B-mode ultrasound examination of canine mammary gland neoplastic lesions of small size (diameter < 2 cm)

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Iacopo Vannozzi1 · Matteo Tesi1 · Marta Zangheri1 · Viola Maria Innocenti2 · Alessandra Rota1 · Simonetta Citi1 · Alessandro Poli1

Abstract
Ultrasonography is a valuable tool for the evaluation of neoplastic lesions in the dog and there is a growing interest in the use of this technique for the stadiation of canine mammary tumours. An accurate assessment of small sized nodules facilitates the stadiation of the mammary lesions and helps the clinician in the choice of the most indicated surgical therapy. The aim of this study was to identify those ultrasound criteria that may be useful in discriminating between benign and malignant lesions of small size (diameter smaller than 2 cm). Sixty-two nodules, < 2 cm in larger diameter, belonging to thirty- ve bitches presented between January 2012 and February 2014 were evaluated. Tumours were observed by conventional ultrasound and assessed for: shape (regular-irregular), limit (de ned-ill-de ned), margins (regular-irregular), echogenicity (hypoechoic-isoechoic-hyperecoic), echotexture (homogeneus-heterogeneus), presence of hyperecoic halo, distal acoustic enhancement or shadowing and surrounding tissue alterations. Among the alterations in surrounding tissues, the disruption of the glandular tissue and the increase in echogenicity of the peritumoral tissues were assessed. Thereafter, bitches were subjected to mastectomy and nodules were evaluated histologically. None of the ultasound criteria considered in the current study showed a statistically signi cant relation with malignancy, except for the presence of alterations in the tissue surround- ing the nodules. According to our results, this characteristic may indicate malignancy, however its subjectivity may a ect the applicability in clinical practice. In conclusions, conventional ultrasound in bitches had a limited ability in discriminating benign and malignant mammary gland neoplastic lesions of small size (diameter < 2 cm).

Keywords Dog · Canine · Mammary tumours · Ultrasound ·

Introduction

Mammary tumours are the second most common neoplasia in dogs, second only to skin tumours (Moulton 1999). They represent approximately 50% of all neoplastic disorders in bitches (Quieroga and Lopes 2002; Sleeckx et al. 2011) and about 30-50% of the recorded masses are malignant (Dorn et al. 1968; Kurzman and Gilbertson 1986; Sorenmo et al. 2000; Feliciano et al. 2017). Canine mammary tumors show epidemiological, patho- logical and prognostic features which are very similar to those of humans (Vail and MacEwen 2000; Mohammed et al. 2011; Queiroga et al. 2011). As in humans, canine mammary neoplasia is age-related. The median age at occur- rence ranges from 8 to 10 years (Sleeckx et al. 2011). Several studies suggest that dogs with tumours smaller than 3 cm have a lower risk of recurrence and a better out- come (Kurzman and Gilbertson 1986; Sorenmo et al. 2000; Cassali et al. 2014). Furthermore, Philibert et al. 2003 observed a higher overall survival in dogs with tumours smaller than 3 cm in comparison to dogs with tumours larger than 3 cm (Philibert et al. 2003). The aforementioned evidences have led to consider nod- ules size as one of the main variables (in addition to disease extent, lymphatic drainage, location of the lesion, etc) to keep in consideration to de ne the therapeutic approach. Small lesions of 0.5 cm can be treated by a simple nodulec- tomy or lumpectomy in absence of paramenters of malig- nancy. Other tumours, with diameter that does not exceed 4 cm, could be removed by simple mastectomy depending on the lymphatic drainage and the existence of muscle adhesion or skin ulcerations. For nodules bigger than 4 cm, regional or unilateral mastectomy is recommended (Cassali et al. 2014). Regarding the treatment of small nodules more therapeu- tic possibilities are available and this suggest as an accurate clinical evaluation of especially these lesions is crucial in de ning the most correct therapeutic choice. Ultrasonography is a non-invasive, well-tolerated tech- nique that allows a real-time evaluation of the mammary tissue. In human medicine, ultrasonography plays a signi - cant role as a method supplementary to the mammography (Skaane and Engedal 1998; Zonderland et al. 1999). The main points of strength of ultrasounds are the ability to dif- ferentiate between cystic and solid lesions, with a reported accuracy of nearly 100% (Skaane and Engedal 1998), and to evaluate lesions in patients with dense breasts (Zonderland et al. 1999). Although in the canine species several stud- ies attempted to nd a single ultrasound characteristic able to discriminate between benign and malignant alterations of the mammary gland, literature is not consistent for their predictive value (Mohammed et al. 2011; Bulnes et al. 1998; Bastan et al. 2009; Tagawa et al. 2016; Nyman et al. 2006a, b; Feliciano et al. 2012). Most of these controversies are closely related to the reproducibility of ultrasound results, which depends on several factors, e.g. US equipment, opera- tor experience and patient populations. According to literature, several ultrasound caractheris- tics are suggestive of benignancy in the dog: regular shape (Bulnes et al. 1998; Bastan et al.

