**Neoplasms, part 3**

Scheme of hematopoietic cell differentiation into derivative cells



HSC – hematopoietic stem cell

HPC – hematopoietic progenitor cell

CMP (CFU-S) – common myeloid progenitor

CLP – common lymphocyte progenitor

CFU-GEMM – colony-forming unit – granulocyte, erythrocyte, monocyte, megakaryocyte;

CFU-GM – colony-forming unit – granulocyte, monocyte

**Neoplasms of myelogenous and lymphocytic origin**

The term **leukaemia *(leucaemia)*** is used to describe hematopoietic neoplasms originating from bone marrow progenitor cells. They can be of the following types:

* **non-lymphoid** (myelogenous leukaemia)
* **lymphoid** (lymphocytic leukaemia)

The following cells may be subject to the processes of neoplastic transformation and proliferation

* **early hematopoietic precursor cells** (acute leukaemia)
* **late hematopoietic precursor cells**, when well-differentiated cells are formed (chronic leukaemia)

The boundary between acute and chronic leukaemia is not always clear, in some lymphocytic leukaemias immature cells may occur next to dominant, well-differentiated cells. Neoplastic cells proliferate in the bone marrow at the expense of normal haematopoiesis, enter the blood and infiltrate internal organs such as the spleen, liver, heart, lymph nodes.

**Acute myeloid leukaemia**

* Subtypes of the disease
	+ AUL – acute undifferentiated leukaemia
	+ AML-M1 – myeloblastic leukaemia without maturation
	+ AML-M2 – myeloblastic leukaemia with maturation
	+ AML-M3 – promyelocytic leukaemia; has been reported only in pigs
	+ AML-M4 – acute myelomonocytic leukaemia; most common AML in dogs, cats and horses
	+ AML-M5 – acute monocytic leukaemia
	+ AML-M6 – erythroleukaemia; reported in cats (mainly in relation to FeLV infection) and poultry
	+ AML-M7 – megakaryoblastic leukaemia

**Acute myeloid leukaemia**

* may occur in animals at any age, but it is more common in young and middle-aged animals
* clinically, the following symptoms are found: lack of appetite, depression, tendency to bleed, fever, vomiting – therefore, these are non-specific symptoms
* **cytopenia** (bi- or pancytopenia) is observed in the circulating blood, with or without the presence of neoplastic blasts
* lymphadenomegaly of one or more lymph nodes, spleen, liver enlargement, mediastinal tumour, fluid in the body cavities may occur; rarely, cancer blasts may infiltrate other organs
* **the diagnosis is based on a bone marrow examination**
* in dogs, AML is most common in middle-aged animals, with myelomonocytic (M4) and monocytic (M5) leukaemias being most common
	+ prognosis is bad, most dogs are euthanized shortly after diagnosis or after 1-4 months of chemotherapy
	+ few cases of longer survival times have also been described
* AML is less common in cats than in dogs, and is most often associated with FeLV infection (hence, it is more common in young animals)
	+ lymphadenomegaly is observed less frequently than in dogs
	+ prognosis is bad (most cats die within 2 months of diagnosis)
* leukaemia is rare in horses (it is much less common than in dogs), but most often it is M4 and M5 type
	+ prognosis is bad, horses survive from a few days to a month after the diagnosis is made

**Acute myeloblastic leukaemia, spleen**

* grossly: even splenomegaly is observed
* microscopically:
	+ leukemic myeloblasts evenly infiltrate the spleen, which leads to obliteration of its architecture and the disappearance of white pulp elements
	+ myeloblasts are cells with a high nuclear-cytoplasmic ratio, the nuclei are round or irregular with an irregular chromatin distribution and distinct nucleoli
	+ the cytoplasm is moderately abundant, slightly grainy
	+ neoplastic myeloblasts may be accompanied by other blood cell precursors such as megakaryocytes

**Acute myeloblastic leukaemia, liver**

* grossly: the liver may be enlarged (hepatomegaly), initially it may have an accentuated and later obliterated lobular structure (depending on the degree of infiltration by neoplastic cells
* microscopically:
	+ leukemic myeloblasts are located in and around the blood vessels, in the sinuses, but over time they can lead to the obliteration of liver architecture and atrophy of hepatocytes
	+ leukemic myeloblasts fill sinus vessels, hepatocytes are compressed, sometimes atrophied
	+ leukemic myeloblasts partially obliterating the lumen of the blood vessel, also present in the lumen of the sinuses between the liver trabeculae

