Ovario-Hysterectomy: An Alternative to Mitigate the Incidence of Mammary Tumors in Canines

Yunayka Mato Lorenzo[1], Leonel Lazo Pérez[2], David del Valle Laveaga[3], José L. Sastre Torres[1], Fredy Peña Rodríguez[2], Raúl A. González Martínez[4], Rigoberto Fimia Duarte[2,5*]

[1]Veterinary Clinic of Rodas municipality, Cienfuegos, Cuba.
[2]Central University "Marta Abreu" of Las Villas, Villa Clara, Cuba.
[3]Juarez University Autonomous of Tabasco, Tabasco, México.
[4]Provincial Center of Epizootiology and Veterinary Diagnosis of Cienfuegos, Cuba.
[5*]Faculty of Health Technology and Nursing (FTSE), University of Medical Sciences of Villa Clara (UCM-VC), Cuba

Abstract— The general objective of the study was to estimate the appearance of recurrence of the mammary tumor in canines after applying the Ovariohysterectomy with previous removal of the mammary tumor. The research was carried out in a veterinary clinic in the municipality of Rodas, Cienfuegos, Cuba. During the first semester of 2017, a descriptive study was carried out, where the sampled population consisted of 80 female canines, diagnosed with mammary tumors. The surgical techniques that were performed were Ovariohysterectomy and/or removal of tumors. An exhaustive analysis of the anamnesis data was performed to assess possible causes and predisposing factors. The variables studied were the location of the tumors, degree of malignancy, histological characteristics, age and race. A retrospective observational study was carried out to determine whether tumor removal with or without the performance of Ovariohysterectomy constituted a risk or protective factor against the appearance or not of recurrence after treatment. The tumors affected the region of the inguinal, middle and anterior mammary glands. The histopathological diagnosis showed tumors of histological malignancy Type I and II and the presence of abscessed granulomatous mastitis is considerable. The highest prevalence of mammary tumors is found in the age groups between seven and nine years of age and in mestizo racial types. The canines that underwent ovary hysterectomy with previous removal of the mammary tumor had a lower risk of suffering recurrences than the animals that underwent only the removal of the mammary tumor.

Keywords— Caninos; glándula mamaria; neoplasias; ovario-histerectomía.

I. INTRODUCTION

Mammary gland neoplasms in bitches have a higher incidence than in other domestic species and three times higher than in humans. This has been related to the hormonal changes of estrous cycles independent of gestation (Núñez and Montes de Oca, 2012), hence mammary tumors are the most frequent neoplasms in unsterilized bitches (Alleman and Bain, 2000; Salas et al., 2015). These come to represent 50% or more of all tumors in females, while in males they are less than 1% (Dobson and Duncan, 2014).

Lujan et al. (2016) defines as mammary gland neoplasms, masses of varying size and shape that appear in any of the anatomical sections that make up this organ, which, as an indispensable requirement is that, the mass is composed of own cells that present an autonomous and uncontrolled growth.

Canine mammary tumors (CMT) represent almost half of the neoplasms in bitches (Sorenmo et al., 2020; Valdivia et al., 2021). In bitches, the protective effect of early ovarian hysterectomy and the presence of steroid hormone receptors in tumor tissues indicate that hormonal factors are involved in the development of mammary tumors (Illera et al., 2006; Beauvais et al., 2012). The clinical presentation of MCTs is very variable, being able to be single or multiple and are exceptional in animals younger than two years, increasing the incidence markedly from the age of six years and continues to do so until the age of ten years, past this age the risk decreases, they are rare in males and young animals of both sexes, this type of tumor has a multifactorial etiology (Hermo et al., 2017).

Mammary gland tumors in canines are commonly diagnosed in clinic, they represent about 50% of tumors occurring in bitches, this incidence being three times higher than that reported in females. Most mammary gland tumors in bitches are of epithelial origin, and approximately 50% are malignant (Arias et al., 2015).

In Veterinary Medicine, an annual incidence of 198 cases of mammary cancer per 100 000 canines was estimated (Meuten, 2016). Currently there are numerous new methods that facilitate diagnosis, including molecular biological tools (Robinson et al., 2000), however, the histopathological study is one of the most reliable and is considered to be the main test for obtaining the definitive diagnosis and tumor classification, based on the morphological characteristics of the tumor (tumor size, nodular status, histological characteristics) and currently takes into account the expression of specific markers associated with the clinical course (Aristizábal et al., 2016).

