INTRODUCTION
Diffuse iris melanoma is the most common primary intraocular neoplasm in cats. The term was developed to indicate the occurrence of these tumors diffusely in the iris. A tumor is first apparent as an asymmetrical hyperpigmentation of the affected iris. Focal areas of hyperpigmentation may persist for months or years until irregular iris masses develop. As the tumor progresses, infiltration of the iridocorneal angle leads to glaucoma and further infiltration can lead to neoplastic infiltration throughout the ciliary body and sclera. Histologically, there is a change in the morphology of pigmented cells that occurs when expanding lesions first infiltrate deeply into the iris stroma. Unfortunately, there are no clinical hallmarks for this change in the histological appearance. Metastatic disease leading to death has been reported at intervals up to several years after enucleation, but there is little indication from published reports about the overall prognosis of diffuse iris melanoma. Clinically measurable features which predict the health risk to the animal are urgently required. This study was undertaken to document the effect upon survival of cats with enucleation due to diffuse iris melanoma, in differing stages of disease, compared to age-matched controls. The results are analysed to document the effect of tumor extent on survival. The extent of tumor spread in the eye is a feature that can be monitored clinically.

MATERIALS AND METHODS
Selection of affected cats
Inclusion criteria for affected cats in this study were cats that had been evaluated by a veterinary ophthalmologist, had enucleation surgery performed for suspected diffuse iris melanoma between 2 and 10 years prior to the study, and had histologically confirmed diffuse iris melanoma. Follow-up reports of each cat admitted to the study were also criteria for inclusion in this study. Thirty-four affected cats qualified for the study.

Selection of control cats
Thirty-eight of the control cats had enucleation after evaluation by a veterinary ophthalmologist. The cause of enucleation was either lymphoplasmacytic uveitis (27 cases), ocular trauma (seven cases), or endophthalmitis (four cases). In these control cats, enucleations were performed between 2 and 10 years prior to this study. Forty-five additional control cats presented for vaccination between 2 and 10 years prior to the study. The extent of diffuse iris melanoma at the time of enucleation in affected cats was graded according to the extent of involvement ofocular tissues and the invasiveness of the tumor. Affected cats have a significantly decreased survival compared with control cats and cats with extensive tumors at the time of enucleation have the lowest survival rates. Cats with tumors confined to the iris survive at the same rate as controls. These results suggest that early enucleation is important to avoid premature death, presumed to be due to cancer metastasis in cats with diffuse iris melanoma.

Key Words: cat, enucleation, eye, feline, melanoma, ophthalmology, survival
performed on all control cases when enucleation was performed. An additional 45 controls were selected from cats which were vaccinated at the University of Wisconsin–Madison Veterinary Medical Teaching Hospital between 2 and 10 years prior to the study. The control sample was age-matched to the cases, not on an individual basis but as a means of making the age distributions in the two samples as similar as possible. Cats were chosen as controls only if the current status of the cat was known. Both groups were used together as a single control group after first testing for variability in survival and finding no significant difference.

**Follow-up information**

Signalment data for each cat were recorded at the time of submission of ocular tissue or by contacting the referring veterinary ophthalmologist. The period of time was recorded as the point when the first iris pigment change was observed until enucleation was performed. Presence or absence of glaucoma was also recorded. The date of death and an estimate of the cause of death were also recorded and the state of health was recorded in surviving animals.

**Extent of involvement**

Results of histopathological examination of eyes with diffuse iris melanoma were reviewed and classified with regard to the extent of involvement of the neoplasm. The following grading system was used to categorized iris melanoma for the purposes of statistical application:

- Grade I (one case): accumulation of small pigmented cells locally confined to the anterior iris surface.
- Grade II (eight cases): neoplastic cells confined to the iris stroma and trabecular meshwork.
- Grade III (nine cases): neoplastic cells extending into the ciliary body stroma but not disrupting the posterior iris epithelium.
- Grade IV (seven cases): neoplastic cells extending throughout the ciliary body stroma and scleral venous plexus but not disrupting the posterior iris epithelium.
- Grade V (three cases): neoplastic cells confined to the iris and trabecular meshwork but also disrupting the posterior iris epithelium. In the experience of the author (R.R.D.) disruption of the iris epithelium is an important indicator of invasiveness of this tumor. As invasiveness can be an important predictor of prognosis this feature was made a factor in Grades V and VI.
- Grade VI (six cases): neoplastic cells extending throughout the ciliary body stroma and scleral venous plexus and also disrupting the posterior iris epithelium.

**Simplified grades**

Using the previously described six grades established at the start of the study a simplified system which characterized only the extent of tumor spread was devised as follows:

- Early (nine cases): these cases had tumor only in the iris and trabecular meshwork (Grade I and Grade II).
- Moderate (12 cases): these cases had tumor in the iris and rostral ciliary body but not the sclera (Grade III and Grade V).
- Advanced (13 cases): these cases had tumor throughout the ciliary body and extending into the sclera (Grade IV and Grade VI).

