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MAGNETIC RESONANCE IMAGING TECHNIQUE FOR THE EXAMINATION OF CANINE MAMMARY TUMOURS

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The aim of this study was to adapt the human magnetic resonance imaging (MRI) sequences for use in the routine examination of canine mammary glands. MRI was performed on 10, middle- to old-aged dogs of different breeds. It was found that T1- and T2-weighted spin echo, short T1 inversion recovery sequences and a gradient echo (GE) dynamic T1-weighted measurement made in the coronal and transversal planes were the most informative MR diagnostic methods for imaging canine mammary tumours. The static MR technique is the most detailed imaging modality for differentiating the tissue types in the substance of the mammary gland. The MRI findings were in close relationship with the histological result (five malignant mixed tumours and five cases of invasive ductal carcinoma). Using the GE dynamic contrast-enhanced sequence the morphological patterns as well as the kinetic parameters proved to be malignant. By the dynamic measurement technique initial information was obtained on the contrast enhancing properties, which are valuable factors during *in vivo* staging and in the prognostic work.

Key words: Mammary tumour, dog, magnetic resonance imaging (MRI), contrast enhancement

Magnetic resonance imaging (MRI) is a very sensitive, noninvasive diagnostic tool that helps to establish accurate diagnosis in tumour patients and enables the staging of neoplastic diseases. MR mammography is widely used in the human oncologic practice.

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Mammary tumour is the most frequent neoplastic lesion in dogs (52% of tumours in bitches affect the mammary glands). Regardless of the breed, tumours occur in middle-aged to old animals at a mean age of 9 years (Yamagami et al., 1996*b*; Perez Alenza et al., 2000). Several studies have shown that mammary tumours have high prevalence in Toy and Miniature Poodles, Cocker Spaniels, English Springer Spaniels, Labrador Retrievers, English Setters, Pointers, German Shepherd dogs, Yorkshire Terriers, Malteses and Dachshunds (Zaninovic and Simcic, 1991; Moe, 2001).

Clinical signs and physical examination. Most of the patients diagnosed with mammary tumours are middle-aged to old. For both women and dogs, mammary tumours are age dependent, rarely occurring before 25 years of age in women and 5 years of age in dogs, respectively, with a median age of occurrence of 10–11 years for dogs and at or after menopause for women (Schafer et al., 1998). The dogs are intact or bitches neutered after maturity, and mostly clinically healthy. Although the 4th and 5th mammary glands are more frequently affected (Zaninovic and Simcic, 1991), the location of the tumour has no influence on the prognosis (Hellemen et al., 1993). In most of the cases (60%) more than one tumour is observed (Benjamin et al., 1999), but a higher number of involved mammary glands does not necessarily mean a poorer prognosis.

Prognosis depends on the age of the animal, the size, type, differentiation, growth rate, clinical evidence of invasiveness, ulceration and oestrogen, progesterone and growth hormone receptor expression of the tumour, the involvement of regional lymph nodes, and the presence of metastases in other organs (Sartin et al., 1992; Yamagami et al., 1996*a*; van Garderen and Schalken, 2002; de Las Mulas et al., 2005).

Laboratory tests. The diagnostic work-up should include a routine haematological and serum chemistry profile as well as urinalysis. A coagulogram may also be indicated because of concurrent association with disseminated intravascular coagulation in cases with inflammatory carcinoma and other tumours considered to carry a high risk of metastasis (Withrow and MacEwen, 2001).

Radiological examination. In cases in which malignancy cannot be excluded, thoracic radiographs in both the right and left lateral and ventrodorsal planes should be taken prior to surgery. Usually conventional radiography is done to evaluate the lungs and sternal lymph node for possible metastasis, but this method is only suitable for detecting pulmonary tumours reaching or exceeding 6–8 mm in size. Computed tomographic (CT) imaging is a more sensitive method for the early detection of metastases, as it can detect tumours as small as 4 mm (Glasspool and Evans, 2000). CT imaging is highly recommended before doing surgical excision. In human patients the most commonly affected distant metastatic sites are the liver, the lungs and the bone marrow.