Canine mammary tumor constitutes the type of neoplasm with the highest incidence in the canine species, whether malignant or benign. It is higher than in other domestic species and three times higher than in humans, this has been related to the hormonal changes of estrous cycles independent of gestation (Núñez and Montes de Oca, 2012), which is why in Veterinary Medicine mammary tumors are the most frequent type of neoplasia in unsprayed bitches (Salas et al., 2015) and can represent 50% or more of all tumors in females however in males less than 1% (Dobson and Duncan, 2014).

Ovario-hysterectomy (OVH) is the surgical technique that involves the removal of the ovaries and uterus, it is performed

with the aim of avoiding estrous cycles, which occur in bitches as well and avoiding unwanted litters (Andrade, 2016).

The OVH prevents diseases of the reproductive tract and is not associated with increased obesity, pathologies of the lower urinary tract, long bone fractures, arthritis, immunosuppression or small urethra, has seven times less risk of acquiring a mammary tissue tumor than one that has not been spayed. When spaying is performed before six months of age, the risk of mammary gland tumors is almost completely eliminated (De Andrés, 2015).

The objective of this study was to estimate the occurrence of mammary tumor recurrence in canines after ovario-hysterectomy with previous removal of the mammary tumor.

II. Material and Methods

The present research was carried out in the veterinary clinic of the municipality of Rodas, province of Cienfuegos, Cuba, during the first semester of the year 2017. A descriptive study was carried out, with the objective of estimating the occurrence of mammary tumor recurrence in female canines after ovario-hysterectomy with previous removal of the mammary tumor. The study population consisted of 80 female canines diagnosed with mammary tumor, representative of 11 breeds, with a predominance of mongrels and aged between 4 and 10 years.

An exhaustive analysis of the anamnesis data was carried out to evaluate possible causes and predisposing factors. The variables studied were tumor location, degree of malignancy, histological characteristics, age and race. A retrospective observational study was carried out to determine whether tumor removal with or without ovarian hysterectomy was a risk or protective factor for the appearance or not of recurrence after treatment.

The patient's clinical history, case number, race, age, presumptive diagnosis, tumor type, location, treatment with ovarian-hysterectomy performed or not and tumor removal were recorded. Of the cases clinically diagnosed with breast tumor, 100% (80) underwent breast surgery or removal of the breast tumor and 43 (representing 53.7%) also underwent ovarian hysterectomy.

To determine the recurrence of the tumors, the appearance or non-appearance of the tumors after surgical treatment (ovarian-hysterectomy with removal of the tumor or only removal of the tumor) was observed during a period of four years.

2.1. Surgical Techniques Used

The surgical techniques performed during the study were ovario-hysterectomy (43 cases) together with breast tumor removal, and breast tumor removal (37 cases). In this research we assume the ovario-hysterectomy (inguinal median) referred by Santiago et al., (2021). In the case of the removal of mammary tumors, the operative techniques according to (Alleman and Bain, 2000) were applied.

The surgical removal of the mammary gland by means of the lumpectomy procedure was applied to seven canines, representing 8.75 % of the total, and consisted of removing the tumor and one centimeter of normal tissue, leaving the adjacent gland intact. This procedure is indicated for small, circumscribed and non-invasive tumors.

Surgical removal of the mammary gland by simple mastectomy procedure was applied to 27 canines, representing 33.7% of the total. It consisted of removing the entire mammary gland and thus avoiding the problems of lymphatic and milk fluid leakage in the wound.

Surgical removal of the mammary gland by means of the regional mastectomy procedure, was applied to 26 canines, representing 32.5% of the total, it was practiced when the tumors were large, and the incision was extended to the contiguous gland or glands to obtain adequate margins.

Surgical removal of the mammary gland by the complete unilateral mastectomy procedure, was applied to 20 canines, representing 25% of the total, for those cases in which the tumors were located in multiple glands, the ipsolateral ones and the intervening tissue were removed. In malignant tumors with metastases, surgical removal of the mass in the mammary gland was used together with removal of the involved regional lymph node.

Thirty mammary tissue samples were collected from canines with clinical diagnosis of tumor for histopathological study of mammary neoplasms. The tissue samples obtained were sent to the Pathology Department of the Provincial Center of Epizootiology and Veterinary Diagnosis of Cienfuegos province, were preserved (fixed) in individual containers (10 mL screw-capped tubes with 10% buffered formaldehyde and kept at room temperature (28°C) until processed by the routine histological technique hematoxylin and eosin. They were then dehydrated and embedded in kerosene blocks, the blocks were cut with microtome at 5 μm and the tissue sections were further stained with Van Gieson's dye. The obtained plates were observed under Olympus CX30 microscope with 40x, 100x and 400x objectives.

