Comparison of ultrasonography and histologic examination for identification of ocular diseases of animals: 113 cases (2000–2010)

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Objective—To compare ultrasonographic and histologic examination findings for eyes of animals with ocular diseases.

Design—Retrospective case series.

Animals—116 eyes of 113 animals examined at 2 facilities.

Procedures—Diseased eyes of animals were examined by means of ultrasonography, removed via enucleation or exenteration, then histologically examined. Ultrasonographic images and histopathologic slides were evaluated, and diseases of eyes were identified with each of those methods and allocated to various categories. For each disease category, agreement between results of ultrasonography and those of histologic examination was assessed via determination of κ statistic values.

Results—Tests had good agreement for identification of iris or ciliary body neoplasia. Overall, intraocular neoplasia was not detected via ultrasonography for only 2 of 31 eyes with histologically detected neoplasia. Hemorrhagic or inflammatory changes were misinterpreted as neoplasia for 8 of 37 (22%) eyes. Tests had moderate to acceptable agreement for identification of retinal detachment. Retinal detachment was not detected by means of ultrasonography for 14 of 38 (37%) eyes with that diagnosis determined via histologic examination at one of the facilities (primarily in eyes with intraocular hemorrhage); however, retinal detachment was not identified via histologic examination for 6 of 38 (16%) eyes with that diagnosis determined via ultrasonography at the other facility.

Conclusions and Clinical Relevance—Agreement between tests evaluated in this study was clinically satisfactory for identification of intraocular neoplasia. Typically, diseases were misdiagnosed via ultrasonography for eyes with poor image contrast. Because determination of ultrasonographic diagnoses of retinal detachment and intraocular neoplasm may be of prognostic importance, performance of additional ultrasonographic techniques may be indicated. (*J Am Vet Med Assoc* 2013;243:376–388)

Ultrasonography is useful for ophthalmologic examination of animals because it is readily available, cost-effective, safe, and noninvasive and can typically be performed without sedation.[1–4] The diagnostic value of ultrasonography is high for animals with opacities of corneas, aqueous humor, lenses, or vitreous humor or pronounced eyelid swelling because direct observation of intraocular structures is not possible for such eyes and assessment of intraocular structures is important for determination of diagnoses and prognoses and for planning of treatments.[2,5–12] Even for animals for which direct observation of intraocular structures is possible, ultrasonography may be helpful for tumor identification, performance of measurements, and comparison of findings to those for the contralateral eye.[6,13] Structures that cannot be observed by use of routine ophthalmologic examination techniques, such as ciliary bodies or retrobulbar spaces, can be evaluated via ultrasonography.[9,14] Of the 2 display modes used during ocular ultrasonography of animals, brightness mode (B-mode) is used more commonly than amplitude mode (A-mode).[2,15]

The ultrasonographic appearances of ophthalmologically normal and diseased eyes of horses, dogs, and cats have been reported.[1,13,14,16–19,a] However, no studies have been performed to determine the accuracy of ultrasonography for identification of ocular diseases, to the authors' knowledge. Diagnoses determined via ultrasonography are typically tentative diagnoses because results are dependent on the examiner's interpretation. Other studies[9,20–24] have been conducted in which ultrasonographic and histologic findings for eyes of animals were compared; however, small numbers of animals were included and such comparison was not the primary outcome objective in those studies.

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To the authors' knowledge, the accuracy of ultrasonography for identification of diseases of eyes of animals has not been determined. The objective of the study reported here was to compare ultrasonographic findings for eyes of animals with ocular diseases to histologic findings for surgically removed eyes of such animals.

Materials and Methods

Animals—Medical records of animals examined by personnel of the ophthalmology services of the Vetsuisse Faculty, University of Zurich, Switzerland, and the Veterinary Medical Teaching Hospital, University of Wisconsin, Madison, Wis, were searched to identify animals that had undergone ocular ultrasonography prior to enucleation or exenteration and for which histologic examination of eyes had been performed within 64 days after removal. Animals with incomplete medical records or low ultrasonographic or histologic image quality were excluded from the study. Animals in which the eye was not involved in the disease process or in which substantial changes in disease were detected after performance of ultrasonography and before surgical removal of an eye were excluded from the study. Sixty-three animals (30 dogs, 15 cats, and 18 horses) evaluated at the University of Zurich from January 2000 through October 2010 were included in the study; data regarding 2 eyes were included for 2 of these animals (2 dogs). Fifty animals (47 dogs, 2 cats, and 1 horse) evaluated at the University of Wisconsin from January 2002 through December 2010 were included in the study; data regarding 2 eyes were included for 1 of these animals (a dog). Medical records were reviewed to determine species, affected eye, medical history, clinical examination findings, and ultrasonographic and histologic findings at the time of examination for each animal.

Ultrasonography—Ultrasonographic images of animals examined at the University of Zurich were obtained by board-certified veterinary radiologists or residents enrolled in a training program approved by the European College of Veterinary Diagnostic Imaging; images were obtained by use of various B-mode ultrasonographic devices[b–f] with linear and curved array probes operating at frequencies from 8 to 14 MHz. Horses were typically sedated, but cats and dogs were sedated only if necessary for performance of ultrasonography. Local anesthesia of corneas was achieved via topical application of 0.4% oxybuprocaine[g] or 0.5% proparacaine.[h] For cats and dogs, ultrasonographic images were typically obtained via transcorneal application of probes. For horses, ultrasonographic images were typically obtained via transpalpebral application of probes. Sterile ultrasonographic gel was applied to eyes to improve contact of probes with tissues. Only still ultrasonographic images were available for animals examined at this facility.

Ultrasonographic images of animals examined at the University of Wisconsin were obtained by board-certified veterinary ophthalmologists or residents enrolled in a training program approved by the American College of Veterinary Ophthalmologists; images were obtained by use of a B-mode ultrasonographic device and a sector scanner probe with an operating frequency of 10 MHz.[i] Horses were typically sedated, but cats and dogs were sedated only if necessary for performance of ultrasonography. Local anesthesia of corneas was achieved via topical application of 0.5% proparacaine.[j] The ultrasonographic transducer was placed directly on corneas for performance of ultrasonography. Still ultrasonographic images were available for all animals examined at this facility; ultrasonography videos were also available for 3 animals.

Ultrasonographic images were evaluated by investigators of the present study because not all ultrasonography reports in medical records were complete (because such reports typically only included information regarding findings relevant to differential diagnoses for animals determined at the time of the initial examinations). For animals examined at the University of Zurich, ultrasonographic images were evaluated by a radiologist (PRK) who was board certified by the European College of Veterinary Diagnostic Imaging, an ophthalmologist (SAP) who was board certified by the American College of Veterinary Ophthalmologists and the European College of Veterinary Ophthalmologists, and an ophthalmology resident (NSG). For animals examined at the University of Wisconsin, ultrasonographic images were evaluated by an ophthalmologist (EB) who was board certified by the American College of Veterinary Ophthalmologists and an ophthalmology resident (NSG). Investigators evaluating ultrasonographic images had knowledge of the medical histories and clinical examination findings of animals but not of the original ultrasonographic and histologic findings. Then, results of these evaluations were compared with results and diagnoses indicated in ultrasonography reports in medical records. Originally determined diagnoses were rarely changed after review; typically, additional diagnoses for eyes were identified that had not been identified at the time of the initial examination. Finally, a list of ultrasonographic differential diagnoses was determined on the basis of the ultrasonographic findings resulting from this evaluation process. From each list of differential diagnoses, the most likely differential diagnosis was selected and listed as the tentative diagnosis on the basis of the level of confidence with the diagnosis determined with clinical and ultrasonographic examination findings. The finalized diagnoses were allocated to various disease categories for statistical comparison of data regarding diagnoses determined via ultrasonography and those determined via histologic examination of tissues.

Histologic examination—Investigators reviewed medical histories and evaluated ultrasonographic images of animals before performing histologic examination of slides of surgically removed eyes of animals. For animals examined at the University of Zurich, slides were reviewed by 2 pathologists (PG and MR) who were board certified by the European College of Veterinary Pathologists, an ophthalmologist (SAP) who was board certified by the American College of Veterinary Ophthalmologists and the European College of Veterinary Ophthalmologists, and an ophthalmology resident (NSG). New histologic sections were prepared from archived tissue samples when necessary and when such tissue samples were available.

For animals examined at the University of Wisconsin, reports of histologic findings in medical records had been approved by an American College of Veterinary Pathologists board-certified pathologist (RRD). Slides of tissue samples were reevaluated by an ophthalmology resident (NSG) and an American College of Veterinary Ophthalmologists board-certified ophthalmologist (EB) or an American College of Veterinary Pathologists board-certified pathologist (RRD).