In dogs, metastases most frequently occur in the lungs but, according to the clinical signs, abdominal ultrasonography or radiography, CT and MRI may also be helpful in detecting distant metastases.

Histology. Histological examination of the tumour is always performed either from a biopsy done before surgery or from a sample taken during the removal of the tumour. If a malignant tumour is small, noninvasive and can be removed with a sharp surgical margin, then excision biopsy is the therapy itself. Samples taken by fine needle aspiration (FNA) technique are not always suitable for differentiating malignant epithelial tumours from benign ones (Sorenmo, 2003). In the human protocol, core biopsy and aspiration cytology are always included in the basic examination, and rarely excision biopsy is also performed.

Clinical staging. Accurate staging is important prior to undertaking treatment. The steps of staging are to (1) evaluate the primary tumour, (2) evaluate the regional lymph nodes, and (3) identify any distant metastatic sites (Owen, 1980).

With a conventional extracellular gadolinium-based contrast agent injected subcutaneously into two periareolar areas overlying each caudal mammary gland and using indirect MR lymphography (MRLG), the sentinel lymph node and the connected lymphatic vessels directly draining from the injection sites are clearly visualised. The 3D MR images help in the accurate identification and surgical biopsy of the sentinel lymph node (Suga et al., 2003).

Treatment. In the veterinary practice, treatment of mammary gland neoplasms consists of surgical removal of the tumour. The most acknowledged surgical method in dogs is to remove any affected tissue with a wide surgical margin. A recent survey did not show benefit regarding recurrence interval or survival following more radical mastectomy (Withrow and MacEwen, 2001).

The objective of this study was to demonstrate the efficacy of MRI in imaging the morphological characteristics and size of canine mammary tumours and to develop an MRI method suitable for the examination of dogs by adapting the sequences used in human mammography.

Materials and methods

Animals

Ten bitches of different breeds (3 German Shepherd dogs, 2 Giant Schnauzers, 2 mongrels, one Dachshund, German Deerhound and Rottweiler each) and sizes were examined. Average age was 9.8 years and the dogs weighed between 10 and 42 kg. The animals were not neutered. Two of the ten animals had frequent oestrus (three times per year) and recurrent false pregnancy (Rottweiler, Dachshund). Detailed history was acquired, then physical and laboratory examinations were performed, including routine haematology (Sysnex SF 3000; Sysnex Co. Ltd.) and routine clinical biochemistry (Konelab 20i; Thermo Electron Corporation) prior to each MRI examination. In the German Deerhound and the 7-year-old mongrel the white blood cell (WBC) count, while in the Rottweiler and the 9-year-old German Shepherd dog the percentage of eosinophil granulocytes was elevated. Lactate dehydrogenase (LDH) activity was elevated in all animals with the exception of the 7-year-old German Shepherd dog. All other laboratory parameters were within the normal ranges.

Six dogs were examined using T1- and T2-weighted and short T1 inversion recovery (STIR) sequences for a morphological study and the other four dogs also by the use of a T1-weighted dynamic contrast-enhanced MRI method. The breed, age, location, staging and histological findings are shown in Table 1.

Anaesthesia

An intravenous injection of propofol (Diprivan 1% inj., AstraZeneca, Macclesfield, Cheshire, United Kingdom; 6 mg/bwkg) was administered for premedication. A mixture of 1.5–2.5 vol. % isoflurane and oxygen (1.5–2 vol. %) was administered via a tracheal tube for the maintenance of general anaesthesia during MRI examination.

MRI examination method

Our aim was to demonstrate the efficacy of MRI in imaging the morphological characteristics and size of canine mammary tumours and the invasion of surrounding tissue.

The objective was to develop an MRI method suitable for the examination of dogs, during which we adapted the sequences used in human mammography. Based on the use of a dynamic sequence we characterised contrast enhancement, morphological patterns and kinetic curves. The following points were considered for the selection of the sequences:

– to optimise the contrast of different tissue types;

– to examine the structure of neoplastic tissue based on differences in their water content;

– to describe characteristic MR mammographic findings in canine mammary tumours and correlate them with the histological findings;

– to adapt the human method for describing the morphological patterns and kinetic parameters of enhancement to the examination of dogs.

