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Evaluation of Mammary Gland Calcification in Dogs; Radiography and Computed Tomography

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ABSTRACT

The mammary gland tumor (MGT) is the most common neoplasia in intact female dogs. Of these, 50% are malignant and metastasis to the other sites are often occurred. Therefore, it is very important for decision of treatment plan and prognosis to differentiate benign tumor from malignancies. Calcification of MGT is a very important imaging finding. The purpose of this study was to investigate the radiological and computed tomographic images of the MGT and the morphology and distribution of calcifications in the MGT using the Breast Imaging Reporting and Data System classification. A total of 42 dogs with MGT were included in this study. The dogs were divided into two groups into benign and malignant groups based upon histologic or cytologic results. The appearance of calcification in the tumor on radiographs and CT images was analyzed for the HU value of pre- and post-contrast injection, margin, surface, and shape of the tumor and the lymph node abnormalities. On radiographs, the positive predictive value of malignant and benign tumors was 72.72 and 85.71%, respectively. On CT examinations, the positive predictive value of malignant and benign tumors was the same value of 83.33%. The maximum diameter of the tumor and the presence of abnormal lymph nodes on CT images showed a strong correlation with malignancies. Therefore, it is thought that radiographs and CT provide useful information for evaluating MGT in dogs.

(Key words: Calcification, CT, Dogs, Mammary gland tumor, Radiograph)

INTRODUCTION

Mammary gland tumors(MGT) are the most common tumors in sexually intact female dogs (Withrow *et al*., 2013). The 4th and 5th glands are most frequently affected due to their bigger volume of gland tissue (Soultani *et al*., 2017). About 50% of the mammary gland tumors are malignant in dogs (Misdorp W., 2002). Due to the risk of metastasis associated with mammary gland tumors, staging before initiating treatment is strongly recommended, especially when benign tumors cannot be histologically confirmed (Simon D *et al*., 2009; Soler *et al.*, 2016). Differentiation between malignant and benign tumors would be of value in judging an individual patient's prognosis and helping therapeutic decision making (Soler *et al.*, 2016).

Human develop breast cancer with similar epidemiologic, clinical, and prognostic features as mammary gland tumors in dogs. In human medicine, mammography is the gold standard for screening test and diagnosing breast cancer (Mohammed *et al.*, 2011; Strandberg et al., 1974). The American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) classifies calcifications on mammograms into two categories, according to types and distribution of calcifications; Typical benign and suspicious morphology. Typical benign calcification includes skin, vascular, coarse or popcorn-like, large rod-like, round, punctate, rim-calcification, dystrophic, milk of calcium, and suture. Suspicious morphology includes amorphous, coarse heterogeneous, fine pleomorphic, fine linear or fine linear branching[1]. In human study of canine model, surgically removed canine mammary gland tumors were imaged mammographically and calcifications were assessed according to BI-RADS categories[11]. In this study, BI-RADS categories showed excellent sensitivity and specificity for canine mammary gland tumors. BI-RADS categories provide standardized classification for canine mammographic reporting (Mohammed *et al*., 2011; Muttarak *et al.*, 2009, Whitman *et al*., 2002). However, application the features of mammography images in alive dogs have limitations. To our knowledge, there

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are no studies about plain radiography, and computed tomography (CT) features of mammary gland tumors in dogs. Radiographic examination is the first screening test that can be performed for mammary gland tumors. CT imaging provides excellent anatomical details good depiction of calcification, and exquisite visualization of the soft tissue components of tumors. CT imaging also provides more sensitive detection of metastasis (Boone *et al*., 2006).

The interest in calcification in the radiological study has largely focused on its identification in many disparate conditions with warnings of its unreliability as a predictor of benign disease (Burkill et al., 2009). This study reviewed cases of calcifying canine mammary gland tumors, comparing them with human breast calcification. The purpose of this study was to identify features in radiographic, and computed tomographic characteristics that could be used to distinguish malignant from nonmalignant lesions focused on calcification and to assess the pattern and significance of calcifications in mammary gland tumors in dogs.

