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ANIMAL SCIENCE

Intraoperative thermal mapping of mammary tumors in dogs

SILVIA MARCELA R. CADENA, PAULA G.A. CABRAL, SCARLATH O.P. DOS SANTOS, JOSÉ EDGARD O. ALVES, HASSAN J. LEANDRO, MARCELO B. DOS SANTOS-JUNIOR, SAULO JOSÉ Q. SILVA, MARIANA S. RIBEIRO, LÍVIA G. AMARAL, JUSSARA P. SCHEFFER, SÁVIO B. DE SOUZA, FERNANDA ANTUNES & ANDRÉ L.A. OLIVEIRA

Abstract: In this study, videothermometry's application in detecting mammary tumors in dogs is explored in-depth. The research hypothesizes that this technique can effectively identify cancerous tissues during surgery by analyzing thermal patterns. The methodology involved comparing thermal imaging results from dogs with palpable mammary nodules against a control group, focusing on capturing real-time thermal patterns. Results were significant, showing distinct thermal patterns in carcinomas. This indicates videothermometry's capability in accurately identifying micro metastases and differentiating between neoplastic and non-neoplastic changes. The study concludes that videothermometry has considerable potential in enhancing surgical precision, especially in tumor resection and safety margin definition, but emphasizes the need for further research to thoroughly understand the thermal signatures of various mammary tumors in dogs.

Key words: Cancer cells, oncologic surgery, surgical margins, micrometastasis, videothermomethry.

INTRODUCTION

Micrometastasis are part of the malignant process in the treatment of mammary tumor and the identification deficiency is related to high mortality rates. Currently the treatment is surgical in association with adjuvant therapies such as radiotherapy and chemotherapy (Cassali et al. 2011).

One out of every four dogs develops new nodules after surgical removal and these may be malignant even if the initial tumor was identified as is benign (Kristiansen et al. 2014, Horta et al. 2015). It is still necessary to explore new approaches that help to improve the choice of safety margins.

The infrared thermometry as a diagnostic method allows the detection of mammary tumors from the thermal difference produced by the release of metabolic energy between normal and carcinogenic cells (Lawson & Chughtai 1963, Bouzida et al. 2009). It is used in the early diagnosis in women, presenting a great accuracy, even in comparison with mammography. It is a method that does not produce pain, does not emit radiation and it is not invasive (Egan et al. 1977, Lahiri et al. 2012).

It has been hypothesized that the thermal pattern of mammary glands affected by palpable nodules will allow the identification of regional metastases, when compared to healthy tissues, based on histopathological diagnosis of the nodules after the surgical procedure. This diagnostic method could represent an important and new approach for improving the resection

of occult neoplastic foci and a better definition of safety margins.

In this way, it will be possible to obtain more information about the standard thermal pattern in the open field and the real time of the alterations found.

MATERIALS AND METHODS

The present study was conducted in full compliance with all applicable research ethics and animal welfare regulations, under a general stranding response authorization by the Animal Use Ethics Committee (CEUA) of the Northern Fluminense State University Darcy Ribeiro, under the protocol number: 344, according to Brazilian federal law n ° 11794/08.

The animals object of the study were patients from the routine of the Universidade Estadual do Norte Fluminense Veterinary Hospital, registered between March 2016 and January 2017. Sixteen animals were divided in groups, ten animals for mastectomy group, presenting mammary nodule(s) in the clinical examination and six animals without comorbities referred to elective ovariohysterectomy (OSH) as part of the control group for thermometric inspection.

The Real-Time Open Field Videothermometry imaging was performed using the

Metabolic Activity in Real Time station (MART). This is a generator with special lenses for capturing multi- and hyperspectral infrared radiation. In addition, it performs the mapping of the multimodal thermal texture, by means of electromagnetic sensors that generate the radiation-free three-dimensional imaging. This allows the recording of videos that are transformed into numerical values of temperature (° C) and time (h), the data are graduated by different colors making them available for medical reading and diagnosis.

The set of stored graded pseudo-colors (palette) in the thermal images comes from a system developed with MART1 software that simplified the inspection, obtaining a subtractive effect of the environment.In the color palette, the highest temperatures are represented by the colors red, white and blue, while the lower temperatures are reflected by orange, yellow and black. It was established a videothermometric parameter for the preoperative distribution of the temperature in the abdomen, throughout the inspection of healthy animals. For the animals presenting mammary nodules the alterations were detected by two methods, palpable tumors and presumptive regions. In accordance to the principles of symmetry and taking into account the thermal pattern of the control group it was analised the presence of hyper or hypo radiant areas and the distribution of thermal emissivity. The demarcation of the biopsy sample regions was made at the MART station using a software of processing segmentation, the mean temperatures were measured by demarcating the selected regions of interest (ROI).

