ETIOPATHOGENY, CLASSIFICATION AND PROGNOSIS OF MAMMARY TUMORS IN THE CANINE AND FELINE SPECIES

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Among all mammals, the canine species presents the highest incidence of mammary tumors. 25 to 50% of bitch tumors are mammary tumors and the frequency of this condition is considered to be 2 to 3 times higher in dogs than the one observed in humans, another species unfortunately known to have a very high incidence of mammary gland tumor. The annual incidence is considered to be as high as 5 to 10 /1000 animals! It is the most frequent tumor in the bitch, the second in importance after skin tumors in the dogs, both sexes included, and the third tumor in the cats after blood and skin tumors. The breed specificity is still controversial and the results are often influenced by the location, the fashion, the time period during which the study has been realized. The incidence seems to be increased in the Spaniels, Setters, Poodles, Labradors and Terriers, but these are also the most current breeds, whereas the incidence seems to be reduced in mongrels (hybrid strength?) , the Boxers and the Chihuahuas. Male mammary tumors are rare (<1%) and are generally secondary to the presence of another lesion including particularly Sertoli cells tumors or hormonal treatments, both having mitogenic effects on the mammary tissue and promoting mammary gland development. The mean age at detection in the bitch is around 9 to 11 years, they are rarely observed before 5 years and when they are detected so early, the lesions are more generally precancerous lesions. The frequency slowly increases from 5-7 years up to 11-12 years. In general, benign tumors are observed earlier than malignant ones.
The 5 pairs of mammary glands in dogs (4 pairs in cats) have important lymphatic and vascular connections (Table 1).

What are the main lymphatic connections

Important and direct between the last 2 pairs
The last 2 pairs directly drain the inguinal lymph nodes
There are numerous physiological anastomoses between pairs 3 and 4 and then 3-4-5 which irrigate the inguinal lymph node
There are connections between the first 3 pairs of mammary glands: direct between 2 and 3, some between 1 and 2.
There are direct connections between these 3 first mammary glands and the axillary lymph nodes.
The anterior mammary glands also drain to the cranial sternal lymph nodes
The third pair is not connected with the inguinal lymph nodes.

In normal mammary glands, there are many vascular connections between the different glands of the same chain, but also between the left and right chains of glands. However, it is important to remember that the lymphatic and vascular connections are dramatically modified in case of cancerous lesions and, depending on the tumor development, extension, type, all the lymphatic and vascular connections can be totally remodeled. For these reasons, the lymphatic and vascular connections are variable between right and left chains and between adjacent glands in the cranial and caudal directions. This is an essential aspect in the establishment of the prognosis, but also in the surgical approach that has to be further developed.

The mammary tissue is under the regulatory control of different factors, some endocrine ones like the ovarian steroids, the mammotrophic hormones and the growth factors, other ones are more paracrine and autocrine factors like GH and somatomedines, EGF and TGF which play a role in the ductal and lobulo-alveolar growths and mammary gland differentiation. The ovarian steroids are essential in mammary gland development: progesterone has some direct mitogenic effects on the epithelium and stroma, it induces full lobulo-alveolar development with hyperplasia of secretory and myoepithelial elements, it potentiates the prolactin and estrogens effects (proliferation during pregnancy), estradiol has apparently a more indirect effect through prolactin, IGF, EGF and TGF, but can also directly stimulate ductal growth. Prolactin, GH and other lactogenic factors belong to the same genomic family and still have ahigh homology and thus similar actions. They induce development and mammary gland differentiation, including lobulo-alveolar development, epithelial growth, induction of cellular and functional differentiations and lactogenesis. Prolactin could also act by increasing the cells sensitivity to the mitogenic action of the ovarian steroids and by modifying steroid receptors sensitivity and affinity. Recently, bitches' mammary glands have been demonstrated to locally produce some GH and prolactin, which may regulate mammary gland development during the estrous cycle and pregnancy. However, when considering the role of hormones in mammary gland tumorigenesis, it is certainly necessary to consider all this as a dynamic process with stages of sensitivity and some others with refractoriness to the same hormonal stimulation. Some factors may be stimulatory at some development stages and inhibitory at some other ones. The figure 2 presents the different factors playing a role in mammary gland development and tumorigenesis with their potential respective site of action.

