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Objective—To determine the effects of treatment with and without adjuvant radiation therapy on recurrence of ocular and adnexal squamous cell carcinoma (SCC) at specific anatomic locations in horses.

Design—Retrospective study.

Animals—91 horses.

Procedures—Medical records of horses with histologically confirmed ocular and adnexal SCC evaluated from 1985 to 2002 were reviewed. Sex, breed, age, type of treatment, location, and recurrence of SCC were recorded. Two treatment groups determined by recurrence of SCCs treated with and without adjuvant radiation therapy were established.

Results—The anatomic site with the highest recurrence rate was the limbus (junction of the cornea and sclera) or bulbar conjunctiva (47.7%), independent of treatment group. There was a significant difference in recurrence rates of ocular and adnexal SCCs between the 2 treatment groups, independent of anatomic location. Recurrence rates of SCCs treated with and without adjuvant radiation therapy were 11.9% and 44.1%, respectively. Recurrence rates for SCCs of the eyelid, limbus or bulbar conjunctiva, and cornea treated with adjuvant radiation therapy were significantly different from those for SCCs treated without adjuvant radiation therapy. The most frequently represented anatomic site for ocular and adnexal SCCs was the eyelid (28.7%). Coat color, breed, and the interaction of age and breed had a significant effect on tumor recurrence regardless of treatment type and anatomic location.

Conclusions and Clinical Relevance—Results indicated that ocular and adnexal SCCs treated with adjuvant radiation therapy had a significantly lower recurrence rate, compared with SCCs treated without adjuvant radiation therapy, independent of anatomic location. (J Am Vet Med Assoc 2004;225:1733–1738)

Squamous cell carcinoma (SCC) is the most common tumor of the eye and adnexa in horses,[12] and the second most common tumor of horses.[3,5,8] An increased prevalence for ocular and adnexal SCC is reported in draft horse breeds,[5] Appaloosas,[6] Paint Horses, Thoroughbreds, and Quarter Horses.[1,4] A predisposition for the development of ocular and adnexal SCC has been reported in geldings.[6,7] Increased exposure to UV light is believed to be a risk factor for the development of ocular and adnexal SCC in light-colored horses and those with nonpigmented skin surfaces. Horses exposed to high-intensity solar radiation for a long duration have a high frequency of ocular and adnexal SCC, regardless of coat color. This suggests an actinic solar response in the pathogenesis of SCC.[6,10]

Treatment of ocular and adnexal SCC with and without adjuvant radiation therapy has been reported. Types of treatment without adjuvant radiation therapy include excision,[11,12] cryotherapy,[13-16] radiofrequency hyperthermia,[17,18] immunotherapy,[18,19] chemotherapy with cisplatin,[20] and carbon dioxide laser ablation.[21] Treatment with adjuvant radiation therapy includes use of strontium 90 (Sr90),[8,22-23] cobalt 60 (Co60),[24] gold 198,[25,26] iridium 192 (Ir192),[27,28] cesium 137,[18,24] iodine 125 (I125),[29,30] and radon 222 (Rn222).[31]

Overall survival rates of horses with ocular or adnexal SCC treated with and without adjuvant radiation therapy have been previously reported.[32] In that study, recurrence rates of SCCs were only determined for individual types of treatment; use of treatments with and without adjuvant radiation therapy was not specifically compared. A second study[33] compared tumor recurrence after treatment with and without adjuvant radiation therapy; however, the effects of anatomic location and treatment on rate of recurrence were not compared. The purpose of the study reported here was to determine the effects of treatment with and without adjuvant radiation therapy on recurrence of ocular and adnexal SCC at specific anatomic locations in horses.

Criteria for Selection of Cases

Medical records from the veterinary teaching hospital at the University of Georgia College of Veterinary Medicine were searched, and records of horses with histologically confirmed ocular and adnexal SCC evaluated from 1985 to 2002 were identified. Horses that did not receive treatment for ocular or adnexal SCC were excluded from the study.

