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An Overview of Cancer and its Tumour Markers

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Abstract: *4th February is celebrated as World Cancer Day. Cancer is the second-leading cause of death worldwide. Near about 10 million people die from cancer every year. 70% of cancer deaths occur in low-to-middle income countries. More than 40% of cancer-related death could be preventable as they are linked to modifiable risk factors such as smoking, alcohol use, poor diet and physical inactivity. Almost at least one third of all deaths related to cancer could be prevented through routine screening, and early detection and treatment.*

Keywords: Cancer

I. INTRODUCTION

Basically cells shows two types of proliferation neoplastic and non neoplastic proliferation.

Non Neoplastic Proliferation of Cells

Hypertrophy is the term for an increase in the size and capacity of an individual cells.
There are two types of hypertrophy: pathological and physiological.
example of a physiological phenomenon: pregnancy-related uterine and breast growth
Pathological - caused by a disease condition, for instance, hypertension causing cardiac enlargement.
Hyperplasia is the medical term for an increase in cell number. In most cases, it results from hormone imbalances or chronic irritation. Prostate nodular hyperplasia is an example.
Metaplasia is a transition from one type of differentiated tissue to another. Although the exact reason is unknown, irritation is frequently a contributing factor. For instance, smoking might cause the stratified squamous epithelium that normally secretes mucus in the bronchi to convert to mucous secreting epithelium.
Dysplasia- it is disordered growth which is frequently the precursor of malignancy.

Neoplastic Proliferation of Cells

Types – according to morbid anatomy and behaviour tumour it has been classified into two types

1. Benign tumours – generally localised, slow growing, circumscribed often encapsulated, compressed normal tissue and effect is due to pressure on adjacent organs/ structures. Histologically benign tumour Mimic structure of their parent organ, Cell resembles to their tissue of origin, show remarkable uniformity in shape size and nuclear configuration, show evidence of normal function, have relatively infrequent mitotic figures[1] .
2. Malignant tumours- it shows metastasis it spread through lymphatics , blood, tissue and serous cavities , rapid rate of growth, it is irregular, ill-defined and non-capsulated , invade and destroy normal tissue and structures. Histologically Malignant tumour shows haphazard arrangement, bear little resemblance to cell of origin, generally cell tend to vary in size , shape and nuclear configuration reflecting an increase in chromosomal number and DNA content(aneuploidy), provide little evidence of normal function, show frequent mitosis often abnormal types [1] .

Histologically it is classified on the basis of involvement of tissue of origin –

1. Epithelial tissue-
2. Mesenchymal tissue
3. Neuroectoderm

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4. Haemopoietic and lymphoid cell
5. Germ cell

Epithelial tissue -Benign Tumors- Papilloma- arise from epithelial surface example skin wart

ADENOMA- ARISE FROM DUCTS AND ACINI OF GLAND. Example – adenoma of gallbladder, intestine, cystadenoma of ovary

MALIGNANT TUMOURS-Carcinoma – arise from epithelial tissue

1. Squamous cell carcinoma
2. Basal cell carcinoma

MESENCHYMAL TISSUE – BENIGN TUMOR - Fibroadenoma- acini and fibrous tissue
Lipoma- masses of fat occur commonly in arms, shoulder, buttocks .
Chondroma- within medullary cavity of tubular bone hand feet. generally occur in small bones
Osteoma- mainly found in skull and sometime in long bone
Leiomyoma – tumour of smooth muscle occur in uterus. These are firm round mases usually begin in myometrium. Also called as fibroid of uterus.
Tumour of fibrous tissue – these are rare example keloid and fibromatosis.

MALIGNAT TUMOR - Exampleleiomyosarcoma, rhabdomyosarcoma, chondrosarcoma, and osteosarcoma.
Aetiological agents- environmental and genetic factors are responsible for cancer. Environmental consist of chemicals, radiation and virusesEnvironmental mutagens are described as physical and chemical elements in the environment that cause genetic mutations or raise the frequency of mutations throughout the lifespan of a person. The majority of mutagens cause cancer in people or have genotoxic effects on the next generation via germ cells.
Numerous mutagens, which contaminate the air, water, and food supply, may cause cancer by inducing mutations in people. It is known that environmental mutagens like heterocyclic amines and polycyclic aromatic hydrocarbons (PAH) attach to nucleotides and produce DNA adducts when they do so.
Chemical carcinogens includes industrial process , social habit and diet.
Industrial process- aniline dyes- consist of Naphthylamine lead to blader cancer
Insulation example buildings- consist of Asbestos – can leads to lung ,laryngeal cancer mesothelioma.
Mineral oil and tar - consist of Benz pyrene and other Hydrocarbon leads to skin cancer
Social habbit – smoking and tobacco chewing leads to oral cancer
Diet –aflatoxins are produced by fungi (aspergillus flavus)[2]aflatoxins Aflatoxin is produced by fungal action during the production, harvest, storage, and processing of food and feed. Contaminate food like milk, egg, chicken and meat , nuts grains , rice it can lead to liver cancer.
physical examination and taking a personal and family medical history also lab testing, imaging tests (scans), or further procedures or examinations A biopsy to determine type of cancer.
Virus-
RNA virus – Hepatis C Virus, Human T-cell Lymphotropic Virus
DNA virus- Epstein – Barr Virus, hepatis B virus, Human herpes virus-8,, human papilloma virus types 16 and 18.

