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**Conventional and alternative treatment methods of canine
mammary gland tumours**

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1. INTRODUCTION

Approximately 80 % of subjects with carcinomas have reoccurrences that lead to death. This indicates that the treatment of mammary gland tumours in dogs cannot be considered a solved problem (BABA, 2007).

1.1. Etiology

Mammary gland tumours are an important health problem in today's companion animals. The incidence of malignant mammary gland tumours in the bitch is higher than of any other cancer (DOBSON and LASCELLES, 2003). In female dogs, mammary tumours represent 50 % of all neoplasms. From these, 41-53% are of malignant character (ANDRADE et al, 2010). Mammary tumours can be small, simple nodules or large, aggressive, metastatic growths. These tumours, originating in the mammary parenchyma, can occur in any of the ten glands. Most mammary gland tumours are located in the caudal mammary glands, probably because of their more abundant parenchymal tissue leading to larger glands. Lymphatic vessels or a plexus of vessels connects all the mammary glands. These connections involve the glands at the same side, as well as the left and right glands. The risk of mammary gland cancer is increasing from six years and onwards, with the average age being 10-12 years (MARTI and FERNANDEZ, 2010). A recent study reported that approximately 70% of dogs have more than one tumour. Mammary tumours in dogs under the age of 5 are rare, unless they have been treated with exogenous hormones (SORENMO et al, 2011).

Even though there is no known genetic predisposition, the incidence is higher in certain breeds. These breeds are Poodle, English setter, Pointer, terrier breeds like Boston and Fox terrier and spaniel breeds like English spaniel, Brittany spaniel and Cocker spaniel. However, there is a lower incidence in Chihuahua and boxer breeds (BABA, 2007). Mammary gland tumours can also occur in males, occurrence ranging from 0 to 2.7% (average <1%) Of the 51 tumours reported, 28 were malignant. In a newer experiment 27 tumours were collected from 18 males, all were benign. This difference may be due to differences in criteria, but these tumours in male are known to most commonly being malignant (BEARSS et al, 2012).

The definite role of sex hormones in the development of mammary gland tumours is unclear, although we do know that about half of canine mammary tumours carry receptors for progesterone, or for progesterone and oestrogen. Benign tumours have a high number of receptors, while malignant tumours have a low number of receptors. Receptor positive

tumours therefore seem to be benign, but they are still susceptible to becoming malignant (ARGYLE, 2008). Controversially to the scientific literature published, there are practical studies questioning this statement. In a study published in 2010, the tumours of nine dogs were examined. Seven of the dogs had stage III, while the last two had stage I mammary gland cancer. Out of these seven tumours, five were positive for oestrogen receptor (ANDRADE et al, 2010).

Oestrogen and progesterone are hormones that promote cellular growth, and therefore it is believed that they increase the number of cells that may be susceptible to malignant transformation. This seems reliable when we know that benign growths are susceptible to becoming malignant. The risk of developing mammary gland tumours is reduced by ovariectomy in early age. The sources of the hormones that cause some mammary cells to lose growth control, leading to malignancy are thereby removed. By performing ovariectomy prior to the first oestrus the risk is reduced to 0.05%, but the effect of ovariectomy decreases, as the dog grows older. Unfortunately there is no apparent effect if it is performed after 2.5 years (ARGYLE, 2008).

In veterinary medicine in Norway, according to the law, it is not allowed to remove healthy tissue. In other words, sterilisation should not be done unless there are strict medical reasons. The Norwegian Animal Welfare Act makes it clear that surgical procedures are not to be used to adapt animals to the needs of humans, unless strictly necessary:

“§9 Medical and surgical treatment must be implemented justifiably with regard to animal welfare in keeping with the animal’s functional abilities and quality of life.”¹

According to the Norwegian Animal Welfare Act, the risk of healthy female dogs getting afflicted, with for example a septic uterus or with mammary gland tumours, is not enough to permit spaying. This has led to Norway having a much higher incidence of mammary cancer than countries like the United States of America. In Sweden, it is allowed to neuter. However, the Swedish Veterinary association informs that less than seven percent of the dogs in their country are neutered or spayed. As one Norwegian veterinarian explains, this law is not in accordance with many veterinarians personal opinion. In many cases, the veterinarians have to say no to owners that want to spay their dog, even though they personally think it would be

¹ <http://lovdata.no/all/tl-20090619-097-001.html#9>

the best for the dog. A pamphlet on mammary tumours by the Norwegian School of Veterinary Science confirms that every fourth female dog in Norway develops malignant tumours in the course of her life and it informs about how to prevent it. According to this pamphlet it's well documented that spaying before the second oestrus leads to a dramatic reduction in the chance of developing for mammary gland tumours later in life. In USA, they rarely see mammary gland tumours, as spaying of dogs at this young age is common (KORNELIUSSEN, 2011).

1.2. Tumour classification

Mammary tumours can be divided into benign and malignant. Simple adenomas, fibroadenomas and benign mixed mammary tumours are of the benign type. Of the malignant tumours, carcinomas are the most common, but sarcomas and complex carcinomas are also represented (ARGYLE, 2008).

Table 1: Histological Classification of Mammary Tumours of the Dog

<ul style="list-style-type: none">1. Malignant Tumors<ul style="list-style-type: none">○ 1.1 <i>Noninfiltrating (in situ) carcinoma</i>○ 1.2 <i>Complex carcinoma</i>○ 1.3 <i>Simple carcinoma</i><ul style="list-style-type: none">▪ 1.3.1 Tubulopapillary carcinoma▪ 1.3.2 Solid carcinoma▪ 1.3.3 Anaplastic carcinoma○ 1.4 <i>Special types of carcinomas</i><ul style="list-style-type: none">▪ 1.4.1 Spindle cell carcinoma▪ 1.4.2 Squamous cell carcinoma▪ 1.4.3 Mucinous carcinoma▪ 1.4.4 Lipid-rich carcinoma○ 1.5 <i>Sarcoma</i><ul style="list-style-type: none">▪ 1.5.1 Fibrosarcoma▪ 1.5.2 Osteosarcoma▪ 1.5.3 Other sarcomas○ 1.6 <i>Carcinosarcoma</i>○ 1.7 <i>Carcinoma or sarcoma in benign tumor</i>
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2. Benign Tumors

- 2.1 *Adenoma*
 - 2.1.1 Simple adenoma
 - 2.1.2 Complex adenoma
 - 2.1.3 Basaloid adenoma
- 2.2 *Fibroadenoma*
 - 2.2.1 Low-cellularity fibroadenoma
 - 2.2.2 High-cellularity fibroadenoma
- 2.3 Benign mixed tumor
- 2.4 Duct papilloma

3. Unclassified Tumors

4. Mammary Hyperplasias/Dysplasias

- 4.1 *Ductal hyperplasia*
- 4.2 *Lobular hyperplasia*
 - 4.2.1 Epithelial hyperplasia
 - 4.2.2 Adenosis
- 4.3 *Cysts*
- 4.4 *Duct ectasia*
- 4.5 *Focal fibrosis (fibrosclerosis)*
- 4.6 *Gynecomastia*

(DOBSON and LASCELLES, 2003: pg. 237)

Table 2: Incidence of malignant tumours in the bitch

Tumour	Classification	Incidence (%)
Carcinoma	Papillary carcinoma	60
	Tubular adenocarcinoma	
	Anaplastic carcinoma	
Complex tumors	Mixed secretory and myoepithelial component	30
Sarcoma		10

(ARGYLE, 2008: pg. 55)

1.3. Clinical diagnostics

Most commonly, the dog will come into the clinic because the owner has noticed little lumps when rubbing their dog's belly, or sometimes this is noticed accidentally when the dog comes in for a standard clinical examination. The veterinarian will then do a Fine Needle Aspiration and look at the aspirated cells in the microscope, or send it to a laboratory. It is important to underline that FNA can also contribute to spreading of the metastatic cells. For differentiating between benign and malignant tumours, the tumour has to be biopsied and sent for histopathological examination. Even if the tumour is benign it is recommended to remove it, as it can, as previously stated, transform into a malignant tumour.

A surgeon will always do an x-ray of the chest, to look for metastasis before any intervention; they may also do a histopathological examination of the lymph nodes.

