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ULTRASONOGRAPHY IN THE STUDY OF CUTANEOUS NEOPLASMS: WHAT IS ITS APPLICABILITY IN DOGS?

(ULTRASSONOGRAFIA NO ESTUDO DE NEOPLASIAS CUTÂNEAS: QUAL SUA APLICABILIDADE EM CÃES?)

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RESUMO

O câncer de pele é o tipo de câncer mais comum em cães e representa uma grande parcela dos distúrbios dermatológicos nesta espécie. A coleta de material para diagnóstico definitivo é invasiva e, em muitos casos, o resultado leva tempo, retardando o início do tratamento adequado. Portanto, o uso de técnicas não invasivas que possam auxiliar no diagnóstico e nas decisões terapêuticas tem sido incentivado. Em humanos, o ultrassom tem sido aplicado no estudo do câncer de pele há algumas décadas. No entanto, sua aplicabilidade na medicina veterinária ainda é limitada devido à falta de informações plausíveis descritas na literatura. Esta revisão fornece informações sobre a aplicabilidade de diferentes técnicas de ultrassom (Modo B, doppler, elastografia e ultrassonografia com contraste) na avaliação de neoplasias da pele e subcutâneo de humanos e cães, para fornecer informações atualizadas aos veterinários sobre o uso dessa ferramenta diagnóstica.

Palavras-chave: Modo B, Doppler, elastografia, microbolhas, oncologia.

ABSTRACT

Skin cancer is the most common cancer type in dogs and represents a large portion of dermatological disorders in this species. The collection of material for definitive diagnosis is invasive, and in many cases, the result takes time, delaying the start of appropriate treatment. Therefore, the use of non-invasive techniques that can assist in diagnosis and therapeutic decisions has been encouraged. In humans, ultrasound has been applied in the study of skin cancer for some decades. However, its applicability in veterinary medicine is still limited due to the lack of plausible information described in the literature. This review provides information on the applicability of different ultrasound techniques (B-mode, doppler, elastography, and contrast-enhanced ultrasound) in the assessment of humans and dogs skin and subcutaneous neoplasms, to provide updated information for veterinarians regarding the use of this diagnostic tool.

Key-words: B-mode, Doppler, elastography, microbubbles, oncology.

INTRODUCTION

Cutaneous and subcutaneous neoplasms are superficial and palpable structures that become easily accessible in ultrasound studies (CRUZ et al., 2021). They may have different cellular origins (epithelial, mesenchymal, melanocytic, or round cells) and consequently there is a wide diagnostic range of neoplasms with different biological behaviors (ARAÚJO et al., 2018; GRAF et al., 2018).

In medicine, ultrasonography has been implemented as an auxiliary method in the diagnosis of several types of skin neoplasms, allowing the associations between imaging findings and malignity (BHATT et al., 2017; BANDERA et al., 2018). It enables the differentiation between specific types of neoplasms, such as squamous cell, basal cell carcinomas, and cutaneous melanomas (BARCAUI et al., 2014). This diagnostic modality is used in monitoring and follow-up of skin lesions, auxiliary method in therapeutic conduct (surgical or not), and prognosis establishment (BADEA et al., 2010; KUČINSKIENĖ et al., 2014; ROLDÁN, 2014; REGINELLI et al., 2020).

In veterinary medicine, few studies have been developed demonstrating the applicability of ultrasound techniques in dermatology. Studies with dogs or rats are predominantly published as an experimental model for humans (SCHROEDER et al., 2001; FORSBERG et al., 2002; SCHÄRZ et al., 2005; LOH et al., 2009; CRUZ et al., 2021). Despite the lack of data regarding the use of these techniques in the study of skin neoplasms, it is believed that they can be implemented in the humans' clinical routine for different purposes.

In dogs, a preliminary study verified an association between ultrasound characteristics in mode-B with malignancy of cutaneous neoplasms (CRUZ et al., 2021). It was also observed that there was a significant difference in stiffness between benign and metastatic lymph nodes when measured by elastography (SEILER and GRIFFITH 2017). Studies have been described demonstrating the applicability of Doppler in the evaluation of some types of neoplasms, such as mast cell tumors, squamous cell carcinomas and soft tissue sarcomas (SCHÄRZ et al., 2005; LOH et al., 2009).

Because of the importance of ultrasonography in the evaluation of skin cancer in medicine and recent development in veterinary research, this study aims to conduct data collection regarding the applicability of different ultrasound techniques (B-mode, elastography, Doppler and contrast-enhanced ultrasound) in the study of cutaneous and subcutaneous neoplasms in both humans and dogs.