**Acute myeloblastic leukaemia, lymph node**

* macroscopically, the lymph nodes in the course of leukaemia may be unchanged or enlarged
* the microscopic image depends on the degree of infiltration of leukemic cells – the node architectonics can be preserved or obliterated to varying degrees
* leukemic myeloblasts form solid foci, demonstrate figures of mitotic division
* neoplastic cells are clearly larger than the surrounding small lymphocytes, they also have a more irregular cell nucleus with light, fine-grained chromatin, the nuclei are distinct and the cytoplasm is moderately abundant

**Avian leukaemia**

* leukaemia in birds includes various types of neoplastic viral diseases (viruses of *Retroviridae* family, genus *Alpharetrovirus*)
* among many forms of avian leukaemia, ***lymphoid leukosis*** and ***myeloid leukosis*** are of the highest importance in hen flocks.

**Lymphoid leukosis (lymphomatosis, organ leukaemia)** – neoplastic bursal-dependent lymphoblasts (B-cells) cause enlargement of the bursa of Fabricius, infiltrate the liver, spleen and other internal organs. It is primarily found in laying hens

**Myeloid leukosis** – neoplastic growth of myeloblasts (*myeloblastosis*) or myelocytes (*myelocytomatosis*) takes place within bones (sternum, ribs), in muscles and in various internal organs (in the liver, spleen, kidneys). It is primarily found in hens of meat breeds

Erythroblastosis and other neoplastic processes are very rare.

**Myeloid leukaemia (myelocytomatosis) within the skeletal muscles**

Grossly: leukemic cell infiltrations in the focal or spilled form are observed. The organs take on a greenish colour, which is associated with eosinophilic infiltration. As a result of leukemic cell infiltration, the parenchymal cells of organs (in this case – muscles) gradually disappear.

Microscopically:

* neoplastic myelocytes have numerous eosinophilic granules in the cytoplasm
* the nuclei are oval or round, bright, with distinct nucleoli
* neoplastic cells demonstrate high mitotic activity
* the muscle fibres are subject to atrophy

**Chronic myeloid leukaemia (neoplasm of the bone marrow)**

It is rare in animals, mainly found in dogs (usually in mature animals) and cats. Types:

* **Chronic granulocytic leukaemia**
	+ neoplastic proliferation of fairly mature neutrophils
	+ it is rare in dogs, cats and horses
* **Chronic eosinophilic leukaemia**
	+ neoplastic proliferation of eosinophils with varying degrees of maturity (but fairly mature)
	+ it is rare in animals (mainly in cats – and must be differentiated from hypereosinophilic syndrome, which is not a neoplastic disease)
* **Chronic basophilic leukaemia**
	+ neoplastic basophiles may have a hypersegmented nucleus
	+ it is rare, but has been described in dogs and cats
* **Chronic myelomonocytic and monocytic leukaemia**
	+ the blood contains fairly mature neutrophils and/or monocytes
	+ hepatosplenomegaly is frequently observed
* **Essential thrombocythemia**
	+ excess platelets are found in blood; they may show signs of atypia
	+ it has been reported in dogs and cats
* **Essential erythrocytosis (*primary erythrocytosis, polycythemia vera*)**
	+ excessive number of erythrocytes, with normal appearance, in blood
	+ it has been described in cats, dogs, cattle and horses
* **Mast cell leukaemia**
	+ it is characterized by the presence of mast cells in the circulating blood, with normal morphology or showing different features of atypia
	+ it is manifested by gastrointestinal symptoms due to the release of vascular mediators such as histamine
	+ it is a primary marrow bone neoplasm that occurs without the presence of cutaneous mastocytoma in dogs or gastrointestinal mastocytoma in cats (and should be distinguished from the leukemic course of these neoplasms)
	+ in cats, splenic mastocytoma often manifests itself as systemic mastocytosis with a leukemic course

**Lymphoid leukaemia**

* consists of neoplastic proliferation of lymphoid cells, occurring in the bone marrow; neoplastic cells are often present in circulating blood (leukemic form), but aleukaemic forms are also reported
* acute and chronic form can be distinguished, depending on the maturity of neoplastic cells
* neoplastic cells often infiltrate lymphatic organs, and in many cases at this stage, it is difficult to distinguish between leukaemia and lymphoma (lymphoma is a neoplasm originating from lymphocytes present in solid lymphatic organs – other than bone marrow, i.e. in lymph nodes, spleen, thymus, lymphatic tissue of various organs, e.g. MALT, SALT)

