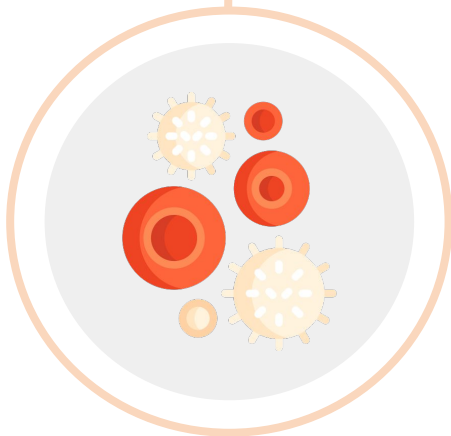




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Introduction to cancer diagnosis & treatment



Objectives :

- ★ Definition of cancer.
- ★ Etiology of cancer.
- ★ Staging of malignant diseases.
- ★ Principles of pathological classification of malignant diseases.
- ★ General symptoms and signs of malignancy.
- ★ Principles of cancer management (curative Vs palliative concept).
- ★ Principles of immuno- oncology

Color index

Original text

Females slides

Males slides

Doctor's notes ⁴³⁸

Doctor's notes ⁴³⁹

Text book

Important

Golden notes

Extra

History

- The origin of the word “cancer” is credited to the Hippocratic physicians, who used the terms karkinos and karkinoma.
- Claims that cancer is only a ‘modern, man-made disease’ are false and misleading.
- This is not only scientifically incorrect, but misleading.
- Cancer has always been with us, from ancient civilizations to today.
- Cancer is the second global cause of death (17.1%) coming after cardiovascular diseases (31.8%)

Defining Cancer

Cancer

A term used for diseases in which abnormal cells divide and escape the body control, **these cells are able to:**

1. Invade surrounding tissues (benign tumors like lipoma and fibroma cannot invade. Locally malignant tumors like Osteoclastoma can invade locally but cannot send distant metastasis. The true malignant tumors can both invade locally and send metastasis.)
2. Send distant metastases.
3. Lose their functions.

Primary tumors:

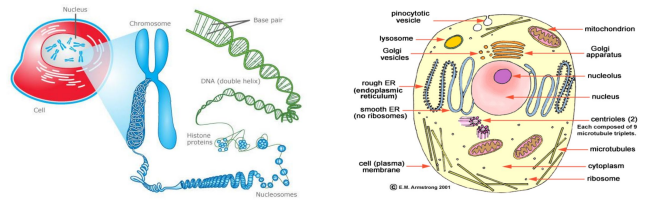
- Represent **de novo** tumors in their initial site e.g. Breast cancer inside the breast tissue.

Metastatic tumors:

- Originate from the **distant** growth of the primary tumors to lymph nodes or other organs like liver, lung, bone, brain, etc..

Basic structure of human body

The body is made of different systems → The systems are made of organs → The organs are made of tissues → The tissues are made of cells → The cell is made of cytoplasm + nucleus → The nucleus has chromosomes which carry the genes which are made of DNA → Nucleolus and DNA controls cell functions → Cell division



