

**THE EFFECT OF COBALT⁶⁰ RADIATION ON
SQUAMOUS CELL CARCINOMAS OF THE
NASAL PLANUM OF THE DOMESTIC CAT**

Georgina Crewe BVSc (Pretoria)

A dissertation submitted to the Faculty of Science, University of the Witwatersrand, in fulfilment of the requirements for the degree of Master of Science.

Johannesburg 2009

University of Witwatersrand, Animal Ethics Committee

Clearance number2000/65

DECLARATION

I declare that this dissertation is my own unaided work. It is being submitted for the Degree of Master of Science in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

(Signature of candidate)

_____ day of _____ 2009

DEDICATION

To my mother, Alice Rita Crewe (1905-1969), my aunt, Vi Robinson (1907-2004) and my friend, Jane Makota (1938-2005), women who yearned for the academic opportunities I have had, and ensured that their children were given these chances.

Also to my children Hilary, Carol and Matthew and their families with appreciation for the love, joy and encouragement I am so abundantly given.

ACKNOWLEDGEMENTS

I would like to thank the following people for the generous help they have given to me in the preparation of this dissertation:

- My supervisors Professors S. Hanrahan and P. Cleaton-Jones (University of the Witwatersrand), for their guidance, interest and patience,
- Colleagues in private practice who referred their patients to me for radiation treatment and to the owners of the cats for their diligence during treatment and for allowing me to monitor the results;
- S. Crewe for her help in recording and retrieving the data used in the study; I. Makato for developing an oncology data collection computer programme that is an invaluable asset to my work;
- Dr. W. Botha (Onderstepoort) for supplying me with paraffin blocks of the different grades of feline nasal planum squamous cell carcinomas; Professor M. Hale and L. Pillman (University of the Witwatersrand) for processing the histological material and Professor M. Hale for his insight in examining them;
- P. Dawson and staff of the Central Animal Services, (University of the Witwatersrand) for access to the Cobalt radiation unit and especially to A. Moosa for her administrative skills in the running of the radiation unit; Professors P. Fatti and Pillay, (University of the Witwatersrand) for their help and guidance with the statistics used in this study;
- P. Nicolson, M. Concha and B. English for their helpful comments and encouragement in the preparation of this dissertation and finally to
- The School of Animal, Plant & Environmental Sciences, (University of the Witwatersrand) for financial support.

SECTIONS OF WORK USED IN THIS DISSERTATION THAT HAVE BEEN PRESENTED AS CONGRESS PAPERS:

1. Crewe, G. (2000) The etiology and control / cure of solar induced squamous cell carcinomas of dogs using cobalt radiation and environmental control. Fourth World Congress of Veterinary Dermatology, San Francisco, California, August 2000.
2. Crewe, G. (2000) The etiology and control / cure of solar induced squamous cell carcinomas of dogs and cats using cobalt radiation and environmental control. South African Veterinary Congress, Durban, September 2000.
3. Crewe, G. (2004) Cobalt radiation therapy of solar induced squamous cell carcinomas of the feline nasal planum. South African Veterinary & Para-veterinary Congress, Cape Town, July 2004.
4. Crewe, G. (2004) A practical approach to Mega-voltage radiation oncology. South African Veterinary & Para-veterinary Congress, Cape Town July 2004.

SECTIONS OF WORK USED IN THIS DISSERTATION THAT HAVE BEEN PRESENTED AS A POSTER:

2. Crewe, G. (2000) The etiology and control / cure of solar induced squamous cell carcinomas of dogs and cats using cobalt radiation and environmental control. South African Veterinary Congress, Durban, September 2000.

ABSTRACT

Squamous cell carcinomas (SCC) are caused by high levels of UVB (B fraction of the ultra violet ray) radiation on susceptible animal tissue. Factors that influence the ultra violet radiation (UV) level in different parts of the world are altitude, intensity and duration of sunlight, and thickness of the ozone layer. South Africa's UV radiation levels are amongst the highest recorded in the world.

The UVB energy enters the squamous cell and damages the DNA, which results in the uncontrolled proliferation of the squamous cells. Ultimately this proliferation of the squamous cells leads to the formation of a squamous cell carcinoma. The normal histology of the well-ordered squamous cell tissue changes from its regular pattern to one of disintegration as the carcinoma grows at the expense of the normal tissue.

This clinical study examines the results of 75 feline patients with solar-induced SCC of the nasal planum treated with Cobalt ⁶⁰ radiation. The cats were grouped clinically according to the severity of the SCC from 1-4, least to worst. The cats were sedated and their nasal planums irradiated on a recognised veterinary fractionated protocol of Monday/Wednesday/Friday. The clinical response was judged by the visual reduction in size and the diminishing aggressiveness of the tumour. This response determined the radiation dose and the number of treatments.

The cats, age, sex, clinical appearance, number of treatments, radiation dose and survival period were recorded. A photographic record was kept of the patient's progress before, during, and after treatment and the cats' subsequent period of monitoring. Environmental compliance by the owners with respect to limiting exposure to solar radiation was also recorded.

The cats were monitored for two years after the initial radiation treatment. The results were statistically analysed and showed that there was a correlation between the initial graded appearance of the nasal planum SCC and the period of survival. There was no statistically significant effect on survival of the independent variables of age, sex, and total radiation dose. However the clinical evidence was, that cats presenting with early nasal planum SCCs and treated with a low dose of radiation survived well. Those with more advanced lesions responded less favourably but enjoyed the palliation of pain that the radiation provided.

This study has shown that mega-voltage radiation can play a most effective part in the treatment of actinic induced nasal planum squamous cell carcinoma. The challenge is to educate the owners and veterinarians to recognise the condition at an early stage and for veterinarians to have access to mega voltage radiation machines.

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LIST OF DEFINITIONS

Nasal planum	Hairless area surrounding the external nares consisting of a thick layer of keratinised squamous cell tissue.
Gy (Grays)	A unit of measure of ionizing radiation.
MED	Minimal Erythematous Dose, which is the amount of UVB light which will cause a fair skin to pinken.
WHO	World Health Organization.
SCC	Squamous cell carcinomas.
UV	Ultra violet radiation.
UVA	A fraction of the UV radiation 320 – 400 nm.
UVB	B fraction of the UV radiation 290 – 320 nm.
.	
UVC	C fraction of the UV radiation 200 – 290 nm.

CHAPTER TWO

MATERIALS AND METHODS

2.1 INTRODUCTION

Practitioners referred domestic cats with solar-induced squamous cell carcinoma of the nasal planum for radiation treatment. This study is therefore one of convenience sampling. Although more than 90 cats were treated for squamous cell carcinoma during the period (1998-2001) only 75 met the criteria of regular check ups (visual or telephonic) for the two years post initial radiation treatment. Of the other 22 cats that were treated during this period, six were squamous cell carcinoma of head and pinnae, one was dead within six months of non-related disease, eight were treated palliatively and seven were untraceable.

