Introduction to Neoplasm : ‘Tumor Classification’
A Review Article

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ABSTRACT:
Generally Tumors are classified into two main Categories:
Benign Tumor: A benign tumor is a tumor that lacks the ability to metastasize.
Malignant Tumor: A Malignant tumor has maximum ability to metastasize.

KEY WORDS: Embryological Classification, Anatomical Classification, Histological Classification, Tumor-Lymph Node-Metastasis Classification,
(Review Article)

INTRODUCTION

The classification of tumors was and is both a practical and theoretic necessity and requirement. Difficulties are numberless, starting with the structural variability and the high number of factors, some of which are suspected, others still unknown, which are involved in the onset and evolution of a tumor, then the response of the organism or even the organ and tissue involved, not to mention the accumulation of a large amount of facts and bibliography, difficult to systematize. And last but not least, the adoption of a unanimously accepted classification.

Over the past decades, the World Health Organization based in Geneva, has succeeded, with the help of internationally reputed specialists, in elaborating a morphological classification, updated with new bibliographic data and recent discoveries in the field of oncology. The World Health Organization has been supported by international bodies and commissions, within which reputed specialists in narrow oncologic areas have elaborated classifications based on clinicomorphological data with predictive support for both humans and animals.

CLASSIFICATION

EMBRYOLOGICAL CLASSIFICATION

The classification of tumors is based on the embryonic origin of tissues and their histological structure. Thus, there are:

- tumors originating from the ectoderm and endoderm: epithelial tumors or carcinomas;
- neuroectodermal tumors: tumors of the nervous system and of the APUD (Amine Precursor Uptake and Decarboxylation) system or DES (diffuse endocrine system) tumors;
- tumors originating from the mesoderm: tumors of the hematopoietic system and connective sarcomas.

A Histogenetic classification, taking into account practical reality, is proposed by Ghilezan (1992), including the following types of malignant tumors:

- epithelial tumors (carcinomas, epitheliomas) which include basal cell tumors, pavement tumors, transitional tumors, adenocarcinomas;
- connective tumors (sarcomas) with bone, cartilaginous and soft tissue tumors;
- hematopoietic tissue tumors, with: lymphomas, leukemias, plasmacytic neoplasms, histiocytosis;
- nerve tissue tumors;
- multiple tissue tumors;
- rare or difficult to classify tumors.

ANATOMICAL CLASSIFICATION

The great majority of anatomical classifications proposed refer to dog and cat tumors but, with small adjustments, they can be used for all species. A short characterization is required for each location:

- description of the tumor location or region;
- strict definition of the region, regional and juxtaregional lymph nodes for each location;
- depending on the case, clinical and surgical methods recommended for the evaluation of TNM categories.
Classification according to Anatomical location

- skin, without lymphosarcoma and mastocytoma;
- skin, mastocytoma;
- mammary gland;
- head and neck;
- digestive tract, including the pancreas and liver;
- urinary system;
- genital system;
- bones and joints;
- lymphatic and hematopoietic system, including malignant skin lymphoma;
- respiratory system;
- Endocrine glands (the thyroid and adrenal glands).

The tumors of the eye, central nervous system, heart and other endocrine glands are not included, as they are difficult to classify and many of these tumors show only a local invasion.

HISTOLOGICAL CLASSIFICATION

The quantified assessment of architectural and especially cytological parameters (cell differentiation grade, mitotic index, etc.) allows to establish a hierarchy of malignancy and to assign the studied tumor to a certain category. The notion of grade is intended to define histoprognosis.

Histological categories have been established for humans, and then they have been adapted or modified, becoming totally specific for animals. According to their histological structure, tumors can be grouped in the following main categories: epithelial tumors, of ectodermal and endodermal embryonic origin; mesenchymal or connective tumors, of mesodermal origin; neuroectodermal tumors and tumors of unknown origin.

Examples of benign and malignant tumors, according to their histological structure

- covering epithelium, at skin level; benign tumor: keratoacanthoma; malignant tumor: squamous cell carcinoma;
- covering epithelium, at intestinal level; benign tumor: papillary adenoma; malignant tumor: papillary carcinoma;
- glandular epithelium, in the pancreas; benign tumor: adenoma; malignant tumor: adenocarcinoma;
- glandular epithelium, in the liver; benign tumor: hepatoma; malignant tumor: hepatocellular carcinoma;
- connective tissue, in the oral cavity; benign tumor: fibroma; malignant tumor: fibrosarcoma;
- connective tissue, in the subcutaneous tissue; benign tumor: lipoma; malignant tumor: liposarcoma;
- Nerve tissue in the brain; benign tumor: astrocytoma; malignant tumor: malignant astrocytoma.

TUMOR-LYMPH NODE-METASTASIS CLASSIFICATION

In 1980, OWEN adapted the TNM classification used in human oncology for domestic animals. The author justified the need for a unique classification of human and animal tumors, given the progress achieved since 1975, when the World Health Organization made the first classification of animal tumors.

The TNM system for the tumors of domestic animals raises the accuracy standard for diagnosis, clinical evolution and prediction. The
The main objective of the international agreement regarding the classification of cancer cases, after the extension of the disease, is to ensure a method that could allow for a unique and clear professional language. The task of the veterinary clinician is to make a provisional diagnosis and to make a decision regarding the most efficient therapeutic approach.

The objectives of tumor staging in animals are:

- to assist the veterinary clinician in planning treatment;
- to assist in the evaluation of treatment results;
- to facilitate the information exchange between veterinary oncologists;
- to contribute to the development of cancer investigations in animals;
- to contribute to the information exchange between human and animal oncology.

These objectives can be achieved through the TNM classification system, in which the basic principles can be applied for all locations, regardless of treatment, with the advantage that it can be subsequently completed with the findings obtained from histopathological and surgical investigations.

The TNM system concerns: the extension of the primary tumor (T); the condition of lymph nodes (N); the absence or presence of distant metastases (M). In order to increase the accuracy of these parameters, numbers are added, which indicate the extension of the malignant tumor.

OWEN (1980) establishes some general rules that can be applied to all tumors, regardless of their location.

In all cases, malignancy should be confirmed by histological and/or cytological examination. The cases in which this confirmation is not possible will be recorded separately. In some locations, several types of cancer may appear which differ not only by their histological appearance, but also by their clinical behavior. Such an example is mammary gland carcinoma in female dogs: in the case of a well differentiated tubular adenocarcinoma, prognosis is favorable after mastectomy, in contrast with anaplastic carcinoma, when prognosis is reserved or even unfavorable.

All cases will be classified using TNM categories and they will be classified and recorded before the initiation of treatment. In the case of an animal with a poor clinical condition, which excludes surgical intervention, the case will not be recorded through the TNM system. The clinical TNM classification performed before treatment is of maximum importance in the reporting and evaluation of the tumor. Detailed histological information is a decisive supplement to clinical diagnosis.

In veterinary oncology, postsurgical TNM classification, pTNM, which also includes histopathological classification, is less used. However, the postsurgical histopathological examination of both the excised tumor and the removed regional lymph nodes is extremely useful in certain cases.

Primary tumors (T) are classified according to their grade in four categories: T1, T2, T3 and T4. There are peculiarities depending on the location, but each tumor should be examined clinically, if possible, in order to define its limits, size, whether it is mobile or fixed and adherent to the adjacent tissues.
An extremely accurate, simple and stereographic record is necessary, which allows cancer specialists to establish, based on a common language, certain criteria for a positive diagnosis and an adequate therapeutic approach. For this purpose, the following definitions are given for primary tumors (T):

- $T_0 \rightarrow$ means a clinically undetectable tumor, which is evidenced through adenopathies or metastases;
- $T_1 \rightarrow$ refers to a small, strictly circumscribed tumor, which does not reach the organ limits;
- $T_2 \rightarrow$ in this case the tumor reaches the organ limits;
- $T_3 \rightarrow$ the tumor is fixed to the neighboring organs;
- $T_4 \rightarrow$ refers to a tumor that has invaded the neighboring organs.

Multiple primary tumors will be evaluated as follows:
- Tumors found simultaneously in pair organs, such as the mammary gland chain, which will be classified independently;
- Tumors found simultaneously in the skin, when the tumor with the highest T category is first identified, and the number of tumors is indicated between brackets: $T_2 (S)$;
- Tumors found in cavitary viscera or tubular organs, such as: bladder, vagina, penis, for which the number of tumors is not important and which are defined by adding the “m” suffix: $T_3 (m)$.

In order to define the local tumor extension, the grades of the T category should be completed by the following symbols:
- $T_0$, for a tumor that cannot be evidenced, such as the cases in which metastases are produced by lymphatic or hematogenous route, while the primary tumor remains occult;
- $T_x$, for a primary tumor whose extension is impossible to appreciate; this category is reserved exclusively for the in situ carcinoma, a preinvasive carcinoma, with locations in the sclera, cornea, eyelid, nose, etc.

Regional lymph nodes (N) are catalogued using indices, $N_0$, $N_1$, $N_2$ and $N_3$, depending on the characteristics of the examination by palpation, lymphangiography and other procedures. For each index of lymph node changing, the following are considered:
- $N_0$ means palpable lymph nodes;
- $N_1$ is used for palpable, mobile lymph nodes, without pathognomonic characteristics;
- $N_2$, for large, hard, still mobile, or with bilateral metastasis in lymph nodes;
- $N_3$, for adherent and fixed, uni- or bilateral metastasis in lymph nodes.