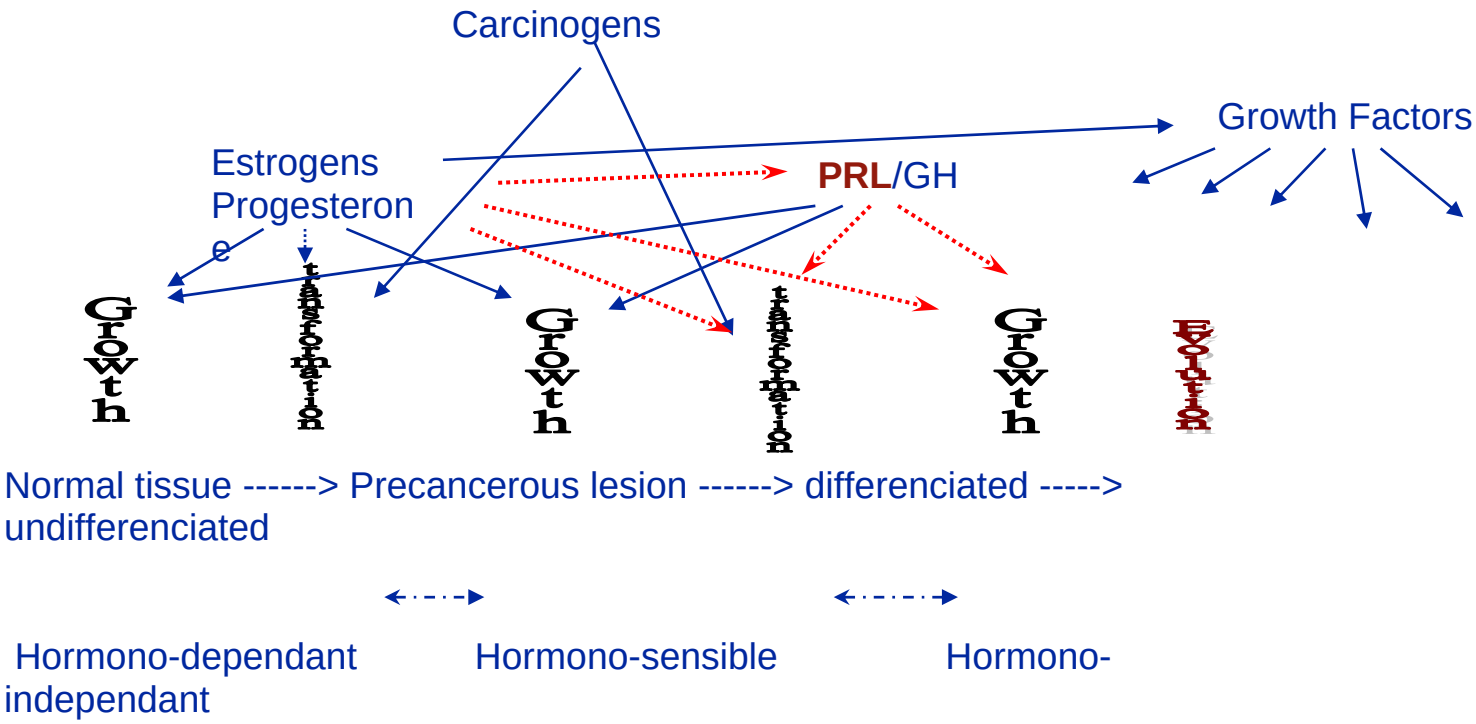


Figure 2.

