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THERMOGRAPHIC ASSESSMENT OF CANINE MAST CELL TUMOURS

KEYWORDS: Mast cell tumours, dogs, thermographic imaging, prognostic factors

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ABSTRACT *Background*

Increasing attention is being directed towards thermographic imaging and is expected to promote technological refinement and broader application of this diagnostic modality. Increased tumouralblood supply, angiogenesis and metabolic rates support the application of thermographic assessment in oncology. Canine mast cell tumours (MCTs) are highly reactive neoplasms with variable behaviour and prognosis. Thermographic assessment of canine MCTs has not been reported to date.

Results

Mean absolute temperatures differed significantly ($p < 0.001$) between tumoural (TA) and non-tumoural (NTA) areas in this study. Mast cell tumours may be colder or warmer than NTAs. Thermographic imaging findings were not correlated with prognostic factors or clinical staging.

Conclusions

Healthy skin temperature differs from skin temperatures in areas affected with MCTs. Temperature differences that cannot be perceived on palpation may be detected by thermographic imaging. Further studies are warranted to investigate potential relationships between thermographic imaging findings and MCT prognosis in dogs.

BACKGROUND

Body surface temperature reflects variations in blood flow in several disease processes (Adams, 1939). While the back of the human hand can only perceive temperature differences greater than 2ºC on average, thermographic imaging is able to detect differences as small as 0.1ºC per square millimeter of tissue (Brioschi et al, 2003).

Standardized interpretation protocols for breast cancer thermograms have been established between the 1960s and the 1970s (Archer&Gros, 1971; Lawson &Chughtai, 1963; Dodd, 1972; Wallace, 1975). Carcinogenesis and associated neoangiogenesis are thought to result in increased temperatures at the periphery of neoplasms (Poljak-Blazi et al, 2009). Also, detection of hotspots and related temperature gradients may help recognize and diagnose tumour malignancy (Arora et al, 2008).

Several advantages of thermographic imaging over other diagnostic modalities have been reported in oncology. Thermographic imaging can be performed in a fast, safe and aseptic manner due to lack of direct contact with tissues; thermal images are easy to obtain and store and are lifetime representative (Lawson &Chughtai, 1963; Nowakowski, 2006). Most studies to date are restricted to thermographic assessment of breast cancer in women (Brioschi et al, 2003; Yahara et al., 2003; Song et al., 2007; Arora et al., 2008; Wishart et al., 010; Kontos et al., 2011; Wang et al., 2011; Boquete et al., 2012). However, temperature changes in one or more cutaneous territories are currently being employed in diagnosis of human neoplastic conditions such as melanoma, thyroid and parathyroid tumours(Brioschi et al, 2003).

Typical infrared images of breast cancer lesions reveal 1 to 3ºC increase in skin temperature at the periphery of tumours. Thermographic imaging can be combined with conventional physical and radiologic assessment to detect hightumour growth rates warranting a more guarded prognosis (Lawson &Chughtai, 1963; Gautherine&Gros, 1980)[5,8]. Despite clear evidences of increased skin surface temperature around breast cancer lesions, core tumour temperatures are sometimes reduced; such temperature discrepancies are not fully understood (Lawson &Chughtai, 1963; Xie, 2004).

In an effort to validate the effectiveness of thermographic imaging in breast cancer diagnosis, Yahara et al. (2003)[15] compared heat patterns in tumoural and peritumoural tissues with healthy tissue temperatures using direct thermography. Song et al. (2007) documented temperature differences following establishment of human breast tumourxenografts in mice and concluded that thermographic imaging may be a promising tool for monitoring of human

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tumourxenografts and their response to anticancer drugs. Arora et al. (2008)analysed the effectiveness of digital infrared thermal imaging (DITI) in breast cancer assessment and diagnosis in women and reported up to 97% sensitivity, anda negative predictive value of 82%.

Thermographic imaging has been employed toinvestigate tissue interactions in carcinoma development studies (experimental carcinoma Walker 256). According to Poljak-Blazi et al. (2009), infrared thermal imaging may have considerable value in assessment of tumour growth, as well asin differentiation between processes such as neoplasia, inflammation and hematoma.

In a study by Wishart et al. (2010)involving 100 patients submitted to DITI imaging prior to core needle biopsy, data analysis using artificial intelligence program (NoTouch Breast Scan) suggested DITI is an effective ancillary tool for breast cancer diagnosis in women under 70 years of age.

Wang et al. (2011)investigated the association of thermographic imaging findings with hormonal and growth factor receptors and concluded thermography may be employed as a prognostic indicator in breast cancer.