The grade of the tumor lesion was assessed by the method of Elston and Ellis, (1991) for the samples that turned out to be carcinomas. This method was based on a grading from I to III (low grade-well differentiated, intermediate grade-moderate differentiation and high grade-poor differentiation).

In addition, a risk analysis was performed to determine the association between the ovarian-hysterectomy factor and the recurrence of mammary tumor in canines, for which a cross-sectional observational analytical study was applied.

2.2. Statistical Processing

The data were collected in a database using the Microsoft Excel tabulator and a frequency distribution was made according to age, breed and number of calving is of the animals. A binomial proportion comparison test was performed to calculate the percentage of recurrence according to the treatments used.

In addition, the associations between ovario-hysterectomy and mammary tumor recurrence were found by forming 2 x 2 contingency tables and applying the χ^2 test, for a confidence level of 95 %; the prevalence ratio and other statistics were estimated. The program for epidemiological analysis of tabulated data EPIDAT version 3.1 was used for these processes. Statistical processing was performed using the

statistical package STATGRAPHICS CENTURION ver XV. II (Statistical Graphic Corp., USA, 2006).

III. RESULTS AND DISCUSSION

With the help of empirical methods of investigation such as observation, interviews with the owners of the animals and the orderly registration of the clinical histories, with emphasis on the anamnesis, it was possible to determine that the causes for the high and frequent occurrence of this pathology in the clinic under study may be varied, such as the abandonment of the animal, pseudo pregnancies, unwanted pregnancies without clinical follow-up, the recurrent use of hormones such as estradiol benzoate after an unwanted mating to avoid gestation, and also the genetic factor. To a lesser degree diet, body weight and obesity may also be a cause to consider.

However, as a notable insufficiency that highly influences the recurrence of this pathology is that the owners of this species have little culture of management and breeding, and much need to know the advantages of early castration (ovary-hysterectomy) in females before the appearance of mammary tumors, i.e. at six months of life, before the occurrence of the first heat.

As a result of clinical examinations, a presumptive diagnosis of mammary tumors was made. The tumor masses were located in the region of the inguinal, middle and anterior mammary glands in 81.81%, 9.09% and 9.09% respectively.

Regarding the anatomical location of mammary tumors, various studies conducted in different parts of the world (Chau et al., 2013; Ruano, 2013; Lipa et al., 2019), showed that 60% of mammary tumors are located in the fourth and fifth mammary gland, which corresponds to what was found in the present study. This result is attributed to the greater volume of mammary tissue susceptible to tumor transformation, an aspect that has been pointed out by (Gerosa, 2007; Sánchez and Guarín, 2014).

The present research points out in its comparative analysis or evaluation of the affectation of the mammary glands that, according to the location of the tumor masses 81.81% appear represented in the inguinal glands, while in the middle and anterior glands they appear in only 9.09 % respectively, which coincides with the criteria of Shafiee (2013) and Bergman (2017) which consider that the location of the lesion is of great importance, as susceptibility must be considered, since there are some lesions in mammary glands (GM) with higher incidence than others, which leads to consider that inguinal GM with 60% incidence and affectation than cranial or medial, only reach 27%, indicating the degree of sensitivity to tumor processes.

In the case of tumors diagnosed as carcinomas, they were classified according to the criteria of Goldschmidt et al. (2011) who used a methodology that adds a gradation from I to III to determine the degree of malignancy (low grade, intermediate grade, high grade). The histopathological diagnosis showed that 18.2% (4/30) of the samples analyzed had Type I histological malignancy tumors, 45.4% (10/30) Type II and Type III 36.36% (8/30), on the other hand, it is of utmost importance to highlight that 8/30 samples sent to the laboratory turned out to be abscessed granulomatous mastitis (Table 1).

TABLE 1. Histological classification of the tumors found

N	Carcinoma grade I (%)	Carcinoma grade II (%)	Carcinoma grade III (%)	Granulomatous mastitis
30	4 (18.2)	10 (45.4%)	8 (36.6)	8 (36.6)

The grading system used is an adaptation of the Elston and Ellis (1991) system currently used in human mammary neoplasms, also known as the Nottingham system, which is based on the scoring of three morphological criteria: the proportion of tubular architecture of the neoplasm, the degree of nuclear pleomorphism and the mitotic index.