In the bitch, the mammary tumors are essentially observed at the level of the last 2 pairs. However, more than 50 % of the bitches have mammary tumors on several glands simultaneously. These can either already be metastasis of primary tumors or totally independent tumors. These multiple tumors could be observed on the same mammary chain or in the 2 different chains. In the queen, the tumors are essentially observed at the level of the first mammary pairs. There is often different histological types of tumors at the same time, these can be observed either at the level of one single tumor or at the level of different tumors (50%). When tumors are observed to metastatise, they use the lymphatic pathway, essentially for the carcinomas, which are the most frequent malignant tumors, or the vascular pathway, typically for the sarcomas which are fortunately rare. In order of frequency, the lymph nodes are the first ones to be colonized, followed by the lungs, the liver (rare), the kidneys (rare), the skin (often skin metastasis for sarcomas and carcinomas with a typical small nodules fleas' bites looking appearance and often rapid extension), the brain, muscles and bones. In general, the extension of mammary tumors follows the described order, but sometime, metastasis can be observed in the skin, brain or other tissues without the presence of lung or liver metastasis.

Epidemiological factors influencing mammary gland cancerisation.

1/ The preventive effect of ovariectomy has been largely described even if there is still some controversy regarding for how long this procedure has some beneficial effects. In a retrospective study on more than 700 bitches with mammary tumors and a similar control population, the statistical analysis using the odds ratio as predictive factors of any beneficial or inducing effects, we were able to demonstrate a positive effect up to 13 year old (table 1). The ovariectomy

prevents the development of mammary tissue observed at puberty and at each ovarian cycle, inhibits the transformation of pre-neoplastic clones in neoplasms or blocks the evolution of the sub-clinical lesions (estrogen receptors?).

Age at sterilization	**Odds ratio (confidence interval 95%) - Significance of the effect**
< 3 years	0.028 (0.01- 0.084) - highly significant protective effect
$3 \leq x \leq 5$	0.082 (0.037 – 0.19) - highly significant protective effect
$5 \leq x \leq 7$	0.31 (0.12 – 0.81) – protective effect
$7 \leq x \leq 9$	0.72 (0.32 – 1.6) – no effect
> 9	0.3 (0.15 – 0.62)
All age categories together	0.23 (0.16 – 0.34)

Table 1: Odds ratio of the effect of sterilization on the incidence of mammary tumors in the bitch. Odds ratio bellow 1 indicates a protective effect, OD over 1 indicates an inductive effects. No effects are observed for the category 7 to 9 due to too few cases in this category. It is important to note that the earliest the sterilization is realized, the best it is.

2/ Progestins treatment effects on mammary tumors.
The same study demonstrated and confirmed some of the already observed observations (table 2). There is an increased risk in bitch treated repetitively and at high dosage with progestins (more than 3 treatments), the detection of the lesions is generally more precocious in progestin treated animals than in non-treated controls, there is apparently no relation with malignity. The progestins may have some effects on the sub-clinic growth and differentiation of the mammary tissue (recruiting effects of the progestins). Some of the progestins effects may be mediated by the local production of GH they have been demonstrated to induce. Some interesting studies have recently advanced some protective effects of very low doses of progestins on the development of mammary tumors. This is an interesting observation, which certainly deserves to be further studied.

Frequency of progestin treatment	**Odds ratio (confidence interval 95%) and significance**
Less than 3 treatments	1.3 (0.75 – 2.2) - non significant effect the CI, between from below to over 1
More than 3 treatments	1.6 (1-2.6) – significant effect
All treatments together	1.4 (1 – 2.1) – significant effect

Table 2: Effect of long lasting progestin treatments on the incidence of mammary tumors. Odds ratio bellow 1 indicates a protective effect, OD over 1 indicates an inductive effect.

3/ Effects of pseudopregnancy of mammary tumors in the bitch.
In our controlled study with a high number of animals (with and without tumors), the statistical analysis clearly demonstrated an increased risk of mammary tumors in animals having presented pseudopregnancies in comparison with animals without ones (table 3). Those animals have tumors detected earlier, and even more interesting, the tumors are more often malignant! This may be explained by the effects of milk retention without let-down, that induced mammary gland distension, responsible for local acini hypoxia by compression of the capillary blood vessels ;

this hypoxia is associated with the release of free radicals known to be carcinogenic. Simultaneously, in the distended mammary glands, food carcinogens directly present in the diet or produced by the local degradation/transformation of the milk, accumulate. All these carcinogens may be responsible for the induction of pre-neoplastic lesions or the development of the pre-existing lesions. A similar observation has also been realized in humans. In physiological post-partum lactation, no similar inductive effects are observed, probably due to the fact that in the lactating animals, there is no milk accumulation (let-down due to suckling) and degradation.

