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).

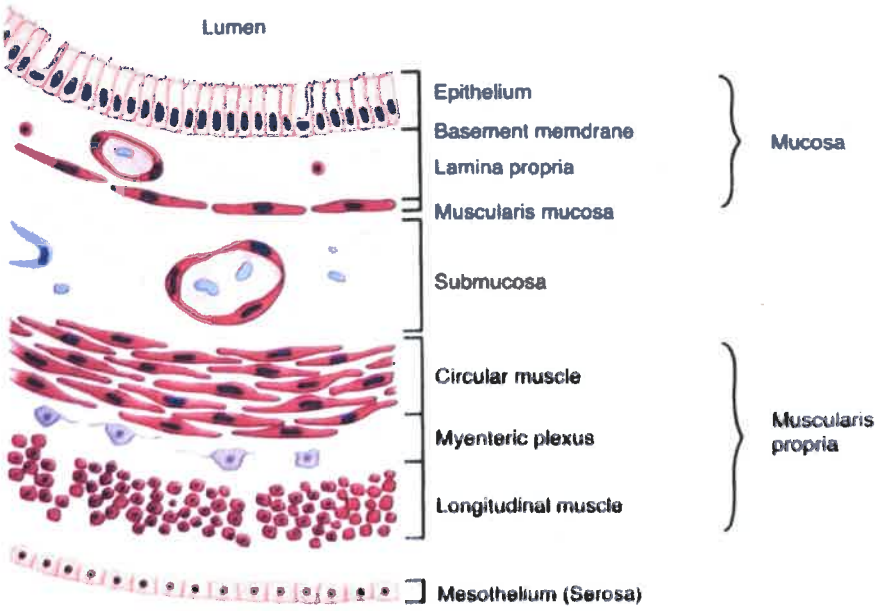
Isolated tumor cells :

- 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 (λ1, λ2 & λ3).
- 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-6, 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
TNFα
IL-1β
IL-8

Factors for angiogenesis
MIF : Endothelial cell activation
TGFβ (Head & neck SCC)
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 & CYP450 3A4.
- 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.