More recently, a novel automated thermal image analysis method has been proposed (ICA; Boquete et al., 2012)for detection ofareas athigh-risk oftumour development, with promising results in early breast cancer diagnosis.

Most studies to date suggest thermal imaging analysis may potentially become a vital tool for accurate diagnosis and prognostication of cancer patients (Brioschi et al, 2003).

Thermographic Imaging in Veterinary Medicine

Thermographic imaging is gaining popularity in Veterinary Medicine as a reliable and accurate diagnostic tool. Recent studies in dogs range from characterization of the normal canine stifle (Loughin& Marino, 2007; Marino &Loughin, 2010)to thermographic assessment of orthopedic conditions such as cranial cruciate ligament rupture (Infemuso et al., 2010).

Canine Mast Cell Tumour

Mast cell tumours (MCTs) have been reported in several species, with higher prevalence in dogs and cats than humans. Mast cell tumours account for 7-21% of cutaneous neoplasms and 11-27% of malignant cutaneous neoplasms in dogs (Macy, 1984; Welle et al, 2008).

Mast cell tumourstend to present as small, firm circumscribed plaques or noduleswhich are often erythematous, alopecic and/or ulcerated (Loughin& Marino, 2007). However, MCTs have variable gross appearance and may resemble other skin tumours or non-neoplastic conditions. Associated edema, erythema, increased local temperature and pruritus suggest poor MCT prognosis(Welle et al, 2008).

Mast cell tumour palpation may elicit local vasodilation, edema and erythema (Darer's Sign) due to mast cell degranulation and subsequent release of histamine and other vasoactive substances (Thamm& Vail, 2007). Mast cell degranulation-related complications occur in approximately 50% of dogs affected with MCT (Loughin& Marino, 2007). Gastrointestinal ulceration and local hemorrhage during tumour resection, fine needle aspiration of lesions for cytology, or following excessive manipulation are often reported in canine MCT patients (Thamm& Vail, 2007).

Histopathology is paramount for MCT grading and prognosticationin spite of potential disparities between tumour grading andtumourbehaviour. Novelstrategies for improved MCT diagnosis and prognostication are currently being investigatedin immunohistochemical, molecular and morphological studies (Abadie et al, 1999; Ayl et al, 1992; Da Costa et al, 2007; Costa-Casagrande et al, 2013).

OBJECTIVES

This study set out to determine the value of thermographic imaging in canine MCT characterization. Potential relationships between thermographic imaging findings, and MCT prognosis and clinical staging were investigated.

METHODS

This study was approved by the Ethics Committee of the School of Veterinary Medicine and Animal Science, University of São Paulo (FMVZ-USP). Samples in this study were retrospectively collected from dogs referred to the Small Animal Veterinary Hospital (HOVET) FMVZ/USPbetween January 2011 and January 2013with a diagnosis of MCT based fine needle aspiration cytology. Informed owner consent was obtained in all cases.

Dogs were submitted to clinical assessment consisting of complete anamnesis and comprehensive physical examination. Tumours were characterized according to progression, location, consistency, presence of bleeding, size, type of surface, presence of alopecia, erythema or ulceration, surface temperature and type of attachment. Laboratory workup included complete blood cell count and serum biochemistry. Chest radiography, transabdominal ultrasonography and regional lymph node cytology were performed as necessary.

Tumour staging was based on the World Health Organization (WHO) mast cell tumour staging system (Welleet al., 2008). Patients were staged 0-13 according topresence of negative prognostic factors. Presence of negative prognostic factors (13) was determined according guidelines published elsewhere (Simoeset al., 1994; Kiupelet al., 2004; Webster et al., 2007; Giantinet al., 2012).

Negative prognostic factors in MCT cases are as follows:

- Histological grade: negative predictive factor (poor differentiation indicates poor prognosis);
- Clinical staging;
- Location: prepuce, scrotum, vulva, subungueal, oral, facial, aural, mucocutaneous junction, visceral, bone marrow involvement – poor prognosis;
- Size of primary tumour;
- Ulceration, edema, erythema, increased local temperature;
- Rapid growth and recent rapid growth;
- Degree of peripheral tissue infiltration;
- Regional or distant metastasis;
- Recurrence following proper treatment;
- Development of new primary tumour at different sites
- Paraneoplastic syndromes;
- Breed: brachycephalic dogs (better prognosis); Sharpei (poor prognosis).

The area of interest was clipped 15 minutes prior to thermographic image acquisition. All thermal images were acquired from the same distance (0.5 m) under identical ambient conditions: isolated,draught-free examination room; windows sealed and protected with film (insulfilm®). Room temperature and humidity were measured using digital

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thermohygrometer and respective datafed into image analysis software (Quick Report®).