Histologic findings determined by investigators of the present study were compared with findings in the histopathology reports in medical records. Additional diagnoses of disease in eyes were identified only after investigators had discussed findings and were confident such diseases were detected in histopathologic slides of eyes. Histologic diagnoses were classified into the same disease categories that were used for classification of ultrasonographic diagnoses. For some animals that had been examined at the University of Zurich, it was not possible to histologically confirm or rule out all ultrasonographic diagnoses because of poor quality of slides of tissue samples and unavailability of archived tissue samples. Such diagnoses were histologically classified as not determined.

Disease categories—Ultrasonographic and histopathologic diagnoses for each animal were allocated to 1 of 23 disease categories (**Appendix**). For animals examined at the University of Wisconsin, 17 disease categories were used because it was not possible to ultrasonographically evaluate anterior portions of eyes (because images of that part of the eye were obtained via high-resolution ultrasonography [probes operating at 20 MHz] at that facility and such images were not available for all animals). Diseases were categorized on the basis of disease type and location in an eye. Diagnoses of ocular melanosis were classified as neoplastic diseases for animals in this study.

Statistical analysis—The statistical comparison of ultrasonographic versus histologic findings was performed for tentative ultrasonographic diagnoses alone and for the complete list of ultrasonographic differential diagnoses (tentative and final differential diagnoses combined) to determine how often the ultrasonographic tentative diagnosis corresponded to histologic diagnoses and how often the correct diagnosis was included in the list of differential diagnoses. Data for eyes evaluated at each facility (University of Zurich and University of Wisconsin) were evaluated separately because findings for each facility were dissimilar.

Agreement between ocular diagnoses determined via ultrasonography and those determined via histologic examination was assessed via calculation of κ statistic values. A κ statistic value of 1 indicated perfect agreement between tests, and a value of 0 indicated agreement only by chance.[25] The κ statistic values indicated poor (< 0.40), moderate (0.41 to 0.60), acceptable (0.61 and 0.75), or good (> 0.75) agreement.[26–28] The actual and expected percentage agreements between the 2 diagnostic modalities were also determined. Expected agreement was defined as the agreement between 2 tests controlled for the agreement for the population distribution that would be detected purely by chance.[25] For a given percentage agreement, as the expected percentage agreement increased, κ values decreased. This was attributable to the high probability of agreement by chance for a near-homogenous population.[25] For the diagnosis category of neoplasia of the iris or ciliary body, histologic examination was considered the criterion-referenced diagnostic method; therefore, sensitivity, specificity, positive predictive value, and negative predictive value of ultrasonography for detection of these diseases were determined. Statistical analyses were performed to test for a lack of independence of data for the 3 animals with bilateral ocular disease. These 6 eyes were excluded from statistical analysis in the affected diagnosis categories. Statistical analyses were performed with software.[k]

Results

Descriptive data—A total of 116 eyes from 113 animals were evaluated (65 eyes of 63 animals examined at the University of Zurich and 51 eyes of 50 animals examined at the University of Wisconsin). Of the 113 animals, 94 (83%) were dogs or cats and 19 (17%) were horses. The left and right eyes were each affected in 55 animals, and both eyes were affected in 3 animals. The median time between performance of the last ultrasonographic examination and enucleation or exenteration was 1 day (range, 0 to 55 days) for animals examined at the University of Zurich and 2 days (range, 0 to 64 days) for animals examined at the University of Wisconsin. For animals examined at the University of Zurich, 41 (63%) eyes were removed within 2 days after performance of ultrasonographic examinations, 53 (82%) within 7 days, and 60 (92%) within 14 days. For animals examined at the University of Wisconsin, 25 (49%) eyes were removed within 2 days after performance of ultrasonographic examinations, 35 (69%) within 7 days, and 43 (84%) within 15 days.

Results regarding diagnoses determined via ultrasonography and those determined via histologic examination of tissue samples were summarized (**Table 1**). Two diagnosis categories for each facility were affected by dependence of data for animals with bilateral ocular disease. Statistical analyses were performed for 61 eyes evaluated at the University of Zurich for the disease categories inflammatory changes or blood near the iris or ciliary body and lens luxation and for 49 eyes evaluated at the University of Wisconsin for the disease categories inflammation in the vitreous cavity and subretinal exudate. For some diagnosis categories (other lens changes, vitreal degeneration, choroidal detachment, choroidal thickening, and scleral thickening), statistical analysis was not performed because the number of eyes with those diagnoses were small. Choroidal detachment was only identified in eyes of animals evaluated at the University of Zurich.

Data for 23 disease categories (diagnoses) for eyes of animals examined at the University of Zurich and 17 disease categories (diagnoses) for eyes of animals examined at the University of Wisconsin were evaluated in the present study (total number, 40). Agreement between ultrasonographic and histologic evaluation results was statistically evaluated for the tentative

Table 1—Agreement between diagnoses determined via ultrasonography and those determined via histologic examination for 116 eyes of 113 animals (65 eyes of 63 animals examined at the University of Zurich and 51 eyes of 50 animals examined at the University of Wisconsin).

Disease category	Facility	No. of ultrasonographic diagnoses	No. of histopathologic diagnoses	Agreement (%)	Expected agreement (%)	κ Value
Corneal perforation	Zurich	9	11	93.85	72.59	0.78
Corneal neoplasia	Zurich	2	3	98.46	92.59	0.79
Anterior chamber neoplasia	Zurich	3	5	96.92	88.4	0.73
Blood, fibrin, or inflammatory changes in the anterior chamber	Zurich	4	40	35.38	39.88	–0.07*
Iris or ciliary body neoplasia	Zurich	21	17	90.77	58.44	0.78
	Wisconsin	8	9	94.12	72.2	0.79
Inflammatory changes or blood near the iris or ciliary body	Zurich	20	38	60.66	44.75	0.29
	Wisconsin	2	16	72.55	67.17	0.16
Cataract	Zurich	19	19	90.77	56.45	0.79
	Wisconsin	8	15	86.27	64.13	0.62
Lens luxation	Zurich	12	6	86.15	59.64	0.66
	Wisconsin	2	8	88.24	81.62	0.36
Lens capsule rupture	Zurich	13	17	89.23	63.08	0.71
	Wisconsin	0	6	88.24	88.24	0
Vitreous cavity neoplasia	Zurich	2	4	96.92	91.15	0.65
	Wisconsin	1	1	96.08	96.16	–0.02*
Vitreous cavity hemorrhage	Zurich	31	31	81.54	48.5	0.64
	Wisconsin	15	18	82.35	56.06	0.60
Inflammation in the vitreous cavity	Zurich	17	19	72.31	58.77	0.33
	Wisconsin	5	24	57.14	50.81	0.13
Retinal detachment	Zurich	27	38	70.77	45.87	0.46
	Wisconsin	38	33	86.27	57.21	0.68
Subretinal neoplasia	Zurich	1	3	96.92	93.99	0.49
	Wisconsin	5	3	92.16	85.47	0.46
Subretinal hemorrhage	Zurich	12	18	84.62	64.07	0.57
	Wisconsin	8	14	76.47	65.47	0.32
Subretinal exudate	Zurich	3	5	90.77	88.4	0.20
	Wisconsin	6	8	91.84	75.43	0.67
Retinal tear	Zurich	1	7	90.77	88.02	0.23
	Wisconsin	1	5	92.16	88.62	0.31
Scleral rupture	Zurich	9	9	93.85	73.49	0.77
	Wisconsin	2	3	98.04	90.66	0.79

The agreement indicates the percentage agreement between diagnoses determined via ultrasonography and those determined via histologic examination for each disease category. The expected agreement indicates the percentage agreement between diagnoses determined via ultrasonography and those determined via histologic examination that would occur purely by chance for each disease category, correcting for the distribution of data for the population of animals in the present study.

*Negative κ values indicate agreement worse than the agreement expected by chance.

ultrasonographic diagnoses alone and for the complete list of differential diagnoses (tentative and differential diagnoses combined). For 19 evaluations, the agreement between ultrasonographic and histologic examination diagnoses decreased when the complete list of differential diagnoses was included in the analysis; for 11 evaluations, agreement did not change, and for 10 evaluations, agreement increased when the complete list of differential diagnoses was included in the analysis. For 22 eyes, not all of the ultrasonographic diagnoses could be identified histologically at the University of Zurich, which corresponded to 9% of all ultrasonographic diagnoses. This was attributable to either a combination of poor tissue sample quality and a lack of archived tissue for repeated sectioning or to the absence of a focal lesion in the examined tissue section. The affected categories were corneal perforation, scleral rupture, cataract, lens luxation, lens capsule rupture, vitreal hemorrhage, vitreal inflammation, vitreal degeneration, and retinal detachment.

