

## Use of Ir<sup>192</sup> interstitial brachytherapy for an equine malignant dermal schwannoma\*

M N Saulez<sup>a</sup>, A Voigt<sup>a</sup>, J C A Steyl<sup>b</sup>, E van Wilpe<sup>c</sup>, J Kotzen<sup>d</sup> and F Daniels<sup>e</sup>

### ABSTRACT

A 10-year-old Hanoverian mare was evaluated for a right buccal swelling that recurred 3 months following surgical resection. Ultrasonographic examination showed a broadly pedunculated subcutaneous mass at the level of 106–109 and 406–409 cheek teeth associated with an erosive mucosal lesion on the inside of the cheek. Histological examination of a biopsy specimen revealed a well-demarcated, malignant, dermal schwannoma. Following subcutaneous placement of platinum coated Ir<sup>192</sup> wires under general anaesthesia, low-dose radiation of 5 gray per day was delivered for 14 days. Short-term complications included loss of patency of the right nasolacrimal duct, erythema, dermatitis, leukotrichia and left-sided deviation of the muzzle. Ten months later, there has been no tumour recurrence. Findings suggest that the use of interstitial brachytherapy should be considered for a malignant, dermal schwannoma that has recurred or is not amenable to surgery.

**Keywords:** horse, implant, iridium-192, radiation therapy.

Saulez, M N, Voigt A, Steyl J C A, Wilpe E van, Kotzen J, Daniels F **Use of Ir<sup>192</sup> interstitial brachytherapy for an equine malignant dermal schwannoma.** *Journal of the South African Veterinary Association* (2009) 80(4): 264–269 (En.). Section of Equine Medicine, Department of Companion Animal Clinical Studies, Faculty of Veterinary Science, University of Pretoria, Private Bag X04, Onderstepoort, 0110 South Africa.

### INTRODUCTION

Schwannomas, also termed neuromas, neurinomas, or neurolemmomas originate from the Schwann cells of nerve roots. In cases described in humans, schwannomas may occur either as a primary brain tumour or as a peripheral nerve tumour. Within the brain, cranial nerve (CN)-8 is most commonly affected and the tumour is termed an acoustic schwannoma, followed by CN-5<sup>11</sup>. Schwannomas may originate from any cranial or spinal root; however, they do not originate from CN-1 and CN-2, since these are myelinated by oligodendroglia<sup>11</sup>. Acoustic schwannomas typically present with progressive, unilateral hearing impairment and can compress neighbouring structures such as the pons and cerebrum, leading to neurologi-

cal deficits. They are typically benign tumours that can be readily detected using MRI and respond to surgical removal. Focal neuropathies may be caused by schwannomas, also termed neurilemmomas, which tend to be solitary subcutaneous tumours that grow within nerve sheaths, are benign, and can be excised<sup>11</sup>.

Schwannomas may occur in adult horses aged 3 to 16 years with no breed or sex predisposition<sup>1</sup>. No typical site exists, and lesions are reported as solitary, firm, <4 cm in diameter with no damage to the overly-

ing skin and hair coat<sup>13</sup>. Schwannomas may also appear as single or multiple firm, rounded, 2–3 mm diameter papules, which occur more commonly on the eyelids<sup>6,15,19</sup>. Following further enlargement, these can attain a diameter of 2 cm before becoming multiloculated, alopecic and ulcerated<sup>13</sup>.

This report details the use of interstitial brachytherapy in a mare with a malignant, dermal schwannoma that recurred and was not amenable to surgical excision.

### CASE HISTORY

A 10-year-old Hanoverian mare was examined at the Onderstepoort Veterinary Academic Hospital (OVAH) for a right buccal schwannoma that recurred 3 months after initial surgical excision. At presentation, there was an externally-visible, localised buccal swelling and a mucosal erosion inside the right cheek. The mare was reported not to be relaxed in the bridle and resisted the bit. Results of histological examination of the mass were suggestive of a schwannoma or peripheral nerve sheath tumour (PNST).

### Clinical findings

At the time of examination at the OVAH, the mare was bright, alert, in good bodily condition, afebrile, with normal cardiovascular and respiratory parameters. Palpation of the right cheek revealed a subcutaneous swelling with poorly-

\*A portion of this work was presented at the South African Society of Clinical and Radiation Oncology and the South African Society of Medical Oncology, Cape Town, 2009.