II. TUMOUR MARKER

It is protein which is helpful in diagnosis and to monitor treatment.
These proteins enter blood stream. where it can be measured. These are biological marker for cancer it includes hormones, enzymes, oncofetal antigens, immunoglobulin and glycoprotein
Histologically identification of these product done by immunostaining in cytoplasm of tumour cells.
Anything that is present in or created by cancer cells, other cells in the body, or certain benign (non-cancerous) disorders in reaction to cancer or other conditions that give information about a cancer is referred to as a tumour marker.

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Some commonly used tumour markers are discussed here

Bence Jones Protein(light chain)- Multiple myeloma

Alpha-fetoprotein (AFP) -To help diagnose liver cancer and follow response to treatment; to assess stage, prognosis, and response to treatment of germ cell tumors

Beta-human chorionic gonadotropin (Beta-hCG) - To assess stage, prognosis, and response to treatment in cases of Choriocarcinoma and germ cell tumors

B-cell immunoglobulin gene rearrangement- To help in diagnosis, to evaluate effectiveness of treatment, and to check for recurrence of B-cell lymphoma

Cyclin D1 (*CCND1*) gene rearrangement or expression -help in diagnosis of Lymphoma, myeloma

CD19 -To help in diagnosis and to help determine treatment of B-cell lymphomas and leukemias

***BCL2* gene rearrangement** -For diagnosis and planning therapy of Lymphomas, leukemias

Beta-2-microglobulin (B2M)- To determine prognosis and follow response to treatmentof Multiple myeloma, chronic lymphocytic leukemia, and some lymphomas

CD20 , CD25 - To help determine treatment of Non-Hodgkin lymphoma

CD30- To help determine treatment of Classic Hodgkin lymphoma, B-cell and T-cell lymphomas

CD22 -To help in diagnosis and to help determine treatment **of** -cell lymphomas and leukemias

CD33 and *IDH1* and *IDH2* gene mutations- To help determine treatment of Acute myeloid leukemia

***FLT3* gene mutations**- To help determine treatment of Acute myeloid leukemia

Chromosome 17p deletion- To help determine treatment of **:** Chronic lymphocytic leukemia.

BCR-ABL fusion gene (Philadelphia chromosome) -To confirm diagnosis, predict response to targeted therapy, help determine treatment, and monitor disease status in cases of Chronic myeloid leukemia, acute lymphoblastic leukemia, and acute myelogenous leukemia

PML/RARα fusion gene- To diagnose Acute promyelocytic leukemia (APL), to predict response to all-trans-retinoic acid or arsenic trioxide therapy, to assess effectiveness of therapy, to monitor minimal residual disease, and to predict early relapse

Programmed death ligand 1 (PD-L1)- To help determine treatment of Non-small cell lung cancer, liver cancer, stomach cancer, gastroesophageal junction cancer, classical Hodgkin lymphoma, and other aggressive lymphoma subtypes

T-cell receptor gene rearrangement- To help in diagnosis of T-cell lymphoma even sometimes use to detect and evaluate residual disease

Terminal transferase (TdT)- : To help in diagnosis of Leukemia, lymphoma

Thiopurine S-methyltransferase (TPMT) enzyme activity or *TPMT* genetic test- here Blood and buccal (cheek) swab taken it is use To predict the risk of severe bone marrow toxicity (myelosuppression) with thiopurine treatment in Acute lymphoblastic leukemia

***IRF4* gene rearrangement** -To help in diagnosis of Lymphoma

LDH – Malignat lymphoma

***JAK2* gene mutation** -To help in diagnosis of few types of leukemia

Lactate dehydrogenase -To assess stage, prognosis, and response to treatment in cases of Germ cell tumors, lymphoma, leukemia, melanoma, and neuroblastoma