Procedures

Details obtained from the medical records included sex, breed, age, number of lesions, location of the ocular...
or adnexal SCC, and types of treatment administered.

Two treatment groups determined by recurrence of SCCs treated with and without adjuvant radiation therapy were established. All SCCs treated with radiation therapy were also treated with cytoreductive surgery. Recurrence of SCCs as determined by histologic examination of biopsy specimens and treatment of recurring SCCs was also recorded. Complications were recorded for each type of treatment. Squamous cell carcinomas at sites other than ocular or adnexal sites were recorded. Evidence of metastatic or invasive SCCs as diagnosed via necropsy was recorded.

**Statistical analyses**—Data were analyzed by use of a logistic regression model with 2 discrete variables, no tumor recurrence and tumor recurrence. A likelihood ratio was used to test treatments with and without adjuvant radiation therapy. A 2-way ANOVA was used to test differences in mean time of follow-up between treatments with and without adjuvant radiation therapy. Values of \( P < 0.05 \) were considered significant.

**Results**

A total of 17,214 horses were evaluated at the veterinary teaching hospital from 1985 to 2002, of which 7,354 (42.7%) were mares, 6,673 (38.2%) were geldings, and 3,100 (18.4%) were stallions. The sex of 87 (0.5%) horses was not recorded. One hundred horses met the search criteria. Ninety-one of those horses were treated for ocular or adnexal SCC. A total of 231 treatments were performed on 157 SCCs, including 172 treatments without adjuvant radiation therapy and 59 treatments with adjuvant radiation therapy. The follow-up period for both treatment groups ranged from 10 to 3,082 days (mean, 420.9 days). The mean follow-up period for ocular or adnexal SCC that did not receive adjuvant radiation therapy was 438.3 and 464.9 days, respectively. There was no significant difference in the follow-up period between the 2 groups (\( P = 0.881 \)). The mean follow-up period for ocular or adnexal SCCs that recurred in both treatment groups was 313.9 days. The mean follow-up period for ocular or adnexal SCCs that did not recur in both treatment groups was 730 days. The mean follow-up period was significantly greater for ocular or adnexal SCCs that did not recur, compared with ocular or adnexal SCCs that recurred in both treatment groups (\( P < 0.002 \)).

The age of all horses ranged from 2.4 to 26.7 years (mean, 12.1 years). There were 56 (31.5%) geldings, 27 (29.7%) mares, and 6 (6.6%) stallions; the sex of 2 (2.2%) horses was not recorded. Quarter Horse was the most common breed (26.4% [n = 24]); other breeds included Appaloosa (17.6% [16]), Paint Horse (12.1% [11]), Tennessee Walking Horse (9.9% [9]), Belgian (6.6% [6]), mixed or crossbreed (6.6% [6]), Thoroughbred (5.5% [5]), Morgan (3.3% [3]), Pony of the Americas (3.3% [3]), Arabian (2.2% [2]), Clydesdale (2.2% [2]), Paso Fino (1.1% [1]), Standardbred (1), Racking Horse (1), and Missouri Fox Trotter (1). The most common coat color was chestnut or sorrel (39.5% [36]), followed by brown or brown and white paint (11% [10]), white (11% [10]), red roan (8.8% [8]), gray (7.7% [7]), bay (6.6% [6]), palomino or blonde (6.6% [6]), and black or black and white paint. The coat color of 5 (3.5%) horses was not recorded.