Human patients who are in remission from cancer for more than five years are considered to be disease free. There is no comparable remission time for animals. But if the lifespan of cats to humans is compared at a ratio of approximately 5:1, it seems reasonable to use a two-year survival period as a successful treatment, as the two-year survival period then approximates to a human survival rate of 10 years.

The end point of the study was survival during this two-year period. All cats, male and female had been sterilized. The tumours were visually graded T1- T4 (least to worst), and there were at least 15 patients in each grade. The fractionated radiation dose of each patient varied according to the visual assessment of the response to the treatment. The fractionated radiation dose, the number of treatments and the total radiation dose were recorded. Digital photographs of each patient were taken

from 01/09/99 onward and stored. The instituting of environmental and behavioural change was strongly recommended.

Each patient was monitored every two to three months either visually or telephonically and the efficacy of the treatment was assessed two years after the initial radiation treatment. The clinical outcome was judged on the length of survival of the patient. Because the nature of this study was based on clinical therapeutic evidence there was no control group. However two clients who decided not to have any treatment for their cat and let nature take its course allowed photographic monitoring of the cats. These photographs are included in the results.

The results of this study were compared to the treatment modalities referred to in the introduction 1.8.

2.2 THE INITIAL CONSULTATION WITH THE OWNER AND PATIENT

The first consultation with the owner was an evaluation of the general condition of the cat together with a visual assessment of the nasal planum tumour. The owner was fully informed of the etiology of the disease, the proposed radiation treatment and the necessity of ensuring that the cat's lifestyle be changed to that of a nocturnal animal to limit further UV exposure.

It was recommended that during the day from 8am to 5pm the cat should be kept in a bright sunny room that had a film of special plastic on the windows that blocked out the UV radiation. The infrared and the visible light were not affected so the cat

had the warmth and brightness from the sun but no UV exposure. The cats usually adapted to this new lifestyle within three days.

After this consultation (approximately 1 hour) the owners were able to make an informed decision on whether or not to proceed with radiation therapy and/or the environmental control. If the owners decided to have their cat treated they completed an "Informed Consent to Treatment" form, Appendix A. The owners did not have to agree to the environmental changes but were requested to inform me of their decision. This decision was recorded.

2.3 VISUAL GRADING OF THE TUMOUR

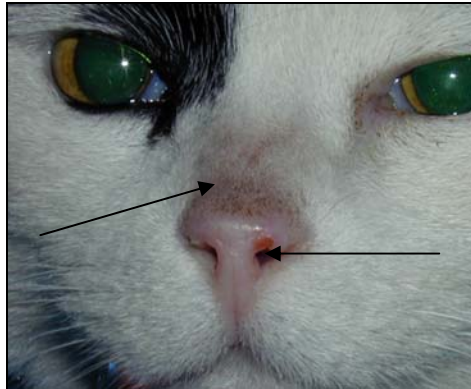
The patients were grouped according to the visual severity of the tumour. The tumours were given a grading of T1 - T4 using an adaptation of the World Health Organization (WHO) classification of tumors in domestic animals (1980). Although the size of the tumour was noted and recorded photographically the criteria for the grading of the tumour was judged on the depth of the tumour rather than the size. It should be noted that the depth depends on the type of tissue that is affected and not on an absolute measurement.

Table 2.1 Tumour grading scheme used in this study.

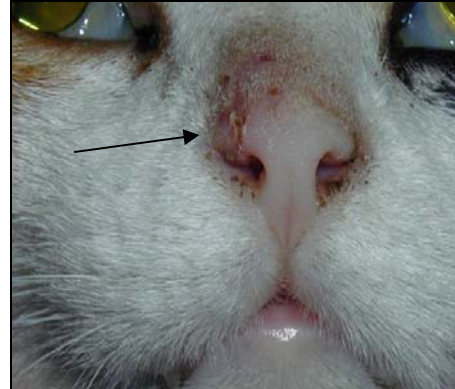
Adaptation from World Health Organisation Classification of tumors in domestic animals (1980).

Tumour Grade	Criteria
T ₁	Small very superficial or exophytic lesion 1-3 mm diameter and 1 mm deep (Figure 2.1 T1)
T ₂	Superficial lesions 3-5 mm diameter and 1-2 mm deep minimal invasion. (Figure 2.1 T2).
T ₃	Lesions more than 5 mm diameter and 2-3 mm deep or invasion of subcutis (Figure 2.1 T3).
T ₄	Lesions more than 8 mm diameter and > 3 mm deep invading nasal septum cartilage, aggressive and painful (Figure 2.1 T4).

The following pictures show the clinical appearance of the tumours graded T1-T4. Note in particular the lack of pigmentation of the nasal planum tumour area also the tiny, black superficial flecks on the nasal planum of Figure 2.1. grade T1.



Grade T1



Grade T2



Grade T3



Grade T4

Key: The arrows point to the early lesions of T1 and T2.

Figure 2.1 The visual grading of the different tumour levels.

2.4 CLINICAL DATA

The clinical data listed below was recorded for each cat (Appendix B)

- a) Breed, sex and age.
- b) History with regard to the squamous cell carcinoma.

c) Visual clinical grading of squamous cell carcinoma was initially described and recorded. This was later supplemented by digital photographs, which were taken before, during and after treatment and during the two-year monitoring period. This data was used to visually record and evaluate the success of the treatment.

The cases were not verified by histopathology as often within days of taking a biopsy, the tumour increases alarmingly in size and aggressiveness (personal observation). The owner's participation with regard to environmental control was scored on an "honesty scale" (owner information) of 1-3 scale (least to best).

2.5 HISTOLOGICAL EXAMINATION OF NASAL PLANUM TUMOURS

In order to try and understand the histopathology of the disease various slides of the nasal planum were examined. The biopsy material was obtained from two sources; the normal pigmented nasal planum tissue was taken, with the owner's permission, from a young cat that had to be euthanased. The slides from normal tissue have been used to illustrate section 1.6, (figures 1.3, page 10; 1.4, page 11 and 1.5, page 12). Other biopsy tissues exhibiting the carcinoma in various stages of development were examined. Veterinarians in private practice who needed to establish the pathology of the lesion on their feline patients' nasal planums had submitted these biopsy tissues. They were not biopsies of the cats in the study. They were then sectioned, mounted and stained. The standard laboratory staining methods were used. Slides were stained using hematoxylin and eosin (Bancroft and Gamble 2002). These slides were then examined and described in section 3.3.

Now to digress; in 1996, radiation therapy for veterinary patients was not available in Johannesburg. However the laboratory animal unit of the University of the Witwatersrand had a Cobalt⁶⁰ Theraton 80 radiation machine used for research. In private practice there were many cases of feline nasal planum squamous cell carcinoma being treated with limited success. The books, *Managing the Veterinary Cancer Patient* by Ogilvie and Moore (1996) and the *Textbook of Veterinary Internal Medicine*, eds Ettinger and Feldman (1995) gave some insight into the exciting practice of veterinary radiation therapy.