Development of Malignant Disease

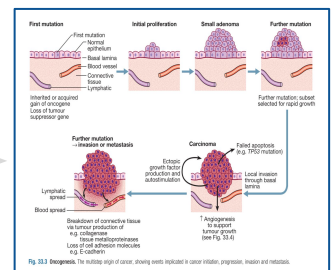
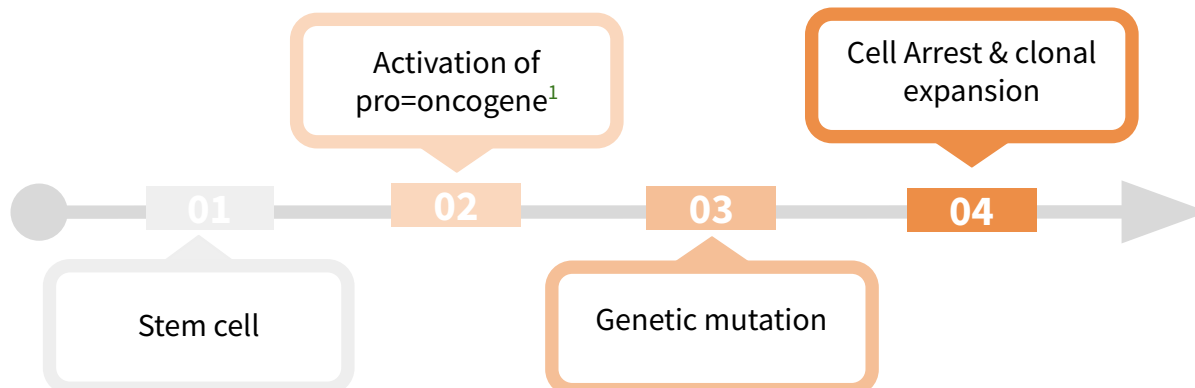


Fig. 33.3 Diagrams, the multiple steps of cancer, showing events indicated in cancer initiation, progression, invasion and metastasis.

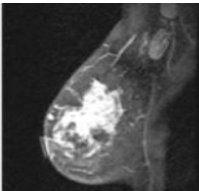
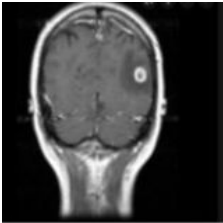

1- Normal genes responsible for division & mutation. when its affected it turns into an oncogene

◀ Hellman's theory :

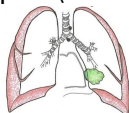
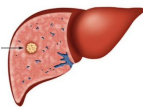
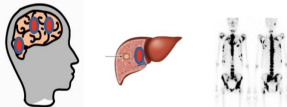
In 1994, What hellman says is that:

- Cancer at initial presentation fell into a spectrum or biological behavior ranging from indolent disease to wide metastatic disease.
- This is proportion to the tumor ability to metastasize Irrespective to its size . The ability of a tumor to metastasize depends mainly on the biology of the tumor rather than its size (The tumor behavior is not related to its size) . We have seen patients with huge tumors that didn't even metastasize to the lymph nodes. The good, bad and ugly are like that since they have been born.
- So, **screening** of a (1 cm) sized tumor that has the biological features to metastasize does **NOT** benefit these patients, he/she will die either with a 1 cm or 10 cm mass .

Approach to patients differ depending on the scenario, 3 different scenarios can happen :

Scenario 1	
<ul style="list-style-type: none"> • A 51 y/o lady with a Dx of left breast cancer in 2009 which is treated, then had another right breast cancer in 2018, and again had a local recurrence in 2021 (no distal metastasis, always coming back locally). • This tumor is considered to be a (Homey tumor state) and has 3 F's (see below) • This patient was treated locally by Sx, radiation therapy & adjuvant systemic therapy 	
Scenario 2	
<ul style="list-style-type: none"> • A 40 y/o lady with a Dx of left breast cancer in 2012 which is treated. After 6 years (in 2018) had a lesion in her brain which is removed and proved to be mammary carcinoma/breast cancer (distant metastasis after long time) . • This type is called oligometastases, it has fine micro-environment and few falling cells migrating into the bloodstream. • These patients are treated with a combination therapy 	
Scenario 3	
<ul style="list-style-type: none"> • A 40 y/o lady just diagnosed with breast cancer and is receiving local treatment with adjuvant therapy, suddenly develops massive lung/pulmonary metastasis (distal metastasis within 1 year / short time) . • This tumor is considered to be systemic type: very aggressive micro-environment, very active tumor with active migrating cells (a lot of cells in the circulation) and the recipient environment (the organ that will be metastasized) is weak -> so tumor can overcome the immunity and metastasize there. • These patients are treated systematically 	

➤ What is the behavioral diversity of malignant tumors?