Thermal image analysis was based on the following parameters:

- Temperature at a central tumoural spot (tumoural spot, SpT);
- Temperature at a non-tumouralspot (> 3 cm away from the tumour; non-tumoural spot, SpNT);
- Quadrangular area encompassing the tumour (tumoural area, TA);
- Quadrangular area (equal size to TA) as far as possible from the tumour – area beyond surgical safety margins (non-tumoural area, NTA).

Mean values were submitted to statistical analysis for investigation of temperature differences.

All tumours were resected and immediately immersed in 10% formaldehyde. Tumour samples were submitted to histological evaluation for preoperative diagnosis confirmation (hematoxylin and eosin stain, HE). Histological assessment of surgical margins and histological grading of lesions were also performed.

Histological grading was based on the degree of cellular differentiation (Da Costa, 2007) and criteria described byKiupell et al. (2011). Toluidine blue staining was employed in cases where cell differentiation and histological grading were not possible in HE stained slides.

Correlations of thermal readings with survival time and disease-free survival time were investigated based clinical and postoperative progression.

Statistical analysis

Summary statistics (mean, standard deviation, median, minimum and maximum values) were employed for quantitative data analysis. Staging was based on absolute and relative frequencies. Spearman correlations between temperature changes, staging and prognostic factors were calculated (Kirkwood&Sterne, 2006).

Mean disease-free survival time was estimated based on marker category (categorization based on medians), staging and prognostic factors. Respective 95% confidence intervals were calculated with the Kaplan-Meier method(Kleinbaum,1996) and compared using log-rank tests. The level of significance was set at 5%.

RESULTS

Thermographic imaging was performed in 15 dogs diagnosed with MCT. All tumours in this study were graded as Grade II (low grade) MCTs.

Mean temperatures recorded in this study in tumoural (SpT) and non-tumoural (SpNT) spots, and tumoural (TA) and non-tumoural (NTA) areas were as follows: 33.18 °C (28.70 to 36.5°C; SpT), 33.39°C (28.50°C to 36.30°C; SpNT), 33.27°C (29.30°C to 36.10°C; TA) and 33.95°C (31.10 to 36.00°C; NTA). Temperatures measured at selected areas of interest differed -0.21°C on average (temperature range, -5.60°C to +4.4°C; Table 1).

Table 1 – Temperature readings in 15 dogs submitted to thermal imaging assessment. SpT – Central Tumoural Spot; SpNT – Spot in a non-tumoural area. TA - Tumoural area; NTA – Non-tumoural area

Dog No	SpT	SpNT	Mean	SpT - SpNT	TA	NTA
1	35.40 °C	34.10 °C	34.75 °C	1.3	34.60 °C	33.40 °C
2	34.50 °C	36.30 °C	35.40 °C	-1.8	34.80 °C	36.00 °C
3	35.60 °C	35.90 °C	35.75 °C	-0.3	36.10 °C	35.70 °C
4	36.00 °C	34.90 °C	35.45 °C	1.1	34.80 °C	35.60 °C
5	30.10 °C	35.70 °C	32.90 °C	-5.6	30.10 °C	34.00 °C
6	36.50 °C	35.00 °C	35.75 °C	1.5	34.50 °C	35.80 °C
7	36.20 °C	31.80 °C	34.00 °C	4.4	35.50 °C	32.90 °C
8	28.70 °C	33.50 °C	31.10 °C	-4.8	35.60 °C	34.30 °C
9	32.30 °C	28.50 °C	30.40 °C	3.8	29.30 °C	32.90 °C
10	32.60 °C	33.60 °C	33.10 °C	-1	32.50 °C	34.10 °C
11	28.70 °C	33.50 °C	31.10 °C	-4.8	31.60 °C	33.60 °C
12	30.90 °C	34.20 °C	32.55 °C	-3.3	31.40 °C	33.70 °C
13	33.30 °C	32.30 °C	32.80 °C	1	31.80 °C	33.10 °C
14	32.30 °C	28.50 °C	30.40 °C	3.8	32.50 °C	31.10 °C
15	34.60 °C	33.10 °C	33.85 °C	1.5	34.00 °C	33.00 °C

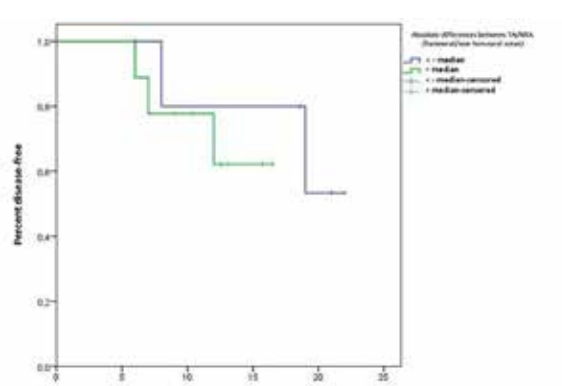
Temperature differences were negative (i.e. tumours colder than distant skin) in 7 cases and positive (i.e. tumours warmer than distant skin) in 8 cases (47% and 53% respectively).