For the accomplishment of the videothermometric images, the pre surgical preparation room and the surgical center were previously conditioned by an air conditioning system; Maintaining the enviromental temperature at 22 ± 2 ° C.

During the clinical evaluation, the necessary data about the animal were collected and they were divided by a classification form. The following pre-operatory exams were performed: complete blood count, blood chemistry (blood urea nitrogen, creatinine, alanine transaminase, alkaline phosphatase, aspartate aminotransferase; Ultrasonography, simple tomography of the thorax and abdomen covering all mammary chains. Cardiac evaluation of animals over 10 years of age was performed by means of an electrocardiographic

and echocardiographic exams. Consequently, were excluded animals with clinical alterations were excluded due to the possible reserved prognostic and the lifethreatening risks for the anesthetic procedure, such as anemia.

The technique of mastectomy adopted was in agreement with Macphail (2015) proceeding to the excision of the block mammary chain. Bitches directed to regional mastectomy were also prepared and operated following the same principles.

The surgical technique used, total unilateral or regional, was chosen based on the clinical evaluation and the preoperative staging of the palpable node (s) using an evaluation form. In this form they were divided by stages, so stage I was considered the animal presenting a tumor with less than 3 centimeters, without lymph node metastasis or an unilateral or bilateral lymphnode involved; stage II, tumors with less than 3 centimeters and tumors with 3-5 centimeters involving unilateral lymph nodes or without lymph node metastasis; stage III, tumors with more than 5 centimeters and with our without lymph node involvement; stage IV, any tumor size and lymph node involvement unilateral or bilateral but presenting metastasis including lymph nodes. In this way bitches in good clinical condition with stage I and II were submitted to unilateral total mastectomy, whereas bitches with stage III presented nodules of great size, ulcerated or not. The dogs with significant hematological alterations and stage III were submitted to regional mastectomy aiming at a better quality of life for the animal.

The anesthetic protocol was standardized when the unilateral total mastectomy technique was performed. Although the protocol was adjusted according to the clinical status of bitches operated with the regional mastectomy technique. Besides, the pre-anesthetic medication of the control group was the same as the one used in the group that underwent mastectomy, to avoid interference of the anesthetic protocol in the thermometric evaluation.

The animals received a pre-anesthetic protocol based on chlorpromazine hydrochloride, at a dose of 1 mg/kg/ intravenously. After obtaining the desired anesthetic effect, a wide trichotomy of the ventral region of the thorax and abdomen was performed, comprising from above the axillary region to the inguinal region. The induction was performed by an intravenous application of propofol at 3 mg/kg and the animals were maintained under anesthesia with isoflurane inhalation, in a universal vaporizer.

In addition, intraoperative pain control was performed, first a bolus of morphine sulfate and then with the aid of an infusion pump for syringe MLK (morphine sulfate, lidocaine hydrochloride and ketamine hydrochloride) at 1 ml/kg/hour rate. The animals remained on spontaneous ventilation throughout the experiment.

A first 10 minutes' inspection was performed through infrared videothermometry immediately before antisepsis of the surgical field and mastectomy. Subsequently, the altered areas were identified with a surgical pen, randomly numbered. These areas were classified according to the detection method by: palpation (PP) corresponding to the nodular alterations perceptible by surgeon touch and presumptive by videothermometry (PVTM) those nonnodular regions with a presumptive thermal pattern of alteration.

The samples of the tissue (fragments) were identified, separated and packed in vials containing 10% formaldehyde. The fragments were sent for processing in the animal pathology department at the Universidade Estadual do Norte Fluminense Veterinary Hospital.

Ovariohysterectomy was adopted as a surgical standard prior to mastectomy for

all patients, in order to avoid future cases of pregnancy, ensuring their quality of life. The surgical technique of unilateral total mastectomy was performed in the affected mammary chain and in case the two mammary chains were involved, the mastectomy was performed in two phases with a difference of four weeks between the procedures, first removing the most affected breast chain. The samples product of the histopathological study were divided into: without alteration, when the normal architecture of the tissue was preserved; non-neoplastic alterations, contemplating inflammation, processes of hyperplasia and cysts; benign neoplasms, such as adenomas, fibroadenomas, mixed breast tumor and malignant neoplasms among the types of carcinomas and sarcomas.

