Surgical technique´s influence on overall survival, disease free interval and new lesion development interval in dogs with mammary tumors

Authors:

Rodrigo dos Santos Horta (Veterinary School - Universidade Federal de Minas Gerais - Brazil)
Gleidice Eunice Lavalle (Veterinary School - Universidade Federal de Minas Gerais - Brazil)
Rúbia Monteiro de Castro Cunha (Veterinary School - Universidade Federal de Minas Gerais - Brazil)
Larissa Layara de Moura (Veterinary School - Universidade Federal de Minas Gerais - Brazil)
Roberto Baracat de Araújo (Veterinary School - Universidade Federal de Minas Gerais - Brazil)
Geovanni Dantas Cassali (Biological Ciences Institute - Universidade Federal de Minas Gerais - Brazil)

Short Title: Surgical technique in dogs with mammary tumors

Keywords: neoplasia, mastectomy, lumpectomy, mammectomy.

Abbreviations: World Health Organization (WHO)

Address:

Escola de Veterinária da UFMG
Av. Antônio Carlos, 6627
PO Box: 567, Campus Pampulha
CEP: 30123-970, Belo Horizonte, MG, Brazil

E-mail: rodrigohvet@gmail.com

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ABSTRACT

Mammary gland tumors represent 42% of all tumors in the bitch. Although there are numerous studies about disease development and progression, some questions remain concerning the surgical treatment. Many surgical techniques may be used for the treatment of canine mammary tumors similar to Medicine, the advantages and disadvantages of each procedure have been extensively discussed. The purpose of this study is to evaluate the influence of surgical procedure on survival, disease free interval and new lesion development interval in dogs with mammary tumors treated according to the biological behavior of these lesions. For this, 143 intact bitches were submitted to surgery for the treatment of mammary tumors between 2007 and 2011. Removal of mammary tumors was performed through the simplest and less invasive surgical procedure necessary for the complete removal of all tumors and main known lymphatic connections between affected glands: lumpectomy, mammectomy, regional mastectomy (including abdominal cranial mammary gland or not) or radical mastectomy. Mean clinical follow-up was 738.5 days. Considering only the first surgical event, 84.6% of animals had more than one mammary tumor, and 52.5% had tumors in both mammary chains. Comparing surgical techniques, there was no difference in ipsilateral and contralateral tumor development. Only 33 dogs developed new lesions in remaining mammary tissue, without correlation with primary lesion. Surgical technique had no effect on overall survival, disease-free interval and new lesion development interval in patients on this study, treated according to oncological surgery principles and established prognostic factors for mammary gland tumors in dogs. It is important to consider these results when deciding on the surgical management of dogs with

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mammary tumors, to avoid aggressive surgical procedures that will not translate into clinical advantages to the patient.

Keywords: Dogs; Surgery; Mammary neoplasm; Lumpectomy; Mammectomy; Mastectomy.

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INTRODUCTION

Mammary gland tumors represent 42% of all tumors in the bitch (Johnson, 1993). Although there are numerous studies about disease development and progression, some questions remain concerning the surgical treatment (Stratmann, 2008).

Similar to human mammary neoplams (Mohammed, 2011), lymphatic system represents the main route of metastasis of mammary malignant pathologies of dogs and cats (Sorenmo, 2003; Lana, Rutteman & Withrow, 2007; Cassali et al., 2011). In the dog, cranial and caudal thoracic glands drain to axillary lymph nodes, whilst inguinal and caudal abdominal glands drain to inguinal lymph nodes. Cranial abdominal gland, however, may drain to either axillary or inguinal lymph nodes (Sorenmo, 2003; Patsikas, Dessiris, 2006). Axillary lymph nodes are rarely involved with mammary cancer in the dog and should not be removed prophylactically. The inguinal lymph node, intimately associated with the ipsilateral inguinal gland, should be removed whenever this gland is surgically removed (Lana, Rutteman & Withrow, 2007). Connections between glands on different sides and between other mammary glands are rare, but may exist (Patsikas, Dessiris, 2006). Pereira et al. (2003) reported that neoplastic lesions may induce the development of lymphatic anastomoses, modifying mammary tissue natural drainage.