Frequency of pseudopregnancy	**Odds ratio (confidence interval 95%) and significance**
Rare (less than 3)	1.5 (0.96 – 2.3) – not significant but close to
Frequent (more than 3)	1.9 (1.15 – 3) – significant effect of frequent PSP on mammary tumors incidence
All categories together	1.6 (1.14 – 2.3) –significant effect of PSP in general

Table 3 : Effect of pseudopregnancy on the incidence of mammary tumors.
Odds ratio bellow 1 indicates a protective effect, OD over 1 indicates an inductive effect.

These observations indicate that the prevention of PSP is essential, not only to correct the behavioral and anatomical troubles associated with this condition, but also to help preventing mammary tumors development. Finally, figure 1 presents the possible site of action of prolactin on mammary gland development and tumorogenesis ; the role of prolactin in the pathogeny of PSP being clearly established, the use of anti-prolactinic agents in the treatment of PSP and prevention of mammary tumors is highly advisable.

Classification of mammary tumors

It is generally admitted that the incidence of benign versus malignant tumors in the dog is nearly equivalent with, depending on the authors, either a 50/50% ratio or a 60/40% ratio. However, it is important to note than the incidence of benign tumors is higher in young animals than in old ones and that, with age, many tumors have the tendency to evolve from benign to malignant.

Many classifications of mammary tumors exist and have been fully described elsewhere, however none has been up-to-now fully accepted. We can describe the easy and clinically relevant WHO adapted classification, which describes 3 categories of tumors, based on their histological origin. However, the clinical significance and the incidence on the prognosis are unfortunately not directly taken into account. The benign tumors of epithelial origin include adenomas, fibroadenomas,…, the malignant tumors include the adenocarcinomas and carcinomas whereas benign tumors of mesenchymal origin include i.e. fibroma, and lipoma, and malignant tumors include all types of sarcomas. The inflammatory carcinoma is of the worst prognosis, the lesions being malignant with a very high metastatic rate and associated with an important inflammatory reaction, an intense congestion with a total remodeling of lymphatic and vascular connections. The neovascularisation process is always observed in this case and favors rapid infiltration and extension of the lesions. There is an important lymphatic and vascular infiltration with edema, the mammary glands are firm, diffuse, erythematous, warm, painful and necrosis can rapidly be detected. DIC is a complication often observed. These animals have to be

treated rapidly (large surgery) or it will often be too late. The prognosis is unfortunately always poor, even with a rapid reaction and aggressive surgery.

The Gilbertson classification is more oriented on the prognosis and includes 5 categories:

1/ benign lesions (50%)
2/ benign with some abnormal figures (30%): numerous figure of mitosis, abnormal chromatin, no longer a benign lesion
3/ in situ carcinoma (5%): no infiltration yet observed, still localized at the mammary gland level
4/ invasive carcinoma without lymph nodes or vascular invasion (10%)
5/ invasive carcinoma with invasion (5%), the basal membrane is broken and extension has begun.

The Hampe and Misdorp classification also distinguishes 5 categories:

1/ dysplasia : similar to category one of Gilbertson
2/ benign lesions: atypic lesions are observed
3/ adenocarcinomas: the glandular structure is still conserved, tubular or papillar. In general, localized non invasive lesions (in situ carcinomas of Gilbertson)
4/ carcinomas without preservation of structure: solid and anaplastic carcinomas: infiltration and tissue invasion
5/ sarcomas but rarely observed in the bitch.