MATERIALS and METHODS

1. Experimental animals

The animal samples were obtained over a four-year period, from dogs referred to Chungnam Veterinary Medicine Teaching Hospitals. Inclusion criteria is the presence of at least one site of the mammary gland tumors in dogs. Physical examination, complete blood cell counts, serum chemistry analysis, radiography, or CT studies were performed. Exclusion criteria is the patients with no results of cytologic or histopathologic examination.

2. Radiography

Right lateral radiographic images were evaluated. If calcifications were present, they were assessed according to the BI-RADS categories. Assessment of categories were based on the description of shape and distribution of calcifications. Based on morphology of calcification divided into 2 groups; Typically benign, and suspicious morphology. Typical benign calcifications include skin, vascular, coarse or popcorn-like, large rod-like, round, rim, milk of calcium, suture, and dystrophic calcifications. Suspicious morphology included amorphous, coarsely heterogeneous, fine, linear, branching, pleomorphic (varying in size and shape), and numerous (Fig. 1 and 2). In cases with two or more types of calcifications are present, predominant descriptor was used.

3. Computed tomography

CT scan was obtained using 32-detector-row CT scanner (Alexion^{TM}, Toshiba, Japan) with following parameters: 120 kVp, 150 mAs, 2-3 mm slice thickness, 0.75 second rotation time and 0.938 collimation beam pitch. Intravenous iodinated contrast medium, iohexol (Omnipaque$^{®}$, GE healthcare Ireland, Ireland), a dose of 600 mg iodine/kg was administered via cephalic vein with injection rate of 2 ml/sec using power injector (Salient^{TM}, Imaxeon Pty. Ltd., Australia). Scan field was the entire abdomen extending from the cranial margin of diaphragm to the rectum, which was performed scanning from cranial to caudal. All patients had CT evaluation that included

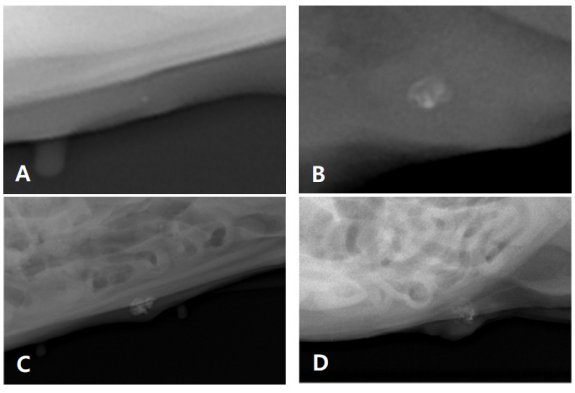

Fig. 1. The representative radiographic images of typically benign calcifications in mammary gland tumors. Punctated (A), rim (B), popcorn-like (C), and dystrophic (D) calcification.

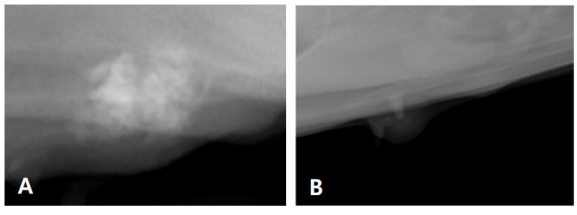

Fig. 2. The representative radiographic images of suspicious morphology in mammary gland tumors. Coarse heterogeneous (A), and fine pleomorphic (B) calcification.

non-enhanced and contrast-enhanced dynamic CT. Anesthetized dogs were placed in the ventral or dorsal recumbency on the CT table and the ventilation of the positive pressure (10-15 cm H_2O) with a breath-holding technique was administered during scan to avoid motion artifact due to respiration.