If the presence of cancer cells is histologically confirmed, $N^+$ is noted, and if no cancer cells are detected, $N^-$ is noted.

Distant metastases (M) are codified as follows:
- $M_0$, no metastases have been clinically and radiologically identified;
- $M_1$, metastases are clinically and radiologically present in organs or tissues, and the metastatic organ (liver, lung, bones, etc.) can be mentioned.

Histopathological extension (P) and grading (G) can offer additional information. The P symbol refers to the depth of the tumor infiltration in an organ or tissue, and the G
symbol to the grade of tumor malignancy. For example, in the case of some cavitory organs, histopathological extension is expressed by four P grades:

- **P₁**, tumor limited to the mucosa;
- **P₂**, the tumor involves the mucosa and submucosa, extending to the serous membrane but without penetrating it;
- **P₃**, the tumor penetrates through the serous membrane, with or without the invasion of adjacent structures;
- **P₄**, the tumor diffusely and completely invades the organ wall, without the evidencing of limits.

The malignancy grade (G) is expressed by three categories:

- **G₁**, low malignancy grade;
- **G₂**, moderate malignancy grade;
- **G₃**, high malignancy grade

**CLINICAL CLASSIFICATION**

The combination of the three elements of the TNM classification allows establishing the clinical stage, with the possibility of prognostic evaluation. An example:

- **Clinical stage I**: T₁ N₀, M₀ or T₂, N₀, M₀;
- **Clinical stage II**: T₂, N₁, M₀ or T₂, N₁, M₀;
- **Clinical stage III**: T₁, N₂, M₀ or T₂, N₂, M₀;
- **Clinical stage IV**: T₃, N₀, 1, 2, 3, M₀ or T₄, N₀, 1, 2, 3, M₀ or any TN + M₁.

Survival at one year in the first group can be 60%, while in the last group this can be only 15%. The TNM classification is more practical than the classification by clinical stages [1].

**CELL TYPE CLASSIFICATION (TUMOR CELL)**

**CARCINOMA**

Carcinoma (Gk. *karkinos*, or "crab", and -oma, "growth") is the medical term for the most common type of cancer occurring in humans. Put simply, a carcinoma is a cancer that begins in a tissue that lines the inner or outer surfaces of the body, and that generally arises from cells originating in the endodermal or ectodermal germ layer during embryogenesis. More specifically, a carcinoma is tumor tissue derived from putative epithelial cells whose genome has become altered or damaged to such an extent that the cells become transformed, and begin to exhibit abnormal malignant properties.

**Histological types and variants of carcinoma**

**Squamous cell carcinoma (SCC or SqCC)**

Squamous cell carcinoma is a cancer of a kind of epithelial cell, the squamous cell. These cells are the main part of the epidermis of the skin, and this cancer is one of the major forms of skin cancer. However, squamous cells also occur in the lining of the digestive tract, lungs, and other areas of the body, and SCC occurs as a form of cancer in diverse tissues, including the lips, mouth, esophagus, urinary bladder, prostate, lung, vagina, and cervix, among others. Despite sharing the name *squamous cell carcinoma*, the SCCs of different body sites can show tremendous differences in their presenting symptoms, natural history, prognosis, and response to treatment.

SCC is a histologically distinct form of cancer. It arises from the uncontrolled multiplication of
cells of epithelium, or cells showing particular cytological or tissue architectural characteristics of squamous cell differentiation, such as the presence of keratin, tonofilament bundles, or desmosomes. SCC is still sometimes referred to as "epidermoid carcinoma" and "squamous cell epithelioma", though the use of these terms has decreased. Cancer can be considered a very large and exceptionally heterogeneous family of malignant diseases, with squamous cell carcinomas comprising one of the largest subsets\(^3\), \(^4\), \(^5\).

The International Classification of Diseases for Oncology (ICD-O) system lists a number of morphological subtypes and variants of malignant squamous cell neoplasms, including\(^6\):

- Papillary carcinoma (Code 8050/3)
- Verrucous squamous cell carcinoma (Code 8051/3) (Carcinoma cuniculatum or Ackerman tumor or Vulvar Cancer)
- Papillary squamous cell carcinoma (Code 8052/3)
- Squamous cell carcinoma (Code 8270/3)
- Large cell keratinizing squamous cell carcinoma (Code 8071/3)
- Large cell keratinizing squamous cell carcinoma (Code 8072/3)
- Small cell keratinizing squamous cell carcinoma (Code 8073/3)
- Spindle cell squamous cell carcinoma (Code 8074/3)
- Adenoid/pseudoglandular squamous cell carcinoma (Code 8075/3)
- Intraepidermal squamous cell carcinoma (Code 8081/3)
- Lymphoepithelial carcinoma (Code 8082/3)

Other variants of squamous cell carcinoma are recognized under other systems, such as:

- Basaloid squamous cell carcinoma
- Clear-cell squamous-cell carcinoma
- Keratoacanthoma
- Signet-ring-cell squamous-cell carcinoma

**Adenocarcinoma** – Adenocarcinoma is a cancer of an epithelium that originates in glandular tissue. Epithelial tissue includes, but is not limited to, the surface layer of skin, glands and a variety of other tissue that lines the cavities and organs of the body. Epithelium can be derived embryologically from ectoderm, endoderm or mesoderm. To be classified as adenocarcinoma, the cells do not necessarily need to be part of a gland, as long as they have secretory properties. This form of carcinoma can occur in some higher mammals, including humans\(^7\).

Most cervical cancer is squamous cell cancer, but sizeable minorities of cervical cancers are adenocarcinomas\(^8\). Adenocarcinoma of the Lung is currently the most common type of lung cancer in life long non-smokers\(^9\). Prostate cancer is Adenocarcinomas. The most common colon cancer cell (Colorectal Cancer) type is adenocarcinoma which accounts for 95% of cases. Other, rarer types include lymphoma and squamous cell carcinoma.

- Linitis plastica
- Vipoma
- Grawitz tumor
- Cholangiocarcinoma
- Fibroadenoma (benign tumor of composed of fibrous and glandular tissue)
- Anal sac adenocarcinoma
- Perianal Gland adenocarcinomas(hepatoid tumor)

**Basal Cell Carcinoma** - Basal-cell carcinoma (BCC) is the most common type of skin cancer.
It rarely metastasizes or kills. However, because it can cause significant destruction and disfigurement by invading surrounding tissues, it is still considered malignant. Basal-cell carcinomas may be divided into the following types:

- Nodular basal-cell carcinoma (Classic basal-cell carcinoma)
- Cystic basal-cell carcinoma
- Cicatricial basal-cell carcinoma (Morpheaform basal-cell carcinoma, Morphoeic basal-cell carcinoma)
- Infiltrative basal-cell carcinoma
- Micronodular basal-cell carcinoma
- Superficial basal-cell carcinoma (Superficial multicentric basal-cell carcinoma)
- Pigmented basal-cell carcinoma
- Rodent ulcer (Jacobi ulcer)
- Fibroepithelioma of Pinkus
- Polypoid basal-cell carcinoma
- Pore-like basal-cell carcinoma
- Aberrant basal-cell carcinoma
- Nevoid basal-cell carcinoma syndrome

For simplicity, one can also divide basal-cell carcinoma into 3 groups, based on location and difficulty of therapy:

- Superficial basal-cell carcinoma or some might consider being equivalent to "in-situ". Very responsive to topical chemotherapy such as Aldara, or Fluorouracil. It is the only type of basal-cell cancer that can be effectively treated with topical chemotherapy.
- Infiltrative basal-cell carcinoma, which often encompasses morpheaform and micronodular basal-cell cancer. More difficult to treat with conservative treatment methods such as electrodessication and curettage, or with curettage alone.

- Nodular basal-cell carcinoma, which essentially includes most of the remaining categories of basal-cell cancer. It is not unusual to encounter morphologic features of several variants of basal-cell cancer in the same tumor.

Carcinoma in Situ / Bowen’s Diseases

Carcinoma in situ (CIS) is an early form of cancer that is defined by the absence of invasion of tumor cells into the surrounding tissue, usually before penetration through the basement membrane. In other words, the neoplastic cells proliferate in their normal habitat, hence the name "in situ" (Latin for "in its place"). For example, carcinoma in situ of the skin, also called Bowen's disease, is the accumulation of neoplastic epidermal cells within the epidermis only that has failed to penetrate into the deeper dermis.

For this reason, CIS will usually not form a tumor. Rather, the lesion is flat (in the skin, cervix, etc.) or follows the existing architecture of the organ (in the breast, lung, etc.). Some CIS, however, do form tumors, such as in the colon (polyps), in the bladder (pre-invasive papillary cancer), or in the breast (more properly called ductal carcinoma in situ). Many forms of invasive carcinoma (the most common form of cancer) originate after progression of a CIS lesion. Therefore, CIS is considered a precursor or incipient form of cancer that may, if left untreated long enough, transform into a malignant neoplasm.

When explaining a laboratory report to a patient, most doctors will refer to CIS as "pre-cancer", not cancer. However, because most forms of
CIS have a high probability of progression into invasive carcinoma, doctors will usually recommend that the lesion be completely removed. Therefore, CIS is usually treated in much the same way as a malignant tumor.

In the TNM classification, carcinoma in situ is reported as TisN0M0 (Stage 0).