<sup>a</sup>Section of Equine Medicine, Department of Companion Animal Clinical Studies, <sup>b</sup>Section of Pathology, Department of Paraclinical Studies and <sup>c</sup>Section of Anatomy, Department of Anatomy and Physiology, Faculty of Veterinary Science, University of Pretoria Private Bag X04, Onderstepoort, 0110 South Africa.

<sup>d</sup>Department of Radiation Oncology, University of Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital.

<sup>e</sup>Department of Radiation Oncology, Steve Biko Academic Hospital.

\*Author for correspondence.  
E-mail: montague.saulez@up.ac.za

Received: August 2009. Accepted: November 2009.

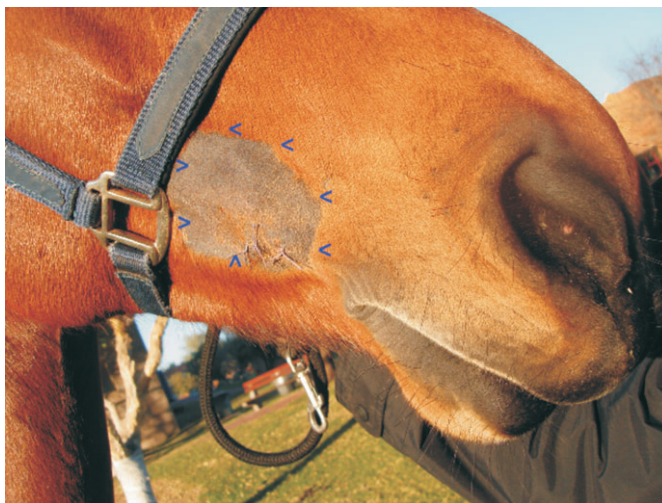


Fig. 1: Photograph of a 10-year-old Hanoverian mare with a right buccal schwannoma (demarcated by arrowheads).

defined margins present in the buccal region (Fig. 1). The horse was sedated with detomidine hydrochloride (Domosedan®, Pfizer) (3 mg, IV) and oroscopy was performed, which revealed a mucosal erosion inside the right cheek (Fig. 2).

Ultrasonography of the right cheek, mandibular lymph node, the parotid and retropharyngeal region was performed. There was an inhomogeneous hyperechoic mass of 7 cm rostrocaudal length and 4 cm dorsoventral height with a lateral wide pedunculated mural base of at least 3.5 cm width at the inside of the right cheek at the level of 106–109 and 406–409 cheek teeth. The mass was well defined where it protruded into the buccal cavity but poorly defined at its base, thus appearing to infiltrate into the cheek musculature. A right oval to round mandibular lymph node (2 × 1.4 cm) was present medial to tooth 107 and was heterogeneously hypoechoic with minimal blood flow. No enlarged lymph nodes were seen in the parotid or retropharyngeal region. Ultrasonographic findings were consistent with a broadly pedunculated mass with reactive mandibular lymphadenopathy. A fine-needle aspirate (FNA) of the right mandibular lymph node revealed an elevated number of plasma cells and prominent numbers of immature lymphocytes consistent with reactive hyperplasia. A FNA of the parotid gland showed no evidence of inflammation and was consistent with a hyperplastic reaction. Ultrasonography of the abdomen revealed no abnormalities, while thoracic ultrasound showed mild dimpling of the visceral lung surface with associated ring down artefacts restricted to the cranioventral lung lobes.

### Histopathology

Punch biopsies were taken from the buccal mass under local anaesthesia following admission to the OVAH. Examination of biopsy specimens at low magnification revealed a well-demarcated, non-encapsulated, mid- to deep-dermal neoplastic mass (Fig. 3). The mass consisted of uniform, interlacing whorls of fusiform cells. The epidermis was ulcerated and contaminated with opportunistic bacterial colonies. Small aggregates of lymphocytes were present along the deeper margins of the mass. No interaction between the neoplastic cells and the epidermis was evident, suggesting that the mass was unlikely to be a sarcoid. This was further supported by negative immunohistochemical staining for papilloma virus (rabbit polyclonal, N1547 Dako, Glostrup, Denmark). At higher magnification, individual neoplastic cells were characterised by long, slender, interconnecting, eosino-