Examinations were performed with a SIEMENS MAGNETOM VISION PLUS, 1.5 Tesla MRI scanner.

Since most of the animals were risk patients (due to age, cardiovascular diseases, endocrine diseases, etc.), we had to reduce the time of examination as much as possible while still obtaining informative images.

Table 1

Breed, age, location, staging and histological results of the dogs

Breed	Age (years)	Location of the tumour	Staging	Histology
German Shepherd dog	9	right caudal abdominal	II	Scirrhous invasive carcinoma
Dachshund	13	right caudal abdominal	IV	Malignant mixed tumour
German Deerhound	12	right and left inguinal	III	Invasive ductal carcinoma
Rottweiler	8	right caudal abdominal	III	Malignant mixed tumour
Giant Schnauzer	9	right caudal abdominal and inguinal	V	Right caudal abdominal: solid invasive ductal carcinoma; right inguinal: *in situ* carcinoma
Mongrel	7	right caudal abdominal and inguinal, left cranial abdominal, caudal abdominal and inguinal	V	Invasive ductal carcinoma
German Shepherd dog (DCE-MR)	13	right and left caudal abdominal and left inguinal	III	Right caudal abdominal: malignant mixed tumour; left caudal abdominal and inguinal: invasive ductal carcinoma
German Shepherd dog (DCE-MR)	7	left inguinal	II	Malignant mixed tumour
Mongrel (DCE-MR)	9	right caudal abdominal	II	Solid invasive ductal carcinoma
Giant Schnauzer (DCE-MR)	11	right caudal abdominal and inguinal	V	Malignant mixed tumour

In human medicine, a specific, dedicated breast coil is available for the simultaneous examination of both breasts. The number and size of mammary glands in dogs do not permit the use of such a specific coil. The examination was carried out in dorsal recumbency, using a local coil appropriate for the region. The average examination time was 40 min per animal. The recovery period after anaesthesia was short, rapid and without any complications in all cases. Following MRI examination, the size and shape of the neoplasms were defined and their tissue structure was analysed and subsequently compared with the results of histological examinations. Additional thoracic and abdominal CT examinations were performed and staging was done according to the TNM system (Owen, 1980).

The analysis of signal intensity–time curves is the main part of interpreting dynamic contrast-enhanced (DCE) MRI examinations. In contrast to DCE-MRI, which is clearly a functional technique providing information on the physiological properties of tumours, conventional static MRI explores the morphological features only. The ideal breast MRI technique should integrate the high temporal resolution dynamic and high spatial resolution static sequences to achieve the optimal diagnostic performance.

Kinetic parameters

Cancer-induced angiogenesis is the main feature that can be depicted *in vivo* by DCE-MRI, and it plays an important role in the differentiation of benign mammary diseases from malignant ones.

Newly formed pathologic vasculature around malignant foci is prone to be highly permeable, typically causing a rapid uptake and elimination of the contrast agent. In contrast, benign lesions exhibit slowly rising, persistent enhancement kinetics.

Qualitative descriptors of enhancement curves are also widely used in human medicine. The most widespread curve shape classification system was described by Kuhl et al. (1999). The four main curve types are: types 1a and 1b, where signal intensity increases persistently with time; type 2, which is a plateau curve; and type 3, which is a wash-out curve. Types 1a and 1b are typical of benign lesions, while types 2–3 are most often found in malignant lesions (Heywang-Köbrunner and Beck, 1995). We examined whether this characteristic could be applied to describe canine mammary tumours.

Morphological criteria

Each enhancement abnormality of the breast should first be characterised according to its distribution. A detected lesion can present a focal mass or non-mass enhancement. *In situ* ductal cancers, lobular invasive carcinomas and hyperplastic changes appear most typically as non-mass lesions in the human practice. Mass lesions can be classified according to their shape, margin and internal structure. In all animals we found mass lesions. Spiculated or irregular borders are highly predictive for carcinoma, and a lobular or smoothly outlined lesion is more likely a benign entity. The more heterogeneous a mass lesion, the more likely it belongs to the malignant group. In a rim-like enhancement the contrast agent uptake appears first at the periphery and then continues towards the centre of the tumour. This centripetal enhancement pattern is suggestive of malignancy, whereas the opposite, centrifugal enhancement is characteristic of benign lesions. Non-enhancing internal septation has a very high negative predictive value for cancer (Szabó, 2004). The mass lesion characteristic is shown in Table 2.

