Results from the treatment of advanced stage squamous cell carcinoma of the nasal planum in cats, using a combination of intralesional carboplatin and superficial radiotherapy: a pilot study

J. P. de Vos, A. G. O. Burm and B. P. Focker

De Ottenhorst, Clinic for Companion Animal Medicine, Terneuzen, The Netherlands

Abstract
Six cats with an advanced stage squamous cell carcinoma (SCC) of the nasal planum were treated with a combination of superficial radiotherapy and intralesional carboplatin therapy. This multimodality protocol was well tolerated by the majority of cats and resulted in complete responses in all cats (100%). Median follow-up for all cats is 268 days, and the median time-to-recurrence, time-to-progression and overall survival have not yet been reached. Our study, although limited in number of animals and with a relatively short median follow-up compared to other studies for this disease, suggests that a combination of radiotherapy and intralesional carboplatin is a useful treatment option for an advanced stage SCC of the nasal planum in cats and warrants further application of the multimodality approach presented here.

Keywords
carboplatin and radiotherapy, carboplatin, intralesional therapy, nasal plane tumour cat, squamous cell carcinoma cat

Introduction
Squamous cell carcinoma (SCC) is suggested to be a sunlight-associated tumour in which photocarcinogenesis is initiated by exposure to UV light (Ogilvie & Moore, 2001; Withrow, 2001). In cats, the tumour is seen mainly in older animals, particularly in those cats who are lightly pigmented. The nasal planum is the most common site of involvement, with the pinnae and eyelids the next most frequent sites. Although the tumour may be focal, the entire region of sunlight-exposed skin is at an increased risk for development of tumours, leading to a synchronous or asynchronous development of SCC of the face. Animals at risk need to be carefully checked on a regular basis and preferably should be protected from sunlight exposure (Ogilvie & Moore, 2001; Withrow, 2001).

The geographical incidence of SCC in cats differs and correlates to the degree of sunlight exposure. For example, in the UK, Germany and Switzerland, the incidence does not exceed 20% of all skin tumours in cats (Théon et al., 1995a; Ogilvie & Moore, 2001).

Several treatment modalities are described in the literature, including radical surgical excision (nasal planectomy) (Withrow & Straw, 1990; Lana et al., 1997; Withrow, 2001), cryosurgery (Clarke, 1991; Lana et al., 1997), radiotherapy (Carlisle et al., 1982; Théon et al., 1995a; Lana et al., 1997; Kaser-Hotz et al., 1997) intralesional therapy (Orenberg et al., 1992; Théon et al., 1996) and photodynamic therapy (Peaston et al., 1993; Frimberger et al., 1998; Stell et al., 1999). In this article, we describe the method and the preliminary results of the...
treatment of an advanced stage SCC of the nasal planum in cats, using a combination of radiotherapy and intralesional injections with carboplatin.

**Materials and methods**

During the period between April 2002 and October 2003, six cats were treated in our clinic for SCC of the nasal planum. The diagnosis was confirmed in five cases via histological biopsy and in one case with fine needle aspirate cytology. All patients were domestic short-haired cats, between 11 and 22 years, with a mean and median age of 14.8 and 13.5 years, respectively. On the basis of clinical evaluation and imaging, one cat had a stage 2 tumour, two cats had stage 3 tumours and three cats had stage 4 tumours (Table 2). According to the WHO staging system (Table 1) (Owen, 1980; Ogilvie & Moore, 2001). Clinical examinations were otherwise unremarkable. There were no macroscopic signs of metastasis, either by palpation of the regional lymph nodes or on thoracic radiography. All cats were hospitalized for the entire 4-week treatment interval.

The radiation therapy protocol prescribed consisted of a total dose of 48 Gray (Gy) divided into 12 equal fractions of 4 Gy each, delivered over 4 weeks on a Monday/Wednesday/Friday schedule. The radiotherapy unit used was a 50-kV orthovoltage unit (Dermatus 50, Enraf-Nonius, Delft, the Netherlands). The radiation tube makes direct contact with the lesion. The treatment volume included all visible tumour along with an additional normal tissue margin of 5–10 mm. The radiation energy was delivered through a one angle dorsal beam. The focus-skin distance was 15 cm, the internal tube diameter 22 mm and a 1.5-mm aluminium filter was used. The decline of the central axis depth dose in this setting is: 80% radiation energy present at 5 mm, 65% at 10 mm and 50% at 15 mm. The minimum depth of penetration by the low energy radiation beam has a sparing effect on the healthy tissue ventral to the tumour.