Corneal neoplasia—The agreement between ultrasonography and histologic examination of tissue samples for determination of a diagnosis of corneal neoplasia was good (κ = 0.79) for eyes examined at the University of Zurich. For 1 of the 3 eyes for which a diagnosis of corneal neoplasia was determined via histologic examination at that facility, that disease had not been identified via ultrasonography. This eye was surgically removed from a cat with intraocular melanoma with extension into the cornea.

Neoplasia in the anterior chamber—The agreement between ultrasonography and histologic examination of tissue samples for determination of a diagnosis of anterior chamber neoplasia was acceptable (κ = 0.73) for eyes examined at the University of Zurich. Diagnoses of neoplasia in the anterior chamber of the eye determined by use of those 2 methods agreed for 3 of 5 animals; for 2 animals, intraocular neoplasia had been identified via ultrasonography but anterior chamber involvement (confirmed via histologic examination) was not identified via that method. These animals included 1 cat and 1 dog with intraocular melanoma that likely originated from the iris or the ciliary body. Those tumors extended into the anterior chamber, vitreous cavity, and subretinal space; in the cat, the tumor also extended into the cornea. On the basis of the ultrasonographic appearance, these tumors were classified as neoplasia of the iris or ciliary body only.

Neoplasia of the iris or ciliary body—The agreement between ultrasonography and histologic exami-

nation for determination of a diagnosis of iris or ciliary body neoplasia was good for eyes examined at the University of Zurich ($\kappa = 0.78$) and for those examined at the University of Wisconsin ($\kappa = 0.79$). Iris or ciliary body neoplasia was not identified via ultrasonography for 1 of 17 eyes for which that diagnosis had been determined via histologic examination at the University of Zurich. Iris or ciliary body neoplasia was not identified via histologic examination for 5 of 21 (24%) eyes for which that diagnosis had been determined via ultrasonography at the University of Zurich. For these eyes, blood clots had been misinterpreted as neoplastic changes. Histologically identified iris and ciliary body tumors were not identified via ultrasonography for 2 of 9 eyes examined at the University of Wisconsin. For one of these eyes, a histologically identified ciliary body adenoma was misidentified as a vitreous cavity neoplasia via ultrasonography (**Figure 1**). For the other eye, an intraocular neoplasm had been identified via ultrasonography but iris or ciliary body involvement had not been detected via that method. Ultrasonographically identified iris or ciliary body neoplasia was not identified via histologic examination for 1 of 8 eyes examined at the University of Wisconsin. For this eye, a blood clot had been misidentified as a tumor (**Figure 2**). Because of the high number of eyes with a diagnosis of iris or ciliary body neoplasia and the fact that histologic examination of tissue samples is the criterion-referenced method for determination of this diagnosis,[29] sensitivities, specificities, and positive and negative predictive values were determined. The sensitivities of ultrasonography for identification of iris or ciliary body neoplasia in eyes evaluated at the University of Zurich and the University of Wisconsin were 94.12% and 77.78%, respectively. The specificities of ultrasonography for identification of iris or ciliary body neoplasia in eyes evaluated at the University of Zurich and the University of Wisconsin were 89.58% and 97.62%, respectively. The positive predictive values of ultrasonography for identification of iris or ciliary body neoplasia in eyes evaluated at the University of Zurich and the University of Wisconsin were 67.19% and 87.50%, respectively. The negative predictive values of ultrasonography for identification of iris or ciliary body neoplasia in eyes evaluated at the University of Zurich and the University of Wisconsin were 97.73% and 95.35%, respectively.

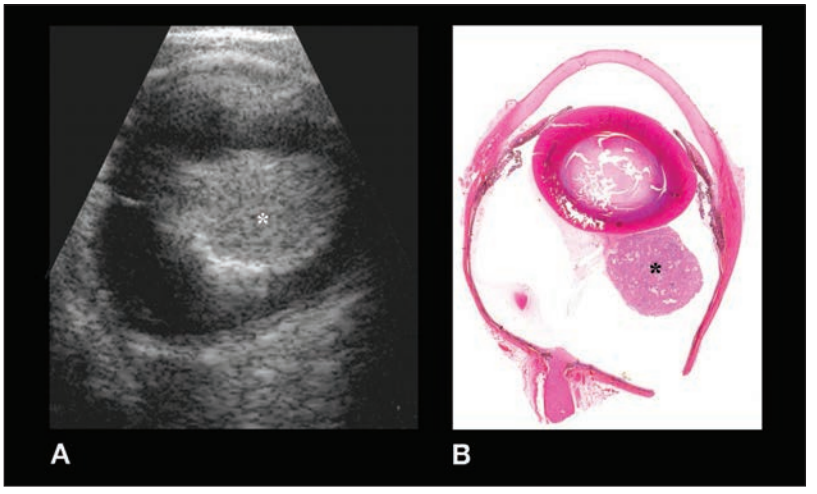

Figure 1—Representative ultrasonographic image (A) and photograph of an H&E-stained histologic slide (B) of an eye of a dog with ciliary body adenoma. In panel A, notice the hyperechoic mass (asterisk), which was ultrasonographically categorized as a tumor in the vitreal cavity. In panel B, notice the mass (asterisk), which was histologically diagnosed as a ciliary body adenoma and was therefore histologically categorized as neoplasia of the iris or ciliary body.

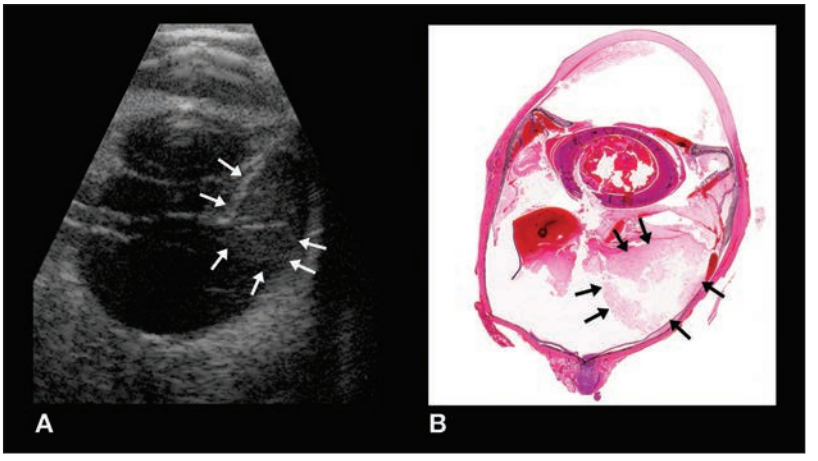

Figure 2—Representative ultrasonographic image (A) and photograph of an H&E-stained histologic slide (B) of an eye of a dog with a blood clot associated with the ciliary body and extending into the vitreous cavity. In panel A, notice the hyperechoic mass (arrows), which was ultrasonographically diagnosed as a neoplasm. In panel B, notice the mass (arrows), which was histologically diagnosed as a blood clot.

Lens capsule rupture—The agreement between ultrasonography and histologic examination of tissue samples for determination of a diagnosis of lens capsule rupture (**Figure 3**) was acceptable ($\kappa = 0.71$) for eyes evaluated at the University of Zurich. Lens capsule rupture was not identified via ultrasonography for 5 of 17 eyes with that diagnosis determined via histologic examination of eyes examined at the University of Zurich. Lens capsule rupture was not identified via histologic examination of tissue samples for 1 of 13 eyes with that diagnosis determined via ultrasonography at that facility. The agreement between ultrasonography and histologic examination of tissue samples for determination of a diagnosis of lens capsule rupture was poor ($\kappa = 0$) for eyes evaluated at the University of Wisconsin because lens capsule rupture was not identified via 10-MHz ultrasonography for any of the 6 eyes with that diagnosis determined via histologic examination.

