Mammography and Ultrasound Imaging of Preinvasive and Invasive Canine Spontaneous Mammary Cancer and their Similarities to Human Breast Cancer

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Grant support: Fondazione Banco di Sardegna 2009

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Running title: Mammography and Ultrasound Imaging of Canine Mammary Lesions

Key word: dog, calcification, animal model, breast lesions
Abstract

Understanding the evolution of proliferative breast disease such as atypical hyperplasia (AH) and carcinoma in situ (CIS) is essential for clinical management of women diagnosed with these lesions. Therefore, an animal model that faithfully represents human breast disease in every aspect from spontaneity of dysplasia onset, histopathological features, genetics, to clinical outcome is needed. Previously, we studied canine spontaneous AH and DCIS (low, intermediate and high-grade) and reported their similarities to human lesions in histopathological and molecular features as well as prevalence. To further validate the resemblance of these lesions to humans, we examined their mammographic and sonographic characteristics in comparison to those of human’s as well as the potential of the human Breast Imaging Reporting and Data System (BI-RADS) to predict canine disease. Non lesional, benign and malignant mammary glands of dogs presented to Sassari Veterinary Hospital, were imaged using mammography and ultrasound. The images where then analyzed and statistically correlated with histopathological findings and to their similarities to humans. Our results showed that canine mammary preinvasive lesions, benign, and malignant tumors have mammographic abnormalities, including the presence, pattern and distribution of macro-calcification and micro-calcifications, similar to their humans’ counterparts. BI-RADS categorization is an accurate predictor of mammary malignancy in canine with 90% of sensitivity and 82.8% of specificity. The mammographic images similarities and the ability of BI-RADS to predict canine mammary malignances with high specificity and sensitivity further confirm and strengthen the value of the dog as model to study human breast pre-malignancies for development of prognostic biomarkers.
Introduction

Most invasive breast cancers are thought to evolve from proliferative breast disease such as atypical hyperplasia (AH) and carcinoma in situ (CIS) lesions. These lesions are currently diagnosed more often due to increase in public awareness and routine mammographic screening (1,2,3). Approximately 54,010 new cases of ductal carcinoma in situ (DCIS) are expected to be diagnosed in 2010 (4). Despite the technological advances in detecting these lesions, their biological significance and natural history is not well understood. Five to ten percent of women diagnosed with DCIS who are treated with lumpectomy alone develop invasive cancer within five years and a similar group develops subsequent DCIS (5). Although adjuvant treatment with radiation and tamoxifen have reduced the rates of subsequent breast cancer, these treatment regimens have not affected death rates from breast cancer (6,7). Studies that attempted to identify women at high risk of developing invasive cancer were not successful thus creating uncertainty in how aggressively clinicians would treat women diagnosed with DCIS (8).

As a result, many animal models of mammary tumorigenesis, such as rodents, were developed to examine pathogenesis and progression of human breast cancer (9-10-11). However, most mouse mammary tumors do not resemble human cancers in morphology and have different patter of metastasis, so there must be still-undetected factors that promote breast cancer development and progression in humans but are not occurring in the rodent. Therefore, rodent models may not accurately represent human breast cancer pathogenesis or reproduce many aspects of the human disease (12- 13).

In contrast to rodents, dogs develop mammary cancer spontaneously with similar epidemiological, clinical, morphological and prognostic features as human breast cancer (14-15-
Mammary tumors constitute about half of all cancers in female dogs. One in four non-ovariohysterectomized dogs over 4 years old is expected to develop mammary tumors. About 30%-50% of canine mammary tumors are malignant (19-20). Furthermore, as in humans, development of canine mammary tumor is hormone dependant. Ovariohysterectomy before the first, second, or third estrus cycle reduces the relative risk of developing mammary tumors to 0.5%, 8%, or 26%, respectively. Ovariohysterectomy later in life had no significant effect on risk of developing mammary tumors. As in humans, advanced age also increases the risk of mammary tumor in dogs. The median age for the dog to develop mammary tumors is about 10-12 years (21).

Most importantly, dysplasias develop spontaneously before tumors in canine mammary tissue (18-22). Intraepithelial lesions (IELs) are common in tumor-bearing glands and in non-tumor-bearing glands in female dogs. In previous study in our laboratory, within dogs without mammary tumors evaluated for prevalence of IEL half had at least one type of IEL, including ductal hyperplasia, atypical ductal hyperplasia, low-grade DCIS, intermediate-grade DCIS, and high-grade DCIS. One fourth of the dogs examined had two or more different IEL types. Furthermore, we have shown that these lesions are remarkably similar in histopathological morphology, and in expression pattern of ER-α, PR, and HER-2 neu to those of the human breast (22-23).