Table 2

Morphological parameters of the mass lesions

Shape	Various
Margin	spiculated, irregular, lobulated, smooth
Internal structure	homogeneous, intermediate, heterogeneous
Rim enhancement	presence, absence
Septation	presence, absence

Histopathology

Samples for histopathological examination were taken from mammary gland tumours, fixed in 8% buffered, neutral formaldehyde solution, and then embedded in paraffin. Five sections were cut with a Reichert sled-type microtome and stained with haematoxylin and eosin (HE). Histopathological examinations were performed at Szent István University, Faculty of Veterinary Science, Department of Pathology and Forensic Veterinary Medicine.

Results

The following sequences, adapted from the human examination protocol, proved to be suitable for MRI examination of the canine mammary glands:

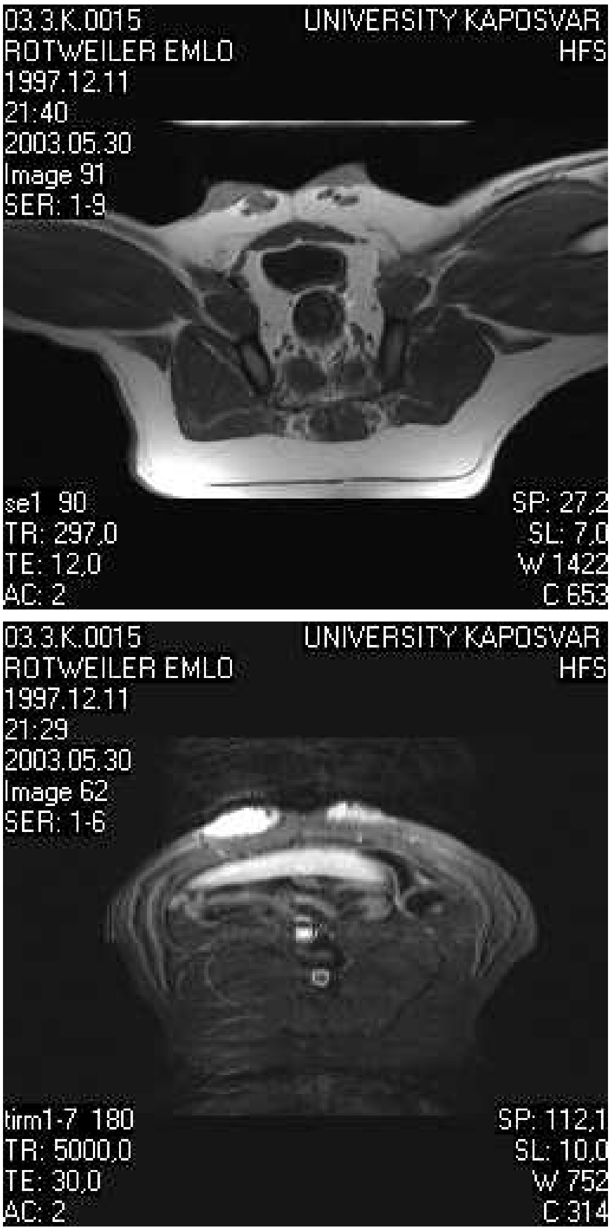
– T1 SE (TR: 450 s, TE: 9.6 s, Aq.: 2 s, SL: 4 mm, FoV: 350 × 200 mm) coronal (Fig. 1a), transversal (Fig. 2a) plane;

– T2 SE (TR: 3800 s, TE: 110 s, Aq.: 2 s, SL: 4 mm, FoV: 350 × 350 mm) coronal (Fig. 1b), transversal (Fig. 2b) plane;

– STIR (short T1 inversion recovery; TR: 4500 s, TE: 36 s, Aq.: 2 s, SL: 4 mm, FoV: 350 × 350 mm) coronal (Fig. 3), transversal plane;

– T1 GE (TR: 12 s, TE: 4.8 s, Aq.: 1 s, SL: 2 mm, FoV: 320 × 320 mm) in a dynamic fashion coronal plane (Figs 4 and 5).

