A NEET SS (SURGERY) PREPARATION COURSE BY MARROW, WITH A TEAM OF SELECTED SUPER-SPECIALITY FACULTY

SURGERY NEET SS

oncology

PREPARATION COURSE BY MARROW, WITH A TEAM OF SELECTED SUPER-SPECIALITY FACULTY

CONTENT

PRINCIPLES OF CANCER STAGING

Introduction

00:00:10

Purpose : To know the extent of the disease.

TNM Staging :
most widely used staging system.
Anatomical staging system.
3 components :

1. T category : Primary tumor.
   - T x.
   - T 0.
   - T is.
   - T 1. } Invasive
   - T 2. } Invasive
   - T 3. } Invasive
   - T 4. } Invasive
2. N category : Regional lymph nodes (LN).
   - N 0 : No nodes.
   - N 1.
   - N 2.
   - N 3.
3. M category : Distant metastasis.
   - M 0 : No distant metastasis.
   - M 1 : Distant metastasis present.
     Has sub-categories like a, b, c, d.

Evidence based system : Upper stage → ↓ Survival.
Eg.: Breast cancer :
T 1 : <2 cm. T 2 : 2-5 cm. T 3 : >5 cm.
1.8 cm and 1.9 cm tumors : No difference in survival.
1.9 cm and 2.1 cm tumors : Sharp difference in survival.
∴ Cut-off for upper stage is 2 cm.

Staging Groups 00:04:10

Group	Based on
cTNM	Clinical examination Radiological examination Surgical exploration without resection
pTNM	Pathology of resected tumor
yTNM : • ycTNM • ypTNM	Post-Neoadjuvant therapy (NACT)
rTNM : • rcTNM • rpTNM	Recurrence
aTNM	Autopsy (incidental detection)

ycTNM : Clinical/radiological examination post-NACT.
ypTNM : Pathology of resected tumor post-NACT.
rcTNM : Clinical/radiological examination of recurrence.
rpTNM : Pathology of resected tumor of recurrence.

TNM Staging 00:09:40

T (Primary tumour) :
Tx : Cannot be assessed/Information not available.
Eg.:
- Primary tumor operated elsewhere with no records.
- Extensive tumor where the primary cannot be identified.

T 0 : No primary tumor.
T is : In situ.
T 1-T 4 : Invasive.

N (Regional nodes) :
N x : Cannot be assessed.
N 0 : No nodes
N 1-N 3 : Nodes present.

M (distant metastasis) :

M 0 : No distant metastasis.

M 1 : Distant metastasis present.

No M x.

Multiple tumors : Highest T mentioned.

Eg.: Breast cancer :

- 3 tumors are present with largest being 6 cm.
- Staging : pT3 (m)/N 0/M 0 (or) pT 3 (3)/N 0/M 0 where (m) means multiple.
- Actual number of tumors can also be specified like (3).

Synchronous vs. metachronous :

- Cut-off of appearance of multiple tumors is 4 months from the diagnosis of primary.
- <4 months : Synchronous.
- >4 months : metachronous.
- metachronous malignancies are staged separately.
- Synchronous malignancies are staged together.
- Paired organs like lung included in the staging criteria.

Unknown primary :

- Evidence of nodal spread is present.
- Expected primary site does not show up.
- Categorized as T 0.
- Eg.:
  a. Axillary nodes present, no primary seen in breast.
  b. Clinically → cT 0.
  c. Mastectomy is done and no primary is found → pT0.
  d. Staging (as per suspected primary site) → Ca. Breast, T 0/N 1/M 0, Stage II.

Regional nodes :

Sentinel node :

- Represented as (sn).
- If only sentinel node biopsy is done then (sn) can be used.
- If complete dissection is done, then (sn) cannot be used.

FNAC proven nodes :

- Represented as (f).
- Eg.: FNAC proven N1 : pN1 (f).