***MYC* gene expression** -it help in diagnosis of Lymphomas, leukemias and to help determine treatment

C-kit/CD117 - To help in diagnosis of Gastrointestinal stromal tumor, mucosal melanoma, acute myeloid leukemia, and mast cell disease and to help determine treatment

CA15-3/CA27.29 -To assess whether treatment is working or if the cancer has recurred in cases of Breast cancer

Estrogen receptor (ER)/progesterone receptor (PR) -To help determine treatment of Breast cancer

***BRCA1* and *BRCA2* gene mutations** - To help determine treatment of Ovarian and breast cancers

CA-125 - To help in diagnosis, assessment of response to treatment, and evaluation of recurrence of Ovarian cancer

HE4 -To plan cancer treatment, assess disease progression, and monitor for recurrence of Ovarian cancer

CA 27.29 - To detect metastasis or recurrence of Breast cancer

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Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor (PAI-1)- To determine aggressiveness of breast cancer and guide treatment

5-Protein signature (OVA1)- To pre-operatively assess pelvic mass for suspected ovarian cancer

21-Gene signature (Oncotype DX)- To evaluate risk of distant recurrence and to help plan treatment of Breast cancer

70-Gene signature (Mammaprint)- To evaluate risk of recurrence of Breast cancer

Gastrin -To help in diagnosis, to monitor the effectiveness of treatment, and to detect recurrence of Gastrin-producing tumor (gastrinoma)

***HER2/neu* gene amplification or protein overexpression**- To help determine treatment of Breast, ovarian, bladder, pancreatic, and stomach cancers

Microsatellite instability (MSI) and/or mismatch repair deficient (dMMR) -To guide treatment of Colorectal cancer and other solid tumors and to identify those at high risk of certain cancer-predisposing syndromes

UGT1A1*28 variant homozygosity- Blood and buccal (cheek) swab taken to predict toxicity from irinotecan therapy of Colorectal cancer

CA19-9 -To assess whether treatment is effective in cases of Pancreatic, gallbladder, bile duct, and gastric cancers, colorectal carcinomas.

Carcinoembryonic antigen (CEA)- To keep track of how well cancer treatments are working and check if cancer has come back or spread in cases of Colorectal cancer and some other cancers

Circulating tumor cells of epithelial origin (CELLSEARCH) -To inform clinical decision making, and to assess prognosis of Metastatic breast, prostate, and colorectal cancers

Somatostatin receptor-To help determine treatment of Neuroendocrine tumors affecting the pancreas or gastrointestinal tract (GEP-NETs)

BRAF V600 mutations - To help determine treatment of Cutaneous melanoma, Erdheim-Chester disease, Langerhans cell histiocytosis, colorectal cancer, and non-small cell lung cancer

Chromosomes 3, 7, 17, and 9p21- help in monitoring for tumor recurrence of Bladder cancer

Bladder Tumor Antigen (BTA)- Bladder cancer and cancer of the kidney or ureter. As surveillance with cytology and cystoscopy of patients already known to have bladder cancer

***FGFR2* and *FGFR3* gene mutations** -To help determine treatment of Bladder cancer

Fibrin/fibrinogen - To monitor progression and response to treatment of Bladder cancer

Des-gamma-carboxy prothrombin (DCP) -To monitor the effectiveness of treatment and to detect recurrence of Hepatocellular carcinoma

***DPD* gene mutation** -To predict the risk of a toxic reaction to 5-fluorouracil therapying cases of Breast, colorectal, gastric, and pancreatic cancers

Cytokeratin fragment 21-1 - To help in monitoring for recurrence of Lung cancer

***EGFR* gene mutation -** help to determine treatment and prognosis of Non-small cell lung cancer.

5-HIAA- To help in diagnosis of Carcinoid tumors and to monitor disease

Immunoglobulins- To help diagnosis of Multiple myeloma and Waldenström macroglobulinemia, and to assess response to treatment, and look for recurrence

***KRAS* gene mutation-** To help determine treatment of Colorectal cancer and non-small cell lung cancer

***MYD88* gene mutation**- To help in diagnosis of Lymphoma, Waldenström macroglobulinemia and to help determine treatment

Myeloperoxidase (MPO) - To help in diagnosis of Leukemia

Neuron-specific enolase (NSE) - help in diagnosis of Small cell lung cancer and neuroblastoma and to assess response to treatment

***NTRK* gene fusion**- To help determine treatment of Any solid tumor

***ALK* gene rearrangements and over expression** -To help determine treatment and prognosis of Non-small cell lung cancer, anaplastic large cell lymphoma, histiocytoses.