B-mode ultrasonography

The first description of the use of ultrasound in dermatology was in the late 1970s by Alexander and Miller (1979), who investigated a fast and non-invasive method that would allow human skin thickness measurements. There has been an expansion of dermatological ultrasound and advancement of technology, and recently it has been observed that ultrasonography performed at frequencies above 20 MHz (high-frequency ultrasound) allows for better detailing of skin layers, contributing to the implementation of this technique in the study of skin in a more precise way (POLAÑSKA et al., 2017).

In medicine, ultrasound of skin cancer has been described since the early 90's, when it was found that it was possible to differentiate between neoplasms, cysts, and panniculitis through echogenicity, echotexture , and presence of septa (NESSI et al., 1999). It is known that a large portion of the human skin neoplasm is hypoechoic and homogeneous in relation to adjacent tissues. However, using B-mode, other characteristics must be evaluated for better diagnosis, such as delimitation of contours, involvement of adjacent structures and measurement of longitudinal, transversal, and axial axes (BARCAUI et al., 2014).

This technique also allows the differentiation between some specific types of neoplasms, such as basal cell carcinomas and squamous cell carcinomas. Although these are similar when evaluated by B-mode (hypoechoic structures, well delimited, with irregular contours, usually located in the dermis, but which may involve deeper tissues), it is possible to verify hyperechogenic points inside the basal cell carcinomas, which can be due to horny cysts, microcalcifications or clusters of apoptotic cells (BARCAUI et al., 2014). Barcaui et al. (2015) found that the majority of hidrocystomas are well-defined, with a hyperechoic surface and an anechoic content that forms a posterior acoustic reinforcement, while basal cell carcinomas were ovaloid hypoechoic structures and difficult to define.

B-mode also proved to be effective in differentiating between benign cavernous hemangioma and cutaneous melanoma, so that the first was characterized as well-defined, hypoechoic, and well-vascularized, while melanoma was also predominantly hypoechogenic but with heterogeneous and poor delimitation (DYBIEC et al., 2015).

Ultrasonography is widespread in medicine because it allows the differentiation of different skin lesions and neoplastic types, used as an auxiliary method in early therapeutic decision, avoiding surgical removal of lesions when there is no need (DINNES et al., 2018). This exam also helps to complement the surgical planning since it allows lesions measurements in different axes and suggests inflammatory/neoplastic infiltrates in the adjacent tissues (NESSI et al., 1990; GUITERA et al., 2008; KUČINSKIENĖ et al., 2014).

Another use of the technique is related to the differentiation of benign lymph nodes from metastatic lymph nodes. It is known that, in cases of cutaneous melanoma, metastatic lymph nodes are hypoechoic and with a length/depth ratio greater than 2 (MOEHRLE et al., 1999).

In dogs, dermatological use is recent and not widespread. First studies concerning skin measurement using this imaging technique were described by Diana et al. (2004) in healthy dogs of different breeds, and Zanna et al. (2012), in Shar-peis, where there was a correlation between skin thickness, histological measurements,and plicometry measurements.

Few studies have demonstrated the applicability of this imaging technique in the evaluation of skin tumors. In a study involving 34 cutaneous neoplasms of dogs (ten mastocytomas, eight soft tissue sarcomas, and 16 neoplasms with other classifications - including malignant and benign neoplasms), it was observed that there was no difference between the ultrasound characteristics evaluated. However, all hyperechogenic neoplasms were soft tissue sarcomas (LOH et al., 2009). There were also no differences between lipomas and malignant skin neoplasms in terms of shape, regularity, echogenicity, and echotexture (LONGO et al., 2018).

In a preliminary study including 42 cutaneous neoplasms of dogs (30 malignant and 12 benign), it was found that those predominantly hypoechogenic, heterogeneous, and with signs of invasiveness, were more prone to malignancy. However, as it is a study with a low experimental number, the authors suggest the use of information cautiously since the predictive values were moderate for all associations obtained (CRUZ et al., 2020).

Elastography

Elastography is an advanced ultrasound technique that allows the study of tissue stiffness/elasticity through qualitative characteristics, assessed by elastogram, or quantitative, by measuring shear wave velocities (FELICIANO et al., 2017). Its use in dermatology was initially described by Coutts et al. (2006), who evaluated the characteristics of skin and subcutaneous stiffness in humans to assist in the future in the diagnosis of skin neoplasms or other skin diseases.