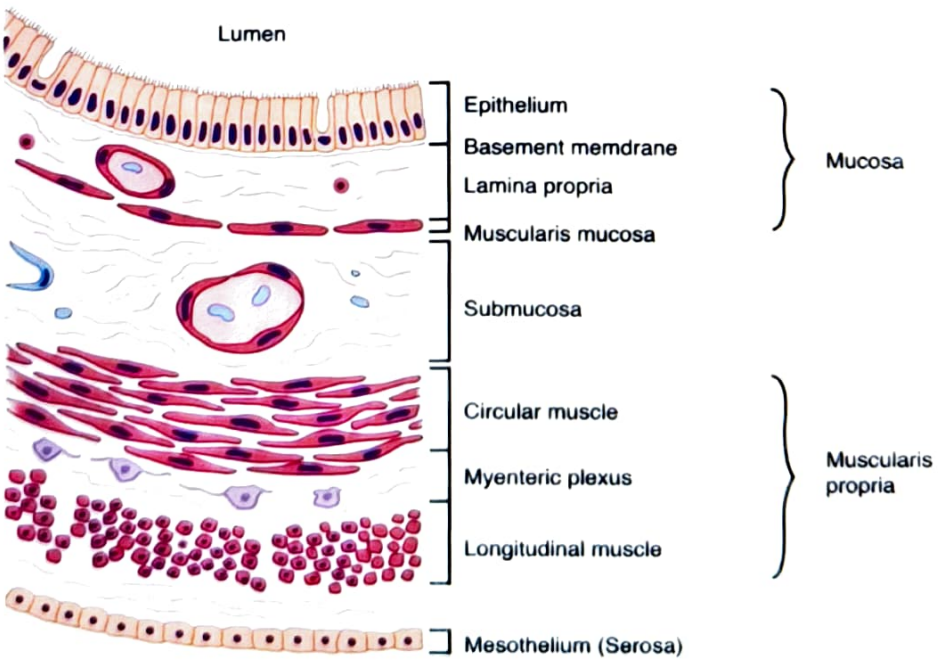
Isolated tumor cells :

- Cluster of < 200 cells.
- Size < 0.2 mm.
- Represented as (i+). Eg.: pN1 (i+).
- It represents in-transit disease and not something that stations and proliferates.
- It is not considered as node +ve.
- Isolated cells are also considered node positive in aggressive malignancies :
  a. Melanoma.
  b. Merkel cell carcinoma.

Stage 0

00:20:13

In situ and non-invasive cancers.



Layers of GIT

Area below the serosa : Subserosa.

If serosa is absent, it is called Adventitia.

1. In situ : Not crossed a boundary to attain spread (no

spreading potential).

- Boundary can be :
  a. Basement membrane : Oral cavity.
  b. Muscularis mucosae : Colon.
- No potential to spread.
- Nodal / distant assessment not needed.

2. Complete Pathological response :

- Seen when tumor disappears after NACT.
- T 0/N 0/m 0.
- Not Stage 0 (stage 0 → in-situ).

3. Non-Invasive : Disease has not crossed basement membrane of epithelium.

- Very few cancers.
- Represented as T a.
- Eg : Bladder cancer : pT a/N 0/m 0.

4. DCIS :

- Can have nodal spread.
- Invasive component maybe missed on pathology.

ETIOLOGY OF CANCER I

Etiology & factors responsible for carcinogenesis

00:00:10

Rudolf Virchow proposed that lymphoreticular infiltrate in a tumor originates from chronic inflammation.

Types of inflammation :

Tumor intrinsic	Tumor extrinsic
Cancer initiates and amplifies the inflammatory pathway → Promote survival, growth & invasion.	macroscopic environment of tumor contributes to carcinogenesis.
E.g. : • Aflatoxin & aspergillus (↑ses mutagenesis) causing HCC. • RET mutations → Non invasive follicular thyroid neoplasm → Promotes tumor development (promotion of inflammatory pathway)	E.g. : • Chronic pancreatitis → Pancreatic carcinoma. • H pylori → Stomach cancer. • GERD → Esophageal ca. • Hepatitis → HCC.