The animals were kept under observation until state of consciousness and sensorial recovery, a compression bandage was performed throughout the wound to reduce dead space and avoid the formation of seromas, being indicated for the owner to maintain it for three days and return after this period for inspection of the wound, to detect any complications of dehiscence and necrosis. In the absence of complications, the next return was indicated 15 days later for removal.

It was prescribed for oral use, cefalexin at the dose of 30 $mg.kg^{-1}$ every 12 hours for 15 days as a preventive treatment of post-surgical infections. For the treatment of pain, meloxicam at the dose of 0.1 $mg.kg^{-1}$ was prescribed every 24 hours for 5 days; tramadol hydrochloride at the dose of 3 $mg.kg^{-1}$ every 12 hours for 6 days; dipyrone monohydrate at the dose of 25 $mg.kg^{-1}$ every 8 hours for 5 days.

Statistical analysis

Sixteen patients were selected to enter the trial. The selection was based on the patient condition and according to the aim of the study, being of non-probabilistic way, thus were performed 12 mastectomies of which 31 samples were obtained and identified by the selected methods palpation pp and videothermometry vtm, and as the standard exam all the fragments from the mastectomies were histopathologically analyzed.

Descriptive analysis was performed by mean and standard deviation to characterize weight and age between the groups. In addition, a correlation of frequencies and absolute temperatures of each mammary gland, histological changes, according to the methods of palpation, videothermometry and histopathological biopsy reports.

The absolute frequencies between histopathological diagnoses identified from the pp and vtm techniques were submitted to the square test (χ^2, $p \leq 0.01$), which if significant confirms a difference between the techniques. In addition, to establish a videothermometry pattern in the control group (6 animals) the average temperatures and standard deviations observed by type of mammary gland were analyzed and the mammary chain was differentiated. It was subjected to the the minitab computer system.

RESULTS AND DISCUSSION

The non-probabilistic design in such a short period of registration and the clinical stage of the dogs, restricted the size of the samples. In the group of nodular presentation (group 1) were performed 12 surgeries with real time thermal inspection and complete histopathological evaluations. Also, six healthy bitches were neutered and inspected as part of the control group (group 2).

The mean age differed by 6.06 years between the groups and the group of cases presented a higher mean. The group of cases presented a

weight of 16.1 ±11.9 kg and the control group had a mean of 18.8 ± 12.2 kg.

The number of nodular alterations identified by palpation was 20, and in all cases, a change in the thermal pattern was evidenced when compared to the control group images. It was possible to identify more 11 abnormal thermal patterns by real-time videothermometry, and only three of all the regions detected had no alteration in the histopathological study.

The proportions of diagnoses between the methods of palpation and videothermometry differed significantly (χ^2 = 39.09 calculated). Since when the proportions between techniques were evaluated according to the type of biopsy report, it was observed significant differences (χ^2 = 23.59 tabulated, GL = 9, p <0.01) using videothermometry allowed to detect with greater precision non-neoplastic changes and carcinomas (Figure 7), in the first case, five more diagnoses were identified and in the second presumptive reports represented four more new cases.

Therefore, the number of alterations detected per presumptive VTM (P VTM) was significantly higher than by palpation. Indicating that regardless of the type of histological report obtained, the videothermometric technique was more efficient. These results are in agreement with that reported in the literature about the ability of thermometric detection of palpable and invisible tumors even when compared to mammography (Gautherie & Gros 1980, Lawson & Chughtai 1963, Ohashi & Uchida 2000), suggesting that the value of abnormal thermograms as a prognostic factor for the development of breast neoplasms is crucial.

The thermal pattern found in the mammary glands in group 2 was homogeneous and symmetrical (Figures 1, 2a,b, 3a,b, 4a,b,c, 5a,b, 6a,b,c). It was characterized by warmer areas around vascularized regions, and cooler areas on the periphery of the ventral abdomen. During the video thermometric assessment of group 1, asymmetrical and abnormal patterns where found when compared to group 2, this goes according to the differentiated temperature of mammary tumors reported by Lawson (1958) and represents an important aspect for the micrometastasis detection.

