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CASE REPORT

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Outcome of external beam radiotherapy for treatment of noncutaneous tumors of the head in horses: 32 cases (1999-2015)

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Abstract

Background: The long-term outcomes of external beam radiotherapy for treatment of noncutaneous tumors of the head in horses is unknown.

Objective: To report the long-term outcomes for treatment of noncutaneous tumors of the head of horses, and report short and long-term clinical adverse effects.

Animals: Thirty-two horses treated in 2 referral hospitals.

Methods: In this retrospective study, medical records of horses receiving radiation therapy for noncutaneous tumors between 1999 and 2015 were reviewed. Signalment, tumor type, treatment protocol, tumor control duration, and survival were recorded. Kaplan-Meier survival curves were generated for overall survival (OS), by tumor type and location, and compared using Log-rank tests, and treatment protocol adherence.

Results: Follow-up ranged from 2 to 145 months (median 14 months). Of 32 horses, 16 (50%) were alive at the time of reporting, with complete tumor response occurring in 12 (38%). Horses with tumors of the maxilla/nasal cavity had significantly shorter median OS compared to horses with tumors in other locations (21 months vs 145 months) (P = .06). Adverse effects resulting from the tumor or the therapy occurred in 20/32 (63%). The occurrence of major adverse effects and delays in treatment protocol were not significantly associated with median survival estimates.

Conclusions and Clinical Importance: External beam radiotherapy can be used to treat a variety of noncutaneous tumors of the head of horses. Adverse effects related to radiotherapy or the tumor are common.

KEYWORDS

complication, remission, teletherapy, tumor

Abbreviations: CR, complete response; PR, partial response.

1 | INTRODUCTION

Tumors of the head of horses, including the nasal and paranasal sinuses, maxilla, and mandible, are often difficult to treat with surgery alone, and can have high rates of recurrence. Squamous cell carcinoma, adenocarcinoma, soft tissue sarcoma, lymphosarcoma, osteoma, osteosarcoma, and ameloblastic odontoma are described as sinonasal tumors in horses.[1] Surgical treatment of paranasal sinus tumors in horses does not result in long-term remission.[2,3] Tumors of the mandible occur in horses, and although surgical treatment has been successful in some cases, extensive mandibulectomy might be needed.[4] In dogs with nasal tumors, external beam radiotherapy is considered the standard of care and has resulted in longer survival times compared to historical survival times for dogs treated with surgery and chemotherapy.[5,6] There are case reports that describe the use of external beam radiotherapy for the treatment of noncutaneous tumors of the head in horses with good results.[7-9]

Important factors influencing the success of radiation therapy are tumor volume, type and location.[10,11] For many tumor types, tumor volume is inversely proportional to the probability of local control achieved with external beam radiotherapy; however, this is not the case with all tumor types.[12] Tumor type affects the success rate of external beam radiotherapy and influences the selection of radiation protocol, and different total radiation doses are required to control different tumor types.[12] Tumor location plays an important role in selection of radiation treatment delivery (brachytherapy vs external beam radiotherapy; photons vs electrons) and the total dose administered. Radiation therapy damages DNA, affecting both normal and tumor cells. The damage created in normal cells can lead to adverse effects. Radiation might not be suitable for treatment of tumors at all locations, and there are negative effects of radiation therapy for tissues in the path of the beam.[12] Well-being of horses plays an important role in determining treatment possibilities, therefore, the stage of the tumor and any comorbidities should be considered when planning therapy.[12]

The purpose of this student was to document the outcome of radiation therapy of the head in horses for a variety of tumor types, and no studies and to the acute and late effects of radiotherapy with long-term follow-up data in horses. The purpose of this study was to provide a retrospective analysis of the treatment of noncutaneous neoplasia of the equine head using external beam radiotherapy. We hypothesized that tumor type and tumor location would affect survival, with carcinomas and nasomaxillary tumors having a worse prognosis for survival.

2 | MATERIALS AND METHODS

2.1 | Case selection criteria and medical records review

Computerized medical records from JT Vaughan Large Animal Hospital, Auburn University and Ohio State Veterinary Medical Center, The Ohio State University between January 1999 and December 2015, were reviewed by 2 authors (Alex Gillen and Margaret Mudge). Records were retrieved using digital codes or keyword searches including the words "radiation," "teletherapy," and "linear accelerator." Horses were considered for inclusion in the study if they had a neoplastic mass diagnosed by clinical examination and either histology or cytology, and underwent radiation therapy using a linear accelerator in either of the 2 hospitals. Horses with cutaneous tumors and tumors not localized to the head were excluded. Recorded details included the signalment of the horse, diagnostic procedures, tumor type, tumor location, previous treatment including debulking surgery or excision, anesthetic protocol, radiation therapy protocol, adjunctive therapy, and any acute adverse effects that occurred during treatment.