Once a week, during the 4-week period, the tumours were intralesionally injected with carboplatin approximately 30 min prior to the next radiation treatment. This way carboplatin was intended to act as a radiopotentiating agent, in addition to its cytotoxic properties. The cats were anaesthetized with medetomidine (Domitor®, Pfizer Animal Health, Capelle a/d Ijssel, The Netherlands) intramuscularly (i.m.) and thiopental sodium (Nesdonal®, 1 g, Merial, Amstelveen, The Netherlands) intravenously through an intravenous catheter (Braunule®, Braun Co, Melsungen, Germany). The medetomidine was antagonist with atipamezole (Antisedan®, Pfizer Animal Health, Capelle a/d Ijssel, The Netherlands) i.m. at the end of the procedure. During the radiation

Table 1. WHO tumour staging system for cutaneous squamous cell carcinoma in cats (Ogilvie & Moore, 2001; Owen, 1980)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Size</th>
<th>Depth</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td></td>
<td>Pre-invasive carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>&lt;2 cm</td>
<td>Superficial</td>
</tr>
<tr>
<td>T2</td>
<td>2–5 cm</td>
<td>Minimal invasion regardless of size</td>
</tr>
<tr>
<td>T3</td>
<td>&gt;5 cm</td>
<td>Invasion of subcutis regardless of size</td>
</tr>
<tr>
<td>T4</td>
<td>Any size</td>
<td>Invasion of fascia, cartilage, muscle or bone</td>
</tr>
</tbody>
</table>

Table 2. Results of the treatment

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age in years</th>
<th>WHO T stage</th>
<th>Time to recurrence (days)</th>
<th>Time to progression (days)</th>
<th>Overall survival (days)</th>
<th>Result of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>3</td>
<td>549*</td>
<td>562*</td>
<td>562**†</td>
<td>Complete remission</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>4</td>
<td>174</td>
<td>190</td>
<td>202</td>
<td>Euthanasia†</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>4</td>
<td>291*</td>
<td>311*</td>
<td>311**†</td>
<td>Complete remission</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>3</td>
<td>224*</td>
<td>249*</td>
<td>249**†</td>
<td>Complete remission</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>4</td>
<td>35*</td>
<td>52*</td>
<td>52†</td>
<td>Complete remission</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>2</td>
<td>249*</td>
<td>286*</td>
<td>286†</td>
<td>Complete remission</td>
</tr>
</tbody>
</table>

*Indicates still has not recurred or progressed at date of analysis.
†Still alive at date of analysis.
‡Euthanasia by owner request.

© 2004 Blackwell Publishing Ltd, Veterinary and Comparative Oncology, 2, 2, 75–81
fractions without intralesional injections, the thiopental sodium was not used.

The tissues surrounding the tumour were infiltrated with a commercially available carboplatin solution containing 10 mg mL$^{-1}$ (Carbosin®, Pharmachemie BV, Haarlem The Netherlands). The injection ports were 5 mm away from the macroscopic visible perimeter of the tumour. The tumour also was infiltrated as deep as possible with carboplatin. A 26-gauge needle attached to a 2 mL Luer Lock syringe was used. Unlike intralesional therapy described in other studies, the carboplatin was not diluted with sesame seed oil. Rather, the first two patients were treated with 1.5-mg carboplatin cm$^{-2}$ tissue, with the carboplatin solution diluted in a ratio of 1 : 1 with the cat’s own serum. The serum was intended to act as a slow-release system for carboplatin bound to the serum proteins. In the remaining four patients, we injected the undiluted carboplatin solution into the tumour and the normal tissues surrounding the tumour. This resulted in a total injection volume of 0.5–1.0 mL, dependent on tumour size, per weekly treatment.

Care was taken during injection to prevent carboplatin back-spray along the needle track due to the high interstitial pressure in the tumour. This was accomplished by angling the needle from one injection port in several directions. If the carboplatin was observed to be leaking from the ulcerated parts of the tumour, the needle was drawn back a millimetre or two and another angle was tried. During this procedure, there is a risk of aerosol formation, in case the carboplatin sprays back from the needle track or topical contamination of the adjacent surfaces through leakage of carboplatin from ulcerated parts of the tumour. Safe handling of chemotherapy drugs is essential, due to the mutagenic and carcinogenic properties of these drugs. Hazardous occupational exposure can be avoided by proper handling techniques and protection measures. Protective clothing, in the shape of polycoted latex gloves (Chemoprotect®, Codan BV), safety pair of glasses and a mouth mask (Chemoprotect®, Codan BV), was worn by the person injecting the carboplatin and the technician assisting. The surrounding surfaces were protected from contamination by covering with disposable polyethylene covers.

