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Cutaneous Neoplasia: Part 1

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Introduction

In clinical veterinary practice, cutaneous neoplasia is frequently presented to you as a clinician, as the skin is something owners can see on a day-to-day basis. Histopathology forms the cornerstone of effective clinical oncology – as it is the primary tool in diagnosis. An integrated histopathology report allows for presentation of relevant prognostic information to animal owners, for them to make informed decisions about their animals' health regarding likely success of treatment modalities, cost and welfare issues. It also enables selection of the most relevant and effective therapeutic protocols for individual patients (e.g. surgery, chemotherapy, radiation etc.).

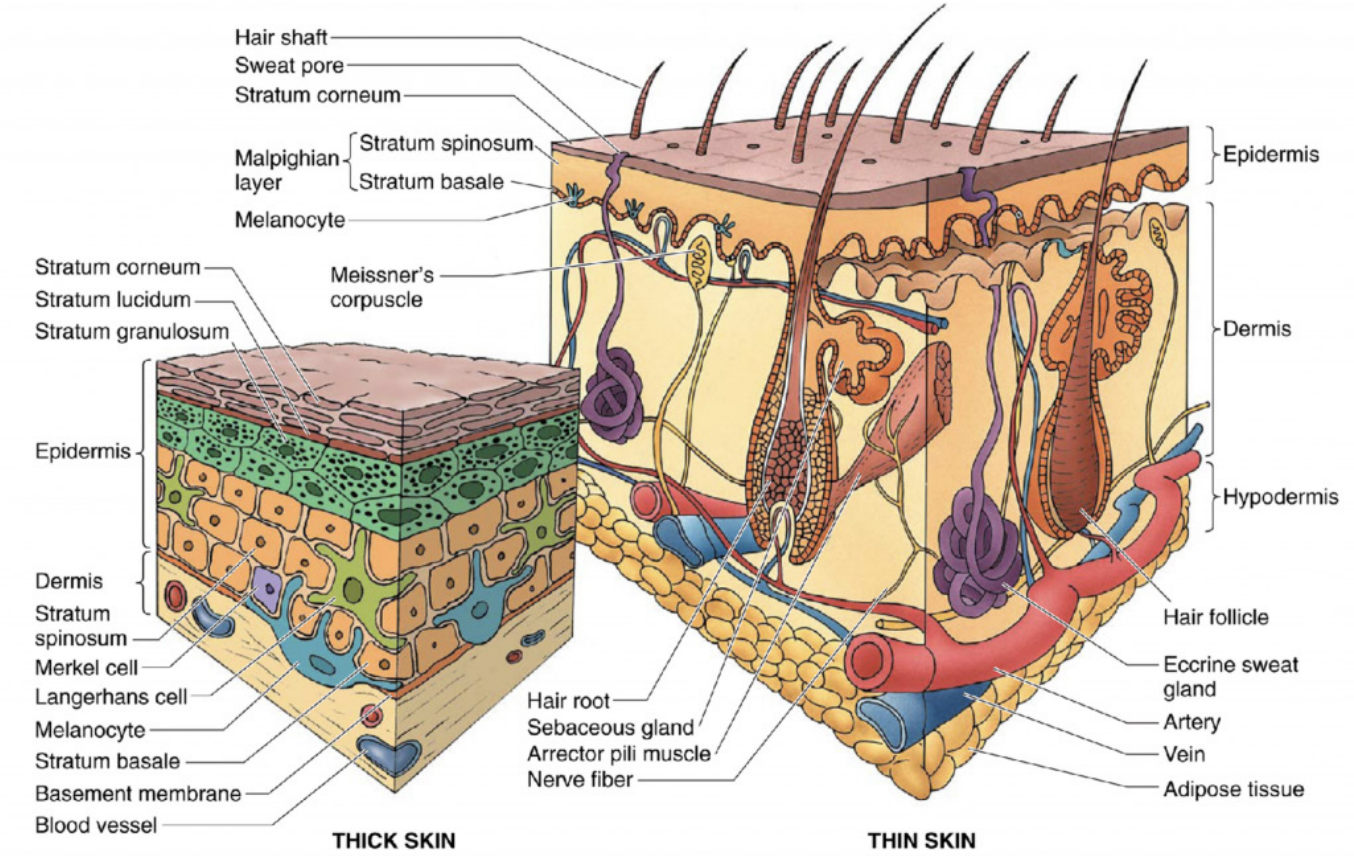

Figure 1. Normal histology structures of skin.