Diagnosis of mammary tumors

The diagnosis of mammary tumors is generally easy, based on history and mammary glands observation. As more than 50% of mammary tumors are detected in dioestrus animals, where pseudopregnancy can be a problem, it is sometimes necessary to treat the animals with the anti-prolactinic drugs to induce mammary gland decongestion and so be able to clearly detect all mammary tumors at the palpation. Indeed, small lesions can be hidden in the hyperplasic tissue. As complementary diagnostic methods, blood samples need to be taken to obtain a clear pre-operative hematological and biochemical picture of the animal. A radiology of the chest needs to be realized to detect the possible lungs metastasis, these are of high prognosis importance. Sensitivity (true positives), specificity (true negatives) and accuracy of thoracic radiographies for detecting metastases at the time of mammary tumors detection are 65%, 97% and 87%, respectively. The interest of pre-operative biopsies is controversial for different reasons and it is the author to not advice mammary gland biopsies. Two kinds of biopsies can be realized: fine-needle biopsies and punch biopsies. FNB may be unconclusive and negative findings should never exclude a more aggressive excisional surgery. Often, the informations obtained by FNB are reduced and not useful for the diagnosis. Do never rely on the results of a FNB , unless the results suggest malignancy! PB allows for obtaining samples large enough to generally get an accurate diagnosis. However, mammary tumors are often complex (37%), heterogenic and multiple (50-67%), that suppose multiple biopsies not only in the different lesions, but also in the same lesions as sometimes, the same lesion can present both malignant and benign aspects, which one biopsy (particularly if FNB) will not reveal. Punch biopsies can induce bleeding, inflammatory reactions and if not lucky, malignant cells diffusion and a more rapid extension of the process. For the authors, the only good mammary tumor biopsy is the excision surgery, particularly as resection of all mammary tumors is advised. Indeed, a benign tumor today, in a

young healthy animal, will always become a malignant tumor in an older and non (or less) healthy animal. So when a mammary tumor is detected, surgical resection should be done as soon as possible. After the surgery, due to the complexity, heterogeneity and multiplicity of the lesions, it is important that all excised tissue including normal tissue surrounding the lesions and all lymph nodes will be submitted for histopathology diagnosis, allowing for a clear identification of the nature of the lesions, detection of local extension and lymph nodes or vascular invasion.

Prognosis

Before the surgery, a prognosis can be proposed to the owner, based on the TNM (tumor – lymph node – metastasis) evaluation system (flowchart 1) and taking into account some important clinical parameters. Tumor size is a factor that correlates with survival time.

TNM system

T = primary tumor size

T0: no tumor, T1 $\leq$ 3, T2: 3 $\leq$ x$\leq$ 5, T3: > 5cm.

N = local lymph node

N0: no invasion, N1: ipsi-lateral invasion, N2 : bilateral invasion

M = distant metastasis

M0: no metastasis, M1: presence of metastasis

Among the important clinical data associated with poor prognosis, there are:

1/ Relation with cycle and estrus: the tumors detected or observed to rapidly grow during estrus or after estrus are often associated with a poorer prognosis than the ones detected in anestrus.