Hepatocellular Carcinoma (Hepatic Carcinoma)

Hepatocellular carcinoma (HCC, also called malignant hepatoma) is the most common type of liver cancer. Most cases of HCC are secondary to either a viral hepatitis infection (hepatitis B or C) or cirrhosis (alcoholism being the most common cause of hepatic cirrhosis)\(^1\). Some of Hepatocellular Carcinoma are:

- Malignant hepatic neoplasms
- Benign hepatic neoplasms
- Fibrolamellar carcinoma

**Ductal Carcinoma:** - Ductal carcinoma is a type of tumor that primarily presents in the ducts of a gland.

**Mammary ductal carcinoma**

Mammary ductal carcinoma is the most common type of breast cancer in women. It comes in two forms: invasive ductal carcinoma (IDC), an infiltrating, malignant and abnormal proliferation of neoplastic cells in the breast tissue, or ductal carcinoma in situ (DCIS), a noninvasive, potentially malignant, neoplasm that is still confined to the milk ducts (lactiferous ducts), where breast cancer most often originates. Many doctors feel that DCIS is overdiagnosed and that many women who are treated for DCIS do not actually have cancer\(^16\).

**Invasive ductal carcinoma**

Invasive ductal carcinoma (IDC) is the most common form of invasive breast cancer. It accounts for 55% of breast cancer incidence upon diagnosis, according to statistics from the United States in 2004\(^17\). On a mammogram, it is usually visualized as a mass with fine spikes radiating from the edges. On physical examination, this lump usually feels much harder or firmer than benign breast lesions such as fibroadenoma. On microscopic examination, the cancerous cells invade and replace the surrounding normal tissues\(^18\).

**Ductal carcinoma in situ (intraductal carcinoma)**

Ductal carcinoma in situ (DCIS, also known as intraductal carcinoma) is the most common type of noninvasive breast cancer or pre-cancer in women. Ductal carcinoma refers to the development of cancer cells within the milk ducts of the breast. In situ means "in place" and refers to the fact that the cancer has not moved out of the duct and into any surrounding tissue.

Ductal carcinoma in situ (DCIS) is noninvasive breast cancer that encompasses a wide spectrum of diseases ranging from low-grade lesions that are not life threatening to high-grade lesions that may harbor foci of invasive breast cancer. DCIS has been classified according to architectural pattern (solid, cribriform, papillary, and micropapillary), tumor grade (high, intermediate, and low grade), and the presence or absence of comedo histology\(^19\).

**Pancreatic ductal carcinoma**

Pancreatic cancer refers to a malignant neoplasm originating from transformed cells arising in tissues forming the pancreas. The
most common type of pancreatic cancer, accounting for 95% of these tumors, is adenocarcinoma (tumors exhibiting glandular architecture on light microscopy) arising within the exocrine component of the pancreas. A minority arise from islet cells, and are classified as neuroendocrine tumors. The symptoms that lead to diagnosis depend on the location, the size, and the tissue type of the tumor. They may include abdominal pain and jaundice (if the tumor compresses the bile duct) 20.

Exocrine pancreas cancers

The most common form of pancreatic cancer (ductal adenocarcinoma) is typically characterized by moderately to poorly differentiated glandular structures on microscopic examination. Pancreatic cancer has an immunohistochemical profile that is similar to hepatobiliary cancers (e.g. cholangiocarcinoma) and some stomach cancers; thus, it may not always be possible to be certain that a tumour found in the pancreas arose from it.

Cross section of a human liver, taken at autopsy examination, showing multiple large pale tumor deposits. The tumor is an adenocarcinoma derived from a primary lesion in the body of the pancreas.

Pancreatic carcinoma is thought to arise from progressive tissue changes. Three types of precancerous lesion are recognized: pancreatic intraepithelial neoplasia - a microscopic lesions of the pancreas, intraductal papillary mucinous neoplasms and mucinous cystic neoplasms both of which are macroscopic lesions 21. The second most common type of exocrine pancreas cancer is mucinous.

Other exocrine cancers include adenosquamous carcinomas, signet ring cell carcinomas, hepatoid carcinomas, colloid carcinomas, undifferentiated carcinomas, and undifferentiated carcinomas with osteoclast-like giant cells 22.

Endocrine pancreatic cancers (Neuroendocrine tumor)

Pancreatic endocrine tumors (PETs) are also called pancreatic neuroendocrine tumors (PNETs) and islet cell tumors 23. The majority of PNETs are usually categorized as benign 24, 25, 26 but the definition of malignancy in pancreas endocrine tumors has been ambiguous. A small subset of endocrine pancreatic tumors are incontrovertible pancreatic endocrine cancers, that make up about 1% of pancreas cancers. Low- to intermediate-grade neuroendocrine carcinomas of the pancreas may be called islet cell tumors. Some sources have also termed these pancreatic carcinoid, a practice that has sometimes been strongly condemned. Definitional migration has caused some complexity of PNET classification, which has adversely affected what is known about the epidemiology and natural history of these tumors. It is probable that some of these tumors have been included in ICD-O-3 histology classifications 8240–8245, in that they were labeled pancreatic carcinoid tumours. but most islet cell carcinomas have been coded as ICD-O-3 system 8150–8155. The more aggressive endocrine pancreatic cancers are known as pancreatic neuroendocrine carcinomas (PNEC). Similarly, there has likely been a degree of admixture of PNEC and extrapulmonary small cell cancer.

- Insulinoma (Pancreatic Endocrine Tumors)
(Review Article)

- Glucagonoma (tumor of the alpha cells of the pancreas)
- Gastrinoma
- Glomangioma (known as a "solitary glomus tumor"
- Nonchromaffin paragangioma
- Pheochromocytoma or Phaeochromocytoma (PCC) is a neuroendocrine tumor of the medulla of the adrenal glands (originating in the chromaffin cells)

Pancreatic cystic neoplasms

Pancreatic cystic neoplasms are a broad group of pancreas tumors that have varying malignant potential.

Anaplastic Carcinoma

Refers to a heterogeneous group of high-grade carcinomas that feature cells lacking distinct histological or cytological evidence of any of the more specifically differentiated neoplasms. These tumors are referred to as Anaplastic or Undifferentiated carcinomas.

Large Cell Carcinoma

Composed of large, monotonous rounded or overtly polygonal-shaped cells with abundant cytoplasm. Large-cell lung carcinoma (LCLC) is a heterogeneous group of undifferentiated malignant neoplasms originating from transformed epithelial cells in the lung. In most series, LCLC’s comprise between 5% and 10% of all lung cancers. According to the Nurses’ Health Study, the risk of large cell lung carcinoma increases with a previous history of tobacco smoking, with a previous smoking duration of 30 to 40 years giving a relative risk of approximately 2.3 compared to never-smokers, and a duration of more than 40 years giving a relative risk of approximately 3.6. The newest revisions of the World Health Organization Histological Typing of Lung Cancer schema include,

- Basaloid
- Clear Cell
- Lymphoepithelioma-like
- Rhabdoid phenotype
- Large-cell neuroendocrine carcinoma (derived from neuroendocrine cells) / LCNEC
- Combined large-cell neuroendocrine carcinoma / c-LCNEC

Small Cell Carcinoma

Small cell carcinoma (sometimes known as "small-cell carcinoma", "small cell lung cancer", or "Oat-cell carcinoma") is a type of highly malignant cancer that most commonly arises within the lung, although it can occasionally arise in other body sites, such as the cervix and prostate.

- Combined small cell lung carcinoma (c-SCLC) - Small cell lung carcinoma can occur in combination with a wide variety of other histological variants of lung cancer, including extremely complex malignant tissue admixtures. When it is found with one or more differentiated forms of lung cancer, such as squamous cell carcinoma or adenocarcinoma, the malignant tumor is then diagnosed and classified as a combined small cell lung carcinoma (c-SCLC). C-SCLC is the only currently recognized subtype of SCLC.

- Small cell carcinoma of the prostate - In the prostate, small cell carcinoma (SCCP) is a
A rare form of cancer (approx 1% of PC)\[^{35}\]. Due to the fact that there is little variation in prostate specific antigen levels, this form of cancer is normally diagnosed at an advanced stage, after metastasis. It can metastasize to the brain\[^{36}\].

**Nasopharyngeal Carcinoma**

Nasopharyngeal carcinoma (NPC) is the most common cancer originating in the nasopharynx, the uppermost region of the pharynx ("throat"), behind the nose where the nasal passages and auditory tubes join the remainder of the upper respiratory tract. NPC differs significantly from other cancers of the head and neck in its occurrence, causes, clinical behavior, and treatment. It is a squamous cell carcinoma or an undifferentiated type. Squamous cells are a flat type of cell found in the skin and the membranes that line some body cavities. Differentiation means how different the cancer cells are from normal cells. Undifferentiated is a word used to describe cells that do not have their mature features or functions\[^{37}\].

**Merkel cell carcinoma**

Merkel cell carcinoma also known as "cutaneous APUDoma," "primary neuroendocrine carcinoma of the skin," "primary small cell carcinoma of the skin," and "trabecular carcinoma of the skin" - is a rare and highly aggressive cancer in which malignant cancer cells develop in hair follicles, or on or beneath the skin\[^{38}\].

The majority of Merkel cell carcinomas appear to be caused in part by a virus, which has been named Merkel cell polyomavirus (MCV). Direct evidence for this oncogenetic mechanism comes from research showing that inhibition of production of MCV proteins causes MCV-infected Merkel carcinoma cells to die but has no effect on malignant Merkel cells that are not infected with this virus\[^{39}\]. MCV-uninfected tumors, which account for approximately 20% of Merkel cell carcinomas, appear to have a separate (and as-yet unknown) cause\[^{40}\].

