Malignant tumours

Classification

Cancers are classified by the type of cell that resembles the tumour and, therefore, the tissue presumed to be the origin of the tumour. These are the histology and the location, respectively. Examples of general categories include:

- **Carcinoma:** Malignant tumors derived from epithelial cells. This group represents the most common cancers, including the common forms of breast, prostate, lung and colon cancer.
- **Sarcoma:** Malignant tumors derived from connective tissue, or mesenchymal cells.
- **Lymphoma**and leukemia: Malignancies derived from hematopoietic (blood-forming) cells
- **Germ cell tumor:** Tumors derived from totipotent cells. In adults most often found in the testicle and ovary; in fetuses, babies, and young children most often found on the body midline, particularly at the tip of the tailbone; in horses most often found at the poll (base of the skull).
- **Blastictumor or blastoma:** A tumour (usually malignant) which resembles an immature or embryonic tissue. Many of these tumors are most common in children.

Signs and symptoms

Symptoms of cancer metastasis depend on the location of the tumor.

Roughly, cancer symptoms can be divided into three groups:

- ***Local symptoms*:** unusual lumps or swelling (*tumor*), hemorrhage (bleeding), pain and/or ulceration. Compression of surrounding tissues may cause symptoms such as jaundice (yellowing the eyes and skin).
- ***Symptoms of metastasis (spreading)*:** enlarged lymph nodes, cough and hemoptysis, hepatomegaly (enlarged liver), bone pain, fracture of affected bones and neurological symptoms. Although advanced cancer may cause pain, it is often not the first symptom.
- ***Systemic symptoms*:** weight loss, poor appetite, fatigue and cachexia (wasting), excessive sweating (night sweats), anemia and specific paraneoplastic phenomena, i.e. specific conditions that are due to an active cancer, such as thrombosis or hormonal changes.

Causes

Cancers are primarily an environmental disease with 90-95% of cases due to environmental factors and 5-10% due to genetics. Most environmental causes, such as naturally occurring background radiation, are not modifiable or controllable. Common environmental factors that lead to cancer death include: tobacco (25-30% of deaths), diet and obesity (30-35%), infections(15-20%), radiation, stress, lack of physical activity, and environmental pollutants.

Chemicals

The incidence of lung cancer is highly correlated with smoking. Prolonged exposure to asbestosfibers is associated with mesothelioma.
Alcohol is an example of a chemical carcinogen that is not a mutagen. Such chemicals may promote cancers through stimulating the rate of cell division. Faster rates of replication leaves less time for repair enzymes to repair damaged DNA during DNA replication, increasing the likelihood of a mutation.

Radiation

Sources of ionizing radiation, such as radon gas, can cause cancer. Prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin malignancies. Non-ionizing radio frequency radiation from mobile phones and other similar RF sources has also been proposed as a cause of cancer, but there is currently little established evidence of such a link.

Infection

Some cancers can be caused by infection. This is especially true in animals such as birds, but also in humans, with viruses responsible for up to 20% of human cancers worldwide. These include ***human papillomavirus***(cervical carcinoma), ***human polyomaviruses*** (mesothelioma, brain tumors), ***Epstein-Barr virus*** (B-cell lymphoproliferative disease and nasopharyngeal carcinoma), ***Kaposi's sarcoma herpesvirus***(Kaposi's Sarcoma and primary effusion lymphomas), ***hepatitis B and hepatitis C viruses*** (hepatocellular carcinoma), and ***Human T-cell leukemia virus-1*** (T-cell leukemias). Bacterial infection may also increase the risk of cancer, as seen in ***Helicobacter pylori*** induced gastric carcinoma.

Hepatitis viruses, including hepatitis B and hepatitis C, can induce a chronic viral infection that leads to liver cancer in 0.47% of hepatitis B patients per year (especially in Asia, less so in North America), and in 1.4% of hepatitis C carriers per year.

The most prominent example is the link between chronic infection of the wall of the stomach with *Helicobacter pylori* and gastric cancer. Although only a minority of those infected with *Helicobacter* go on to develop cancer, since this pathogen is quite common it is probably responsible for most of these cancers.

HIV is associated with a number of malignancies, including Kaposi's sarcoma, non-Hodgkin's lymphoma, and HPV-associated malignancies such as anal cancer and cervical cancer.

Heredity

Most forms of cancer are *sporadic*, meaning that there is no inherited cause of the cancer. There are, however, a number of recognised syndromes where there is an inherited predisposition to cancer, often due to a defect in a gene that protects against tumour formation. **Famous examples are:**

- certain inherited mutations in the ***genes BRCA1 and BRCA2*** are associated with an elevated risk of breast cancer and ovarian cancer
- tumors of various endocrine organs in multiple endocrine neoplasia***(MEN types 1, 2a, 2b)***
- ***Li-Fraumeni syndrome*** (various tumors such as osteosarcoma, breast cancer, soft tissue sarcoma, brain tumors) due to mutations of ***p53***
- ***Turcot syndrome***(brain tumors and colonic polyposis)
- ***Familial adenomatous polyposis*** an inherited mutation of the **APC gene** that leads to early onset of colon carcinoma.
- ***Hereditary nonpolyposis colorectal cancer***(HNPCC, also known as Lynch syndrome) can include familial cases of colon cancer, uterine cancer, gastric cancer, and ovarian cancer, without a preponderance of colon polyps.
- ***Retinoblastoma***, when occurring in young children, is due to a hereditary mutation in the retinoblastoma gene.
- ***Down syndrome*** patients, who have an extra chromosome 21, are known to develop malignancies such as leukemia and testicular cancer, though the reasons for this difference are not well understood.