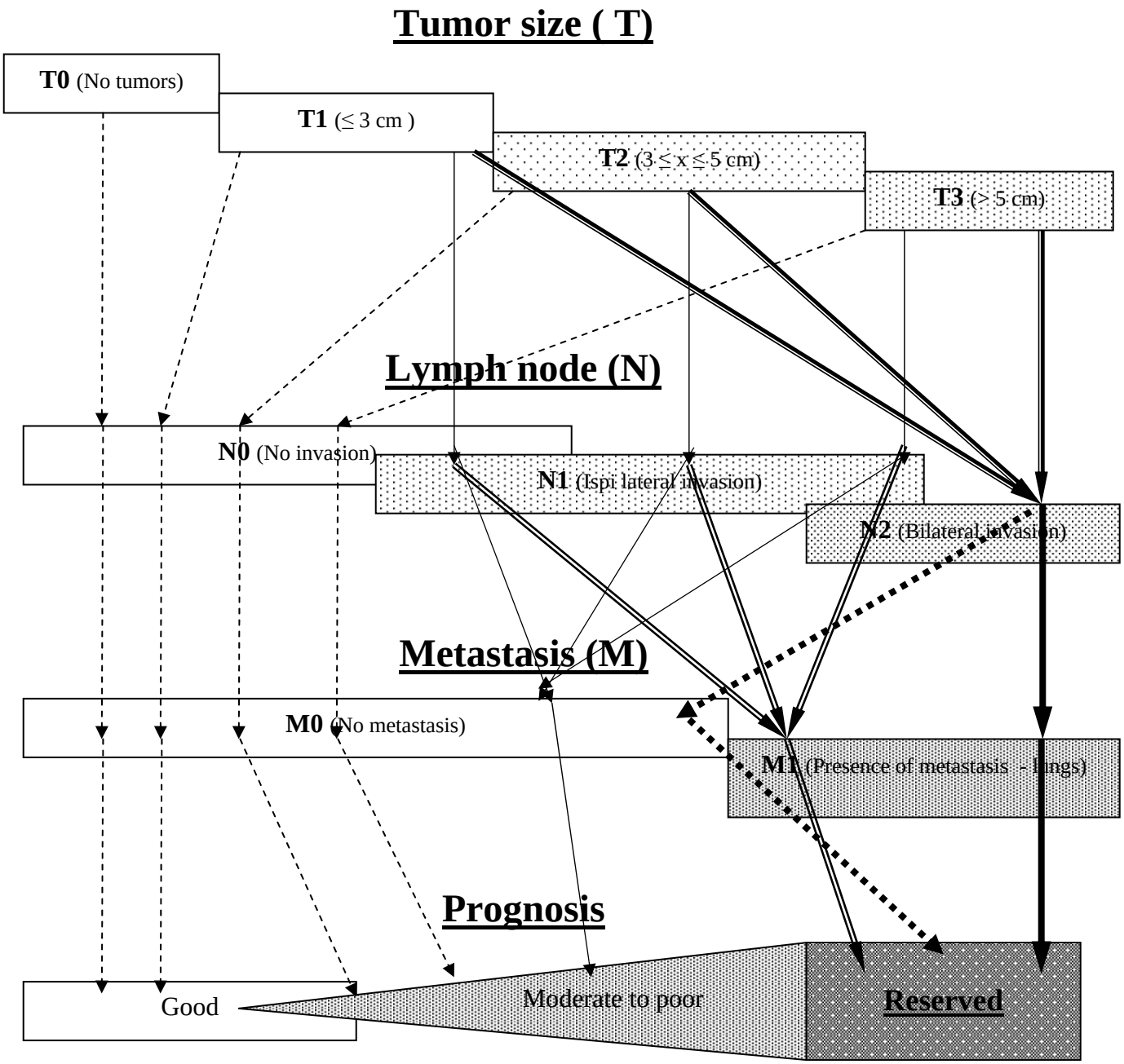
2/ The tumor called “ sleeping beauty” is a tumor characterized by a long period of quiescence (months or years) and a sudden rapid development.

3/ The unlocalized and poorly delimitated tumors are more often associated with poor prognosis than the well delimitated ones.

4/ The tumors with clear evidence of invasion of the surrounding tissues

5/ The inflammatory tumors are always of poor prognosis

6/ The presence of metastases



Survival rate is directly related to the size of primary tumors in absence of lymph nodes or vascular extension. However, if invasion is observed, the primary tumor size does no longer correlate with the survival time after surgery. The detection of invasion through post-surgery histological analysis of all surrounding tissues and lymph nodes is thus essential for the prognosis.

Evaluation of the canine tumor by counting silver-stained nucleolar organizers regions (AgNOR) has demonstrated a correlation between an increased NOR count and one year post-surgical survival prognosis in dogs with mammary carcinomas. Dogs with a NOR count below 8.0 generally have a good one year survival prognosis whereas dogs with an increased NOR generally have a poor prognosis. Unfortunately, these preliminary interesting data have not yet been fully confirmed and further studies are warranted to confirm the usefulness of NOR count in establishing the prognosis in dogs with mammary carcinomas.