The computed tomographic images examined included the presence of calcification (yes or no), Hounsfield unit (HU) value (hyper-, hypo-, isoattenuation), margin (distinct or indistinct), surface (smooth or irregular), morphology (round, lobulated, spiculated), maximal diameter (cm), and presence of abnormal lymph nodes (yes or no). In cases with two or more masses, the largest and more heterogeneous mass was analyzed. If calcifications were found, they were assessed according to the BI-RADS categories (Fig. 3 and 4). Attenuation of tumors was measured using the maximum circular or ellipse regions of interest (ROI) that could be fitted to each mass. Identical ROIs were used for measurements in pre- and post-contrast images. On post contrast CT images, hyperattenuation was defined as at least 10 HU greater than normal parenchyma; hypoattenuation was defined as at least 10 HU less than normal parenchyma; isoattenuation was defined as attenuation within 10 HU of normal parenchyma. Large mammary mass generally displayed necrosis at their center, and they were evaluated based on the exterior areas of

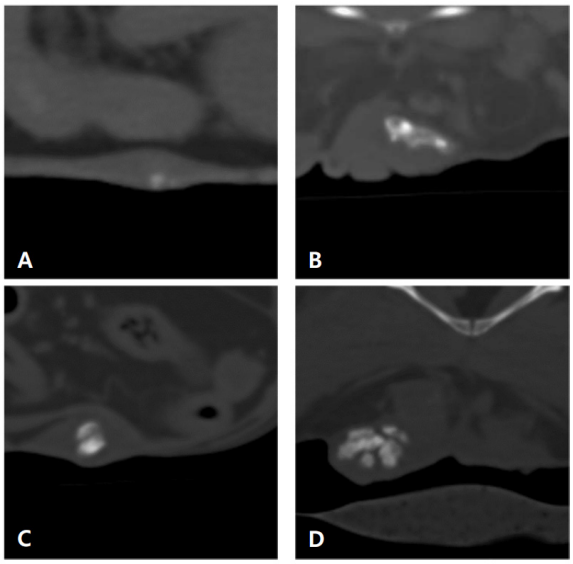

Fig. 3. Transverse precontrast CT images of typically benign calcifications in dogs with mammary gland tumor. Punctate (A), rim (B), popcorn-like (C), and dystrophic (D) calcifications.

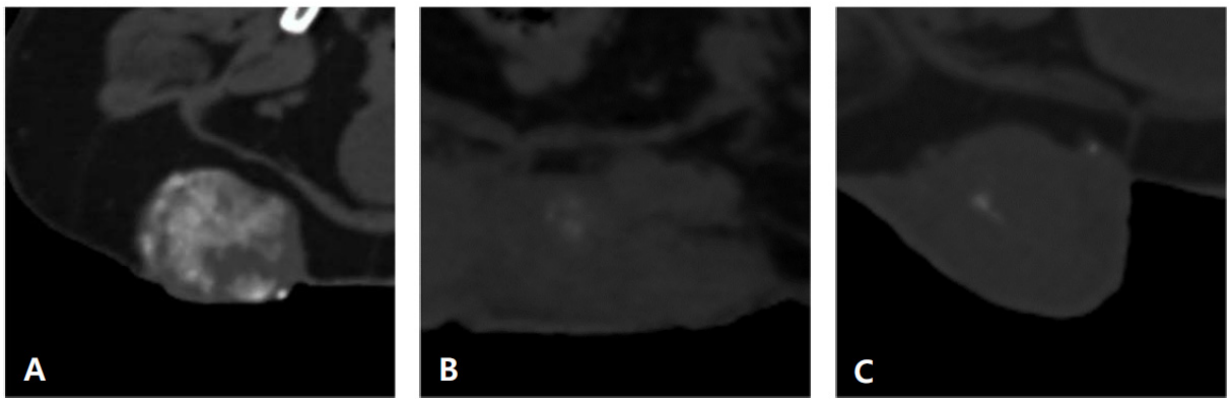

Fig 4. Transverse pre contrast CT images of suspicious morphology calcification in dogs with mammary gland tumor. Coarse heterogeneous (A), amorphous (B), and fine linear (C) calcifications.

the lesions. The maximal transverse diameter of each mass were evaluated with two-dimensional transverse images of the CT and measured using electronic calipers. Abnormal lymph node was noted when ovoid or round lymph nodes were showed and had a ratio of > 0.7 (short axis/long axis) or when the lymph nodes had a long axis of >10 mm and a heterogeneous or ring contrast enhancement pattern was observed.