Human DCIS are currently detected using X-ray mammography as mentioned above (3-24). The ability of mammogram to identify these lesions is based on the presence of microcalcification. Microcalcifications are present in 42-72% of DCIS (25-26). About 90% of non-palpable DCIS were diagnosed on the basis of microcalcifications alone (27). The American College Radiologists recommendations, Breast Imaging Reporting and Data system (BI-RADS),
classifies mammogram findings into three categories as following; typical benign, intermediate concern, higher probability of malignancy according to morphology and distribution of calcifications (28).

Mammographically detected DCIS is usually excised immediately and currently is not possible to estimate the fraction of untreated lesions that would progress to invasive cancer (8). Despite the increase in detection of DCIS, the probability of definitive studies in human to demonstrate whether detection of DCIS by mammography would contribute to the reduction of breast mortality is very slim (8). Unless these studies are conducted in animal model, that develop DCIS with similar characteristics as human. For that reason, our laboratory’s focus is to characterize the dog as a model for breast cancer pre-invasive and invasive cancer.

Therefore, to complement our previous work, the purpose of this study was to determine whether the routinely used imaging techniques in human, mammography and sonography as well as interpretations of their results according to BI-RAD, could be used to detect and discriminate between preinvasive, benign and malignant mammary lesions in the dog. Our results showed that canine mammary preinvasive lesions, benign, and malignant tumors have mammographic abnormalities, including the presence, pattern, and distribution of macro-calcification and micro-calcifications, similar to their humans’ counterparts. BI-RADS categorization is an accurate predictor of mammary malignancy in canine with high sensitivity and specificity. The mammographic images similarities and the ability of BI-RADS to predict canine mammary malignances with high accuracy and sensitivity further confirm and strengthen the value of the dog as model to study human breast pre-malignancies. This is important for development of prognostic biomarkers to stratify women diagnosed with DCIS according to risk of developing subsequent disease.
Material and Methods

Animals:

This study was conducted “ex vivo” in 88 excised mammary glands from forty female dogs that underwent mastectomy at Sassari Veterinary Hospital during 2006-2008 years. Dogs belonged to the following breed: Poodle (4), Dachshund (2), Mixed breed (13), Yorkshire (12), one each of Bobtail, German hounds, German shepherd, Giant Schnauzer, Mastiff, Dalmatian, Doberman, Siberian husky, English setter. The dogs’ ages ranged from 5 to 15 years (median age 10) of which 36 were adult spayed and 4 were intact females. Mammary tissues were surgical removed. Fresh samples were mammographically and ultrasonographically imaged and subsequently processed for histopathology. All procedures from handling, anesthesia, and surgeries were in accordance with the Sassari University Animal Care and Use Committee guidelines.

Mammography experiment:

Eighty-eight mammary specimens were imaged with a Diamond Premier Analog DMR Mammography System (General Electric). Images were examined by two radiologists (human and veterinarian) and calcifications were assessed according to the Breast Imaging Reporting and Data System (BI-RADS) categories. Mammographic features of 78 lesions and 10 normal-looking mammary glands were described according to BI-RADS lexicon. Assessment of categories were based on the description of shape (round, oval, lobular, irregular) and margins (circumscribed, indistinct) of mammary masses, and shape (popcorn-like, round, pleomorphic, amorphous, linear branching) and distribution (regional or diffuse) of macro- and microcalcifications.
Ultrasound experiments:

Forty-six of 88 mammary specimens that were mammography imaged were also examined by ultrasound. All ultrasound scans were performed with Esaote MyLab 70 equipped with a 15–18 MHz linear multifrequency transducer. Longitudinal and transverse scans of each surgical specimen were evaluated. Ultrasound features of mammary lesions and tumor were described for mass shape (round, oval, irregular), margins (circumscribed, indistinct), echogenicity (Hyperechoic, hypoechoic, anechoic, complex mass) and also for the presence of macro- and micro-calcifications as illustrated by BI-RADS lexicon.