Type 1 (Homey)	Type 2 (Oligo-metastatic)	Type 3 (Disseminated)
		
<p>3 Fs:</p> <p>1- Fine micro environment 2- Rare Falling migrating cells 3- Failure recipient soil</p>	<p>3 Fs:</p> <p>1- Fine micro environment 2- Falling migrating cells 3- Failure recipient soil</p>	<p>3 As:</p> <p>1- Aggressive micro environment 2- Actively migrating cells 3- Accepting recipient soil</p>

Causes of Cancer

- ❖ Cancer is a disease of **both DNA & RNA**. Not any defective DNA would lead to cancer, you have to find a defective protein. So if a mutation happens without effective RNA, it will not lead to cancer.
- ❖ Alter in immunity in cases of autoimmune or immunodeficiency diseases (e.g. AIDS) will alter the process of capturing cancer cells and killing it which can predispose to cancer.

Environmental etiology	Processes	Diseases
Occupational exposure (see Tobacco below)	Use and abuse; manufacturing (various amines)	Bladder cancer
	Asbestos mining, construction work, insulating materials	Lung cancer and mesothelioma
	High-dose X-ray irradiation	Lung neoplasms
	Polycyclic aromatic hydrocarbons	Acute leukemia
Chemicals	Chemicals (e.g., asbestos, nitrophenols)	Acute myeloid leukemia
 cigarette smoking	Exposure to carcinogens from inhaled smoke	Lung and bladder cancer
Food ingestion	Excess fat intake	Bladder neoplasms and esophageal cancer
	Human papillomavirus	Cervical cancer
	Hepatitis B and C viruses	Hepatocellular carcinoma
Bacterial infection	Helicobacter pylori	Gastric, MALT lymphoma, gastric cancer
	Campylobacter	Colorectal cancer
	Shigella flexneriae	Colorectal cancer
Parasitic infection	Liver fluke (Clonorchis sinensis)	Cholangiocarcinoma
	Schistosoma haematobium	Squamous cell bladder cancer
Dietary factors	Low red-meat/animal-protein diet	Colorectal cancer
	High cholesterol intake	Hepatocellular carcinoma
	Alcohol, non-caloric sweeteners or Aspartame flavor	Bladder cell carcinoma
Radiation	UV exposure	Melanoma
	Nuclear fallout following explosion (e.g., Hiroshima)	Non-melanocytic skin cancer
	Diagnostic exposure (e.g., CT)	Lung cancer, e.g., thyroid
	Occupational exposure (e.g., benzene and chromium mining)	Cholangiocarcinoma, leukemia, thyroid cancer
	Therapeutic radiotherapy	Lung cancer, bladder, thyroid cancer, leukemia
Inflammatory diseases	Chronic colitis	Colorectal cancer
Hereditary	Clas of dysplastic polyps	Topical cancer
	Neuropilin	Endometrial cancer
		Bladder cancer

1 DNA Mutations

- Cancer arises from the **mutation** of a normal gene.
- Mutated genes that cause cancer are called **oncogenes** (the process should be completed by a competent RNA system)

What causes DNA to be mutated?

- Radiation and other environmental factors (Tobacco, Alcohol, Radon, Asbestos, etc).
- Random somatic mutations.
- Inherited germline mutations (Not every pt carrying germline mutation will develop cancer)

2 Genetic Predisposition

- Retinoblastoma, p53 (tumor suppressor gene), APC, CDKN2A, BRCA1, BRCA2

3 Infectious agents

- **Viral:**
 - HPV – cervical cancer
 - Hepatitis – liver cancer
 - EBV - Lymphoma
- **Bacterial**
 - H. pylori – stomach cancer

Hallmarks of Cancer

1 Self-sufficiency in growth signals.

2 Insensitivity to growth inhibitory signals .

3 Absence of apoptosis.

4 Limitless proliferative capacity.

5 Sustained angiogenesis
Blood vessel formation

6 Tissue invasion and metastasis.



In order of occurrence, the most common cancers in **males** are prostate, lung, and colon. The cancer with the highest mortality in **males** is lung, followed by prostate and colon.
In order of occurrence, the most common cancers in **females** are breast, lung, and colon. The cancer with the highest mortality in **females** is lung, followed by breast and colon.