This cancer is considered to be a form of neuroendocrine tumor. While patients with a small tumor (less than 2 cm) that has not yet metastasized to regional lymph nodes have an expected 5-year survival rate of more than 80 percent, once a lesion has metastasized regionally, the rate drops to about 50 percent. Up to half of patients that have been seemingly treated successfully (i.e. that initially appear cancer-free) subsequently suffer a recurrence of their disease\[^{41}\]. Recent reviews cite an overall 5-year survival rate of about 60% for all MCC combined. Merkel cell carcinoma (MCC) occurs most often on the sun-exposed face, head, and neck.

**Bronchioloalveolar carcinoma**

Bronchioloalveolar carcinoma (BAC) is a rare type of lung cancer. It occurs more frequently among never-smokers, women and Asians. By definition, BAC is not an invasive tumor. Therefore, pathologists classify it as a form of carcinoma in situ (CIS). However, unlike other forms of CIS, its behavior is malignant, often lethal. Major surgery, either a lobectomy or a pneumonectomy, is needed to control it, and recurrences are frequent. For this reason, oncologists classify it among the other malignant tumors, which are invasive tumors. Bronchioloalveolar carcinoma is a sub-type of lung adenocarcinoma. However it is distinct from other lung adenocarcinomas by different clinical features, prognosis and response to treatment\[^{44}\].
Choroid Plexus Carcinoma

Choroid plexus carcinoma is a papillary, intraventricular tumor derived from choroid plexus epithelium that shows clear signs of malignancy. Choroid plexus papilloma corresponds to WHO Grade III glioma. Choroid plexus carcinoma accounts 30-60% of all choroids plexus tumors in children. These lesions are most common among children less than five years of age. These tumors arise most frequently in the lateral (50%), 4th (40%) and 3rd (5%) ventricles. Choroid plexus carcinoma is a malignant solid tumor. Nuclear pleomorphism, frequent mitoses, high nucleus:cytoplasm ratio, and increased cellularity are characteristic. The papillary pattern underlying the biologic origin of these tumors may be blurred by the poorly structured sheets of tumor cells, frank necrosis and often diffuse areas of brain invasion. Papillary serous carcinoma

Probably better referred to simply as "serous carcinoma" (a papillary architecture may be inconspicuous), this is a carcinoma that most commonly arises in the ovary. Less common sites of origin include the endometrium, the cervix uteri and fallopian tube (the last of these sites being particularly represented among women with germline BRCA mutations). A small number of cases occur in the peritoneum with no/minimal involvement of the female genital organs, and these are referred to as primary peritoneal serous carcinoma. The large majority of these tumors are high grade (aggressive) malignancies. A small number of cases are of low-grade type. There is significant recent evidence that these latter tumors are histogenetically distinct.

Cervical Carcinoma

Cervical cancer is the term for a malignant neoplasm arising from cells originating in the cervix uteri. One of the most common symptoms of cervical cancer is abnormal vaginal bleeding, but in some cases there may be no obvious symptoms until the cancer has progressed to an advanced stage. Human papillomavirus (HPV) infection appears to be a necessary factor in the development of almost all cases (90+ %) of cervical cancer.

Histologic subtypes of invasive cervical carcinoma include the following: Though squamous cell carcinoma is the cervical cancer with the most incidences, the incidence of adenocarcinoma of the cervix has been increasing in recent decades. Non-carcinoma malignancies which can rarely occur in the cervix include melanoma, lympho.

Renal Carcinoma - (Renal Cell Carcinoma/ Hyernephroma/ Grawitz Tumor / Kidney Tumor)

Renal medullary carcinoma is a rare type of cancer that affects the kidney. It tends to be...
aggressive, difficult to treat, and is often metastatic at the time of diagnosis. Most individuals with this type of cancer have sickle cell trait or rarely sickle cell disease, suggesting that the sickle cell trait may be a risk factor for this type of cancer. Renal medullary carcinoma has been termed "the seventh sickle cell nephropathy" because it is found almost exclusively in individuals with sickle cell trait or occasionally in those with sickle cell disease.

Follicular Thyroid Carcinoma

Thyroid neoplasm or thyroid cancer usually refers to any of four kinds of malignant tumors of the thyroid gland: papillary, follicular, medullary or anaplastic. Papillary and follicular tumors are the most common. They grow slowly and may recur, but are generally not fatal in patients under 45 years of age. Medullary tumors have a good prognosis if restricted to the thyroid gland and a poorer prognosis if metastasis occurs. Anaplastic tumors are fast-growing and respond poorly to therapy.

- Follicular carcinoma tends to metastasize to lung and bone via the bloodstream.
- Papillary thyroid carcinoma commonly metastasizes to cervical lymph nodes.
- Medullary Thyroid Cancer which originates from the parafollicular cells (C cells), which produce the hormone calcitonin
- Medullary Breast Carcinoma

Adenoid Cystic Carcinoma (AdCC)

A malignant tumor arising from the epithelial cells. Microscopically, the neoplastic epithelial cells form cylindrical spatial configurations or Cylindroma (cribriform or classic type of adenoid cystic carcinoma), cord like structures (tubular type of adenoid cystic carcinoma), or solid structures (basaloid variant of adenoid cystic carcinoma). Adenoid cystic carcinomas mostly occur in the salivary glands. Adenoid cystic cancer (AdCC) is a rare type of cancer that can exist in many different body sites. It most often occurs in the areas of the head and neck, in particular the salivary glands; but has also been reported in the breast, lacrimal gland of the eye, lung, brain, Bartholin gland, trachea, and the paranasal sinuses. It is sometimes referred to as adenocyst, malignant cylindroma, adenocystic, adenoidcystic, ACC, AdCC. It is the second most common malignant salivary gland tumor overall (after mucoepidermoid carcinoma).

Transitional cell carcinoma

Transitional cell carcinoma (TCC, also urothelial cell carcinoma or UCC) is a type of cancer that typically occurs in the urinary system: the kidney, urinary bladder, and accessory organs. It is the most common type of bladder cancer and cancer of the ureter, urethra, and urachus. It is the second most common type of kidney cancer, but accounts for only 5% to 10% of all primary renal malignant tumors.

TCC arises from the transitional epithelium, a tissue lining the inner surface of the hollow organs. When the term "urothelial" is used, it specifically refers to a carcinoma of the urothelium, meaning a TCC of the urinary system.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is the most common type of salivary gland malignancy in adults. Mucoepidermoid carcinoma can also be found in other organs, as bronchi, lacrimal sac and thyroid. Mucicarmine staining is one stain used by pathologist for detection.
Acinic cell carcinoma

Acinic cell carcinoma is a tumor most commonly found in the parotid gland. The disease presents as a slow growing mass, sometimes associated with pain or tenderness. These tumors which resemble serous acinar cells vary in their behavior from locally aggressive to blatantly malignant. It can also appear in the breast. The pancreatic form of acinic cell carcinoma is a rare subtype of exocrine pancreatic cancer. Exocrine pancreatic cancers are the most common form of pancreatic cancer when compared to endocrine pancreatic cancer65.

Acinic cell carcinomas arise most frequently in the parotid gland. Other sites of primary tumors have included the submandibular gland and other major and minor salivary glands. There have been rare cases of primary tumors involving the parapharyngeal space and the sublingual gland.

Sebaceous lymphadenoma

Sebaceous lymphadenoma is a benign tumour of the salivary gland.

Surface epithelial-stromal tumor (Ovarian Cancer)

Surface epithelial-stromal tumors are a class of ovarian neoplasms that may be benign or malignant. Neoplasms in this group are thought to be derived from the ovarian surface epithelium (modified peritoneum) or from ectopic endometrial or Fallopian tube (tubal) tissue. This group of tumors accounts for the majority of all ovarian tumors. Serum CA-125 is often elevated but is only 50% accurate so it is not a useful tumor marker to assess the progress of treatment.

Dermal cylindroma

In dermatologic pathology, a dermal cylindroma, also dermal eccrine cylindroma56 and (less specifically) cylindroma, is a benign adnexal tumor57, which occurs on the scalp and forehead. Multiple cylindromas may grow together in a "hat-like" configuration, the so-called "turban tumor." Cylindromas are uncommon dysplasias of skin appendages58.

Spiradenoma - Spiradenoma, also eccrine spiradenoma59, is a cutaneous condition that is typically characterized, clinically, as a solitary, deep-seated dermal nodule of approximately one centimeter, occurring on the ventral surface of the body66, 67. The histological origin is controversial59, 62.

Pancreatic serous cystadenoma

Pancreatic serous cystadenoma, also known as serous cystadenoma of the pancreas and serous microcystic adenoma, a benign tumour of pancreas. It is usually found in the tail of the pancreas63, and may be associated with von Hippel-Lindau syndrome64. In contrast to some of the other cyst-forming tumors of the pancreas (such as the intraductal papillary mucinous neoplasm and the mucinous cystic neoplasm), serous cystic neoplasms are almost always entirely benign. There are some exceptions; rare case reports have described isolated malignant serous cystadenocarcinomas65.