**Acute lymphoblastic leukaemia**

* in cats, it is mostly derived from T lymphocytes (and accompany FeLV infection, but there have also been reported cases in FIV+, FeLV- cats)
* in dogs, it can be derived from T, B, NK and null lymphocytes

**Chronic lymphocytic leukaemia**

* it is most commonly found in older animals
* neoplastic lymphocytes resemble normal, small lymphocytes
* most cats with chronic lymphocytic leukaemia are FeLV-

**Enzootic bovine leukosis**

* it is an infectious chronic disease in cattle (controlled *ex officio*)
* caused by BLV(***bovine leukaemia virus***) of *Retroviridae* family
* the disease has a long incubation period (from several months to even 2-3 years)
* subclinical stage (haematological period) – chronic lymphocytosis, may last for life
* clinical (nodular) stage – characterised by infiltration of neoplastic B lymphocytes in the lymph nodes, spleen and many other organs, also in the myocardium – neoplastic foci may be nodular or diffused (infiltrated)
* in the heart **(*lymphadenosis cordis*)** infiltrations of leukemic cells (small lymphocytes) are observed between myocardial fibres. Through pressure, infiltrations gradually lead to the disappearance of cardiomyocytes. Leukemic cells can also accumulate under the endocardium, epicardium or cover the whole heart. They can also form heaped-up thickenings around coronary vessels. The left and the right auricle are usually covered by massive leukemic cell infiltration. The result is myocardial failure, which contributes to the death of the animal.

**Lymphoma/lymphosarcoma**

* are the result of neoplastic transformation and proliferation of lymphocytes (B or T) of solid lymphatic organs
* may occur without any change in the blood image or neoplastic lymphoid cells may secondarily be present in the bone marrow, causing myelosuppression and leukemic course of the disease (neoplastic cells are present in circulating blood) – in these cases, the term lymphoma/leukaemia is used interchangeably
* lymphomas can primarily originate from:
	+ the skin: epitheliotropic and non-epitheliotropic lymphomas (T lymphocytes)
	+ mucous membranes, mainly of the gastrointestinal tract: they may be derived from B lymphocytes or T lymphocytes
	+ subcutaneous and mesenteric lymph nodes (B, T, NK lymphocytes)
	+ spleen
	+ thymus

**Lymphoid lymphoma (*lymphoma lymphonodi*)**

Grossly: lymph nodes are enlarged:

* lymph nodules fuse, forming thick clusters of neoplastic tissue
* on the cross-section, lymph nodes are whitish, the parenchyma often has pulpy consistency, necrosis foci are present, sometimes blood extravasations
* The microscopic image depends on the length of the neoplastic process:
	+ initially, neoplastic cell infiltration is visible in the form of foci, streaks **(nodular, focal form)**
	+ over time, they start to dominate the lymph node, then uniform masses of neoplastic lymphoid cells infiltrating the entire lymph node are found **(diffused, infiltrating form)**
* neoplastic cells can penetrate the lymph node capsule and infiltrate surrounding tissues
* neoplastic cells may originate from lymphocyte line cells of different maturity: small lymphocytes, lymphoblasts, centrocytes, centroblasts, immunoblasts
* depending on the size of neoplastic cell nuclei, lymphomas are classified as small lymphocytic lymphomas (nuclei size: 1-1.5 RBC), intermediate lymphocytic lymphomas (nuclei size: 1.5-2 RBC) and large lymphocytic lymphomas (nuclei size: 2 RBC and greater). Mixed forms are also possible

**Large lymphocytic lymphoma of the lymph node**

* the architecture of the lymph node is obliterated (the structure of the lymph nodules, the paracortical zone, sinuses and medullary cords is completely invisible)
* atypical lymphocytes cross the lymph node capsule, infiltrating adjacent adipose tissue
* atypical lymphocytes have large nuclei (about 2 RBC, sometimes larger than 2 RBC, round or slightly irregular, the nucleoli are numerous and peripheral (corresponding to centroblasts) or a solitary, large central nucleolus is observed (corresponding to immunoblasts)
* numerous figures of mitotic division are visible
* atypical cell cytoplasm is scanty
* numerous macrophages phagocytising cellular debris give the histological image a starry sky appearance
* they indicate a large number of apoptotic neoplastic cells

**Large lymphocytic lymphoma (liver)**

Grossly: lymphoma affecting the liver may lead to its enlargement, and because the neoplastic cells are located around the central veins and portal areas, accentuated lobular structure is present.

