

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

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### **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-hyperechoic), echotexture (homogeneous-heterogeneous), presence of hyperechoic 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 ultrasound criteria considered in the current study showed a statistically significant relation with malignancy, except for the presence of alterations in the tissue surrounding the nodules. According to our results, this characteristic may indicate malignancy, however its subjectivity may affect 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; Sleenckx 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, pathological 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 occurrence ranges from 8 to 10 years (Sleenckx et al. 2011). Several studies suggest that dogs with tumours smaller than 3 cm have a lower risk of recurrence and a better outcome (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 nodules size as one of the main variables (in addition to disease extent, lymphatic drainage, location of the lesion, etc) to keep in consideration to define the therapeutic approach. Small lesions of 0.5 cm can be treated by a simple nodulectomy or lumpectomy in absence of parameters of malignancy. 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 therapeutic possibilities are available and this suggest as an accurate clinical evaluation of especially these lesions is crucial in defining the most correct therapeutic choice. Ultrasonography is a non-invasive, well-tolerated technique that allows a real-time evaluation of the mammary tissue. In human medicine, ultrasonography plays a significant 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 differentiate 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 studies attempted to find 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, operator experience and patient populations. According to literature, several ultrasound characteristics 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), homogeneous echotexture (Bulnes et al. 1998; Nyman et al. 2006a, b). In contrast, the presence of irregular shape, ill-defined and non-circumscribed margins, heterogeneous echotexture, 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, however, include nodules of different developmental stages and size. The aim of this study was to identify those ultrasound criteria that may be useful in the canine species in differentiating between benign and malignant lesions with diameter smaller than 2 cm and to define their specific predictor value.

## **Materials and methods**

**Animals** - This study was performed at the Veterinary Teaching Hospital 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 anestrus according to vaginal cytology. The age of bitches was  $9.5 \pm 2.4$  years (range 5.1–14.3 years) and they belonged to mixed or different pure breeds. The median number of nodules 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 history 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 (defined, ill-defined), margins (regular, irregular), echogenicity (hypoechoic, isoechoic, hyperechoic), echotexture (homogeneous, heterogeneous), presence of hyperechoic halo, distal acoustic enhancement or shadowing. Besides the aforementioned characteristics, alterations in surrounding tissues was taken into consideration 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 buffered formalin and then embedded in paraffin wax. Sections of 5  $\mu$ m were cut and stained with hematoxylin and eosin (H & E) for histological examination. Histological 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% confidence intervals. A t-test was used to compare measures of major and minor axis between benign and malignant tumours. Data are presented as means  $\pm$  standard deviations. P-values lower than 0.05 were considered statistically significant. 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 identified 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  $8.5 \pm 4.5$  mm (range 3.6–20 mm), the mean size of tumor minor axis was  $6.7 \pm 3.1$  mm (range 2–19.4 mm). No differences were observed between the major and minor axes of benign ( $7.32 \pm 2.42$  and  $5.71 \pm 2.37$  mm) and malignant tumour ( $8.55 \pm 3.52$  and  $6.62 \pm 2.88$  mm) ( $P > 0.05$ ). Univariate logistic regression models assessing the relations between ultrasonographic and histological findings are shown in Table 2. With respect to shape, margins (Fig. 1), echogenicity, echotexture, anterior echogenic rim and posterior acoustic features (Fig. 2), no statistically significant differences were found between benign and malignant tumours. Presence of surrounding tissue alterations was the only feature which showed a significant difference between the two groups in the univariate logistic regression ( $P < 0.05$ ) (Fig. 3).

## Discussion

The histopathologic examination revealed that the proportion of malignant tumours was larger than