Granulomatous mastitis is a benign entity of the breast, of unknown cause, which in many cases resembles a carcinoma. It is characterized by multinucleated and epithelioid giant cells, limited to the mammary lobules with micro abscesses. In other species such as sheep, granulomatous mastitis produced by the filamentous fungus *Aspergillus fumigatus* has been reported (Lazo, 2022).

The histopathological study identified cases that showed various degrees of malignancy (tubular carcinoma, fibrosarcoma, tubular carcinoma grade I) where epithelial cells with different and very diverse atypia, multiple tubular structures, nuclear and cellular pleomorphism and mitosis figures were observed. Abscessed granulomatous mastitis and benign tumors were also observed.

Figure 1A shows a histologic section of breast with diagnosis of abscessed granulomatous mastitis. The inflammatory infiltrate and areas of caseous necrosis can be seen at the periphery of the lesion.
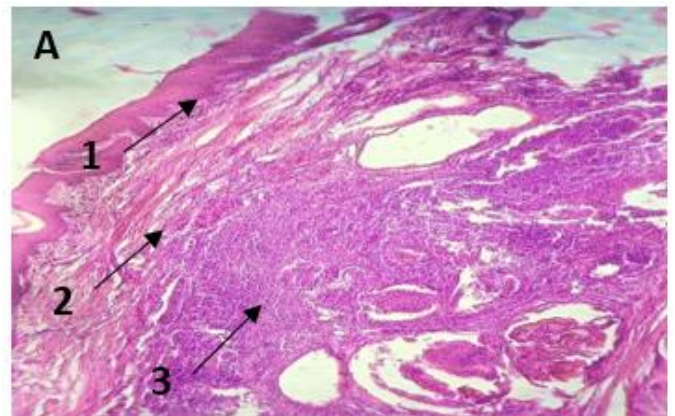

Figure 1A Granulomatous abscessed mastitis 100X. Hematoxylin Eosin (H. E)

Legend: 1 Epidermis, 2 Dermis and elastic fibers, 3 Granuloma with inflammatory cells.