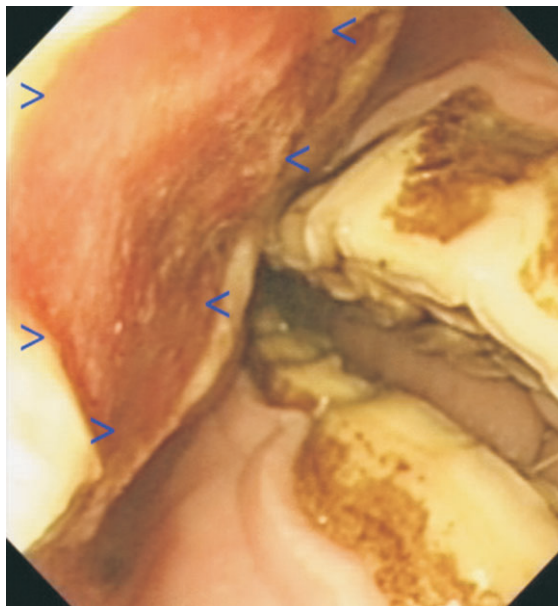


Fig. 2: Orosopic view of the right cheek of a 10-year-old Hanoverian mare with a right buccal schwannoma. Note the mucosal erosion present on the buccal aspect of cheek teeth 106–109 and 406–409 (demarcated by arrowheads), rostral is to the left.

philic cytoplasmic processes, separated by clear slits (Fig. 4). The nuclei were cigar-shaped, elongated and heterochromatic. In longitudinal sectioned regions of the mass, nuclei were large and oval, suggesting a flattened, disc-shaped morphology. The mitotic rate was low (less than 1/hpf). Immunohistochemical staining for S-100 antigen (rabbit polyclonal, Z0311 Dako, Glostrup, Denmark) yielded patchy positive staining of tumour cells (Fig. 5). All neoplastic cells were strongly positive for vimetin (mouse monoclonal, Dako, Glostrup, Denmark). Staining for glial fibrillary acidic protein (rabbit polyclonal, Z0334 Dako, Glostrup, Denmark) was negative.

Relevant areas of the tumour in the

paraffin embedded tissue sample were processed for electron microscopy and revealed narrow spindle cells with elongated cytoplasmic extensions arranged in a whorling fashion in a collagenous matrix (Fig. 6a). The tumour cells exhibited elongated nuclei (Fig. 6a) with smooth or indented outlines and with prominent nucleoli (Fig. 7b). Dilated cisternae of the endoplasmic reticulum with electron-dense and electron-lucent contents were seen (Fig. 6b). Intermediate filaments were present in the cytoplasm (Fig. 7a). Numerous proteoglycan particles were found in the extracellular matrix. Fibroblasts and a few histiocytes were present among the tumour cells. No external lamina surrounding the tumour cells or

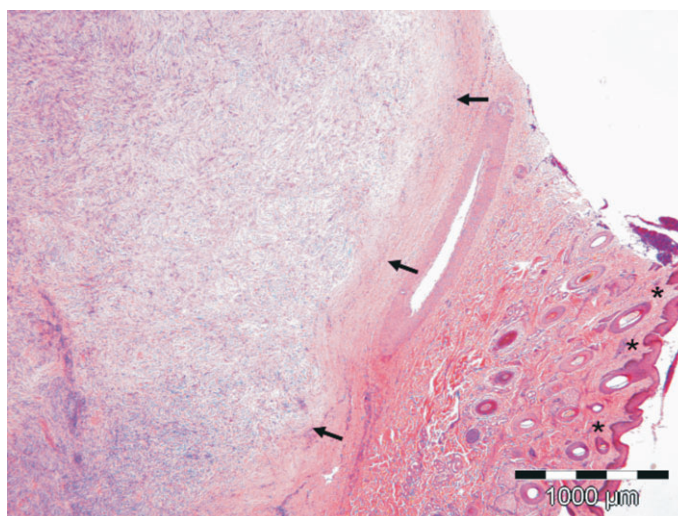


Fig. 3: Photomicrograph of a section of the buccal mass from the horse in Fig. 1. There was a well-demarcated, non-encapsulated, mid- to deep-dermal neoplastic spindle cell mass (arrows) that consisted of uniform, interlacing whorls of fusiform cells. Small aggregates of lymphocytes were present along the margins of the mass. Note the lack of interaction between the epidermal junction and neoplastic cells (\*). H&E stain; scale bar = 1000 µm.



cytoplasmic filaments forming focal densities could be demonstrated.

### Diagnosis

The histopathological features were consistent with a diagnosis of sarcoma (absence of nuclear palisading and dense cellular arrangement) and the immunohistochemical results were suggestive of a schwannoma or PNST<sup>2</sup>. The tumour cells that did not stain positively for S-100 were most likely poorly differentiated Schwann cells or perineural cells.