Just follow the normal histological structures of the skin to establish your list of most common cutaneous neoplasms for example

- Neoplasms of the epidermis.
- Neoplasms of the hair follicles.
- Neoplasms of the adnexal glands (sweat glands, sebaceous glands)
- Neoplasms of mesenchymal tissue (collagen, blood vessel, nerve).
- Neoplasms of resident inflammatory cells (mast cells, histiocytes, dendritic cells).

Nomenclature of cutaneous tumours

The particular name bestowed on a tumour is based on the specific cell of origin from which neoplasm has arisen. This cell of origin actually forms the basis of clonality. Polymerase chain reaction (PCR) based clonality testing is emerging as a useful diagnostic technique with certain tumours, for example PAAR (PCR for antigen receptor rearrangements), which helps distinguish inflammatory from neoplastic lymphoid cells.

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The anatomical sites where tumours are found are also important components of the nomenclature, as the same type of tumour may behave in very different ways at different anatomical locations. For example **cutaneous** squamous cell carcinomas are far less aggressive tumours than **tonsillar** squamous cell carcinomas, which carry a poor prognosis. The name assigned to a tumour generally indicates if it is **benign** or **malignant**.

Epithelial		Mesenchymal
Benign	…oma(or papilloma if papillary) adenoma (if glandular)	…oma
Examples *Exceptions* • *haematoma* • *granuloma*	Squamous papilloma Laryngeal papilloma Thyroid adenoma Prostatic adenoma Mammary adenoma	Fibroma Haemangioma Lipoma Chondroma Osteoma
Malignant	carcinoma Adenocarcinoma (glandular)	...sarcoma
Examples *Exceptions* • *seminoma* • *melanoma*	Squamous cell carcinoma Thyroid adenocarcinoma Prostatic (adeno) carcinoma Breast adenocarcinoma	Fibrosarcoma Haemangiosarcoma Liposarcoma Chondrosarcoma Osteosarcoma

Figure 2. Nomenclature of neoplasms.

Cutaneous Tumour Staging vs Tumour Grading

Tumour staging is a clinical procedure making use of clinical assessment, cytology and histopathology and can be performed on all tumours. Clinical grading on the other hand is exclusively used in histopathology and only certain tumours (e.g. mast cell tumours) can be graded.

Clinical Staging

Stage	Definition
Tis	In situ, non-invasive (confined to epithelium)
T1	Small, minimally invasive within primary organ site.
T2	Larger, more invasive within primary organ site.
T3	Larger and/or invasive beyond margins of primary organ site.
T4	Very large and/or very invasive, spread to adjacent organs.
N0	No lymph node involvement.
N1	Regional lymph node involvement.
N2	Extensive regional lymph node involvement
N3	More distant lymph node involvement
M0	No distant metastases
M1	Distant metastases present

Figure 3. Clinical tumour staging.

- **Simple/basic staging** – detailed physical examination looking for new cutaneous lesions and regional lymph node involvement. If regional lymph node involvement confirmed or primary tumour located at site with potential drainage to internal nodes then complete staging recommended.
- **Complete staging** = basic staging + diagnostic imaging. If metastasis suggested then move to extended staging.
- **Extended staging** = cytological examination of suspected metastatic lesions and compare to primary mass histopathology + bone marrow cytology.
- All tumours can be staged.

Tumour Grading

Tumour grading systems are designed specifically to estimate probable biological behaviour of a particular type of tumour, based on its histopathological features which;

- Enables selection of appropriate therapeutic options.
- Can predict likely outcomes with various treatment modalities.
- Guestimate survival times based on published data.

Currently there are histological grading systems available for various cutaneous tumours (mast cell tumours, melanomas, lymphomas, soft tissue sarcomas), but remember not all cutaneous tumour types can be graded.

Classification System of the Cutaneous Neoplasms.

1. Cysts, hamartomas and tumour-like lesions

2. Benign and malignant epithelial neoplasms
   - Epidermal
   - Follicular
   - Adnexal glands (sebaceous glands, sweat glands).

3. Round cell tumours
   - Plasmacytic
   - Lymphocytic
   - Histiocytic
   - Mastocytic
   - Melanocytic

4. Benign and malignant mesenchymal neoplasms
   - Soft tissue
   - Vascular
   - Neural
   - Other (lipoma, infiltrative lipoma, liposarcoma)

5. Metastatic dermal lesions.

1.1 Cysts

Cysts are sac-like structures that are lined by an epithelial lining. They can arise from hair follicles, apocrine/eccrine glands and sebaceous gland ducts. Cysts are benign, however can elicit a marked inflammatory reaction if they leak or rupture and this can

impart a gross appearance of a malignant process. Complete local surgical excision is usually curative.