Vitreous cavity neoplasia—The agreement between ultrasonography and histologic examination of tissue samples for determination of a diagnosis of vitreous cavity neoplasia was acceptable

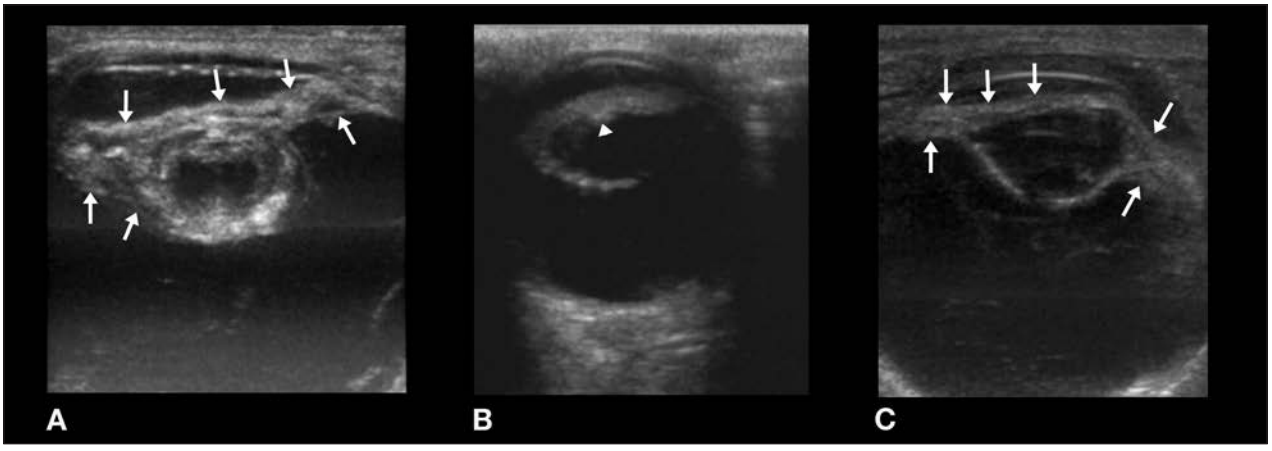

Figure 3—Ultrasonographic images of eyes of 2 representative horses (panels A and C) and 1 representative dog (panel B) with lens capsule rupture. In panels A and C, notice the hyperechoic material (arrows) surrounding the cataractous lens, which was attributed to debris caused by inflammation. In panel C, notice the irregular and flattened lens contour. In panel B, notice the dense material over the anterior aspect of the lens capsule with an adjacent intralenticular opacity (arrowhead). The normal interface and distinct reflection of the anterior and posterior aspects of an intact lens capsule could not be identified ultrasonographically in these eyes.

(κ = 0.65) for eyes examined at the University of Zurich. Vitreous cavity neoplasia was not identified via ultrasonography for 2 of 4 eyes with that diagnosis determined via histologic examination at that facility; these were in the 2 animals with intraocular melanomas of greater extent than expected. The agreement between ultrasonography and histologic examination of tissue samples for determination of a diagnosis of vitreous cavity neoplasia was poor (κ = –0.02) for eyes evaluated at the University of Wisconsin. At that facility, only 1 eye had a diagnosis of vitreous cavity neoplasia determined via histologic examination; that neoplasm was a metastatic malignant melanoma. Neoplastic cells had been detected in the vitreous cavity but nowhere else in the eye. Ultrasonographically, that tumor had appeared to be a subretinal neoplasm, which was not supported by histologic findings. One eye of an animal evaluated at the University of Wisconsin had been determined to have vitreal neoplasia via ultrasonography; results of histologic examination indicated that eye had ciliary body neoplasia (Figure 1).

Retinal detachment—The agreement between ultrasonography and histologic examination of eyes for determination of a diagnosis of retinal detachment was moderate (κ = 0.46) for eyes evaluated at the University of Zurich. Retinal detachment was not identified via ultrasonography for 14 of 38 (37%) eyes for which that diagnosis had been determined via histologic examination at the University of Zurich; 5 of these eyes had scleral rupture, which caused poor contrast in ultrasonographic images. For 3 of these eyes, vitreal hemorrhage or inflammatory changes without scleral rupture had caused poor contrast in ultrasonographic images. Two of these eyes had small focal areas of retinal detachment. For 4 of these eyes, the retina could not be observed in ultrasonographic images. Of 27 eyes with an ultrasonographic diagnosis of retinal detachment at that facility, 2 (7%) did not have that histologic finding; results of histologic examination of these eyes indicated vitreal hemorrhage or inflammation. In 2 more eyes with that ultrasonographic diagnosis, the histologic diagnosis could not be determined. The agreement between ultrasonography and histologic examination of tissue samples for determination of a diagnosis of retinal detachment was acceptable (κ = 0.68) for eyes evaluated at the University of Wisconsin. Retinal detachment was not identified via ultrasonography for 1 of 33 (3%) eyes with that diagnosis determined via histologic examination; that eye had vitreal hemorrhage. Retinal detachment was not identified by means of histologic examination for 6 of 38 (16%) eyes with that diagnosis determined by means of ultrasonography at the University of Wisconsin. Four of these eyes had intravitreal changes (eg, vitreal hemorrhage or debris attributable to inflammation) that had been falsely interpreted as retinal detachment. Two of these eyes had v-shaped proteinaceous material in the vitreous cavity, and 1 eye had asteroid hyalosis; these changes appeared similar to retinal detachment in ultrasonographic images (**Figure 4**).

Subretinal neoplasia—The agreement between ultrasonography and histologic examination of tissue samples for determination of a diagnosis of subretinal neoplasia was moderate for eyes evaluated at the University of Zurich (κ = 0.49) and the University of Wisconsin (κ = 0.46). Subretinal neoplasia was identified via ultrasonography for 1 of 3 eyes with that diagnosis determined via histologic examination at the University of Zurich. The other 2 eyes were of the animals with intraocular melanoma. Subretinal neoplasia was identified via ultrasonography for 2 of 3 eyes with that diagnosis determined via histologic examination at the University of Wisconsin. Of 5 eyes with subretinal neoplasia detected by means of ultrasonography, 2 had that diagnosis determined via histologic diagnosis. For one of these eyes, neoplasia had been diagnosed but the location of the tumor had been incorrectly determined; this was the eye with metastatic malignant melanoma, for which results of histologic examination indicated the tumor was in the vitreal cavity rather than in a subretinal location. For the other 2 eyes, blood clots were misidentified as neoplastic lesions via ultrasonography. One eye had a medulloepithelioma; that tumor was de-