There is a central region with an amorphous and acidophilic substance characteristic of caseous necrosis, surrounded by multinucleated giant cells (Langhans giant cells). A halo of inflammatory cells was also observed, mostly represented by lymphocytes and macrophages with some neutrophils. All of these defensive berries are encapsulated in fibrous tissue.
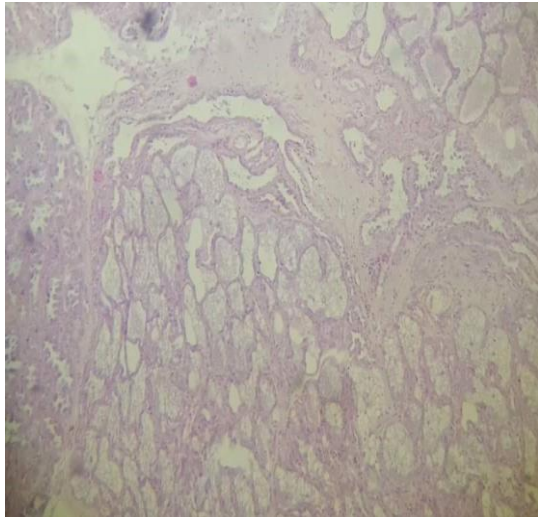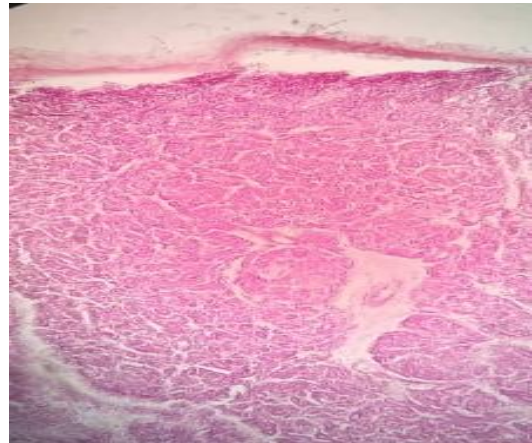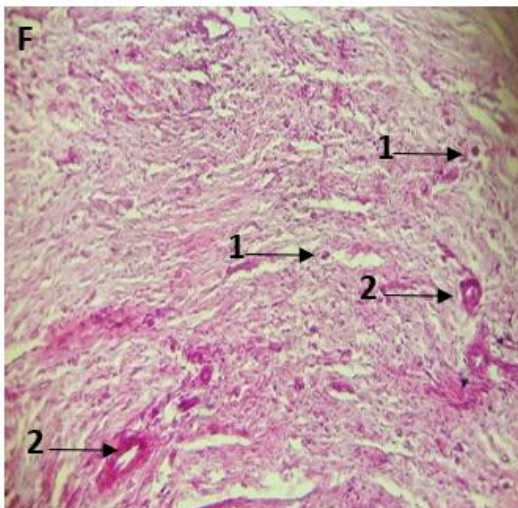
B: Tubular type carcinoma40x (HE)
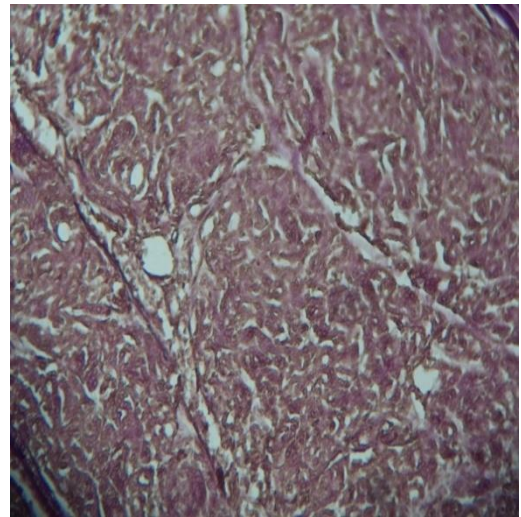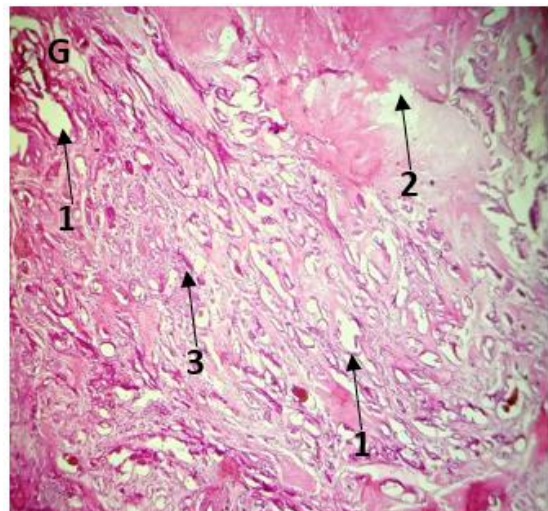

C: Fibrosarcoma40x (Van-Ginson)
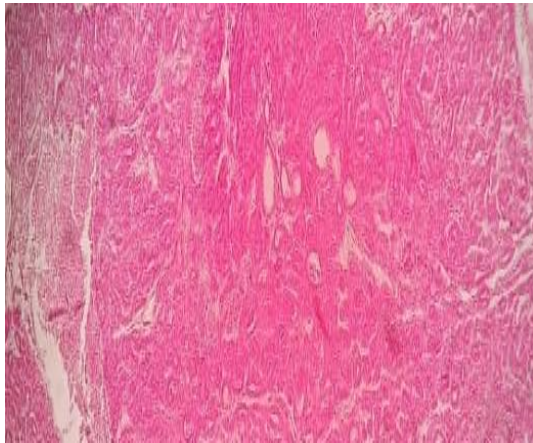
D: Tubular adenocarcinoma grade II (HE)
Anisokaryosis and abundant mitotic bodies were observed.

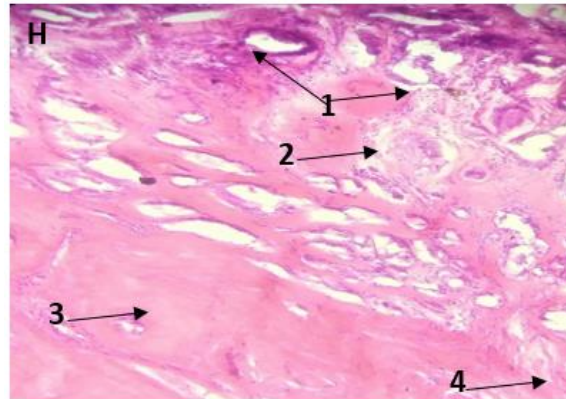E: Tubular carcinoma grade I 40 x (HE)

F: Fibrosarcoma 40 x (HE)