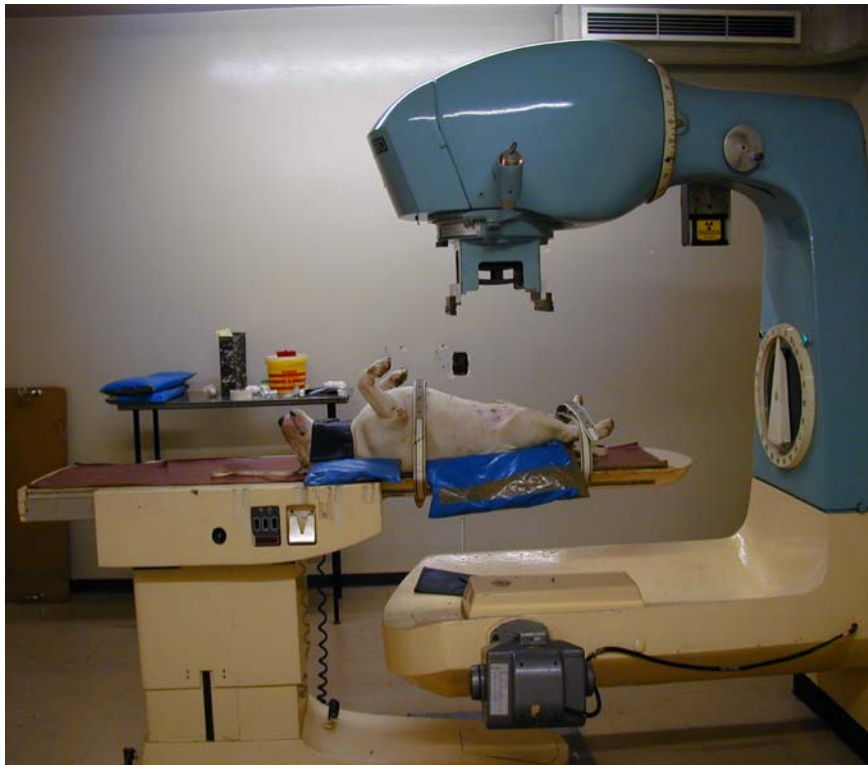


Figure 2.2 Cobalt⁶⁰ Theraton 80 radiation machine.

Fortuitously, Ogilvie and Moore (1996) reported on a study by Theon et al. (1995) describing the treatment of feline nasal planum SCCs using ortho-voltage radiation therapy (10 x 4 Gys), which seemed to have encouraging results. As a consequence of this article and remembering the two adages "do no harm" and "nothing

ventured nothing gained” the decision was made to treat feline patients exhibiting SCC of the nasal planum, with cobalt radiation. Being cautious it was decided to halve the radiation dose used by Theon et al. (1995) on the early tumours (T1 and T2) and to carefully monitor the visual effect of the radiation.

Accordingly the fractionated radiation dose was between 2 – 4 Gy per session depending on the severity of the tumour. T1 and T2 were radiated with 2 Gy at each session,. T3 with 3 Gy per session and T4 started off with 4 Gy and was reduced to 3 Gy as the tumour responded to the treatment. The number of treatments depended on the clinical response of the lesion with regard to aggressiveness and size, the patients being individually assessed before each treatment.

The fractionated radiation dose, the total radiation dose (Gy) and the number of treatments were recorded. From 01/09/99 the cats were photographed (Olympus C-2000Z) before, during treatment and at check-up visits (Crewe, 2004). The university subsidized the capital expense and the maintenance of the Theratron machine and that meant the cost of radiation per treatment was R75.00 exclusive of drugs.

Unfortunately the cats’ overall general behaviour was not recorded before, during or after treatment. However the owners were delighted as their cats’ pain diminished, their general condition improved and their behaviour returned to that exhibited before the squamous cell carcinoma had become apparent.

2.6 PROCEDURE FOR RADIATION THERAPY

Food was withheld from the patient for at least 8 hours prior to treatment, whilst water was freely available. A recognised fractionated radiation veterinary protocol treatment is a Monday, Wednesday and Friday schedule and this was the programme that was followed. The cat was sedated with "Domitor" (Medetomidine hydrochloride) at 0.05-0.1 ml/kg. The cat was then positioned on its back supported by sand bags under the Cobalt⁶⁰ Theratron 80 radiation machine. The skin to source distance was 80 cms. The nasal planum area to be radiated was the clinical tumour volume (CTV) plus a margin of at least a 0.5 cm. The nasal planum was then irradiated. The sedative was afterwards reversed with "Antisedan" (Atipamizole hydrochloride) at 0.04-0.06 ml/kg.

2.7 MONITORING OF THE PATIENTS AFTER TREATMENT

After the completion of the treatment the cat was monitored for the tumour recurrence, monthly for the first two months and thereafter every three months. However, the owners were often unable to adhere to this time interval and telephonic assessment had to be made. This method was unreliable, as the owners were unable to "read" the lesion correctly. As a result of this the survival rate was found to be a more precise method of monitoring the outcome of the treatment.

The survival time was defined as the period from the first radiation treatment to that of death. Cats dying of non-related disease during the two-year follow up period were included in this study of 75 cats.

The compliancy of the owner with regard to UV exposure control was scored on an 'honesty basis' of:

1. Did nothing
2. Tried
3. Successfully changed the cat to being a nocturnal animal. During the day, the cat was confined to a room that had a special plastic film placed on the windows that filtered out the UV radiation.

2.8 STATISTICAL ANALYSIS

The results for sex and age in relation to tumour grade were first tested separately to see if there was any relationship to tumour grade; sex using the Chi Square test, and age using the Kruskal Wallis test (Zar 1996). The mean total radiation and number of treatments were also analysed using the Kruskal Wallis test. These last two are dependent variables and one would expect them to be linked to tumour grade.

Combined factors were then subjected to the Cox proportional hazard model (Cox and Oakes 1984). This test was chosen because it is not based on assumptions about the nature and shape of the hazard function and is essentially a non-parametric method of analysis. It does however have an assumption that there is a log-linear relationship between the independent variables and the underlying hazard function, in this case death. It allows the analysis of several risk factors on survival. Survival curves were calculated using the Kaplan Meier method.

CHAPTER THREE

RESULTS

3.1 INTRODUCTION

The criterion for judging the efficacy of the treatment in this study was straightforward; two years after the initial radiation treatment, the patients had either survived or succumbed. It was not possible to run a control group of cats but the photos of two patients that were not treated, but tracked, are shown below.