All cats wore neck-collars to prevent self-trauma from scratching. These collars also served to prevent the cats from spreading carboplatin over their fur through licking. Touching and handling of the cats during the hospitalization period was done with care and kept to a minimum, while the technician who was taking care of the cats was wearing protective clothes when handling them. Special attention was paid to avoid touching the head of the cat and feeding bowls. The cats were hospitalized in isolated cages with smooth surfaces and disposable feeding bowls were used.

All materials used, during the intralesional injections, the litter from the cat’s box, disposables and cleaning material from the cages, were removed in special boxes for chemotherapy-associated hospital waste, which can be permanently closed and incinerated. Special attention was paid to prevent carboplatin-polluted material spreading into the environment of the cage, by using cages with semi-closed fronts.

Response to therapy was categorized as complete response (CR: complete regression of all measurable disease), partial response (PR: $>50\%$ but $<100\%$ regression of measurable disease), stable disease (SD: $<50\%$ regression or $<25\%$ progression) and progressive disease (PD: $>25\%$ increased in measurable disease or appearance of new lesions). Time to recurrence (TTR) was defined as time from documentation of response until the progression of disease. Time to progression (TTP) was defined as the time from first treatment until subsequent progression of disease, loss to follow-up or death. Overall survival (OS) was defined as the time from first treatment until subsequent death.

© 2004 Blackwell Publishing Ltd, Veterinary and Comparative Oncology, 2, 2, 75–81
at the end of study, or were lost to follow-up or died of disease other than SCC. All analyses were performed in an intention-to-treat basis.

Results
In all cases, a PR was seen after 4 weeks of treatment. CR was achieved in all six cats (100%) after approximately 1-month post-treatment (Fig. 1). The results of the treatment are listed in Table 2. Survival analysis revealed that TTP, TTR and OS have not yet been reached with a median follow-up for all cats of 268 days. A representative curve for TTR is presented in Fig. 2.

Cat number 2 was euthanized at the request of the owner, 202 days after the treatment. This cat, obtained from an animal shelter 3 years previously, suffered from chronic rhinitis and already had one pinna surgically removed because of SCC. The rhinitis had evolved into a therapy-resistant disease. At the time of euthanasia, there was an ulcer, with a diameter of 2–3 mm, visible at the cranial part of the septum of the nasal planum. The owner declined further examinations and treatment. Because no postmortem histopathology was available on this cat, for the purpose of analysis, this cat was considered to have died of SCC disease. All the other cats were still alive and in complete remission at the time of analysis.

All cats tolerated therapy well except for cat number 6 which developed a treatment-induced dermatitis (i.e. moist desquamation) that let the owner to terminate therapy after only one intralesional treatment and five of 12 radiation fractions. This cat was included in analysis on an intention-to-treat basis. Despite only receiving one-quarter of his prescribed treatment, this cat experienced a CR and is still in remission at the time of analysis. All cats developed temporarily self-limiting periods of sneezing, which started during the initial treatment and persisted for a few weeks after treatment. This was due to a mild radiation-induced mucositis involving the entrance of the nose.

Discussion
In previous studies, radiotherapy proved to be an efficient treatment option for an early stage (T1 and T2) SCC of the nasal planum in cats (Carlisle et al., 1982; Théon et al., 1995a; Ogilvie & Moore, 2001). However, recurrence of the tumour within
1 year was likely to occur in cats with $T_3$- and $T_4$-staged tumours. In one study, 90 cats with SCC of the nasal planum were treated with orthovoltage radiotherapy (10 fractions of 4 Gy). The median TTP of cats in this study with a $T_1$ tumour was 53.2 months, and this was significantly better than those animals with a $T_3$ and $T_4$ lesion, who had a median TTP of 18.8 and 15.3 months, respectively (Théon et al., 1995a; Ogilvie & Moore, 2001). Megavoltage radiotherapy showed no obvious advantage over orthovoltage radiotherapy in this kind of superficial skin tumours (Lana et al., 1997; Kaser-Hotz et al., 1997; Ogilvie & Moore, 2001).