More common types of cutaneous cysts include:

- Isthmus follicular cyst.
- Infundibular follicular cysts.
- Dilated pore of Winer.
- Keratomas.
- Apocrine cysts.
- Apocrine cystadenoma.

1.2 Hamartomas

Benign tumour-like nodules composed of histologically normal mature tissue, which is disorganised, present in excessive amounts or abnormally enlarged. Complete local surgical excision is usually curative.

The more common types of cutaneous hamartomas include

- Fibroadnexal hamartomas
- Collagenous hamartomas
- Sebaceous gland hamartomas
- Apocrine gland hamartomas.

1.3 Non-neoplastic tumour-like lesions.

- Idiopathic squamous papilloma. Anatomical predilection sites include eyelids, face, conjunctiva, paw pads (dogs>cats), penile (horses). No viral component has been demonstrated.
- Cutaneous horn. Cylindrical formations of keratin that extend from the epidermis outwards (exophytic growth).
- Fibro-epithelial polyp (skin tag). Portion of dermis containing redundant dermal collagen which lacks follicular and adnexal structures.

2.1 Epidermal neoplasms (benign/malignant).

2.1.1 Viral papillomas

Induced by specific papilloma viruses. Immunocompromised animals are more susceptible and they are seen more commonly in younger versus older animals.

Tumours can regress depending on a cell-mediated generated attack.

Animals with good CMI responses rid themselves of the tumours, while in animals with impaired CMI responses tumours tend to persist. Development of multiple lesions due to PV is common.

There is potential for viral papillomas to progress to more invasive subtype, although this is the exception rather than the norm.

Cutaneous papilloma viral infections may also be associated with squamous papilloma, inverted viral papilloma, feline viral plaques, canine pigmented viral plaques, Bowenoid *in situ* carcinoma, invasive squamous cell carcinoma, fibropapillomas, and feline and equine sarcoids.

Species	
Cattle	•BPV-1 –PV on teats and penis •BPV-2 –fibropapillomas on head, neck, dewlap, shoulder •BPV-5 –Teat frond warts •Bovine papillomatosis
Horses	•3 distinct clinical syndromes •Classic–verrucous mass on muzzle and lip <3 years of age. Spontaneous remission in ~2-3 months. •Genital papillomas–associated with malignant transformation to SCC •Ear papillomas (aural plaques) –confined to pinna. Rare, spontaneous remission. •Sarcoids discussed in mesenchymal neoplastic section.
Dog	•Cutaneous (exophytic) papillomas–most common. Mainly on head, eyelids and paw. These lesions can spontaneously regress •Cutaneous inverted papillomas – more common in adult dogs. Mainly on ventral abdomen, groin>limbs and digits. Most do not spontaneously regress. •Canine pigmented plaques – possibly heritable due to breed predisposition (e.g. miniature schnauzers, pugs). Most common on ventral abdomen and groin.
Cat	•Cutaneous papillomas and viral plaques are rare in cats. •Bowenoid in situ carcinoma.

Figure 4. Cutaneous Papillomaviruses of domestic animals.

2.1.2 Cutaneous squamous cell carcinoma.

These are common cutaneous neoplasms of animals which are generally locally invasive, but do occasionally metastasise to the regional lymph nodes and lungs.

There is a strong association with UV radiation induction and promotion and so they are commonly seen in geographical regions with high average daylight hours of sunshine. Tumours are often accompanied by features of solar dermatitis. Some useful facts about SCC include

- In sun-bathing dogs, distribution of lesions is ventral abdomen and inner legs.
- In cats sunlight associated SCC occurs most commonly on the head (ear tips, nose) and tumours are frequently multiple.
- Digital SCC arising from the nailbed (subungual) have a high potential for metastasis, although not as high as digital SCC arising from non-subungual sites. The majority are cured by complete removal via digital amputation before progression of the neoplasm.

Feline Bowenoid *in situ* carcinoma is associated with papillomavirus (PV) infection and seen at sun protected sites.

2.2 Follicular (hair follicle) neoplasms.

The most commonly encountered hair follicle tumours are:

- Infundibular keratinising acanthoma (IKA)

- Trichoepithelioma (malignant trichoepithelioma)
- Trichoblastoma. Common in dogs and less common in cats. Predilection sites include head, neck and back.
- Pilomatricoma (malignant pilomatricoma)

All of these neoplasms are amenable to complete surgical excision. Due to the presence of keratin, these neoplasms can rupture leading to granulomatous inflammation, as the keratin which is normally "immunologically" protected within the hair follicle, is released into the dermis where it acts as a foreign body.