2.2 | Radiation therapy

Radiation therapy was delivered to all horses using a linear accelerator (Siemens Mevatron, Seimens Medical Laboratories, Walnut Creek, California) at the JT Vaughan Large Animal Teaching Hospital, Auburn University and The Ohio State University Veterinary Medical Center. Depending on tumor location, radiation delivery was achieved with 6MV photons using a single field, parallel opposed, 3-field, or isocentric arc technique, or with a single field of 7 or 12 MeV electrons based on tumor location and at the discretion of the radiation oncologist (GA, EG). When required, a tissue-equivalent bolus of varying thickness was used to achieve appropriate depth dose distribution. Radiation therapy protocol was determined by tumor type and owner and clinician preference. Treatment planning was achieved using either manual calculations or 3D plans were made using Oncentra treatment planning system, based on CT scans (Nucletron BV, Veenendaal, The Netherlands) (hospitals A and B).

Horses were anesthetized for all treatments and positioned to achieve a source to surface distance (SSD) of 100 cm, in all cases, for electron therapy, or a source to axis distance (SAD) for photons. Positioning for treatment was verified either by visual inspection or MV portal imaging. Field size varied and was achieved with varying size electron applicator cones (5 cm radius; 10 × 10 cm, 15 × 15 cm, and 20 × 20 cm square). The electron field was shaped using the applicator cones described, and the photon field sizes were defined by the X-Y collimator jaws. Where appropriate, lead blocks were inserted in a tray for photon beams to block normal structures. Fractions were administered either weekly for hypofractionated protocols, or on a Monday, Wednesday, Friday basis for finely fractionated protocols. Horses not completing their intended treatment protocol were identified.

2.3 | Anesthetic protocol

Horses were sedated with xylazine hydrochloride (0.05 mg/kg, IV) prior to induction. Ketamine (2.2 mg/kg, IV) and diazepam or midazolam (0.02 mg/kg, IV) were used for induction. The initial anesthetic episode for all horses was maintained with inhaled isoflurane delivered via an endotracheal tube. Subsequent anesthetic episodes were maintained using intravenous triple drip (5% guaifenesin solution in 1 L 0.9% sodium chloride solution with 1000 mg ketamine and 500 mg xylazine) at a dose of 2 mL/kg or to effect at hospital A; or intravenous triple drip or inhaled isoflurane or sevoflurane at hospital B. Horses at Auburn University were provided endotracheal intubation during the first 2 anesthetic episodes, whereas the airway was protected with an endotracheal tube for all horses at The Ohio State University for all anesthetic episodes.

2.4 | Follow-up information

Long-term follow-up for horses from each hospital was obtained via a telephone questionnaire conducted with the owner or trainer by 2 surgeons (Alex Gillen and Margaret Mudge). Clients were asked, via a questionnaire, if the tumor regressed completely, partially, remained the same or increased in size. In addition, clients were asked at what point, if any, recurrence occurred. Clients were asked if the horse remained alive and if not, when the horse died or was euthanized, and for what reason death or euthanasia occurred. For cases treated within the last 5 years, follow-up was performed as part of patient care. Follow-up in cases treated more than 5 years previously was performed for the purpose of this study. Initial follow-up was performed by the primary care veterinarian; however, it was decided to contact the owners regarding the horses' status due to the duration of the majority of the follow-up. Some horses which experienced complications or required further external beam radiation therapy were reevaluated and additional treatment provided. All complications related to anesthesia, the tumor itself or external beam radiotherapy were included, with the exception of white hair growth and alopecia as these were anticipated and not expected to impact the quality of life of the horse. Horses were deemed to have a complete response (CR) if the tumor and its associated clinical signs abated and were not apparent for the duration of the follow-up. Horses were deemed to exhibit a partial response if some improvement in either tumor size or clinical signs occurred for any duration. Recurrence of the tumor described an initial regression of the tumor, followed by a regrowth.