Figure 3.1 The appearance at presentation and the lesion two months later, before euthanasia

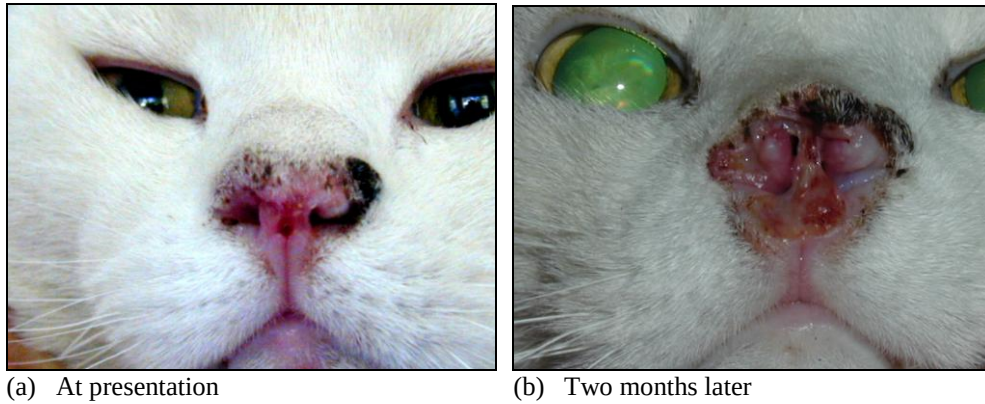


Figure 3.2: The appearance at presentation and the lesion two months later before euthanasia

These patients emphasise the rapid growth of the tumour once it is clinically visible. Both cats were monitored from the time of first presentation when they were graded as T3 to two months later when the cats were euthanased. Without treatment the tumour at stage 3 progressed very rapidly.

The data retrieved for each cat in the study were age, sex, total radiation dose (Gy) and the survival rate measured at six monthly intervals up to twenty-four months (Table 3.1). The total population was 75 and this consisted of the four groupings with reference to the severity of the nasal planum tumour T1 (n=16 i.e. 21%), T2 (n=15 i.e. 20%), T3 (n=24 i.e.32%) and T4 (n=20 i.e.27%) as summarised in Table 3.1 page 42.

During the two year period, twelve of the 75 cats died of non-related disease, four from group T1, four from group T2, one from group T3 and three from group T4 see Table 3.1. It is interesting to note that of the cats that survived the two year period, up until 2004, only one cat from the T1 group had died from squamous cell

carcinoma after 44 months, one cat from the grade T2 group after 41 months and one from the grade T3 group at 33 months. The other surviving cats were either still alive or had died from non-related diseases.

3.2 STATISTICAL ANALYSIS OF THE RADIATION TREATMENT

It should be noted that statistically these are small sample sizes. The results were submitted to statistical analysis to establish whether the factors of age, sex and total radiation dose were significantly related to tumour grade. The analysis was started by testing for differences in sex using the Chi squared test. The differences of the age of the cat, the tumour levels, the total radiation dose and the tumour level were examined by using the Kruskal Wallace test with tied ranks (Zar 1996) as the data were not normally distributed. The total data set was analysed using Cox's regression analysis.

Table 3.1 shows the data collected for survival, age, sex, number of treatments, total number of Gy., number of re-treatments, (censored or complete) tumour grade, number of individual patient per grade, and the patients that died of non-related diseases. divided into the four tumour level groups T1, T2, T3 and T4.

**Table 3.1 Data collected in this study grouped into tumour levels
T1, T2, T3 and T4**

Group T1 –Tumor 1

Survival (mnths)	Age (yrs)	Sex	No.treat	Tot Gys	Re- treats	Censored	Tumour Grade	Cat number	N/R
24	9	F	2	4	0	censored	Tumour 1	1	
24	4	M	3	4	1	censored	Tumour 1	2	
24	9	M	2	4	0	censored	Tumour 1	3	
24	13	F	2	4	0	censored	Tumour 1	4	
24	7	F	2	6	0	censored	Tumour 1	5	
24	13	M	2	6	0	censored	Tumour 1	6	
24	10	M	1	2	0	censored	Tumour 1	7	
24	7	F	2	4	0	censored	Tumour 1	8	
24	18	F	2	4	0	censored	Tumour 1	9	
24	9	M	5	13	2	censored	Tumour 1	10	
24	16	F	2	6	0	censored	Tumour 1	11	
24	8	F	2	4	0	censored	Tumour 1	12	
18	10	F	2	6	0	censored	Tumour 1	13	N/R
6	10	F	2	5	0	censored	Tumour 1	14	N/R
12	7	M	2	6	0	censored	Tumour 1	15	N/R
12	12	F	1	3	0	censored	Tumour 1	16	N/R

Group 2 – Tumour Grade 2

Survival (mnths)	Age (yrs)	Sex	No.treat	Tot Gys	Re- treats	Censored	Tumour Grade	Cat number	N/R
24	15	M	2	6	1	censored	Tumour 2	1	
24	17	F	2	6	0	censored	Tumour 2	2	
24	14	F	3	6	0	censored	Tumour 2	3	
24	13	F	3	9	0	censored	Tumour 2	4	
12	8	M	4	11	1	complete	Tumour 2	5	
24	8	M	1	4	0	censored	Tumour 2	6	
12	10	F	4	9	0	complete	Tumour 2	7	
24	6	M	2	6	0	censored	Tumour 2	8	
24	10	F	2	6	0	censored	Tumour 2	9	
24	7	M	6	20	1	censored	Tumour 2	10	
12	10	M	4	12	1	censored	Tumour 2	11	N/R
12	8	F	6	18	1	censored	Tumour 2	12	N/R
4	14	F	3	6	0	censored	Tumour 2	13	N/R
14	7	M	10	31	2	censored	Tumour 2	14	N/R
24	9	F	2	4	0	censored	Tumour 2	15	

Group 3 – Tumour Grade 3

Survival (mnths)	Age (yrs)	Sex	No.treat	Tot Gys	Re-treats	Censored	Tumour Grade	Cat number	N/R
24	10	F	3	8	0	censored	Tumour 3	1	
24	12	M	5	24	1	censored	Tumour 3	2	
24	8	F	5	10	1	censored	Tumour 3	3	
24	8	M	3	9	0	censored	Tumour 3	4	
6	18	F	5	10	1	complete	Tumour 3	5	
4	14	F	5	23	1	complete	Tumour 3	6	
11	7	M	4	8	0	complete	Tumour 3	7	
5	8	F	6	15	1	complete	Tumour 3	8	
3	14	F	2	4	0	complete	Tumour 3	9	
24	13	F	8	19	1	censored	Tumour 3	10	
17	8	F	11	29	3	complete	Tumour 3	11	
9	12	M	5	15	0	complete	Tumour 3	12	
17	7	F	11	29	1	complete	Tumour 3	13	
8	11	F	4	8	0	complete	Tumour 3	14	
24	9	M	5	14	1	censored	Tumour 3	15	
14	7	F	7	14	1	complete	Tumour 3	16	
7	9	F	7	21	1	complete	Tumour 3	17	
12	9	F	6	23	0	complete	Tumour 3	18	
24	8	F	4	12	0	censored	Tumour 3	19	
12	10	M	5	15	0	censored	Tumour 3	20	N/R
12	12	M	15	35	1	complete	Tumour 3	21	
12	10	F	9	20	2	complete	Tumour 3	22	
24	13	F	6	18	0	censored	Tumour 3	23	
24	12	F	9	25	1	censored	Tumour 3	24	