Hyper-radiant regions were present in the affected mammary chains when compared with the control group and it was associated with the histopathological finding of malignant tumors (Figures 2a,b, 3a,b, 4a,b,c, 5a,b, 6a,b,c) also, the reports corresponding to carcinomas are characterized by underlying hyper-radiant regions signaling that the malignant tumors have a greater activity represented in higher emissivity. Gautherie & Gros (1980) described a directly proportional relationship observed

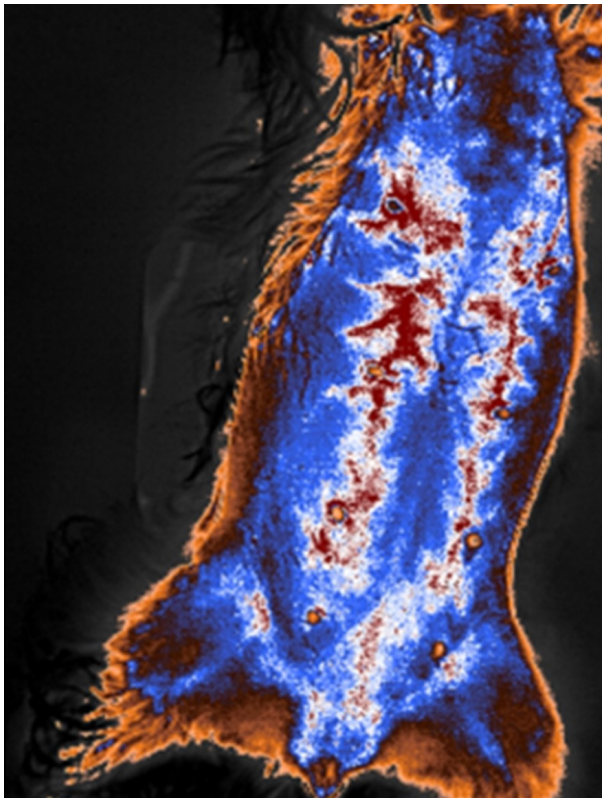

Figure 1. Thermal images of the inspection of the mammary glands of the control showed thermal symmetry evaluated using MART software.

between the tumor cell growth rate and the metabolic heat production displayed in the thermometric evaluation which is in accordance with the current findings.

Non-neoplastic changes and benign tumors exhibited a subtle thermal difference between the central and peripheral areas when compared with the malignant processes. Therefore, it is necessary an accurate observation of the thermologist to recognize differences even if subtle in the thermal patterns, considering that the excision of benign mammary tumors in dogs is highly recommended because of the existence of a malignization process (Stratmann et al. 2008).

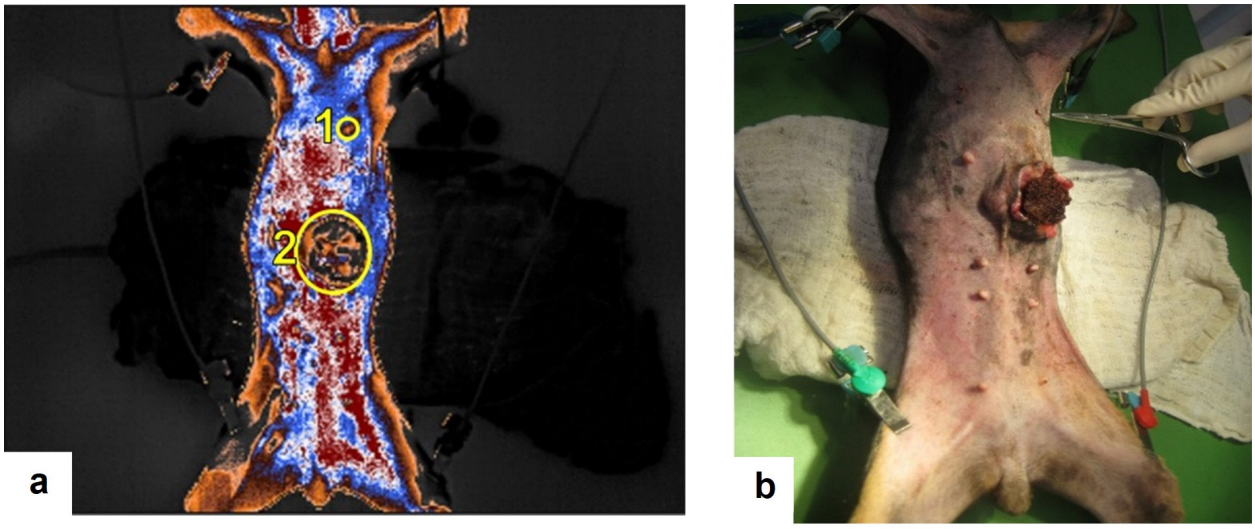

Figure 2. Procedure 3 of the case group, (a) Thermal image showing by ROI in yellow; Sample 1, VTM corresponding to metastatic focus of tubular carcinoma; Sample 2 PP, solid mammary carcinoma. (b) Actual view of the study animal.