2.5 | Statistical analysis

Horse and disease characteristics, treatment modality, follow-up time (time from diagnosis to end of follow-up) and outcomes were summarized overall and by institution. Means and standard deviations or medians and range were calculated for continuous variables, and percentages were calculated for categorical variables. Kaplan-Meier methods were used to estimate the median OS and progression free survival (PFS), both overall and by subgroups, where there were sufficient number of events. Progression free survival was defined as the duration after therapy during which the tumor was no longer evident. The end of the progression free period was defined as recurrence of the tumor, death of the horse, or the end of follow-up. Kaplan-Meier survival curves were generated for OS by tumor location and tumor type. OS was defined as the time from the date of diagnosis to the date of death or euthanasia. Horses were censored at the date they were last recorded as being alive. PFS was defined as the time from the end of initial treatment to any recurrence of clinical signs being noted by the owner, or until death occurred, regardless of the cause. The Log-rank test was used to compare Kaplan-Meier curves for tumor location and tumor type. All statistical analyses were performed with SAS 9.4 (SAS Institute, Inc, Cary, North Carolina) and Stata 16.0 (StataCorp, College Station, Texas). Significance was determined by P-value <.05.

3 | RESULTS

3.1 | Signalment and presentation

Thirty-two horses meeting the inclusion criteria, with follow-up information, were identified (12 mares, 18 castrated males). The mean age was 13.0 years (SD 7.32; range, 5 months to 27 years). Breeds were: Thoroughbred (6), American Quarter Horse (4), Warmblood (4), Tennessee Walking Horse (3), American Paint Horse (3), Standardbred (2), Morgan (2), Arabian (1), Pony (1), Irish Draught (1), Percheron (1), Saddlebred (1), Lusitano (1), Belgian (1), and Dutch Harness (1).

Tumor types consisted of squamous cell carcinoma (11), ossifying fibroma (8), lymphoma (2), fibrosarcoma (3), carcinoma (other than squamous cell) (3), osteosarcoma (2), ameloblastoma (1), myxosarcoma (1), and melanoma (1). All 5 of the horses less than or equal to 2 years of age had ossifying fibroma compared to 9% of the horses older than 2 years.

3.2 | Therapeutic protocols

Horses underwent definitive intent therapy (n = 27 available for follow-up) with 45 to 54 Gy per tumor site, delivered over 9 to 12 fractions of 4 to 5 Gy per fraction per tumor site. Nine horses underwent hypofractionated protocols consisting of 4 fractions of 6 to 8 Gy (total dose 24-32 Gy). The remaining cases underwent finely fractionated protocols consisting of 9 to 12 treatments (on a Monday, Wednesday, Friday basis) of less than or equal to 4.8 Gy. The total dose per tumor site administered to horses ranged from 34 to 54 Gy, with the median and mean being 44 and 40.5 Gy, respectively. The field size data was available for 24 cases at 1 hospital. The data was normally distributed. Mean field size was 242 cm^2 (range, 42-625 cm^2; SD 153 cm^2).

3.3 | Oncologic outcome

The median overall follow-up time for horses in this study was 13 months and ranged from 2 months to 145 months. Although the range of follow-up was similar between the institutions, the median follow-up for institute A was 49.0 months but was only 13.0 months for institution B. Sixteen (50%) of horses were alive at the time of follow-up with complete tumor response occurring in 12 (38%) of cases. The median OS was 25 months (95% CI: 14-145 months). Four (12%) horses were alive with tumor recurrence at the time of follow-up. Eight (25%) horses were euthanized due to a lack of tumor response or tumor recurrence and 5 (15%) horses were euthanized due to unrelated issues (Figure 1). The median time to recurrence, in cases where recurrence occurred, was 3.5 months (range, 2-14 months).

Three horses had treatment delays (longer intervals between treatments than originally intended) in their treatment protocol of 1 to 2 weeks due to 1 or more of: pyrexia (2), pharyngitis (1), colic (1), respiratory difficulties (1) or soreness of the surgery site (1); 2 horses had 2 of the above complications. The duration of the delay was determined by clinician preference. Treatment was resumed when the horse was determined fit to undergo general anesthesia and receive further treatment. Nine horses underwent hypofractionated treatment (4 × 6-8 Gy); of these, 4 were based on tumor type (hence receiving definitive intent therapy), and the remainder (5) were based on owners' financial restrictions and the occurrence of complications (these horses received nondefinitive intent therapy). When nondefinitive intent horses were considered, horses undergoing hypofractionated protocols had a median OS of 7.5 months (95% CI: 1.0-21.8 months). Progression free survival in horses receiving a hypofractionated protocols ranged from 3 to 42 months; however, 1 horse showed no tumor resolution. Seven horses had treatments limited by complications or financial restrictions; these horses received fewer treatments than intended.