Signs & Symptoms of Cancer

◀ If you decided to be an oncologist, what should you know ?

How to diagnose cancer ?

How to treat cancer ?

01

02

03

04

05

When & how to suspect cancer ?

What the essential work up for staging ?

What is the prognosis of your patient ?

What did change the face of oncology recently?

- The change in our understanding of the ways of cancer development and dissemination.
- Improvement in: Screening & Early detection.
- The Change of the Therapeutic Strategies

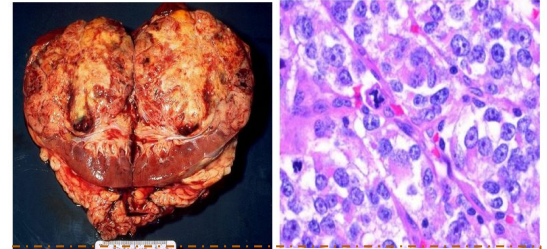
◀ Q1: When to suspect cancer? Cancer Signs & Symptoms :

- Cancer gives most people **no** symptoms or signs that **exclusively** indicate the disease.
- Unfortunately, **every complaint or symptom of cancer can be explained by a harmless condition as well** for example:
 - The most common cause of hemoptysis is not lung cancer or TB, it's bronchitis.
 - The most common cause of hematemesis is not stomach cancer or PUD, it's gastritis.
- **Do not forget the constitutional symptoms:**
 - **Fatigue, fever, sweating, weight loss.**
 - DDX of weight loss: unintentional weight loss with increased appetite → thyrotoxicosis, unintentional weight loss with anorexia → chronic infection, e.g. TB, brucellosis and malignancy.
 - Sometimes cancer patients present only with constitutional symptoms, especially leukemia and lymphoma patients
- **What are the clues?**
 - **PPD: Persistent, Progressive, Disabling** (prevent the patients from doing daily activity)
 - **Symptoms & Signs** change **according to the site** of origin, e.g. stomach cancer causes hematemesis, colon cancer causes bleeding per rectum.
- **Think about the pathology and site:**
 - The Mass is able to **invade locally** and **spread distantly** → To bone, brain, lung, liver
 - **With any mass you have to rule out cancer**
 - **Mass (lump):**
 - **Pressure** on vital organs e.g. Stomach cancer → abdominal discomfort (fullness, vomiting, dyspepsia). Brain cancer → raised ICP, Intracranial hemorrhage, tension symptoms like headache, vomiting, blurry vision. Lung cancer → dyspnea, atelectasis.
 - **Obstruction** of lumens e.g. colon cancer will cause constipation, obstruction and abdominal distention . Bladder cancer → urinary retention, weak stream.
 - **Invasion :**
 - Blood vessels → **bleeding** . Bladder cancer → hematuria. Lung cancer → hemoptysis.
 - Nerves → **pain** (if sensory), weakness or paralysis (if motor).
- **Other examples:**
 - >40 elderly pt developed his/her first grand-mal seizure → brain tumor until proven otherwise
 - >60 elderly pt developed T1DM → could be pancreatic tumor or pancreatic fibrosis
 - Patient with bleeding per rectum → number 1 cause is piles (hemorrhoids)→ if continuous + Hb levels less than 10 then you should do colonoscopy