4. Statistical analysis

Descriptive statistics including mean, range (minimum to maximum) and standard deviations (SD) were calculated for the age and diameter of tumors. The difference of age and tumor size were assessed using independent t-test. The correctness of radiographic and computed tomographic interpretation, using the BI-RADS, assessment was determined by means of accuracy, sensitivity, specificity rates, and positive and negative predictive values (PPV and NPV) to differentiate between benign and malignant tumors. The differences between benign and malignant MGTs were analyzed by use of a one-way ANOVA test. The statistical significance was set to be $p < 0.05$. All data were statistically analyzed with SPSS statistical software program (IBM SPSS Statistics 24.0, IBM Corp., USA).

RESULTS

A total of 42 female dogs were included in this study. 40 dogs were intact female and 2 dogs were spayed female. The dogs belonged to the following breeds: Maltese (*n*=9), Mongrel (*n*=9), Shih-tzu (*n*=7), Yorkshire terrier (*n*=6), Cocker spaniel (*n*=4), Poodle (*n*=2), Golden retriever (*n*=1), Jindo (*n*=1), Minipin (*n*=1), Papillon (*n*=1), and Pekingese (*n*=1). Weight range was from 2.1 to 33kg (mean 6.7 ± 5.7kg). The age of the animals ranged from 4 to 16 years (mean ± *SD* 11.78 ± 2.7 years) (Table. 1).

All mammary gland tumors were evaluated by histopathologic or cytologic study. Tumors were surgically removed and submitted for histopathologic examination (*n*=26), and only cytologic examination were performed that tumors were not surgically removed (*n*=16). Nineteen out of 42 (45.2%) mammary gland tumors analyzed were benign and 23 (54.8%) were malignant. Complex adenoma was the most common in benign tumors and adenocarcinoma was the most common in malignant tumors (Table 2). The average age in animals with benign tumors was 11.11 ± 3.05 years (range: 4 ~ 15 years), and it was 12.35 ± 2.29 years (range: 8 ~ 16 years) in group of animals with malignant tumors. Dogs with malignant tumors found to be older than dogs with benign tumors.

Calcifications were identified in 18 out of 42 dogs on radiographic examination, whereas 9 of 18 were associated with malignant tumors. Seven out of 18 contain typically benign calcifications and 11 out of 18 contain suspicious morphology. Benign calcifications were punctate (3/18; 16.7%), rim (2/18; 11.1%), and dystrophic (2/18; 11.1%) calcification. Suspicious morphology was coarse heterogeneous (7/18; 38.9%), fine pleomorphic (4/18; 22.2%) calcification. The radiographic results are summarized in table 3. The PPVs for BI-RADS category typically benign and suspicious morphology are 14.29% and 72.72%, and NPVs for BI-RADS category typically benign and suspicious morphology are 85.71% and 27.28%. The sensitivity, specificity, and accuracy were 88.89%, 66.67%, and 77.78 respectively.

Calcification was identified in 12 out of 24 dogs in CT examination. Six out of 12 were malignant tumors. Six out of 12 contain typically benign calcifications and 6 out of 12 contain suspicious morphology. Benign calcifications were rim (2/12; 16.7%), dystrophic (2/12; 16.7%), punctate (1/12; 8.3%), and popcorn-like (1/12; 8.3%) calcification. Suspicious

Table. 1. Clinical information of mammary gland tumor patients.

	Animals
Number	42
Breed	Maltese (9), Mongrel (9), Shih-tzu (7), Yorkshire terrier (6), Cocker spaniel (4), Poodle (2), Golden retriever (1), Jindo (1), Minipin (1), Papillon (1), Pekingese (1)
Sex	Female (40), Spayed female (2)
Body weight (kg)	2.1 ~ 33 (6.7 ± 5.7)
Age (years)	4~16 (11.8 ± 2.7)

Table 2. Cytologic or histopathologic type of benign and malignant tumors.