that of benign tumours (71 and 29%, respectively). These findings are close to the results observed by Feliciano et al. who observed a higher prevalence of malignant nodules. In the aforementioned study, out of the 300 mammary masses evaluated, 82% were classified as malignant and 18% as benign (Feliciano et al. 2017). With a mean overall age of 9.5 years, our study confirms how age is one of the main risk factors for developing mammary tumors in dogs, as reported in literature (Sleeckx et al. 2011; Sorenmo et al. 2000). No difference was seen in size between benign and malignant nodules. This finding 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 differences might be not yet evident even if the histological differentiation 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 ultrasonographic 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 findings were not observed in the current study. No difference was observed in definition and regularity of margins either. This result contrasts with the results of other authors who noticed as defined and regular margins were associated with benign tumours while ill-defined 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 differences compared to benign ones. Although these results differ from those obtained in other studies, where benign nodules were more often hypoechoic and hypoechoic than malignant nodules (Nyman et al. 2006b), they are supported by those of Tagawa et al. (2016) who concluded that echogenicity is not useful for classification of nodules in benign or malignant. In several studies, ecotexture was a significant feature for lesions classification, with malignant tumours are more likely to have an heterogeneous ecotexture (Bulnes et al. 1998; Bastan et al. 2009; Nyman et al. 2006a; Soler et al. 2016). In contrast, we did not observe differences 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 heterogeneity, the presence of necrosis in malignant 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, calcification showed no significant difference between benign and malignant lesions. Contradictory findings 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, Paulinelli 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 mammary tumour have considered this ultrasound characteristic. We could not find any significant difference 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 enhancement 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 enhancement 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 associated 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 differences 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 statistically significant differences 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, margins, echogenicity and acoustic shadowing were evaluated in B-mode but none of these showed efficacy 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 differentiation between benign and malignant tumours, which is consistent with observations by Skaane and Engedal (1998) regarding the differentiation between adenoma and invasive ductal carcinoma in human medicine. The malignant nature of a mammary nodule may cause alterations of the surrounding tissue. The application of a new technique, elastography, has shown that many malignant breast lesions exhibited high stiffness not only in the lesion but also in the surrounding tissue (Itoh et al. 2006). The higher stiffness 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 mammary lesions might indicate the infiltration of cancer cells into the peritumoral tissue or might be caused by the desmoplastic reaction (Itoh et al. 2006). Further prospective studies with a large population is warranted to define the correspondence between the histopathologic findings and the ultrasound modifications. However, an ultrasound feature needs three characteristics to have a practical applicability in differentiating malignant from benign tumours: frequency, reliability and reproducibility (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 affects 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 evaluation 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 difficult. Possible explanations could be the higher variability 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, echogenicity, echotexture, anterior echogenic rim and posterior acoustic features did not show any relevant difference between benign and malignant tumours. The only ultrasound parameter that had a different 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 differentiated histologically, it was not possible to identify a group of B-mode ultrasound characteristics able to discriminate between benign and malignant canine mammary tumors of small size (diameter < 2 cm).

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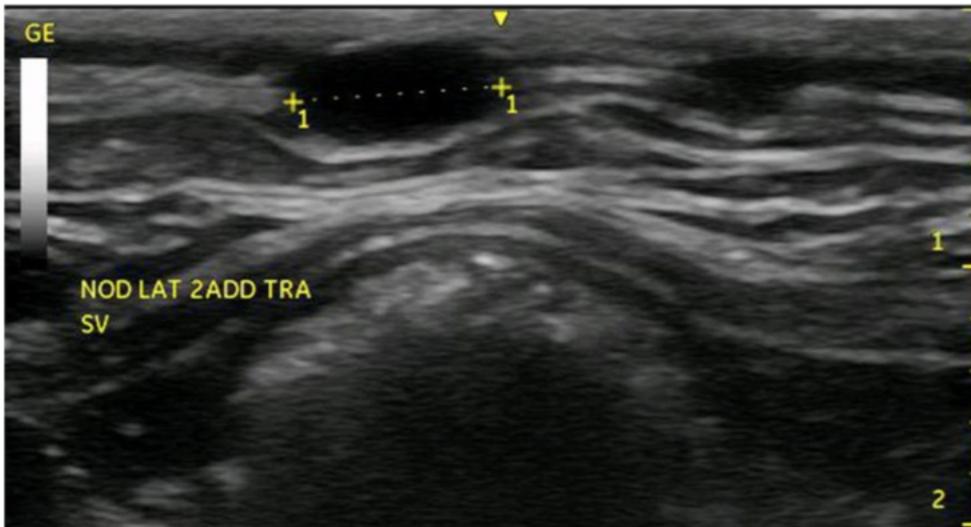
## Figures and tables

Tumour group	Histologic diagnosis	N.
Benign	Adenoma	11
	Duct papilloma	4
	Fibroadenoma	3
Malignant	Simple tubulopapillary adenocarcinoma	20
	Complex tubulopapillary adenocarcinoma	21
	Solid carcinoma	3
Total		62