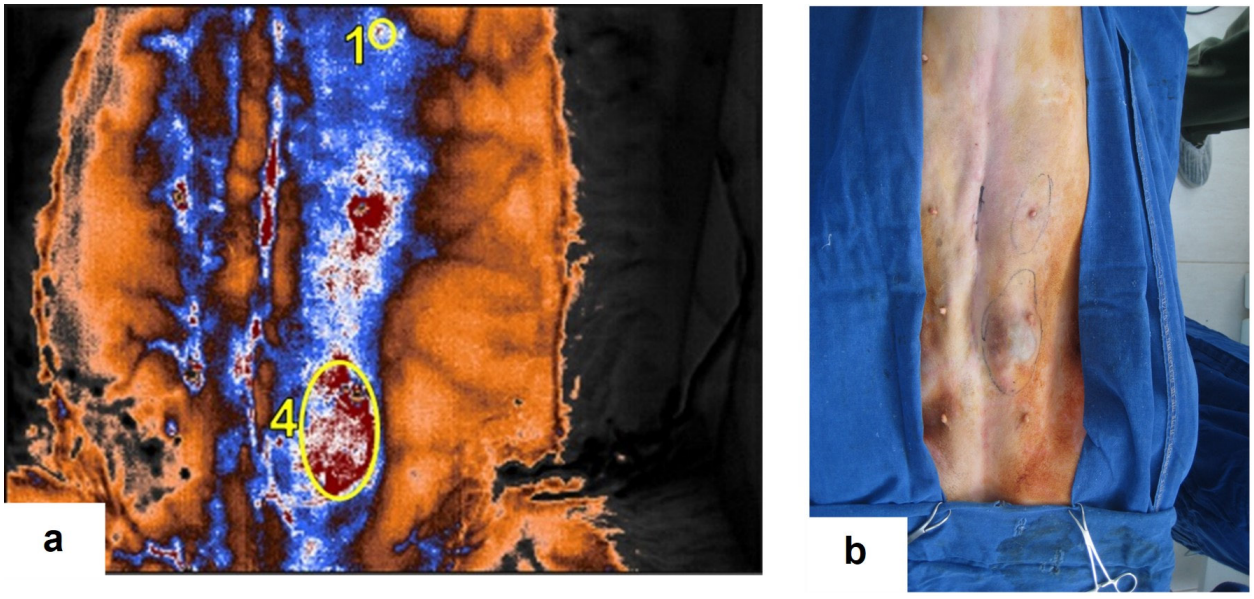

Figure 3. Fourth mastectomy, (a) Thermal image showing ROI in yellow; Sample 1, VTM corresponding to a neoplastic embolus in a blood vessel; Sample 4 PP, tubular carcinoma. (b) Actual visualization of the animal being studied.

During the current real-time inspection, no significant response to cold stress was observed after the topical application of the antiseptic solutions; in contrast to the reported by Ohashi & Uchida (2000), who describes a dynamic evaluation after cold stress that improves the identification of neoplastic lesions in wich is important for the differentiation of cold tumors.

The specimens with non-neoplastic alterations had a significant difference and five new cases were identified through videothermometry. Four specimens of carcinomas non detectable by palpation were identified by videothermometry. It was also possible to detectquantitatively the thermal pattern of the control group. It was recognized a homogeneous behavior in the thermal pattern, and there were not a significant difference between the temperatures of the mammary chains nor between the mammary glands (Figure 8).