Microscopically: atypical large lymphocytes infiltrate liver parenchyma with obliteration of its architecture, accompanied by numerous macrophages (Kupffer-Browicz cells) loaded with blood pigments.

**Alimentary/gastrointestinal lymphomas**

* gastrointestinal lymphoma in dogs is much less frequent than multicentric lymphoma (causing generalized lymphadenomegaly and/or affecting liver/spleen/bone marrow)
	+ represents about 5-7% of all lymphomas in this animal species
	+ males are predisposed to the disease
	+ it can develop at any age, but usually affects middle-aged or older dogs
	+ it occurs mainly within the small intestine, less frequently within the stomach and the large intestine
	+ may be derived from lymphocytes B or T
	+ large lymphocyte lymphomas are more common (unlike in cats)
	+ prognosis is grave, dogs rarely survive longer than 6 months after diagnosis
* gastrointestinal lymphomas also occur in horses (T-cell rich large B-cell lymphoma, and T-cell lymphomas), and in other animal species

**Feline gastrointestinal lymphomas**

* gastrointestinal lymphoma is the most common form of lymphoma in cats
* it occurs in older cats, usually FeLV-
* the most common type of gastrointestinal lymphoma in cats is T-cell small lymphocytic lymphoma
	+ may emerge as consequences of chronic inflammatory bowel disease (IBD)
	+ in most cases, it is observed within the jejunum
	+ is a slowly progressing lymphoma, and relatively long survival periods are reported
	+ its characteristic feature is its location within the mucosa (but may also infiltrate deeper layers of the intestinal wall) and epitheliotropism (infiltration of the covering epithelium and intestinal glands)
* the second most frequent is T-cell large lymphocytic lymphoma, also most frequently found within the jejunum
* large granular lymphocyte, derived from T-cells or NK cells is also observed, often with a leukemic course
* lymphomas originating from the stomach and the area of the ileo-cecal-colic junction more often derive from B-cells (and large lymphocytes)

**Intestinal small lymphocytic lymphoma**

* atypical small lymphocytes may massively infiltrate mucosa and submucosa, reaching the muscle tissue (they may also only infiltrate mucosa, reaching submucosa)
* atypical small lymphocytes can surround intestinal glands, they can also infiltrate them
* atypical lymphocytes infiltrate the intestinal villi leading to their widening, deformation and fusion
* atypical cells have round hyperchromatic nuclei, demonstrate low mitotic activity (no visible figures of mitotic division)

**Cutaneous lymphomas**

* Cutaneous lymphomas are quite rare skin diseases, classified into epitheliotropic lymphomas and non-epitheliotropic lymphomas
* they can occur in different animal species

**Epitheliotropic lymphoma**

* occurs in dogs, rarely in cats, usually in older animals (but also in other species of animals)
* generally derived from T-cells
* neoplasm infiltration covers the skin, neoplastic cells demonstrate epitheliotropism (infiltrate epidermis and skin appendages)
* in dogs, it represents up to 1% cutaneous tumours, it is a progressive disease, developing within several months up to 2 years
	+ four clinical categories are observed: exfoliative erythroderma, mucocutaneous localization, solitary or multiple plaques or nodules, ulcerative disease of the oral mucosa
	+ it can probably develop in atopic dermatitis sites
* atypical lymphocytes massively infiltrate epidermis, forming the so-called Pautrier’s microabscesses
* atypical lymphocytes have large nuclei and round or irregular nucleoli are often numerous, peripheral
* numerous figures of mitotic division are visible
* Demodex mites are sometimes present in the follicar lumen. Demodicosis is sometimes diagnosed as a complication of neoplastic diseases, it can develop as a result of immunosuppression

**Non-epitheliotropic lymphoma**

* may occur as a primary tumour, or as part of systemic (diffuse) lymphoma
* it occurs in dogs and cats
* it is more frequent in cats than epitheliotropic lymphoma, while in dogs it is less frequent
* infiltration of neoplastic lymphocytes – most often T-lymphocytes – does not demonstrate epitheliotropism
* solitary or multiple tumours, often accompanied by lymphadenopathy
* in the case of solitary tumours, surgical excision may lead to recovery, but most cases have a rapid course, with metastases to lymph nodes and internal organs
* neoplastic infiltration is found deeply in the skin and subcutaneous tissue, the cells form packets, and are located perivascularly
* neoplastic cells usually do not infiltrate hair follicles or epidermis (no epitheliotropism)

