the tissue. Used in ENDOSCOPY, colonoscopy, and bladder biopsy.
	-Excisional biopsy (complete removal of the lesion) FNA > Core needle biopsy > incisional biopsy > excisional biopsy. Picture

Basal cell carcinoma "rodent ulcer"	Diffuse basal cell carcinoma
Since it's localized, you could take excisional biopsy	since it's diffuse, you can only take incisional biopsy (wedge biopsy, which is biopsy of normal + abnormal tissue)

*It is not about the tumor type. The idea here basically is that when we have diffuse/large tumor we go with incisional biopsy, but with localized/small tumors we could use excisional biopsy "which could be part of the treatment"

ما فيها فكرة جديدة بس نعرف ان الهرمونز لها علاقة بالكانسر اما بالتريتمنت او بالبرزنتيشن :Hormones and cancer

- In relation to tumor growth: usually sex hormones (testosterone and estrogen). We can use them in treatment by using the concept of hormonal receptors. Ex. Tamoxifen in breast cancer and LHRH agonists in prostate cancer (lower the amount of testosterone).
- **Hormones produced by the tumor**: either originally hormone-producing organs or non hormone producing organs. (remember what examples we've mentioned before?)

⁵ You take the biopsy either by needle, taking the whole lump or removing the whole organ.

⁶ During urine cytology, it's normal to find cells, as a part of the apoptosis process where all the cell above the basement membrane get regenerated and the old ones get excreted in the urine.

Tumor markers:

- They're basically substances found in the blood or the affected tissue and may indicate malignancy.
 - Important principles to know: Most of them are not specific but important in diagnosis, screening and follow up. With the background of the clinical and investigation and biopsy. When there is another elevation of the marker after the surgical treatment you suspect recurrence.

CEA	Colon cancer, lung cancer, breast cancer, stomach cancer, pancreas cancer and ovaries cancer	
CA125	Lung cancer, breast cancer, pancreas cancer and ovaries cancer.	
AFP	Testicular cancer and liver cancer	
PSA	Prostate cancer	
HCG	Testicular cancer	
HER2	Breast cancer	
CA 19-9	pancreas cancer	

Screening:

the goal of screening is to catch dysplasia early or detect cancer before clinical feature appear.

- Screening methods:
 - \circ Pap smear → cervical cancer.
 - \circ Mammography \rightarrow breast cancer.
 - \circ PSA and digital rectal exam \rightarrow prostate cancer.
 - \circ Hemoccult test and colonoscopy \rightarrow colon cancer.

Treatment and Prognosis:

- ➤ First start with establishing cancer diagnosis → define type and stage → decide curative or palliative treatment.
 - o Curative: Aggressive, expensive and complex. Long term irreversible toxicity.
 - **Palliative**: Simplest, good to avoid hospitalization, available and least toxic. Short term toxicity . enhance quality of life.

> Modalities of treatment:

Solid tumors (according to the stage)	Early	Local +/- systemic treatment "why would we use systemic therapy in early disease? to prevent recurrence or metastasis"	
	Locally advanced	Local <u>and</u> systemic treatment	
	Metastatic	Systemic +/- without local treatment "why would we use local therapy in metastatic disease? Palliative, to relieve symptoms"	
Liquid tumors	Systemic treatment		

^{*}Local treatment: Surgery & Radiotherapy, Systemic treatment: Chemotherapy, hormonal & biological⁷.

Prognosis:

> It depends on the cancer type and extent (stage), host factors (age, sex, and co-morbidities) and available tools.

Tumors can be cured	Tumors with prolonged survival	Tumors that can be palliated
Lymphomas/Leukemia/ Early solid tumors	Locally advanced tumors and some of the metastatic tumors	Metastatic solid tumors

⁷ The problem with biological treatment for cancer is that cancer cells are smart & they change the receptor or the whole pathway + even the same type of cancer can have variation in receptors بعض المرضى يتحسنون بالبداية للعلاج بعدين ترجع تسوء حالتهم كذا

Surgical recall

Define:

Surgical oncology

Surgical treatment of tumors

XRT

Radiation therapy

In situ

Not invading basement membrane

Benign

Nonmalignant tumor—does not invade or metastasize

Malignant

Tumors with anaplasia that invade and metastasize

Adjuvant RX

Treatment that aids or assists surgical treatment = Chemo or XRT

Neoadjuvant RX

Chemo, XRT, or both BEFORE surgical resection

Brachytherapy

XRT applied directly or very close to the target tissue (e.g., implantable radioactive seeds)

Metachronous tumors

Tumors occurring at different times

Synchronous tumors

Tumors occurring at the same time

What tumor marker is associated with colon cancer?

CEA

What tumor marker is associated with hepatoma?

Alpha-Fetoprotein (AFP)

What tumor marker is associated with pancreatic carcinoma?

CA 19-9

What is paraneoplastic syndrome?

Syndrome of dysfunction not directly associated with tumor mass or mets (autoimmune or released substance)

What are the most common cancers in women?

- 1- Breast
- 2- Lung
- 3- Colorectal

What are the most common cancers in men?

- 1- Skin cancer
- 2- Prostrate
- 3- Lung
- 4- Colorectal

What is the most common cancer causing death in both men and women?

Lung

MCQs

- 1) A 19-year-old college student presents with a testicular mass, and after treatment he returns for regular follow-up visits. Which of the following is the most useful serum marker for detecting recurrent disease after treatment of nonseminomatous testicular cancer?
- a. Carcinoembryonic antigen (CEA)
- b. Human chorionic gonadotropin (hCG)
- c. Prostate-specific antigen (PSA)
- d. CA125
- e. p53 oncogene
- 2) A 37-year-old woman has developed a 6-cm mass on her anterior thigh over the past 10 months. The mass appears to be fixed to the underlying muscle, but the overlying skin is movable. Which of the following is the most appropriate next step in her management?
- a. Above-knee amputation
- b. Excisional biopsy
- c. Incisional biopsy
- d. Bone scan
- e. Abdominal CT scan
- 3) A 38-year-old woman who underwent a cadaveric renal transplant 8 years ago presents with fevers, fatigue, and weight loss. Evaluation included CT scans of the head, neck, chest, abdomen, and pelvis; she is noted to have diffuse lymphadenopathy and pulmonary nodules. A biopsy and histologic examination of a lymph node is performed. Which of the following viruses is most likely to be present in the lymph node?
- a. Cytomegalovirus
- b. Human papillomavirus
- c. Human herpesvirus 8
- d. Epstein-Barr virus
- e. Coxsackie virus
- 4) A 19-year-old college student presents with a testicular mass, and after treatment he returns for regular follow-up visits. Which of the following is the most useful serum marker for detecting recurrent disease after treatment of nonseminomatous testicular cancer?
- a. Carcinoembryonic antigen (CEA)

- b. Human chorionic gonadotropin (hCG)
- c. Prostate-specific antigen (PSA)
- d. CA125
- e. p53 oncogene

An edentulous 72-year-old man with a 50-year history of cigarette smoking presents with a nontender, hard mass in the lateral neck. Which of the following is the best diagnostic test for establishing a diagnosis of malignancy?

- a. Fine-needle aspiration cytology
- b. Bone marrow biopsy
- c. Nasopharyngoscopy
- d. Computed tomography (CT) scan of the head and neck
- e. Sinus x-ray

Answer key:

1 (b) | 2 (c) | 3 (d) |

4 (b) | 5 (a) |