Grading and staging

- Staging is the process of assessing the extent of local and systemic spread of a malignant tumour or the identification of features that are risk factors for spread
- Grading is the process of assessing the degree of differentiation of a malignant tumour

The objectives of staging and grading a tumour are:

- to plan appropriate (treatment) for the individual patient;
- to give an estimate of the prognosis;
- to compare similar cases when assessing outcomes or designing clinical trials

Staging and grading methods

Staging

The commonest system is the internationally agreed TNM classification. It is not appropriate for leukaemia lymphomas, or myeloma. A four-stage classification (I. II, III, IV) is also often used and is compatible with TNM. Specific staging systems also exist for some tumour sites (e.g. Duke's stage in colorectal cance.

Staging may be either radiological or pathological.

- Radiological (often performed preoperatively) indicated by the prefix before the letter (e.g. rT3, rM1). If different radiological modalities are used separate prefixes can be used, e.g. for ultrasound (uT2). Radiological staging is used to plan treatment (e.g. neoadjuvant therapy, selection for surgery, planning of surgery).
- Pathological (performed on surgical specimens) indicated by the prefix before the letter (e.g. pT3, pN2, pM1). If there has been preoperative radiotherapy, the prefix is used to denote that the pathological stage may have been modified by this, e.g. ypT2. Pathological staging is used to plan adjuvant treatment (chemotherapy or radiotherapy) and for informing prognosis.

An example of lung cancer staging

- **Stage I** (T1 NO, T2NO): 85% 5y survival with surgery.
- **Stage II** (T1 N1, T2N1, T3N0): 60% 5y survival with surgery.
- **Stage IIIa** (T3 N1 or any N2): 20% 5y survival with surgery.
- **Stage IIIb** (Any T4, any N3): < 20% 5y survival; no benefit with surgery.
- **Stage IV**(M1): < 10% 5y survival; no benefit with surgery.

Other pathological features may be included with the TNM system for some tumours, e.g.

- The presence of extratumoural vascular invasion V0 or V1;
- Presence of extratumoural lymphatic invasion LyO or Ly1;
- Presence of viable tumour cells at or within 1mm of the surgical margin of excision R0, R1 (microscopic), R2 (macroscopic).

Histological grading
Gives a guide to the behaviour of a cancer by describing the degree of differentiation of the tumour (e.g. breast cancer).

- **Grade 1:** represents the least malignant tumours.
- **Grade 2:** 25-50% of the cells are undifferentiated.
- **Grade 3:** 50-75% of the cells are undifferentiated.
- **Grade 4:** more than 75% of the cells are undifferentiated.

Grading predicts the aggressiveness of a malignant neoplasm by characterising its microscopic appearance taking into account

1. The degree of differentiation,
2. Nuclear and cellular appearance,
3. Architectural integrity and
4. The proportion of active mitoses.

• **Grade 1:** well differentiated;
• **Grade 2:** moderately well differentiated;
• **Grade 3:** poorly differentiated.

Factors affecting the prognosis of malignant tumour

The prognosis of any tumour depends on four main features:

1) **Extent of spread**
2) **Microscopic appearance**
3) **Anatomical situation**
4) **General condition of the patient**

- ***The extent of spread***

The extent of the tumour (it's staging) on clinical examination, operation and on studding the excised surgical specimen, is of great prognostic importance. Obviously, the clinical findings of palpable distant secondaries or gross fixation of the primary tumor are serious. Similarly, the local invasiveness of the tumour at operation and evidence of distant spread are of great significance. Finally histological study may reveal involvement of the nodes which had not detected clinically or microscopic extension of the growth at the edges of the resected specimen with consequent worsening of the outlook for the patient.

- ***Microscopic appearance of the tumour (histological differentiation)***

  As general principle, the prognosis of tumor is related to it's degree of histological differentiation (its grading) which is a spectrum between well differentiated and anaplastic.

  The spread of the tumour and it's histological differentiation should be considered in conjunction with each other.

  A small tumour with no apparent spread at the time of operation may still have poor prognosis if it is highly anaplastic, whereas, an extensive tumour is not incompatible with long survival of the patient after operation if the microscopic examination reveals a high degree of differentiation.

- ***Anatomic Situation***

The site of the tumour may preclude it's adequate removal and thus seriously affect the prognosis e.g. tumour at the lower and of the esophagus may be easily removable whereas an exactly similar tumour situated behind the arch of the aorta may be technically inoperable. A brain tumour located in the frontal lobe may be resected whereas similar tumour in the brain stem will be not.

- ***General condition of the patient***

A patient apparently curable from the point view of the local condition may be inoperable because of poor general health. For example, a gross congestive heart failure may convert what is technically operable carcinoma of the rectum into a hopeless anesthetic risk.

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