Six anatomic tumor locations were identified: eyelid (28.7% [n = 45]), third eyelid (26.1% [41]), cornea (19.1% [30]), limbus (the junction of the cornea and sclera) or bulbar conjunctiva (17.8% [28]), palpebral conjunctiva (7.6% [12]), and orbit (0.64% [1]). Eighteen (19.8%) horses had bilateral ocular or adnexal SCC. Invasive SCC involving the bony orbit, maxillary sinus, frontal sinus, or nasal turbinates was diagnosed in 4.4% (n = 4) of the horses. Squamous cell carcinoma of the nares or perianal regions was diagnosed in 2.2% (n = 2) of the horses prior to referral. Both of those horses had been treated by the referring veterinarian, and recurrence of the SCC had not been detected at nonocular sites during the study. Squamous cell carcinoma at sites other than the eyes or adnexa was not diagnosed in any horse after referral. Necropsies were performed on 4.4% (n = 4) of the horses, and no metastatic disease was found.

Single and combined treatments were used to treat horses. Seven types of treatment were allocated to the 2 groups. Horses that did not receive adjuvant radiation therapy were treated with enucleation or exenteration, ≥ 1 cytoreductive surgical procedure, surgery and cryospray (1 mg/cm², q 2 weeks for 4 treatments) injected into the tumor, or ≥ 1 surgical procedure followed by ≥ 1 cryotherapy treatment. Horses that received adjuvant radiation therapy were treated with ≥ 1 cytoreductive surgical procedure followed by ≥ 1 treatment with Ir¹⁹², Co⁶⁰, Sr⁹⁰, or cryotherapy and Sr⁹⁰. All cryotherapies were performed by use of a double freeze-thaw method. The dose of Ir¹⁹² implanted into the tumor ranged from 58 to 65 Gy. The implants were removed after 5 to 13 days depending on the intended dose to be delivered. Strontium 90 was administered as a single dose of 80 to 100 Gy to SCCs of the cornea, 100 to 120 Gy to SCCs of the conjunctiva, and 120 to 200 Gy to SCCs of the eyelid. The dose of Co⁶⁰ that was administered ranged from 32 to 36 Gy divided into 4 weekly treatments.

Overall, 41.3% (n = 96) of the treatment outcomes were lost to follow-up. Of the 172 treatments without adjuvant radiation therapy, 34.9% (n = 60) were lost to follow-up. Of the 59 treatments with adjuvant radiation therapy, 61.0% (n = 36) were lost to follow-up (Table 1). The overall recurrence rate in both treatment groups was 35.9% (n = 83 SCCs), regardless of treatment. The anatomic site with the highest recurrence rate, regardless of treatment group, was the limbus or bulbar conjunctiva (45.7% [21/46]), followed by the third eyelid (33.3% [20/60]), eyelid (39.0% [27/69]), cornea (27.9% [12/43]), and palpebral conjunctiva (23% [3/13]).

There was a significant (\( P < 0.001 \)) difference in recurrence rates of ocular and adnexal SCCs between the 2 treatment groups, independent of anatomic location. Squamous cell carcinomas that were treated without adjuvant radiation therapy had a recurrence rate of 44.1% (n = 76), whereas those treated with adjuvant radiation therapy had a recurrence rate of 11.9% (7). There was a significant difference in recurrence rate between the 2 treatment groups for SCCs located on the eyelid, cornea, and limbus or bulbar conjunctiva (Table 2).
There was no significant difference in the recurrence rate of SCCs located on the third eyelid ($P = 0.158$). Because of inadequate sample size, the recurrence rates of SCCs located on the palpebral conjunctiva were not analyzed statistically.

Squamous cell carcinomas of the eyelid received 69 treatments. The recurrence rate of tumors that had been treated without adjuvant radiation therapy was significantly ($P = 0.006$) different from that of tumors that had been treated with adjuvant radiation therapy. Tumors that had been treated without adjuvant radiation therapy had a 54% (27/50) recurrence rate, whereas tumors that had been treated with adjuvant radiation therapy ($n = 19$) did not recur during the study period. Two tumors of the eyelid that were treated with $^{192}$Ir implants had complications. Both eyelids developed secondary infection, blepharitis, and skin depigmentation after treatment with $^{192}$Ir.