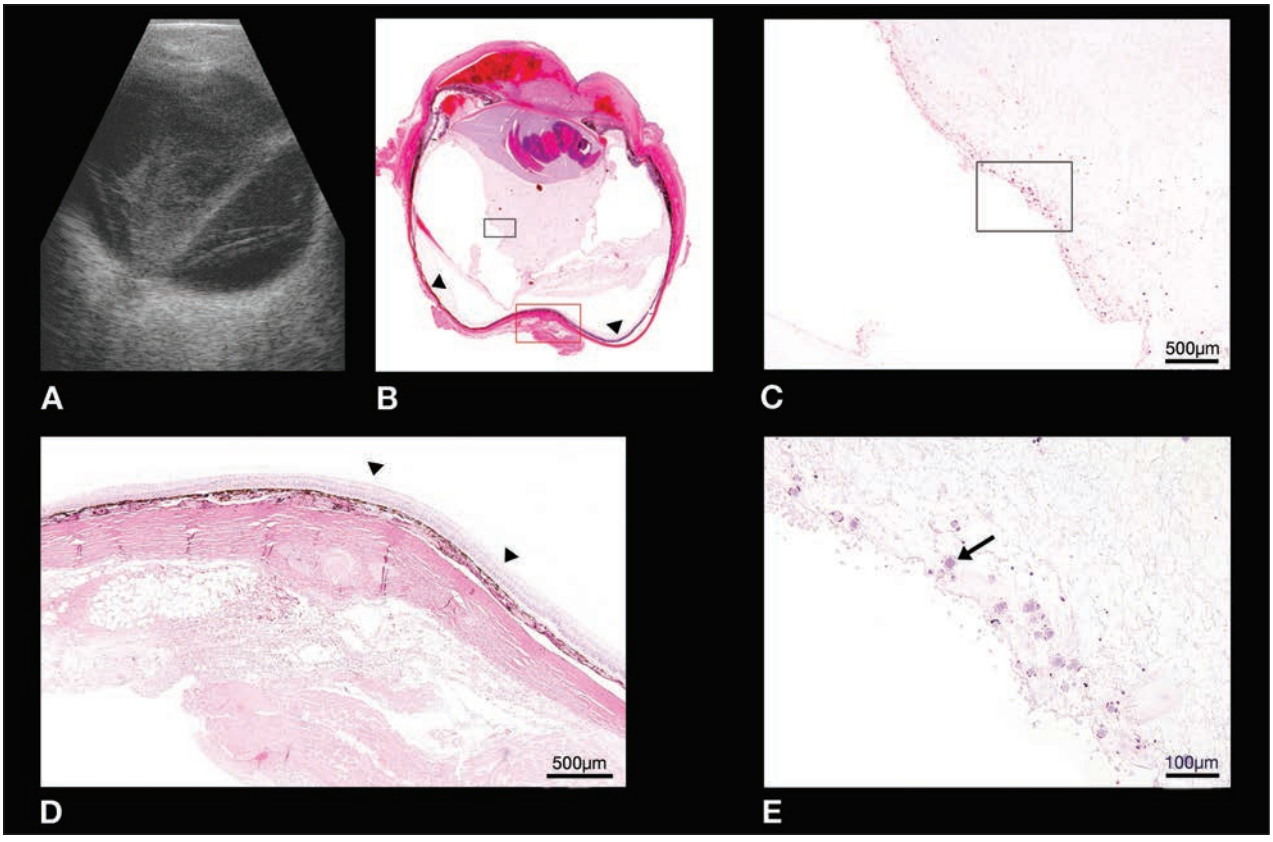

Figure 4—Representative ultrasonographic image (A), photograph of an H&E-stained histologic slide (B), and photomicrographs (C through E) of an eye of a dog with vitreous humor protein condensation. The black boxed area in panel B corresponds to the area depicted in panel C. The red boxed area in panel B corresponds to the area depicted in panel D. The boxed area in panel C corresponds to the area depicted in panel E. In panel A, notice the hyperechoic v-shaped lines, which were ultrasonographically diagnosed as retinal detachment. In panel B, notice the membranous structures corresponding to the v-shaped lines identified in the ultrasonographic image; these membranous structures were histologically diagnosed as condensed vitreous humor and proteinaceous material. The retina was determined to be attached (arrowheads in panels B and D). In panels B, C, and E, notice the pale eosinophilic v-shaped proteinaceous material in the vitreous cavity with asteroid hyalosis material lining the free edge of that proteinaceous material; the hyperechoic ultrasonographic signal was attributed to this material. The thin black arrow in panel E indicates an asteroid hyalosis particle. Bars = 500 µm (panels C and D) and 100 µm (panel E).

tected and correctly localized via ultrasonography as a subretinal neoplasia (**Figure 5**).

Overall intraocular neoplasia—An intraocular neoplasm was identified via ultrasonography in 37 eyes at both study locations. In 29 of these eyes, the diagnosis was confirmed via histologic examination. In the 8 remaining eyes, hemorrhagic or inflammatory changes were misidentified as neoplastic lesions via ultrasonography. An intraocular neoplasm was identified via histologic evaluation in 31 eyes at both locations. In 2 of these eyes (1 at each location), the diagnosis had not been identified via ultrasonographic examination. The neoplasm was misidentified as hemorrhage in one of these eyes and as inflammation in the other.

Subretinal exudate—The agreement between ultrasonography and histologic examination of eyes for determination of a diagnosis of subretinal exudate was poor (κ = 0.20) for eyes evaluated at the University of Zurich; subretinal exudate was not identified via ultrasonography for 4 of 5 eyes with that diagnosis determined via histologic examination, and that problem was not identified via histologic examination for 2 of 3 eyes with that diagnosis determined via ultrasonography. The agreement between ultrasonography and histologic examination of tissue samples for determination of a diagnosis of subretinal exudate was acceptable (κ = 0.67) for eyes evaluated at the University of Wisconsin. Subretinal exudate was not identified via ultrasonography for 3 of 8 eyes with that diagnosis determined via histologic examination at that facility, and that problem was not identified by means of histologic examination for 1 of 6 eyes with that diagnosis determined by means of ultrasonography. Both eyes of 1 dog with systemic blastomycosis were excluded from statistical analyses because of a lack of independence of data. All animals with systemic mycosis had subretinal granulomas (**Figure 6**).

Retinal tear—The agreement between ultrasonography and histologic examination of tissue samples for determination of a diagnosis of retinal tear (**Figure 7**) was poor (κ = 0.23) for eyes evaluated at the University of Zurich; retinal tear was not identified via ultrasonography for 6 of 7 eyes with that diagnosis detected via histologic examination. The agreement between ultrasonography and histologic examination of tissue samples for determination of a diagnosis of retinal tear

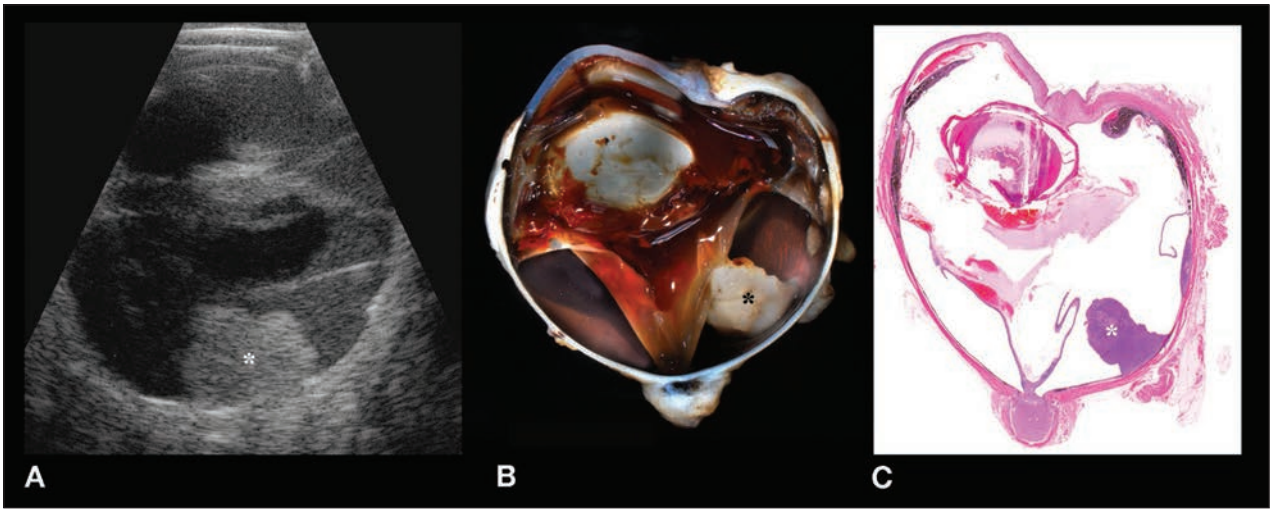

Figure 5—Representative ultrasonographic (A) and gross (B) images and photograph of an H&E-stained histologic slide (C) of an eye of a dog with subretinal medulloepithelioma. In the ultrasonographic image in panel A, notice the hyperechoic mass (asterisk) that seems to be under a membrane, which was assumed to be the retina. In the gross (panel B) and histologic (panel C) images, the mass (asterisks) has a similar appearance to that detected in the ultrasonographic image. The mass was correctly identified and localized via ultrasonography as a subretinal neoplasm.