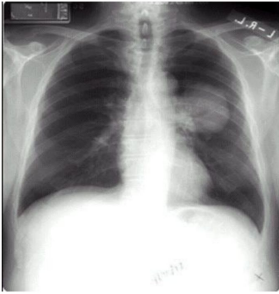
33.7 Non-metabolic manifestations of malignant disease	
Feature	Common cancer site associations
Weight loss and anorexia	Lung, gastro-intestinal tract
Fatigue	Any
Hypercalcaemia	Myeloma, breast, kidney
Prothrombotic tendency	Ovary, pancreas, gastro-intestinal tract
SIADH	Small cell lung cancer
Ectopic ACTH	
Lambert-Eaton myasthenic syndrome	Small cell lung cancer
Subacute cerebellar degeneration	Small cell lung cancer, ovarian cancer
Acanthosis nigricans	Stomach, oesophagus
Dermatomyositis/polymyositis	Stomach, lung
ACTH = adrenocorticotropic hormone; SIADH = syndrome of inappropriate antidiuretic hormone (secretion) secretion	

Q2: How to diagnose cancer?

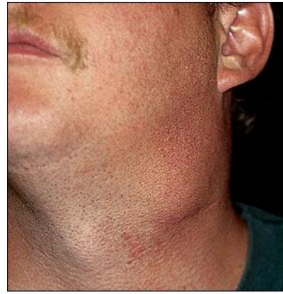
1	<ul style="list-style-type: none"> IT IS NOT A CLINICAL DIAGNOSIS
2	<ul style="list-style-type: none"> IT IS NOT A RADIOLOGICAL DIAGNOSIS
3	<ul style="list-style-type: none"> IT IS NOT SEROLOGICAL DIAGNOSIS
4	<ul style="list-style-type: none"> IT IS A PATHOLOGICAL DIAGNOSIS
5	<ul style="list-style-type: none"> IT IS A TISSUE DIAGNOSIS¹



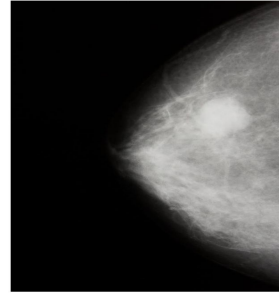
GROSS AND MICROSCOPIC PICTURE OF Renal Cell Carcinoma



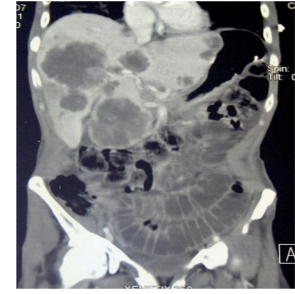
Lung cancer



Lump in the neck (lymphoma)