3.4 | Oncologic outcome by tumor type

Squamous cell carcinoma was the most common tumor treated in this study, representing 11 (34%) out of 32 cases. Four horses were treated using a coarsely fractionated (4 × 6-8 Gy) protocol. Three (27%) of the cases (all of which received finely fractionated protocols [9-12 × 4-4.5 Gy]) had complete tumor response (CR), with no recurrence during the follow-up time period. The remaining 8 (72%) cases had evidence of recurrence and 6 (55%) of these horses were ultimately euthanized due to the tumor. Progression-free survival ranged from 2 to 48 months and OS ranged from 2 to 48 months (median 6 months; 95% CI: 4.36-19.64). Three cases remained in CR and 4 cases were alive at the time of follow-up. Two horses received intratumor carboplatin in addition to radiotherapy, and they remained progression free for the duration of follow-up (6 and 48 months). Four horses received debulking surgery prior to radiation therapy. Three horses had recurrence (2, 3, and 13 months after therapy). The remaining horse had regression but the tumor remained and resulted in euthanasia 5 months after treatment.

Ossifying fibroma (n = 8) was the second most common tumor treated. Seven cases were treated with a finely fractionated (10-12 × 4-4.5 Gy) protocol. One received a hypofractionated (4 × 6 Gy) protocol. Of these cases, 6 (75.0%) cases, including the case receiving a hypofractionated protocol, obtained complete resolution of the tumor with no recurrence. One of these horses were euthanized 25 months after therapy for unrelated causes. Four cases exhibited a complete response and remained alive for the duration of follow-up. One case, a 6 month-old foal, had no signs of tumor recurrence, but was euthanized 2 months after therapy due to pneumonia. Response times and OS follow-up ranged from 2 to 132 months. The majority (7 out of 8) of the ossifying fibromas were located on the mandible or maxilla; however, 1 case with successful tumor control was located in the nasal passages. Surgical debulking/rostral mandibulectomy was performed in 3 cases. Two cases exhibited PFS for 2 and 18 months (complete response was present in both cases for the duration of follow-up; however, the foal with PFS for 2 months died due to pneumonia), whereas 1 tumor recurred after 7 months.

Of the 2 cases of lymphoma, 1 tumor, located at the larynx, remained in CR for the duration of the study (104 months) and the other tumor, located in the nasal passage, was alive 12 months after treatment; however, a recurrence of the mass occurred at 8 months posttreatment. The case remaining progression-free was treated with a hypofractionated (4 × 8 Gy) protocol and surgical debulking within 1 month of treatment.

Follow-up was available for 3 horses with fibrosarcoma. One horse was euthanized immediately after treatment due to a lack of response; this horse underwent a hypofractionated (4 × 8 Gy)

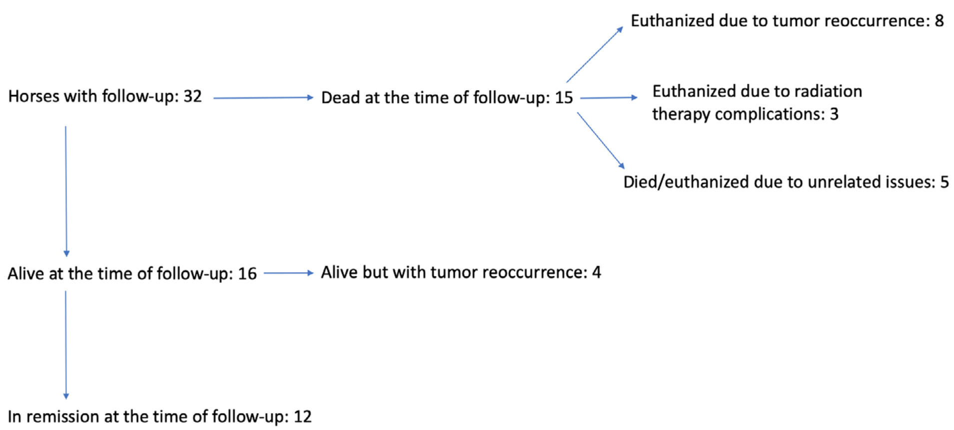

FIGURE 1 A flow chart exhibiting the number of patients showed a complete response, a recurrence, or no response at all to external beam radiotherapy

