Long-term Follow-up of Canine Mammary Gland Neoplasia in Eight Dogs Treated with Surgery and a New Chinese Herbal Formula

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ABSTRACT

Eight dogs with histologically confirmed mammary adenocarcinoma were enrolled in a study to determine if an herbal formula, Mammosol (a proprietary blend of 28 herbal ingredients), could prolong survival times compared to two previous reports in dogs having surgical excision alone or surgical excision in combination with chemotherapy. Dogs were excluded from the study if they had had chemotherapy or radiation therapy before, during or after the herbal supplement, in order to determine if the supplement alone would extend survival times. All dogs had surgical excision of their cancer and no evidence of metastasis on thoracic radiographs. All dog were administered 0.022 gm/kg of Mammosol twice daily for 2 years and monitored with thoracic radiographs and physical examinations at 3, 6, 9, 12, 18 and 24 months post surgery. Serum biochemical tests for liver and kidney function were evaluated during the study period to monitor for unexpected toxicity. In this study, 7 of the 8 dogs lived greater than 2 years. The dog that lived less than 2 years only received half the dose of herbs due to improper caretaker compliance. Survival rates were significantly increased in the dogs that had surgical excision and Mammosol as compared to previously published results of dogs that had surgery alone (*p* value 0.001) and dogs with surgery and chemotherapy (*p* value 0.05) using the discrete Bonferroni method. Further investigations of Chinese herbal treatments for mammary cancer therapy are warranted.

Keywords: Chinese herbal medicine, mammary adenocarconoma, dogs

Disclosure: Drs. Wen and Johnston co-own Natural Solutions Inc., the provider of the herbal formula, Mammosol, investigated in this study.

Mammary tumors are commonly reported in female dogs and approximately half of these are found to be neoplastic upon histopathological examination.[1] There are several factors that affect the development of mammary tumors. The most significant impact on lifetime risk of disease is the age at which an ovariohysterectomy is performed. Female dogs undergoing ovariectomy prior to the first estrus had a 0.05% risk of developing mammary neoplasia during their lifetime as opposed to 8% in dogs who were spayed between the first and second estrus and 25% in dogs who underwent sterilization after the 3rd estrus.[2] Another study showed that intact females have a seven-fold increased risk of developing mammary cancer compared to spayed females.[3]

Diet may play a role in the risk of mammary cancer development as well. Dogs that were fed home cooked meals, especially containing red meat, such as beef and pork, had a significantly higher incidence of mammary tumors.[4] Further, obesity may influence the risk of mammary cancer as spayed female dogs with a thin body condition at 9-12 months of age have a decreased risk for mammary carcinoma.[5] Breed susceptibilities have been identified and Poodles, Terriers, Cocker Spaniels, and German Shepherds were over-represented compared to other breeds.[6]

Iatrogenic factors have been cited as having a potential role in the occurrence of disease. It has been theorized that exogenous progestogens may instigate tumor development and studies estimate that 50% of canine mammary tumors are estrogen-receptor positive and 44% are estrogen-and progesterone-receptor positive.[7]

Mammary neoplasms are divided into different classes according to histological evaluation. Adenomas and benign mixed tumors account for nearly one half of all canine mammary tumors and the remaining tumors are malignant and classified as carcinomas, adenocarcinomas, sarcomas or inflammatory (or anaplastic) carcinomas.[8]

Approximately half of malignant mammary tumors have already metastasized when initially diagnosed.[9] Metastases most frequently involve regional lymph nodes and lungs. Therefore thoracic radiographs should be obtained to evaluate for evidence of pulmonary metastasis on all cases. Less common sites of metastasis include the kidney, heart, liver, adrenal gland, bone, and

From: Hampton Veterinary Hospital, Speonk, NY

brain.[3] The entire mammary chain should be examined to determine if the primary tumor is accompanied by other mammary nodules as these tumors may occur at multiple sites.