Group 4– Tumour Grade 4

Survival (mnths)	Age (yrs)	Sex	No.treat	Tot Gys	Re-treats	Censored	Tumour Grade	Cat number	N/R
4	19	M	12	38	1	complete	Tumour 4	1	
5	16	F	6	18	0	complete	Tumour 4	2	
14	13	F	6	18	0	complete	Tumour 4	3	
6	11	F	5	10	0	complete	Tumour 4	4	
18	13	F	15	38	1	complete	Tumour 4	5	
15	15	M	8	26	2	complete	Tumour 4	6	
19	11	M	9	27	1	complete	Tumour 4	7	
6	13	M	6	15	0	complete	Tumour 4	8	
11	14	F	11	37	3	complete	Tumour 4	9	
12	8	M	11	34	2	complete	Tumour 4	10	
2	15	M	4	12	0	complete	Tumour 4	11	
4	13	M	15	61	0	complete	Tumour 4	12	
2	7	F	6	23	0	complete	Tumour 4	13	
6	17	M	12	39	0	complete	Tumour 4	14	
2	10	F	6	17	1	complete	Tumour 4	15	
5	13	F	11	38	1	complete	Tumour 4	16	
6	3	M	10	27	2	censored	Tumour 4	17	N/R
6	8	M	6	21	0	censored	Tumour 4	18	N/R
5	13	F	2	6	0	complete	Tumour 4	19	
6	23	M	5	15	0	censored	Tumour 4	20	N/R

Key: S - survival, D- dead, No r - number of treatments, N/R-non-related disease
Re-treats - number of repeat treatments. Cats were numbered individually within the groups.

3.2.1 Male to female ratio at different tumour levels

Overall there were more female cats (44) than males (31) presented. Equal numbers of cats could have been expected in each group.

Table 3.2 The distribution of male and female cats at the different tumour grades.

	T1	T2	T3	T4	Total
Male	6	7	7	11	31
Female	10	8	17	9	44

When tested using the Chi-square test it was found there were no significant differences between groups and that the tumour grade is independent of sex ($\chi^2 = 4.4922$, $v = 3$, $0.25 > P > 0.10$).

3.2.2 Male to female ratio radiation dose

The mean number of Gys given was slightly higher for males (mean = 17.33 Gys) than females (mean = 14.22 Gys). When compared using the Chi-square test the results were not found to be significantly different, ($\chi^2 = 0.3183$, $0.50 < P < 0.75$). On the basis of these two results, the data from male and female cats were pooled for each tumour grade.

3.2.3 Age and tumour levels.

The ages of the 75 cats ranged from 3 to 23 years. The overall mean age was 10.96 years $\pm$ 3.7. The mean age was relatively constant in groups T1-T3 (T1-10.1 years; T2-10.4 years; T3-10.4 years), but as expected was higher in the group T4 being 12.8 years. Surprisingly one cat in Group 4 was only three years old. When results were compared using the Kruskal Wallis test, differences were not significant ($H = 2.952$, $\chi^2_{0.05} = 7.815$, $v = 3$, $0.25 > P < 0.10$).

3.2.4 Mean total radiation dose Gys at different tumour levels

The mean total radiation dose for each group was T1=5 Gy, T2=10 Gy, T3=17 Gy and T4=26 Gy. When results were compared using the Kruskal

Wallis test with paired ranks they were found to be highly significant ($H = 43.88$, $\chi^2_{0.001} = 16.266$, $v = 3$, $P=0.001$).

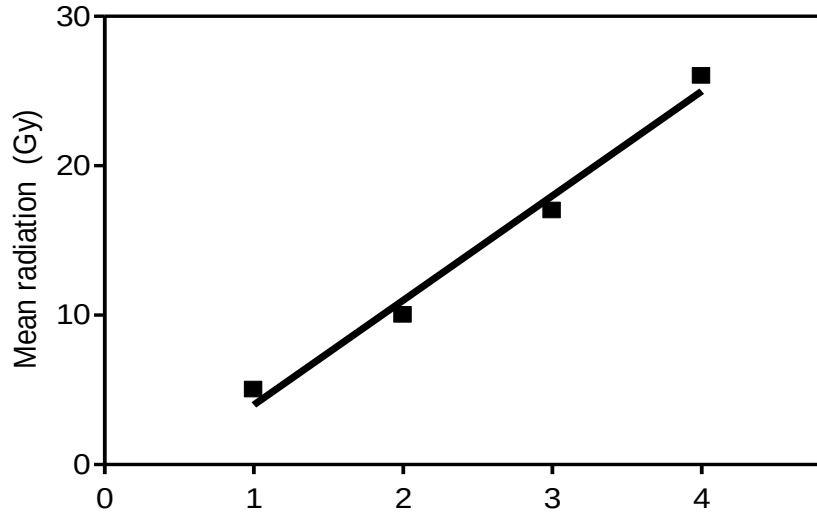


Figure 3.3 The mean total radiation dose (Gys) at the different tumour levels

Clinically this result would be expected, as a higher radiation dose would be required to eliminate a greater tumour volume (T4) than a smaller tumour volume (T1).

3.2.5 Number of treatments

One would expect that the cats with the smaller tumours would need fewer treatments than those with larger tumors. The mean number of treatments for each group is as follows: T1 - 2, T2 - 4, T3 - 6 and T4 - 9 treatments. When tested with one way Kruskal Wallis test with tied ranks these results were found to be significantly different ($H=35.348$, $\chi^2 = 16.2266$, $v = 3$, $P = 0.001$).

3.2.6 Survival analysis

A Cox regression analysis was prepared with SAS for Windows (Version 9.1; SAS Institute Inc, Cary NC, USA) using the proportional hazards procedure.

The overall survival was calculated using all the dependent variables of age, sex, number of treatments, re-treatments, total Gy, tumour grade (Figure 3.4).