1.4. Clinical staging

Table 3: For canine mammary gland tumour, the TNM classification is used:

<p>T: Primary tumour size</p> <p>T1: < 3 cm maximum diameter</p> <p>T2: 3-5 cm diameter</p> <p>T3: > 5 cm maximum diameter</p> <p>T4: Inflammatory carcinoma</p>
<p>N: Regional lymph node status</p> <p>N0: No metastasis</p> <p>N1: Metastasis to ipsilateral lymph node</p> <p>N2: Metastasis to contralateral lymph node</p>
<p>M: Distant metastasis</p> <p>M0: No distant metastases detected</p> <p>M1: Distant metastasis detected</p>

(DOBSON and LASCELLES, 2003: pg. 237)

Table 4: Stage grouping of tumours

1	T1	N0	M0
2	T0-1	N1	M0
	T2	N0-1	M0
3	T3	Any N	M0
	Any T	N2	M0
4	Any T	Any N	M1
	T4	Any N	Any M

(DOBSON and LASCELLES, 2003: pg. 237)

1.5. Therapy

When a dog is diagnosed with mammary gland tumour, the owner is left with an important decision; concerning what treatment they want their animal to go through.

It must be kept in mind that the best treatment for a certain tumour is not necessarily the best treatment from the owner's perspective. The animal's general health and performance is the most important patient-related factor to be considered (COUTO, 2009).

Surgery, radiotherapy and chemotherapy, being conventional methods, are today the most frequently used methods in treatment of mammary cancer in dogs. Acupuncture, heat treatment, homeopathy and herbs are alternative methods with an increasing popularity.

Conventional medicine considers cancer to be a localized disease caused by mutated cells dividing and multiplying uncontrollably, leading to a tumour mass (DEMERS, 2005). On the other hand, alternative medicine considers cancer to be a systemic disease coming from a diseased immune system. Therefore they treat the dogs systemically by boosting the immune system or correcting any in-balance in the dog which they believe lead to cancer. They also mean, that if a cure cannot be achieved the two main goals of treatment are to induce shrinkage of the tumour while remaining a good quality of life (COUTO, 2009).

There needs to be a fine line between extreme conservatism which leads to blinding of the veterinary practitioners to newer alternative medicine, and a uncritical approval of these alternative medicines, however how impressive they are (ROLLING, 1995).

The incident of cancer in pet animals is increasing worldwide. The cure for cancer is constantly being searched for and there are continuously new research and new methods being created. If a dog is diagnosed with mammary gland tumours, what options do we stand with? Should we simply go for the conventional methods, because they are familiar and well recognized? Or is it worth considering the more alternative methods as well? In that case, what are these methods and how safe are they?

2. CONVENTIONAL METHODS

2.1. Surgery

Surgery is the oldest and still the most commonly recommended treatment of mammary gland tumours. It is also the most widely accepted treatment. According to notes from the North American Veterinary conference held in Florida in 2004; *“Surgery is, and will remain for the near future the most widely applied modality for cancer control”* (STRAW, 2005:128). The conventional western treatment aims to eliminate all cancer cells from the body, both at the primary site and at other, more distant sites (STRAW, 2005). Canine patients with small tumours and no metastasis have an 80% chance of still being alive 2 years after their surgery, if the tumours are removed cleanly with a good margin. Those with larger tumours and metastasis have only a 40% chance of still being alive after 2 years (ELDREDGE and BONHAM, 2005).

When removing tumours surgically, it is important that the excision include a wide margin around the tumour, minimum 2 cm. If the dog has several tumours this means that the incision will be quite long. In dogs with multiple tumours this may lead to an incision almost along the whole belly. Owners can get very terrified about this, but what they don't think about is that a wound heals from side-to-side, not end-to-end. Still, there is no secret that surgery might be quite invasive. It is also important to remember that there is no guarantee that there will be no reoccurrence. What surgical procedure that will be done depends on many things, one of them being the size and number of tumours present in the dog (ELDREDGE and BONHAM, 2005).

Table 5: Surgical procedures for mammary tumours:

Surgical procedure	Comments
Nodulectomy	Used for masses <0.5 cm, but generally considered to be a biopsy procedure only
Mamnectomy	Removal of a single gland. This is an ideal procedure for confirmed benign masses.
Regional mastectomy	Removal of sets of glands according to lymphatic and venous drainage
Unilateral mastectomy	For multiple lesions affecting one mammary chain.
Bilateral mastectomy	Applied when there are multiple tumours affecting both mammary chains. This is carried out as two unilateral mastectomies, 2-3 weeks apart.

(ARGYLE, 2008 pg. 57)

Table 6: Prognostic factors in survival of mammary tumours

Factor	Effect on prognosis
Tumour size	Tumours < 3 cm carry a better prognosis than larger tumours
Degree of invasion and ulceration	Invading, ulcerating tumours carry a poorer prognosis
Lymph node involvement	Metastasis to local lymph nodes increases the risk of tumour reoccurrence. There is no evidence that removal of affected lymph nodes increases survival or disease-free interval
Histopathological grading	Poorly differentiated tumours carry a poorer prognosis. Presence of an immunological infiltrate correlates with increased survival times.
Hormone receptor status	Progesterone/oestrogen receptor-positive tumours are often benign.

(ARGYLE, 2008, pg.57)

“According to the Tufts University school of Veterinary Medicine, some cancers can actually be cured. But the word cure is defined as the cancer not reoccurring within a three to five-year period” (STRAW, 2005: p.127). Walter Last, the author of “The Self Help Cancer Cure and Problem Food” notes that surgery is not always successful. According to him, surgery leaves cancerous cells behind in 25-60% of human cancer patients. Also, there are certain risks performing the surgery, the tumour might be disrupted, also the preceding biopsy might contribute to the cancer spread in the body (STRAW, 2005).

The main cause of death in dogs after surgical removal of mammary carcinoma is metastatic spread. Canine mammary carcinoma usually metastasises to the lymph nodes through the lymphatic system, then to the lungs. The detection of lymphatic vessels invasion and/or metastasis to the regional lymph nodes is related with poor survival after surgery (RASOTTO et al, 2012). In addition, surgery is not indicated in case of patients with inflammatory carcinoma. Due to the extensive tumour involvement and a high incidence of distant metastasis, survival is poor even when treated (SORENMO et al, 2011).

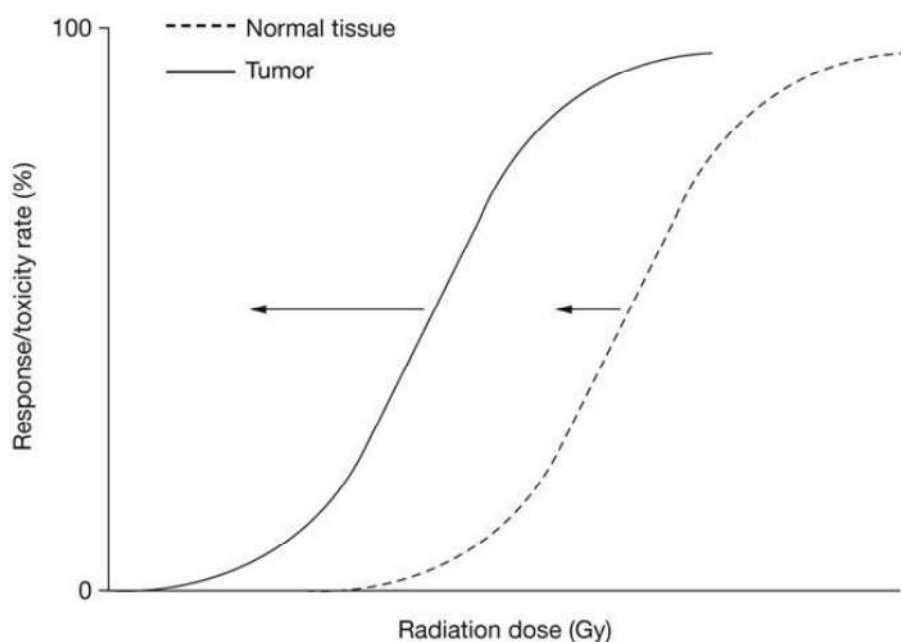
Today, there are no scientific studies supporting the theory that radical surgery will produce significantly longer survival time than more simple approaches (MARTI and FERNANDEZ, 2010).

2.2 Radiation therapy

Radiation therapy is used to kill the cancer cells and/or stopping them from dividing. Most scientific evidence suggests that the effect of radiation is caused by the interaction of radiation with the nucleus of the cell and with the cell’s DNA in particular. There has also been increasing evidence that radiation has significant cytoplasmic effect. The interaction of radiation leading to breakage in the DNA strand is probably the most important in killing of the cells. In addition, the radiation may also interact with other molecules; mainly water, to form free radicals, which then cause damage to the DNA. In human medicine, radiation therapy has established as one of the principal methods of cancer treatment. In veterinary medicine, however, radiation has been uncommon compared to the use of surgery and chemotherapy. This is not caused by a lack of medical indications, rather from a shortage of funding and knowledge. However, it has been an enormous increase in the availability of radiation therapy in veterinary medicine in the USA during the last years (DOBSON and LASCELLES, 2003).