### Interstitial tumour therapy

On re-admission to the OVAH, trimethoprim-sulfamethoxazole (Purbac<sup>®</sup>, Aspen Pharmacare) (25 mg/kg, PO, q 12h), phenylbutazone (Phenylbutazone BP, Kyron Laboratories) (2 mg/kg, PO, q 12h) was started 72 hours prior to day of surgery. Results of a complete blood count and serum biochemistry were unremarkable. On the day of radiotherapeutic implant, romifidine hydrochloride (Sedivet<sup>®</sup>, Boehringer Ingelheim) (0.04 mg/kg, IV) and butorphanol tartrate (Torbugesic<sup>®</sup>, Fort Dodge Animal Health) (0.04 mg/kg, IV) were administered prior to induction of general anaesthesia using ketamine hydrochloride (Anaket-V, Centaur Laboratories) (2.2 mg/kg, IV) and GGE (GGE powder, Kyron Laboratories) (50 mg/kg, IV). The horse was transferred to the surgery suite and positioned in left lateral recumbency and maintained using halothane to effect and partial intravenous anaesthesia (PIVA) using a combination of ketamine (1 mg/kg/hr, IV), lidocaine (Lignocaine Injection, Bayer (Pty) Ltd) (0.01 mg/kg/min, IV) and romifidine (0.03 mg/kg/hr, IV). Following surgical preparation of the right buccal region, 9 parallel-placed stainless steel pins (10 cm in length) were placed subcutaneously at

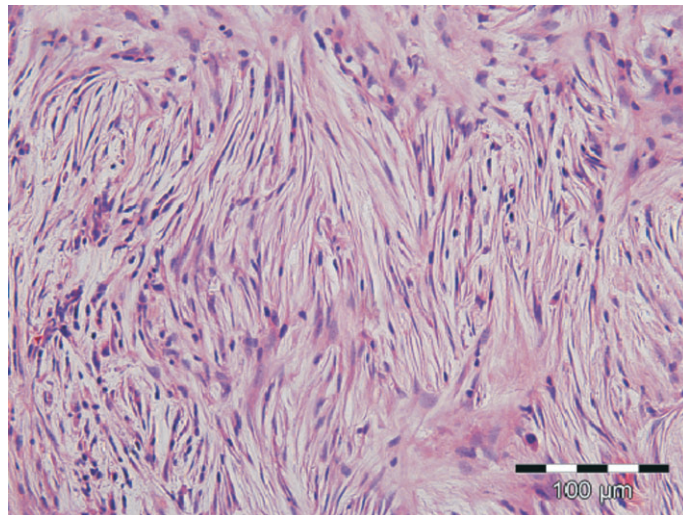


Fig. 4: Photomicrograph of a section of the buccal mass from the horse in Fig. 1. Neoplastic spindle cells are characterised by long, slender, interconnecting, eosinophilic cytoplasmic processes, separated by clear slits. The nuclei are cigar-shaped, elongated and heterochromatic. In longitudinal sectioned regions of the mass, nuclei are large and oval in shape, suggesting a flattened, disc-shaped morphology. The mitotic rate was low (less than 1/hpf). H&E stain; scale bar = 100  $\mu$ m.

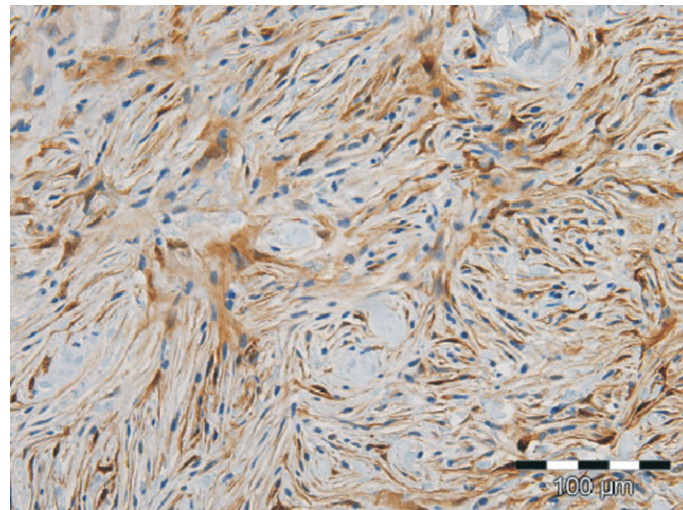


Fig. 5: Photomicrograph of a section of the buccal mass from the horse in Fig. 1 following immunohistochemical staining for S-100 antigen. Immunoreactivity (brown staining) is observed in the cytoplasm and nuclei of neoplastic cells. Haematoxylin counterstain; scale bar = 100  $\mu$ m.

