Canine mammary tumors
Canine mammary tumors are the most common tumor of the intact female dog and are 25-50% of all canine neoplasia. The median age at diagnosis ranges from 10-11 years. It rarely occurs in dogs under the age of 4. Females are more often affected than males, but males can develop breast cancer as well. Certain breeds are at a higher risk of developing the cancer. These predisposed breeds include Poodles, Spaniels, Dachshunds, Terriers and Setters.

Estrogen and progesterone play an important role in the development of normal mammary gland tissue. These hormones also play a role in the development of malignant tumors (carcinogenesis). Early spaying (OVE or OHE) has been shown to be protective in preventing the development of these tumors. If dogs are spayed before their first estrus, they have a 0.5% risk in their lifetime of developing the tumors. After the first estrus this risk increases to 8%, and 26% if spayed after the second estrus. Dogs spayed after the age of 2.5 years or after their 3rd estrus no longer have any protective effect from spay surgery.

In dogs about half (40-50%) of canine tumors are malignant. Also, about half (60%) of dogs have tumors in multiple glands. The majority (65%) of tumors occur in the 2 most caudal glands. Often multiple nodules are found within a mammary gland. Metastatic spread is most often to the regional lymph nodes, lungs, and other organs.

Feline mammary tumors
Mammary gland carcinoma is the 3rd most common cancer in cats (12% of all tumors). The mean age of first detection is about 10-12 years. Both intact and females spayed late in life are most often affected. A genetic predisposition is proposed in cats because Siamese (34%) and Persian (16%) cats are overrepresented. Hormonal factors are also associated with the development of feline tumors. Progestin administration increases the risk of benign and malignant tumors developing threefold. Similar to dogs, spaying cats at an early age is protective for developing these tumors. Cats spayed at 6 months of age had a sevenfold reduced risk of tumor development. There is a risk reduction associated with time of spay (earlier = better) as cats spayed at 6 months have a 91% reduced risk of developing these tumors. When spayed at 12 months this risk was 86%. If cats were spayed at a later age, the risk reduction was much lower (24 months: 11%).

In contrast to dogs, the vast majority (85-90%) of tumors in cats are aggressive cancers (malignant). These tumors tend to infiltrate local tissues and can ulcerate (18-25%) the overlying skin. About half of cats have multiple gland involvement. The tumors generally grow rapidly and can metastasize to regional lymph nodes, lungs, and other organs.

Types of mammary tumors
There are many different types of mammary tumors, ranging from adenomas to carcinomas and sarcomas. Inflammatory mammary carcinoma (IC) is a separate type of tumor in dogs. It is very uncommon for cats, but has recently also been reported. IC is an aggressive type of mammary tumor. Generally it presents as a diffuse, firm, painful swelling involving one or both chains. Patients present with signs of inappetence, weight loss, weakness and extensive lymph edema. For treatment, surgery is generally not recommended due to short survival (on average 60 days). Instead, the focus of treatment is pain control and anti-inflammatory drugs to alleviate symptoms.

Diagnosis & staging
As always, a thorough history is essential in the work up of mammary tumors. The spay status and when the surgery was performed is helpful in knowing if a mass around the mammary gland could be a tumor. On the physical exam, evaluate the size, number, and fixation of the tumor. Also, palpate and consider aspirating the draining lymph nodes. For the chest radiographs, always perform three views to screen for metastatic nodules. A CT scan of the chest is considered more accurate at screening for metastasis. If large lymph nodes are present, an abdominal ultrasound is helpful for screening for metastatic disease internally.

To diagnose a tumor, a tissue sample is needed. A fine needle aspirate (FNA) in dogs can be unreliable as many tumors consist of a mixed population of cells. It has been shown that for FNA, 86% of samples were diagnostic. 93% of these correlated with benign tumors. 81% of these correlated with a malignant phenotype. Therefore, in dogs, an FNA is good initial screening tool. However, a biopsy is more informative and considered the gold standard for diagnosis. Usually an excisional biopsy is performed, but an incisional biopsy is recommended for inflammatory carcinoma. However, in cats, an FNA is diagnostic as many tumors are carcinomas. For biopsies in cats, an incisional biopsy is recommended. These tumors need to be removed with aggressive margins (unilateral mastectomy).
The mammary glands in dogs are connected through lymphatic drainage. However, in cats, no lymphatic connections are found connecting the two mammary chains or between two adjacent glands. Multiple concurrent nodules in different glands are all independent primary tumors. For this reason, local metastatic spread is thought to occur through venous drainage.

**Treatment**

For treatment, surgery is the most important step. If needed, chemotherapy and (palliative) radiation therapy can be indicated. In the future, immunotherapy and hormonal therapy will likely play an increasingly important part in treatment in veterinary medicine, similar to humans.

Surgical excision consists of lumpectomy to remove the tumor. This can be in the form of a simple mastectomy, regional mastectomy, unilateral mastectomy or a bilateral mastectomy. Which procedure to choose from, depends on tumor and species.

In dogs, the type of surgery has not been shown to influence survival, as no difference was found in survival and recurrence rate between simple mastectomy and unilateral radical mastectomy. Also, no difference in the 2 year survival mark was found between dogs treated with a lumpectomy, mastectomy, regional, unilateral, and bilateral radical mastectomy. The debate continues whether or not a concurrent overiectomy (OHE) or ovariohysterectomy (OHX) is beneficial but recent reports suggest a benefit in outcome with spaying concurrently.