When it comes to radiation therapy, the main concern is the response of tumours and normal tissue to irradiation, rather than the response of individual cells. The response of a tumour or the occurrence of side effects in tissue can be described in a dose-response curve. (Fig.1) The sigmoidal shape of these curves indicates that tumour control and toxicity increase rapidly. All tumours would be cured if we delivered high enough radiation dose, but unfortunately, as showed in the curve, the effects in normal tissue is parallel to the response of the tumour. The goal of radiation therapy is to increase the probability of tumour control, at the same time minimizing the effect on normal tissue (DOBSON and LASCELLES, 2003).

Fig. 1: Schematic dose-response curve for tumour and normal tissue damage with radiation.



Source: http://www.nature.com/nrclinonc/journal/v4/n2/fig_tab/ncponc0714_F3.html

“Clinical and experimental observations supports delivery of radiation therapy in multiple small fractions, but the optimal radiation fractionation has not been determined” (DOBSON and LASCELLES, 2003:107)

The French radiologist, Henri Coutard, recognized one of the most important concepts in radiology; that radiation therapy is more effective and better tolerated when delivered in small multiple doses. This is a standard in radiation therapy today, and the effects of fractionation can be explained by a concept called the 4 R's.

Repair: If the radiation dose is delivered in small fractions, many cells will survive due to their ability to repair in between the doses. This will help sparing normal tissue from the effects of irradiation.

Reoxygenation: Cells that are in a low oxygen environment at the time of radiation therapy are more resistant to killing than well-oxygenated cells. Therefore, when a tumour is treated with radiation, hypoxic cells are spared. Reoxygenation in between the doses will therefore be expected to improve the tumour control.

Redistribution: Cells occupy different stages in the cell cycle, and the sensitivity of cells to killing by irradiation depends upon what stage they are in the cell cycle. When time is allowed between the doses, cells in insensitive stages will have progressed, and may be in a more sensitive stage when the next dose is given.

Repopulation: When treated with radiotherapy, tissues and tumours replace dying cells by accelerated repopulation. This is one of the reasons for limiting the overall time period in which radiation therapy is given (DOBSON and LASCELLES, 2003).

When deciding to use radiation therapy, the first consideration is the goal of the therapy. Radiation therapy can be used as curative treatment, or palliative treatment. In curative treatment the goal is a high probability of tumour control, whilst in palliative treatment, the goal is to improve the patient's quality of life. Palliative treatment is often used when the tumour is inoperable but still causing discomfort. When palliative treatment is chosen, it is most commonly given in a few large doses, since the animal is not expected to live that long, and late radiation complications by large doses is unlikely to be of concern. It is important still, that the dose is low enough to prevent acute radiation injury (DOBSON and LASCELLES, 2003).

Radiotherapy is most commonly used in combination with surgery or chemotherapy. The goal of combining therapies is to increase tumour control, while decreasing normal tissue damage. The advantage of using radiotherapy together with chemotherapy is that the chemotherapeutic drug dose can be lowered, leading to a reduction in the side effects of chemotherapy. The dosages of radiation are much higher than those used for X-ray, but the beam is much narrower. The machines being used have special collimators that force the radiation into narrow beams. In this way, the damage to normal tissue around the tumours is minimized. Still, radiation does not differentiate between healthy and diseased tissue (ELDREDGE and BONHAM, 2005).

When the decision is taken to do surgery, there are several things to think about when considering using chemotherapy or radiotherapy in combination; one is resistance. In radiation therapy, most cells are killed when they are attempting to divide in mitosis. Cells rendered incapable of reproduction are considered death, as cell death in radiation is defined as a reproductive cell death. In chemotherapy, the agents induce programmed cell death or apoptosis. This means that cellular damage by radiation and cellular damage by chemotherapy differs mechanically, and as a result, mechanisms of resistance also differ. If a patient seems to be resistant to chemotherapeutic treatment, it might be worth trying radiation therapy

There are theoretical and clinical data supporting the belief that therapeutic gain exists when surgery and radiation therapy is combined. One of the reasons for this is that the cells of the periphery of the tumour seem to be well oxygenized, meaning they are more sensitive for radiation (DOBSON and LASCELLES, 2003).

One example where radiotherapy is used in combination is when the tumor is inoperable or if there is uncertainty that wide enough margins were excised. When combined with surgery, it is most commonly used after the surgical procedure, although it can also be used before surgery to reduce the size of the tumour. The patient will most commonly be treated for 5 days a week for a definite treatment. Most pets get worse about 7-10 days after treatment, and then they slowly recover (ELDREDGE and BONHAM, 2005).

Table 7: Comparison of pre- and postoperative radiation:

PREOPERATIVE RADIATION THERAPY	
Advantages	Disadvantages
<ul style="list-style-type: none"> ▪ Smaller radiation field may be used when entire surgical field does not need to be included ▪ No disruption of vasculature with surgical dissection ▪ Smaller surgical resection may be possible after irradiation ▪ Surgically induced exfoliation of tumour is decreased 	<ul style="list-style-type: none"> ▪ Altered wound healing in irradiated skin ▪ Histopathology and staging may be delayed or require a separate surgical procedure ▪ No opportunity to place radiopaque markers or secure normal tissue out of the surgical field.

POSTOPERATIVE RADIATION THERAPY	
Advantages	Disadvantages
<ul style="list-style-type: none"> ▪ May obtain histopathology, staging and information about margins ▪ Placement of radiopaque markers may aid in planning radiation field ▪ Normal tissue may be secured out of the radiation field 	<ul style="list-style-type: none"> ▪ Larger radiation field due to the inclusion of surgical field and margins ▪ Disruption of vasculature which may result in hypoxia ▪ Surgical complications may delay irradiation

(DOBSON and LASCELLES 2003, pg.110)

There is still little evidence in veterinary medicine to prove or disprove the effectiveness of radiotherapy (ARGYLE, 2008). Another thing to think about when considering radiation therapy is that it is quite expensive, so the owner has to be able and willing to go through with the treatment. In addition, the health of the dog has to be considered, as it has to be put under anesthesia for each treatment in order for it to lie completely still.

2.3. Chemotherapy

Simply put, chemotherapy is the use of medications to fight and kill cancer cells. The therapy is most often used for cancers that have already spread and cancers that are in blood and lymphoid tissue. One major concern with chemotherapy is that the drugs do not differentiate between cancerous cells and normal cells. Therefore, it is quite invasive on normal healthy tissue as well. Another important factor is that chemotherapy, being toxic drugs has several side effects, which can be quite severe. It is therefore important to consider the current health and the life expectancy of the animal before starting the treatment (ELDREDGE and BONHAM, 2005). Chemotherapy works by killing rapidly dividing cells, like tumour cells. Since it does not differentiate tumour cells from healthy cells, it also attacks the healthy rapidly dividing cells. Therefore it makes sense that a common toxicity associated with chemotherapy is bone marrow suppression. Because of its high dividing fraction, bone marrow is the prime target (MACDONALD, 2009).

“Since these agents possess the lowest therapeutic indices of any class of drugs, they produce frequent and predictable multisystem toxicities” (MACDONALD, 2009: 665)

Vomiting is also a common side effect in the use of chemotherapy. Haemorrhagic diarrhea may develop in breeds like collies, boxers and West Highland White terriers. It may occur 3-7 days after start of treatment, but usually resolves within 24-48 hours without specific treatment. Cyclophosphamide is known to produce a risk of haemorrhagic cystitis (MARTI and FERNANDEZ, 2010).

Table 8: Possible chemotherapy protocols for mammary gland tumours

Agent	Dose
Doxorubicin	Dogs (<15 kg) or cats: 25 mg/m ² or 1 mg/kg i.v. Dogs (>15 kg): 30 mg/m ² i.v Every 3 weeks, 4-6 cycles
FAC protocol*	Doxorubicin (same dose as above) day 1 Cyclophosphamide (100mg/m ²) iv or orally day 1 5-Fluorouracil (150 mg/m ² i.m) days 1 and 15 Every 3 weeks, maximum of 6 cycles
Mitoxantrone	5,5 mg/m ² i.v Every 3 weeks, 4-6 cycles
Doxorubicin + Cyclophosphamide	Doxorubicin (same dose as above) Cyclophosphamide (200mg/m ² iv) divided on days 4-7 of the first week of each treatment cycle Cyclophosphamide (cats:25 mg/m ² orally) divided on days 2-4 of the first week
Other chemotherapeutics accepted	Carboplatin Cisplatin Paclitaxel

(MARTI and FERNANDEZ, 2010: pg. 17.)

* FAC is the acronym for the trade names of the 3 drugs used in combination. These preparations are fluorouracil, doxorubicin and cyclophosphamide. (MARTI and FERNANDEZ, 2010: 164).