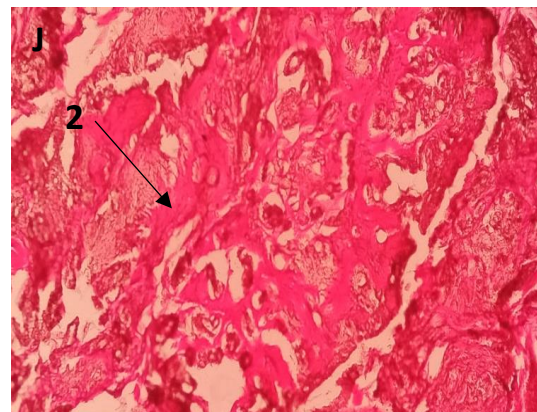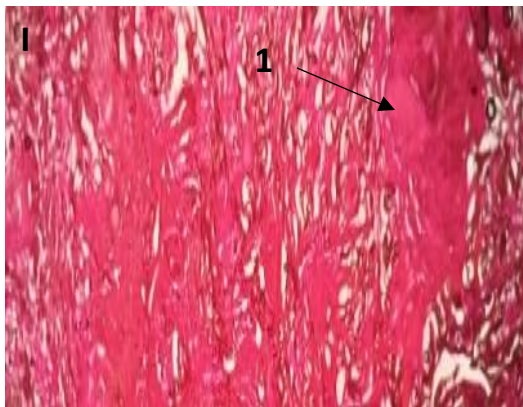G: Mixed tumor fibrous hyperplasia (HE)

Legend: F. 1 Mitotic bodies, 2 tubular Legend: G. 1 tubules, 2 myoepithelial hyperplasia and 3 fibrous hyperplasia

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H: Mixed tubulopapillary tumor with bone metaplasia (100x). (HE)

Legend: 1 bone trabeculae, 2 myoepithelial tissue, 3 compact bone, 4 tubular structures.

The histologic slides (I, J) correspond to the aforementioned mixed tumor with connective tissue hyperplasia. The large amount of collagenous fibers in the fibrous tissue can be observed and the myoepithelial cells are of a dark yellowish color.

I, J: Mixed tumor with connective tissue hyperplasia (I 40x, J and K 100x and L 400x) (Van-Gieson).

Legend: 1 collagenous fibers, 2 fibrous tissue with myoepithelial cells.

Table 2 illustrates that 65% (52/80) of the female canines in the study were in the seven to nine years age group, which indicates a clear prevalence of mammary tumor at those ages.

The results of the present study correspond with those obtained by Graham and Myers (2000) who reported a wide age range in patients with MCT investigated in the veterinary clinic of the municipality of Rodas, Cienfuegos province They also correspond with those obtained by Cruz et al. (2015) in a study conducted in Colombia, where more than half of the canines sampled were between 6 and 10 years old.

TABLE 2. Ratio of canines diagnosed with mammary tumor according to age group

Age groups	n	Percentage	IC: 95%
Under 3 years old	0	0	-
4 to 6 years old	19	23.75	4.61 – 42.89
7 to 9 years old	52	65.00	52.04 – 77.96
10 years and older	9	11.25	-9.39 – 31.89
Total	80	100	-

Legend: (n) number, (CI) Confidence Interval.

In this study, the predominant age range was between 4 and 9 years. Similarly, Kuldip et al. (2012) reported the disease in bitches between 2 and 16 years, with a mean of 9 years, the incidence was higher in those aged 10 to 12 years (31.37 %), which differs somewhat with the results of that study. On the other hand, Sanchez and Guarin (2014) identified that the age of presentation with the highest number of cases is found in canines between 7 and 13 years of age.

The risk of developing a mammary tumor is higher for bitches that present many pseudo-gestations. This increased risk linked to many pseudo-pregnancies could be secondary to the association of the effect of age and the accumulation of secretion products within the mammary (Zatloukal et al., 2005). The reviewed bibliography refers that older animals have a higher probability of developing canine mammary tumor and also a worse prognosis. Some authors have related age with a higher growth rate and lower disease-free time (DFT) and overall survival (OS) (Jaramillo et al., 2016).

Table 3 shows that the racial type with the highest prevalence of mammary tumor was in the mestizo breed, with 43.75% (35/80).

Among the risk factors associated with mammary gland tumors in bitches are sex and breed (Sorenmo, 2003).