Shortly thereafter, it was found that, in a case of invasive squamous cell carcinoma, metastatic lymph nodes appeared, using elastograms, asymmetrical and with areas of greater rigidity, suggesting that this technique could be used as a complementary method for the identification of malignancy in lymph nodes of patients with different types of skin cancer (AYOAGI et al., 2009). This hypothesis was confirmed a few years later in patients with cutaneous melanoma where increased rigidity was observed in metastatic lymph nodes, showing good sensitivity and specificity for predicting malignancy (HINZ et al., 2012; CAUDRON et al., 2013; OGATA et al., 2013).

Regarding its use in the evaluation of the neoplasms themselves, it was observed that in a case of T-cell lymphoma of a man, there was a predominance of dark blue color in the elastogram obtained by compressive elastography, that is, the mass had stiffness, higher than that of adjacent tissues (SCHMID-WENDTNER et al., 2011). On the other hand, the elastogram of a benign fibrous histiocytoma showed a mixed aspect with greater rigidity in the peripheral region than in the central region (CRISAN et al., 2014b). Yet, this technique did not show significant results in differentiating between benign tumors and basal cell carcinomas (CRISAN et al., 2014a).

Elastography proved to be effective in predicting malignancy in skin lesions (neoplastic and non-neoplastic) (DASGEB et al., 2015), where malignant neoplasms (basal and squamous cell carcinomas) were more rigid while benign lesions (dermoid cyst, keloid, seborrheic keratosis, hyperkeratotic actinic keratosis, benign nevus, acrochordons and angiokeratoma) were less rigid.

Cutaneous melanomas have high or medium stiffness and there is a significant difference between the stiffness of the lesion and the hypodermis or adjacent tissues (BOTAR-JID et al., 2016), information relevant for surgical planning on removing these neoplasms. However, elastography was not useful in differentiating between thin and thick melanomas when comparing using the Breslow index (measuring the thickness of the melanoma, in millimeters), rate of deformation of the dermis and hypodermis of these neoplasms (BERGHE et al., 2019).

In dogs, the use of elastography in skin cancer studies are recent and with little described data. As in humans, it was also found that metastatic lymph nodes are more rigid than benign lymph nodes, both by qualitative and quantitative evaluation, using a tissue stiffness score (SEILER and GRIFFITH, 2017). In a preliminary study involving 34 malignant neoplasms and 18 lipomas, elastography technique proved to be efficient to differentiate the groups, since malignant lesions showed greater rigidity by both the qualitative and quantitative studies, through Tsukuba elasticity score (> 1.5) (LONGO et al., 2018). More recently, a study involving 65 skin tumors (neoplasms and inflammatory tumors) demonstrated that mast cells and benign follicular tumors showed greater rigidity. However, the method was not effective for differentiating between neoplasms and inflammatory lesions (BRIZZI et al., 2021).

Doppler

Doppler is a non-invasive ultrasound technique that allows real time qualitative and quantitative assessment of tissue vascularization and, through this, it is possible to differentiate benign from malignant lesions (GIOVAGNORIO et al., 1999; KARAMAN et al., 2001).

In humans, Color Doppler is widely used in dermatology, being able to significantly increase the specificity of ultrasonography use in the evaluation of skin nodules and differentiation between malignant and benign neoplasms. Benign neoplasms were avascular or with few peripheral-colored spots during the exam. Most malignant neoplasms present multiple peripheral-colored spots or with central vascularization (GIOVAGNORIO et al., 1999).

Crisan et al. (2014a) verified that differentiation between malignant and benign neoplasms were possible by using both color Doppler and pulsed Doppler. Malignant neoplasms showed irregular and central or mixed vascularization on the qualitative evaluation, and vascular speed greater than 2 cm/s in the quantitative study.

Even though Doppler allows differentiation between benign and malignant lesions, it is not always possible to establish this relationship. Giovagnorio et al. (2003) found that all benign lesions and all B-cell lymphomas showed no vascularization using Color Doppler. They described that other metastatic malignant skin neoplasms had at least one pole of peripheral vascularization and intratumoral vessels.

Neoplasms have characteristics on Doppler. Basal cell carcinomas have intra and peritumoral vascularization, but with low flow (WORTSMAN, 2013) while squamous cell carcinomas have internal and peripheral vascular components with a mixed pattern (MARMUR et al., 2010).

Another use of Doppler is to monitor and set up a surgical plan for patients with cutaneous melanoma, so that there is an association between vascularization, Breslow index and tumor stiffness, verified by elastography. It is known that melanomas with intense vascularization have a higher average Breslow index than those classified with discrete or moderate flows, in addition to the fact that most melanomas with high elasticity have discrete or moderate vascularization (JID et al., 2015).