Surgery is the basic treatment of canine mammary tumors and is the most effective for disease regional control (Sorenmo, 2003).

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Many surgical techniques may be used for the treatment of canine mammary tumors (Lana, Rutteman & Withrow, 2007; Hedlund, 2008) and similar to Medicine (Fisher et al., 1977; Bland, 1981), the advantages and disadvantages of each procedure have been extensively discussed (Fergunson, 1985). When studying biological behavior of canine mammary tumors, Gilbertson et al. (1983) indicated radical mastectomy as the best surgical option. In the same year, Brodey et al. (1983) advocated individual treatments; surgical procedure should respect known lymphatic connections and base itself on tumor location, number and size of lesions and existence of skin or muscular adhesions. Radical surgeries were thoroughly performed on women with mammary tumors between 1910 and 1964, without any clinical benefits (Olson, 2002, Cotlar, Dubose, Rose, 2003). As from the 1950´s, Halsted´s mastectomy was questioned (Bland, 1981), however, the lack of clinical benefits of the radical mastectomy was only proved by the end of the 1970´s (Fisher et al., 1977). Similar to Medicine, a prospective study conducted by MacEwen et al. (1985), with 144 dogs, did not find any difference between recurrence rate and survival when single mastectomy was compared to chain mastectomy.

A greater understanding about canine mammary pathology and new therapeutic modalities enabled the definition of distinct groups regarding prognosis and treatment (Cassali et al., 2011). Aggressive surgical procedures for the treatment of localized lesions may reduce the risk of developing new lesions in a small number of dogs, especially in young intact bitches (Lana, Rutteman & Withrow, 2007). Stratmann et al. (2008) also indicated radical mastectomy as the best surgical option, regardless of number and size of lesions. Authors reported a superior probability of new tumor

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growth ipsilateral to the first surgery, although without statistical significance assessment.

The purpose of this study is to evaluate the influence of surgical procedure on survival, disease free interval and new lesion development interval in dogs with mammary tumors treated according to the biological behavior of these lesions.

MATERIALS AND METHODS

Inclusion criteria:

143 intact bitches were submitted to surgery for the treatment of mammary tumors between 2007 and 2011.

Animals with malignant lesions and compromised surgical margins accessed by histopathological evaluation and dogs submitted to targeted adjuvant therapies with the use of cyclooxygenase inhibitors or hormone-therapy through ovariohisterectomy were excluded. Adjuvant chemotherapy was allowed. Candidates to chemotherapy were patients with lymph node or distant metastasis and patients with guarded to poor prognostic tumor diagnoses including: micropapilar carcinoma, high degree tubular carcinoma, mucinous, secretory or lipid-rich carcinoma, solid carcinoma, malignant mioepitelioma, carcinosarcoma and other sarcomas (Cassali et al., 2011).

Prior to surgery, all animals went through a complete clinical exam and two-view thoracic radiographs were taken to evaluate metastasis. Lymph nodes with size, shape or

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consistency alterations were submitted to fine-needle aspiration cytology for metastasis evaluation. Positive cases were removed during surgery.

This study was approved by the ethics committee in animal experiments (023/2011).

Choosing the surgical technique

Removal of mammary tumors was performed through the simplest and less invasive surgical procedure necessary for the complete removal of all tumors and main known lymphatic connections between affected glands, as suggested by Brodey et al. (1983) and Lana et al. (2007).

It was not possible to separate surgical technique from staging and type of disease, since surgical technique was chosen according to lesion number and site, respecting lymphatic drainage and established prognostic factors such as size of lesions and existence of skin or muscular adhesions.