BI-RADS

All lesions examined by mammography and ultrasound were classified in consultation between both human and veterinary radiologists according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) lexicon, which provide standardized classification for mammographic and ultrasound reporting (28). This system classifies findings into 6 assessment categories and provides 4 management outcomes. These assessment categories have been shown to correlate with the likelihood of malignancy in human breast cancer (29,30). Depending on the level of suspicion, the lesions can be placed on the following BI-RADS categories; Category 0 when additional image evaluation is recommended, category 1 when there is no abnormality to report; category 2 for benign findings, category 3 for likely benign lesions where 6 month follow up is recommended; category 4 for suspicious abnormality and category 5 for highly suspicious lesions or diagnostic of malignancy.

Histopathological evaluation:
Mammary gland samples were formalin fixed and paraffin embedded. Cut sections (5μm) were stained with H&E. Tumors were classified according to WHO Histological Classification of Mammary Tumors of the Dogs and Cats (31). Mammary glands were also evaluated for the presence of IELs in tumor-bearing glands and in non-tumor-bearing glands as previously described (22-23). Lesions were imaged using Nikon Eclipse 80i and digital computer images were recorded with a Nikon Ds-fi1 camera.

Statistical analysis
Accuracy of mammogram interpretation using the BI-RADS final assessment was determined by means of sensitivity, specificity rates, positive and negative predictive value (PPV and NPV) to differentiate between benign and malignant lesions. Histological findings were utilized as the gold standard. Statistical measures for overall lesions were calculated considering BI-RADS categories 1-2-3 as reporting of benign findings and categories 4-5 as malignant findings according to the methodology included in the BI-RADS guideline. In addition, PPV were calculated for each BI-RADS category as follows: the number of lesions in one of the categories with malignant diagnosis divided by the total number of lesions classified into this category. All statistical calculations were performed using statistical software (Stata software, version 11.2).

Results
Mammography and ultrasound
The mammographic features such as macrocalcifications, microcalcifications, mass shape and margin, and their correlation with histological diagnosis were assessed in 78/88 mammary glands and the results were showed in table 1. Normal mammographic appearance of ten mammary gland were confirmed at histology.

Calcification was identified in 42 of 78 (54%) lesions examined, of which 19/78 (24%) contained macrocalcifications and 23/78 (29%) had microcalcifications. Of the 19 lesions with macrocalcifications, 11 (57%) had popcorn-like shape with regional (4/19; 21%) and diffuse (7/19; 36%) distribution; while 8/19 (42%) were round in shape with regional localization. Lesions with macrocalcifications were diagnosed as intraepithelial lesions (IELs) without atypia and as benign and malignant tumors mostly of complex type. On the other hand, lesions with microcalcifications (23/78; 29%), generally were either pleomorphic regional and diffuse (14/23; 61%), amorphous/indistinct (5/23; 22%) or linear branching (4/23; 17%) and were associated mostly with atypical IELs and malignant tumors.

In addition, we evaluated mass shape and margins by mammography in 54/78 (69%) lesions. Of the 26 benign lesions, 21 (81%) exhibited round or oval shaped masses, and 12/26 (46%) had circumscribed margins. Twelve of 25 malignant lesions (48%) displayed irregular shape and 22/25 (88%) had indistinct margins. Figure 1 shows canine and human proliferative lesions (DH, ADH, and DCIS) mammograms and their corresponding histopathology.

Similarly, we correlated the ultrasound abnormalities of 46/78 mammary lesions with histological findings. Calcifications were found in 19/46 (41%) lesions, whereas 11/19 (53%) were associated with malignant tumors. The oval shape was the most common form of masses and was found in 25/40 (62.5%) either in benign (12) and malignant (11) tumors. Benign lesions are usually presented with well circumscribed margin 14/18 (78%), while malignant lesions were
typically indistinct in margin 16/20 (80%). Figure 2 and 3 shows the mammograms and ultrasound images of canine benign and malignant tumors.

Histopathological evaluation and BI-RADS classification:
Tissues from mammary glands (88) were examined histologically and included normal (10) and tissues that carried abnormal histology (78). These lesions were classified as IELs (11), benign lesions (37) and malignant mammary tumors (30). Additionally, we diagnosed other 9 IELs (5 DH, 2 ADH) associated to benign lesions and 2 DCIS high grade associated to invasive carcinoma (comedo type). Palpable masses were 58 out of the 78 lesions (30 were classified as benign and 28 as malignant tumors) whereas 20/78 were non palpable masses (11 were IELs, 7 were benign and 2 were malignant tumors).