Infections causing cancer :

Cancer	Infection
Bladder cancer	Schistosoma haematobium
Burkitt's lymphoma	EBV. HHPV 4
Cervical cancer	HPV
Cholangiocarcinoma	Salmonella typhi, Opisthorchis viverrini, Clonorchis sinensis
Colorectal cancer	JC virus, Streptococcus bovis
Glioma	JC virus

HCC	Hepatitis B, C, D, Schistosoma japonicum, Aflatoxin
Hodgkin's lymphoma	EBV
merkel cell cancer	merkel cell polyoma virus
mesothelioma	SV 40
Adult T cell leukemia/ lymphoma	HTLV I
Prostate cancer	Xenotropic murine leukemia virus
Kaposi's sarcoma	HHV 8

Inflammatory mediators 00:08:48

The following have a role in interaction b/w tumor & host immune cells (cytokines) :

- Chemokines.
- Interleukins : IL-1, IL-6, IL-8, IL-17.
- Interferons : I (α & β), II (γ), III ($\Delta 1$, $\Delta 2$ & $\Delta 3$).
- Prostaglandins.
- TNFα.

TNF : 1° mediator of inflammation.

NFKB pathway :

- Major role in cancer.
- Activator of TNF.
- Initiation & transformation.

Mechanism :

Inflammation → Cytokines → Promote release of inflammatory cells → Oxidative damage, DNA mutation → microenvironment in tissue is more conducive to increased cell growth, survival & transformation.

Survival of cell :

- Pro-inflammatory cytokines : IL-1β, IL-8, TNFα & CRP ↑sed levels → Reduced survival (poor prognosis).

- STAT 6 & STAT 3 ↑ expression (↑ inflammation) → inverse association of survival in mesothelioma.

Invasion :

- mmp 9 (matrix metalloproteinase 9) :
  a. Gelatinase which degrades type IV collagen.
  b. High expression shows poor prognosis (High chance of tumor invasion).
- HIFα : Increased vascular invasion in HCC → Poor prognosis.
- Cathepsin D : Increased association in inflammatory breast cancer.

Angiogenesis :

Pro-angiogenic factors	Factors for angiogenesis
TNFα	MIF : Endothelial cell activation
IL-1β	TGFβ (Head & neck SCC)
IL-8	Angiopoietin-2

Factors for metastasis
VEGF
FGF 2
PDGF
ICAM-1
VCAM-1
E-selectin
P-selectin
mmP-9

Molecular mechanism of carcinogenesis 00:18:00

1. NFKB pathway : Pro-tumorogenic.

mechanism :

i. Chronic inflammation → EMT (epithelial mesenchymal transformation) activation → ↑ sed cell survival by promoting anti-apoptotic proteins → MYC & BCL-XL.

ii. Extracellular matrix remodeling by MMP & VEGF.

2. STAT 1 & 3 : Persistent STAT → Tumor inflammatory signal

+

NFKB

↓

Tumor cell survival & angiogenesis

3. Inflammasome :

- Silica & asbestos can trigger inflammosome.
- Activates IL-1β & IL-8 and other mediators (pro-inflammatory).

4. Toll like receptors (TLR) :

- Role in :
  a. Host defense mechanism.
  b. Tissue injury.
- Chronic inflammation → Chronic TLR pathway activation → Carcinogenesis.

Chemical factors

00:23:06

Scrotal cancer in chimney sweepers : First environmental cancer discovered by Percivall Pott.

Cancer	Chemical carcinogens
Lung	Tobacco, asbestos, nickel.
Pleura	Asbestos.
Oral cavity	Tobacco, alcohol.
Esophagus	Tobacco, alcohol.
Gastric	Tobacco.
Colon	Tobacco, alcohol.
Liver	Aflatoxin, vinyl chloride, tobacco, alcohol.
Kidney	Tobacco, trichloroethylene.
Bladder	Tobacco, 4-amino biphenyl, 2-naphthylamine, cyclophosphamide, phenacetin.
Prostate	Cadmium.

Skin	Arsenic, coal tar, PAH, benzopyrenes, cyclosporin A.