The prognosis for malignant canine mammary tumors varies and disease-related mortality depends upon tumor type, infiltration into blood vessels, nuclear differentiation and tumor size.[8,10-12] The median survival time after surgical excision of mammary carcinomas has been reported to range from 7-16 months. [14] A very poor prognosis has been reported for two subsets of malignant mammary tumors: sarcoma and inflammatory carcinoma. According to one study, the median survival time for dogs with sarcoma of the mammary gland was only 3 months.[14] Local tumor control is often difficult for inflammatory carcinoma and metastases are frequently present at the time of diagnosis.[15]

Treatment options remain limited for malignant mammary tumors. Surgery is the main therapeutic modality used for canine mammary neoplasia, but unilateral or bilateral mastectomy has not shown any survival advantage compared with more conservative surgery such as lumpectomy or partial mastectomy.[11] Results of investigations concerning concurrent ovariohysterectomy and tumor removal have been conflicting. In one study, concurrent ovariohysterectomy did not show any clear beneficial effect, where as another study indicated that ovariohysterectomy with tumor removal produced a mean survival time of 18.5 months compared to 6.1 months for mastectomy alone.[3,16] There is no data showing that affected lymph node removal during tumor removal increases survival time.[17] In one study 75% of dogs with malignant mammary tumors did not survive more than two years with surgery alone.

The authors are not aware of any chemotherapy protocol that has shown consistent efficacy against malignant mammary tumors or the ability to prolong survival in dogs. Side effects associated with the use of chemotherapeutic agents include gastrointestinal upsets, lethargy and immunosuppression that may significantly affect the animal's quality of life.[18] Dogs treated with chemotherapy do not necessarily show significant increases in overall survival time, metastasis, or recurrence-free intervals.[18]

The purpose of this study was to investigate whether surgical excision and a combination of 28 Chinese herbs in a formula called Mammosol[a] could affect the expected life span of female dogs with a histological diagnosis of malignant mammary cancer as compared to published studies of surgical excision alone or in combination with chemotherapy.

MATERIALS AND METHODS

A total of eight cases were collected over a two year period between 2003 and 2007. No dogs were included after 2007 in order to allow a 2 year interval between diagnosis and the end of the study. The dogs ranged in age from 7 to 12.5 years. None of the dogs had known metastases prior to beginning treatment based on no evidence of tumors on thoracic radiographs. All dogs had a histological diagnosis of malignant disease established by a veterinary pathologist. The histological diagnoses included 1 dog with carcinoma, 6 dogs with adenocarcinoma and 1 dog with both adenocarcinoma and sarcoma. In order to be included in the study, the diagnosis must have been made within three months of beginning the herbal supplement. All dogs had surgical tumor removal, but none of them had radiation or chemotherapy before, during or after the study period. No vaccines were given during the study.

The ingredients of the Chinese herbal formula, Mammosol[a] and their properties are listed in Table 1. All single herbs were prepared as a 1:5 ratio extracted powder (5 pounds of dried herb to produce 1 pound of powder). The separate herbal powders were mixed together and encapsulated in size "0" gelatin capsules. Each capsule contained 0.5 gram mixed extracted powder. The herbal formula was then administered at a dose of one capsule per 4.54 kg (10#) body weight or 0.1 gm/kg twice daily for a period of 2 years.

Patients were monitored by thoracic radiographs and physical examination at 3, 6, 9, 12, 18 and 24 months after surgery and beginning the Mammosol[a]. Serum blood urea nitrogen (BUN), creatinine, phosphorus, alanine amino transferase (ALT), aspartate aminotransferase (AST), bilirubin and albumin were monitored via blood chemistry and urinalyses were performed to monitor specific gravity.