The predisposition of certain breeds to MCT is very diverse. Uncastrated females are at the highest risk, due to the tropism of natural estrogens for the mammary gland (Salas, 2016).

These results agree with those obtained by Flores and Cattaneo (2001) in a study conducted in Chile, where he observed a predominance of the mestizo breed in female canines affected by mammary tumor. It agrees with Lipa et al.

(2019) who in a study conducted in Peru found that the racial group with the highest frequency of mammary neoplasms was represented by mestizo dogs (32%) and the age stratum between 9 and 12 years the most affected with (49.3%).

TABLE 3. Relationship of canines diagnosed with mammary tumor according to breed

Races	n	Percentage	IC: 95%
Pekinese	4	5.00	-16.36 – 26.36
Mongrel	35	43.75	27.31 – 60.19
Husky Siberiano	8	10.00	-10.79 – 30.79
Teken	3	3.07	-16.45 – 22.59
CockerSpaniel	2	2.05	-17.59 – 21.69
Labrador	4	5.00	-16.36 – 26.36
Doberman	10	12.50	-8.00 – 33.00
Havanese Bichon	1	1.25	-20.53 – 23.03
Pitbull	4	5.00	-16.36 – 26.36
Dalmatian	7	8.75	-12.18 – 29.68
Afghan Hound	2	2.05	-17.59 – 21.69
Total	80	100	-

In Mexico and Venezuela, the most frequently reported breeds included mestizos, Poodle, Cocker (Briceño et al., 2014; Salas et al., 2015) and in Colombia were the Poodle, mestizos and Cocker (Caicedo et al., 2012).

The results of this study demonstrate a higher incidence of MCT in the mongrel breed, however, the occurrence of mammary tumors has been increasing in large-sized breeds, probably due to the popularity of these breeds in different geographical areas (Salas, 2016).

Espinoza (2016) found that English SpringerSpaniels showed a 36% predisposition to generate breast cancer. For his part, reported an elevated incidence in Spaniel, Doberman, German Shepherd and Boxer breeds, results that do not coincide with those of the present investigation (Cala, 2014).

It is well known that the popularity of a breed varies between countries, which can influence breed predisposition analyses (Salas, 2016), in this study it was identified that the mixed breed showed greater predisposition to develop malignant mammary tumors, which coincides with a study conducted by Fariña and Ramírez (2017) who also found that these breeds have greater predisposition to MCT.

In another retrospective study conducted in the Czech Republic from 1977 to 2001 (Zatloukal et al., 2005) found that the Poodle, Schnauzer, Cocker Spaniel and Dachshund were breeds predisposed to develop malignant neoplasms, however, these authors found no risk for TMC in mixed-breed types of different breeds, contrary to what was found in the present study.

Of 43 bitches that underwent removal of the mammary tumor and ovarian hysterectomy, in two of them the operative technique was lumpectomy, in 12 cases simple mastectomy, while regional mastectomy was used in 14 patients and finally 15 of them underwent complete unilateral mastectomy, supported by the clinical physical examination based on the author's own medical experience.

Considering the total number of cases that underwent removal of the mammary tumor and ovarian hysterectomy (43), there was recurrence of the mammary tumor in only five (11.62%).

Out of 37 bitches that underwent removal of the mammary tumor, in five of them the operative technique was by lumpectomy, in 15 cases simple mastectomy, while regional mastectomy was used in 12 patients and finally in five of them complete unilateral mastectomy was applied, supported by the clinical physical examination based on the author's own medical experience.

Regarding the surgical techniques applied, it was determined that the ones with the highest incidence were simple and regional mastectomy, with 27 and 26 cases respectively, while complete unilateral mastectomy was applied to 20 canines and to a lesser degree the surgical technique of lumpectomy with only seven cases.

In the present investigation, out of 43 bitches that underwent mammary tumor removal and ovarian hysterectomy, only five (11.62%) had recurrence of the mammary tumor and 38 (88.3%) had no recurrence after treatment. However, of 37 bitches that underwent removal of the mammary tumor but were not ovariohysterectomized, 31 (83.7%) had recurrence of the mammary tumor and only six (16.21%) did not show recurrence of the tumor. This shows highly significant differences between the treatments used.

The analysis showed that in female canines that underwent ovariohysterectomy, the percentage of animals with mammary tumor recurrence was lower than in bitches that were not ovariohysterectomized, with statistically significant differences for $p \leq 0.05$ (Table 4).