Squamous cell carcinomas of the cornea received 43 treatments. The recurrence rate of tumors that had been treated without adjuvant radiation therapy was significantly ($P = 0.006$) different from that of tumors that had been treated with adjuvant radiation therapy. Tumors that had been treated without adjuvant radiation therapy had a 34% (27/80) recurrence rate, whereas tumors that had been treated with adjuvant radiation therapy ($n = 19$) did not recur during the study period. Two tumors of the cornea that were treated with $^{192}$Ir implants had complications. Both tumors developed secondary infection, blepharitis, and skin depigmentation after treatment with $^{192}$Ir.
Squamous cell carcinomas of the limbus or bulbar conjunctiva received 46 treatments. The recurrence rate of tumors that had been treated without adjuvant radiation therapy was significantly \((P = 0.008)\) different from that of tumors that had been treated with adjuvant radiation therapy. Tumors that had been treated without adjuvant radiation therapy had a 51.5\% (17/33) recurrence rate, whereas tumors that had been treated with adjuvant radiation therapy had a 30.8\% (4/13) recurrence rate.

Squamous cell carcinomas of the third eyelid received 60 treatments. There was no significant difference in the recurrence rate between the 2 treatment groups \((P = 0.158)\). Tumors that had been treated without adjuvant radiation therapy had a 40\% (18/45) recurrence rate; tumors that had been treated with adjuvant radiation therapy had a 13.3\% (2/15) recurrence rate.

Squamous cell carcinomas at the palpebral conjunctiva received 13 treatments. Tumors that had been treated without adjuvant radiation therapy had a 20\% (2/10) recurrence rate; tumors that had been treated with adjuvant radiation therapy had a 33.3\% (1/3) recurrence rate.

The overall recurrence rate of ocular and adnexal SCCs for horses 5 to 10 (30/84), 10 to 15 (26/73), and 15 to 20 years old (22/60) was 36\%, regardless of treatment type. The recurrence rate of ocular and adnexal SCCs for horses 20 to 25 years (1/2) was 50\%. Geldings (34.3\% [49/143]), Thoroughbreds (61.5\% [81/133]), and bay coat color (56\% [14/25]) had the highest recurrence rates for ocular and adnexal SCCs. Coat color \((P = 0.028)\), breed \((P = 0.044)\), and interaction of age and breed \((P < 0.001)\) had a significant effect on tumor recurrence, regardless of treatment type and anatomic location. Coat color had a significant \((P = 0.003)\) effect on tumor recurrence on the cornea, regardless of treatment type.

**Discussion**

Results of our study indicated that ocular and adnexal SCCs treated with adjuvant radiation therapy had a lower recurrence rate than those that were treated without adjuvant radiation therapy. Treatments with adjuvant radiation therapy resulted in significantly lower recurrence rates of SCCs on the cornea, limbus or bulbar conjunctiva, and eyelid than treatments without adjuvant radiation therapy. Treatments without adjuvant radiation therapy resulted in a higher recurrence rate of SCCs located on the third eyelid, compared with the recurrence rate of SCCs in this location after adjuvant radiation therapy, although this difference was not significant. The lack of significant results may have been due to the low number of SCCs of the third eyelid that received adjuvant radiation therapy.

We examined recurrence rates rather than progression free survival time or overall survival rate. The recurrence rate of SCC was determined by gross appearance and histologic confirmation. This approach provides a more accurate determination of SCC recurrence than overall survival rate or progression free survival time. Overall survival rate would overestimate the number of the tumors that had not recurred because SCC is a locally invasive tumor with a low rate of metastasis. Dunn et al and Schwink compared overall survival rates of horses after treatment with and without adjuvant radiation therapy; neither found an association between survival and type of treatment. A true progression free survival time for each case was difficult to determine because of the lack of owner compliance with returning horses for follow-up examinations after treatment.