2009; Tagawa et al. 2016), circumscribed and regular margins (Bastan et al. 2009; Mohammed et al. 2011), homogeneus ecotexture (Bulnes et al. 1998; Nyman et al. 2006a, b). In contrast, the pres- ence of irregular shape, ill-de ned and non-circumscribed margins, heterogeneus ecotexture, anterior echogenic rim, acoustic posterior shadowing and vertical orientation may indicate malignancy (Bulnes et al. 1998; Bastan et al. 2009; Calas et al. 2007; Paulinelli et al. 2011). These studies, how- ever, include nodules of di erent developmental stages and size. The aim of this study was to identify those ultrasound criteria that may be useful in the canine species in di eren- tiating between benign and malignant lesions with diameter smaller than 2 cm and to de ne their speci c predictor value.

Materials and methods

Animals - This study was performed at the Veterinary Teaching Hos- pital of the Department of Veterinary Sciences, University of Pisa, Italy, between January 2012 and February 2014. Sixty-two spontaneous nodules of the mammary glands were obtained from 35 bitches of which 27 were adult spayed and 8 were intact females. All intact bitches were in anestrous according to vaginal cytology. The age of bitches was 9.5 ± 2.4 years (range 5.1-14.3 years) and they belonged to mixed or di erent pure breeds. The median number of nod- ules for each dog was 2.

Ultrasound examination - The ultrasound examination of each tumor was performed using a GE Healthcare Venue 40 equipped with a 5-13 MHz linear array transducer by a single experienced physician. At the time of the evaluation the physician was unaware of the lymph node status, histological type, grading, and family his- tory of the bitch under examination. The size of the tumour was calculated by measuring the major and minor axes. We decided to consider only nodules whose main axis was not larger than 2 cm. The following criteria were assessed: shape (regular, irregular), limit (de ned, ill-de ned), mar- gins (regular, irregular), echogenicity (hypoechoic, isoec- hoic, hyperecoic), echotexture (homogeneus, heterogeneus), presence of hyperecoic halo, distal acoustic enhancement or shadowing. Besides the aforementioned characteristics, alterations in surrounding tissues was taken into considera- tion as secondary sign. Among the alterations in surrounding tissues, we considered the disruption of the glandular tissue intended as the loss of the normal echotexture at the border of the neoplastic lesion and the increase in echogenicity of the subcutaneous, peritumoral tissues.

Histological evaluation - After the excision, tumors were submerged and preserved in 10% neutral bu ered formalin and then embedded in para n wax. Sections of 5 µm were cut and stained with hematoxy- lin and eosin (H & E) for histological examination. Histo- logical type, tumor size, and nodal status were determined according to WHO criteria (Misdorp et al. 1999).

Statistical analysis - Ultrasound criteria were all categorized and assessed against the result of histological assessment (benign or malignant) by univariate logistic regression model, expressing the result as odds ratio (OR) with 95% con dence intervals. A t-test was used to compare measures of major and minor axis between benign and malignant tumours. Data are pre- sented as means ± standard deviations. P-values lower than 0.05 were considered statistically signi cant. The statistical software Minitab 16.1 (Minitab Inc., State College, USA) was used for statistical analysis.

Results

Among the 62 nodules histologically evaluated, 18 tumours were identi ed as benign (29%) and 44 as malignant (71%). The nodules' histologic diagnosis is shown in Table 1. The mean size of tumors' major axis was 8.5 ± 4.5 mm (range 3.6-20 mm), the mean size of tumor minor axis was 6.7 ± 3.1 mm (range 2-19.4 mm). No di erences were observed between the major and minor axes of benign (7.32 ± 2.42 and 5.71 ± 2.37 mm) and malignant tumour (8.55 ± 3.52 and 6.62 ± 2.88 mm) ($P > 0.05$). Univariate logistic regression models assessing the relations between ultrasonographic and histological ndings are shown in Table 2. With respect to shape, margins (Fig. 1), echogenity, echotexture, anterior echogenic rim and posterior acoustic features (Fig. 2), no statistically signi cant di erences were found between benign and malignant tumours. Presence of surrounding tissue alterations was the only feature which showed a signi cant di erence between the two groups in the univariate logistic regression ($P < 0.05$) (Fig. 3).