The correlation of BI-RADS categories with histological diagnosis of IELs, benign and malignant tumors were illustrated in table 2. Lesions classified and placed into BI-RADS category 1 (i.e. without positive finding); 10/25 were normal mammary gland, 7/25 palpable lesions [intraductal papilloma (2), tubular adenoma (2), sclerosing papilloma (1), fibroadenoma (1), and benign mixed tumor (1)]; and 8/25 were non-palpable masses [duct ectasia (2), intraductal papilloma (2), adenosis (2), and ductal hyperplasia (2)]. The PPV for this category was 0%; no malignant lesions were identified using histological evaluation and all lesions were benign. For BI-RADS category 2 (indicate that the lesions are benign), 4/7 lesions were palpable [benign mixed tumor (3), intraductal papilloma (1)]; and 3/7 were not- palpable [sclerosing papilloma (1), adenosis (1), and ADH (1)]. The PPV for category 2 was also 0% (i.e. no lesion was identified as malignant). For BI-RADS category 3 (which denote that the lesions are
probably benign), 16/19 lesions were benign and also palpable [complex adenoma (5), benign mixed tumor (4), intraductal papilloma (2), tubular adenoma (1), fibroadenoma (1), complex carcinoma (2), and tubular carcinoma (1)]; and 3/19 were benign not palpable [adenosis (1), ADH (1), and complex adenoma (1)]. The PPV for this category is 16% because 3 lesions of the 19 were found pathologically to be malignant. For BI-RADS category 4 (which means that it is a suspicious lesion for malignancy and further action should be taken), lesions were mostly palpable 29/35 [complex adenoma (6), tubular carcinoma (6), carcinoma comedo type (7), carcinosarcoma (4), complex carcinoma 2), squamous cell carcinoma (1), fibrosarcoma (1), liposarcoma (1), osteosarcoma (1)], except 6 lesions, whereas 1 was DH, 2 were ADH, 1 complex adenoma and 2 tubular carcinomas. This category is consisted mostly of malignant lesions 25/35, and 10/35 were benign lesions. The PPV for category 4 was 71% because 25 of 35 lesions were malignant lesions. For BI-RADS category 5 (lesions which bestow highly suggestive of malignancy), two out of 2 malignant lesions were carcinoma comedo type. The PPV for this category was 100%. For all lesions, the PPV was 73% [95% CI.: 55.9% -86.2%] and the NPV was 94.1% [95% CI.: 83.3% -98.8%]. The mammography test compared with histopathological findings used as golden standard showed 90% of sensitivity [95% CI.: 73.5%-97.9%] and 82.8% of specificity [95% CI.: 70.6% -91.4%].

Discussion

We showed for the first time that mammography and ultrasound imaging as well as interoperation of their findings according to the Breast Imaging Reporting and Data System (BI-RADS) can be used to detect intraepithelial lesions (ADH and DCIS) as well as benign, and invasive mammary lesions in dogs. Currently, mammography is gold standard procedure for
screening and diagnosing breast abnormalities (25). Mammography ability to detect these abnormalities is based on the presence of microcalcifications (26-27). Thus this study confirms that as in humans, canine malignant mammary lesions are associated with microcalcifications, underscoring the physiological similarities between the dog and human breast disease. Until now, there has been no animal model of human breast malignancies that showed reproducible microcalcifications. Although many were developed using MMTV vectors or BRCA1/BRCA2 knockouts, however, calcification in the produced tumors is rare and unpredictable (32-33). Usually suspicious microcalcifications vary in size, shape and form clusters in linear or segmental pattern that signify that the tissue may be malignant. While benign calcifications or macrocalcification tend to be large with round or oval shape and scattered in the breast (34-36). Thus, calcifications are considered to be one of the most important diagnostic markers of both benign and malignant lesions (26-37). Correlation of mammographic features with histopathology, in this study, revealed that calcifications were present in 54% of canine mammary cases. Macrocalfications were present in 24% while microcalcifications occurred in 29% of mammary cases. Similarly in study conducted by Sickles (38) evaluating mammographic features in human breast cancers, reported that more than half of breast cancers examined in their study had mammographic ally visible calcifications. Whereas, tumor mass was the sole mammographic finding in another 26% of breast cancers. However, another 20% of cancers presented with neither mass nor calcifications (38). In another study of 1261 occult breast abnormalities 50.4% lesions were found to have calcification and 18.8% were found to be malignant (39).