protocol. One of the remaining 2 horses (both undergoing finely fractionated protocols [11-12 × 4-4.4 Gy]) with a fibrosarcoma located on the maxilla remained in partial response (PR) for 7 months and was euthanized due to recurrence of the tumor. The second case with a fibrosarcoma located on the mandible had stable disease after therapy (PR) and was alive at follow-up (13 months). Two cases of osteosarcoma were available for follow-up. One horse with osteosarcoma located in the nasal passage had PFS for 21 months; this horse underwent surgical debulking within 1 month of external beam radiation therapy. A second horse with osteosarcoma of the maxilla was in CR 14 months after treatment. Both horses received finely fractionated protocols (12 × 4.3 Gy) and had no signs of recurrence for the duration of follow-up.

Three horses with carcinoma (other than squamous cell carcinoma) were treated. All horses underwent a finely fractionated protocols (10-12 × 4-4.8 Gy). One of these cases, located on the mandible, exhibited a complete response after treatment and was alive 72 months after therapy. A second horse died 3 months following therapy due to a medication reaction, and the third horse remained alive and progression free 9 months after therapy. The horse that died at 3 months after treatment had signs of recurrence revealed by necropsy. The 2 successful cases had carcinoma located on the mandible and both underwent debulking surgery within 1 month prior to treatment.

3.5 | Oncologic outcome by location

The OS curves for horses with tumors of the maxilla/nasal region differed with lower survival times in the maxilla/nasal region compared to horses with tumors at other locations (*P* = .06) (Figure 2). Although the median survival time was 21 months for SCC/Carcinomas/Sarcomas compared to 133 months for other tumors, numbers in categories were small (20 sarcomas/carcinomas; 12 other tumors), and the survival curves were not significantly different (*P* = .48). One horse with SCC of the temporal region received a second course of radiation therapy 3 months after the initial treatment. No other treatments were administered after radiation therapy.

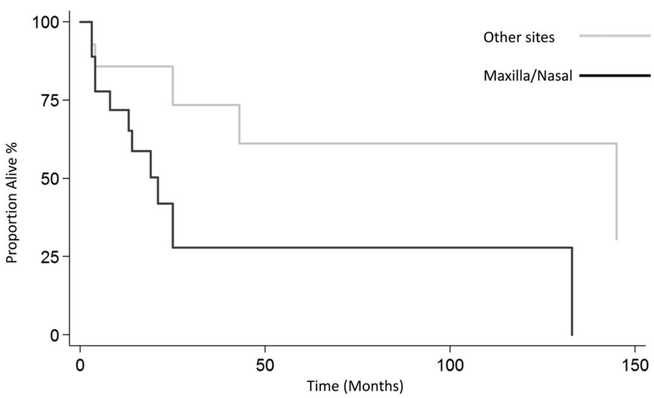

FIGURE 2 Kaplan-Meier survival estimate for horses with tumors involving the maxilla/nasal region vs horses with tumors involving other sites. The y-axis shows the proportion of patients remaining alive. The x-axis shows time in months. Patients with tumors located in the nasal and maxilla region had a significantly shorter median survival time than those with tumors in other locations (*P* = .06)

3.6 | Adjunctive therapies

Adjunctive therapy involving intratumoral carboplatin (1.5 mg/cm^3 of tissue) was performed in 2 horses with squamous cell carcinoma within 24 hours of commencement of the course of radiation therapy. Neither horse received more than 1 carboplatin treatment and both horses had CR. One of these horses had a squamous cell carcinoma of the left hemimandible and the horse was alive and in CR 48 months after treatment. The second horse had a squamous cell carcinoma of the right muzzle and mandible; the patient was alive and in CR 6 months after treatment.