Fig. 1. T1- (a) and T2- (b) weighted spin echo sequences in coronal plane (11-year-old Giant Schnauzer)



(a)

(b)

Fig. 2. T1- (a) and T2- (b) weighted spin echo sequences in transversal plane (8-year-old Rottweiler)

Fig. 3. Short T1 inversion recovery (STIR) sequence in coronal plane (13-year-old German Shepherd dog)

The neoplasms in five dogs proved to be malignant mixed tumours according to the histological findings. On the static MR images these tumours had an inhomogeneous structure. Three of them contained fluid, did not involve abdominal muscle and had no fixation to skin or fascia. The other five animals had a histological diagnosis of invasive ductal carcinoma. These tumours were of variable intensity on scans, and were sharply distinct from the abdominal muscles, having fixation to skin or fascia. In one dog we found a malignant mixed tumour and also invasive ductal carcinoma. Three animals with invasive ductal carcinoma had a large number of cyst-like structures containing fluid in the tumour. They were different in size, could be distinctly differentiated from each other and had the same signal intensity. Their size and location could be determined exactly by MRI before taking a sample or removing the tumour surgically. The morphological characteristics of the examined tumours are shown in Table 3 according to the human model.

The scans in the coronal and transversal planes of the animal positioned on its back proved to be the most informative of the tumours.

Fig. 4. T1-weighted coronal gradient echo sequence in a dynamic fashion at the beginning (a) and at the end (b) of dynamic measurement using gadolinium contrast agent (13-year-old German Shepherd dog)