MAMMARY TUMORS IN THE QUEEN

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Another abstract from the same authors concerns mammary tumors in the bitch and queen. The readers are thus proposed for the general information that is valid for the 2 species to refer to the previous paper. This paper only focuses on aspects specific of cats. When dealing with mammary lesions in cats, we certainly should begin by making the distinction between the tumors observed in the young animals (more often below 5 years) and the lesions observed in the older animals (over 5-7 years). The first type of lesions are most often fibroadenomatosis, which is a tumor-like lesion, but mainly benign and reversible, whereas the later ones are much more severe cancerous lesions, as benign tumors are exceptional and represent less than 15% of the cases in older cats. Indeed, most studies agree that nearly all mammary tumors of the old queens are adenocarcinomas, mixed tumors being rare and sarcomas exceptional. Invasion of the lymphatic system is a common observation.

a) mammary tumors

Mammary tumors are among the most frequent malignant neoplasms in the cat. They represent the third tumors after blood and skin tumors. The incidence is relatively high, even if it is lower than the one observed in dogs. Per year, 0.25/1000 new cases are described. Mammary tumors represent 14% of all tumors and 76 % of the reproductive tract tumors in this species. The mean age of the cats at the time of diagnosis is around 10-11 years, and Japanese domestic and Siamese breeds are the predominant breeds (doubled risk). Survival rates after 1 and 2 years of diagnosis are reported to be 31.8% and 17.7%, respectively, suggesting a poor prognosis related to this malignancy.

Among the factors playing a role in the pathogeny of the disease, we have, in cats like in dogs, the effects of sexual steroids. The ovariectomy reduces the risk of mammary tumor development by a factor of 7, but does not reduce the risk to nearly zero, like in dogs. The risk to develop mammary tumor increases significantly with age (significantly over 6 years) with an incidence over 2/1000 at 10-11 years old. Like in dogs, progestin treatments increase the risk and the tumors are observed earlier.
The estrogen and progesterone receptors are present on mammary tissue, indicating a hormonal sensitivity, if not a dependency. The PR is present in ± 37.5% of malignant tumors and 66.7% of both benign tumors and dysplasia, and both in immunocytochemical and radioreceptor studies. The presence of PR was linked to the absence of ovariectomy ($P<0.02$). Estrogen receptors, detected by either method, were also noticed in half the cases in which PR had been detected. In malignant tumors, the most prevalent groups were the ER + PR + and ER- PR + groups.
The role of viruses in the pathogeny of mammary tumors in queens has been questioned after several studies that demonstrated the presence of viral particles (FeLV) in around 30% of feline

mammary tumors . The role of this viral infection in the pathogeny of feline mammary tumors is not yet determined.
The mammary tumors in the queens are essentially observed at the level of the first pairs of mammary glands.
The mammary tumors in queens are generally malignant with around 86% of carcinomas (89% of adenocarcinomas and 11 % of carcinomas), 0.8% of sarcomas and 12% of benign tumors. At detection time, the tumors are often numerous, large and poorly delimited. Invasion is rapidly observed and, 50 to 90 of cats presented for mammary tumors have already lung metastasis at radiography.

The prognosis can also be established using the TNM system. Table 1 gives the mean survival time based on TNM grading and clearly shows that the most important prognosis factor is the size of mammary lesions at detection. In general, the interval between first detection by the owner and presentation to the veterinarian is around 7 months, explaining easily why the prognosis is generally poor.

TNM system

T = primary tumor size

T0: no tumor, T1 $\leq$ 2 estimated survival time: over 2 to 3 years,
T2: 2 $\leq$ x$\leq$ 3 : estimated survival time below 2 years
T3: > 3 cm: estimated survival time below 6 months
It is important to note that, in queen the mean interval time between detection and death in absence of treatment is one year!

N = local lymph node

N0: no invasion,
N1: ipsi lateral invasion: estimated survival time below 6 months,
N2 : bilateral invasion: ??

M = distant metastasis

M0: no metastasis,
M1: presence of metastasis: estimated survival time below 6 months.

However, some recent studies apparently questioned these data. In one study, they observed that cats with tumors greater than 3 cm in diameter had a 12-months median survival period with an interval ranging from 4 to 12 months, whereas those with tumors of less than 3 cm in diameter had a 21-month survival period, ranging from 3 to 54 months. Therefore, the tumor size alone seems to be of limited prognostic value in cats with tumor smaller than 3 cm in diameter. In cats with tumor larger than 3 cm in diameter, tumor size appears to have much higher prognostic relevance. Conservative versus radical surgery seems to have a relation with the disease free-interval but no clear relation with the mean survival time. Breed and age do not correlate with prognosis at the tumors detection time.
To improve the prognosis, many studies correlated the histological grade with the survival time. However, histological grounds alone can be unsatisfactory, because they do not always correspond to the clinical behavior of the neoplastic disease and the results are also highly variable. Nowadays, many studies try to correlate post-surgical survival time with other parameters, but up-to-know, without real success. Recently, some studies have tried with some relative success to correlate several parameters assessing the proliferative activity - mitotic