3.7 | Adverse effects

Fifteen out of 32 (47%) horses had complications related to anesthesia, the presence of the tumor itself or radiation therapy (excluding the presence of leukotrichia and hair loss). Complications were categorized as either major or minor. Fourteen horses had major complications (44%) including 1 or more of: acute respiratory difficulty, thrombophlebitis, corneal ulceration, colic and trismus. Minor complications (9.4%) included 1 or more of redness or pain at the site of therapy, tooth loss due to regression of the tumor, and transient fever. When all complications were considered, 8 out of 15 (53%) horses with adverse effects were progression-free at the time of follow-up, whereas only 4 out of 17 (24%) horses who had no adverse effects were alive and with no signs of disease progression at the time of follow-up. When only major complications were considered, 7 out of 14 (50%) horses were progression-free at the time of follow-up, compared to 6 out of 18 (33%) horses who had no major complications. Only 1 case had a late (occurring more than 90 days after treatment) major complication. This horse underwent a finely fractionated protocol (12 × 4 Gy) and at 7 months, experienced respiratory difficulties which resulted in its euthanasia. The initial tumor evaluation was a fibrosarcoma located on the maxilla. The remaining 3 cases with respiratory difficulties had clinical signs during their first 1 to 2 months after treatment. Horses with trismus had clinical signs within 2 months of treatment and those with fever, pharyngitis, colic, leucopenia or thrombophlebitis all exhibited clinical signs during the course of treatment. Horses that had major complications had a mean total tumor dose of 42.7 Gy, and, horses that did not have a major complication had a mean total tumor dose of 40.4 Gy. It should be noted that the horse with the highest total tumor dose (54 Gy), developed trismus. Horses receiving total tumor doses of less than 32 Gy did not develop major complications.

4 | DISCUSSION

Results of the present study indicate that external beam radiotherapy might be used for treatment of a variety of noncutaneous tumors of the head of horses. Overall, durable complete tumor response with no tumor recurrence during the follow-up period occurred in 12 out of 32 horses. Although tumor type did not have a statistically significant association with survival, we identified variation among tumor types, with sustained CR in only 3 out of the 11 squamous cell carcinoma cases and in 6 of the 8 ossifying fibroma cases. Successful treatment of ossifying fibroma with radiation therapy is reported in the equine literature. Complete tumor response in a case of ossifying fibroma after treatment with cobalt 60, with a follow-up period of 3 years,[8] as well as a further successful case[9] has been documented. The reason for the success with this tumor type might be related to the fact that malignant transformation of ossifying fibromas is not reported in horses.[13]

Treatment of osteosarcoma was positive. Two horses were treated in this study and had complete resolution of the tumor. Osteosarcomas are typically aggressive and metastatic in nature and usually carry a poor prognosis regardless of the treatment method employed.[14] However, the 2 successful outcomes in this retrospective study suggest that radiation therapy might be a viable option in certain cases. Osteosarcoma biology varies with anatomic site in dogs.[15] Sinonasal osteosarcomas behave more like other potentially less aggressive sinonasal tumors compared to appendicular osteosarcomas which have a high tendency to metastasize.

The most common tumor type treated in our investigation was squamous cell carcinoma; however, durable tumor control in only 3 out of 11 cases compares poorly to other literature describing regression rates of 50% to 100% in horses.[7,16] A possible reason for this disparity includes the fact that the follow-up periods in both studies were shorter (4-24 months[16] and 2-6.5 years[7]) than the current investigation. The current study demonstrated that squamous cell carcinoma can recur up to 13 months after therapy. Delayed metastasis or delayed extension occurring in cases of squamous cell carcinoma occurs[17] with tumor recurrence observed 30 to 36 months after treatment.

Lymphoma (2 cases with follow-up) carried a good success with both cases achieving PFS for the duration of follow-up. Historically, there is a high success rate with this type of tumor, with a 100% long-term response described in 4 horses treated using radiation treatment,[18] and complete response in 2 horses treated with surgical debulking and treatment with 3 fractions of 3 Gy at 7-day intervals.[19,20] However, evidence in small animal species suggests that surgical debulking of lymphomatous tumors prior to radiation therapy might not be beneficial.[21]

Tumor location had an impact on median survival times, with shorter median survival in horses with tumors of the maxilla and nasal cavity. This might be related to respiratory compromise associated with tumors in these locations. It is also possible that tumors arising from the paranasal sinuses might have delayed detection, and result in treatment at a more advanced stage. The internal nature of these tumors also makes accurate localization and treatment more challenging, thereby increasing the risk of inaccurate dosing. The survival of dogs receiving radiation therapy for nasal tumors is also variable, possibly due to the large size of sinonasal tumors, and potential inherent radio-resistance.[22]