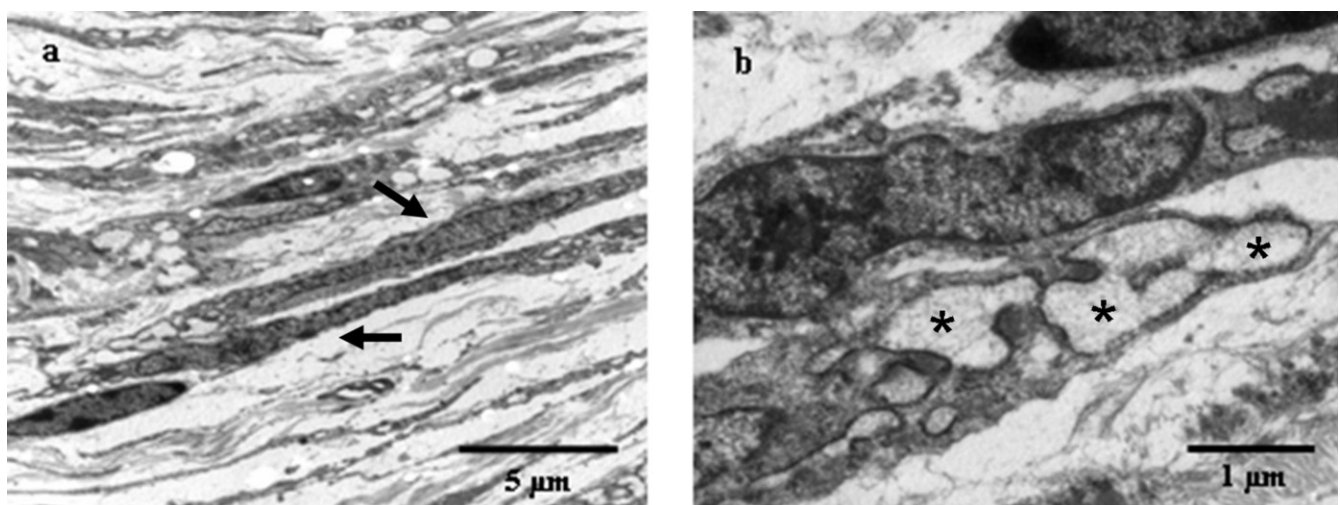


Fig. 6: Photomicrograph of a section of the buccal mass following electron microscopy. a, Narrow spindle cells (arrows) with elongated nuclei and slender cytoplasmic extensions; scale bar = 5  $\mu$ m. b, Dilated cisternae of the endoplasmic reticulum with electron-dense and electron-lucent contents (\*) were noted; scale bar = 1  $\mu$ m. Stain: Reynold's lead citrate and uranyl acetate.