2.3 Adnexal gland tumours.

2.3.1 Sebaceous gland tumours.

There are classical and modified sebaceous glands which occur in the skin and all may be affected by hyperplasia, benign and malignant neoplasia.

Sebaceous glands	Modified Sebaceous Glands
•Sebaceous gland hyperplasia •>50% of all sebaceous gland tumours •Cocker spaniels and poodles •Head, eyelids, trunk and limbs •Lesions are waxy to hyperkeratotic.	**•Meibomian gland (eyelids)** •Hyperplasia •Adenoma •Epithelioma •Carcinoma.
•Sebaceous adenoma •Grossly similar to sebaceous hyperplasia.	**•Perianal (hepatoid glands) of the perianal ring** •These neoplasms are believed to hormonally driven. •Recommendation for intact males with multiple lesions is castration. •Hepatoid gland hyperplasia vs hepatoid gland adenoma •Hepatoid gland epitheliomas – low-grade malignancy. •Hepatoid gland carcinomas – Uncommon. Metastasis to regional lymph nodes in 30% of cases.

Figure 5. Sebaceous and modified sebaceous gland growth disturbances.

Hepatoid gland adenomas are sometimes found at aberrant sites including;

- Base of tail.
- Dorsal lumbosacral area.
- Lateral prepuce / vulva.
- Ventral midline.

2.3.2 Sweat gland tumours.

Apocrine gland	Eccrine gland

• **Apocrine cystadenoma**
  • Mass containing multiple cysts
  • Cats>dogs
  • Head, ear canal and eyelid
  • Himalayan and Persian cats can get multiple lesions
	• Extremely rare
	• Arise from the foot pads of dogs and cats
	• Aggressive neoplasms that often locally recur and may metastasise to the regional lymph nodes and lungs.

• **Apocrine adenoma** • Amenable to complete surgical excision	

• **Apocrine gland adenocarcinoma**
  • Dogs – legs
  • Cats – head, legs and abdomen
  • Lymphatic, regional lymph node and pulmonary metastasis have been reported	

• **Ceruminous gland neoplasms**	

• **Anal sac gland adenocarcinoma**
  • Unilateral or bilateral
  • Paraneoplastic hypercalcaemia
  • Metastasis is common to lymph nodes, lung, spleen, liver and bone (50-80%)
  • Tend to grow into the pelvic canal. Only ~50% of cases grossly seen.	

Figure 6. Sweat gland tumours.

3.1 Plasma cell tumours.

Plasma cell tumours are benign dermal neoplasms. They are common in dogs, but rare in cats. Middle-aged to older dogs are most commonly affected and there is a site predilection for feet, ear canal and oral cavity. Some animals are predisposed to developing multiple cutaneous or oral lesions. Some but not all of these tumours contain amyloid. They are cured by complete surgical excision.

3.2 Histiocytic Diseases.

Table: Canine and feline histiocytic diseases

Disease	**Species**	**Cell of origin**
Histiocytoma	Dog	Langerhans cell
Cutaneous LCH	Dog	Langerhans cell
Cutaneous histiocytosis	Dog	Activated interstitial DC
Systemic histiocytosis	Dog	Activated interstitial DC
Histiocytic sarcoma	Dog, cat	Interstitial DC
Histiocytic sarcoma – haemophagocytic	Dog, cat	Macrophage
Feline progressive histiocytosis	Cat	Interstitial DC
Pulmonary Langerhans cell histiocytosis	Cat	Langerhans cell

Courtesy of Meuten – *Tumours in Domestic Animals*. 5th edn 2016.

3.2.1 Canine cutaneous histiocytoma

Very common dermal neoplasms of young dogs (< 3 years of age), but may be uncommonly found in middle aged and old dogs. These are benign tumours which may arise anywhere within the dermis. They usually undergo spontaneous immune-mediated regression. They are most commonly encountered on the head, pinna and feet. They are amenable to complete surgical excision. They can look pleomorphic and very anaplastic "scary" on FNA to the untrained eye (e.g. high mitotic index, pleomorphic).

3.2.2 Langerhans cell histiocytosis (multiple histiocytomas).

This is a progressive cutaneous condition with the development of multiple cutaneous masses, which histologically are indistinguishable from histiocytoma. There is frequent regional lymphnode involvement. They are also found at mucocutaneous junctions and within the oral cavity. Systemic involvement is rare, but well documented. The Shar-pei breed is over-represented with this condition.