Macrocalfication are associated with benign lesions as well as in some malignant tumors in dogs (Table 1). Of these lesions 58% had popcorn-like shape with diffused or regional
localization. Ovoid shape with regional calcifications was seen in 32% of samples. These were mostly intraepithelial lesions without atypia (11%) and benign tumors (37%). Ten lesions (52%) belong to this group (lesions with macrocalcification) were malignant but of complex type. These tumors are of epithelial and myoepithelial origin and characterized by the presence of cartilaginous metaplasia and chondroid matrix depicted as dense calcifications by mammography (17). Typical benign calcifications in human are similar to that we have seen in the dog, are large, smooth, popcorn-like, round, dense, and scattered over a large area. These lesions in human do not need further investigations or close follow-up (26, 34).

About 47% of malignant tumors in this study showed microcalcification. Likewise, microcalcifications occur in about 30-50% of human breast cancers (26). In our study, only 14% of non palpable benign lesions showed microcalcification, consistent with what observed in women where microcalcifications were seen in 14.5% of 198 and 4.5% of 1818 benign cases of asymptomatic and symptomatic women, respectively. Also microcalcifications occurred in 83% of atypical IELs in dogs. These lesions were identified histopathologically to be ADH and DCIS. Similar to what we observed in the dog, the incidence of calcification in human DCIS ranges between 42-72% (26-40). Up to 90% of DCIS lesions in human are detected based on mammographically visible microcalcifications (26-41). All canine DCIS were associated to carcinoma comedo type and contain microcalcification, and, interestingly, were mammography detected.

In addition, to the presence of microcalcifications, we examined the types and patterns of microcalcifications. Distributions and type of microcalcifications seen in human proliferative lesions (42) that are suggestive of malignancy also occurred in canine lesions (figure 1).
Microcalcifications present in canine DCIS and cancer tissues were predominantly pleomorphic/ granular diffuse or linear/branching.

Mammographic features other than calcifications that were examined in this study included mass shape and margin. About 50% of malignant palpable and non-palpable lesions in dogs have irregular shape and indistinct margin consistent with findings found in human (38). While majority of benign tumors were ovoid or round in shape with circumscribed margin (Table 1).

In other hand sonography plays an important role in the differentiation of solid and cystic masses. It is used in evaluating palpable masses in radiographically dense breast and young women susceptible to radiation. It used in combination with mammography to reduce the negative to positive biopsy ratio (43). Features that characterize an invasive carcinoma by ultrasound include irregular shape, irregular margin, internal hypoechogeticity, and non-uniform distribution of internal echo texture (44). Reviewing the sonogram of canine mammary palpable masses, we found that the sonographic features of these lesions correlated with their histopathology as well as mammography findings (Figure 2). Lesions with well circumscribed margins were found to be mostly benign (78%) whereas lesions with indistinct margin were found to be malignant (80%). These results were in conformity to what observed in humans where oval shape and well circumscribed margins are most predictive of a benign diagnosis, whereas irregular shape and non-circumscribed margins indicate malignant features (44-45).

Our results showed that mammography can be successfully applied to non-palpable mammary lesions in dog to detect cancer at early stages. In human medicine, mammography detects occult breast cancer with high sensitivity, which ranged from 71% - 98% for annual screening mammography (46). However, there are variations in findings interpretation between radiologists. To reduce the discordance in the interoperation of mammographic findings and to
standardize terms for reporting, the American College of Radiology has developed the Breast Imaging Reporting and Data System (BI-RADS). This system provides specific final assessment category that correlate with the likelihood of malignancy in human breast cancer. Under the Mammography Quality Standards Act (MQSA) in the United States, all screening mammograms must be interpreted using BI-RADS final assessment categories (47-48). Therefore, we calculated the PPV for each BI-RADS assessment category to determine if BI-RADS categorization is a good predictor of malignancy in our canine model. Based on presence or absence of masses and calcification characteristics we were able to classify our findings according to BI-RADS, which were then confirmed by pathology. The PPV for BI-RAD category 1, 2, 3, 4, and 5 are 0%, 0%, 15.79%, 71.43% and 100% respectively (Table 2). According to BI-RADS category in our study the sensitivity and the specificity of diagnostic mammography was of 90% and 83%, making this system an excellent predictor of mammary malignancy in palpable and non-palpable mammary canine disease. This is the first time that BI-RADS are applied to other species than humans. This study has demonstrated that the dog mammary neoplasm form micro and macro-calcification similar to humans. The study also suggests that the process of cancer pathogenesis may be similar in the two species. Furthermore, mammography and sonography features of canine mammary IELs, benign and invasive cancer correlate with the histopathological findings and the BI-RADS classification is a good predictor of malignancies in the dog. This further provides more evidences to the value of the dogs as model for breast cancer. The research might allow examination of breast pre-malignancies for development of prognostic biomarkers.