“Most of the chemotherapy protocols designed for veterinary patients have a <5% incidence of severe life-threatening complications. Most veterinary patients enjoy a good quality of life while on therapy” (MACDONALD, 2009: 665)

Doxorubicin is currently one of the most commonly used chemotherapeutic drugs, even though it is known to be cardiotoxic and can cause irreversible dilated cardiomyopathy. Long-term doxorubicin administration can lead to diffuse myocardial damage, dogs being more sensitive than humans. There are currently no sensitive predictor tests for monitoring these patients. A case was reported by where an 8-year-old German Shepard suffered a fatal cardiomyopathy after being treated with doxorubicin for splenic haemangiosarcoma. All the blood values were physiological when starting the treatment and the dose was less than 240 mg/m² according to published protocols. The dog received the combination of cyclophosphamide and doxorubicin every 3 weeks for a total of 6 treatments. After the 6th treatment the dog developed a fatal cardiomyopathy. The myocardial fibre vacuolisation and myocytolysis were highly suggestive for doxorubicin cardiotoxicity (BANCO et al, 2011). Epirubicin or mitoxandrone should be used instead if there is cardiomyopathy in the patient (MARTI and FERNANDEZ, 2010).

Chemotherapy is most commonly used when the surgical margins are not clear, and it is best that it is given in the morning. There are no ideal drugs or protocol, which have proved particularly effective in the treatment of canine mammary gland tumours. It has been suggested that the combination of cyclophosphamide and adriamycin is the most effective combination, but there are no data from large clinical trials to support this claim (ARGYLE, 2008).

Chemotherapy has until now been little used in Norway. This will probably change in the future, because of the increasing interest from veterinarians, and increased demand from the owners reading about the treatment online (DAHL et al, 2009).

3. UNCONVENTIONAL METHODS

“Holistic medicine is nothing if not a therapy of hope: until the animal dies, there’s hope of recovery from even the direst condition, cause when you allow for miracles by persisting with the right natural supplements, sometimes they occur” (STRAW, 2005:141)

Alternative medicine has had an increasing popularity in the veterinary field, also in the treatment of mammary gland tumours. Owners are seeking for more alternative methods and they have become more open for new treatment methods, which may be less invasive for their animal. At the same time they are willing to pay more in order to prolong their animal’s life, or at least improve the quality of it (STRAW, 2005).

The amounts of veterinarians becoming aware, and showing interest in alternative medicine is increasing as well. There are professional courses, all 150-200 hours in length that deliver a good basic understanding of these methods. In 1998, the International Veterinary Society (IVAS) had 1400 members and the American Holistic Veterinary Medical Association over 800 members (VOCKEROTH, 1999).

Conventional practitioners believe that cancer is a localized disease of mutated cells growing and dividing uncontrollably. In contrast, holistic practitioners believe cancer is a systemic disease. They believe as the mutated cells would be recognized and removed by a healthy immune system, the disease is caused by a deficient immune system. As they believe the reason behind it all is a deficient immune system, it makes for them no sense to use methods as radiotherapy and chemotherapy, which is highly toxic for the body, nevertheless, the immune system (DEMERS, 2005).

Dr. Myrna M. Milani, a veterinarian and author explains that one of the major problems when it comes to alternative medicine today is the mind of the people. All alternative methods are based on a philosophy of helping the mind and body to heal itself. This takes time, and a lot of commitment, which simply do not fit the quick fix mentality of our society. Dr. Milani also states that if veterinarians see their commitment as helping animals regain and maintain their health, then it seems that any treatment that achieves this is valid (STRAW, 2005).

Some people do not believe in alternative medicine simply because they believe it is too good to be true. The common arguments from these people are that veterinarians practising

alternative medicine are simply trying to make money out of other peoples misfortune. What they don't think about, is that everyone in medicine is trying to make money out of other people's misfortune, irrespective if they are practicing conventional or alternative medicine (GREENWORD, 2011).

There is little data to prove whether alternative medicine works, with the exception of anecdotal evidence. Therefore it is largely debatable if it actually does work. Many respectable alternative practitioners agree that there are many dishonest people in the field and that some of the things termed "alternative" are simply quackery. On the other side, there are many veterinarians that are certified in certain methods and that know alternative medicine. Also a lot of the therapies seem to work even though we don't know exactly why. There is enough anecdotal evidence to suggest that some alternative therapies work but until there are more studies and data we won't know with certainty. Unfortunately, it happens too often that the dog's owner chooses alternative medicine rather than conventional, without discussing with a veterinarian. Even though alternative medicine may affect cancer, this choice may lead to the cancer progressing to a point where not even conventional medicine can help (ELDREDGE and BONHAM, 2005).

When choosing alternative medicine, one first needs to decide if the goal is to try and cure the cancer, or to provide palliative care. Palliative care is focusing on relieving the pain and other symptoms related to cancer and its treatment, and the goal is to improve the quality of life. It can be used together with curative treatment, for example in order to relief the side-effects resulting from chemotherapy. According to the World Health Organisation (WHO), 80% of human patients use complementary and alternative medicine for palliative care when undergoing conventional treatment. By complementary and alternative medicine, WHO refers to acupuncture, herbal medicine, homeopathy, and vitamins and as such (LIAO et al, 2013).

3.1. Acupuncture

Acupuncture is probably the most widely accepted form of alternative medicine. It can either be used as an attempt to cure, or to help with pain or other side-effects resulting from treatments like surgery or chemotherapy.

In human medicine, acupuncture is a well-accepted treatment method when it comes to conditions like back pain, knee pain and nausea associated with chemotherapy. Also in animals, acupuncture has becoming more and more usual. The amount of veterinarians specialising in acupuncture is increasing, both in the veterinary clinics and out in the field, especially when it comes to back-pain in horses. However, when it comes to treatment of cancer, acupuncture is still very much discussed and most conventional practitioners are very sceptical, despite several eye-opening results. This would be understandable if conventional methods like chemotherapy, radiotherapy and surgery were universal solutions, but they are not. Not only can they be very invasive, they can even be destructive, and there is no guarantee that there will be no reoccurrences (GREENWORD, 2011).

Dr. Are Thoresen is a well-known man in the world of acupuncture. He is a Norwegian Veterinarian, Homeopath and Acupuncturist and has treated human and canine patients with combinations of acupuncture, homeopathy and herbs about 150.000 times (THORESEN, 2005). Acupuncture and homeopathy works by the stimulation of the self-healing mechanisms of the body. According to Dr. Thoresen, most Acupuncturists and Homeopaths agree that these methods work through information and regulation to/of the somatic processes (THORESEN, 1984). A study of how the immune system is affected by acupuncture has been done. *“These studies report substantial increase of T- lymphocyte proliferation, increase in NK cell activity, activation of the complementary system, heat stable mitogenic humoral factors and increase in OKT cells”* (THORESEN, 2005).

The explanation behind acupuncture is that vital life energy, also known as “qi” or “Chi” flows through the body in energy channels, also called meridians. There are 12 meridians connecting most of the 400 known acupuncture points. Each of the 12 meridians supports one meridian and controls another meridian. Therefore each meridian has a generative (sheng) and control (ko) functions. Each meridian consists of two parts; one outer part on the surface of skin, which collects energy, and one inner part. The inner part serves internal organs by transporting energy to an organ. The meridians can become obstructed, and any obstruction or

blockage can eventually lead to disease. It is believed that through acupuncture, the blockage is released and the energy re-balanced leading to recovering of the animal (STRAW, 2005).

The 12 meridians

YIN

Yin meridians of arms

1. Lung
2. Heart
3. Pericardium

YANG

Yang meridians of arms

1. Large intestine
2. Small intestine
3. Triple warner

Yin meridians of legs

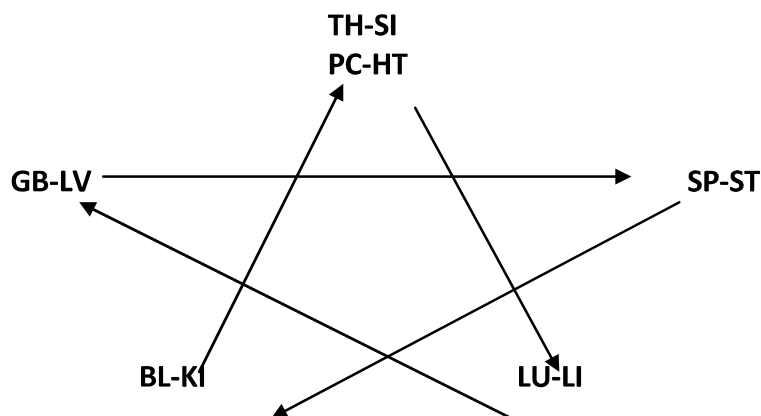
1. Spleen
2. Kidney
3. Liver

Yang meridians of legs

1. Stomach
2. Bladder
3. Gallbladder

(THORESEN, 2005)

Figure 2: The control cycle of the meridians



(THORESEN, 2005)

In Dr. Thoresen`s protocol, he only uses the ko cycle, and only the yin meridian for bringing control to the affected organ as well as the controlling organ. For mammary cancer he uses the liver (LV) meridian. The liver meridian controls the spleen and stomach meridian (SP-ST), stomach being the meridian where mammary gland tumour develops. (Fig. 2) Thoresen underlines that the most important is to stimulate the controlling meridian, not necessarily the

controlling points itself. It is also important that during the stimulation of that meridian, no other meridian should be stimulated (THORESEN, 2005).