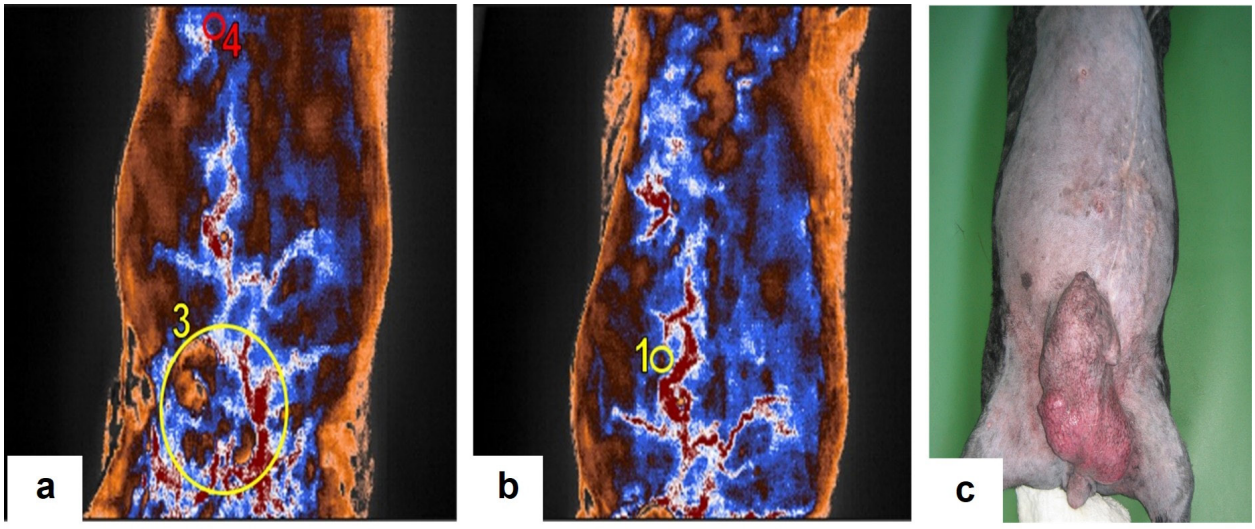

Figure 4. **Sixth mastectomy, Thermal images showing with ROI in yellow, (a) sample 1 VTM, vascular hamartoma and mammary micometastasis carcinoma, (b) sample 3 PP, solid carcinoma; in red, sample 4 PP, tissue without change. (c) Actual visualization of the animal under study.**

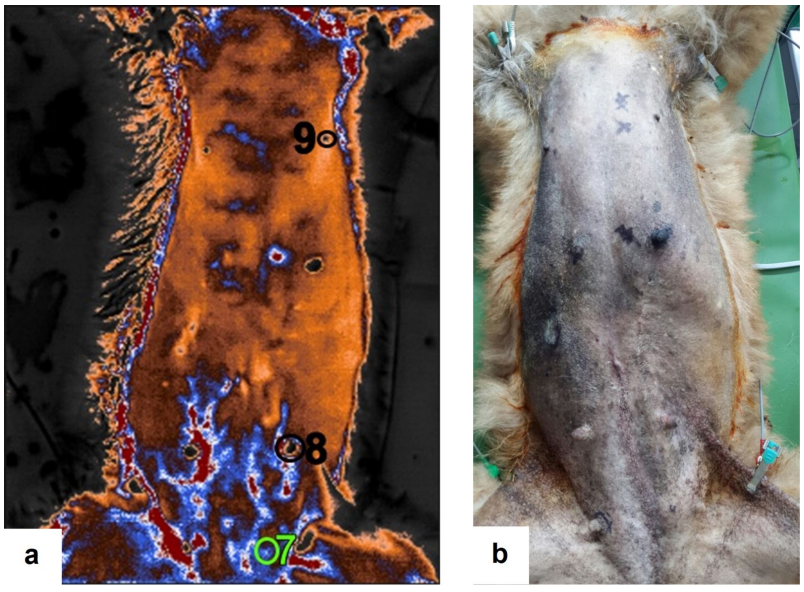

Figure 5. **Ninth mastectomy, (a) Thermal image signaling with green ROI, sample 7 PP, regular gland with some dilated units; in black sample 8 PP, adenoma with cystic dilatation; Sample 9 VTM, adenoma (b) Real visualization of the animal ventral region under study.**