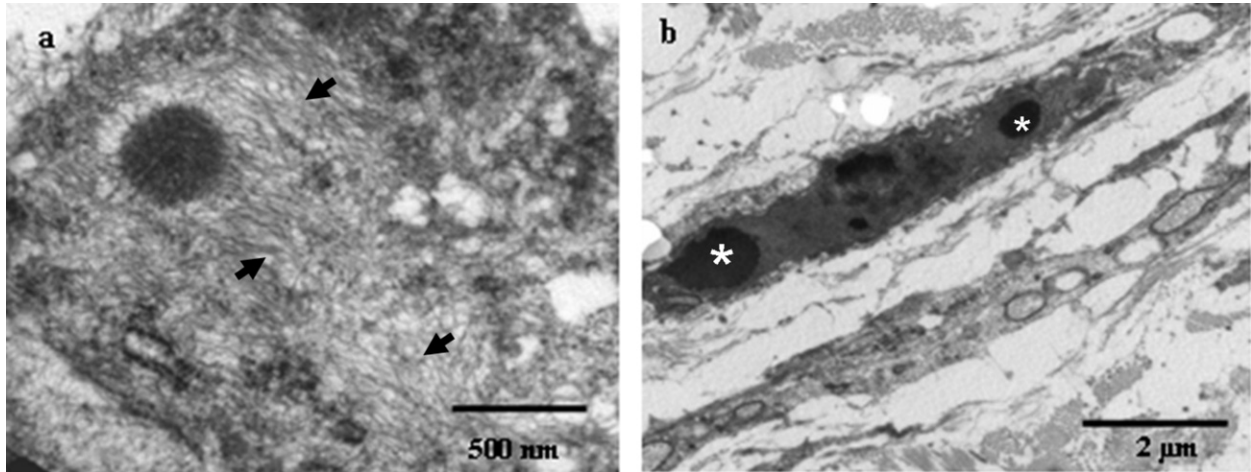


Fig. 7: Photomicrograph of a section of the buccal mass following electron microscopy. There were (a) cytoplasmic intermediate filaments (arrows); scale bar = 500 nm; and (b) prominent nucleoli (\*); scale bar = 2 µm. Stain: Reynold's lead citrate and uranyl acetate.

1.5 cm intervals, entering the schwannoma dorsally and exiting ventrally. Plastic guide tubes were then attached to each pin and threaded dorsoventrally by pulling each pin ventrally. Platinum-coated Ir<sup>192</sup> wires (AEC-Amersham) were then loaded into the guide tubes and the tubes sealed with studs (Fig. 8). Oroscopy was performed to ensure that implant penetration into the oral cavity was prevented during implantation. No attempt was made to surgically debulk the buccal tumour. Following recovery from general anaesthesia, the horse was isolated in a radiation-controlled area of the hospital until the precalculated radiation dose had been delivered, after which the guide tubes containing the Ir<sup>192</sup> wires were removed. During this period, the mare was monitored for any discomfort, swelling or discharge associated with the implantation. The implants were removed after 14 days without sedation by releasing the studs and sliding the plastic guide tubes containing the platinum-coated Ir<sup>192</sup> wires out of the subcutaneous tissues.

The pattern of implantation was deter-

mined by ultrasonographic evaluation of the right buccal region, digital palpation and the size and shape of the tumour. The standard planar implant protocol (Paris system) was used and the radiation calculation dose was determined for a treatment depth of 1.5 cm pre-implant to be 50 gray (Gy) at a low-dose radiation (LDR) of 0.5 mCi/cm. The actual implant region was 9 × 7 cm. The post-implant recalculated radiation dose was 65.0 Gy over a 14-day period. This allowed a LDR protocol of approximately 5 Gy per day. Radiation source of 50 cm Ir<sup>192</sup> wire with activity of 0.5 mCi/cm was used with a lead shielding of 2.8 cm (source strength = 500 µGy/h/m<sup>2</sup>). The physical properties of Ir<sup>192</sup> are a half life of 74.1 days, a principle gamma mean energy of 0.38 MeV with a half value layer (HVL) in lead of 6 mm and an exposure rate constant of 4.8 Rh-m/Ci at ref air-kemma rate of 100 µGy/h.

#### Radiation control

Radiation protection was ensured by discussing procedures with all relevant personnel and students. A microcom-

puter-based instrument that measured Gamma, Beta and X-ray radiation (Smart-ION Chamber Survey Meter 2130, Thermo Scientific, Erlangen, Germany) and an electronic pocket dosimeter (EPD) ('MYDOSE-mini' pocket dosimeter, Aloka Co Ltd., Tokyo, Japan) was available for monitoring radiation exposure. Post-implant procedures also included providing a dedicated radiation stall with appropriate radiation warning signs, a notice of the isolation period, and daily monitoring charts for the mare and for isolation stall contamination.

#### Outcome

Short-term complications from the interstitial brachytherapy included loss of patency of the right nasolacrimal duct with increased tear flow of the right eye (fluorescein eye stain could not be visualised at the external puncta of the nasolacrimal duct), erythema and moist dermatitis at the entry and exit sites of the guide tubes, leukotrichia, localised soft tissue swelling and mild left-sided deviation of the muzzle. Follow-up consultation 3 months later revealed no visible tumour recurrence following digital palpation, slight muzzle deviation to the left most likely due to trauma of the *N. facialis* secondary to pin placement and the right nasolacrimal duct appeared patent. Although no further biopsy was performed, the mare continues to be in remission 12 months after the use of interstitial brachytherapy.