In cats, surgery can consist of a simple lumpectomy, mastectomy or regional mastectomy. All of these procedures are discouraged due to high local recurrence rate of the tumor. A radical mastectomy is considered standard of care as the survival rates are much better (Disease Free Interval: 575 -1300 days for radical surgery vs. 300-325 days for conservative surgery; Median Survival Time: 917 days for bilateral radical surgery vs. 348 days for unilateral radical surgery vs. 428 days for regional surgeries).

My personal recommendation for surgery for dogs is the simplest technique available to remove the tumor with clean margins. If needed, also remove the draining lymph node and spay an intact dog concurrently. For cats, plan for a staged bilateral radical mastectomy, if possible, but at minimal a unilateral radical mastectomy. Although often difficult in cats, try to also remove the closest draining lymph node to the tumor for staging purposes.

**Prognostic factors**

Postoperative survival is influenced by multiple factors. It can vary depending on the histological type and differentiation, stage of disease and type of treatment chosen. Prognostic factors cats and dogs include size of tumor (most important), stage of disease, presence of metastasis at diagnosis, histopathological type and grade.

Post-operative survival in dogs is strongly associated with tumor size. Smaller tumors have a better outcome than larger tumors (<3cm: 22 months; >3cm: 14 months; >5cm worse prognosis). Higher stage (>II) of disease is associated with shorter survival times. Several studies have proved this, but individual numbers vary. (Stage: I: 24 months; II: 12 months; III: 15 months; IV: 19 months).

The stage of disease is also important in cats, but the postsurgical outcome varies for this depending on which report is referenced. (Regional lymph node: 1543 dogs, pleural metastasis 188 days, pulmonary metastasis 1-11 months). The prognosis depends on location of metastasis at time of diagnosis. Also, the subtype of the grade of the tumor affects outcome. Low grade tumors (100% alive at 1 year) have a better outcome after surgery than high grade tumors (0% alive >1 year).

In cats, similar prognostic factors count as for dogs and size is once again the most important factor. There are various reports that reviewed outcome based on size. Smaller tumors have a better outcome than larger tumor (<3cm: 12-54 months, 2-3cm: 6-36 months, >3cm: 4-12 months). The stage of disease is also important in cats, but the postsurgical outcome varies for this depending on which report is referenced. (Regional lymph node: 1543 dogs, pleural metastasis 188 days, pulmonary metastasis 1-11 months). The prognosis depends on location of metastasis at time of diagnosis. Also, the subtype of the grade of the tumor affects outcome. Low grade tumors (100% alive at 1 year) have a better outcome after surgery than high grade tumors (0% alive >1 year).

There are many other prognostic factors in dogs and cats, and the research continues in these. The main future factors of interest include vascular or stromal invasion, proliferation indices (mitotic index, AgNOR, PCNA, MIB-1 or Ki-67), angiogenic factors, P-Glycoprotein, steroid receptor status (Her-2/neu status), BRCA1/BRCA2 gene status.

**Medical management**

Chemotherapy is often recommended following surgery, if the tumors are considered at risk of spreading systemically, or if metastatic disease has been found. The optimal protocol for dogs is still to be determined, but current treatments are based on drugs that are effective in humans as well. The anthracyclines (e.g. doxorubicin) are still considered the most effective, but other chemotherapeutics often used include 5-FU, cyclophosphamide, methotrexate, and paclitaxel. Multiple chemotherapy protocols are used commonly, but new drugs are being developed and studied.

For dogs, chemotherapy is effective in the gross and adjuvant tumor setting. For cats, chemotherapy has been shown to be beneficial for survival and pain relief (in palliative setting). No definitive benefit has been proven for adjuvant chemotherapy (after surgery). Doxorubicin-based protocols are most often used and other chemotherapeutics have not been well studied.
The enzyme COX-2 is expressed in aggressive tumors and is not found in healthy mammary tissue in dogs and cats. Cox-2 expression in tumors is associated with poorer prognosis, development of lymph node or distant metastasis and angiogenesis. Cox-2 inhibition with NSAIDs is often used, but more work is needed to know how much it actually impacts survival.

VEGF (Vascular Endothelial Growth Factor) is a possible marker of malignancy and a prognostic indicator. In cats, increased VEGF levels are found in poorly differentiated carcinomas. This increase is related to a poor prognosis. For dogs, VEGF expression is stronger in malignant tumors. Increased angiogenesis correlates with malignancy. Targeting tumor vasculature may be a future therapeutic direction (tocenarib, masitinib etc.), but Avastin’s (antibody against VEGF, bevicuzamab) benefit has been questioned in the past years.

Mammary gland tumors express hormone receptors such as estrogen (humans 50-70%, dogs 50-80%, cats 20-40%). Generally there is an inverse relationship between ER expression and histological differentiation. ER positive status is associated with benign or well differentiated tumors. ER negative status is associated with undifferentiated or anaplastic tumors. Hormone ablation is used to prevent continued estrogen stimulation to the tumor. Surgically, this is achieved with spaying (OHE). Medically, this is done through blocking estrogen receptors (with a receptor agonist/antagonist such as Tamoxifen) or suppressing synthesis of estrogen (Aromatase inhibitors). These medications are not often used in veterinary medicine due to cost and side effects.

**Conclusion**

For small, well differentiated mammary tumors without lymph node invasion, surgery alone may be adequate. Adjuvant chemotherapy may not be indicated for these types of low risk tumors. Larger, more poorly differentiated or high grade and invasive tumors with lymph node invasion, require multimodality management and surgery and chemotherapy are generally both indicated.