Like other ultrasound techniques, Doppler still has limited applicability in canine species. In a study with 34 canine skin neoplasms, it was observed that vascularization was seen more easily by power Doppler than by color. Squamous cell carcinomas showed more intense vascularization than the other evaluated tumors (SCHÄRZ et al., 2005).

Loh et al. (2009) verified that all cutaneous mast cell tumors and soft tissue sarcomas showed vascularity that could be evaluated. However, only 37.5% of the other masses (including benign and malignant neoplasms) were able to perform this type of study. Fractional area was smaller in mast cells and sarcomas than in other neoplasms, both by color and by power Doppler. It was observed that cutaneous mast cell tumors had a lower resistivity index than the other groups.

In a study of 132 superficial neoplasms of dogs, it was found that no lipoma presented vascularization that could be studied using the Doppler, as well as four other neoplasms types and concluded that the technique associated with the B-mode, reduced the errors of classification of neoplasms to 24%, where three out of four neoplasms were correctly classified using these techniques (NYMAN et al., 2006).

Contrast-enhanced ultrasound

Contrast-enhanced ultrasound (CEUS) is a recent advanced ultrasound technique that complements the evaluation of tissue vascularization. Unlike Doppler, this test allows evaluation of tissue perfusion at microvascular level (DUDAU et al., 2014).

Use of CEUS in dermatology is still restricted, both in medicine and veterinary medicine. When cutaneous melanomas were induced in rats, it was observed that there was a significant reduction in the number of tumors that did not present vascularization visualized by power Doppler after administration of ultrasound contrast. It also increased the intensity of the Doppler signal after the application of contrast agent (SCHROEDER et al., 2001).

Forsberg et al. (2002) released a preliminary study comparing CEUS results with angiogenesis biomarkers in human cutaneous melanomas xenoimplanted in rats, and a direct correlation was found between the findings of power Doppler and harmonic image of pulse inversion (after contrast administration) with COX-2, suggesting that the technique is effective in the vascular study in this type of neoplasm.

CEUS has also been used in post-surgical follow-up of patients undergoing excision of cutaneous melanomas, through the evaluation of lymph nodes not removed during surgery. Rubaltelli et al. (2011) observed that after administration of the contrast lymph nodes with cortical thickening and presence of filling gaps were characterized as metastatic. In this work, the technique showed sensitivity of 100% and specificity of 99.5% in the diagnosis of malignancy.

It is possible to differentiate between human benign metastatic lymph nodes and squamous cell carcinomas in the head and neck region. Malignant lymph nodes will have a shorter peak contrast time than lymph nodes without alteration, and this characteristic is a predictor of malignancy with 100% sensitivity and 85.7% specificity (DUDAU et al., 2014).

In a patient with cutaneous dermatofibroma (benign fibrous histiocytoma), it was observed a intense vascularization and tissue filling characteristics by Doppler and CEUS, despite being a benign neoplasm, so that this neovascularization was confirmed after histopathological analysis. (CRISAN et al., 2014b). Crisan et al. (2014a) observed that between benign cutaneous neoplasms included in the study, only dermatofibromas presented vascularization visualized by Doppler, and malignant neoplasms showed heterogeneity of contrast filling.

In dogs, the only study demonstrating the use of CEUS studying skin neoplasms was described by Ohlerth et al. (2010), who evaluated the correlation between power

Doppler findings after administration of CEUS with immunohistochemical results in 45 neoplasms. They reported an intense vascularization in squamous cell carcinomas, a moderate in oral melanomas and low in soft tissue sarcomas. Authors found that the measurement of vascularization correlated with microvascular density in all tumors, but there was no correlation within histological groups and concluded that, although the technique is non-invasive and provides important results on the characteristics of vascularization, its measurement may present different biological information.

CONCLUSION

Ultrasonographic techniques can provide a large amount of information and can be used to aid diagnosis, therapeutic planning and post-surgical follow-up in cases of cutaneous and subcutaneous neoplasms. These techniques are gaining ground in veterinary medicine and even though few studies have demonstrated the applicability in canine species, it is likely that they can and will be used for different purposes in the future.

Author's contributions

Igor Cezar Kniphoff da Cruz: literature review and document writing

Luciana Cristina Padilha-Nakaghi: support in writing the document

Rafael Kretzer Carneiro: literature review and document writing

Marcus Antônio Rossi Feliciano: support in writing the document

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