Trichoepithelioma

Trichoepithelioma is a neoplasm of the adnexa of the skin. Its appearance is similar to basal cell
carcinoma. One form has been mapped to chromosome 9p21⁶⁷. Trichoepitheliomas consisted of nests of basaloid cells. They lack the myxoid stroma and artefactual clefting seen in basal cell carcinoma. Mitoses are uncommon when compared to basal cell carcinoma⁶⁸. Trichoepitheliomas may be divided into the following types⁶⁸:

- Multiple familial trichoepithelioma
- Solitary trichoepithelioma
- Desmoplastic trichoepithelioma
- Giant solitary trichoepithelioma
- Generalized trichoepithelioma

Malignant Acrospiroma

An acrospiroma (also known as a "Clear cell hidradenoma," "Dermal duct tumor," "Hidroacanthoma simplex," "Nodular hidradenoma," and "Poroma") is a tumor of the distal portion of a sweat gland. Acrospiromas are usually benign, and treatment consists of surgical excision. A malignant acrospiroma (also known as "Malignant poroma, "Porocarcinoma" and "Spiradenocarcinoma") is a sweat gland carcinoma of the hand, which may recur locally in 50% of patients after excision, with distant metastases occurring in 60% of patients⁶⁸,⁷⁰,⁷¹.

- Acrospiroma
- Syringoma
- Hidrocystoma

Craniopharyngioma

Craniopharyngioma is a type of brain tumor derived from pituitary gland embryonic tissue. It arises from nests of odontogenic (tooth-forming) epithelium within the suprasellar/diencephalic region and, therefore, contains deposits of calcium, which are evident on an x-ray. Histologically, craniopharyngiomas resemble adamantinomas (the most common tumors of the tooth). Patients may present with bitemporal inferior quadrantanopia leading to bitemporal hemianopia, as the tumor may compress the optic chiasm. Craniopharyngiomas are also known as Rathke pouch tumors, hypophyseal duct tumors, or adamantinomas(tumors of tooth)¹²⁶,¹²⁷. The histologic pattern consists of nesting of squamous epithelium bordered by radially arranged cells. It is frequently accompanied by calcium deposition and may have a microscopic papillary architecture. Two distinct types are recognized⁹⁸,⁹⁹:

- Adamantinomatous craniopharyngioma
- Papillary craniopharyngioma.

Histocytoma

A histocytoma is a tumour consisting of histiocytes. Histiocytes are cells that are a part of the mononuclear phagocytic system, a part of the body's immune system that consists of phagocytic cells, which are responsible for engulfing solid particles by the cell membrane to form an internal phagosome by phagocytes and protists¹⁵². Types include:

- benign fibrous histiocytoma
- malignant fibrous histiocytoma
- histiocytoma (dog)

Oncocytoma

An oncocytoma is a tumor made up of oncocyes, a special kind of cells. An oncocye is an epithelial cell characterized by an excessive amount of mitochondria, resulting in an abundant acidophilic, granular cytoplasm. Oncocytes can be benign or can undergo malignant transformation. Thyroid oncocytomas
can be benign (adenomas) or malignant (carcinomas)\textsuperscript{100}.

Endometrial Carcinomas

Endometrial carcinomas originate from cells in the glands of the endometrium (uterine lining). These include the common and readily treatable well-differentiated endometrioid adenocarcinoma, as well as the more aggressive uterine papillary serous carcinoma and uterine clear-cell carcinoma.

SARCOMA

A sarcoma (from the Greek σάρξ (σάρκα) meaning “flesh”) is a cancer that arises from transformed cells of mesenchymal origin. Thus, malignant tumors made of cancerous bone, cartilage, fat, muscle, vascular, or hematopoietic tissues are, by definition, considered sarcomas. This is in contrast to a malignant tumor originating from epithelial cells, which are termed carcinoma. Sarcomas are quite rare - common malignancies, such as breast, colon, and lung cancer, are almost always carcinoma. Sarcomas are given a number of different names based on the type of tissue from which they arise. For example, osteosarcoma arises from bone, chondrosarcoma arises from cartilage, liposarcoma arises from fat, and leiomyosarcoma arises from smooth muscle\textsuperscript{72}.

Ewing Sarcoma

Ewing sarcoma is a malignant round-cell tumour. It is a rare disease in which cancer cells are found in the bone or in soft tissue. The most common areas in which it occurs are the pelvis, the femur, the humerus, the ribs and clavicle. Because a common genetic locus is responsible for a large percentage of Ewing sarcoma and primitive neuroectodermal tumors, these are sometimes grouped together in a category known as the Ewing family of tumors. The diseases are, however, considered to be different: peripheral primitive neuroectodermal tumours are generally not associated with bones, while Ewing sarcomas are most commonly related to bone. Ewing sarcoma occurs most frequently in teenagers, with a male/female ratio of 1.6:1. Although usually classified as a bone tumour, Ewing sarcoma can have characteristics of both mesodermal and ectodermal origin, making it difficult to classify. James Ewing (1866–1943) first described the tumour, establishing that the disease was separate from lymphoma and other types of cancer known at that time. The Ewing family of tumors is a group of cancers\textsuperscript{93} that includes

- Ewing tumor of bone (ETB or Ewing sarcoma of bone),
- extraosseous Ewing tumors (EOE tumors),
- primitive neuroectodermal tumors (PNET or peripheral neuroepithelioma), and
- Askin tumors (PNET of the chest wall). These tumors all come from the same type of stem cell. Also called EFTs.

Kaposi’s Sarcoma - Kaposi's sarcoma (KS) is a tumor caused by Human herpesvirus 8 (HHV8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV). It was originally described by Moritz Kaposi (KAP-o-shee), a Hungarian dermatologist practicing at the University of Vienna in 1872. It became more widely known as one of the AIDS defining illnesses in the 1980s. The viral cause for this cancer was discovered in 1994. Although KS is now well-established to be caused by a virus infection, there is widespread lack of awareness of this...
even among persons at risk for KSHV/HHV-8 infection. Since Moritz Kaposi first described this malignant neoplasm, the disease has been reported in five separate clinical settings, with different presentations, epidemiology, and prognoses.

- Classic Kaposi sarcoma
- African cutaneous Kaposi sarcoma
- African lymphadenopathic Kaposi sarcoma
- AIDS-associated Kaposi sarcoma
- Immunosuppression-associated Kaposi sarcoma

**Soft Tissue Sarcoma** - A soft-tissue sarcoma is a form of sarcoma that develops in connective tissue, though the term is sometimes applied to elements of the soft tissue that are not currently considered connective tissue.

- Alveolar soft part sarcoma (9581/3)
- Angiosarcoma (9120/3)
- Cystosarcoma Phyllodes
- Dermatofibrosarcoma protuberans (DFSP) (8832/3-8833/3)
- Desmoid Tumor (8821/1-8822/1)
- Desmoplastic small round cell tumor (8806/3)
- Epithelioid Sarcoma (8804/3)
- Extraskeletal chondrosarcoma (9220/3)
- Extraskeletal osteosarcoma (9180/3)
- Fibrosarcoma (8810/3)
- Hemangiopericytoma (9150)(Also known as "solitary fibrous tumor". Only a subset of these tumors are classified as malignant.)
- Hemangiosarcoma (9120/3) (More commonly referred to as "angiosarcoma")
- Kaposi's sarcoma (9140/3)
- Leiomyosarcoma (8890/3-8896/3)
- Liposarcoma (8850/3-8858/3)
- Lymphangiosarcoma (9170-9175)
- Lymphosarcoma (Not considered to be sarcomas)
- Malignant fibrous histiocytoma (8830/3)(This is an obsolete term that is no longer recognized by the World Health Organization. Many of these tumors would currently be classified as "undifferentiated pleomorphic sarcoma").
- Malignant peripheral nerve sheath tumor (MPNST)
- Neurofibrosarcoma (9540/3)
- Rhabdomyosarcoma (8900-8920)
- Synovial sarcoma (9040/3-9043/3)
- Undifferentiated pleomorphic sarcoma (previously referred to as Malignant fibrous histiocytoma)

**Osteosarcoma(Osteogenic Sarcoma)**

Osteosarcoma is an aggressive malignant neoplasm arising from primitive transformed cells of mesenchymal origin (and thus a sarcoma) that exhibit osteoblastic differentiation and produce malignant osteoid. It is the most common histological form of primary bone cancer.

**Leiomyosarcoma** – Leiomyosarcoma (Gr. "smooth muscle connective tissue tumor"), aka LMS, is a malignant cancer of smooth muscle. (When such a neoplasm is benign, it is a leiomyoma.) Leiomyosarcoma is a relatively rare form of cancer, and accounts for between 5–10% of soft tissue sarcomas, which are in themselves relatively rare. Smooth muscle cells make up the involuntary muscles, which are found in most parts of the body, including the uterus, stomach and intestines, the walls of all blood vessels, and the skin. It is therefore
possible for leiomyosarcomas to appear at any site in the body (including the breasts); they are most commonly found in the uterus,[84] stomach, small intestine and retroperitoneum.

**Pleomorphic undifferentiated sarcoma** - Pleomorphic undifferentiated sarcoma (abbreviated PUS), also undifferentiated pleomorphic sarcoma and previously malignant fibrous histiocytoma (abbreviated MFH), is a type of soft tissue sarcoma.[86, 87] PUS occurs most commonly in the extremities and retroperitoneum, but has been reported in other sites. Metastasis occur most frequently in the lungs (90%), bones (8%) and liver (1%). In the extremities, it presents as a painless enlarging soft tissue mass. The histomorphology, otherwise, is characterized by high cellularity, marked nuclear pleomorphism, usually accompanied by abundant mitotic activity (including atypical mitoses), and a spindle cell morphology. Necrosis is common and characteristic of high grade lesions[88].