Nuclear matrix protein 22- To monitor response to treatment of Bladder cancer

PCA3 mRNA- To determine need for repeat biopsy after negative biopsy of Prostate cancer

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Prostate-specific antigen (PSA)- To help in diagnosis, to assess response to treatment, and recurrence of Prostate cancer

Prostatic Acid Phosphatase (PAP) To help in diagnosing poorly differentiated Metastatic prostate cancer

17-Gene signature (Oncotype DX GPS test)And 46-Gene signature (Prolaris)- To predict the aggressiveness of cancer help manage treatment of prostate cancer

***ROS1* gene rearrangement**- To help determine treatment of Non-small cell lung cancer

Soluble mesothelin-related peptides (SMRP)- To monitor progression or recurrence of Mesothelioma

Urine catecholamines: VMA and HVA- urine test help in diagnosis of Neuroblastoma

FoundationOneCDx (F1CDx) genomic testAnd Guardant360 CDx genomic test: As a companion diagnostic blood test to determine treatment and for general tumour mutation profiling of Any solid tumour

Calcitonin - To aid in diagnosis, check whether treatment is working, and assess recurrence of Medullary thyroid cancer

Thyroglobulin- this blood test help to evaluate response to treatment and to look for recurrence of Thyroid cancer

Chromogranin A (CgA) - help in diagnosis, assessment of treatment response, and evaluation of recurrence of Neuroendocrine tumors.

Special stains are utilized by pathologist for identification of cells example Cytokeratin stain positive for epithelial tissue origin of cancer

Vimentin stain positive – connective tissue origin

CD 45 positive – malignant lymphoma.

Grading and staging of cancer -

Grading - It has been done on the basis of differentiation and nuclear features, invasiveness

Based on differentiation - most tumours are graded as X, 1, 2, 3, or 4.

- Grade X: Grade cannot be assessed (undetermined grade)
- Grade 1: Well differentiated (low grade)
- Grade 2: Moderately differentiated (intermediate grade)
- Grade 3: Poorly differentiated (high grade)
- Grade 4: Undifferentiated (high grade)

Staging and spread of tumour- it is important prognostic factor for survival

TNM System –It is most important and widely used method. T denotes the primary tumor's size and location. The N stands for the quantity of cancerous lymph nodes in the area. The M indicates whether or not the cancer has spread. The most used cancer staging method is the TNM system

Primary Tumour (T) –

TX: The primary tumour is immeasurable.

T0: The primary tumour is undetectable.

T1, T2, T3, and T4T -the major tumor's size or extension is indicated. The size of the tumour or the extent of its invasion into neighbouring tissues is indicated by the number after the T. To provide further information, Ts can be further separated into T3a and T3b.

Localised Lymph Nodes (N) -

NX: It is impossible to detect cancer in surrounding lymph nodes.

N0: The lymph nodes in the area are cancer-free.

N1, N2, and N3: These terms describe the quantity and location of lymph nodes that are cancerous. The more cancerous lymph nodes there are, the higher the number following N.

Remote Metastasis (M) –

MX: Metastasis is impossible to quantify.

M0: The cancer has not spread to other organs.

M1: The cancer has spread to additional body locations.

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TNM combinations are grouped into five less-detailed stages.

Stage 0 - Abnormal cells are present but have not spread to nearby tissue. Also called carcinoma in situ, or CIS. CIS is not cancer, but it may become cancer.

Stage I, Stage II, and Stage III (may also be written as Stage 1, Stage 2, and Stage 3)- Cancer is present. The higher the number, the larger the cancer tumor and the more it has spread into nearby tissues

Stage IV (may also be written as Stage 4)- The cancer has spread to distant parts of the body.

The staging system, which is used for all cancer types, divides cancer into five major categories.

In situ – abnormal cells are present, but they haven't invaded the tissue around them.

Localized cancer- shows no signs of spreading and is contained to the area where it first appeared.

Regional—Lymph nodes, tissues, or organs nearby have developed cancer.

Distant—The cancer has spread to far-flung organs.

Unknown—The stage cannot be defined based on the available information.

Effect of cancer on individual- cachexia – weight loss, anorexia, muscle waisimg loss of subcutaneous fat and fatigue Anaemia- Anaemia seen in cancer commonly anaemia of chronic disease . other types also seen like macrocytic Hypochromic or microcytic Hypochromic Anaemia .and autoimmune haemolytic anaemia .

III. CONCLUSION

Neoplastic and nonneoplastic proliferation of cells are discussed in detail in this article different types of benign and malignant tumours are discussed in detail .. causative agents of carcinoma is discussed in detail with environmental factors . different tumour markers with their indications are mentioned. tumour markers these are biological markers of cancer it is use for diagnosis of cancer, recurrence , and can predict response to treatment.

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