The specific point on the meridian where the needle is placed is called an ECIWO point. ECIWO is an acronym for Embryo Containing Information Of the Whole Organism, and was first described in 1973 by Zingqing Zang. ECIWO indicates that all cells and parts of the body contain information of the whole body. Zingqing Zang hypothesized that cancer itself is a cellular ECIWO *“that has arrested at the morula stage of embryological development, in which the cells are undifferentiated and are in the process of rapid cellular division”* (GREENWORD, 2011:46). He further postulated that all the ECIWO systems are interconnected and this is why they can be used as healing device. Interference in one system will automatically restore all other systems as well and by this the whole body (THORESEN, 2005).

When performing acupuncture, first one must make a thorough meridian diagnosis. This is done by a simple observation of where the tumours have developed. In the case of mammary gland tumour this will be in the area of the nipple line. The cancer ECIWO point is then found by the sensitivity of the finger, as the finger is moved along the metatarsal bone along the path of the meridian. The needle is then inserted, left for 20 minutes in situ with no stimulation. To stimulate the body to bring the cancer under control usually takes 1-3 acupuncture sessions and the intervals between the sessions are of around 4 weeks, depending on each patient. Treatment of very severe cancers may continue for 1-2 years. The use of chemotherapeutic drugs in combination is not recommended as they usually decrease or expel the self-healing of the body, which will lead to a poorer result. The result of acupuncture in patients with mammary gland tumours are good compared to other kinds of cancer, as the meridian for mammary gland tumour is known (THORESEN, 2005).

On request of Dr.Med.Ottestad, Chief Medical Officer of the mammary cancer department at the Radium Hospital of Norway, Dr. Thoresen noted and measured all his veterinary patients between April 22nd 2003 and January 26th 2004. These were not handpicked and all were followed up until 31.12.2009 or until they died (THORESEN, 2005).

Table 9: Summary of the outcomes of Dr. Thoresen's patients with mammary gland tumours

# Cancer type /description of tumour /malignancy and indication of malignant (M) or benign (B)	Patient, year of birth	Acupoint(s) used/date of first treatment/description of progression or development and indication or positive (P), uncertain (?) and negative (N)
Mammary carcinoma / 10 & 8 mm tumours in both sides/malignant	Female dog, Chihuahua, born 1999	LV03/22/4-03 / the tumours went almost totally away, then reappeared, and are now stable. No other treatment (P)
Mammary tumours (2): diameter 1,4 cm, 1,2 cm /benign (B)	Bitch, English setter, born 1998	LV03/17/7-03/ after one year the tumours are 0,3 and 0,2 mm. No other treatment has been performed (P)
Mammary tumour: diameter 1.1 cm/benign (B)	Bitch, English setter, born 1996	LV03/17/7-03/ After one year the tumour was totally gone. No other treatment has been performed.
Mammary carcinoma /multiple tumours in both sides, size varying between 5 mm to 20 mm /malignant (M)	Icelandic sheep-dog bitch, born 2001	LV03/30-9--03/she was not operated or given any other form of treatment. The tumours went almost away, and can now not be detected (P)
Mammary carcinoma on left side; operated but had metastasis, new cancer is developing on the right side/malignant (M)	Tibetan temple dog, bitch, born 1991	LV03 bilateral/20/1-03/ since the treatment started the tumour is somewhat reduced (P) #2

(THORESEN, 2005)

Table 10: Clinical outcome in 34 patients during 1 year

Clinical outcome (interim)	Number of cases
Humans	18
Dogs	15
Horses	1
Total Benign tumours	8
Total Malignant tumours	26
Reduced growth in benign tumours	2
Reduced growth in malign tumours	12
Total disappearance of visible benign tumours	2
Total disappearance of visible malignant tumours	4
Overall positive development in number of benign tumours	4
Overall negative development in number of benign tumours	1
Overall positive development in number of malign cancer	18
Overall negative development in number of malign cancer	5

(THORESEN, 2005)

All of the dogs in the presented case series experienced significant regression of their mammary cancer without relapse (Table 9). No side effects were noted. The dogs became playful again; they got their shiny coat and appetite back. According to Thoresen, there is no conceivable reason to indicate that these dogs represent cases with a condition much more likely to spontaneously regress than dogs presenting in other practices (THORESEN, 2005).

“Whether you choose to believe it is the Chi or that acupuncture somehow works with nerves or through stimulating biochemicals in the body, most people agree that it works in some fashion, so much that the American Veterinary Medical Association recognizes it as well” (ELDREDGE and BONHAM, 2005:164).

3.2 Heat therapy

"Who cannot cure disease with medicine, should operate. Who cannot operate, should heal with heat." Hippocrates

3.2.1. Hyperthermia

Hyperthermia is the procedure of raising the body temperature above the normal level for a definite period of time. The heat can be applied to the whole body or just parts. In oncology, hyperthermia refers to the treatment of malignant diseases by administering heat in various ways. In general, hyperthermia is not accepted as a conventional cancer treatment, mainly because of its controversial performance. The main concern is the complications and effect of the high temperature on the body. In order to avoid tissue damage, the goal is to keep the local temperatures under 44 degrees and the whole body temperature under 42 degrees, which is the upper limit. (SZÀSZ A. et al, 2013).

Hyperthermia is usually used in combination with chemotherapy, but can also be combined with radiotherapy. The heat treatment may make the malignant cells more susceptible to the ionization of radiation or certain chemotherapeutic drugs. When combined with chemotherapy, the chemotherapeutic drug-dose can be reduced, resulting in fewer side effects. Performing hyperthermia before radiation treatment will increase the oxygen level to that area, which not only makes radiation more likely to kill the cells, but also preventing the cells to repair the damage induced during radiation. The goal of hyperthermia research is to find the molecular mechanism by which the heat kills the tumour and the mechanism of how hyperthermia makes the cells more radiosensitive. The different types of hyperthermia are still under clinical investigation, and a few positive comparative trials have already been completed (SZÀSZ A. et al, 2013).

3.2.2. Oncothermia

Oncothermia is a method of hyperthermia that brings a new hope in the treatment of pets with cancer. Oncothermia has been used in human clinical oncology since 1989, and many of their methods were also tested in the veterinary clinical practice. Its clinical results are excellently showing the advantages of the method. Because the classical whole body hyperthermia showed serious side effects, locoregional hyperthermia techniques became more prevalent. Oncothermia uses the energy of modulated electromagnetic field to heat up the tumours (ANDOCS et al, 2013).

In Oncothermia, the locally applied deep heat is controlled by selectively targeting the cellular membrane of the malignant cells. There are several differences between malignant and

healthy cells, which can be used for selection by heat targeting. The main selection factor is the different metabolic activity of malignant cells (SZÁSZ O, 2013).

Malignant cells have an enormous requirement for nutrients, and due to this they will compete for the nutrients leading to disruption of the cells harmony. Their healthy network is damaged, the order of the tissue is lost and the signals between the cells are destroyed. Another important selection factor is that the dielectric constant and optimal refractive index also differs from normal healthy cells. This helps marking off the malignancies (SZÁSZ O, 2013). Hyperthermia has limited effect on healthy cells, while it may kill or weaken tumour cells. Tumour cells have difficulties tolerating heat because of their disorganized structure. Oncothermia may therefore cause the tumour cells to undergo apoptosis in direct response to applied heat (SZÁSZ A. et al, 2013).

The setup of oncothermia is quite simple. The modulated radiofrequency current (RF) flows through the cancerous lesion. The current will mainly flow in the extracellular electrolyte, because their membrane electronically isolates the cells. The membrane disruption is one of the targeted aims. The main advantage of the application of electric field is the missing control of the organism, so no physiological feedback is directly limiting the electric fields, resulting in that only its consequences could be regulated. As stated, oncothermia has its main energy delivery into the extracellular liquid. The liquid is heated up, creating a little difference between the inner and outer temperature of the cell. This starts a heat flow from outside into the cell through the membrane, and acts until the temperature difference exists. The main energy absorption will be in the membrane and the extracellular electrolyte. The treated tissue will be in-homogeneously heated and the heat will flow from the extracellular to the cytosol. The current will continue until the extracellular and intracellular temperature reaches equilibrium (SZÁSZ A. et al, 2013).