	Tumor type	Number of tumor
Benign tumors	Complex adenoma	8 (19.0%)
(19/42, 45.2%)	Adenoma	7 (16.7%)
	Benign mixed tumor	3 (7.1%)
	Complex and mixed mammary adenoma	1 (2.4%)
Total		19 (C:3, H:16)
Malignant tumors	Adenocarcinoma	12 (28.6%)
(23/42, 54.8%)	Complex adenocarcinoma	2 (4.8%)
	Malignant mixed tumor	2 (4.8%)
	Mammary gland carcinoma	2 (4.8%)
	Complex carcinoma	1 (2.4%)
	Inflammatory adenocarcinoma	1 (2.4%)
	Mixed mammary gland carcinoma	1 (2.4%)
	Sarcoma	1 (2.4%)
	Spindle cell sarcoma	1 (2.4%)
Total		23 (C:13, H:10)

C, cytology; H, histopathology

Table 3. Radiographic results evaluated by BI-RADS categories for calcifications of MGTs

No.	Tumor type	Morphology	Classification
1	Benign mixed tumor	Coarse heterogeneous	Suspicious morphology
2	Benign mixed tumor	Dystrophic	Typical benign
3	Adenoma	Dystrophic	Typical benign
4	Adenoma	Rim calcification	Typical benign
5	Adenoma	Punctate	Typical benign
6	Adenoma	Punctate	Typical benign
7	Complex and mixed adenoma	Coarse heterogeneous	Suspicious morphology
8	Complex adenoma	Coarse heterogeneous	Suspicious morphology
9	Complex adenoma	Punctate	Typical benign
10	Adenocarcinoma	Fine pleomorphic	Suspicious morphology
11	Adenocarcinoma	Fine pleomorphic	Suspicious morphology
12	Adenocarcinoma	Fine pleomorphic	Suspicious morphology
13	Adenocarcinoma	Coarse heterogeneous	Suspicious morphology
14	Inflammatory adenocarcinoma	Fine pleomorphic	Suspicious morphology
15	Malignant mixed tumor	Fine pleomorphic	Suspicious morphology
16	Mixed mammary gland carcinoma	Coarse heterogeneous	Suspicious morphology
17	Complex adenocarcinoma	Rim calcification	Typical benign
18	Complex carcinoma	Coarse, Popcorn	Typical benign

Table 4. CT results evaluated by BI-RADS categories for calcifications of MGTs.

No.	Tumor type	Morphology	Classification
1	Benign mixed tumor	Coarse heterogeneous	Suspicious morphology
2	Benign mixed tumor	Dystrophic, popcorn	Typical benign
3	Adenoma	Dystrophic, popcorn	Typical benign
4	Adenoma	Rim, popcorn	Typical benign
5	Complex adenoma	Punctate	Typical benign
6	Complex and mixed mammary adenoma	Rim, dystrophic	Typical benign
7	Adenocarcinoma	Fine linear	Suspicious morphology
8	Adenocarcinoma	Amorphous	Suspicious morphology
9	Adenocarcinoma	Amorphous	Suspicious morphology
10	Adenocarcinoma	Fine linear, dystrophic	Suspicious morphology
11	Malignant mixed tumor	Fine linear branching, rim	Suspicious morphology
12	Complex carcinoma	Popcorn	Typical benign

morphology was fine linear (3/12; 25%), amorphous (2/12; 16.7%), and coarse heterogeneous (1/12; 8.3%) calcification. The CT results are summarized in table 4. The PPVs for BI-RADS category typically benign and suspicious morphology are 16.67% and 83.33%, and NPVs for BI-RADS category typically benign and suspicious morphology are 83.33% and 16.67%. The sensitivity, specificity, and accuracy were all 83.33%, respectively (Table 5). The correlation of calcification features of mammary gland tumors in radiography and CT are summarized in table 6.

The computed tomographic results are summarized in Table 7. When comparing benign and malignant groups, significant

Table 5. Correlation of BI-RADS categories with benign and malignant tumors.