To the authors' knowledge, the study reported here is the only study that has specifically examined whether there was a significant difference between recurrence rates of ocular and adnexal SCCs at specific anatomic locations in horses after treatment with and without adjuvant radiation therapy. A recurrence rate of 11.9\% for ocular and adnexal SCCs after treatment with adjuvant radiation therapy across all anatomic locations is comparable to that reported in other studies. Rehbun and Frauenfelder et al reported recurrence rates of 16.7\% and 11\%, respectively, after treatment with adjuvant radiation therapy using Sr\(^{90}\) \((250 \text{ Gy})\) alone for ocular SCCs in horses. In our study, adjuvant radiation therapy with Sr\(^{90}\) resulted in a 15.1\% recurrence rate independent of anatomic location. The low recurrence rate reported by Frauenfelder et al may have been due to use of a higher dose of Sr\(^{90}\) radiation \((250 \text{ Gy})\) than used in our study. A smaller number of horses were treated \((n = 91)\) in that study, compared with our study. Results of 1 study in horses examining use of adjuvant radiation therapy with Ir\(^{192}\) for ocular and adnexal SCC reported a recurrence rate of 18.2\%, compared with a 10.5\% recurrence rate for adjuvant Ir\(^{192}\) treatment independent of anatomic location in our study.

In our study, horses receiving treatments without adjuvant radiation therapy had a higher recurrence rate \((44.1\%)\) of ocular and adnexal SCC than those receiving adjuvant radiation therapy \((11.9\%)\). Surgery alone had the highest recurrence rate at all anatomic locations, except the eyelid. King et al reported a higher recurrence rate for surgery and cryotherapy \((66.7\%)\), compared with surgery alone \((44.4\%)\), independent of anatomic location; however, in that study, only 2 horses were treated with surgery followed by cryotherapy, whereas 18 horses were treated with surgery alone.

Differences in recurrence rates for ocular and adnexal SCC at specific anatomic locations among studies may be affected by treatment options that are available at that location, which are dependent on size and depth of the tumor, differences in doses among studies, and differences in criteria for choosing treatment modalities. The absence of exact tumor locations, measurements, and radiation dosages used in other studies may have been due to the low number of SCCs of the third eyelid that received adjuvant radiation therapy.
studies makes comparison of recurrence rates among studies difficult.

Radiation therapy has specific indications and limitations for its use. Strontium 90 is only indicated for superficial tumors that are or have been debulked to a tumor depth ≤ 3 mm because 80% of the radiation dose is absorbed in the first 2 mm of tumor. A more appropriate treatment for tumors > 3 mm is Ir¹⁹² interstitial implants that have a radiation penetration depth of approximately 1 to 1.5 cm. Because of the delivery mechanism, this treatment is most often used for eyelid and periorcular tumors. Cobalt 60 teletherapy has a large penetration depth and is used for more invasive tumors, particularly as a palliative therapy. Potential complications should also be considered when choosing a treatment type. Theon and Pascoe reported secondary complications of corneal and palpebral ulcerations in 10.3% of horses treated with Ir¹⁹². Doses of Ir¹⁹² used in the study reported here caused minimal complications such as skin and hair depigmentation, secondary infection, and blepharitis. Overall, the risk associated with radiation therapy using Sr⁹⁰ is low, making its use for a neoplastic disease process justifiable. There has been only 1 report of Sr⁹⁰-induced keratopathy in a horse. This diagnosis was determined on the basis of the late onset in nature of the disease, exclusion of other disease processes, and consistent histologic findings. Two factors may have contributed to the keratopathy in this horse: a large keratectomy site (20 × 16 mm) and the high dose of Sr⁹⁰ (200 Gy) that was administered. In humans, Sr⁹⁰ has been used for pterygia treatment. Complications with use of Sr⁹⁰ in humans include telangiectasia of the conjunctiva, punctate corneal ulceration, corneal edema, corneal neovascularization and scarring, iris atrophy, symblepharon, and ptosis. Similar complications secondary to use of Sr⁹⁰ include cataracts, endophthalmitis, and scleral or corneal thinning or rupture. Similar complications have not been reported in horses and were not observed in our study. In the study reported here, the mean follow-up period after treatments was 420.9 days. Of the treatment group outcomes, 61% of tumors that had been treated with adjuvant radiation therapy were lost to follow-up and 34.9% of tumors that had been treated without adjuvant radiation therapy were lost to follow-up. The reason for this difference is unknown. The incidence of tumor recurrence in horses treated with adjuvant radiation therapy may have been lower than that in horses treated without adjuvant radiation therapy; therefore, follow-up examinations may not have been performed because of owner noncompliance. In our study, the mean follow-up period was significantly greater for tumors that did not recur, compared with tumors that did recur. This adds validity to our results, which indicated lower recurrence rates for ocular and adnexal SCC that received adjuvant radiation therapy, compared with those that were treated without adjuvant radiation therapy. It is also possible that the owners did not return horses for follow-up examinations because of the increased costs associated with radiation therapy.