Lumpectomy was the removal of single solid superficial non-adherent tumors less than one centimeter. Lesions larger than one centimeter implied the need to remove the role gland. Mammectomy was indicated for lesions up to three centimeters, affecting only one gland whilst regional mastectomy was indicated for the removal of lymphatic connections of glands affected by lesions larger than three centimeters. The removal of cranial abdominal gland during regional mastectomy was sometimes necessary to obtain adequate surgical margins or for lesions between one and three centimeters in this gland. Radical mastectomy was the removal of all mammary chain unilaterally, when

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lesions larger than three centimeters affected the cranial abdominal gland. Regional and radical mastectomies were also performed on multiple lesions, of one to three centimeters, to obtain a single surgical wound through a continuous incision and resection of mammary tissue.

Surgically removed tumors were submitted to surgical margin review, histopathological exam and classification, as proposed by Cassali et al. (2011).

Clinical follow-up:

Throughout clinical follow up (median 738.5 days), dogs were examined, including thoracic radiographic examinations, in three to six months intervals or sooner, in case the owner recognized changes on the mammary chain or in case the patient was submitted to adjuvant chemotherapy. Subsequent surgery was indicated and performed in dogs that developed recurrences or new tumors on the remaining mammary tissue.

Survival time, in days, was defined as the time from original surgery until death caused by the disease. Disease free interval, in months, was defined as the time from original surgery until development of local recurrence or distant metastatic disease. New mammary lesion development interval, in months, was defined as time from original surgery until development of subsequent lesions in the remaining mammary tissue.

Experimental design e statistical analysis:

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Each animal represented a repetition and each surgical technique a group: lumpectomy (P1), mammectomy (P2), regional mastectomy without cranial abdominal gland involvement (P3), regional mastectomy with cranial abdominal gland involvement (P4), and unilateral mastectomy (P5).

After descriptive analysis of data and determination of malignant lesion frequency according to the surgical technique, groups were compared with chi-squared test.

Spearmann´s test was used to determine correlation between number of lesions and number of histological diagnoses in dogs that presented multiple mammary lesions at initial diagnoses or that underwent new surgical procedures, due to development of new lesions in the remaining mammary tissue.

Spearman´s correlation was used to assess the association between surgical technique and patient staging. The ages of animals in each surgical technique group were submitted to analysis of variance and the median values were compared with Fisher exact test and Tukey´s post-test.

New tumor development could only happen on the same gland of dogs treated by lumpectomy and radical mastectomy precludes new tumor development ipsilaterally, therefore, new mammary lesion development contralateral and ipsilateral, in each surgical technique (with the exception of evaluation of frequency of ipsilateral lesions for radical mastectomy) was compared with a chi-squared analysis.

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Overall survival, disease free interval and new mammary lesion development interval (unrelated to primary tumor) were calculated using the Kaplan-Meier product limit method. Longrank statistics of Cox-Mantel was used to compare groups. Cases were censored for analysis if lost to follow-up or dead from another disease.

Statistical significance for all testing procedures was set at 5%.

RESULTS

One hundred forty-three dogs were included in the study. Ages of the dogs ranged from 3 to 16 years (mean 9.2 ± 2.3 years). There were 23 mixed breed dogs (16%) with the other 120 dogs, representing 25 breeds. Poodle was the most common (n = 52; 36.4%), followed by Cocker Spaniel (n = 11; 7.7%) and Yorkshire terrier (n = 10; 7%) (Table 1).

Considering only the first surgical procedure, 121 (84.6%) of 143 dogs had more than one mammary lesion, and 52.5% of animals had tumors on both mammary chains. Histopathological diagnosis was established for 391 lesions, and 219 (56%) were classified as malignant neoplasms, 121 (31%) were benign neoplasms and 49 (12.5%) were non-neoplastic lesions. Histological types, in each surgical technique, are demonstrated on Table 2. Benign mixed tumor represented 56.2% of benign neoplasms, followed by papilloma (23.1%) and adenomas (17.4%). Carcinoma in mixed tumor was

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the most frequent mammary cancer (47.5%), followed by malignant lesions “in situ” (23.3%) and papillary carcinoma (7.7%).