**Vaccine-associated sarcoma** -

A vaccine-associated sarcoma (VAS) is a type of malignant tumor found in cats (and rarely, dogs and ferrets) that has been linked to certain vaccines. VAS has become a concern for veterinarians and cat owners alike and has resulted in changes in recommended vaccine protocols. These tumors have been most commonly associated with rabies and *feline leukemia virus* vaccines, but other vaccines and injected medications have also been implicated[89].

**Fibrosarcoma (Fibroblastic Sarcoma)**

Fibrosarcoma is a malignant tumor derived from fibrous connective tissue and characterized by the presence of immature proliferating fibroblasts or undifferentiated anaplastic spindle cells. It originates in fibrous tissues of the bone and invades long or flat bones such as femur, tibia, and mandible. It also involves periosteum and overlying muscle[90].

**Fibromas**

Fibromas (or fibroid tumors or fibroids) are benign tumors that are composed of fibrous or connective tissue. They can grow in all organs, arising from mesenchyme tissue. The term "fibroblastic" or "fibromatous" is used to describe tumors of the fibrous connective tissue. When the term *fibroma* is used without modifier, it is usually considered benign, with the term fibrosarcoma reserved for malignant tumors:

- dermatofibroma
- angiofibroma
- cystic fibroma (*fibroma cysticum*)
- myxofibroma (*fibroma myxomatodes*)
- cemento-ossifying fibroma
- chondromyxoid fibroma,
- desmoplasmic fibroma,
- nonossifying fibroma,
- ossifying fibroma,
- nuchal fibroma,
- collagenous fibroma,
- fibroma of tendon sheath,
- perifollicular fibroma,
- pleomorphic fibroma,
- uterine fibroma
- Ovarian fibroma
- Giant Cell Fibroma

**Neurosarcoma**

A malignant peripheral nerve sheath tumor (also known as "Malignant schwannoma,"[91] "Neurofibrosarcoma,"[91] and
"Neurosarcoma"[91] is a form of cancer of the connective tissue surrounding nerves. Given its origin and behavior it is classified as a sarcoma. About half the cases are diagnosed in people with neurofibromatosis; the lifetime risk for an MPNST in patients with neurofibromatosis type 1 is 8-13%[92]. MPNST with rhabdomyoblastomatous component are called Malignant triton tumors.

Hemangioendothelioma

Hemangioendothelioma is used to describe a group of vascular neoplasms that may be considered benign or malignant in their activity. They have been described as masses that fall between a hemangioma and angiosarcoma. They are vascular tumors that commonly present with an enlarging mass and most commonly involve the lungs, liver, and musculoskeletal system, although many other body sites have been reported, including the head and neck, intestines, lymph nodes, pleura, retroperitoneum, stomach[94,95,96].

- Epithelioid
- Kaposiform
- Retiform
- Infantile hemangioendothelioma

Sarcoma botryoides

Sarcoma botryoides or botryoid sarcoma[91] or botryoid rhabdomyosarcoma is a subtype of embryonal rhabdomyosarcoma, that can be observed in the walls of hollow, mucosa lined structures such as the nasopharynx, common bile duct, urinary bladder of infants and young children or the vagina in females, typically younger than age 8. The name comes from the gross appearance of "grape bunches" (botryoid in Greek). Under the microscope one can see rhabdomyoblasts that may contain cross-striations. Tumor cells are crowded in a distinct layer beneath the vaginal epithelium ( cambium layer)[97,98].

Chondrosarcoma

Chondrosarcoma is a cancer composed of cells derived from transformed cells that produce cartilage[100]. Chondrosarcoma is a member of a category of tumors of bone and soft tissue known as sarcomas. About 30% of skeletal system cancers are chondrosarcomas[101]. While the disease can affect people (or animals) of any age, unlike most other forms of skeletal system cancer, it is more common among older people than among children, and more often affects the axial skeleton than the appendicular skeleton[102].

- Chondrosarcoma
- Juxtacortical chondrosarcoma
- Myxoid chondrosarcoma
- Mesenchymal chondrosarcoma
- Clear cell chondrosarcoma
- Dedifferentiated chondrosarcoma
- Enchondroma or Osteochondroma
- Ecchondroma (Benign tumor on the surface of cartilage or bone)

Granuloma

The term "granuloma" loosely to mean "a small nodule". Since a small nodule can represent anything from a harmless nevus to a malignant tumor, this usage of the term is not very specific. granulomas often contain calcium, although the cells that form a granuloma are too tiny to be seen by a radiologist. The most accurate use of the term "granuloma" requires a pathologist to examine surgically removed and specially colored (stained) tissue under a microscope[149]. Macrophages (also known as histiocytes) are
the cells that define a granuloma. They often, but not invariably, fuse to form multinucleated giant cells (Langhans giant cell). The macrophages in granulomas are often referred to as "epithelioid". An epithelioid cell is a cell that resembles epithelial cells in that it directly contacts its neighboring cells via cell surface molecules or junctions. Unlike epithelial cells, however, epithelioid cells make contacts over their entire surface, rather than at restricted (e.g., basolateral) portions. The term epithelioid cell also refers to a specialized cell type of the immune system.

- Choristoma (AKA infundibuloma and granular cell tumor)
  - Osseous choristoma of the tongue

**Angiomyolipoma**

Angiomyolipoma (AML) are the most common benign tumour of the kidney and are composed of blood vessels, smooth muscle cells and fat cells. Angiomyolipoma are tumours consisting of perivascular epithelioid cells (cells which are found surrounding blood vessels and which resemble epithelial cells). A tumour of this kind is known as a PEComa, from the initials of perivascular epithelioid cell. Older literature may classify them as hamartoma (benign tumours consisting of cells in their correct location but forming a disorganised mass) or choristoma (benign tumours consisting of normal cells in the wrong location). PEComas are themselves a kind of mesenchymal tumour which involves cells that form the connective tissue, cardiovascular and lymphatic systems. An angiomyolipoma is composed of varying proportions of vascular cells, immature smooth muscle cells and fat cells. These three components respectively give rise to the components of the name: angio-, myo- and lip-. The -oma suffix is indicates a tumour. Angiomyolipoma are typically found in the kidney but have also been commonly found in the liver and less commonly the ovary, fallopian tube, spermatic cord, palate and colon.

**Endometrial stromal sarcomas**

Endometrial Stromal sarcomas originate from the connective tissues of the endometrium.

**Mesothelioma**

Mesothelioma (or, more precisely, malignant mesothelioma) is a rare form of cancer that develops from transformed cells originating in the mesothelium, the protective lining that covers many of the internal organs of the body. It is usually caused by exposure to asbestos. There are three histological types of malignant mesothelioma: (1) Epithelioid; (2) Sarcomatoid; and (3) Biphasic (Mixed). Epithelioid comprises about 50-60% of malignant mesothelioma cases. It is also called Sarcoma of Kidney.

**BLASTOMA**

A blastoma is a type of cancer that is caused by malignancies in precursor cells, often called blasts. Examples are nephroblastoma, medulloblastoma and retinoblastoma. The suffix blastoma is used to imply a tumor of primitive, incompletely differentiated (or precursor) cells, i.e., chondroblastoma is composed of cells resembling the precursor of chondrocytes. Blastomas usually occur in children.

Many types of blastoma have been linked to a mutation in tumor suppressor genes. For example pleuropulmonary blastomas have been
linked to a mutation of the coding for p53. However, the mutation which allows proliferation of incompletely differentiated cells can vary from patient to patient and a mutation can alter the prognosis. In the case of retinoblastoma, patients carry a visibly abnormal karyotype, with a loss of function mutation on a specific band of chromosome 13. This recessive deletion on the rb gene is also associated with other cancer types and must be present on both alleles for a normal cell to progress towards malignancy. Thus, in the case of common blastomas, such as retinoblastomas, a practitioner may go directly into treatment, but in the case of rarer, more genetically linked blastomas, practitioners may karyotype the patient before proceeding with treatment.

**Neuroblastoma (NB)**

Neuroblastoma is the most common extracranial solid cancer in childhood and the most common cancer in infancy. It is a neuroendocrine tumor, arising from any neural crest element of the sympathetic nervous system or SNS. It most frequently originates in one of the adrenal glands, but can also develop in nerve tissues in the neck, chest, abdomen, or pelvis. Neuroblastoma is one of the few human malignancies known to demonstrate spontaneous regression from an undifferentiated state to a completely benign cellular appearance.

Esthesioneuroblastoma, also known as olfactory neuroblastoma, is believed to arise from the olfactory epithelium and its classification remains controversial. However, since it is not a sympathetic nervous system malignancy it is a distinct clinical entity and is not to be confused with neuroblastoma.

**Hepatoblastoma**

Hepatoblastoma is an uncommon malignant liver neoplasm occurring in infants and children and composed of tissue resembling fetal or mature liver cells or bile ducts. Affecting 1 in 1.5 million. They are usually present with an abdominal mass. The disease is most commonly diagnosed during a child's first three years of life. Alpha-fetoprotein (AFP) commonly is elevated, but when AFP is not elevated at diagnosis the prognosis is poor. Hepatoblastomas originate from immature liver precursor cells, usually unifocal and affect the right lobe of the liver more often than the left lobe, can metastasize. Patients with familial adenomatous polyposis (FAP), a syndrome of early-onset colonic polyps and adenocarcinoma, frequently develop hepatoblastomas. Also beta-catenin mutations have been shown to be common in sporadic hepatoblastomas, occurring in as many as 67% of patients.