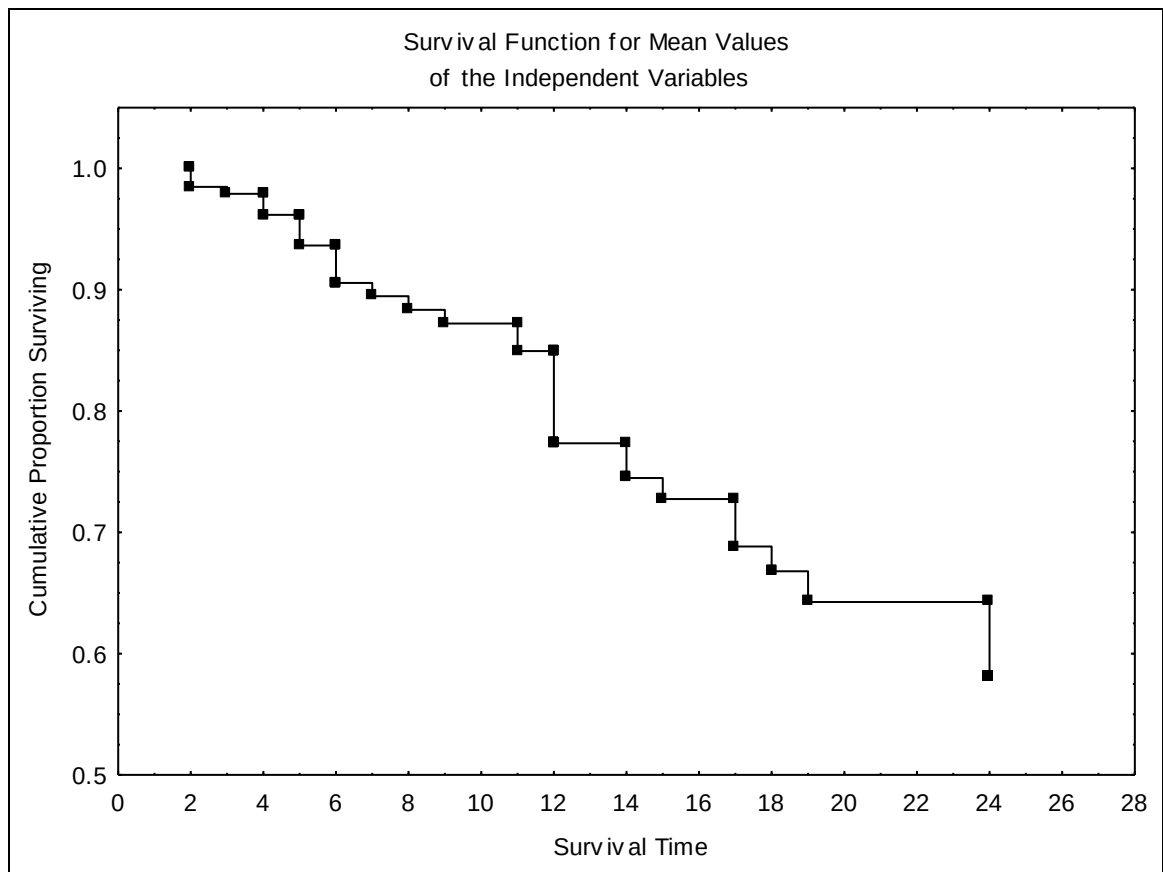


Figure 3.4 Survival function for mean values of all independent variables.

Dependent Variable: survival Censoring var.: censored

Chi² = 48.7749 df = 6 p = .00000 N = 75

	Beta	Std. Err.	t-value	Exp beta	Wald St	P
Age	0.011121	0.056203	0.19787	1.011183	0.03915	0.843148
Sex	-0.467905	0.384804	-1.21595	0.626313	1.47855	0.224011

No. Treat	-0.068422	0.143820	-0.47575	0.933866	0.22634	0.634257
Total Gys	0.022761	0.048874	0.46572	1.023022	0.21689	0.641422
Retreats	-0.065125	0.244784	-0.26605	0.936950	0.07078	0.790201
Grade	1.452949	0.317201	4.58053	4.275707	20.98126	0.000005

The results showed a highly statistically significant effect of tumour grade on cat survival ($P < 0.0000$), but no significant effect for the other independent variables.

Maximum likelihood estimates for tumour pre-treatment group indicator, sex and age (explanatory variables) can be seen in Table 3.3

Table 3.3 Analysis of maximum likelihood estimates

	Parameter		Standard			Hazard
Variable	DF	Estimate	Error	Chi-Square	Pr>Chi Square	Ratio
Tumour	1	0.80682	0.19224	17.6137	<.0001	2.241
Age	1	0.04849	0.05623	0.7435	0.3886	1.050
Sex	1	0.11872	0.34336	0.1196	0.7295	1.126

The tumour was considered here as a continuous variable and further analysis with separated tumour groups showed that the differences between tumour groups were highly significant. The results for T4 were used as the baseline for the calculations. See Table 3.4. Although T1 (H (1)) and T2 (H (2)) differed significantly from T4 they did not vary substantially from each other. The results were combined to produce the graph below (Figure 3.5).

Table 3.4 Cox (proportional hazards) regression

Deviance (likelihood ratio) chi-square = 7.554558 df = 4 P = 0.1093

H (1)	b1 = -2.041194	z = -3.829192	P = 0.0001
H (2)	b2 = -2.61781	z = -3.433797	P = 0.0006
H (3)	b3 = -1.054874	z = -2.778781	P = 0.0055
H (4)	b4 = 0	z = *	P < 0.0001

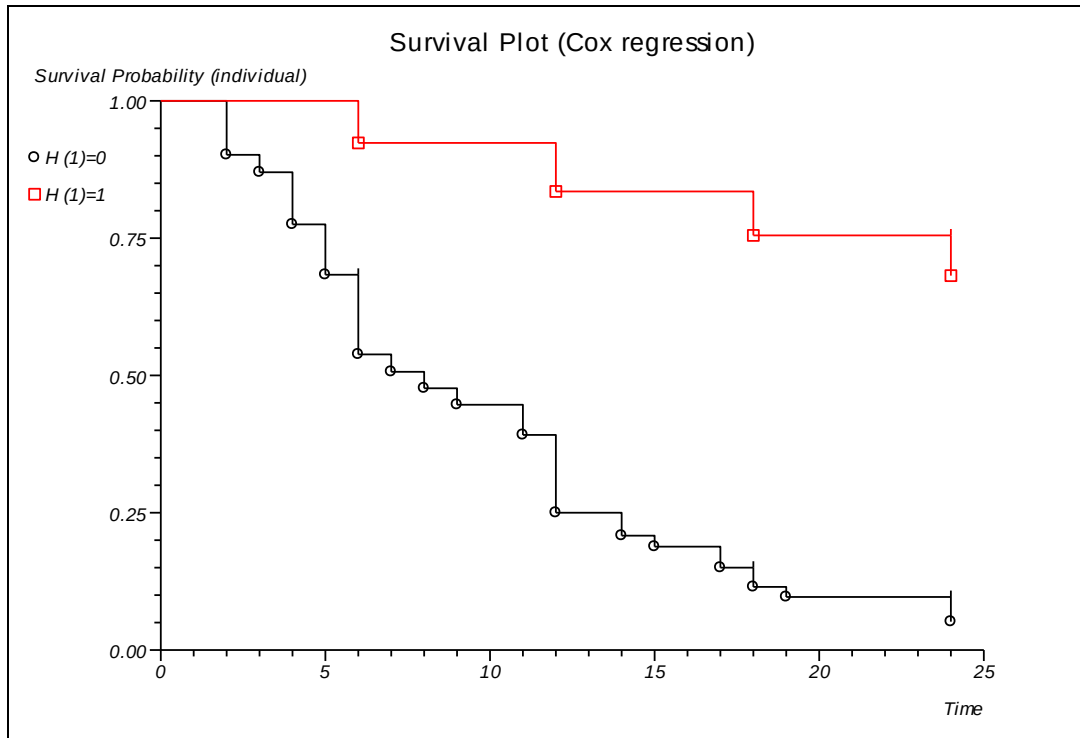


Figure 3.5 Survival graph using Cox regression combining the results of T1 and T2 (red) and T3 and T4 (black) showing the survival probability of the individual together with the tumour levels

A simple Kaplan Meier analysis also showed that tumour grade at presentation had a highly statistically significant effect on survival ($P < 0.00001$) as illustrated by the all graphs below (See Figure 3.6). Deaths among T1 and T2 cats were from non related causes.