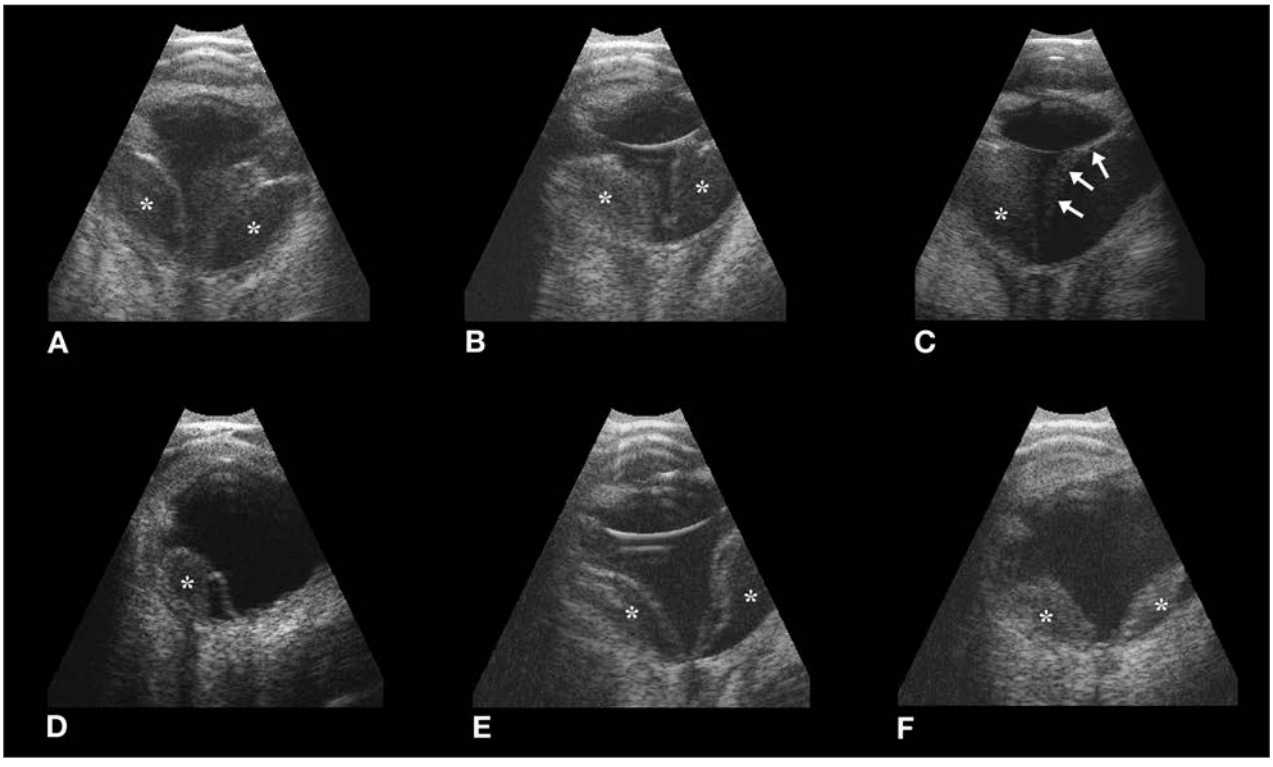

Figure 6—Ultrasonographic images of eyes of representative dogs with intraocular lesions attributable to blastomycosis. In panels A through F, notice the seagull-shaped retinal detachment with hyperechoic homogenous subretinal exudate (asterisks); this finding was detected in ultrasonographic images for all animals with blastomycosis in the present study. In panel C, notice the hyperechoic membranous appearance of the detached retina (arrows).

was poor ($\kappa = 0.31$) for eyes evaluated at the University of Wisconsin; retinal tear was not identified via ultrasonography for 4 of the 5 eyes with that diagnosis determined via histologic examination.

Scleral rupture—The agreement between ultrasonography and histologic examination of tissue samples for determination of a diagnosis of scleral rupture (**Figure 8**) was good for eyes evaluated at the University of Zurich ($\kappa = 0.77$) and those evaluated at the University of Wisconsin ($\kappa = 0.79$). Scleral rupture was not detected via ultrasonography for 2 of 9 eyes with that diagnosis determined via histologic examination at the University of Zurich; scleral rupture was not identified by means of histologic examination for 2 of 9 eyes with that diagnosis determined by means of ultrasonography at this facil-

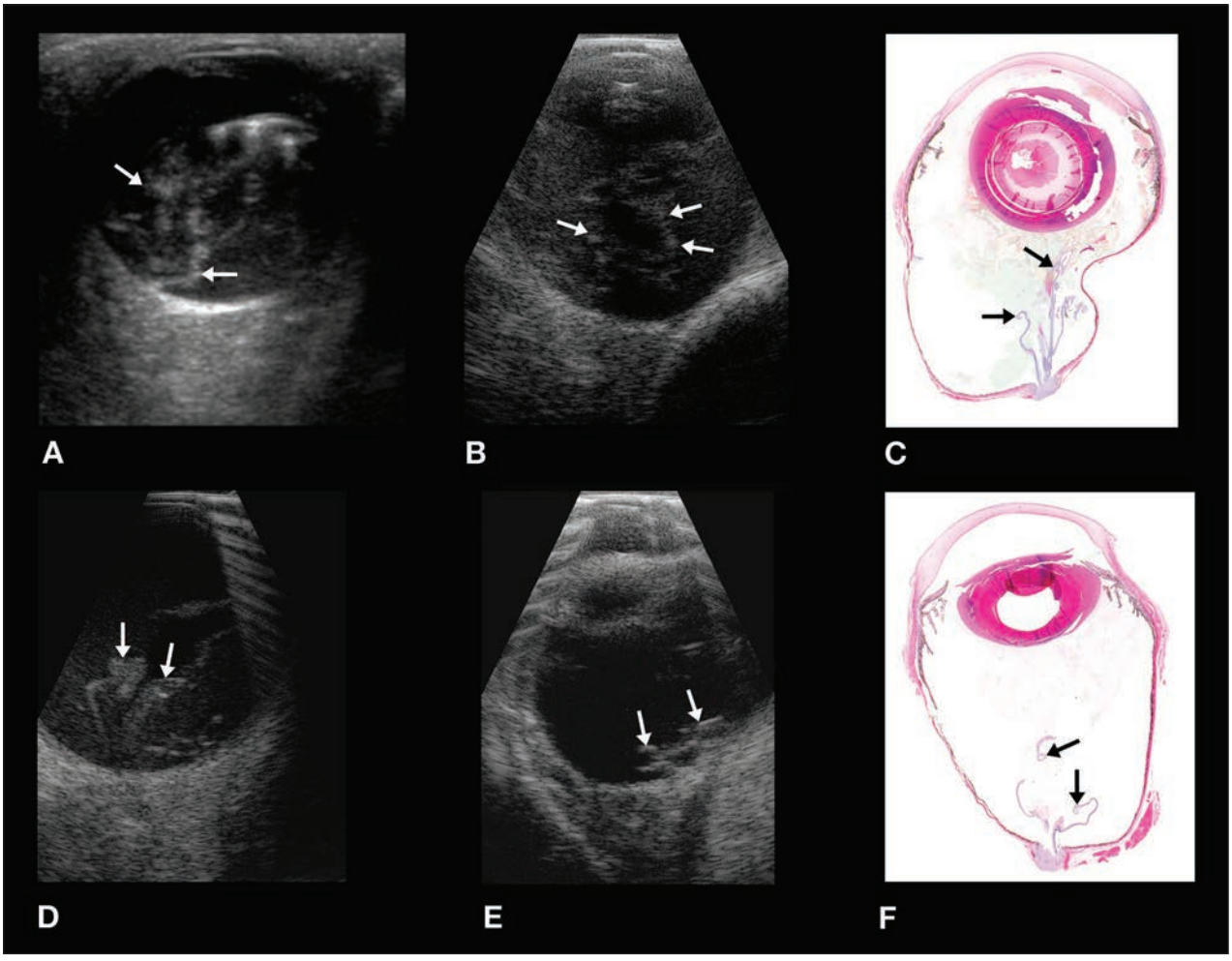

Figure 7—Images of eyes of animals with retinal tears. A—Ultrasonographic image of an eye of a dog. B—Ultrasonographic image of an eye of a dog. C—Photograph of an H&E-stained histologic slide of the eye in panel B. D—Ultrasonographic image of an eye of a dog. E—Ultrasonographic image of an eye of a dog. F—Photograph of an H&E-stained histologic slide of the eye in panel E. In panels A, B, D, and E, notice the hyperechoic structure with an irregularly shaped strand-like structure in the vitreous cavity (white arrows), connected to the area of the optic disk; this was the typical ultrasonographic appearance of retinal tears in completely detached retinas. In panels C and F, notice the typical appearance of retinal tears with curled ends (black arrows).

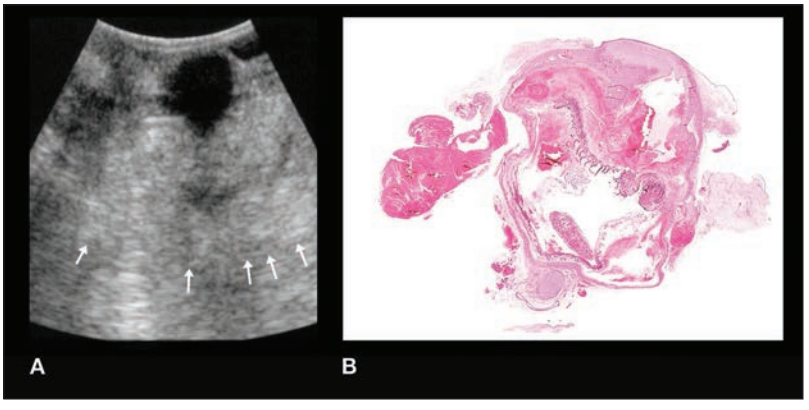

Figure 8—Ultrasonographic image (A) and photograph of an H&E-stained histologic slide (B) of an eye of a dog with scleral rupture. In panel A, notice the poor image contrast; the posterior outline of the globe was difficult to identify (arrows).

ity. For 2 more eyes with that diagnosis determined via ultrasonography, the diagnosis could not be determined histologically because the site of rupture was not located in the plane of the tissue section. Scleral rupture was not identified via ultrasonography for 1 of 3 eyes with that diagnosis determined via histologic examination at the University of Wisconsin. All ultrasonographic diagnoses of scleral rupture (n = 2 eyes) were histologically confirmed for eyes evaluated at that facility.