RESULTS

The patient age and sex, histological diagnoses, interval from surgical removal to initiation of herbal therapy and survival times are outlined in Table 2. No patients experienced any adverse reactions to the herbal formula during the treatment period and no vomiting or diarrhea was reported. The BUN, ALT, AST, bilirubin and albumin remained in the normal ranges. One dog received only one half of the recommended dosage due to poor caretaker compliance not related to side effects. This dog died 10.5 months after beginning the supplement due to the mammary cancer. At that time the tumor had metastasized to the lungs based on the radiographs and the client decided to euthanize the pet. Another dog in this study died at 14 years of age due to renal failure 3 years after a diagnosis of mammary cancer. At that time, there had been no recurrence of the cancer based on thoracic radiographs and palpation of the mammary region and regional lymph nodes. Six dogs are still alive. None of these dogs have shown evidence of tumor recurrence. Using the discrete Bonferroni method, the survival rate using the herbal formula in this study was significantly better than the survival rate observed in two previous studies using either surgery alone or surgery with chemotherapy (Table 4) at p values of 0.001 and 0.05.[18]

Table 1: Ingredients of the Chinese herbal formula, Mammasol[a], and their pertinent actions

***Pin Yin* Name**	**English Name**	**Actions**[19]
Niu Jiao	Bubali	Analgesic and anti-neoplastic effects
Ru Xiang	Olibanum	Anti-neoplastic effects
Mo Yao	Myrrh	Analgesic and anti-neoplastic effects
Huang Qi	Astragalus	Prolongs survival in mice with tumors
Shan Ci Gu	Cremastra	Anti-neoplastic effects
Xiang Yu	Dioscorea	Improves the intestine's digestive function
Shen Qu	Massa	Protects gastrointestinal tract and facilitates digestion to balance other herbs in the formula that may cause decreased appetite
Shan Zha	Crataegus	Anti-neoplastic effects
Mai Ya	Hordeum	Protects gastrointestinal tract from side effects of other herbs in formula
Xia Ku Cao	Prunella	Anti-inflammatory effects
San Qi	Notoginseng	Cox-2 inhibition; Cox-2 inhibitors have shown to have anti-neoplastic effects against several forms of cancer (e.g., transitional cell tumors of the bladder)
He Shou Wu	Polygonum	Anti-neoplastic effects and enhances the activity of NK cells in mice
Yi Yi Ren	Coix	Anti-tumor effects
Zi Hua Di Ding	Viola	Anti-inflammatory effects
San Leng	Sparganium	Anti-neoplastic effects
E Zhu	Zedoaria	Anti-neoplastic effects
Yin Yang Huo	Epimedium	Anti-inflammatory effects
Quan Xie	Buthus	Anti-neoplastic effects
Wu Gong	Scolopendra	Anti-neoplastic effects
Mu Li	Ostrea	Anti-neoplastic effects
Hai Zao	Sargassum	Immune-stimulant effects
Kun Bu	Laminaria	Inhibits the generation of blood vessels and has demonstrated anti-neoplastic effects in rats
Tai Zi Shen	Pseudostellaria	Stimulates appetite, protects the digestive system
Ji Xue Teng	Millettia	Stimulates a marked increase in neutrophils
Dang Gui	Angelica	Immune-stimulant and analgesic and anti-inflammatory effects
Gou Qi Zi	Lycium	Immune-stimulant, anti-neoplastic effects
Ban Zhi Lian	Scutellaria	Anti-neoplastic effects
Bai Hua She She Cao	Oldenlandia	Anti-neoplastic effects

Mammasol[a] is a proprietary blend of ingredients

DISCUSSION

Using chemotherapy, after surgical removal of tumors, can still result in relapse or metastatic disease in 66.7% of patients (Tables 3 and 4).[18] However, in this report, only 1 of 8 dogs treated with herbal supplements had a recurrence of disease. This dog however only received approximately one half of the recommended dose due to lack of caretaker compliance.

Aside from the possible increased survival rate in dogs receiving herbal supplementation, there are several other benefits associated with this approach. Patients can begin herbal supplementation as soon as the cancer is diagnosed. It is not necessary to delay herb administration after surgery as is often advised with cytotoxic chemotherapy. It seems logical that the sooner anti-neoplastic therapy can be initiated in the peri-surgical period, the greater the chance for a successful outcome.

In comparison with chemotherapy and radiation therapy, which commonly cause unpleasant or life threatening side effects, the herbal therapy had fewer side effects and no dog in this study exhibited any adverse reactions. Although not specifically measured caretakers reported that a high quality of life was maintained.