Overall, 12 of 32 horses experienced a major complication due to anesthesia, hospitalization, the tumor itself, or radiation therapy. Although 3 out of 32 horses had minor complications, many of which included soreness or swelling of the site and during follow-up owners did not express any dissatisfaction with the cosmesis of the treatment site, providing the tumor regressed. One horse had a major complication (respiratory difficulties) later than 3 months after treatment. The remaining horses developed clinical signs of complications either while in hospital or during their first 2 months after discharge. The authors suggest additional monitoring should be employed during this period. Five of the recorded adverse effects were related to anesthesia or hospitalization. Two of the horses had thrombophlebitis or swelling of the catheter site. All horses that had complications with the catheter site were patients that maintained a long-term catheter for the duration of treatment, consistent with the likelihood of thrombosis being directly correlated with the duration the catheter remains in situ.[23] Horses that received a new polyurethane catheter prior to each general anesthetic episode and had the catheter removed upon recovery did not have complications. Although use of multiple catheters is costly, the lack of thrombophlebitis using this method makes this worthy of consideration.

A common perception is that the number of anesthetic episodes undergone by horses undergoing radiation therapy can be an important factor in complications. However, recovery from anesthesia actually improves with repeated episodes.[24,25] In the current study, despite the incidence of thrombophlebitis and colic, there were no anesthesia related neuropathies, myopathies or injuries during the recovery period. The comparatively low numbers in this study, the short duration of anesthetic episodes and the minimal use of inhalant anesthesia are likely explanatory factors.[26]

This investigation also brought to light external beam radiotherapy-associated adverse effects not previously reported in horses. Two of the horses in the current study had pharyngitis which presented as hypersalivation. Both horses were intubated for their first 2 treatments but not for subsequent treatments. Pharyngitis occurred 14 to 21 days after the start of treatment. These horses had tumors located on the muzzle region and the left orbit. Both horses received similar doses to other horses in the study. One horse, with a SCC, received 8 Gy per fraction (32 Gy total dose), the second horse, with a SCC received 4 Gy per fraction (36 Gy) total dose. Pharyngitis occurs in dogs and cats undergoing radiation therapy due to inflammation resulting from the proximity of the beam to the pharynx.[27] This should be considered in horses with tumors of the head and neck, and possible treatment with modified diet and topical anti-inflammatories or analgesics could be used.[28] Two horses developed trismus at 2 and 5 months after treatment. Both horses received radiation therapy to the mandibular region. One horse, with lymphoma, received a hypofractionated protocol with 8 Gy per fraction (32 Gy total dose), the second horse, with an SCC received finely fractionated protocol with 4.5 Gy per fraction (54 Gy total dose; no horses received more than 8 Gy per fraction in this study). One of these cases resolved with manipulation under general anesthesia and administration of dexamethasone, flunixin meglumine and methocarbamol. However, the other case resulted in euthanasia due to lack of resolution. This complication occurs in humans after radiation therapy.[29] Although rare, it is important to inform owners of this possible complication. The horses afflicted with pharyngitis and trismus underwent similar radiation protocols to the majority of horses in this study, with 1 horse receiving 8 Gy per fraction and the second receiving 4.5 Gy per fraction. However, given the occurrence of 2 cases of trismus when external beam radiation therapy was performed toward the middle or caudal aspects of the mandible, it might be prudent to evaluate the horse's jaw movement between treatments to ensure the movement remains normal. The severity of acute normal tissue effects like pharyngitis will be related to the fractionation protocol chosen and the volume of sensitive normal tissue that is included in the radiation field. These adverse effects occurred near the end of the radiation treatment and in the first few weeks that follow. Protocols delivering smaller doses per fraction over a longer treatment period allow normal tissues to repair radiation-induced DNA damage between doses. This will result in less severe normal tissue adverse effects. Utilizing radiation delivery techniques that geographically avoid inclusion of large volumes of normal tissues by physically blocking the beam using lead blocks or collimation will limit the adverse effects to a smaller area. The probability of late normal tissue effects like trismus is related to the size of the dose per fraction, with larger doses having a higher likelihood for development. Late effects take months to years to develop and do not resolve without some form of intervention. When selecting a radiation protocol and radiation delivery technique, one must weigh the risks associated with acute and late effect development and the tumor control expected.