**Statistical analysis**

Survival times were measured from dates of vaccination (among vaccination cats) or enucleation (all others). Median follow-up was 5 years in cases and 4.5 years in controls. Univariate comparisons were conducted via the log-rank test or its generalization to more than two groups. The proportional hazards model was used to adjust for age, using linear and quadratic terms.

**RESULTS**

Survival was not associated with sex or neutering. The ages of affected and control cats at the time of enucleation or vaccination were closely matched (Fig. 1): control cats had a median age of 9 years (25th percentile, 7 years, 75th percentile, 12 years) while the cases had a median age of 9.5 years (25th percentile, 7.1 years, 75th percentile, 11.8 years). Compared to the vaccination controls, cats with lymphoplasmacytic uveitis had a virtually identical survival time (Fig. 2). The hypothesis of no difference in survival among controls is marginally significant, i.e. \( P = 0.075 \). Because of this we combined the groups and used them all together as one control population.

Survival after enucleation surgery in cats with diffuse iris melanoma was significantly shorter than survival of control cats (Fig. 3), \( P = 0.016 \). After adjustment for the age the \( P \)-value decreased to 0.004. When the affected eyes were evaluated for the extent of disease, the effect on survival time was accentuated (Fig. 4). Cats with grade I and II involvement tended to have survival rates close to that of the controls (54/83 = 65%), while those with grade III–VI involvement tended to have lower survival. There was a significant association \( (P = 0.007) \) of survival with grade of neoplastic involvement after adjustment for age (the adjustment is necessary because cats with greater neoplastic involvement also tend to be older). Survival of cats with tumor confined to the iris stroma and trabecular meshwork was comparable from the control cats; however, none of the cats with grade VI neoplasms survived. Five of six cats with grade VI neoplasms had documented metastatic disease at the time of death.

The six grades of involvement address both the extent of involvement and a factor of invasiveness. As the extent of involvement is a measurement that can be evaluated clinically it is useful to re-evaluate the data to look only at the relationship between the extent of tumor spread and...
the survival. This is done by simplifying the grading as described earlier, creating three categories of extent of tumor: early, moderate, and advanced. Figure 5 depicts the survival rates and Fig. 6 depicts the survival curve of cats in the three new categories. Clearly the extent of tumor within the eye is an excellent predictor of survival.

Cats with diffuse iris melanoma having secondary glaucoma had shorter survival times compared to affected cats that did not have secondary glaucoma. Four of 19 cats (21%) with diffuse iris melanoma and concurrent secondary glaucoma survived compared to 11 of 15 cats (73%) with diffuse iris melanoma that did not have secondary glaucoma. Median ages for cats with diffuse iris melanoma and concurrent glaucoma and cats with diffuse iris melanoma that did not have secondary glaucoma were 8 and 11 years, respectively. The age-adjusted $P$-value for glaucoma and survival was 0.07. Glaucoma was associated with histopathologic grade of neoplasm but there was not enough data to adjust for survival.
DISCUSSION

In most cases we were not able to obtain an exact confirmation of the cause of death. Our data hinted that the deaths of cats with advanced tumors were associated with metastatic disease because of statements such as palpable abdominal masses or weight loss. Death of a control cat was often related to signs not suggestive of neoplasia.

A previous author reported on survival in a small number of cases related to amount of pigmentation, anisokaryosis,
vascular scleral invasion, tumor location, and cell types. In addition, survival was related to mitotic index, nuclear-to-cytoplasm ratio, and number of nucleoli. A trend of positive results was found in vascular scleral invasion and mitotic index. Our findings support the significance of invasion of the sclera and survival. As one goal of this study was to look for predictors of survival that could be useful as clinical indicators, we did not look at mitotic activity. We did record information about cell type but the results were not useful because there were too many categories to be analysed with such a small number of cases.

Diffuse iris melanoma in cats is a slowly progressive disease and death attributable to metastasis has been reported. Typically, affected cats first present with pigmented foci on the surface of the affected iris. These foci may remain static for the life of the cat or they may expand with no affect on vision or health for several years. In some cats, a morphological change occurs at the time the pigmented foci expand and the pigmented cells begin to infiltrate the iris stroma. The cells change from small angular cells to rounded cells with a round nucleus and a prominent nucleolus. Morphologically, this change in cellular appearance marks the beginning of diffuse iris melanoma; however, this change is not detectable by clinical observation.

In the three cats that had grade V neoplasms the tumors did not extend throughout the ciliary stroma or invade the sclera, but were focally invasive causing disruption of the posterior iris pigmented epithelium. All three of these cats survived. Disruption of the iris epithelium in tumors which are not extensive may not be an accurate prognostic indicator for cats with diffuse iris melanoma. When the data is analysed to reclassify the six grades into early, moderate, and advanced tumors based only on the extent of infiltration, then there is a strong correlation between the extent of the tumor infiltration and survival. This data is recorded in Figs 5 and 6.

Our findings suggest that when enucleation is done in the early stages of disease, while the tumor is confined to the iris stroma, affected cats survive as long as control cats. Conversely, when enucleation is done after invasion of the ciliary body stroma, or later, there is a progressively poorer prognosis. Similarly, cats with glaucoma attributable to tumor infiltration of the ciliary body are likely to die earlier then control cats.

REFERENCES