Discussion

Results of the present study suggested that the accuracy of ultrasonography for diagnosis of ocular problems varies among diseases. High agreement between results of ultrasonography and those of histologic examination was detected for diagnosis of intraocular neoplasia. Only 2 ocular neoplasms of animals detected via histologic examination were not detected via ultrasonography (1 eye for animals evaluated in each of the facilities of the present study). In addition, ocular tumors detected via ultrasonography for which

locations were incorrectly determined via that method (as determined via histologic examination) were considered incorrect diagnoses in this study. Results of the study suggested that it was difficult to identify the ocular location and extent of a tumor via ultrasonography, but that method was accurate for detection of tumors. Besides the category iris or ciliary body neoplasia, this finding affected the percentage agreement values for ultrasonography and histologic examination regarding 4 other diagnosis categories (corneal neoplasia, anterior chamber neoplasia, vitreous cavity neoplasia, and subretinal neoplasia) for which a low number of eyes were included in the study.

For 5 eyes evaluated at the University of Zurich and 3 eyes evaluated at the University of Wisconsin, blood clots identified via histologic examination were incorrectly identified as neoplasms via ultrasonography. Because such ultrasonographic findings may lead to performance of incorrect treatments, results should be cautiously interpreted for animals with large amounts of intraocular blood.

Results of the present study indicated ultrasonography was moderately accurate for detection of retinal detachment. For 37% of eyes with histologically detected retinal detachment evaluated at the University of Zurich, that problem was not detected via ultrasonography. This finding was attributed to poor contrast in ultrasonographic images of 8 eyes that had scleral rupture or vitreous humor hemorrhage or inflammation. Interestingly, scleral rupture was detected in approximately 3 times as many eyes evaluated at the University of Zurich versus the University of Wisconsin. In contrast, retinal detachment was identified more often in ultrasonographic images of eyes without a histologic diagnosis of retinal detachment at the University of Wisconsin versus the University of Zurich. At the University of Wisconsin, ophthalmologists performed ultrasonographic examinations and determined ultrasonographic diagnoses, whereas at the University of Zurich, such examinations were performed by radiologists. Ophthalmologists may have been more likely than radiologists to identify membranous intravitreal structures as retinal detachments.

Interestingly, hyperechoic v-shaped lines were identified in ultrasonographic images of 2 eyes examined in this study; this appearance was similar to that for eyes with retinal detachment. However, results of histologic examination indicated retinas were not detached in those 2 eyes and the v-shaped lines identified in ultrasonographic images were eosinophilic proteinaceous material in the vitreous humor. One of these 2 eyes had asteroid hyalosis material lining the edge of the proteinaceous material, which may have caused a strongly hyperechoic ultrasonographic signal.[10] To avoid misinterpretation of ultrasonographic images, information regarding medical histories and results of clinical examinations and other imaging tests should be considered when determining a diagnosis for animals with ocular disease.

Results of the present study indicated high κ values for diseases that were consistently identified via ultrasonography (eg, corneal or scleral perforation, cataracts, and iris or ciliary body neoplasia). This finding may have been attributable to the characteristic ultrasonographic appearance of eyes for some diseases (eg, cataracts). Alternately, knowledge of the medical histories of animals may have aided ultrasonographic diagnosis for some diseases (eg, corneal perforation). However, differentiation between intraocular hemorrhage and inflammatory changes via ultrasonography was difficult; results of this study indicated low κ values for such diagnoses. This finding was not surprising, considering that inflammatory cells and hemorrhage in vitreous humor may have identical ultrasonographic appearances (small moving pinpoint lesions),[19] whereas inflammatory cells and hemorrhage can be easily distinguished via histologic examination. Differentiation between hemorrhagic and inflammatory changes may not be as important as correct identification of neoplasms because tumor diseases may have markedly different prognoses.

For lens capsule rupture, subretinal exudate, and retinal tear, pathological changes detected via histologic examination were detectable in ultrasonographic images when we reexamined such images with knowledge of histologic findings. Lens capsule rupture was not identified via ultrasonography in eyes evaluated at the University of Wisconsin; this finding was attributed to the low near-field resolution of the 10-MHz ultrasonography probe used in this study. For eyes in which lens capsule rupture is suspected, a technique such as offset or high-resolution ultrasonography should be used, as is the case in the clinical setting at this facility.[20] At the University of Zurich, lens capsule rupture was correctly identified via ultrasonography in 12 of 17 (71%) eyes and was not detected via ultrasonography in 5 of 17 (29%) eyes (as determined via histologic evaluation). In retrospect, for most of the lens capsule rupture eyes, this disease was detectable in ultrasonographic images. The normal interface with distinct reflection of the anterior and posterior aspects of an intact lens capsule could not be appreciated ultrasonographically in these images. Instead, an ultrasonographically irregular and discontinuous lens contour or hyperechoic material suggestive of inflammatory deposits surrounding the lens was observed in ultrasonographic images. This was similar to the typical histologic appearance of septic implantation syndrome.[30,31] Irregularity of the lens capsule and the suspected presence of lens material on the outer surface of the capsule have been described as a typical ultrasonographic appearance of lens capsule ruptures.[17,18]

Both eyes of 1 dog from Wisconsin with systemic blastomycosis were included in the study, but because of dependence of data for animals with bilateral ocular disease in this diagnosis category, these 2 eyes were excluded from statistical analysis for this category. The other 4 of the remaining 8 eyes evaluated at the University of Wisconsin with histologically diagnosed subretinal exudate had blastomycosis-induced granulomas. The ultrasonographic appearance of these eyes was different from that of all other eyes with retinal detachment and subretinal material such as hemorrhage or exudate. A seagull-shaped area of retinal detachment with homogenous hyperechoic subretinal exudate was detected in ultrasonographic images of

eyes with blastomycosis-induced granulomas. This ultrasonographic appearance may be typical for eyes of animals with mycosis-induced subretinal granulomas.[19] Subretinal exudate was detected in more eyes evaluated at the University of Wisconsin versus the University of Zurich; this finding was attributed to the geographic distribution of blastomycosis. The κ statistic value for subretinal exudate was much higher for the University of Wisconsin, compared with the University of Zurich, for this category.

For eyes evaluated at both facilities of the present study, irregular, curved, strand-shaped hyperechoic structures connected to the optic disk region were detected in the vitreous cavity in ultrasonographic images of eyes with completely detached retinas and retinal tears. This ultrasonographic appearance distinguished eyes with retinal tears from those with retinal detachments without retinal tears or vitreal cavity inflammation or hemorrhage.

Limitations of the study were identified that were attributed to the retrospective study design. Most available ultrasonographic images were still images; evaluation of ultrasonographic still images may be more difficult than real-time ultrasonographic evaluation of eyes for determination of a diagnosis. Availability of ultrasonography reports in medical records was important for evaluation of ultrasonographic images by investigators of the present study. Personnel with various amounts and types of experience had originally performed the ultrasonographic examinations. Evaluation of all ultrasonographic images by the same group of people, consisting of personnel who were board certified in radiology or ophthalmology, was considered important in the present study.

The quality of some histologic slides of eyes made comparison of diagnoses determined via ultrasonography and those determined via histologic examination difficult. Proper tissue sample processing is important for determination of histologic diagnoses. Additionally, several ultrasonographic diagnoses could not be confirmed via histologic examination of eyes because the area of interest was not included in the histologic tissue section plane. Archived ocular tissue samples were not available for all animals for preparation of additional slides. Certain diagnoses (eg, globe perforations) could be confirmed on the basis of sufficient indirect signs (eg, if the perforation itself was not included in the histologic tissue section plane). These signs could have been funnel-shaped inflammatory cell infiltrates leading toward a perforation site, the presence of foreign body material within the globe, or the presence of microorganisms in the globe in combination with a history and clinical signs of focal trauma.