Also, the oncothermia has self-focusing property in the tumours. As the tumour cells has higher metabolic rate than the environment, they form and transfer more metabolites into the extracellular space. Many of these molecules raise the conductivity of the liquid close proximity to the tumour cells. The current, however always tries to flow through the materials where the least resistance is occurred. So, putting together the two mentioned effects, better conductance (hence less electric resistance) is found in the tumours, so the electric current,

caused by the oncothermia, will flow through this area in much higher amount. This is the theoretical basis of the self-focusing ability of the application. (SZÀSZ A. et al, 2013).

Oncothermia is certified by TÜV, Munich by medical CE certificate, both the safety and efficacy are certified. No serious toxicity or side effects were reported. Of all the large number of treatment, only 3% experienced minor adipose burns. Patients report fewer side effects from the conventional treatment if oncothermia is used in combination. Most importantly, they report furthermore an improved well-being and a better quality of life (SZÀSZ A. et al, 2013).

3.2.3: Comparison of the methods

There are several differences between the traditional hyperthermia and oncothermia. In traditional hyperthermia only the temperature is controlled, while in oncothermia, energy-dose control is used. Here, instead of temperature, energy (measured in Gy) is used to characterize the dosing of the treatment.

The traditional hyperthermia has to heat up if there are multiple lesions overlapping over an area. Oncothermia, however, automatically focuses on the lesions in their multiple locations without treating the healthy tissue in-between. One important advantage of oncothermia is that it does not require high temperature for the treatment. Energy and thermodynamic effects cause the distortion of the selected malignant cells. Oncothermia is based on modulated electric effect, working together with the classical temperature-based hyperthermia concept. The main advantage of oncothermia is that the heating creates a heat-flow through the membrane into the cytosol, which is active until equilibrium is reached. This gains the efficacy and reability of the treatment (SZÀSZ A. et al, 2013).

In the classical hyperthermia the main effect is necrosis of the malignant cells, while the effect of oncothermia is apoptosis. The apoptosis is investigated by several methods (DNA-laddering, Tunel, morphology etc.) Another important effect of oncothermia is that it works parallel with immune reactions leading to a promotion of the immune reactions, which again result in a systemic action. The process is also non-toxic and no inflammatory reactions are seen afterwards (SZÀSZ A. et al, 2013).

In classical hyperthermia, dissemination of malignant cells is often promoted. Oncothermia also differs here, as it blocks the dissemination avoiding the motility of the malignant cells. This blocking of dissemination is due to the reestablishment of the junction between the

malignant cells leading to their reconnection. This is a very important effect of oncothermia as it improves the chances of success. The mechanism is unclear, but it is clear that the immune system acts against the metastatic lesions. The local treatment of the primary tumour also aids in distant metastasis as well. Oncothermia is applied in advanced cases. Indications can be if conventional methods fail to work, if there is distant metastasis or if there are multiple drug resistance in the case of chemotherapy. Today, oncothermia in human medicine is widely spread around the world, represented in 30 countries on five continents (SZÁSZ A. et al, 2013).

3.2.4. VetEHY510 system

Today, there are no really effective and at the same time relatively cheap treatments to help the veterinarians curing the tumour in the pet. Therefore Oncotherm GmbH (Páty, Hungary) created a specialized device, the VetEHY510 system. The goal of this system is to provide veterinarians with an easy and effective device for treating cancer, provide information about the efficacy and collecting information in order to optimize the treatment protocol. The veterinary medical centre in Tottori University has used the VetEHY510 system when treating dogs and cats with different kinds of tumours, including soft tissue sarcomas, lung tumours etc. Because fewer "gold standard" treatments exist in veterinary medicine, it is ethically acceptable to try new forms of therapy in untreated cancer rather than to wait until all "known" treatments has failed (ANDOCS et al, 2013).

Case study: A 9-year-old castrated male golden retriever was diagnosed with lymphoma in the thoracic cavity. It was treated with a low-dose of COP (Cyclophosphamide-Oncovin-Prednisolon cocktail) + oncothermia (15 times at the first session then 1-2 times/month).

Before the treatment the CT showed a large tumour mass compressing a large part of the lung, leading to serious difficulties in breathing. 11 months after the treatment started, the size of the lesion had significantly decreased and the lung had been partially released from the compression. This case was a typical example when a rapidly progressing deadly disease became a manageable chronic disease (ANDOCS et al, 2013).

Several impressive results have come out from the use of VetEHY510 system in in oncotherapy. The tumour size decrease, the pain associated with the tumour decreased, and the animal's quality of life improved. However, better results were observed when

oncothermia was used in combination with low-dose chemotherapy. Veterinary oncothermia clinical investigations are still in progress (ANDOCS et al, 2013).

3.2.5. Xiao-Aiping TCM decoctum and oncothermia

In the past years, the interest in using natural products in cancer treatment has increased, *Marsdenia Tenocissima* being one of these. *Marsdenia* is an ancient Chinese herb and its extracts have in several cancer types been reported to have anticancer activity, inhibiting the growth of cancer, and induce apoptosis (ZHENGRONG, 2012). *Marsdenia* is known to have anti-inflammatory and detoxification effect and it is indicated in the treatment of phlegmon, tumors of oesophagus, stomach, lung and liver. Also it is suggested to have synergic effect with radiation and chemotherapy (KŐVÁGÓ 2013).

Dr. Kővágó Csaba is currently working on a scientific research on Xiao-Aiping TCM-decoctum and oncothermia. The main goal of this research is to test and find materials that can expand the local treatment effect of the treatment systematically to the oncothermic untreated regions of the body. The main treatment used in this experiment is Xiao-Aiping (Xi) injection. Xiao-Aiping is an injectable solution with the extracts of *Marsdenia Tenacissima*. Its main active ingredient is Chlorogenic-acid (11mg/ml) and polydatin. (concentration is not specified) For application in mouse it is suggested to inject the solution intraperitoneal or intratumoral with a dose of 7, 5 ml/ttkg once per day for more days (KŐVÁGÓ 2013).

For this experiment, 12 female conventional BALB-C breed mice were divided into four groups. The tumour, C26 (colo-rectal tumour cell line) was injected subcutaneously to both limbs of each group. (750 000 cells, 01.1 ml) The incubation period was 2 weeks.

Table 11: Treatment of the different groups:

Group 1:	Control group
Group 2:	Xi: IP 7,5 ml/bwkg Xi (0.15-0,25 ml) during 4 days
Group 3:	OTM: 30` OTM right limb, max 42 degrees tumour core temperature
Group 4:	OTM-xi: 4 days Xi, on the 4 th day OTM.

(KŐVÁGÓ, 2013)

After 24 hours incubation, the tumours were excised and examined. The examination consisted of histopathology with HE staining, Tunnel Assay (Nucleic –acid fragmentation), CD3 (lymphocyte, Rhodamine) and HSP70 (Rhodamine). For evaluation, the

Relative Dead Area ratio was compared in pairs of each group with HistoQuant and 3D Histotech.

For the oncothermia treatment, the RF parameter was 13.56; AM modulation with 1/f noise and capacitive coupled-Impedance tuned was used. The system used was LAB-EHY 100, the output power was 1-3 W and the duration was 30 minutes.

Table 12: Results from the experiment:

Group 1:	Control group
Group 2:	Application of Xi alone has no effect on the tumour
Group 3:	Partly tumour damage on both sides
Group 4:	Application of Xi 24 hours before OTM has no effect, since Xi is eliminated before the oncothermic treatment. However, the Xi application + OTM together resulted in partly tumour damage on both side. The damage were at the same level as when OTM was used alone (group 3). The level of damage was the same on both sides.

(KÖVÁGÓ, 2013)

HSP70 level suggested that there is stress on the OTM untreated side, while Tunel Assay suggested that there is programmed cell death happening in both sides. The most important result is the programmed cell death on the OTM-Xi treated side. Time-course study is presently going on (KÖVÁGÓ 2013).

3.3. Homeopathy

“Those who treat animals using either of the two modalities believe that at the root of health is an innate, instinctive life force or energy, and that animals have a natural capacity and ability to heal” (STRAW, 2005:172)

Many people today consider homeopathy as a modern alternative treatment method, but it actually developed in the time of Hippocrates, the father of medicine. It was a medical doctor in Germany, Samuel Christian Hahnemann that, in 1790, developed the system being used today. He discovered that extremely small amounts of certain herbs could treat the side effects that they would cause in massive amounts. This meaning that a substance causing fever could be used in a lower amount to actually treat fever. He decided to experiment it, and the only

way was for him to take it himself and see what it did to him. The results astonished him. Dr.Hahnemann tested many substances this way, building up a basic library of seventy homeopathic medicines, which are today several thousands (ELDREDGE and BONHAM, 2005).