There were no significant differences between surgical techniques with regard to malignant lesion frequency ($p>0.05$), however, there was a correlation between patient staging and surgical technique ($p<0.0001$; $rs = 0.409$) and between staging and patient age ($p<0.002$; $rs = 0.247$). The number of animals submitted to each technique and mean age in each group are demonstrated on Table 3. Dogs submitted to lumpectomy (P1) were younger than dogs on other groups, and so were animals submitted to regional mastectomy without removal of cranial abdominal gland (P3) compared with those submitted to radical mastectomy (P5) ($p<0.0001$).

There was no significant correlation between lesions, but there was a strong association between number of mammary tumors and histological diagnoses variety ($p<0.0001$; $rs = 0.833$), as shown on Table 4. Thirty-three (24.8%) dogs developed new tumors on the remaining mammary tissue, and the number and percentage of animals that developed new tumors on the same gland where the first tumor was removed (only for lumpectomies), the ipsilateral chain adjacent or not (except for radical mastectomy) or the contralateral mammary chain, according to surgical technique, is shown on Table 5. No new lesions were observed in 30%, 72.7%, 72.7%, 71.4% and 90.2% of dogs in groups P1, P2, P3, P4 and P5, respectively. There was no significant difference between development of tumors ipsilaterally or contralaterally with regard to surgical technique ($p>0.05$).

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During follow-up, only fifteen, of 33 animals that developed new mammary lesions on the remaining tissue after the first surgery were submitted to subsequent surgery. There was no correlation between lesions ($p>0.05$), and only five (33.3%) dogs had the same histological type on both procedures.

None of the patients submitted to lumpectomy and mammectomy died due to the disease or developed signs of the disease during follow-up. It was observed greater survival ($p <0.03$) and disease free interval ($p <0.05$) in patients of groups P1 and P2, when compared with P5, as shown in Figures 1 and 2, respectively. New lesion development interval (Figure 3) was random and there was no evidence of reducing the development of new lesions by use of a more extensive surgical technique ($p>0.05$).

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DISCUSSION

The mean age of dogs diagnosed with mammary tumors and the search for veterinary assistance were in accordance with earlier reports (Daleck et al., 1998; De Nardi et al., 2002; Sorenmo, 2003; Zatloukal et al., 2005). The high incidence of crossbreds, Poodles and Cocker spaniels may be related to population profile. However, in a study by Zatloukal et al. (2005), of 214 dogs, Poodles and Cocker spaniels had a statistically significant relative risk of developing mammary gland neoplasia.

Multiple mammary tumors, seen in 84.6% of animals in this study, are not related with the possibility of multicentric disease and do not imply a worse prognosis (Sorenmo, 2003). Fowler et al. (1974) and Benjamin et al. (1999) describe multiple lesions in over 60% of the cases, and each tumor should be examined separately, because there is a great possibility of distinct histopathological diagnoses. The strong correlation between number of lesions and distinct diagnoses, which occurred in 83.3% of the study population, is in accordance with Fowler et al. (1974) and Cassali et al. (2011).

In this study, malignant neoplasm frequency of 56% was superior to the 50% ratio reported by Sorenmo (2003) and Lana (2007). However, De Nardi et al. (2002) and Filho et al. (2010), reported malignancy ratios of 68.4% and 73.3%, respectively. These

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differences may relate to regional characteristics as contraceptive use (De Nardi et al., 2002) and delay in the search for veterinary assistance. In this study, benign mixed tumor was the most frequent benign neoplasm (56.2%), but it was the second most frequently diagnosed (40%) by Filho et al. (2010). Likewise, carcinoma in mixed tumor represented 47.5% of malignant neoplasms in this study, and 20.5% on the study by Filho et al. (2010). Frequencies reported in this study for each histological type differ from international literature reports (Gilbertson, 1983; Brodey, Goldschmidt, Roszel, 1983; Stratmann et al., 2008), probably due to a lack of histological standardization for canine mammary tumors (Salgado, Cassali, 2012).