Radical nasal planectomy in eight cats resulted in three of the cats with $T_3$ and $T_4$ lesions in tumour recurrence within 5 months of surgery (Withrow & Straw, 1990; Ogilvie & Moore, 2001). In another study, which showed the results of nasal planectomy in 21 cats with SCC, the median TTP was 20 months, although this TTP included a group of cats with SCC of the pinnae (Lana et al., 1997; Ogilvie & Moore, 2001). Megavoltage radiotherapy showed no obvious advantage over orthovoltage radiotherapy in this kind of superficial skin tumours (Lana et al., 1997; Kaser-Hotz et al., 1997; Ogilvie & Moore, 2001).

Photodynamic therapy, if available, should be reserved for $T_{is}$, $T_1$ or $T_2$ lesions and showed minor response rates in advanced stage tumours (Peaston et al., 1993; Frimberger et al., 1998; Stell et al., 1999).

The purpose of intratumoral administration of cytotoxic agents is to increase, for a certain amount of time, the tumour versus plasma drug-concentration ratio. Intralungal injection of SCC of the nasal planum in cats with carboplatin in purified sesame seed oil was described in one study. Fifteen cats were treated once a week during 4 weeks with an intratumoral administration of carboplatin in a water–sesame-oil emulsion, at a dosage of 1.5-mg cm$^{-3}$ of tissue. CR rate was 73.3% and the median TTP was 16 months. The 1-year progression-free survival rate was 55.1%. Local recurrence was observed in seven cats (Ogilvie & Moore, 2001; Théon et al., 1996).

Platinum-derived drugs have been historically used as radiopotentiating agents for radiochemotherapy of cancer, with carboplatin as one of the commonly used drugs. Important mechanisms in the interaction between carboplatin and radiotherapy are the increased production of radiation-induced DNA single-strand and double-strand breaks, in combination with impaired intracellular DNA-repair mechanisms (Théon et al., 1995b; Yang et al., 1995a, c). Radiation can also enhance the binding of carboplatin to doublestrand DNA under hypoxic conditions (Yang et al., 1995b). The combination of chemotherapy and radiotherapy has produced improved response and survival rates among cancer patients, but the most effective way of delivering the drugs into the tumour has still to be established. The radiation-enhancing effects of carboplatin, when given systemically compared to intratumoral administration, can be limited by a lower drug concentration in the tumour. Most likely, the radiosensitizing effects of cytotoxic agents can be improved when the drug is delivered at an optimal concentration in the tumour and maintained at this site for a prolonged period (Ke et al., 2001).

The initial approach in our study, diluting the carboplatin with the cat’s own serum, was based on the protein-binding capacity and subsequent release kinetics of the protein-bound fraction of cisplatin (Pretorius et al., 1981; Deurloo et al., 1990; Deurloo et al., 1991; Théon et al., 1994). The serum protein, particularly the albumin fraction,
was intended to act as a slow-release matrix for carboplatin. Several studies showed, however, that carboplatin has a lower protein-binding capacity compared to cisplatin (Perera et al., 1992; van der Vijgh & Klein, 1986; van der Vijgh, 1991). *In vitro*, carboplatin does not bind instantaneously and reversibly to the plasma proteins (Gaver et al., 1987). The protocol was changed to the injection of undiluted carboplatin.

Our study, although limited in number of animals and with a relatively short median follow-up compared to other studies for this disease, suggests that a combination of radiotherapy and intraläsional carboplatin is a useful treatment option for an advanced stage SCC of the nasal planum in cats. Most cats tolerated the therapy well, and the 100% response rate in the face of an advanced disease is promising. The responses appear to be durable; five of the six cats achieved a minimum of 6-month control with a median follow-up of 268 days. The median TTR, TTP and OS have not yet been reached. Only one cat had recurrence, and this recurrence was assumed rather than histologically documented. Importantly, the therapy was well tolerated in the majority of the cats. Therefore, this multimodality approach warrants further application. Incorporation of sustained release systems of carboplatin in the protocol could possibly improve the results of this therapy (Théon et al., 1996; Emerich et al., 2002).

**Acknowledgments**

We thank the owners and their cats whom we were able to treat and our animal health technicians Beata, Bianca, Cathy, Ella, Kelly, Mena and Monique for their assistance during treatment and care of our patients. We acknowledge Dr David M. Vail of the University of Wisconsin-Madison, School of Veterinary Medicine for manuscript review and performance of survival analysis.

**References**