Homeopathic medicines are prepared with substances from the animal, vegetable, and mineral kingdoms. Specialists harvest the plants in their natural habitat and bring them fresh into the laboratory, where the venoms, hormones and organs of animals are used as extract. The mother tincture results from maceration of plants and other base products in alcohol. This tincture is the original source and it is diluted for the preparation of a given homeopathic medication into infinite small doses (STRAW 2005).

Homeopaths state that *“By diluting the substance, the healing properties are greatly enhanced and the potential poisonous attributes are removed”* (ELDREDGE and BONHAM, 2005:160).

What is surprising to many is that the more diluted the medication is, the more potent it actually is. When the medicine is made, on part of the substance is diluted nine times with a dilutant, usually distilled water. This is turned over several times to release the energy of the substance. As homeopathic medicines are more potent the more diluted they are, they are often diluted over and over again. This is one of the main problems of the sceptics. If a substance is diluted so many times that there nearly are any molecules left, how can it then work? On the other hand, this makes homeopathic medicines extremely safe, as they simply have no more side effects than distilled water may have (ELDREDGE and BONHAM, 2005). The goal of homeopathy is to find a medicine which fits the total physical or psychological signs in a patient, in order to affect the animal in a deep and lasting way (VOCKEROTH, 1995).

When choosing the right homeopathic medicine or remedy, all the animals clinical signs are taken into consideration, included the ones that seems unrelated to the primary problem. These symptoms are taken together and analysed, and then the most suitable remedy is chosen based on the description of remedies previously used. This chosen remedy should match the signs and the disease process affecting the animal. It is then administered per os in the appropriate strength or dose, in order to try to push the animal to heal itself (VOCKEROTH, 1995). One of the challenges when using homeopathy, is to find the right person with the

appropriate knowledge in order to not have the remedy be overused or that the wrong remedy is chosen. This does not harm the disease but it does no good, and this is why homeopathy was in the past seen as a treatment with little or no effect. The importance of the right use of homeopathy cannot be emphasized enough (VOCEROTH, 1995).

D.V.M Richard Pitcairn is one of the most famous and respected practitioners in USA. He is known to have said “*Gradually we are training veterinarians in methods of healing instead of suppressing*” (STRAW, 2005:173). He explains how homeopathy can get to the deeper levels of the disease development, and that that’s where the ultimate cure exists in. Another well-known practitioner is D.V.M George Glanzberg. He has a small animal clinic in Vermont, where he has combined conventional medicine and homeopathy for twenty years. He explains that in many cases they have done well without the conventional methods, and that the animals still have lived long, happier and healthier life (STRAW 2005).

There are several success stories of Dr. Glanzberg treating animals with cancer. In August 1995 an older dog had a mammary tumour removed. The dog was in addition severely arthritic; it has a bloated stomach and was on two medications. Dr. Glanzberg decided to put it on natural food diet while treating him with homeopathic medicines. First the tumours began to shrink, but they then started growing again. Another tumour was removed in July 1999, and the homeopathic remedy was changed. Six years after the treatment, the dog is free of tumours and is still in relatively good condition (STRAW 2005).

Homeopaths state that homeopathic medicine works on strengthening the immune system, helping the animal to fight the cancer itself. In a scientific study, the effects of the homeopathic medicine “Canova” were studied in normal and sarcoma-bearing mice. Canova is a complex medicine composed of 19x *Thuja occidentalis*, 18x *Bryonia alba*, 11x *Aconitum napellus*, 19 x *Arsenicum album* and 18x *Lachesis muta* (BELLAVITE et al, 2006).

The mice were examined daily and the tumours were examined histologically. Compared to the control group, it was in the treated group noticed a delay in development, a reduction in size of the tumours and increased infiltration by lymphoid cells, granulation tissue and fibrosis surrounding the tissue. No regression of tumour was found in the control group, whilst a total regression of the tumour was found in 30% of the treated animals. 30% of control group died, while all the animals from the treated group died. This study suggests that

due to the homeopathic medicine, the immune response of the host was increased, leading to a protection against the experimental sarcoma (BELLAVITE et al, 2006).

In Norway, cancer is one of the diseases homeopaths are not allowed to treat. According to the law:

§ 7. *Treatment of serious diseases and illnesses.*²

“Treatment of serious diseases and illnesses other than included in § 6, (Treatment of serious transmittable diseases) shall not be performed by other than health personnel.

Other than health personnel can still perform treatment that extensively has the purpose to soothe or lower the symptoms of, or because of the disease or illness or side effects given by the treatment that is given, or that has as goal to strengthen the body’s immune system or the capacity of self-healing. “

Therefore, when it comes to canine cancer, homeopaths do not treat the disease itself, instead they focus on treating the symptoms. They have as a starting-point to treat the individual as a whole, and they use the symptoms and signs to create a complete picture of the individual’s balance/unbalance and prescribe homeopathic medicines out from this. For that reason, there are no homeopathic medicines listed for cancer itself, because the medicine is chosen based on the main symptoms. Homeopathic medicines are mostly used as a supplement in the treatment of canine mammary gland tumours. Of course there will be certain homeopathic medicines that are more suiting with a mammary cancer diagnosis than others, but in classical homeopathy they cannot say that “this” or “that” medicine is used in the case of mammary cancer. Homeopathic medicines like Pulsatilla, Sepia, Phytolacca, Conium, Carinosinum, are examples of herbs that are more subscribed in the case of mammary gland tumour (HATLEDAL, 2013)

“One of the benefits to homeopathic medicine is that it is extremely safe. Because the dangerous qualities of the original substance are diluted, there are no chance of getting ill from them” (ELDREDGRE and BONHAM, 2005: 161)

²<http://www.lovddata.no/all/hl-20030627-064.html> (Personal translation)

3.4. Herbal medicine

The use of herbs is one of the oldest forms of medicine in the world, and it seems to have been rediscovered. Many are turning to the potential of plants when their dog is diagnosed with cancer, in hope to ease the discomfort, help the immune system and relieve the emotional stress. Cheryl Schwartz is a veterinarian, and the author of the popular book “Four Paws Five directions; A guide to Chinese Medicine for Cats and Dogs”. Dr. Schwartz tributes the use of herbs in cancer treatment for three reasons: They can be used in the combination of chemotherapy or radiotherapy in order to strengthen the patient and reduce the side effects. In addition, they can also act as first line of defence in older, weakened animals. Herbs can also be used to treat pain, and are suitable in drug-sensitive animals as the herbs are better tolerated (STRAW, 2005).

3.4.1. Artemisinin

Artemisinin is an ancient Chinese medical herb, also called wormwood. The herb has been used successfully for many years in the treatment of malaria and is also found to be effective in the treatment of cancer. According to veterinarian Narda Robinson, D.O., D.V.M., of Colorado State University Veterinary Teaching Hospital; two researches: Henry Lai and Nardndra Singh of the University of Washington, reported that “*artemisinin kills breast cancer cells selectively with only minimum impact on normal breast cells*”. (STRAW, 2005:147) Dr. Robinson also states that a dog that received artemisinin was cured, within 5 days of treatment. The dog which previously could not walk at all was able to walk normally and X-rays confirmed the tumour was gone (STRAW 2005).

3.4.2. Essiac

In 1922, a woman named Renée Caisse received a formula from a patient who had treated her own breast cancer successfully. Later, Caisse’s aunt developed terminal breast cancer, and with support of her physician she tried the formula. The aunt lived for twenty years after the treatment (STRAW, 2005). Caisse named the formula “Essiac”, and used it for many of her patients. JFK’S physician, Dr. Charles Brush is known to have said: “*Essiac is the cure for cancer, period. All studies in the United States and Canada support this conclusion*” (STRAW 2000:148). Clare E. Middle, B.V.M.S in Australia has been using Essiac, sold under the name T-Can on animals for some period. Dr. Middle frequently uses Essiac as an alternative treatment to chemotherapy and has had some success. She treated dogs, cats and a canary, all together twenty cases. All the cases, except two was diagnosed with malignancy before starting the treatment. According to both Dr. Middle and the owners, more than half of

the animals showed noticeable improvement under the treatment of Essiac. They felt better within a few days and survived longer with a better quality of life than expected without any treatment. After one year, seven of these patients were still alive, bright and active (STRAW, 2005).

3.4.3. Garlic

Garlic has been given medicinally to both humans and animals for at least four thousand years. “According to the article “Cancer-Fighting Botanicals” by Baddock Ray, The National Cancer Institute research has found garlic to be effective in inhibiting the growth of cancer cells”(Straw 2005:150). Referring to research by Dr. Walter Last, garlic inhibits the growth of existing tumours and protects against metastasis. In addition, it increases the detoxification ability of the liver and strengthens the immune system. Another researcher, Dr. Sujatha Sundaram found that one of the components in cancer, Diallyl disulphide caused human bowel cancer cells to shrink when transplanted into mice. He also found another component that slowed the progress of breast cancer in rats (STRAW 2005).