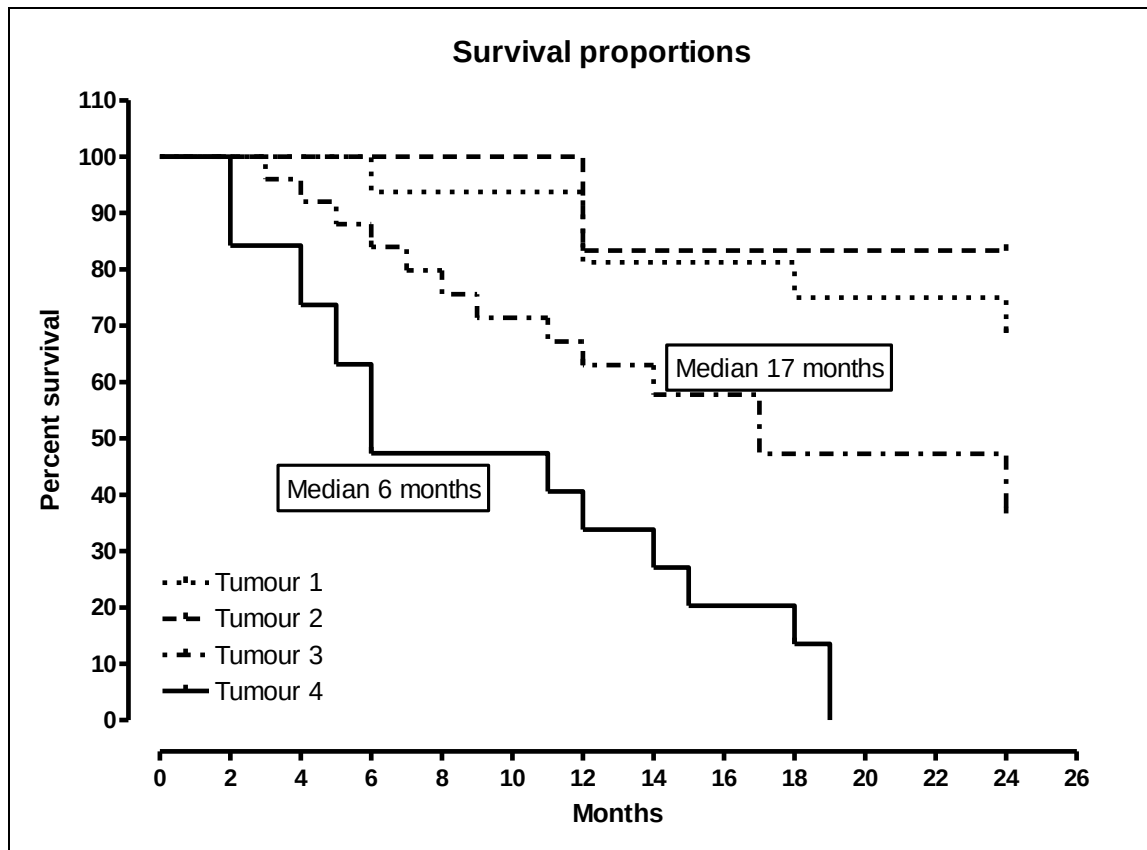


Figure 3.6 Kaplan –Meier survival graph for cats at the different tumour levels and the median values for T3 and T4.

3.3 THE LONG-TERM FOLLOW UP OF CATS THAT SURVIVED THE 24-MONTH STUDY

Although the results of this study were based on a twenty-four month survival period, the surviving cats were tracked until November 2004 and, for interest and for the sake of completion, these results are recorded in Table 3.4. Because environmental control was not followed by most owners it was not possible to know if the recurrence of the tumour was due to insufficient initial radiation of the tumours or if they were newly acquired squamous cell carcinomas.

Table 3.5 Additional information on cats that survived longer than 24 months

T1				
Cat No	Alive (Months)	Dead SCC (Months)	Dead N/R (Months)	Comments
1			25	
2	71			Re-treated (3X2Gys) after 52m. Compliance scored 3
3			45	
4			55	
5	63			Recurred after 29m re-treated
6	72			
7		44		
8			25	Compliance scored two
9			45	
10	27			Re-treated (3X3Gys) cannot trace
11			37	

T2				
Cat no	Alive (Months)	Dead SCC (Months)	Dead N/R (Months)	Comments
1			36	Compliance scored two
2	52			Re-treated after 41 months
3			61	
4	33			Cannot trace after 01/02
6		41		
8	51			
9	51			
10			37	

T3				
Cat no	Alive (Months)	Dead SCC (Months)	Dead N/R (Months)	Comments
1			81	
2		26		
3			61	
4			54	
10		33		
19	43			

Key: N/R- death due to non-related causes. Cat no - the individual cats recorded.

Alive - living x months after first radiation treatment. Com - compliance. Grade T1 number 2*- compliance score of three (cat is still alive aged 11years, seven years after first treatment)

Two cats could not be traced, T1 (No 10) after 27 months and T2 (No 4) after 33 months. Only one cat in Grade T1 died of squamous cell carcinoma, 44 months after treatment. In the Grade T2 group one cat died of squamous cell carcinoma, 41 months after treatment. In the T3 group of the six that survived the 24-month period, one was alive after 43 months, two succumbed to squamous cell carcinoma and three died from non-related diseases. None of the cats in T4 group survived the 24 months post radiation period and all died due to squamous cell carcinoma of the nasal planum.