Surgical technique, performed as proposed by Brodey et al. (1983) and Lana et al. (2007), was related to patient staging in 40.9% of the population in this study. There was a correlation between staging and patient age in 24.7% of cases, which implied the need for more aggressive surgery on older animals. World Health Organization (WHO) stage III, IV or V in older patients may be related to interval between tumor development and veterinary assistance, leading to the need of more aggressive procedures in these animals (Campos et al., 2012). Gilbertson et al. (1983) reported that some mammary lesions are associated with a higher risk for the development of invasive malignant neoplasms. Cassali et al. (2011), reported alterations on the mammary epithelium molecular expression pattern suggesting intraepithelial and intraductal lesions, as the ones reported in this study, which may represent pre-neoplastic lesions and a premature level of canine breast cancer development, and substantiates premature and simpler surgical procedures.

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Unlike the report by Stratmann et al. (2008), there was no significant difference in ipsilateral and contralateral tumor development between surgical techniques, probably because, in this study, surgical technique was not randomly chosen, but based on disease macroscopic and clinical features. In addition, there was no correlation between subsequent lesions, probably due to a more detailed histopathological evaluation of each lesion.

Survival and disease free interval estimates were higher for dogs submitted to lumpectomy or mammectomy. This result may be related to early staging of these patients, which has better prognostic factors.

As MacEwen et al. (1985) reported for dogs and Fisher (1977) for Medicine, surgical technique must be chosen based on prognostic factors described on literature and there is no benefit on survival, disease free interval and new lesion development interval in dogs treated randomly by radical mastectomy (Lana, Rutteman & Withrow, 2007). The effectiveness of a surgical treatment depends on the surgeon's overall understanding of the overall health of the patient, type and stage of cancer, adjuvant therapies available and expected prognosis (Fisher, 2008).

Therefore, we conclude that surgical technique does not influence overall survival, disease free interval and new lesion development interval, as long as oncological surgery principles and established prognostic factors are respected; patients must have routine checkups and, any lesion, however small, must be prematurely removed by surgery and; canine mammary tumors must be removed by the simplest procedure, with the goal of removing the role lesion and the main lymphatic connections.

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464 **FIGURES**

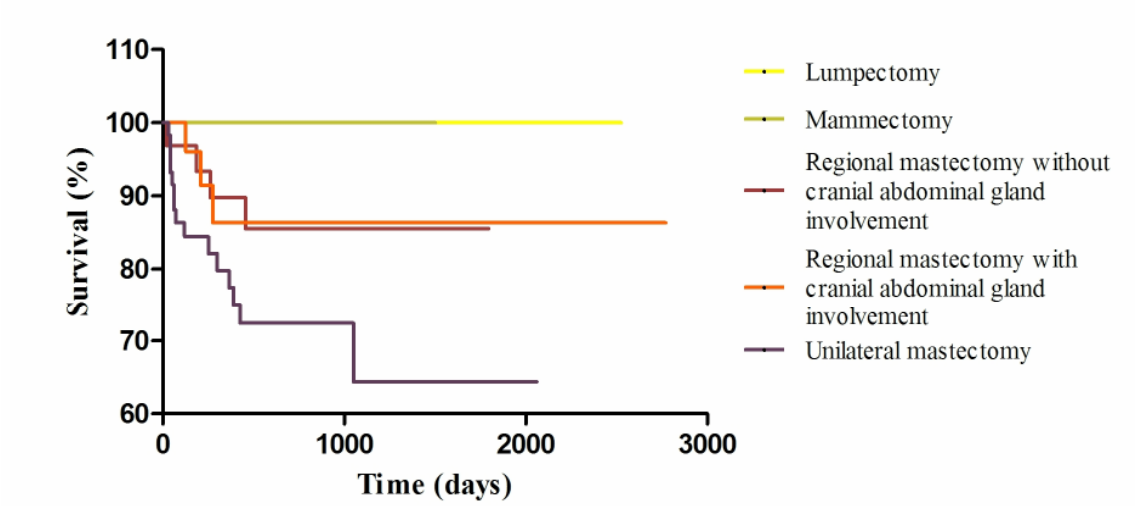

Figure 1 - Graphical representation (Kaplan-Meier curve) of survival evaluation of 143 dogs with mammary tumors, by surgical technique.