**Disclosure of Potential Conflicts of Interest**
No potential conflicts of interest were disclosed.

Grant Support

Fondazione Banco di Sardegna 2009

Acknowledgements

We are deeply grateful to Luigi Foddi for his radiology technical assistance and to Silvia Melis and Dolores Addis for technical support for histology.

References


### Tables

**Table 1:** Correlation of mammography features and histopathogy of IELs, benign and malignant tumors*

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*IELs: Intraepithelial lesions; NP= not palpable lesions*
Table 2: Correlation of mammography BI-RADS categories with histopathogy of IELs, benign and malignant tumors*

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<th>NPV %</th>
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*IELs: Intraepithelial lesions
Figure Legends

Figure 1
Panel A, D: mammography shows the presence of round regional microcalcification in dog and in women (BI-RADS 2). Panel G, L: Histological diagnosis of adenosis in dog and blunt duct adenosis in woman. Ductules lined by epithelial proliferating cells with occasional varying in size nuclei. A luminal eonophilic material (secretory calcification) is also present. H&E stain, scale bar, 10 μm

Panel B, E: mammography with scattered pleomorphic/granular microcalcification in dog and in women (BI-RADS 3). Panel H, M: Histological diagnosis of atypical hyperplasia. Part of enlarged duct lined by more than three columnar cell layer showing atypical features (loss of polarity, nuclear pleomorphism). A cluster of irregular calcifications are clearly evident. H&E stain, scale bar, 10 μm


Figure 2:
Panel A, D, G: Mammogram show oval and regular masses with well-defined margins (BIRADS-2). Ultrasound imaged the lesion as regular mass with circumscribed margin. (BIRADS-2). Histological diagnosis: intraductal papillomas. H&E stain, scale bar, 50 μm.
Panel **B, E, H:** Mammogram depict round and regular mass with defined margins and evident round macrocalcifications (BIRADS-1). Ultrasounds examination show same mass with well circumscribed margin. (BIRADS-1). Histological diagnosis: tubular adenoma. H&E stain, scale bar, 100 μm

Panel **C, F, I:** Mammogram reveal an oval ill-defined mass with small and round microcalcifications (BIRADS-3). Ultrasounds examination well defined the mass as regular with circumscribed margins. Calcifications are also seen. (BIRADS-2). Histological diagnosis: Complex adenoma. H&E stain, scale bar, 100 μm

**Figure 3:**

Panel **A, D, G:** Mammographic image reveal an irregular mass with indistinct margins. Notice mixture of pleomorphic/granular diffuse microcalcifications and some round macrocalcification (BIRADS-4). Ultrasounds show an irregular not circumscribed mass with a complex pattern. (BIRADS-4). Histological diagnosis: invasive carcinoma comedo type. H&E stain, scale bar, 50 μm

Panel **B, E, H:** Mammography depict a round lobulated mass with indistinct margins. (BIRADS-4). Ultrasounds examination reveal an irregular mass with not well-circumscribed margins. Histological diagnosis: complex carcinoma. H&E stain, scale bar, 50 μm

Panel **C, F, I:** Mammography shows popcorn like diffuse macrocalcification with any mass evidence. (BIRADS-4). Ultrasounds examination depict an irregular not circumscribed mass with a complex pattern. ((BIRADS-4). Histological diagnosis: carcinosarcoma. H&E stain, scale bar, 50 μm
Cancer Prevention Research

Mammography and Ultrasound Imaging of Preinvasive and Invasive Canine Spontaneous Mammary Cancer and their Similarities to Human Breast Cancer

Sulma I Mohammed, Giovanni B. Meloni, Maria L. Pinna Parpaglia, et al.

_Cancer Prev Res_ Published OnlineFirst July 29, 2011.

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