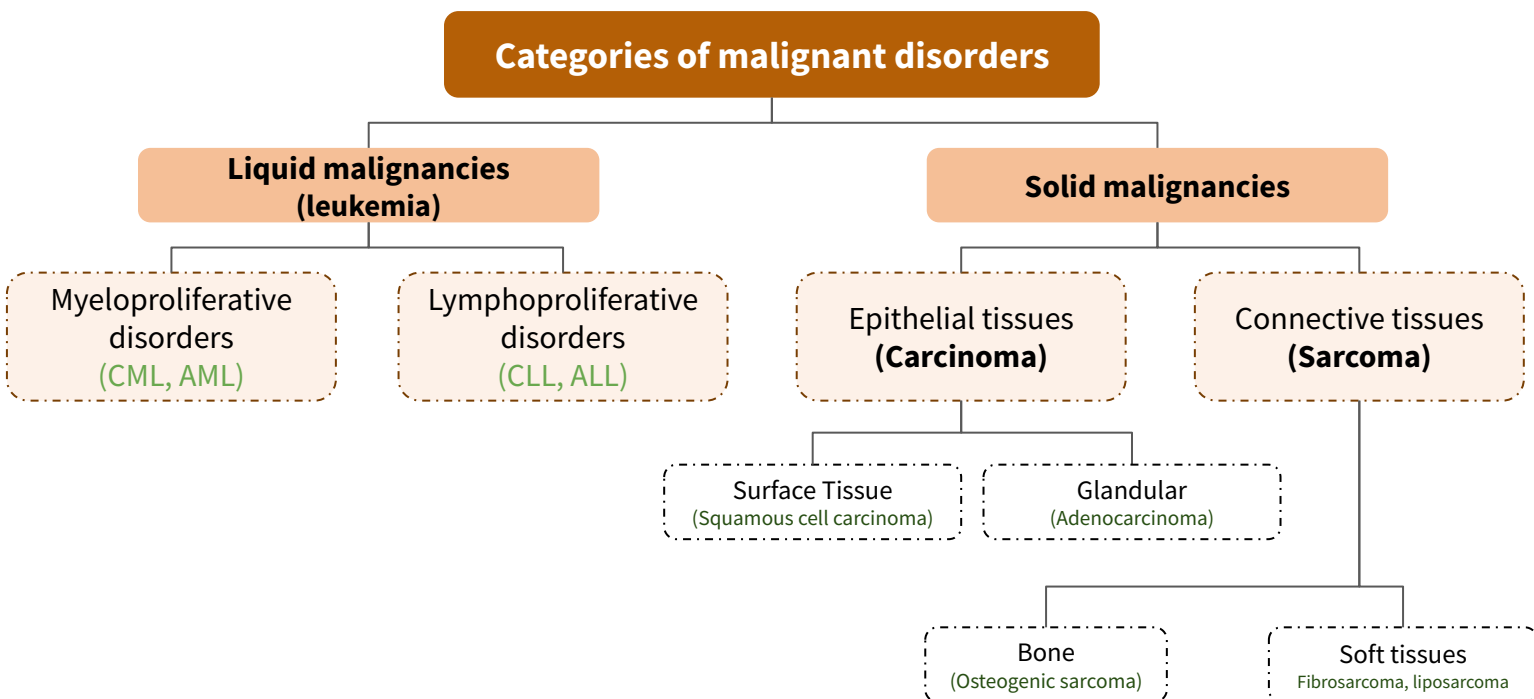


Breast cancer with nodule in the breast



liver metastasis in the left and right lobes

Categories of malignant disorders



1- "The tissue is the issue" you cannot accurately diagnose cancer without having a biopsy.

Staging of Cancer

Screening Vs. Early diagnosis

	Early Detection (Screening)	Early Diagnosis
S&S	non / asymptomatic	minimal
Invasive Cancer	+/-	yes
Mass Screening	yes, in a random region	no
Focus On High Risk Group	essential	needed
Impact On Survival	may be	more definite
What Is Needed?	public & health care givers awareness	physician awareness

- **A perfect screening test is not found yet**
 - Simple & accurate (Highly sensitive & Highly specific)
 - Cheap & cost effective
 - Widely accepted, non invasive and non Morbid
- **So far, we have screening programs for only 5 out of >100 cancer types:**
 - Breast Cancer
 - Colon Cancer
 - Lung cancer
 - Prostate cancer
 - Cervical cancer

- **Early diagnosis**: (less expensive, done by physicians) is better than screening (expensive/asymptomatic pts) in the case of cancer, but it is still challenging due to the vagueness of cancer symptoms (e.g. the most common cause of hemoptysis is chronic bronchitis, although it could be a presentation of cancer)
- Doing a mammogram for women with family Hx of breast cancer is not screening because they have a risk factor.

Q3: What the essential work up for staging?

- **TNM** (T= tumor, N= Node, M= Metastases)
 - **Clinical** TNM
 - **Radiological** TNM
 - **Pathological** TNM
- **Radiology:**
 - **XR**ay
 - **MRI**: preferred technique for brain and pelvic imaging. It is widely employed for the staging of rectal, cervical and prostate cancers.
 - **CT**: is a key investigation in cancer patients and is particularly useful in imaging the thorax and abdomen.
 - **US**: is useful in characterising lesions within the liver, kidney, pancreas and reproductive organs. Endoscopic ultrasound is helpful in staging upper gastrointestinal and pancreatic cancers.
 - **PET scan**: It can accurately assess the severity and spread of cancer by detecting tumour metabolic activity following injection of small amounts of radioactive tracers such as fluorodeoxyglucose (FDG).
- **Surgical Staging**