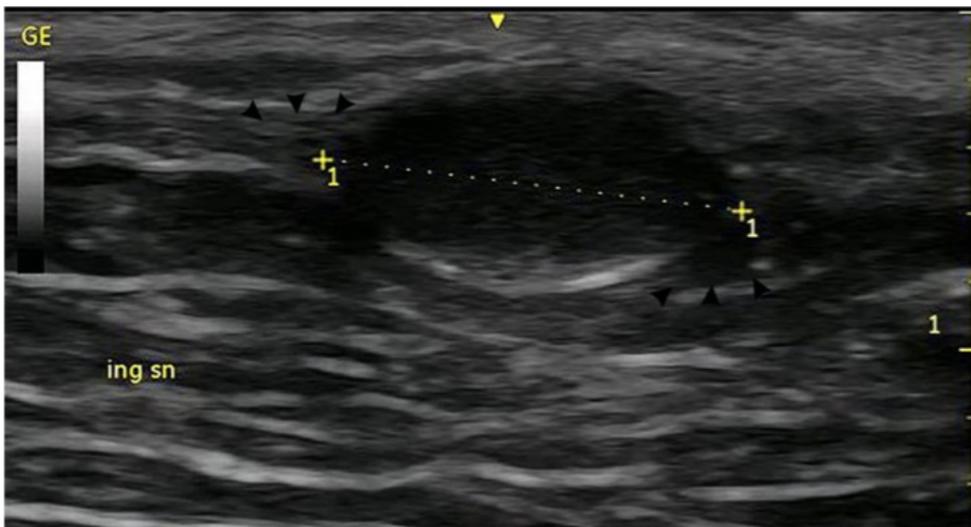
**Table 1** Distribution of the histologic diagnosis of the 62 nodules

Feature	Histological assessment		Univariate analysis	
	Benign	Malignant	p-value	OR (95% CI)
<b>Shape</b>				
Regular	10	27	0,67	1,27 (0,42–3,86)
Irregular	8	17		
<b>Margin</b>				
Defined	9	16	0,32	0,57 (0,19–1,73)
Ill-defined	9	28		
<b>Margin contour</b>				
Regular	13	30	0,75	0,82 (0,24–2,77)
Irregular	5	14		
<b>Echogenicity</b>				
Hypoechoic	15	41	0,25	0,37 (0,07–2,01)
Hyper-, isoechoic	3	3		
<b>Echotexture</b>				
Homogeneous	14	29	0,35	0,55 (0,15–1,98)
Heterogeneous	4	15		
<b>Anterior echogenic rim</b>				
Absent	15	28	0,11	2,86 (0,72–11,40)
Present	3	16		
<b>Post. acoustic features</b>				
Absent	4	16	0,27	2 (0,56–7,12)
Present	14	28		
<b>Enhancement</b>				
Absent	6	24	0,13	0,42 (0,13–1,31)
Present	12	20		
<b>Shadowing</b>				
Absent	16	36	0,48	1,78 (0,34–9,33)
Present	2	8		
<b>Modified surround. tissue</b>				
Absent	16	26	0,015	5,54 (1,13–27,11)
Present	2	18		

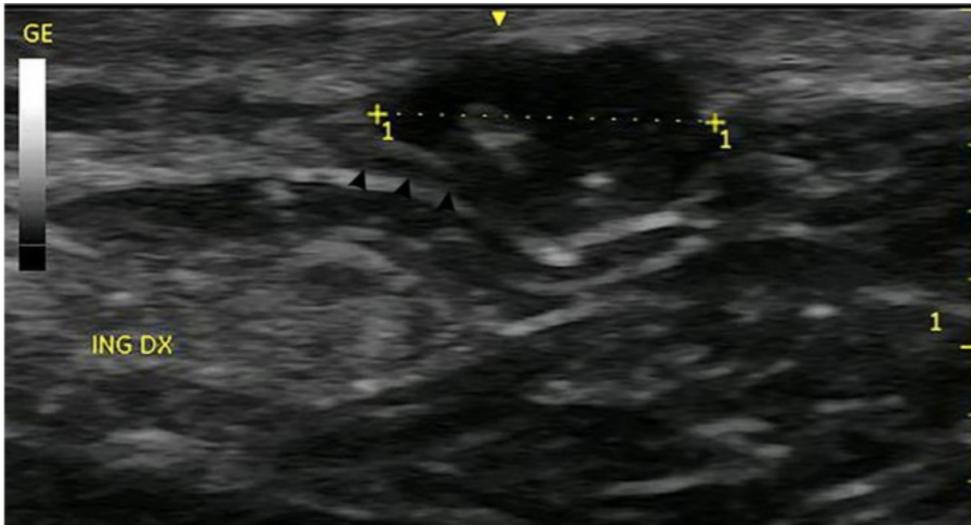
**Table 2** Associations between the ultrasound characteristics of mammary nodules observed and histological assessment



**Fig. 1** A grey-scale image of a mammary simple adenoma in a 8-year-old intact German Shepherd. Note the regular and defined margins of the tumour, the homogeneous echotexture 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 defined margins, homogeneous echotexture, posterior enhancement and the presence of disruption of the glandular tissue at the border of the lesion (arrowheads)



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