Chemical carcinogens

Genotoxic	Non-genotoxic
Directly altering genetic material.	Independent of direct insult.
Damages DNA by : • DNA adducts. • Inducing DNA ssb (single stranded breaks) & dsb (double stranded breaks).	MAP (mitogen activated protein) Kinase pathway (or) NFKB pathway They are epigenetic modifiers : • Cytotoxic. • Receptor mediated. (steroid receptors & tamoxifen)
• Direct genotoxic : Cause cancer at site of exposure. E.g : UV induced skin cancer. • Indirect genotoxic : Require metabolic transformation from procarcinogen to carcinogen E.g : Aflatoxin.	

Both can cause reactive oxygen species DNA damage alter gene expression.

Aristolochic acid :

- From genus of Aristolochia (plant).
- Used as herbal remedy for weight loss.
- Class I carcinogen.
- Causes A : T to T : A transversion.

- Diseases caused :
  c. Balkan endemic nephropathy.
  d. Nephrotoxic → Interstitial fibrosis.
  e. Upper tract urothelial carcinoma.

PAH (Polycyclic aromatic hydrocarbons) :

- ≥3 fused benzene rings.
- >200 chemicals.
- Benzopyrene : most studied PAH.
- metabolized by CYP450IA1 & CYP4503A4.
- Mechanism of action : DNA adducts formation.
- Excretion : Glutathione pathway.
- ↑ sed lung & skin cancer.
- Found in overcooked food, coal burning and tobacco smoke.

IARC group I pharmaceutical carcinogens 00:35:13

Drug	Cancer
Azathioprine	Non-hodgkin's lymphoma, SCC of skin, HCC, cholangiocarcinoma.
Cyclophosphamide	Bladder cancer, leukemia.
Chlorambucil	Leukemia
Cyclosporine	Leukemia, lymphoma, non-melanomatous skin cancer.
Tamoxifen	Endometrial cancer
Estrogen /OCP /HRT.	Breast cancer, endometrial cancer.

Physical factors :

- Ionising radiations : Ionize molecules (electron is displaced from orbit) by linear energy transfer (LET)
- Electromagnetic radiation : X rays & γ rays (have low LET).
- Particulate matter : Electron, proton, neutron, Carbon ion, α particles (have high LET).

m/c source of radiation exposure :

- 80% : Radon gas.
- 20% : medical sources.

Mechanism of action of ionising radiations 00:39:29

Direct action	Indirect action
High LET : Direct DNA damage	LOW LET
Direct energy transfere to molecule.	Hydrolysis of H_2O releases → OH^- radical → DNA damage.

Both causes similar lesions in DNA.

1 Gy of ionizing radiation :

- 40 dsb formed → Critical lesions → Cell lethality.
- 1000 ssb formed.
- 1000 single base lesions destroyed.
- 150 DNA protein crosslinks formed per cell.

Cell response to radiation :

1. Base excision repair : For ssb.
2. Homologous repair :
    a. High fidelity repair (requires a contralateral DNA strand).
    b. For dsb.
3. Non homologous end joining repair :
    a. m/c mechanism of repair in ionising radiations.
    b. For dsb.
    c. Not accurate : Results in mutation.

Theoretical risk models for radiation induced cancer 00:43:46

1. Linear, no threshold model :
    - most accepted.
    - Induction of cancer is directly proportional to dose of radiation (even in low dose).

2. Sublinear / threshold model : Below threshold dose, risk is negligible.

3. Supralinear / Stealth model :
   - Doses below threshold can trigger activation of DNA damage surveillance & repair mechanism → Sub-optimal activation of cell cycle.
   - ↑ sed chance of mutation accumulation → Cancer.

4. Linear quadratic model : Radiation at low doses → Single tract of radiation hitting multiple targets → Quadratic induction rate.

Tissue vulnerable to radiation :

Vulnerability	Tissue / cells
most Vulnerable	Hematopoietic cell line (↑ all leukemia except CLL) > Thyroid gland.
Intermediate	Breast, lung, salivary gland.
Radioresistant	Skin, bone, GIT.