Similar to results of other studies, the most prevalent tumor location for ocular and adnexal SCC in horses was the eyelid followed by the third eyelid, cornea, limbus or bulbar conjunctiva, palpebral conjunctiva, and orbit. In our study, the recurrence rate of 35.9%, independent of treatment group and tumor site, was similar to that in a previous study; however, SCCs treated with adjuvant radiation therapy had a significantly lower recurrence rate, compared with SCCs treated without adjuvant radiation therapy, independent of tumor location.

Bilateral ocular involvement was found in 19.8% of horses, which is similar to results of other studies. King et al and Lavach and Severin reported bilateral ocular involvement in 11.6% (n = 5) and 16.3% (8) of horses, respectively. Metastasis rates for ocular and adnexal SCC range from 0.3% to 18.6% in horses, respectively. In our study, necropsies were performed in only 4.4% (n = 4) of horses. This may account for the absence of documented metastatic disease; however, 4.4% of horses had invasive SCC extending into the surrounding periorbital tissues.

Horses with light coat colors or areas of skin hypopigmentation have a higher prevalence of ocular SCC secondary to an actinic solar response. Results of our study indicated that the most prevalent color of horses with ocular and adnexal SCC was sorrel or chestnut (39.5% [n = 36]). This suggests that dark-colored horses have a high prevalence of ocular and adnexal SCC, which contradicts results of previous studies; however, facial markings and the prevalence of periorbital hypopigmentation were not available retrospectively. The increased number of dark-colored horses with ocular and adnexal SCC in our study may have been associated with the breed distribution in the total hospital population at the veterinary teaching hospital.

The prevalence of ocular SCC is reported to be higher in draft horse breeds, Thoroughbreds, Quarter Horses, and Paint Horses. The increased prevalence of ocular and adnexal SCC in Quarter Horses at the veterinary teaching hospital may have been associated with the breed distribution in the total hospital population of horses. Quarter Horses (33.4% [n = 3,750]) were the most frequently examined breed in the overall hospital population of horses during the study.

Mean age of horses with ocular and adnexal SCC was 12.1 years, which is similar to results of other studies that report an age range of 8.0 to 11.8 years. The increased prevalence of ocular and adnexal SCC in geldings is also similar to results of other reports. From 1985 to 2002, 42.7% of horses evaluated at the teaching hospital were mares, 38.2% were geldings, and 18.4% were stallions; however, ocular and adnexal SCC was most frequently diagnosed in geldings (61.5%). Dugan et al and Lall proposed that sexually intact male and female cattle are significantly less likely to develop horn SCC because of increased circulating androgens and estrogens than castrated males. The difference in these hormones between castrated and sexually intact animals may provide an explanation for the increased frequency of ocular and adnexal SCC in geldings.

**SAS, version 8, SAS Institute Inc, Cary, NC.**
References