	Radiography		CT	
	Typical benign	Suspicious morphology	Typical benign	Suspicious morphology
Benign tumor	6	3	5	1
Malignant tumor	1	8	1	5
PPV %	14.29	72.72	16.67	83.33
NPV %	85.71	27.27	83.33	16.67

Table 6. Calcification features of mammary gland tumors.

Calcification	Radiography			CT		
	Benign	Malignant	Total	Benign	Malignant	Total
Punctate	3		3	1		1
Rim calcification	1	1	2	2		2
Popcorn					1	1
Dystrophic	2		2	2		2
Total	6	1	7	5	1	6
Coarse heterogeneous	3	4	7	1		1
Amorphous					2	2
Fine pleomorphic		4	4			
Fine linear					3	3
Total	3	8	11	1	5	6

Table 7. Summary of computed tomographic results of benign and malignant tumors.

	Benign	Malignant
Contrast enhancing		
Enhancing	8 (72.7%)	8 (72.7%)
Non-enhancing	3 (27.3%)	3 (27.3%)
Margins		
Distinct	9 (75%)	7 (58.3%)
Indistinct	3 (25%)	5 (41.7%)
Surface		
Smooth	5 (41.7%)	3 (25%)
Irregular	7 (58.3%)	9 (75%)
Morphology		
Round	5 (41.7%)	3 (25%)
Lobulated	7 (58.3%)	8 (66.7%)
Spiculated		1 (8.3%)
Calcification	6	6
Abnormal lymph node	2	8

differences (p<0.05) were not found between 2 groups for contrast enhancement, margins, surface, and morphology. For contrast enhancing pattern, the two groups of tumors had same presentation. Margins and surface were had also similar presentation between benign and malignant tumors. Most benign tumors showed distinct margins, and malignant tumors had a higher frequency of indistinct margins than in benign tumors. Both groups showed irregular surface. Abnormal lymph nodes were found 8 dogs in malignant group and 2 dogs in benign group. The mean maximal diameter of malignant group (4.59 ± 3.32 cm) is bigger than benign group (1.68 ± 0.96 cm) and showed significant difference. In malignant group, the patients with abnormal lymph node (6.15 ± 2.98cm) tend to have bigger primary tumor maximal diameter than the patients with normal lymph node (1.46 ± 0.32cm) (Table 8 and 9).

Table 8. Maximal diameters of mammary masses on CT images in benign and malignant group.

	Maximal diameter(cm)
Benign group (n=12)	1.68 ± 0.96 (range: 0.6 ~ 3.7)
Malignant group (n=12)	4.59 ± 3.32 (range: 0.9 ~ 11.3)
t-value(p)	-2.915(0.012)

p<.05

Table 9. Primary tumor maximal diameters of malignant group with abnormal lymph and normal lymph node on CT images.

	Primary tumor maximal diameter(cm)
Malignant group with abnormal LN (n=8)	6.15 ± 2.98 (range: 2.6~11.3)
Malignant group with normal LN (n=4)	1.46 ± 0.32 (range: 0.98~1.66)
t-value(p)	4.394(0.003)

p<.05

DISCUSSION

Evaluating imaging features of canine MGT can be useful for prognosis, and thus select the appropriate surgical procedure for complete tumor removal, since incomplete resection is the most important cause of recurrence after surgery (Misdorp W. 2002). In this study, 23 out of 42 tumors (54.8%) were considered malignant, while 19 out of 42 tumors (45.2%) were benign. These results are similar to the findings obtained in a previous study (Feliciano *et al*., 2012; Soler et al., 2016). Dogs with malignant tumors have been found to be significantly older than with benign tumors (Misdorp 2002; Withrow *et al*., 2013). In this study, the results are consistent with previous findings.

The type of mammary gland tumors in dogs differ from human breast cancer. Complex adenoma is the most common benign tumors in dogs whereas, fibroadenoma is more common in human. However, in both species, simple type of carcinomas is the most common malignant tumor (Misdorp W. 2002; Sorenmo *et al*., 2009; Whitman et al., 2002). In this study, the results are consistent with these findings.