ETIOLOGY OF CANCER II

Physical factors leading to carcinogenesis 00:00:08

UV light :

- UV A (320 to 400 nm) : mainly produces ROS → Single strand breaks & base lesions in DNA.
- UV B (290 to 320 nm).
- UV C (240 to 290 nm) : most damaging to DNA. most of the UV C is absorbed by ozone layer.
- UV B & UV C : Forms pyrimidine dimers. And also 6 - 4 photoproducts that consists of covalent ring structures → Bending of DNA helix → Interfere in DNA synthesis.

Cellular reponse to UV radiation :

UV radiation

↓

DNA damage (pyrimidine dimers & 6 - 4 photoproducts)

↓

Nucleotide excision repair (NER) : Removes pyrimidine dimers

↓

1. Major mutagenic lesions in melanoma.
2. NER deficiency : Xeroderma pigmentosa (2000 times more prone to develop UV induced skin CA).

Asbestos :

- Contributes in causing 5 -7 % of all lung cancers.
- Mechanism of action : ROS → Single strand breaks + base lesions.
- Asbestos + tobacco : more chance of causing lung CA.
- Tumor suppressor genes p53 & p16INK4A + K-RAS oncogene are associated with lung CA caused by asbestos.

- Malignant mesothelioma :
  - Major cause : Asbestos fibres.
  - Associated with p16INK4A & NF2 gene mutation.

Radiofrequency radiation and microwave radiation :

- Radiofrequency radiation : 3 KHz to 300 MHz.
- Microwave radiation : 300 MHz to 300 GHz.
- Cellphones :
  - Brain peak specific absorption rate : 4 to 8 W/Kg.
  - > 10 yrs of cellphone usage : Increased chance of glioma and acoustic neuroma. It is inconclusive as large prospective studies have shown no risk.

Electromagnetic fields :

- Not carcinogenic (energy is not high enough to break chemical bonds).

Dietary factors

00:09:34

Dietary fibre :

- All plant polysaccharide & lignin → Resistant to hydrolysis by the digestive enzymes.
- No association b/w dietary fibre and colorectal cancer.

	Increased incidence of	Decreased incidence of
Red meat	Colorectal CA	
Regular milk consumption	Prostate CA	Colorectal CA
Coffee		HCC Endometrial CA Prostate CA
Vit D		Colorectal CA Breast CA Prostate CA
Selenium (acc to SELECT RCT)	No protective effect in prostate CA.	

mechanisms of redmeat being carcinogenic :

- ↑ Anabolic hormones in red meat.
- Polycyclic aromatic hydrocarbons (cooking at high temperature).
- ↑ Heme in red meat.
- Nitrates → Nitrosamines (in smoked, salted and processed meat).

Obesity and carcinogenesis 00:13:41

mechanisms of carcinogenesis in obese :

- Steroid hormone pathway.
- IGF pathway.

These 2 pathways are overactive in obese and lead to :

1. Increased endogenous estrogen → Increased incidence of breast and uterine CA.
2. Increased levels of insulin & C-peptides.
3. Increased levels of inflammtory mediators.

Physical activity :

Decreases the chances of cancer by following mechanisms.

- Increases immune surveillance.
- Decreases inflammation.
- Promotes insulin sensitivity.
- GF production & activation.
- Decreases obesity & central adiposity.
- Optimizes DNA repair capacity.
- Reduces oxidative stress.

Breast CA (in pre & post menopausal women) :

- Physical activity : Protective effect.
- Obesity : Increased incidence.

Inadequate evidence to say that obesity has a role in following CA	Sufficient evidence to say that obesity has a role in following CA
Non cardia gastric CA. Extrahepatic biliary tract CA. Lung. Melanoma. Testes. Urinary bladder. Brain/ Spinal cord glioma.	Cardia gastric CA. Esophagus. Liver. Pancreas. Breast (post menopausal). Uterus. Ovary. Kidney. Meningioma. Thyroid.

Lack of physcial activity & obesity is associated with poor outcomes in :

- Breast CA.
- Colorectal CA.
- Prostate CA.

ONCOGENIC VIRUSES I

Introduction 00:00:09

7 families of viruses, mainly seen in immunosuppressed patients.
most common : HPV.