Discussion

The histopathologic examination revealed that the propor- tion of malignant tumours was larger than that of benign tumours (71 and 29%, respectively). These ndings are close to the results observed by Feliciano et al. who observed a higher prevalence of malignat nodules. In the aforemen- tioned study, out of the 300 mammary masses evaluated, 82% were classi ed as malignant and 18% as benign (Feli- ciano et al. 2017). With a mean overall age of 9.5 years, our study con rms how age is one of the main risk factors for developing mammary tumors in dogs, as reported in litera- ture (Sleeckx et al. 2011; Sorenmo et al. 2000). No di erence was seen in size between benign and malig- nant nodules. This nding is in disagreement with those of previous studies where malignant tumors were on average larger than the benign ones (Bastan et al. 2009; Nyman et al. 2006b). However, we included only nodules whose major diameter did not exceed 2 cm. Malignant tumours have a tendency to grow faster and become larger than benign tumours (North and Banks 2009) but with a size lower than 2 cm these di erences might be not yet evident even if the histological di erentiation is completed. Several studies in humans (Calas et al. 2007; Rahbar et al. 1999) and in dogs (Bulnes et al. 1998; Bastan et al. 2009; Tagawa et al. 2016), reported that one of the ultrasono- graphic feature that most reliably characterizes masses of the mammary glands as benign is a regular shape. A round/ oval shape seems to be indicative of benignancy while an irregular shape is more likely seen in malignant lesions. In a study conducted in bitches, it was reported that 84% (59/70) benign tumours were oval in shape (Tagawa et al. 2016). However, such ndings were not observed in the current study. No di erence was observed in de nition and regular- ity of margins either. This result contrasts with the results of other authors who noticed as de ned and regular margins were associated with benign tumours while ill-de ned and irregular margins characterized malignant tumours (Bulnes et al. 1998; Bastan et al. 2009; Nyman et al. 2006a). It can be hypothesized that when the size is still below 2 cm, shape and margins irregularity is still not appreciable. With regard to echogenicity, malignant tumours showed no di erences compared to benign ones. Although these results di er from those obtained in other studies, where benign nodules were more often hypoechoic and hysoechoic than malignant nodules (Nyman et al. 2006b), they are sup- ported by those of Tagawa et al. (2016) who concluded that echogenicity is not useful for classi cation of nodules in benign or malignant. In several studies, ecotexture was a signi cant feature for lesions classi cation, with malignant tumours are more likely to have an heterogeneus ecotexture (Bulnes et al. 1998; Bastan et al. 2009; Nyman et al. 2006a; Soler et al. 2016). In contrast, we did not observe di erences between the two groups, which is however consistent with results of other authors (Tagawa et al. 2016; Feliciano et al. 2012). Nyman et al. (2006a) indicated as possible main source of ecotexture heterogenicity, the presence of necrosis in malig- nant tumours and bone/ brocartilage tissue in benign ones. In that same study, the presence of histologic elements like necrosis and metaplastic phenomena, but also like edema, hemorrhage, cyst, calci cation showed no signi cant di er- ence between benign and malignant lesions. Contradictory ndings were reported concerning anterior echogenic rim in human medicine. Early studies suggested a good predictive value for malignancy of this echographic feature but then it was scaled-down over the years (Skaane and Engedal 1998; Rahbar et al. 1999). Nevertheless, Paul- inelli et al. (2011) conducted a study on 1403 breast lesions and included anterior echogenic rim in the group of features suggestive of malignancy in the woman. To the author's knowledge none of the studies conducted on canine mam- mary tumour have considered this ultrasound characteris- tic. We could not nd any signi cant di erence in presence of anterior echogenic rim between the groups of benign (16,7%) and malignant (36,4%) tumours. According to Nyman et al. (2006a) posterior enhance- ment was correlated with the presence of necrotic and cystic areas. Considering that necrosis was detected in a larger proportion in the malignant tumors (73%), compared with the benign tumors (36%), these authors associated posterior enhacement with malignancy. Such relation was not found in the current study and this is in agreement with the results reported by several authors in both canine (Bastan et al. 2009; Tagawa et al. 2016) and human species (Calas et al. 2007). In humans as in dogs, the ability of the presence of shadowing to discriminate between benign and malignant tumours is controversial. Shadowing seems to be likely asso- ciated with malignancy in human species (Paulinelli et al. 2011). In the bitch, however, most of the authors (Tagawa et al. 2016; Nyman et al. 2006b; Feliciano et al. 2012; Soler et al. 2016) agree that there are no di erences between the two groups concerning both bilateral and central shadowing, and the results obtained in the present study support such assessment. Concerning the presence of posterior acoustic features, in the present study this was low in both groups, and no stastistically signi cant di erences emerged, similarly to what described by Bastan et al. (2009) and Tagawa et al. (2016). In 2017, Feliciano et al. proposed a large prospective cohort study which included 153 bitches with a total of 300 mammary nodules. As in our study, echotexture, mar- gins, echogenicity and acoustic shadowing were evaluated in B-mode but none of these showed e cacy in predicting malignancy in canine mammary nodules (Feliciano et al. 2017). Alterations in surrounding tissue turned out to be the only ultrasound characteristic valuable in the di erentiation between benign and malignant tumours, which is consistent with observations by Skaane and Engedal (1998) regarding the di erentiation between broadenoma and invasive ductal carcinoma in human medicine. The malignant nature of a mammary nodule may causes alterations of the surrounding tissue. The application of a new technique, elastography, has shown that many malignant breast lesions exhibited high sti ness not only in the lesion but also in the surrounding tissue (Itoh et al. 2006). The higher sti ness of malignant tumour surrounding glandular tissue has been described by subjective visual inspection and quantitative analysis and correlates with invasiveness in both humans (Adamietz et al. 2011; Yi et al. 2012; Zhou et al. 2014) and dogs (Feliciano et al. 2014, 2017). The alterations in surrounding tissue of malignant mam- mary lesions might indicate the in ltration of cancer cells into the peritumoral tissue or might be caused by the des- moplastic reaction (Itoh et al. 2006). Further prospective studies with a large population is warranted to de ne the correspondence between the histopathologic ndings and the ultrasound modi cations. However, an ultrasound feature needs three characteristics to have a practical applicability in di erentiating malignant from benign tumours: frequency, reliability and reproduc- ibility (Rahbar et al. 1999). Alterations in surrounding tissue were present in 20 of the 62 nodules. The reported frequency (32%) was not very high and this a ects the accuracy (only 55%) and thus the applicability of this feature. Furthermore, despite an inter- observer agreement evaluation was not performed in this study, it is possible that it would be low for this ultrasound characteristic. In humans, even for very small nodules, ultrasound evalu- ation seems to be more reliable and thus predictive models of malignancy have been developed (Paulinelli et al. 2011). In dogs, the development of such models appears to be more di cult. Possible explanations could be the higher varia- bility of histotypes observed in this species and the lower number of lesions evaluated in most studies. Recent studies suggest how other techniques, such as Doppler ultrasound and ARFI elastography, might be more reliable than B-mode ultrasound in malignancy prediction of canine mammary masses (Soler et al. 2016; Feliciano et al. 2017).