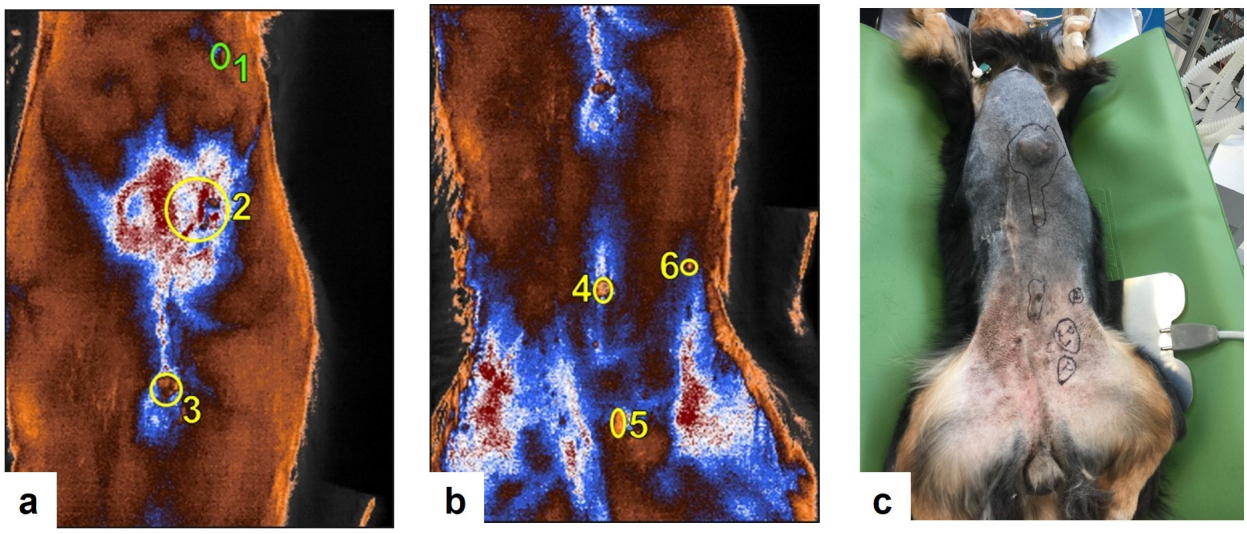

Figure 6. Procedure 12th, (a) Thermal image signaling with green ROI, sample 1 PP, epidermoid cyst; in yellow sample 2 PP, multicentric tubular carcinoma; Sample 3 PP, tubular and papillary carcinoma (b) 4 PP sample signaling, cystic carcinoma and papillary carcinoma; 5 PP sample, complex carcinoma; Sample 6 VTM; micrometastasis of Carcinoma cells; (c) Real visualization of the ventral region under study.

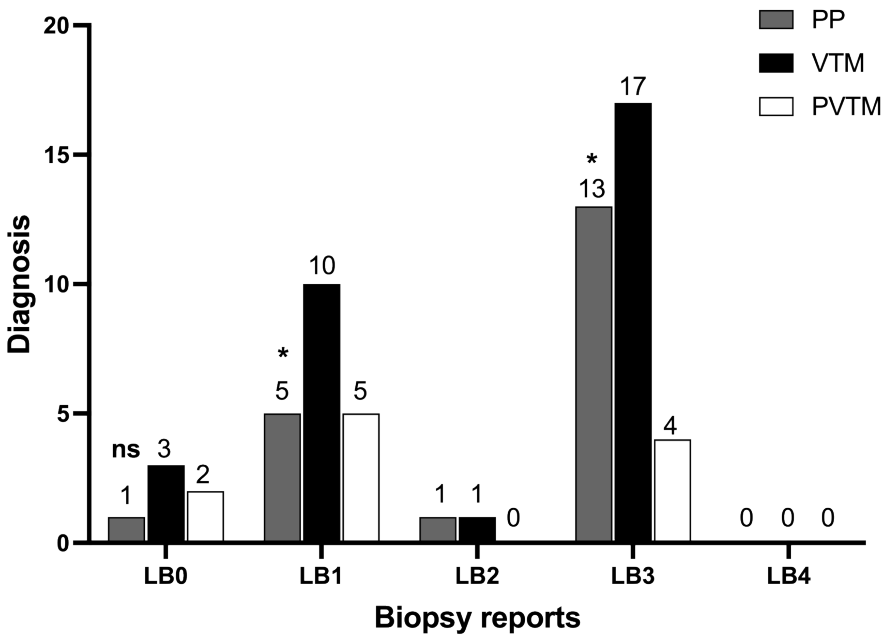

Figure 7. Differences in the number of diagnosed cases of breast neoplasia of bitches, between the palpation (PP), videothermometry on nodular regions (VTM) and presumptive VTM (PVTM – non-nodular regions with a presumptive thermal pattern of alteration.) methods confirmed by histopathological biopsy reports (*significant, according to the χ 2 test at 1% (LB1) with non-neoplastic alterations, (LB2) benign neoplasia, (LB3) carcinomas and (LB4) sarcomas.

CONCLUSIONS

Videothermometry allows the identification of abnormal patterns corresponding to micrometastasies, palpable and micro metastatic mammary carcinomas, and non-neoplastic alterations through transoperative image processing, without interfering with field and normal surgical flow. However, it is necessary to study a greater number of cases to determine the thermal pattern of all types of breast tumors in bitches. Even if the surgical margin was chosen following the current principles of oncologic surgery, the method was efficient in identifying the tumor delimitation.