HPV :

- Non enveloped DNA virus (alpha papilloma virus family).
- Causes cancer cervix, penile, anus, vagina ,vulva, tonsils, base of tongue and bladder.
- Infection rate > 70 %.

HBV & HCV :

HBV	DNA virus	Infection rate : 2 to 8 %	Hepatocellular carcinoma
HCV	RNA virus	Infection rate : < 3 %	

Epstein Barr virus (EBV)/HHV 4 :

- DNA virus.
- Infection rate : 90 %.
- mainly found in B cell & pharyngeal mucosa.
- Causes Burkitt's, NHL, nasopharyngeal Ca.

Kaposi sarcoma Herpes virus (KSHV)/HHV 8 :

- DNA virus.
- Causes Kaposi sarcoma, multicentric castleman disease.

merkel cell polyoma virus :

- DNA virus.
- Causes merkel cell carcinoma.

Human T cell leukemia virus (HTLV) :

- RNA virus.

- Cause Adult T-cell leukemia, topical spastic paraparesis.

B K polyoma virus :

- DNA virus.
- Cause bladder cancer.

Mechanism of viral oncogenesis 00:04:17

1. Direct mechanism :
   - Virus infects cell → makes it malignant.
     Viral oncogene expression → Direct genotoxin effect by viral gene products.
   - Inactivation of p53/RB gene.

2. Indirect mechanism :
   - Cells are not infected.
   - Inflammatory response to virus → accelerated tissue damage & regeneration of non infected cells.

HPV :

- High risk : HPV 16, 18, 45, 31, 33, 52, 58, 35.
  99 % : Cervical Ca.
  HPV 16, 18 : 70 % of cases.
  80 % : Anal canal Ca.
  43 % : Vulval Ca.
  70 % : Vaginal Ca.
- Increased incidence of head and neck Ca.
- HPV association & cancer : Nobel prize for Medicine in 2008 → Harald zur Hausen.

Mechanism of action of HPV 00:08:20

1. Late phase proteins :
   - L1, L2 (capsid proteins).
   - Found in differentiating keratinocytes in skin & mucosa.
   - HPV induced cancers are seen in the zone of

transition b/w stratified squamous & simple columnar.

- HrHPV : Lifetime risk > 70 %.

2. Early phase proteins → (E1-E7) :
   - E2 :
     1. Transcriptional repressor.
     2. E2 expression → Integrates viral episome into host DNA.
     3. Loss of E2 expression Increase upregulation of early gene expression.
   - E6 : p53 destruction & telomerase activation.
   - E7 : Interacts with RB → Blocks RB to trigger cell cycle arrest.

Epidermodysplasia verruciformis (EV) :

- Rare immunodeficiency.
- Numerous flat warty lesions containing beta papilloma virus will present → HPV 5/HPV 8.
- Develop squamous cell carcinoma in sun exposed areas.
- UV radiation is a cofactor.

HPV vaccines :

- Each vaccine contain L1 capsid protein of HPV 16, 18 → Organised into virus like particles → Given as vaccines.
- Immunogenic → High titre antibodies are produced against this.

Gardasil vaccine : HPV 6, 11, 16, 18.

Cervarix vaccine : HPV 16, 18.

ONCOGENIC VIRUSES II

Polyoma virus

00:00:09

Includes :

- BK/Human Polyoma Virus 1 : Kidney disease, bladder cancer.
- John Cunnigham virus/Human Polyoma Virus 2 : Causes Progressive multifocal leukoencephalopathy (PMFLE).

Both affects immunocompromised individuals.

merkel cell polyoma virus/Human Polyoma Virus 5 : 80% merkel's carcinoma, class 2A (probably carcinogen)

carcinogens.

Affects patients with immunocompromised states like HIV, post organ transplants.

Ebstein Barr virus

00:02:30

History :

- Dennus Burkett noticed unusually B cell derived tumor involving jaw bones of children.
- Micheal Ebstein and Yvonne Barr : Pathology of tumor.

Burkitt's tumor : EBV/HHV 4 (class 1 carcinogen).

EBV is also responsible for infectious mononucleosis and endemic burkitt's lymphoma (100 %).