**Epidermal neoplasms**

1. **Neoplasms derived from the covering epithelium** (skin, mucous membranes):
* benign: **papilloma**
* locally malignant: **basal cell carcinoma**
* malignant: **squamous cell carcinoma**
1. **Cancers originating from glands** (for example, cutaneous glands**)**:
* benign – adenomas:
	+ **sebaceous adenoma**
	+ **Meibomian adenoma**
	+ **hepatoid gland adenoma**
	+ **apocrine adenoma**
	+ **ceruminous adenoma**
* malignant – adenocarcinomas:
	+ **sebaceous carcinoma**
	+ **Meibomian carcinoma**
	+ **hepatoid gland carcinoma**
	+ **apocrine carcinoma**
	+ **ceruminous carcinoma**

**Papilloma**

* benign neoplasm, may have a viral aetiology (papillomavirus) or occur spontaneously
* viral papilloma is more common in young animals and may occur as multiple lesions
* most lesions undergo spontaneous regression and do not require treatment
* in the case of spontaneous papilloma, surgical excision leads to recovery
* this neoplasm originates from the epithelium, and its stroma is built of connective tissue rich in blood vessels, growing into the parenchyma of the tumour in the form of finger-like processes
* the type of the epithelium from which papilloma is derived depends on its location:
	+ cutaneous papillomas are derived from keratinized stratified squamous epithelium – **hard papillomas** (stroma is formed by the solid fibrous tissue)
	+ papillomas of the buccal, throat, larynx, and oesophagus mucosa originate from the non-keratinized stratified squamous epithelium – **soft papillomas** (limp, richly vascular stroma)
	+ gastrointestinal papillomas from simple columnar epithelium
	+ urinary bladder papillomas from transitional epithelium (often transform into carcinomas)
* papilloma forms numerous polyp, villiate, cauliflower-like structures, growing on the surface of the skin or mucous membranes – **exophytic growth**
* less frequently, it grows downward, e.g. in the upper respiratory tract – **endophytic growth (inverted papilloma *papilloma inversum*)**
* the neoplasm can be bond to the surface with a wide base or it can be thin and long – **pedunculated papilloma** **(*papilloma pendulum*)**
* papillomas are solitary or multiple tumours **(*papillomatosis universalis*)**, grow slowly and do not infiltrate the substrate
* in cutaneous papilloma, the parenchyma of the neoplasm is formed of keratinized stratified squamous epithelium, showing features of hyperplasia and hyperkeratosis, containing all layers of cells, i.e. starting from the basement membrane:
	+ **stratum basale cells** – cylindrical, cubic cells with large nucleus and small amount of cytoplasm
	+ **stratum spinosum cells** – polygonal, large nucleus, more cytoplasm
	+ **stratum granulosum cells** – often several layers, they are polygonal, flattened, tightly adhered to each other, with keratohyalin granules in the cytoplasm
	+ **stratum lucidum** **cells** – very flat, few organelles
	+ **keratinized cells**
* it is often hyper-keratinized and then referred to as ***keratopapilloma***
* connective tissue stroma, in the form of finger-like processes, penetrates the parenchyma of the neoplasm
* buccal mucosa papilloma looks similar (but its stratified arrangement corresponds to non-keratinized stratified squamous epithelium)

**Viral papilloma**

* cytopathic effects of the virus include:
	+ koilocytes – keratinocytes with pyknotic nuclei and vacuolated bright cytoplasm – present in stratum spinosum and stratum granulosum
	+ presence of giant keratohyalin granules in the keratinocytes of stratum granulosum
	+ presence of intranuclear inclusion bodies at the edge of stratum corneum

**Basal cell tumours**

Basal cell tumour is a collective term for:

1. Neoplasms originating from the germinal layer of the epidermis
* **Basal cell tumour/basalioma**; benign neoplasm
* **Carcinoma basocellulare**;locally malignant neoplasm
1. Neoplasms originating in the germinal layer of hair follicles (benign tumours)
* **Trichoblastoma**
* **Infundibular keratizing acanthoma**
1. Neoplasms originating from the germinal layer of the cutaneous glands, i.e. **epitheliomas (*epitheliomata*)**, which are locally malignant neoplasms

Differentiation of these tumours in the cytological image is difficult, histopathological examination is necessary.