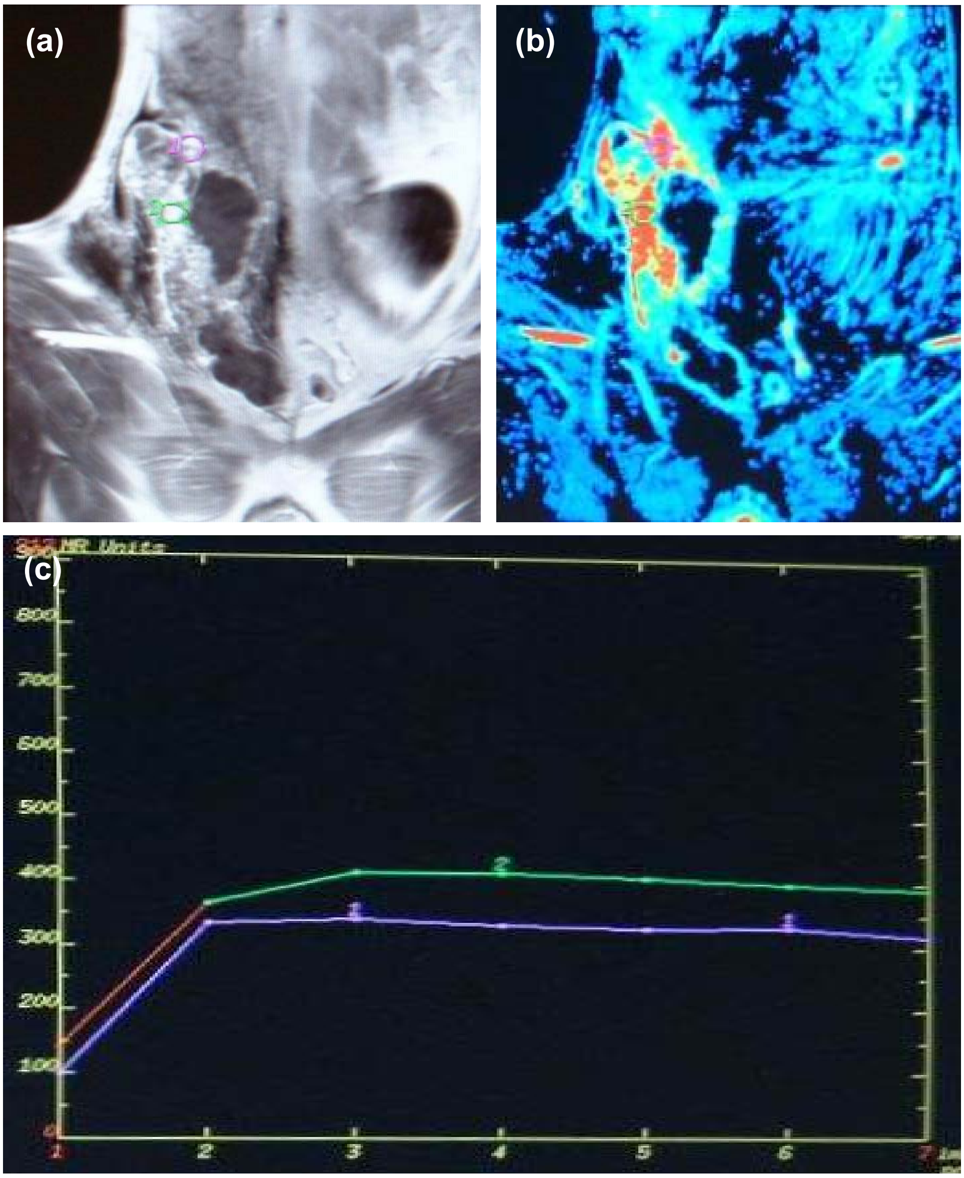


Fig. 5. Eleven-year-old Giant Schnauzer, T1-weighted dynamic contrast-enhanced MRI (a). After the administration of contrast agent on the functional map (b) the region of interest (ROI) shows the most active part of the tumour. The lesion (invasive ductal carcinoma) reaches the peak signal intensity in the first two minutes (early enhancement) and then wash-out occurs in 6 minutes (c)

Table 3

Morphological characteristics of the tumours examined

Breed (age in years)	Shape	Margin	Internal structure	Septation	Histology
German Shepherd dog (9)	longish	smooth	intermediate	absent	scirrhous invasive carcinoma
Dachshund (13)	oval	irregular	heterogeneous	present	malignant mixed tumour
German Deerhound (12)	oval	lobulated	heterogeneous	present	invasive ductal carcinoma
Rottweiler (8)	longish	smooth	intermediate	absent	malignant mixed tumour
Giant Schnauzer (9)	longish	irregular	heterogeneous	present	right caudal abdominal: solid invasive ductal carcinoma; right inguinal: *in situ* carcinoma
Mongrel (7)	longish	smooth	heterogeneous	absent	invasive ductal carcinoma
German Shepherd dog (13) (DCE-MR)	oval	lobulated	heterogeneous	present	right caudal abdominal: malignant mixed tumour; left caudal abdominal and inguinal: invasive ductal carcinoma
German Shepherd dog (7) (DCE-MR)	oval	smooth	intermediate	absent	malignant mixed tumour
Mongrel (9) (DCE-MR)	oval	smooth	intermediate	absent	solid invasive ductal carcinoma
Giant Schnauzer (11) (DCE-MR)	longish	irregular	heterogeneous	present	malignant mixed tumour

Table 4

Characteristics of the tumours found in the dogs examined by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)

	13-year-old German Shepherd dog	7-year-old German Shepherd dog	9-year-old mongrel	11-year-old Giant Schnauzer
Shape	oval	oval	oval	longish
Margin	lobulated	smooth	smooth	irregular
Internal structure	heterogeneous	intermediate	intermediate	heterogeneous
Rim enhancement	present	absent	absent	absent
Septation	present	absent	absent	present
Histology	malignant mixed tumour, invasive ductal carcinoma	malignant mixed tumour	invasive ductal carcinoma	malignant mixed tumour
Curve type	early enhancement and wash-out	delayed enhancement	early enhancement and wash-out	early enhancement and wash-out

In four animals examinations were performed by obtaining T1-weighted images in a dynamic fashion, one sequence before and six repetitive sequences after intravenous bolus administration of paramagnetic agent (gadolinium contrast agent injected in a quick bolus of 2 ml/sec in a 0.1 mmol/kg dose, injected within 1 to 2 min). The dynamic examination was analysed using a General Electric Flextrial Software.