Mammography is the gold standard for screening and diagnosing breast abnormalities in human. The ability of mammography to detect these abnormalities is based on the presence of macro- and microcacifications. Usually, benign calcifications tend to be large with round or oval shape and scattered in the breast, whereas malignant calcifications vary in size and shape and form clusters in linear or segmental pattern. Thus, calcifications are considered one of the most important diagnostic markers of both benign and malignant lesions (Mohammed *et al*., 2011; Muttarak et al., 2009).

In this study, 18 out of 42 dogs showed calcification in radiography, and the half of calcified tumors were benign. Twelve out of 24 dogs identified calcification in CT, and the half of them were benign. According to BI-RADS category in this study, the sensitivity, specificity, and accuracy were 88.89%, 66.67%, and 77.78%, in radiography. In CT study, the sensitivity, specificity, and accuracy were all 83.33%, respectively. The PPVs for BI-RADS category typically benign and suspicious morphology are 14.29% and 72.72%, and the NPVs for BI-RADS category typically benign and suspicious morphology are 85.71% and 27.28%, respectively in radiography. In CT study, the PPVs for BI-RADS category typically benign and suspicious morphology are 16.67% and 83.33%, and the NPVs for BI-RADS category typically benign and suspicious morphology are 83.33% and 16.67%, respectively. This study shows calcification features, assessed according to the BI-RADS classification, are good predictor of malignancy in canine mammary gland tumors. In one patient, calcification was identified that was not shown in radiograph. This result reveals that CT has better accuracy in evaluating calcification than radiography. This is the first time that BI-RADS categories are applied to radiography and CT images in dogs.

In this study, both groups showed enhancing pattern on post contrast images and showed no significantly difference between two groups. In previous ultrasonography (US) study, both group showed similar vascular pattern. Mixed vascular patterns were predominant in all tumor types (Nyman *et al*., 2005; Nyman *et al.*, 2006).

Regarding margins, no significant differences between both groups of tumors were found in this study. Benign tumors had mostly distinct margins and malignant tumors showed a higher frequency of indistinct margins. In previous study, lesions with well circumscribed margins were found to be mostly benign, whereas uncircumscribed margins suggest an invasive growth and could be interpreted as a sign of malignancy (Mohammed *et al*., 2011; Nyman *et al*., 2006). Both groups showed irregular urface, and no significant differences were found. These results disagree with previous US results those found in dogs and humans. In previous US study, benign tumors showed smooth and malignant tumors irregular appearance (Mohammed *et al*., 2011; Nyman *et al*., 2006).

Malignant tumors have larger diameter and a statistically significant difference between two groups. In previous study, tumors bigger than 5cm in diameter proved to be mostly malignant. It is associated with loss of hormone receptors. Big tumors with higher malignancy show lower expression of hormone receptors (Feliciano *et al*., 2012; Macewen *et al*., 1985; Philibert *et al*., 2003; Polton G., 2009).

Eight patients, in malignant tumor group, abnormal lymph nodes were found in CT examination, and this can be thought of as metastasis to lymph nodes. Malignant group with abnormal lymph nodes had bigger primary tumor size than the same group with normal lymph node. In previous study, the size of the primary tumor was not significant in dogs with local lymph node involvement (Kurzman *et al*., 1986). However, in human study, primary tumor size was significant

predictive factor for lymph node metastasis on multivariated analysis (Han *et al*., 2011).

There were several limitations to the current study. We consider that the they are related to the low number of cases. A larger number of cases perhaps we could found more difference between the two groups of tumors. And not all cases of histologic examination have been performed. Malignant tumors often lack of cytologic signs of malignancy, and a benign diagnosis on cytologic examination cannot exclude malignancy (Tobias *et al*., 2013).

CONCLUSION

Although canine MGT cannot be imaged mammographically, calcifications in tumors can be evaluated by radiographic and CT studies. In this study, primary tumor size and abnormal lymph node showed a significant correlation with malignancy of tumor. We concluded that mammary gland tumor calcification cannot reliably be used to distinguish benign and malignant. In conclusion, calcification is not a sign of malignancy and characteristics of MGT calcification, evaluated in radiography and CT images, are good predictor of malignancy in dogs.

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