**Retinoblastoma**

Retinoblastoma (Rb) is a rapidly developing cancer that develops in the cells of retina, the light-detecting tissue of the eye. In the developed world, Rb has one of the best cure rates of all childhood cancers (95-98%), with more than nine out of every ten sufferers surviving into adulthood. There are two forms of the disease; a heritable form and non-heritable form (all cancers are considered genetic in that mutations of the genome are required for their development, but this does not imply that they are heritable, or transmitted to offspring). Approximately 55% of children with Rb have the non-heritable form. If there is no history of the disease within the family, the disease is labeled...
"sporadic", but this does not necessarily indicate that it is the non-heritable form.

In about two thirds of cases, only one eye is affected (unilateral retinoblastoma); in the other third, tumours develop in both eyes (bilateral retinoblastoma). The number and size of tumours on each eye may vary. In certain cases, the pineal gland is also affected (trilateral retinoblastoma). The position, size and quantity of tumours are considered when choosing the type of treatment for the disease.

Nephroblastoma (Wilms` Tumor)

Wilms` tumor is cancer of the kidneys that typically occurs in children, rarely in adults.[115] Its common name is an eponym, referring to Dr. Max Wilms, the German surgeon (1867–1918) who first described this kind of tumor.[116] Most nephroblastomas are unilateral, being bilateral in less than 5% of cases, although patients with Denys-Drash syndrome mostly have bilateral or multiple tumors.[117] They tend to be encapsulated and vascularized tumors that do not cross the midline of the abdomen. In cases of metastasis it is usually to the lung. This type of cancer is curable. If the tumor is only in the kidney (typical), it can be removed along with the whole kidney (a nephrectomy).[118]

Medulloblastoma

Medulloblastoma is a highly malignant primary brain tumor that originates in the cerebellum or posterior fossa. Previously, medulloblastomas were thought to represent a subset of primitive neuroectodermal tumor (PNET) of the posterior fossa. However, gene expression profiling has shown that medulloblastomas have a distinct molecular profile and are distinct from other PNET tumors. Tumors that originate in the cerebellum are referred to as infratentorial because they occur below the tentorium, a thick membrane that separates the cerebral hemispheres of the brain from the cerebellum. Another term for medulloblastoma is infratentorial PNET. Medulloblastoma is the most common PNET originating in the brain[119]. All PNET tumors of the brain are invasive and rapidly growing tumors that, unlike most brain tumors, spread through the cerebrospinal fluid (CSF) and frequently metastasize to different locations in the brain and spine.

Pancreatoblastoma

Pancreatoblastoma is a rare tumor of the pancreas[120]. It occurs mainly in childhood and has a relatively good prognosis. Resected pancreatoblastomas can be quite large, ranging from 2 centimeters to 20 centimeters in size (1 to 8 inches). They are typically solid, soft masses. Under the microscope, at least two cell types are seen- 1) cells with “acinar” differentiation, and cells forming small “squamoid” nests. The cells with acinar differentiation have some features of the normal acinar cell of the pancreas (the most common cell in the normal pancreas)[121,122,123].

Pleuropulmonary blastoma

Pleuropulmonary blastoma (PPB) or Lungs Cancer is a rare cancer originating in the lung or pleural cavity. It occurs most often in infants and young children but also has been reported in adults. In a retrospective review of 204 children with lung tumors, pleuropulmonary blastoma and Carcinoid tumor (type of Neuroendocrine tumor, originating in the cells of the neuroendocrine system.) were the most common primary tumors (83% of the 204 children had secondary tumors spread from cancers elsewhere in the
body). Pleuropulmonary blastoma is regarded as malignant\textsuperscript{124,125}.

**Pineoblastomas**

Pineoblastoma is highly malignant, primitive embryonal tumor of the pineal gland. Pineoblastoma accounts for about 4\% of all pineal parenchymal tumors. Pineoblastomas arise from the parenchyma of the pineal gland. Pineoblastomas are composed of patternless sheets of densely packed small blue cells with round-to-irregular nuclei and scant cytoplasm. Homer-Wright and Flexner-Wintersteiner rosettes may be seen. The high cellularity, presence of multiple mitoses, and lack of pineocytomatous rosettes differentiate pineoblastoma from pineocytoma. Pineoblastoma may occur in patients with bilateral retinoblastoma ("trilateral retinoblastoma syndrome."). The genetic basis of sporadic pineoblastoma has not been elucidated.

**Ameloblastomas**

Ameloblastoma (from the early English word *amel*, meaning enamel + the Greek word *blastos*, meaning germ) is a rare, benign tumor of odontogenic epithelium (ameloblasts, or outside portion, of the teeth during development) much more commonly appearing in the lower jaw than the upper jaw\textsuperscript{153,154}. It was recognized in 1827 by Cusack\textsuperscript{155}. This type of odontogenic neoplasm was designated as an *adamantinoma* in 1885 by the French physician Louis-Charles Malassez\textsuperscript{156}. It was finally renamed to the modern name *ameloblastoma* in 1930 by Ivey and Churchill\textsuperscript{157,158}.

While these tumors are rarely malignant or metastatic (that is, they rarely spread to other parts of the body), and progress slowly, the resulting lesions can cause severe abnormalities of the face and jaw. Additionally, because abnormal cell growth easily infiltrates and destroys surrounding bony tissues, wide surgical excision is required to treat this disorder.

**GERM CELL TUMOR**

A Germ Cell Tumor (GCT) or Testicular Cancer is a neoplasm derived from germ cells. Germ cell tumors can be cancerous or non-cancerous tumors. Germ cells normally occur inside the gonads (ovary and testis). Germ cell tumors that originate outside the gonads may be birth defects resulting from errors during development of the embryo\textsuperscript{130}. Germ cell tumors are classified by their histology, regardless of location in the body\textsuperscript{131}.

- **Germinomatous or Seminomatous germ cell tumors (GGCT, SGCT)**
  - Germinoma (including dysgerminoma and seminoma)
  - Dysgerminoma
  - Seminoma

- **Nongerminomatous or Nonseminomatous germ cell tumors (NGGCT, NSGCT)**
  - Embryonal carcinoma
  - Endodermal sinus tumor, also known as yolk sac tumor (EST, YST)
  - Choriocarcinoma (Trophoblastic tumor)
    - Gestational choriocarcinoma
  - Teratoma including mature teratoma, dermoid cyst, immature teratoma, teratoma with malignant transformation
  - Polyembryoma
Gonadoblastoma

- Mixed Tumors
  - a common form is Teratoma with Endodermal sinus tumor
  - Teratocarcinoma refers to a germ cell tumor that is a mixture of Teratoma with Embryonal carcinoma, or with Choriocarcinoma, or with both

Despite their name, germ cell tumors occur both within and outside the ovary and testis.

- Head - inside the cranium — pineal and suprasellar locations are most commonly reported
  - Inside the mouth — a fairly common location for teratoma
- Neck
- 1% to 5% in the mediastinum (Mediastinal germ cell tumor)
- Pelvis - particularly Sacrococcygeal Teratoma
- Ovary - Ovarian cancer
- Testis - Testicular cancer
- Pineal Region Tumors - tumors found in this area include other embryonal type tumors, teratomas, astrocytomas, pineocytomas, and pineoblastomas.

LYMPHOMA

Lymphoma is a cancer of the lymphocytes, a type of cell that forms part of the immune system. Typically, lymphomas present as a solid tumor of lymphoid cells. These malignant cells often originate in lymph nodes, presenting as an enlargement of the node (a tumor). It can also affect other organs in which case it is referred to as extranodal lymphoma. Extranodal sites include the skin, brain, bowels and bone.

Lymphomas are closely related to lymphoid leukemias, which also originate in lymphocytes but typically involve only circulating blood and the bone marrow (where blood cells are generated in a process termed haematopoiesis) and do not usually form static tumors. There are many types of lymphomas, and in turn, lymphomas are a part of the broad group of diseases called hematological neoplasms.

Thomas Hodgkin published the first description of lymphoma in 1832, specifically of the form named after him, Hodgkin's lymphoma. Since then, many other forms of lymphoma have been described, grouped under several proposed classifications. The 1982 working formulation classification became very popular. It introduced the category non-Hodgkin lymphoma (NHL), divided into 16 different diseases.

Although older classifications referred to histiocytic lymphomas, these are recognized in newer classifications as of B, T or NK cell lineage. True histiocytic malignancies are rare and are classified as sarcomas.