**Trichoblastoma**

* benign neoplasm, quite common in dogs and cats
* is derived from germinal cells of hair follicles
* grows as a well-circumscribed lesion, hairless, not infiltrating the surrounding tissues
* histological types:
	+ **ribbon type**
	+ **with outer root sheath differentiation**
	+ **trabecular type**
	+ **spindle cell type**

**Ribbon type trichoblastoma**

* oval cells with a serial, sometimes medusoid arrangement, with a high nuclear-cytoplasmic ratio
* sometimes quite numerous figures of mitotic division
* oval, round nuclei, usually with finely stippled chromatin
* scanty cytoplasm
* stroma can be quite abundant, often with oedema

**Basal cell carcinoma *(carcinoma basocellulare)***

* locally malignant neoplasm (does not give metastases, but recurrences are frequent)
* derives from the cells of the basal layer of the epidermis
* often occurs in dogs and cats in the skin of the head area, especially eyelids, nose
* has the form of single, less frequently, multiple tumours, well-circumscribed but unencapsulated, it can also evenly infiltrate the dermis
* the parenchyma of the neoplasm is formed of cells derived from the basal layer cells of the epidermis, they are slightly larger than normal, with a cylindrical, cubic or oval shape
* neoplastic cells have a large, chromatin-rich nucleus (hyperchromasia) and scanty cytoplasm
* they form relatively regular nests or strands, with palisade arrangement of cells at the periphery
* the centre of neoplastic islands sometimes undergoes regressive changes
* connective tissue stroma is variably abundant and may contain cellular infiltrations

**Squamous cell carcinoma (*carcinoma planoepitheliale*)**

* malignant neoplasm derived from the stratified squamous epithelium
* often found in the skin and oral mucosa of cats, but also occurs in dogs
* tumours most often develop in older animals, in light-coloured cats, in short-haired breeds of white or multi-coloured dogs
* they grow infiltrating the surrounding tissues
* have a quite low metastatic potential
* Grossly: squamous cell carcinomashave the form of tumours, infiltration, papillary or cauliflower-like formations often ulcerated
* the parenchyma of the neoplasm is made up of cells proliferating in the form of nests, binding with each other; the cells show a variable degree of keratinization depending on the degree of differentiation
* based on the degree of differentiation of cancer cells, four malignancy grades are distinguished:
	+ well-differentiated squamous cell carcinomas (grade I)
	+ moderately differentiated squamous cell carcinomas (grade II)
	+ moderately differentiated squamous cell carcinomas (grade III)
	+ poorly differentiated squamous cell carcinomas (grade IV)
* in **well-differentiated squamous cell carcinomas,** the arrangement and the appearance of cells in the clusters resembles normal epidermis, with polygonal, non-keratinized cells resembling the cells of stratum basale and stratum spinosum of the epidermis at the perimeter of the foci which in more central areas are polygonal, larger and keratinized; in the very centre of the foci, keratinized cells are flattened, sometimes without nuclei; they are arranged concentrically, forming spheres of various sizes (resembling the cut surface of an onion), the so-called ‘**squamous pearls’.** The formation of squamous pearls is the result of three processes, i.e.:
	+ hyperkeratosis
	+ defective keratosis
	+ unification of excessively built-up carcinoma cells; central areas often become necrotic
* in **poorly differentiated squamous cell carcinomas,** the cells are anaplastic, demonstrate a higher mitotic activity, with numerous atypical division figures; the cells of these carcinomas are less mature and have a limited ability to produce keratin; no squamous pearls are then observed in the tumour parenchyma, but, features of dysceratosis of single cells or foci of partially keratinized cells may be visible.
* moderately differentiated squamous cell carcinomas (grade II, grade III) present intermediate forms between the above-described types
* connective tissue stroma is usually affected by desmoplasia, inflammatory cell infiltrations are frequent