3.4.4. Other herbs

Other herbs commonly used: (EDREDGE and BONHAM: 2005: 163)

- *Aloe Vera* is said to help fight infections and cancer
- *Cats Claw (uña de gato)* is a Brazilian herb that is purported to shrink tumours
- *Chaparral* is a desert plant said to treat tumours
- *Chinese Astragalus* is a herb said to boost the immune system.
- *Hoxsey* is a mixture of different roots. When mixed as a salve it is applied to the area above the tumour.
- *Pau d`arco* is a Brazilian herb that is said to boost the immune system and has cancer-fighting properties.
- *Red clover* is said to have cancer-fighting properties.
- *Tumeric* is an herb said to have strong anti-inflammatory properties that also boosts the immune system.
- *Tian xian* is a Chinese herbal supplement to fight cancer.

The Veterinary Botanical Medicine Association states in the article “Herbs for Animals”: *“It is unwise to assume that herbs alone are used to treat ill-health in our pets. Most holistic veterinarians recommend nutritional support, in addition to conventional therapy if the problem is acute, severe or life threatening”* (STRAW, 2005: 147).

3.5 Future alternative methods

3.5.1 Near-Infrared imaging

In human medicine, up to 40% of patients leave the operating room with deposits of cancer cells left after surgery. Intra-operative detection of retained cancer cells is challenging, and residual disease is one of the most common reasons for local failure, also in veterinary medicine. The cancer cells left after surgery is most commonly found near the resection site, at the margins. Studies have shown that it would take 3000 sections, each 6 µm thick, to fully evaluate the margins of a 2 cm breast biopsy in human patients, which of course is impossible (MAFAJEWSKI et al, 2012).

A method that might be used for detection of retained cancer cells in the future is intra-operative Near-Infrared imaging of surgical wounds after tumour resections. According to a scientific study this can detect residual disease and help informing about the remaining tissue, if the cancerous cells are completely removed or not. In this study, the visual enhancement of tumours was hypothesized using near-infrared imaging in identifying tumour deposits in the wound after resection (MAFAJEWSKI et al, 2012).

Three dogs with soft tissue sarcomas were resected between December 2011 and April 2012 by standard veterinary practise. All the three tumours could easily be palpated and tumour margins were evident by visualisation and palpation. All tumours had 12 to 15 fold-increased fluorescence compared to surrounding tissue. No residual tumour deposits were discovered in the surgical bed after tumour resection. After removing the soft tissue sarcomas, the hand-held Near Infrared device was used to analyse the tumour margins. All resection margins were negative for any evidence of cancer deposits and they were finally discovered to have negative margins by histopathology. The patients were followed up to 45-110 days and no local recurrences were detected (MAFAJEWSKI et al, 2012).

3.5.2 Photodynamic therapy

Photodynamic therapy is a newer method, still under scientific research. In Norway, they are currently performing the first clinical trial on dogs. For this therapy, a chemical drug called Amphinex is used in connection with the chemotherapeutic drug Bleomycin. Amphinex is a

photosensitizer that makes the cells more sensitive for light. It is not activated, and has no effect until it is exposed for light by a laser. By making the cells more sensitive, it will increase the effectiveness of the chemotherapeutic drugs. Chemotherapeutic drug is then given 3-4 days later and after a few hours the tumour will be lightened with laser to release the drug and thereby destroy the cancer cells (JONASDOTTIR, 2013). Elsa Beck, a veterinarian in Detroit, has been using photodynamic therapy for a period. She explains that the therapy has been from 40-95% successful in curing her several hundred patients, depending on the location of the tumours. She states that as a one-time treatment, photodynamic therapy has less side effects than radiation (STRAW, 2005).

3.5.3 BP-CI

The Norwegian Veterinary School is currently doing another scientific research, of the medicament "BP-CI." The research is currently in the phase 1 dose-response stage. This study is for dogs with mammary tumours who metastasised before or after surgical removal of the tumour, dogs with inflammatory carcinoma, inoperable malignant mammary tumour, or malignant mammary tumours where the owner does not want the dog to go through surgery.

BP-C1 is a combination of platinum and an ammonium salt from an acid originating from the bark of a special tree. The platinum has a cytotoxic effect. Results from previous experiments on this particular medicine have been promising and shown to have a positive effect on the development of cancer. In addition, the side effects in humans are reported to be mild and passing. These studies are the first that have been done and make the foundation of future scientific research. The dose that was then given was low, and it is assumed that it will result in better effect if the dose is increased to achieve the optimal effect. The goal of this study is to decide on the optimal, tolerant total dose of BP-C1 on dog at the same time as the effect of the medicament on the dog's cancer is registered. There is a corresponding study going on in humans in parallel with this study (KRISTIANSEN, 2013).

4: DISCUSSION

In the treatment of mammary gland tumours there are several methods to choose between. There has not been found a method that is cheap, effective, and relatively harmless which at the same time lead to a cure. All the present methods have positive and negative sides. Surgery is currently the treatment of choice, and it will probably be in the near future as well. In a dog with good health, surgery is probably the most suitable treatment option. However, if the cancer in the dog has already spread, surgery will remove the tumour, but not the metastasis. This is why a thoracic radiograph always is done before surgery, as surgery is in most of the cases not indicated if there is evidence of metastasis. Chemotherapy and radiotherapy are also popular methods, especially in the combination with surgery for example in the case of metastasis; unfortunately their side effects can be quite severe. Therefore, there are situations where conventional methods simply are not an option. It can be due to the current health status of the dog, that the cancer has metastasized or that the owners feel it is too invasive for their dog. If the dog is old or there is evidence of widespread metastasis, it may not be fair to put the dog through surgery or chemotherapy, when it may end up spending its last lifetime trying to recover. In situations like this, maybe more alternative methods shouldn't be so quickly dismissed. After all, both acupuncture and homeopathy are treatment methods where no side effects have been described. If it will not do any harm, and the owner wants to try it, why not? Acupuncture is quite expensive, but it is not painful for the dog, there are no side effects and most importantly there are several successful cases proving its efficacy.

There are many owners that insist on alternative methods when it comes to treatment of illnesses. If these methods do not disturb any on-going treatment, the owner should be able to try it on their dog, at least be informed that it is possible. It is then important that the veterinarians are open to these more alternative treatments. However, it is important to underline that in most cases, methods like homeopathy and herbs will not be the treatment of choice, but it may help on the dog's well-being. It is also important to explain the owner that if the dog is undergoing treatment like chemotherapy, they should always check with the responsible veterinarian, so they do not give any medications or herbs that can disturb the on-going treatment.

There will always be people who do not accept alternative medicine as an option for canine mammary tumours, and they have many arguments for why. As stated earlier, there is no

doubt that there is some quackery in the world of alternative treatments. But still, there are many professional veterinarians specialising in different alternative treatment methods, and they have had impressive results. Therefore, if choosing alternative medicine, it is important for the owner to find a professional, who can guide them and treat their animal the best way,

Oncothermia, which is a newer method, have also had very promising result during the scientific research. In the future, Oncothermia will most probably be an important method when fighting cancer, as well as canine mammary gland tumours.

It is not possible to decide what treatment is the best for mammary gland tumours, as every case, and every dog is different. Also, it is important that the owner feels confident and agrees with the treatment. In the management of canine mammary gland tumours, or cancer in general, we are still searching for a treatment that will lead to an absolute cure, at the same time provide the highest quality of life as possible. In the meantime, it is important that we, as veterinarians keep ourselves updated in new research and available methods. In that way we are able to explain the owner the different treatment options and offer our patients the treatment, which is most suitable for the dog as an individual.

5: SUMMARY

The incident of cancer in pet animals is increasing worldwide, mammary gland tumours in female dogs having the highest occurrence.

The aim of this thesis was to give an overview over the treatments available for canine mammary gland tumours today.

The conventional methods, which are most frequently used are; surgery, radiotherapy and chemotherapy. The approach and outcome of these treatments are briefly described.

The main focus has been on the more alternative methods, as their popularity is increasing. Each method is described with an attempt to give a deeper understanding of what they consist of and what one can expect. In the acupuncture section there are cases describing the procedure and the outcome of acupuncture done on mammary gland tumours in dogs. The homeopathy and herbal medicine section gives a look into the history and describes the practise of these methods. Some future alternative methods are also briefly described, although their importance in the future cannot be certain. As alternative treatment of animals is becoming more popular, hopefully this thesis will inspire veterinarians practising conventional medicine to take a look into the world of alternative medicine.

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Figure 2:http://www.wingmakers.co.nz/Meridian_Earth.html

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