Unlike chemotherapeutic agents, there is no need for special precautions when handling animal wastes when herbal treatment is administered as no dangerous drugs or metabolites are excreted. As well, no special precautions are required for handling herbal supplements which can easily be administered at home without the use of gloves or the cost of hospitalization.

Table 2: Age, sex, breed, lesion number, lymphatic infiltration, cancer type, mitotic rate and outcome of eight dogs with mammary adenocarcinma treated with the Chinese herbal formula Mammosol[a]

Age Years	Sex	Breed	Lesion number	Lymp infilt	Cancer type	Cancer in SM	MR	Time from surgery until herbs	Metastasis Post Treatment	Survival time
8	F/S	Rottweiler	M	N	A	Y	M	8 days	N	>2yrs
8.5	F/S	Lab cross	S	Y	A	Y	M	12 days	N	>2yrs
7.5	F/S	Lab cross	S	N	A	N	L	6 weeks	N	>2yrs
7	F/S	Mix breed	S	N	C	Y	H	10 days	N	>2yrs
11	F/S	Beagle	M	N	A	N	M	11 weeks	N	>2yrs
11	F/I	Lab cross	M	N	A	N	M	4 days	N	>2yrs
12.5	F/I	Miniature pinscher	S	Y	A, Sa	Y	M	10 days	N	>2yrs
7.5	F/I	Mix	S	N	A	N	M	8 days	Y	10 ½* months

F/S=female spayed, F/I=female intact, M=multiple lesions, S=a single lesion, N=no, Y=yes, A=adenocarcinoma, C=carcinoma, Sa=sarcoma, SM=surgical margins, Lymp infilt=lymphatic infiltration, MR=mitotic rate. M=moderate, H=high, L= low. * dog received only ½ the recommended dose

Table 3: Comparison of survival times for dogs receiving Mammosol herbal formula in this study and two other previously published studies using conventional methods of treatment

Study Author	Number of cases	Number surviving >2 years	Median survival time	Percent relapsed or metastasized
A	8	7/8 (87.5%)	>678 days	12.5%
B	19	3/19 (15.8 %)	370 days	84.2%
C	12	4/12 (33.3%)	231 days	66.7%

A=Wen J, Johnston K. Study with surgery and Mammosol[a] herbal formula (Current study),
B=Simon D, Schoenrock D, Baumgartner W et al. Study with surgery alone[18],
C=Simon D, Schoenrock D, Baumgartner W et al. Study with surgery and doxorubicin and docetaxal chemotherapy[18]

Table 4: *P*-values using the discrete Bonferroni method to statistically compare the outcomes for the mammosol herbal formula treated group and two other previously published studies using conventional treatments

Study Comparisons	*p*-value
p-value for whole study	0.0018
p-value (A) versus (B)	0.001
p-value (A) versus (C)	0.05
p-value (B) versus (C)	0.3839

A=Wen J, Johnston K. Study with surgery and Mammosol[a] herbal formula (Current study), B=Simon D, Schoenrock D, Baumgartner W et al. Study with surgery alone[18], C=Simon D, Schoenrock D, Baumgartner W et al. Study with surgery and doxorubicin and docetaxal chemotherapy[18]

This study suggests that the herbal supplement Mammosol[a] can be a safe and effective treatment for canine mammary gland cancers. Safety of long term use of the herbal preparation is enhanced by several factors. First, the herbs are processed properly. Only herbs with GMP (good manufacturing practice) ratings are used. The herbs in the formula all had certificates of analysis that guaranteed there was no pesticide or heavy metal contamination. The lowest effective dose of all herbs was used in the formula and the herbs were combined and processed to minimize toxicity. *Quan Xie* (Buthus) and *Wu Gong* (Scolopendra) can have toxic effects, but the heads and tails were removed and extremely small amounts (well below the safety level recommended for dogs) were used in the formula, which greatly reduced the chance of toxic effects and

none were seen. Since the case number in this report is low, further studies on a larger number of dogs are needed to further characterize the role of this supplement in dogs with mammary cancer. These studies are currently underway.

FOOTNOTE

[a] Mammosol, Natural Solutions, Inc at 176 Montauk Highway Speonk, NY

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