TABLE 4. Percentage of recurrence according to treatment employed

Surgical techniques	n	Recurrence	Percentage	p value
Breast tumor and ovarian-hysterectomy removal	27	3	11.11[b]	0.00
Breast tumor removal	23	19	82.60[a]	

Unequal letters in the same column indicate differences for $p \leq 0.05$ according to binomial ratio comparison test.

In the risk analysis performed, the prevalence ratio in the exposed animals (PR = 0.13) shows that this surgical procedure (removal of the mammary tumor plus ovarian-hysterectomy) constitutes a protective factor, because the animals exposed to this procedure showed less recurrence (11.11%) than those not exposed (82.60%) and this association is statistical ($p \leq 0.00$) and significant CI: 95 % [0.04 - 0.39] (Table 5).

TABLE 5. Risk analysis of mammary tumor recurrence in canines subjected to two surgical procedures

Variables	n	Association		Statistical significance		
		Recurrence (%)	PR	CI: 95%)	χ^2	p value
RTM y OH	27	3 (11.11)	0.13	0.04 – 0.39	25.76	0.0000
RTM	23	19 (82.60)				

Legend: RTM removal of breast tumor. OH ovarian-histectomy. PR: prevalence ratio. CI: confidence interval. χ^2: chi-square

These results are in correspondence with those obtained by Pereira et al. (2014) in a study conducted in Argentina, which showed that ovarian-hysterectomy performed together with the removal of the mammary tumor, prolonged survival time not only in bitches with benign tumors, but also in malignant

tumors. In addition, the study showed that, in bitches spayed less than two years from the time of surgical ablation, survival was 45% longer than if it had not been done. Therefore, spaying all bitches at the time of mammary tumor removal should be considered.

Result attributed to exposure to endogenous ovarian hormones from early and prolonged stages of life (Queiroga et al., 2005).

According to Guerra and David (2017) is the most important cause of mammary tumor development in bitches and the protective benefit of castration is achieved before the first estrus. This means that the protective effect of ovario-hysterectomy decreases rapidly after the first few years of life. Estrogens can be activated by epoxidation, which damages DNA and will initiate the process of mammary carcinogenesis (Pereira et al., 2013).

Castration of females at an early age has been observed to significantly reduce the occurrence of these tumors. However, the protective effect of ovario-hysterectomy decreases as estrus elapses and may disappear if the surgery is performed after the third estrus (Cruz et al., 2015).

Studies reveal that early ovario-hysterectomy or ovariectomy in bitches that will not be destined for breeding is a key element to strongly decrease the risk of contracting mammary gland tumors. Owners should be advised to routinely examine their bitches' breasts themselves to increase the chances of early diagnosis and appropriate treatment (Sorenmo, 2003; Salas, 2016).

These results agree with those obtained by Mato and Sastre (2017) in a study conducted in the same territory where they concluded that mammary gland tumors are one of the main problems of the reproductive system in canines, the highest prevalence is found in mongrel breed types and the application of ovario-hysterectomy is an adequate treatment conduct to avoid the recurrence of this pathology in female canines.

Sixty percent of mammary tumors are located in the fourth and fifth mammary glands (Lipa et al., 19), which coincides with the present study with 60% of tumors present in these two mammary glands, occurring 37.7% in the inguinal mammary gland and 22.9% in the caudal abdominal mammary gland, probably due to the greater volume of mammary tissue susceptible to tumor transformation (Moe, 2001; Sánchez and Guarín, 2014).

IV. CONCLUSION

The histopathological diagnosis showed tumors of histological malignancy Type I and II, with a marked presence of abscessed granulomatous mastitis, being the regions of the inguinal, middle and anterior mammary glands the most affected. The highest prevalence of mammary tumors was in the age groups between seven and nine years of age, and in mixed breed types. Canines that underwent ovario-hysterectomy with prior mammary tumor removal had a lower risk of recurrence than animals that underwent only mammary tumor removal.

Compliance with ethical standards

Disclosure of conflict of interest
The authors declare that there is no conflict of interest regarding the publication of this article.

Statement of informed consent
Informed consent was obtained from all individual participants included in the study.

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* Corresponding author: Prof. Rigoberto Fimia Duarte, Ph.D.; Phone: +53-59740716; ORCID: https://orcid.org/0000-0001-5237-0810 Scopus author ID: 23472337200. Email: rigoberto.fimia66gmail.com Faculty of Health Technology and Nursing (FTSE), University of Medical Sciences of Villa Clara (UCM-VC), Cuba.