index, MIB1 index, and AgNOR index to survival. Histological stage (local invasion 21.83+/-7.83 months, blood vessels and/or lymphatic invasion 13.38+/-8.99, $P<0.01$), mitotic index (low 22.43+/-88.78, high 12.37+/-7.49, $P<0.001$), and AgNOR index (low 21.86+/-10.68, high 13.82+/-7.11, $P<0.05$) revealed a significant association with survival in univariate analyzis and had an independent prognostic value in multiparametric survival test ($P<0.001$) ; however, if statistically, these parameters seem to have some prognostic values, the benefit of their use is not evident in comparison to the simple TNM approach. But again, if the post-excisional survival period of affected cats is inversely proportional to tumor size, the reported median survival period for different tumor size categories is quite variable. This variability diminishes the prognostic value of reported data.
Recently, the expression of mRNA for several proteins have been used, including the chemokine receptor CXCR4, which was demonstrated to be related to lymphatic infiltration by neoplastic cells, but unfortunately there was no significant relationship between its expression and the one-year survival of the cats.

The survival time appears thus significantly associated with tumor size or WHO clinical stage, but not with breed, age, or gender. Cats with pulmonary metastasis died in general within 5 months following metastases detection. Postoperative prognosis is significantly related to the tumor size at surgery, but not to the type of surgery, nor to adjuvant chemotherapy using cyclophosphamide and/or vincristine.

b) Fibroadenomatous mammary hyperplasia.

Fibroadenomatous hyperplasia (FAH) is characterized by a rapid proliferation of mammary stroma and duct epithelium of 1 or more glands and predominantly affects younger female cats. This pathology is characterized by a massive enlargement of the mammary glands which develop rapidly, in general beginning by the posterior glands, but reaching often the 2 mammary chains in a quasi symetrical development. The glands are firm, unpainful, not inflammatory, but infected or necrosed. As associated clinical signs, tachycardia, skin ulceration, painful mammary glands due to secondary lesions, lethargy and anorexia can be detected. A papillary type structure is often observed with intra-cystic proliferation. The stroma is loose and some arborescent glandular structures can be seen. The animals are in general in perfectly normal condition, not really affected by the tremendous development of the mammary glandsbsometimes. No milk is observed.
The trouble is generally observed in young animals after their first ovulation or after the progestin treatment used either to prevent estrus in female or to treat behavioral or skin diseases, both in male and female. It is exceptionally observed soon after pregnancy.
The pathology is clearly benign and has to be differentiated from mammary tumors, that are in general observed in older animals, more in the thoracic glands and are rarely symmetrical with lesions of the majority of glands. The pathology appears to be hormono-dependant and related to over-sensitivity to progesterone secretion. The influence of progesterone either present as an exogenous therapy in the male or the female cat or as an endogenous steroid of ovarian origin has been demonstrated, both directly and indirectly in cats with mammary hypertrophy. The

presence of progesterone receptors in fibroadenomatous tissue allows for targeted endocrine therapy with progesterone receptor blockers.

The treatment is surgical when due to spontaneous or induced ovulation and consists in an ovariectomy to withdraw the origin of progesterone. In most cases, the mammary gland regresses of 50% in around 2 weeks. Partial or radical mastectomy is not indicated, except if large ulcers or skin necrosis are observed. When the disease is related to progestin treatment, the treatment arrest is indicated. In case of treatment with long-acting progestin, anti-progestins, when available, could be used to fasten recovery and give interesting results. Aglepristone has for example been used by the authors at the dose of 10mg/kg injected 3 times at 48-72 hours intervals, and then, if needed, once weekly or every other week to prevent reoccurrence in animals treated by depot injection of progestin. Fibroadenomatosis hyperplasia in cats can be treated successfully with the progesterone receptor blocker.