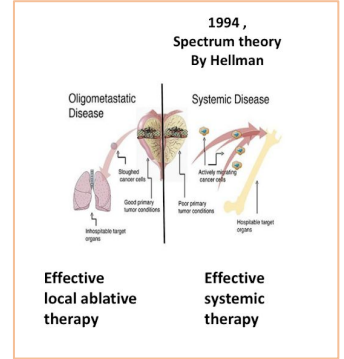
33.4 TNM classification	
Extent of primary tumour*	
TX	Not assessed
T0	No tumour
T1	Increases in primary tumour size or depth of invasion
T2	
T3	
T4	
Increased involvement of nodes*	
NX	Not assessed
N0	No nodal involvement
N1	Increases in involvement
N2/3	
Presence of metastases	
MX	Not assessed
M0	Not present
M1	Present

*Exact criteria for size and region of nodal involvement have been defined for each anatomical site.

Q4: How to treat cancer?

1) Types of oncology problems:

- Patient with Suspected Cancer diagnosis
- Patient with Established Cancer diagnosis (Answer the following questions):
 - Does the patient have cancer?
 - What type of cancer?
 - What stage of cancer?



2) Management Multidisciplinary:

- Surgery, Radiation, Medical Onc.
- Others Disciplines: Radiology, Pathology, Lab, Combined clinics, Tumor board.

3) Determine the treatment Objective:

- Either **Curative** or **Palliative**
- (Surgical procedures are often the quickest and most effective way of palliating symptoms.)

Curative

Therapy:

- Aggressive, Expensive, recent, updated, complex.

Toxicity:

- Long term, irreversible

Palliative

Therapy:

- Simplest, Avoid hospitalization, Availability, Least toxic

Toxicity:

- Short term, acute, quality of life

Different Treatment Modalities

Local therapy:

- Surgery & Radiation therapy

Systemic therapy:

- Chemotherapy
- Hormones
- Biologicals
- Immune therapy

4) Now, moving towards more of Personalized therapy : (we define the molecular target)

Targeted Chemotherapy

- Histologic subtyping for chemotherapy

Targeted biological Therapy

- Genomics-driven TKIs:
- EGFR, ALK, ROS1

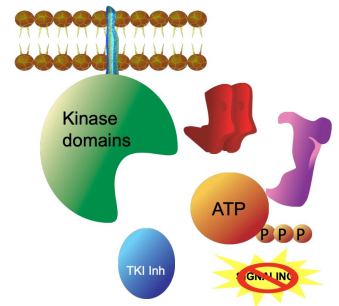
Checkpoint Inhibitors (Targeted Immunotherapy)

- Anti-PD-1
- Anti-PD-L1
- Anti-CTLA-4

Q4: How to treat cancer? cont.

What do we use now to treat cancer?

- **We use tyrosine kinase inhibitor (TKI)**
- Tyrosine kinases are enzymes responsible for the activation of many proteins by signal transduction cascades. The proteins are activated by adding a phosphate group to the protein, a step that TKIs inhibit. (So it blocks the protein not the DNA itself and decrease effect of cancer)
- It is a targeted therapy that identifies and attacks specific types of cancer cells while causing less damage to normal cells. In CML, TKIs target the abnormal BCR-ABL1 protein that causes uncontrolled CML cell growth and block its function, causing the CML cells to die.