The accuracy of ultrasonography for detection of diseases may be increased via several methods, particularly for differentiation of neoplastic from nonneoplastic lesions or for detection of retinal detachment. Performance of standardized ultrasonographic examination protocols with consistent probe orientations and scanning planes should be used. Saving and correct labeling of ultrasonographic images are important for comparison with results of subsequent examinations and for consultation with other clinicians. Performance of repeated ultrasonographic examinations with measurement of structures can be helpful for detection of changes in sizes of masses and differentiation between blood clots and tumors[32]; results of the present study suggested that it was difficult to differentiate blood clots from tumors in eyes via ultrasonography. Use of alternate ultrasonographic techniques may be indicated, including Doppler ultrasonography and contrast techniques such as contrast harmonic imaging. The use of contrast harmonic imaging has been described for examination of eyes of humans[33] and other animals.[34] Results of another study[34] indicate contrast-enhanced ultrasonography is 100% accurate for the detection of retinal detachment and differentiation between that problem and vitreous cavity membranes. Results of that study[34] indicate vascular perfusion of retinas can be detected via that technique, which suggests that the technique may be useful for differentiating between nonvascularized blood clots and vascularized neoplasms as well.

Standardized amplitude mode (A-mode) ultrasonography can be used to identify various types of intraocular tumors via determination of information regarding the internal structure of a mass, which is regularly performed in the human ophthalmology field[32] and has been described for the diagnosis of anterior uveal melanomas in dogs.[35] Primarily, A-mode ultrasonography is used in veterinary ophthalmology for determination of biometric measurements or as a vector A-scan procedure for measurement of structures during B-mode ultrasonography.[1,36]

Results of the present study suggested that the accuracy of ultrasonography for identification of ocular problems varies among diseases. Results indicated performance of B-mode ultrasonography was helpful for determination of diagnoses for various intraocular diseases. However, diagnoses for some animals with ocular disease may not be correctly determined by use of that method. Use of additional diagnostic methods may be necessary for correct determination of diagnoses for animals with ocular diseases.

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c. Aloka Prosound SSD α-10, Aloka Holding, Zug, Switzerland.
d. Phillips IU 22, Philips AG Healthcare, Zurich, Switzerland.
e. GE Logiq 400, GE Medical Systems AG, Glattbrugg, Switzerland.
f. Aloka Prosound α -7, Aloka Holding, Zug, Switzerland.
g. Novesine, Merck-Sharp & Dohme-Chibret, Paris, France.
h. Alcaine, Alcon, Basel, Switzerland.
i. I3 B-scan, Ellex Innovative Imaging, Sacramento, Calif.
j. Proparacaine hydrochloride ophthalmic solution USP, 0.5%, Bausch & Lomb Pharmaceuticals, Tampa, Fla.
k. Stata Software, version 12.1, StataCorp, College Station, Tex.

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Continued on next page.

Appendix

Ultrasonographic and histologic diagnoses included in various disease categories for eyes of animals.

Disease category	Included ultrasonographic diagnoses	Included histologic diagnoses
Corneal perforation	Corneal perforation	Corneal perforation
Corneal neoplasia	Corneal mass	Corneal squamous cell carcinoma
		Diffuse iris melanoma extending into cornea
Anterior chamber neoplasia	Mass in anterior chamber	Anterior chamber squamous cell carcinoma
	Mass in entire globe	Diffuse or iris melanoma extending into anterior chamber
Blood, fibrin, or inflammatory changes in the anterior chamber	Hyphema (blood clot or hemorrhage in the anterior chamber)	Hyphema (blood clot, hemorrhage, or erythrocytes in the anterior chamber)
	Globe completely filled with hyperechoic material	Globe completely filled with blood
	Hypopyon	Fibrin in the anterior chamber
	Fibrin in the anterior chamber	Inflammatory cells or infiltrate in the anterior chamber
	Inflammatory or membranous changes in the anterior chamber	Purulent exudate in the anterior chamber
	Granulation tissue in the anterior chamber	Accumulation of protein in the anterior chamber
	Panophthalmitis	Granulation tissue in the anterior chamber
		Endophthalmitis or panophthalmitis
Iris or ciliary body neoplasia	Mass in or arising from the iris or ciliary body	Diffuse or iris melanoma
	Mass in entire globe	Anterior uveal melanocytoma
		Ciliary body neoplasia (eg, adenoma or adenocarcinoma)
		Ocular melanosis
Inflammatory changes or blood near the iris or ciliary body	Anterior or posterior synechia	Anterior or posterior synechia
	Inflammatory thickening of the iris or ciliary body	Inflammatory thickening of the iris or ciliary body
	Deposits on lens capsule	Inflammation or granulation tissue of the iris or ciliary body
	Lens surrounded with hyperechogenic material	Fibroblastic tissue around lens
	Iridocyclitis	Preiridal fibrovascular membrane
	Iris bombé	Uveitis or iridocyclitis
	Cyclitic membrane	Iris bombé
	Iris cysts	Cyclitic membrane
	Fibrin or hemorrhage in the posterior chamber	Iris cysts
	Globe completely filled with hyperechoic material	Protein or inflammatory infiltrate in the iris or ciliary body
	Panophthalmitis	Fibrin or hemorrhage in the posterior chamber
		Globe completely filled with blood
		Endophthalmitis or panophthalmitis
Cataract	Cataract excluding nucleosclerosis	Cataract
Lens luxation or subluxation	Anterior or posterior lens luxation or subluxation	Macroscopically or microscopically identified lens luxation or subluxation
Lens capsule rupture	Lens capsule rupture	Lens capsule rupture
	Irregular lens contour	
Other lens changes	Intraocular lens	Intraocular lens
	Lens capsule remnants	Lens capsule remnants
	Lens not present	Lens not present
	Resorbing lens	Resorbing lens
Inflammation in the vitreous cavity	Membranous hyperechoic structures in the vitreous cavity	Protein or exudate in the vitreous cavity
	Inflammatory changes in the vitreous cavity	Inflammatory infiltrate in the vitreous cavity
	Fibrin, proteinaceous, or cellular material in the vitreous cavity	Fibrin in the vitreous cavity
	Hyperechogenicity of the vitreous humor with linear structures and moving small particles	Suppurative vitreitis
		Granulation tissue in the vitreous cavity
	Endophthalmitis or panophthalmitis	Endophthalmitis or panophthalmitis
Vitreous cavity hemorrhage	Blood clot, hemorrhage, or hematoma in the vitreous cavity	Blood clot, hemorrhage, or hematoma in the vitreous cavity
	Globe completely filled with hyperechoic material	Globe completely filled with blood
Vitreous cavity neoplasia	Vitreous cavity mass	Melanoma in the vitreous cavity
	Mass in the entire globe	Metastatic osteosarcoma in the vitreous cavity
		Metastatic malignant melanoma in the vitreous cavity
		Choroidal melanocytoma in the vitreous cavity
Degenerative vitreous cavity changes	Irregular membranous structures of low echogenicity	Pale eosinophilic irregular strand-like material in the vitreous cavity
	Liquefied corpuscular material in the vitreous cavity	Proteinaceous exudate in the vitreous cavity
	Hyperechoic densities in the vitreous cavity	
	Degenerative changes in the vitreous cavity	
Retinal detachment	Retinal detachment (focal or complete)	Retinal detachment (focal or complete)
		Retinal pigment epithelium hyperplasia
Subretinal hemorrhage	Subretinal hemorrhage	Subretinal hemorrhage
	Globe completely filled with hyperechoic material	Globe completely filled with blood
Subretinal neoplasia	Subretinal mass	Neoplastic cells or mass in the subretinal space
	Mass in entire globe	Uveal malignant melanoma with invasion into sclera and optic nerve
		Choroidal neuroectodermal tumor (medulloepithelioma) or choroidal melanocytoma
Subretinal exudate	Subretinal inflammatory material	Endophthalmitis or panophthalmitis (subretinal pyogranulomatous material)
	Subretinal granuloma	Subretinal eosinophilic protein and inflammatory infiltrate
	Subretinal empyema	Extensive subretinal inflammation with yeast
	Panophthalmitis	
Retinal tear	Retinal tear	Retinal tear
Choroidal thickening	Choroidal thickening	Neovascular and fibrous proliferation in the choroid
		Distention, expansion, or thickening of the choroid
Choroidal detachment	Choroidal detachment	Choroidal detachment
	Subchoroidal hemorrhage	Subchoroidal hemorrhage
Scleral rupture	Scleral rupture	Scleral rupture
Scleral thickening	Scleral thickening	Scleral thickening

Ultrasonographic and histologic diagnoses may be allocated to > 1 disease category.