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466 Figure 1 – Graphical representation (Kaplan-Meier curve) of survival evaluation of 143
467 dogs with mammary tumors, by surgical technique.

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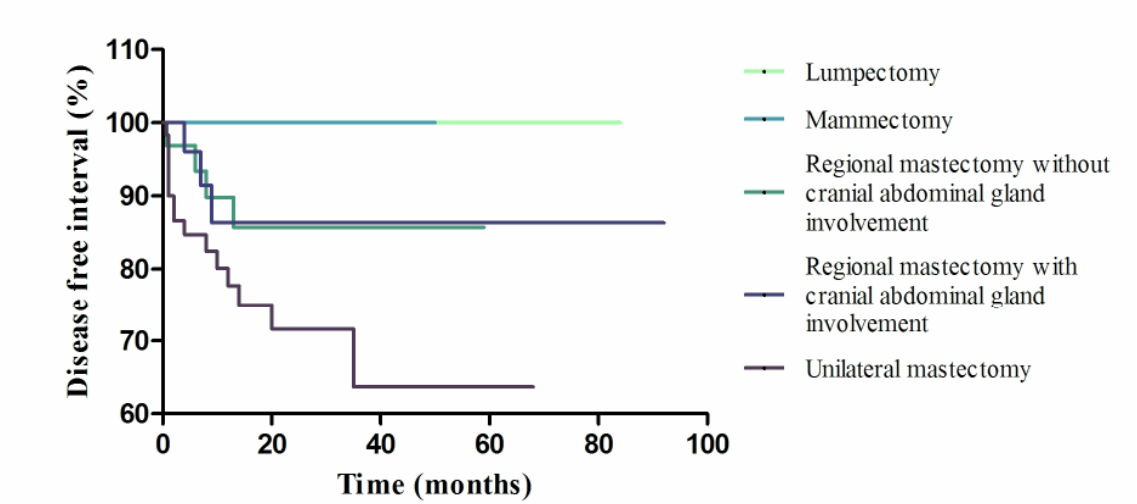

Figure 2 - Graphical representation (Kaplan-Meier curve) of disease free interval evaluation of 143 dogs with mammary tumors, by surgical technique.

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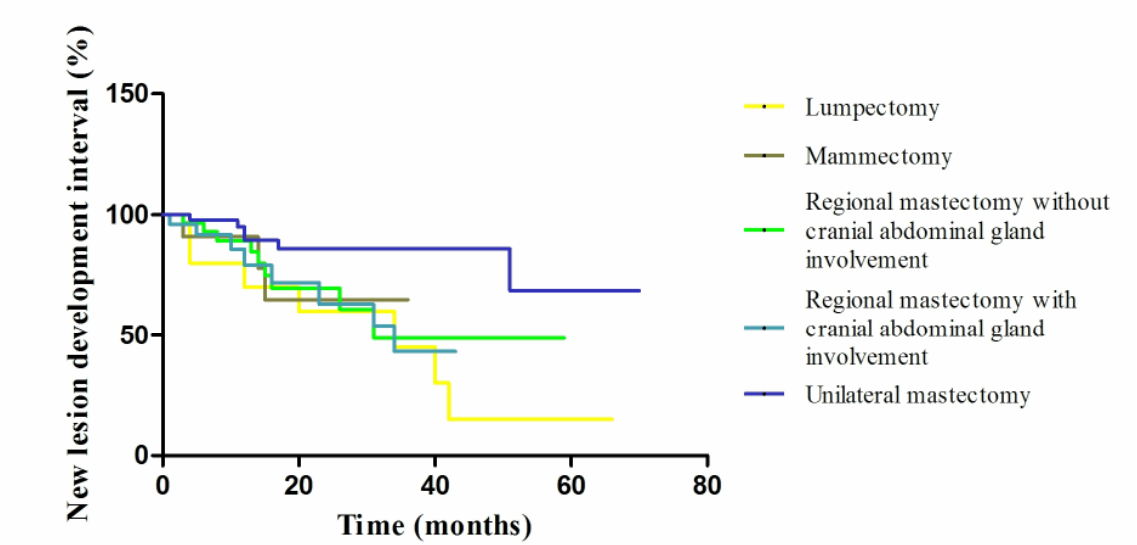

Figure 3 - Graphical representation (Kaplan-Meier curve) of new lesion development interval evaluation of 143 dogs with mammary tumors, by surgical technique.