**Adenoma**

* benign neoplasm, derived from the glandular tissue, of:
	+ tubular structure **(*adenoma tubulare*)**
	+ follicular structure (***adenoma folliculare s. alveolare*)**
	+ mixed structure **(*adenoma tubulo-folliculare s. adenoma mixtum*)**
* neoplastic glands can produce secretion, and since they generally have no excretory ducts, it accumulates in large quantities, causing the gland to expand **(cystadenoma)**
* stroma of the neoplasm is formed of simultaneously growing connective tissue
* grossly: adenomas have the form of polyps, especially if they occur on the surface of the mucous membranes or the skin, or as solid, tumours or nodules, encapsulated, of a spherical shape growing deep inside the organs (ovary, mammary gland, thyroid)

**Perianal gland adenoma / hepatoid gland adenoma *(adenoma glandulae perianales)***

* a benign neoplasm derived from the perianal (hepatoid) glands
	+ perianal glands occur **in dogs** in the skin of the anal, femoral, gluteal, perineal and tail regions (scattered skin glands)
* the neoplasm grows slowly, develops under the influence of androgens – castration is recommended at surgical excision of the tumour (in case of males)
* it is much less frequent in females
	+ the literature describes the occurrence of multiple perianal glandular adenomas in a sterilized bitch as a consequence of hypertestosteronism caused by pituitary-dependent hyperadrenocorticism
* a lobular tumour built of hepatoid cells with abundant eosinophilic cytoplasm
* a layer of basaloid reserve cells occurs on the perimeter of the lobes.

**Adenocarcinoma**

* malignant epithelial neoplasm, derived from the glandular epithelium of mucous membranes, excretory ducts of the glands and cysts lined by glandular epithelium (e.g. ovarian adenocarcinoma)
* the glandular carcinoma mimics glandular ducts **(*adenocarcinoma tubulare*)** or the glandular follicles **(*adenocarcinoma alveolare*),** but they have an irregular shape and arrangement, with a larger number of cells, often built-up, with hyperchromatic nuclei
* carcinoma cells divide rapidly and atypically, growing into the stroma they destroy their basement membrane, the less differentiated they are, the less glandular structure is visible
* in case the ducts and the follicles alveoli have no lumen, the neoplasm is referred to as **solid adenocarcinoma (*adenocarcinoma solidum*)**
* if mucus is produced, the neoplasm is referred to as **mucus adenocarcinoma (*adenocarcinoma muciparum*)**
* sometimes mucus can be deposited in carcinoma cells, pushing their nuclei to the periphery (signet ring cells); in this case the lesion is referred to as **signet-ring cell carcinoma (*adenocarcinoma mucocellulare*)**
* the connective tissue parenchyma is usually scanty or divides the tumour parenchyma into lobules
* the parenchyma of the neoplasm may undergo regressive changes (mainly necrosis), cell infiltration (lymphocytes, histiocytes, plasmocytes) is often observed in the stroma
* adenocarcinomas often occur in the mammary gland, gastrointestinal tract, reproductive system, lungs, exocrine and endocrine organs.

**Mammary gland neoplasms**

1. **Benign:**
* Simple adenoma **(*adenoma simplex*) –** benign neoplastic proliferation of glandular cells
* complex adenoma **(*adenoma complex*; previously referred to as *fibroadenoma*)** – benign proliferation of glandular cells and proliferation of myoepithelial cells, fibroblasts
* benign mixed tumour **(tumor mixtum benignum) –** benign proliferation of glandular cells and proliferation of myoepithelial cells, fibroblasts, with the additional presence of bone and cartilage metaplasia
1. **Malignant:**
* non-invasive, usually ductal carcinoma in situ **(*carcinoma in situ*)** – malignant neoplastic proliferation of glandular cells that do not spread beyond the basement membrane
* simple carcinoma **(*carcinoma simplex*)** – malignant neoplastic proliferation of glandular cells that spread beyond the basement membrane (infiltrating growth):
	+ tubopapillary carcinoma ***(carcinoma tubulopapillare*)**
	+ solid carcinoma **(*carcinoma solidum*)**
	+ anaplastic carcinoma **(*carcinoma anaplasticum*)**
* complex-type carcinoma **(*carcinoma complex*)** – malignant neoplastic proliferation of glandular cells and proliferation of myoepithelial cells, fibroblasts
* mixed-type carcinoma – malignant neoplastic proliferation of glandular cells, proliferation of myoepithelial cell, fibroblasts, and the presence of bone, cartilage, myeloma metaplasia, hyalianization
* **carcinosarcoma** –malignant neoplastic proliferation of glandular cells and malignant proliferation of stromal cells (fibroblasts)