The tissue of the mammary gland is characterised by variable contrast accumulation, depending on the age and oestrous cycle of the animal. Every animal was examined during anoestrus.

Using morphological patterns we can describe the tumour masses found in the four animals which were also examined with DCE-MRI sequences. On the basis of the DCE examination a functional map was obtained, which clearly shows the differences in relative enhancement within the inhomogeneous tumour areas. This allows the placement of the region of interest (ROI) in the fastest enhancing and most active part of the tumour. The inhomogeneity of the MR parameter images corresponds very well to the histology of the tumours. All the four animals had a malignant lesion and the morphological patterns as well as the kinetic parameters proved to be satisfying for the diagnostic work. The characteristics of the tumours are shown in Table 4.

Discussion

It is known from human medicine that soft tissues can be imaged and precisely differentiated from each other and from other tissues by MRI much better than by ultrasonography or CT imaging of the region (Berquist et al., 1990).

The static MR sequences we used fulfilled our aims: the neoplastic mammary gland and the neighbouring anatomical structures could be examined in great detail with optimal contrast conditions. In this way we can picture the morphological characteristics of neoplasms, which can be compared to the histological findings.

Since the introduction of contrast-enhanced MRI of the breast, this method has gained increased attention and acceptance because it offers new and different information as compared with other imaging modalities. This method is probably the most sensitive means of detecting mammary gland pathology. In fat- or blood-containing lesions it may improve the specificity (Friedrich, 1998) and gives higher confidence and sensitivity in breast cancer examination than do conventional mammography and sonography only (Müller-Schimpfle et al., 1997). However, due to its own limitations (high costs, large number of slices per breast), contrast-enhanced MRI cannot be used alone, and it will not replace mammography (Heywang-Köbrunner and Beck, 1995).

Dynamic contrast-enhanced MRI is a method suitable for imaging the physiology of microcirculation. Recent advances in MR technology provide enhanced spatial and temporal resolution, which allows the application of this methodology in the management of cancer patients. In several types of tumours this method has already been shown to correlate well with traditional outcome measures, such as histopathological studies, and with survival. These new measures are sensitive to tumour physiology and to the pharmacokinetics of the contrast agent in individual tumours (Taylor et al., 1999).

The enhancement characteristics over time of spontaneous breast tumours in dogs were compared using gadopentate dimeglumine and a blood-pool agent (24-gadolinium [Gd]-DPTA-cascade polymer). Five carcinomas, 4 adenomas and 9 benign mixed-tissue tumours underwent dynamic magnetic resonance imaging (MRI). For gadopentate dimeglumine, a fast signal increase was found immediately after intravenous injection, with a subsequent signal decay in all tumours. No difference was observed between different tumour types in enhancement kinetics. Similar kinetics were found in benign lesions after injection of blood-pool agent (Adam et al., 1996).

The contrast accumulation methods and curves prepared for human medicine (Kuhl et al., 1999) are of great promise in veterinary use but need to be adapted and a highly sensitive standard protocol should be completed, which makes the detection of canine mammary tumours possible. In all cases we found malignant morphology, in three cases early enhancement with wash-out, while in one case delayed enhancement. The tumours proved to be malignant lesions, so the method must be tested also on benign tumours and on a large number of patients.

One-to-one correspondence with the human patterns cannot be spoken about either in the morphological or in the kinetic analysis of canine mammary glands. In this study the adapted human protocol proved to be applicable for screening mammary tumours, but more research is needed, as at present we cannot yet tell if a tumour is benign or malignant on the basis of MR imaging.

Different methods of human MR mammography are still under research and development (Heywang-Köbrunner and Beck, 1995). Their importance in the complex examination of mammary glands will grow, which hopefully will allow MRI to gain ground in the diagnosis of mammary tumours in companion animals.

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