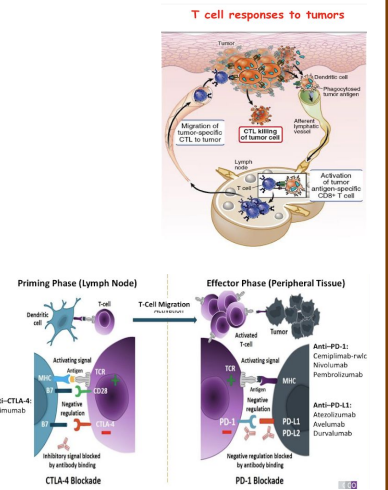
Mechanism of Action of Immunomodulators

The theory is to use the immune system (which is inhibited by the tumor) by removing the inhibition and allowing the cytotoxic T cells kill the cancer cells.

- PD-1 (cell receptor) is overexpressed on tumor
- infiltrating **T cells** and these are functionally exhausted cells
- Programmed cell death ligands: PDL-1 and PDL-2 (**tumor cell** /APC)
- Higher tumoral PDL-1 expression correlates with decreased OS

Rationale:

- Blocking the PD-1 or PDL-1 pathway would restore/promote the function of chronically exhausted tumor-specific T cells and decrease tumor-induced immune suppression



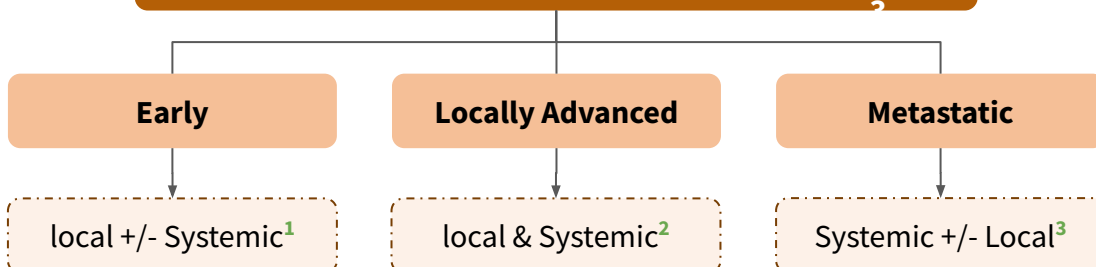
- **Liquid malignancies:**

- Treated systemically

- **Solid malignancies:**

- Treated according to stage

General Staging of solid malignancies



1- local treatment mainly, systemic treatment is adjuvant.
 2- start systemic to decrease the size then local to remove it.
 3- mainly systemic, local for symptoms control.

◀ Q5: What is the prognosis of your patient?

❖ What can medicine offer the cancer patient?

- The cancer type & extent (stage)
- The host factors (age, sex, comorbidities)
- The available tools

Tumors that can be cured

- lymphomas
- leukemia
- early solid tumors.

Tumors that can have prolonged survival

- Locally advanced
- some of the metastatic tumors.

Tumors that can be palliated

- Metastatic solid tumors.

◀ Take home messages:

- **Early diagnosis** is more important than early detection (screening) and it requires physician's awareness.
- Late diagnosis is more expensive and has less outcomes .

Lecture Quiz

Q1: Cancer is diagnosed:

- A- Clinically.
- B- Radiologically.
- C- Serologically.
- D- Tissue & Pathology.

Q2: Which ONE of the following is a characteristic of locally malignant tumors?

- A) Invade locally but cannot send distant metastasis
- B) Invade locally and can send distant metastasis
- C) Cannot invade locally but can send distant metastasis
- D) Cannot invade locally and cannot send distant metastasis

Q3: Which ONE of the following is considered a characteristic of malignant tumors?

- A) Ability to form their own blood vessels
- B) Consuming and responding to the host growth factors
- C) High apoptotic activity
- D) Low mitotic activity

Q4: All of the following are hallmarks of cancer , except:

- A- Sustained angiogenesis .
- B- Tissue invasion .
- C- Insensitivity to growth inhibitory signal .
- D- Presence of apoptosis .

Q5: In liquid malignancies , the proper treatment is:

- A- Systemic therapy .
- B- Local therapy .
- C- Local & systemic .
- D- Local , +/- systemic .

GOOD LUCK!

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