#### DISCUSSION

In published reports, benign schwannomas account for 2 to 5% of equine cutaneous neoplasms<sup>9,10,12,15,19</sup>. However, the prevalence may be falsely increased owing to sarcoids being misdiagnosed as schwannomas<sup>13</sup>. Often, these tumours may be mistaken for fibroma, fibrosarcoma or sarcoid and confirmation of



Fig. 8: Post-operative photograph of the horse after 9 platinum-coated Ir<sup>192</sup> wires were loaded and sealed in guide tubes.

Schwann cell origin requires immunohistochemistry<sup>16</sup>.

Histopathological, immunohistochemical and electron microscopy results in this case were suggestive of the malignant form of schwannoma, also known as malignant PNST or neurofibrosarcoma. This was based on the absence of external lamina<sup>5</sup> and electronmicroscopic evidence of similar tissues that occasionally may be positive with the S-100 immunohistochemical stain such as myofibroblastic, melanocytic and chondroblastic tissue. The malignant form of schwannoma is poorly described in horses and is considered extremely rare in large domestic animals<sup>2</sup>. To the authors' best knowledge, the use of brachytherapy for a malignant dermal schwannoma that recurred and could not be surgically excised owing to location or ill-defined borders has not been reported previously.

Despite the treatment of choice being wide surgical excision, schwannomas may recur. Tomographic mapping to determine areas of disease extension and vascularity was unavailable but may have assisted the procedure. Cutaneous tumours in horses tend to have poorly-defined margins, may be locally infiltrative and have a high recurrence rate. Fifty per cent of periocular schwannomas recurred following surgical removal within a 6-month period<sup>6</sup>. Apart from surgical resection, reported therapeutic interventions have included interstitial brachytherapy using Au<sup>198</sup> for periocular schwannomas<sup>19</sup>, intralesional cisplatin and intralesional BCG<sup>7</sup>. When recurrence takes place, and especially when wide excision may not be possible either due to anatomical location or ill-defined tumour margins for the reasons indicated above, an adjunctive therapy may be necessary. Although the efficacy is unknown at this stage, such therapy may include the use of a Nd:YAG or CO<sub>2</sub> laser, intralesional chemotherapy using cisplatin or 5-fluorouracil, cryotherapy, brachytherapy or teletherapy.

Although surgical resection is the mainstay for primary treatment of all localised soft tissue sarcomas of the extremity and superficial trunk, brachytherapy is used as an adjunct to resection in human sarcomas. However, brachytherapy is not recommended for low-grade sarcomas because it did not influence local recurrence rates in a randomised prospective study of human patients<sup>8</sup>. The success of this treatment, although anecdotal, may suggest a difference between human and equine low-grade sarcomas.

Brachytherapy involves the use of radioactive sources such as Ir<sup>192</sup>, I<sup>125</sup> and Sr<sup>90</sup> to deliver radiation directly to affected tissue



Fig. 9: Post-operative photograph of the horse following implant removal.

either as interstitial (through the use of Ir<sup>192</sup> as in this report) or surface therapy, also termed plesiotherapy<sup>3</sup>. The radioactive sources can be beads, wires, seeds or needles and its use is limited to soft tissue tumours only. Following sedation or general anesthesia, Ir<sup>192</sup> implant wires are inserted through guide tubes placed approximately 1 cm apart in the target tissue, providing a LDR of 0.3 to 0.5 Gy/h and the total radiation dose is typically 60–70 Gy over a 5–7-day period<sup>3</sup>. Alternatively, an automated remote loading technique<sup>14</sup> may be used to insert Ir<sup>192</sup> wires with a high activity into the guide wires for 5–10 minutes, which may be repeated 7 days later, allowing a total radiation dose of 25–30 Gy<sup>3</sup>.

Reported success rates using brachytherapy for the treatment of tumours have ranged from 74 to 100 % at 1 year<sup>17,18,20</sup>, while a 98 % success rate was reported using Ir<sup>192</sup> implantation for periocular sarcoids<sup>4</sup>. Since brachytherapy may be gaining popularity in the treatment of equine cutaneous tumours, certain precautions need to be followed. Radiation licensing restricts the use of Ir<sup>192</sup> to referral hospitals with radiation isolation facilities, personal safety must be adhered to, and the cost of treatment may be prohibitively high.

Personal radiation monitoring was performed using EPDs worn in the operator's left handed vest pocket. These instruments use semiconductor detectors to show the integrated radiation dose equivalent on a liquid crystal display. Other advantages include ease of operation and high sensitivity. Additionally, a larger advanced ion chamber meter with an audible alarm preset and large digital and analogue display was provided for radiation control of the isolation stall.