Several horses developed adverse effects related to the tumor itself. Two horses with tumors extending into the oral cavity had tooth loss after treatment. This occurs in dogs.[30] Although this is perhaps an expected consequence of tumor regression, owners should be informed of this likelihood. In addition, 3 horses with tumors located in the maxilla (2) and proximal neck (1) had respiratory difficulties during the course of treatment. These difficulties were attributed to the size of the tumor and the potential swelling and inflammation at the site of treatment.[8] Due to the possibility of perilesional inflammation with radiation treatment, it is particularly important that horse with tumors close to the respiratory tract receive anti-inflammatory medication and close monitoring.

Important questions regarding external beam radiation therapy involve the patient's horse's of life, and, whether or not survival is prolonged beyond what would have been expected without it. Owners were not asked to assess quality of life after treatment; however, horses were euthanized when quality of life was considered poor, and the incidence of major complications specifically due to radiation therapy was relatively low (4/32). There were 6 horses, 3 of which had nasomaxillary tumors, which either did not achieve complete tumor response, or only showed a complete response for less than or equal to 3 months. In these horses, it is our clinical impression that neither survival, nor quality of life, were markedly improved by the treatment. For the remainder of the cases, which had a complete response for a longer period, some comparison with the literature is possible. Seven malignant tumors in the paransal sinuses were treated surgically with a median survival of 6 months.[2] No horses received radiation therapy. The only horses to show a complete response to treatment for more than 12 months were horses whose histological evaluation revealed tumors which were likely benign. This comparison potentially suggests that external beam radiation therapy can have a positive effect on survival times, compared to patients undergoing no treatment at all, or patients undergoing surgical excision alone. In a series of 8 equine osteosarcoma, 6 tumors were located on the head.[31] Two were lost to follow-up but the remainder died or were euthanized. Although comparing outcomes between different populations is not without its limitations, this comparison suggests that external beam radiation therapy might be beneficial in cases of osteosarcoma, particularly when complete surgical excision is not possible. There are multiple cases reports detailing good results with radical surgical excision of an undifferentiated sarcoma[32] an ameloblastoma[33] and, an ossifying fibroma.[34] All horses exhibited progression free disease at the time of follow-up (9-24 months). Although radiation therapy was not utilized in any of these cases, it should be noted that, at least in the cases of ossifying fibroma, external beam radiation therapy provided the majority of horses with a complete response, with only 1 horse showing recurrence and 1 experiencing life-threatening adverse effects of treatment.

Treatment performed before presentation included surgical debulking, intratumoral carboplatin, intralesional cisplatin beads, cryotherapy and topical treatment with 5-fluorouracil. Due to the low number of cases and variable nature of previous treatment attempts, this factor was not included in the analyses.

This study found no association between the occurrence of complications and the likelihood of tumor resolution. Several horses had delays in treatment during the course of their therapeutic protocol in order to manage complications such as pharyngitis, respiratory difficulties and colic. The delays ranged from 2 days to 1 week and, in our study population, did not appear to affect the success of therapy. The data also showed that horses that failed to complete their course of treatment had a lower rate of tumor regression, with none of these horses achieving long-term tumor control. Conversely, although uncommon, some horses receiving a hypofractionated protocol achieved a PFS of over 6 months. However, this was not the case for all tumor types. Furthermore, the hypofractionated protocols can be considered definitive intent protocols for both lymphoma and melanoma.[35] This study included data on 1 lymphoma and 1 melanoma undergoing hypofractionated protocols. Although our investigation found no negative effect to delaying treatment part-way through a protocol, corroborating evidence in the literature is lacking and it has been well documented in human medicine that delays in treatment protocols have a negative impact on outcome.[36]

There are limitations to this study, including the fact that the retrospective design renders the results prone to selection bias and misclassification bias. In addition, no control groups were employed, resulting in difficulties in making comparisons between groups. There were no reliable measurements of tumor size recorded in the medical records, so we could not investigate the association of tumor size on outcome. Although the numbers presented in this study are larger than any other retrospective evaluating the use of external beam radiotherapy in horses, when examining OS and PFS in subset groups, such as adverse events of tumor type, the small numbers of horses and especially the events in the subsets are a major limitation to this study. It must also be acknowledged that using phone conversations with owners, rather than follow-up with a veterinarian, might have resulted in both a poor evaluation of the tumor status and treatment-related complications, as well as the presence of recall bias. The lack of standardized follow-up periods might have impacted the estimated duration of tumor control.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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