The WHO Classification, published in 2001 and updated in 2008, is the latest classification of lymphoma and is based upon the foundations laid within the "Revised European-American Lymphoma classification" (REAL). This system attempts to group lymphomas by cell type (i.e. the normal cell type that most resembles the tumor) and defining phenotypic, molecular or cytogenetic characteristics. There are three large groups: the B cell, T cell, and natural killer cell tumors. Other less common groups are also recognized. Hodgkin lymphoma, although considered separately within the World Health Organization (and proceeding) classifications, is now recognized as being a tumor of, albeit
markedly abnormal, lymphocytes of mature B cell lineage.135

- Mature B cell neoplasms

  - Chronic lymphocytic leukemia/Small lymphocytic lymphoma
  - B-cell prolymphocytic leukemia
  - Lymphoplasmacytic lymphoma (such as Waldenström macroglobulinemia)
  - Splenic marginal zone lymphoma
  - Plasma cell neoplasms:
    - Plasma cell myeloma
    - Plasmacytoma
    - Monoclonal immunoglobulin deposition diseases
    - Heavy chain diseases
  - Extranodal marginal zone B cell lymphoma, also called MALT lymphoma
  - Nodal marginal zone B cell lymphoma (NMZL)
  - Follicular lymphoma
  - Mantle cell lymphoma
  - Diffuse large B cell lymphoma
  - Mediastinal (thymic) large B cell lymphoma
  - Intravascular large B cell lymphoma
  - Primary effusion lymphoma
  - Burkitt lymphoma/leukemia

- Mature T cell and natural killer (NK) cell neoplasms

  - T cell prolymphocytic leukemia
  - T cell large granular lymphocytic leukemia
  - Aggressive NK cell leukemia
  - Adult T cell leukemia/lymphoma
  - Extranodal NK/T cell lymphoma, nasal type
  - Enteropathy-type T cell lymphoma
  - Hepatosplenic T cell lymphoma
  - Blastic NK cell lymphoma
  - Mycosis fungoides / Sezary syndrome
  - Primary cutaneous CD30-positive T cell lymphoproliferative disorders
    - Primary cutaneous anaplastic large cell lymphoma
    - Lymphomatoid papulosis
  - Angioimmunoblastic T cell lymphoma
  - Peripheral T cell lymphoma, unspecified
  - Anaplastic large cell lymphoma

- Hodgkin lymphoma

  - Classical Hodgkin lymphomas:
    - Nodular sclerosis
    - Mixed cellularity
    - Lymphocyte-rich
    - Lymphocyte depleted or not depleted
  - Nodular lymphocyte-predominant Hodgkin lymphoma

LEUKAEMIA

Leukemia (American English) or leukaemia (British English) (from the Greek leukos λεύκος - white, and haima αίμα - blood) is a type of cancer of the blood or bone marrow characterized by an abnormal increase of immature white blood cells called "blasts". Leukemia is a broad term covering a spectrum
of diseases. In turn, it is part of the even broader group of diseases affecting the blood, bone marrow, heart, and lymphoid system, which are all known as hematological neoplasms. Leukemia can also cause multiple organ failure\textsuperscript{136}.

In 2000, approximately 256,000 children and adults around the world developed some form of leukemia, and 209,000 died from it\textsuperscript{137}.

Clinically and pathologically, leukemia is subdivided into a variety of large groups. The first division is between its acute and chronic forms:

**Acute leukemia** is characterized by a rapid increase in the numbers of immature blood cells. Crowding due to such cells makes the bone marrow unable to produce healthy blood cells. Immediate treatment is required in acute leukemia due to the rapid progression and accumulation of the malignant cells, which then spill over into the bloodstream and spread to other organs of the body. Acute forms of leukemia are the most common forms of leukemia in children.

**Chronic leukemia** is characterized by the excessive build up of relatively mature, but still abnormal, white blood cells. Typically taking months or years to progress, the cells are produced at a much higher rate than normal, resulting in many abnormal white blood cells. Whereas acute leukemia must be treated immediately, chronic forms are sometimes monitored for some time before treatment to ensure maximum effectiveness of therapy. Chronic leukemia mostly occurs in older people, but can theoretically occur in any age group.

Additionally, the diseases are subdivided according to which kind of blood cell is affected. This split divides leukemias into lymphoblastic or lymphocytic leukemias and myeloid or myelogenous leukemias:

- In **lymphoblastic or lymphocytic leukemias**, the cancerous change takes place in a type of marrow cell that normally goes on to form lymphocytes, infection-fighting immune system cells. Most lymphocytic leukemias involve a specific subtype of lymphocyte, the B cell.

- In **myeloid(non lymphocytic) or myelogenous leukemias**, the cancerous change takes place in a type of marrow cell that normally goes on to form red blood cells, some other types of white cells, and platelets.

Combining these two classifications provides a total of four main categories. Within each of these four main categories, there are typically several subcategories. Finally, some rarer types are usually considered to be outside of this classification scheme.

- **Acute lymphoblastic leukemia (ALL)** is the most common type of leukemia in young children. This disease also affects adults, especially those age 65 and older. Standard treatments involve chemotherapy and radiotherapy. The survival rates vary by age: 85% in children and 50% in adults. Subtypes include precursor B acute lymphoblastic leukemia, precursor T acute lymphoblastic leukemia, Burkitt's leukemia, and acute biphenotypic leukemia\textsuperscript{138}.
Chronic lymphocytic leukemia (CLL) most often affects adults over the age of 55. It sometimes occurs in younger adults, but it almost never affects children. Two-thirds of affected people are men. The five-year survival rate is 75%. It is incurable, but there are many effective treatments. One subtype is B-cell prolymphocytic leukemia, a more aggressive disease. T-cell prolymphocytic leukemia (T-PLL) is a very rare and aggressive leukemia affecting adults; somewhat more men than women are diagnosed with this disease. Despite its overall rarity, it is also the most common type of mature T cell leukemia; nearly all other leukemias involve B cells. It is difficult to treat, and the median survival is measured in months.

Acute myelogenous leukemia (AML) occurs more commonly in adults than in children, and more commonly in men than women. AML is treated with chemotherapy. The five-year survival rate is 40%. Subtypes of AML include acute promyelocytic leukemia, acute myeloblastic leukemia, and acute megakaryoblastic leukemia.

Chronic myelogenous leukemia (CML) occurs mainly in adults. A very small number of children also develop this disease. Treatment is with imatinib (Gleevec in US, Glivec in Europe) or other drugs. The five-year survival rate is 90%. One subtype is chronic monocytic leukemia.

Hairy cell leukemia (HCL) is sometimes considered a subset of CLL, but does not fit neatly into this pattern. About 80% of affected people are adult men. There are no reported cases in children. HCL is incurable, but easily treatable. Survival is 96% to 100% at ten years. Carcinosarcoma

Carcinosarcoma is a malignant tumor that is a mixture of carcinoma (cancer of epithelial tissue, which is skin and tissue that lines or covers the internal organs) and sarcoma (cancer of connective tissue, such as bone, cartilage, and fat). Also called malignant mixed Müllerian tumor, also known as malignant mixed mesodermal tumor, MMMT.

MIXED TUMORS

Carcinosarcoma
Lymphosarcoma

Lymphoma is a type of cancer defined by a proliferation of malignant lymphocytes within solid organs such as the lymph nodes, bone marrow, liver and spleen. The disease also may occur in the eye, skin, and gastrointestinal tract. It is also known as lymphosarcoma.

Glioblastomas (Spongiblastoma)

Glioblastoma multiforme (GBM) is the most common and most aggressive malignant primary brain tumor in humans, involving glial cells and accounting for 52% of all functional tissue brain tumor cases and 20% of all intracranial tumors. Despite being the most prevalent form of primary brain tumor, GBMs occur in only 2–3 cases per 100,000 people in Europe and North America. According to the WHO classification of the tumors of the central nervous system, the standard name for this brain tumor is "glioblastoma"; it presents two variants: giant cell glioblastoma and gliosarcoma. Glioblastomas are also an important brain tumor in canines, and research continues to use this as a model for developing treatments in humans[151].

Chondroid syringoma (malignant mixed tumor or Malignant chondroid syringoma) - Chondroid syringoma is a cutaneous condition characterized histologically by nests of cuboidal or polygonal epithelial cells in the dermis and it's of two types: 1-derived from a single germ cell layer that differentiates into more than one cell type 2-derived from more than one germ cell layer(totipotent cells)[159].

Pleomorphic Adenoma

Pleomorphic adenoma is a common benign salivary gland neoplasm characterised by neoplastic proliferation of parenchymatous glandular cells along with myoepithelial components, having a malignant potentiality. It is the most common type of salivary gland tumor and the most common tumor of the parotid gland. It derives its name from the architectural pleomorphism (variable appearance) seen by light microscopy. It is also known as "Mixed tumor, salivary gland type", which describes its pleomorphic appearance as opposed to its dual origin from epithelial and myoepithelial elements.

Warthin’s Tumor

Warthin's tumor or Warthin tumour, also known as papillary cystadenoma lymphomatosum or adenolymphoma, is a type of benign tumor of the salivary glands. The gland most likely affected is the parotid gland. Though much less likely to occur than pleomorphic adenoma, Warthin's tumor is the second most common benign parotid tumor.

GLIOMAS

A glioma is a type of tumor that starts in the brain or spine. It is called a glioma because it arises from glial cells. The most common site of gliomas is the brain. Gliomas are named according to the specific type of cell they share histological features with, but not necessarily originate from. The main types of gliomas are:

- Ependymomas — ependymal cells.
- Astrocytomas — astrocytes (glioblastoma multiforme is the most common astrocytoma).
- Oligodendrogliomas — oligodendrocytes.
Review Article

- Mixed gliomas, such as oligoastrocytomas, contain cells from different types of glia.
- Optical nerve glioma - common cell type is pilocytic astrocytoma.
- Brain stem glioma - tissue from which they arise, they can be either astrocytomas, anaplastic astrocytomas, glioblastoma multiforme, or a mixed tumor.
- Gangliogliomas - They arise from ganglia (a ganglion is a group of nerve cells).
- Choristomas - are distinctive low-grade gliomas arising along the distribution of the neurohypophysis (also AKA infundibuloma and granular cell tumor)
  - Osseous choristoma of the tongue

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