Conclusions

In the conditions of the present study shape, margins, echo- genicity, echotexture, anterior echogenic rim and poste- rior acoustic features did not show any relevant di erence between benign and malignant tumours. The only ultrasound parameter that had a di erent prevalence between the two groups of nodules was the presence of surrounding tissue alterations. It can thus be concluded that, although the lesions were already fully di erentiated histologically, it was not possible to identify a group of B-mode ultrasound characteristics able to discriminate between benign and malignant canine mam- mary tumors of small size (diameter < 2 cm).

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Figures and tables

Table 1 Distribution of the histologic diagnosis of the 62 nodules

Table 2 Associations between the ultrasound characteristics of mammary nodules observed and histological assessment

Fig. 1 A grey-scale image ofa mammary simple adenoma in a 8-year-old intact German Shepherd. Note the regular and de ned margins of the tumour, the homogeneus ecotexture and the absence of anterior echogenic rim

Fig. 2 A grey-scale image of mammary simple carcinoma in a 13-year-old intact Labrador Retriever. Note the regular shape, regular and de ned mar- gins, homogeneus echotexture, posterior enhancement and the presence of disruption of the glandular tissue at the border of the lesion (arrowheads)

Fig. 3 Sonographic image ofa mammary complex tubulo- papillary adenocarcinoma in a 9-year-old intact Lagotto. Note the irregular shape, the irregular and ill-de ned margins, the heterogeneus ecotexture, the absence of anterior echogenic rim and the presence of alterations in surrounding tissue (arrowheads)