Mean absolute temperatures differed significantly ($p < 0.001$)between tumoural (TA) and non-tumoural (NTA) areas in this study (Table 2).

Table 2 – Absolute temperature differences between tumoural (TA) and non-tumoural (NTA) areas andtumoural (SpT) and non-tumoural (SpNT) spots, and results of comparative tests.

Variable	Mean	SD	CI (95%)	P value *
Absolute difference between spots (SpT-SpNT)	2.67	1.75	1.70 to 3.63	< 0.001
Absolute difference between areas (TA-NTA)	1.73	0.99	1.18 to 2.28	< 0.001

SD = standard deviation; CI = confidence interval; * Student's t test



Graph 1. Kaplan-Meier estimates of disease-free survival time according to temperature differences in areas sub-

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mitted to thermographic assessment.

DISCUSSION

Thermographic imaging in 15 dogs in this study was performed according to guidelines given elsewhere[2]. Images were acquired under ideal conditions (i.e. room shielded from direct sunlight and free from draughts; cold light illumination; ambient temperature and humidity control). Patients were kept in the room for a minimum of 15 minutes prior to image acquisition for thermal equilibrium purposes.

The clipping strategy adopted in this study (i.e. minimum of 15 minutes between clipping and image acquisition) was based on previous studieson long haired dogs (Loughin&Marino, 2007).

Significant absolute temperature differences between tumoural and non-tumoural areas in this study suggest healthy skin temperatures differ from skin temperatures in areas affected with MCT, even though such differences may go undetected on palpation (Brioshci et al., 2003). Confirmation of temperature abnormalities measured by direct thermography in subsequent thermographic imaging analysis has been reported (Yahara et al., 2003).

Surface temperature increases ranging from 1 to 3ºC have been documented at the periphery of breast cancer lesions in vivo(Gautherine&Gros, 1980). Mammary tumours are significantly warmer than surrounding tissues in women and tumour temperature is thought to be associated with breast cancer prognosis(Yahara et al., 2003). Negative differences between healthy skin and tumour lesions have been reported in carcinoma xenograft studies (Poljak-Blazi et al, 2009;Mikulska, 2006); despite increased surface skin temperatures at the periphery of carcinoma lesions, core tumour temperatures may be lower than surrounding healthy skin in some stages of tumour development. Such heat pattern discrepancies are not clearly understood; however, associations with local neoangiogenesis have been suggested (Xie et al, 2004).

Tumours in this study were either warmer or colder than distant skin (53% and 47% respectively). Therefore, different from breast carcinomas, MCTs are not necessarily warmer than distant skin. Results of this study suggest highly variable temperature patterns in MCTs.

Skin surface temperature changes were not correlated with histological grade or clinical data (clinical staging, disease-free survival time and survival time) in this study.

CONCLUSIONS

Thermographic imaging revealed marked differences between healthy and tumoural skin surfaces; however, skin surface temperature changes were not correlated with MCT histological grade or clinical data (clinical staging, disease-free survival time and survival time) in this study.

Homogeneous histological grade of MCTs in this study contrasted with tumour surface temperature variation (i.e. tumours colder or warmer than healthy skin).

There is extensive evidence to supportthe use of thermographic imaging in breast cancer diagnosis in women (Arora et al, 2008; Wishartet al, 2010; Wang et al, 2011).Canine studies with larger samples or including investigations of potential correlations between temperature changes and immunohistochemicalstaining patterns may yield more conclusive outcomes.

Novel thermal imaging analysis methods and further studies correlating thermographicfindings with MCT clinical and histological variables may contribute to the consolidation of thermographic imaging as a valuable tool for MCT diagnosis and prognostication.

Thermographic imaging is a promising ancillary modality for accurate diagnosis and prognostication of canine MCTs. However, thermal images should be interpreted in the light of comprehensive clinical history, physical examination findings and other diagnostic tests where applicable.

COMPETING INTERESTS

Authors of this study declare not to have any competing interests.

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