Pathophysiology :

- Chronic infection of mature B cells.
- Patients with X-linked agammaglobulinemia are immune to this infection.

EBV associated malignancies :

Lymphoma (express CD20) :

- Burkitt's lymphoma : 20 % are sporadic (associated with EBV).
- Hodgkin's lymphoma.
- NK /T-cell lymphoma.

- Primary CNS lymphoma and Plasmablastic lymphoma.
- DLBCL.
- Post transplant lymphoproliferative disorder.

Carcinoma :

- 100 % association in nasopharyngeal carcinoma.
- 90 % of gastrolymphoepithelioma like carcinoma.

Kaposi sarcoma herpes virus/HHV 8 :
Mainly sen in mediterranean region, eastern part of sub saharan Africa.
HIV/AIDS pandemic : Highly aggressive variants were seen.
Endemic region : 3rd m/c cancers in adults.
2 forms of B-cell proliferative disorders a/w HHV 8 :

1. Primary effusion lymphoma.
2. multicentric castleman's disease.

Oncogenic retrovirus 00:11:13

SSRNA virus.
HTLV-I :

- Belongs to genus Delta.
- Only oncogenic retrovirus.
- Causes Adult T-cell leukemia/lymphoma :
  Characterized by circulating tumor flower cells.
- Trasmitted only via breastfeeding.

Hepatitis virus :
80 % HCC : HBV + HCV.
Developed countries : > 60% of HCC is by HCV.
Developing countries : 60% of HCC is by HBV.
Pathophysiology : Depress innate immunity.
Transmitted via body fluids, blood, semen (hepadna dsDNA virus).
Co-infection of HBV with HDV (ssRNA).
HBV vaccination reduces infection by > 70 %.

HCV :

Flaviviridae.

7 genotypes present.

Genotype 1 causes > 70 % infection.

Treatment : NS5B polymerase inhibitor (sofosbuvir), NS3-4A (telaprevir, boceprevir, simprevir).

Also causes B-cell NHL, DLBCL, marginal zone lymphoma and lymphoplasmacytic lymphoma.

Efficacy of antiviral therapy : Reduces chances of HCC by 50 %. Hence continuous surveillance is required.

Infectious carcinogens 00:18:35

1. Bacteria : H. pylori → Gastric adenocarcinoma, MALToma, gastric DLBCL.
2. Parasites :
   - Clonorchis sinenses
   - O.vivereni

   } Cholangiocarcinoma, HCC
   - S. hematobium : Bladder cancer.

H. pylori :

- Class 1 carcinogen.
- Non cardia gastric cancer, DLBCL and maltoma.
- Virulence factors : Cag A gene & VAC gene.
- Antibiotics & hygiene measures decreases infection.
- Eradication : Associated with increased risk of cardiac, gastric and esophageal cancers.

CANCER SCREENING

US preventive services task force (USPSTF) 00:00:12

Grade	Definition	
A	USPSTF recommends the service	High certainty, that the net benefit is substantial.
B	Recommends	High certainty that the net benefit is moderate.
C	Recommends	moderate certainty that the net benefit is small.
D	Recommends against the service	moderate or high certainty that the service has no net benefit.
I	Insufficient evidence.	

USPSTF guidelines for breast cancer 00:01:52

USPSTF	ACS (American Cancer Society)
Against self breast examination (Recommendation D)	> 20 yrs : Self breast examination is an option.
Without mammography : >40 yrs : Insufficient evidence for clinical examination	Without mammography : 20 – 39 yrs : Clinical examination every 3 yrs. >40 yrs : Annual clinical examination
With mammography : 40 – 49 yrs : Individualized decision (Recommendation C). 50 – 74 yrs : Screen every 2 yrs (Recommendation B). >75 yrs : Insufficient evidence (Recommendation D).	With mammography : >40 yrs : Screen annually.

Indication of MRI in screening :

- 20 % lifetime risk : MRI annually + Mammography.
- 15 – 20 % lifetime risk : Can be discussed as an option.
- < 15 % lifetime risk : Do not screen with MRI.