In conclusion, the use of interstitial

brachytherapy allowed a localised radiation dose to be delivered to a malignant, dermal schwannoma that recurred 3 months after surgical excision while avoiding signs of systemic toxicity. Typical post-implantation symptoms consisting of localised tissue swelling, erythema, leukotrichia and moist dermatitis occurred. An excellent cosmetic result was achieved with minimal disfigurement and scarring (Fig. 9).

#### ACKNOWLEDGEMENTS

The authors thank Mr Wayne Flowers (AEC-Amersham (Pty) Ltd) for technical assistance and Dr Roy Gottschalk for the referral.

#### REFERENCES

1. Fernandez C J, Valentine B A, Smith C, Summers B A 1996 Equine dermal schwannoma. *Veterinary Pathology* 33: 607
2. Goldschmidt M H, Hendrick M J 2002 Tumors of the skin and soft tissues. In Meuten DJ (ed.) *Tumors in domestic animals*. Iowa State Press, Iowa: 95–96
3. Henson FMD, Dobson JM 2004 Use of radiation therapy in the treatment of equine neoplasia. *Equine Veterinary Education* 6: 405–408
4. Knottenbelt D C, Kelly D F 2000 The diagnosis and treatment of periorbital sarcoid in the horse: 445 cases from 1974–1999. *Veterinary Ophthalmology* 3: 169–191
5. Ordóñez N G, Mackay B 1998 Electron-microscopy in tumor diagnosis: indication for its use in the immunohistochemical era. *Human Pathology* 29: 1403–1411
6. Pascoe R R, Summers P M 1981 Clinical survey of tumors and tumor-like lesions in horses in southeast Queensland. *Equine Veterinary Journal* 13: 235–239
7. Pascoe R R, Knottenbelt D C 1999 Principles of dermatological therapeutics. In *Manual of equine dermatology*. W B Saunders, Philadelphia: 35–62
8. Pisters P W T, Harrison L B, Woodruff J M, Gaynor J J, Brennan M F 1994 A prospective randomised trial of adjuvant brachytherapy in the management of low-grade soft tissue

- sarcomas of the extremity and superficial trunk. *Journal of Clinical Oncology* 12: 1150–1155
9. Ragland WL, McLaughlin CA, Spencer GR 1970 Equine sarcoid. *Equine Veterinary Journal* 2: 168–172
  10. Runnels RA, Benbrook EA 1941 Connective tissues tumors of horses and mules. *American Journal of Veterinary Research* 2: 427–429
  11. Sagar SM, Israel MA Tumors of the nervous system 1998 In Fauci A S, Braunwald E, Isselbacher K J, Wilson J D, Martin J B, Kasper D L, Hauser S L, Longo D L (eds) *Harrison's principles of internal medicine* (14th edn). McGraw-Hill, New York: 2398–2409
  12. Sastry G A 1959 Neoplasms in animals in India. *Veterinary Medicine* 54: 428–430
  13. Scott D W, Miller W H Jr 2003 Neoplastic and non-neoplastic tumours. In *Equine dermatology*. W B Saunders, St Louis: 698–795
  14. Theon A 1998 Radiation therapy in the horse. *Veterinary Clinics of North America: Equine Practice* 14: 673–688
  15. Thomsett L R 1979 Skin diseases of the horse. *In Practice* 1: 15–26
  16. Valentine B A 2006 Neoplasia. In Bertone J (ed.) *Equine geriatric medicine and surgery*. W B Saunders, St Louis: 147–167
  17. Walker M A, Goble D, Geiser D 1986 Two year non-recurrence rates for equine ocular and periorbital squamous cell carcinoma following radiotherapy. *Veterinary Radiology* 27: 146–148
  18. Walker M A, Adams W, Hoskinson J, Held J P, Blackford J, Geiser D, Goble D, Henton J 1991 Iridium-192 brachytherapy for equine sarcoid, one and two year remission rates. *Veterinary Radiology* 32: 206–208
  19. Wyn-Jones G 1979 Treatment of periocular tumours of horses using radioactive gold<sup>198</sup> grains. *Equine Veterinary Journal* 11: 3–10
  20. Wyn-Jones G 1983 Treatment of equine cutaneous neoplasia by radiotherapy using iridium<sup>192</sup> linear sources. *Equine Veterinary Journal* 15: 361–365