3.2.3 Histiocytic sarcoma (HS)

Typically presents as a solid lesion on the extremities. When HS spreads beyond the regional lymphnode to a distant site, it is then referred to as disseminated HS. If identified and treated early with complete surgical excision or limb amputation, prior to lymphnode spread, the prognosis is more favourable. Those treated aggressively with surgery and chemotherapy have a reported medial survival time of 1-1.5 years. This condition is well recognised in Bernese mountain dogs, but has also been reported in other breeds including Rottweiler, golden retriever and flat coated retriever. Clinical signs can be vague, especially if disseminated (e.g. coughing, weight loss, anorexia, lethargy).

3.2.4 Canine cutaneous reactive histiocytosis

There are two specific diseases that fall within this reactive histiocytosis and they are canine cutaneous reactive histiocytosis and systemic reactive histiocytosis. As the name suggests these are reactive and not neoplastic conditions, believed to be aberrant immune mediated diseases. Cutaneous reactive histiocytosis primarily involves skin and subcutis of young to middle aged dogs. Lesions typically do not extend beyond the local draining lymph node. If lesions do spread beyond the draining lymphnode, then the condition becomes systemic reactive histiocytosis. It is important to note that not all cutaneous reactive histiocytic cases progress to systemic reactive histiocytosis.

Solitary skin lesions are uncommon with multiple cutaneous nodules being the more common presentation. Lesions can regress and develop at new sites, or wax and wane overtime. Spontaneous regression has also been known to occur. Prognosis is good for survival, however is guarded without long-term immunomodulatory therapy. These tumours exhibit specific histologic features and unique immunohistochemical findings.

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QUESTION 1

Which of the following statements about tumour staging is INCORRECT?

a. Simple / basic staging involves a detailed physical examination looking for new cutaneous lesions and regional lymphnode involvement
b. If regional lymphnode involvement is confirmed or the primary tumour is located at site with potential drainage to internal nodes then complete staging recommended
c. Complete staging composes basic staging + diagnostic imaging. If metastasis suggested then move to extended staging
d. Extended staging involves cytological examination of suspected metastatic lesions and compare to primary mass histopathology + Bone marrow cytology
e. Not all tumours can be staged

QUESTION 2

Which of the following tumours would not be considered a benign cutaneous neoplasm?

a. Sebaceous adenoma
b. Melanoma
c. Apocrine adenoma
d. Squamous papilloma
e. Thyroid adenoma

QUESTION 3

Cutaneous papillomavirus infection can lead to all of the following tumours EXCEPT?

a. Viral pigmented plaques
b. Bowenoid in-situ carcinoma
c. Fibrosarcoma
d. Squamous cell carcinoma
e. Sarcoid

QUESTION 4

Which of the following is a benign non-neoplastic lesion?

a. Fibro-epithelial polyp
b. Haemangioma
c. Meibomian gland adenoma
d. Sarcoid
e. Trichoblastoma

QUESTION 5

Which of the following anatomical sites are most commonly affected with sunlight induced squamous cell carcinoma in cats?

a. Ventral abdomen
b. Inner legs
c. Digits
d. Nose
e. Axilla

QUESTION 6

Which of the following neoplasms is not derived from the hair follicle?

a. Infundibular keratinising acanthoma
b. Ceruminous gland tumour
c. Trichoepithelioma
d. Trichoblastoma
e. Pilomatricoma

QUESTION 7

Which of the following anatomical locations are considered the prime anatomical location for hepatoid gland tumours?

a. Peri-anal ring
b. Base of tail
c. Dorsal lumbosacral area
d. Lateral prepuce / vulva
e. Ventral midline

QUESTION 8

What is a common clinicopathological finding in dogs diagnosed with anal-sac gland adenocarcinoma?

a. Hypokalaemia
b. Lymphocytosis
c. Hypergammaglobinaemia
d. Anaemia
e. Hypercalcaemia

QUESTION 9

Which of the following cells is the cell of origin of canine cutaneous histiocytomas?

a. Activated interstitial dendritic cell
b. Interstitial dendritic cell
c. Tissue macrophage
d. Langerhans dendritic cell
e. Blood macrophage

QUESTION 10

Which of the following canine breeds shows a breed predisposition to the development of Langerhans cell histiocytosis?

a. Cocker Spaniel
b. Rottweiler
c. Shar-Pei
d. Boxer
e. Bernese mountain dogs

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