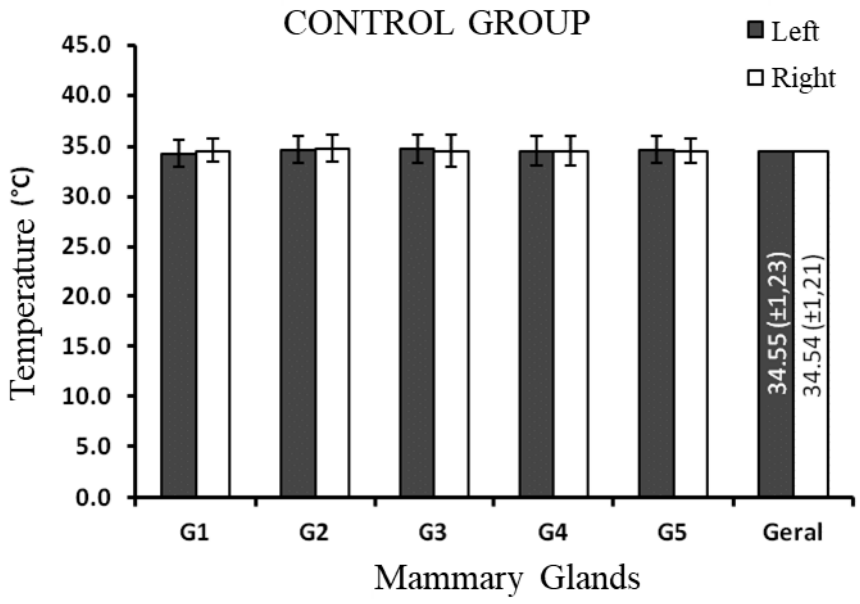

Figure 8. Temperatures of the mammary glands of bitches of the control group discriminated by the mammary chain, right and left. Cranial thoracic gland (G1), caudal thoracic (G2), abdominal cranial (G3), caudal abdominal (G4), inguinal (G5) and general mean temperature. (Ns), according to the F test (p ≤0.01).

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SILVIA MARIA R. CADENA[1]
https://orcid.org/0000-0003-3422-0338

PAULA G.A. CABRAL[1]
https://orcid.org/0000-0002-4405-6511

SCARLATH O.P. DOS SANTOS[1]
https://orcid.org/0000-0002-9914-9168

JOSÉ EDGARD O. ALVES[2]
https://orcid.org/0000-0001-5776-5467

HASSAN J. LEANDRO[3]
https://orcid.org/0000-0002-2373-2453

MARCELO B. DOS SANTOS JÚNIOR[1]
https://orcid.org/0000-0002-6539-7593

SAULO JOSÉ Q. SILVA[1]
https://orcid.org/0009-0001-7686-8338

MARIANA S. RIBEIRO[1]
https://orcid.org/0000-0003-0012-6298

LIVIA G. AMARAL[1]
https://orcid.org/0000-0002-9665-8450

JUSSARA P. SHEFFER[1]
https://orcid.org/0000-0003-3939-234X

SÁVIO B. DE SOUZA[4]
https://orcid.org/0000-0003-3169-7309

FERNANDA ANTUNES[2]
https://orcid.org/0000-0002-2885-9322

ANDRÉ L.A. OLIVEIRA[1]
https://orcid.org/0000-0003-0530-0785

[1]Universidade Estadual do Norte Fluminense, Departamento de Clínica Cirúrgica do Hospital Veterinário, Unidade Experimental Animal, Av. Alberto Lamego, 2000, 28015-622 Campos dos Goytacazes, RJ, Brazil

[2]Universidade Estadual do Norte Fluminense, Departamento de Anestesiologia e Farmacologia, Av. Alberto Lamego, 2000, 28015-622 Campos dos Goytacazes, RJ, Brazil

[3] Universidade Estadual do Norte Fluminense, Departamento de Morfologia e Patologia Animal, Av. Alberto Lamego 2000, 28015-622 Campos dos Goytacazes, RJ, Brazil

[4]Instituto Galzu, Centro de Alta Complexidade, Av. Pelinca, 115, 28035-053 Campos dos Goytacazes, RJ, Brazil

Correspondence to: **André Lacerda de abreu Oliveira**
E-mail: andrevet@uenf.br

Author contributions

Article writing and statistical analysis: Silvia Marcela Ruiz Cadena; Paula Gebe Abreu Cabral; André Lacerda de Abreu Oliveira. Article review: André Lacerda de Abreu Oliveira; Sávio Bastos de Souza. Surgery: Silvia Marcela Ruiz Cadena; Paula Gebe Abreu Cabral; Scarlath Ohana Penna dos Santos; Jussara Peters Scheffer; Marcelo Borges dos Santos-Junior; Saulo José Quina Silva; Mariana da Silva Ribeiro, Lívia Gomes Amaral and André Lacerda de Abreu Oliveira. Pathology: Hassan Jerdy Leandro. Anesthesia: José Edgard De Oliveira Alves and Fernanda Antunes.