Figure 3 – Graphical representation (Kaplan-Meier curve) of new lesion development interval evaluation of 143 dogs with mammary tumors, by surgical technique.

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477 **TABLES**

Table 1 – Breed total from the 143 dogs submitted to surgical treatment for the removal of mammary tumors

Breed	Number
Poodle	52
Cocker Spaniel	11
Yorkshire Terrier	10
Dachshund	7
Pinscher	6
German Shepherd	6
Bichon frise	4
Others	24
Crossbred	23
TOTAL	143

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Table 2 – Histopathological exam results and number of lesions found for each tumor type for each surgical technique on 143 dogs.

Histological type	Surgical technique					
Malignant neoplasms	**P1**	**P2**	**P3**	**P4**	**P5**	**TOTAL**
Carcinoma in mixed tumor	6	5	25	12	56	104
"in situ" carcinoma	1	2	6	13	29	51
Papillary carcinoma	0	1	2	4	10	17
Tubular carcinoma	0	0	0	1	10	11
Solid carcinoma	0	0	0	5	4	9
Tubulopapillary carcinoma	1	0	4	0	3	8
Carcinosarcoma	0	0	1	1	4	6
Complex carcinoma	0	0	2	1	0	3
Mucinous, secretory or lipid-rich carcinoma	0	0	0	0	3	3
Malignant mioepitelioma	0	0	0	0	2	2
Hemangiosarcoma	0	1	1	0	0	2
Sarcoma in mixed tumor	0	0	0	0	1	1
Osteosarcoma	0	0	0	0	1	1
Micropapillary carcinoma	0	0	0	0	1	1
TOTAL	8	9	41	37	124	219
Benign neoplasms						
Benign mixed tumor	3	4	16	19	26	68
Papilloma	1	5	5	5	12	28
Simple, basaloid and complex adenoma	0	2	2	6	11	21
Adenomioepitelioma	0	0	1	0	0	1
Lipoma	0	0	1	0	0	1
Hemangioma	0	0	0	0	1	1
Fibroadenoma	0	0	0	0	1	1
TOTAL	4	11	25	30	51	121
Non-neoplastic lesions						
Ductal and lobular hyperplasia	1	0	7	5	19	32
Mastitis	0	0	2	6	7	15
Columnar cell lesion	0	0	0	0	2	2
TOTAL	1	0	9	11	28	49

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Table 3 – Number of animals, mean age and standard deviation in each group, by surgical technique

Surgical technique	n	Age ($x \pm s^2$)
Lumpectomy	10	6,2 ± 2,2
Mamectomy	11	10,0 ± 2,3
Regional mastectomy without involvement of cranial abdominal gland	33	8,9 ± 2,2
Regional mastectomy with involvement of cranial abdominal gland	28	10,2 ± 2,5
Unilateral mastectomy	61	10,5 ± 2,2

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Table 4 – Number of lesions and mean distinct diagnoses on 143 dogs

Number of lesions	Number of animals	Mean of distinct diagnoses
1	33	1,00
2	43	1,74
3	31	2,45
4	24	2,96
5	4	3,50
6	3	4,00
7	4	4,75
13	1	6,00

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Table 5 – Number and percentage of animals that developed new tumors by surgical technique

Surgical technique	P1	P2	P3	P4	P5
Same mammary gland	4 (40%)	-	-	-	-
Ipsilateral mammary chain adjacent	2 (20%)	0 (0%)	2 (6,1%)	0 (0%)	-
Ipsilateral mammary chain non adjacente	1 (10%)	2 (18,2%)	4 (12,2%)	2 (7,1%)	-
Contralateral mammary chain	3 (30%)	2 (18,2%)	5 (15,2%)	7 (25%)	6 (9,8%)

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