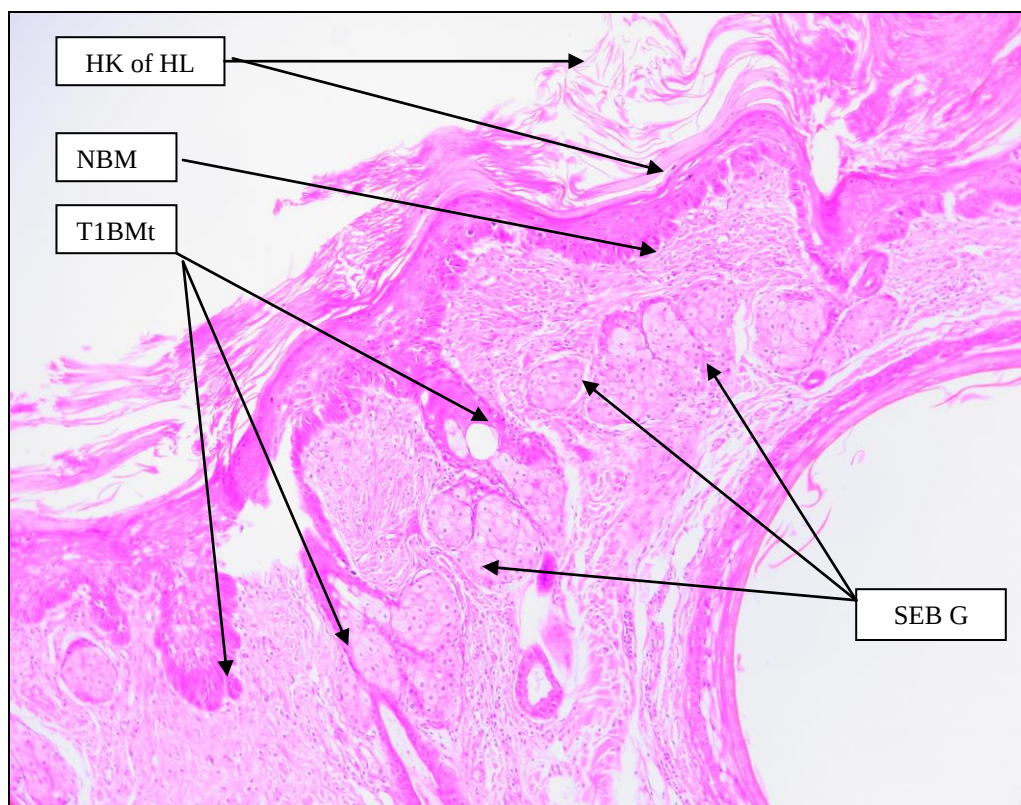
3.4 HISTOLOGICAL CHANGES OF THE NASAL PLANUM TISSUE DURING THE COURSE OF THE DISEASE

In examining the slides of normal tissue of the nasal planum, it was found to be unique. Although visually the nasal planum appears to be thick skin, histologically it seems to fall between the thick epidermis of the pads of the paws and the thin epidermis of the body. Thick epidermis has five strata: cornium, lucidum, granulosum, spinosum and basale whilst thin epidermis has three strata: corneum, spinosum and basale. The nasal planum tissue has three strata: cornium, spinosum and basale and although these layers are those of thin skin, the depth of the spinosum reflects that of the thick epidermis. The histology of the normal healthy tissue has been described in Section 1.6 (page 9) of this study.

The sectioned and stained biopsy material the origin of which was recorded in Section 2.5 on page 34, is now examined and the histology described.

3.4.1 The histopathology of an early well-differentiated squamous cell carcinoma

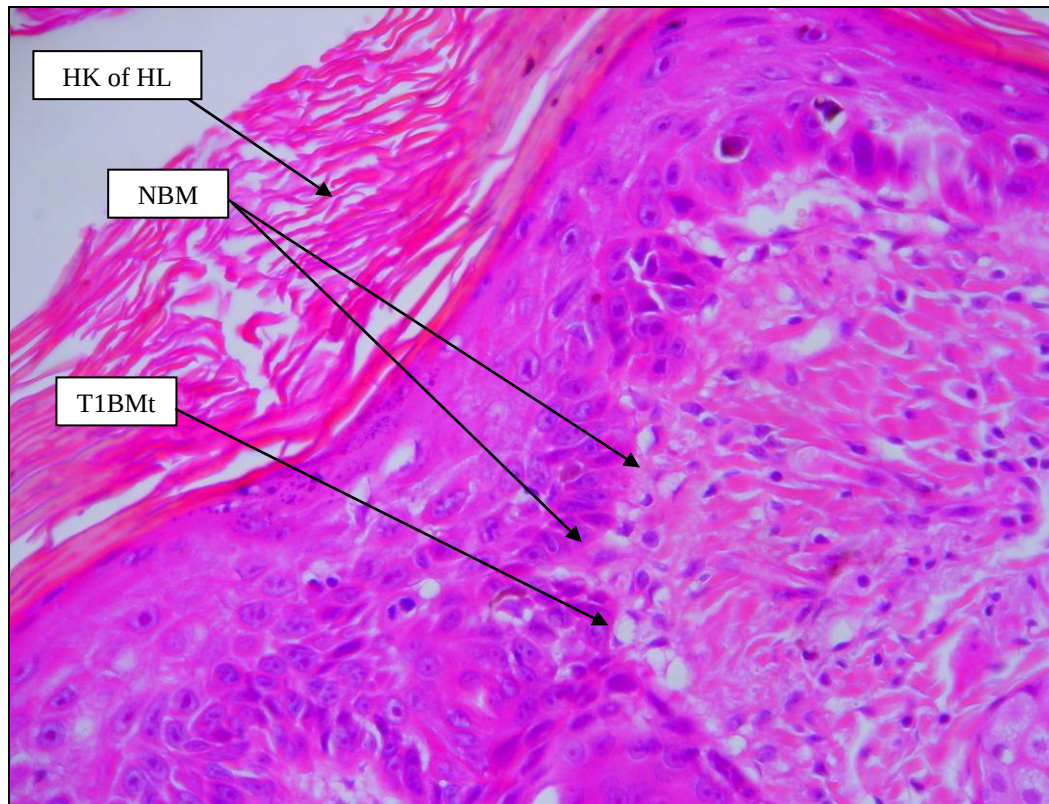
The section (Figure 3.7) shows an early well-differentiated tumour of the non-pigmented nasal planum. There is hyperkeratosis and crust formation in the horny layer and early dysplastic changes in the basal cells of the epidermis. Note that there is no melanin in the basal cells. Trabeculae of neoplastic cells are starting to infiltrate into the dermis. The sebaceous glands are clearly visible. The glands appear to be stimulated in the early stages of the disease, the waxy exudate traps dust and fine dirt and often the first warning sign of pre-cancerous tissue is the observant owner recognising this symptom (see Figure 2.1 on page 33).



Key: HK of HL - hyperkeratosis of the horny layer, NBM- normal basement membrane, T1 BMt - tumour showing dysplasia of the basement membrane (the start of SCC) with trabeculae of neoplastic cells infiltrating the dermis, SEB G - sebaceous gland

Figure 3.7 Well-differentiated squamous cell carcinoma (X 40)

The following section (Figure 3.8) is also of an early well-differentiated tumour and is at a higher magnification than that of (Figure 3.7). It shows the strands of hyperkeratosis, the disturbance of the basement membrane and the infiltrating trabecula of the squamous cell carcinoma.



Key: HK of HL - Hyperkeratosis of the horny layer, NBM - normal basement membrane, T1 B Mt - tumour showing dysplasia of the basement membrane and infiltrating trabecula.

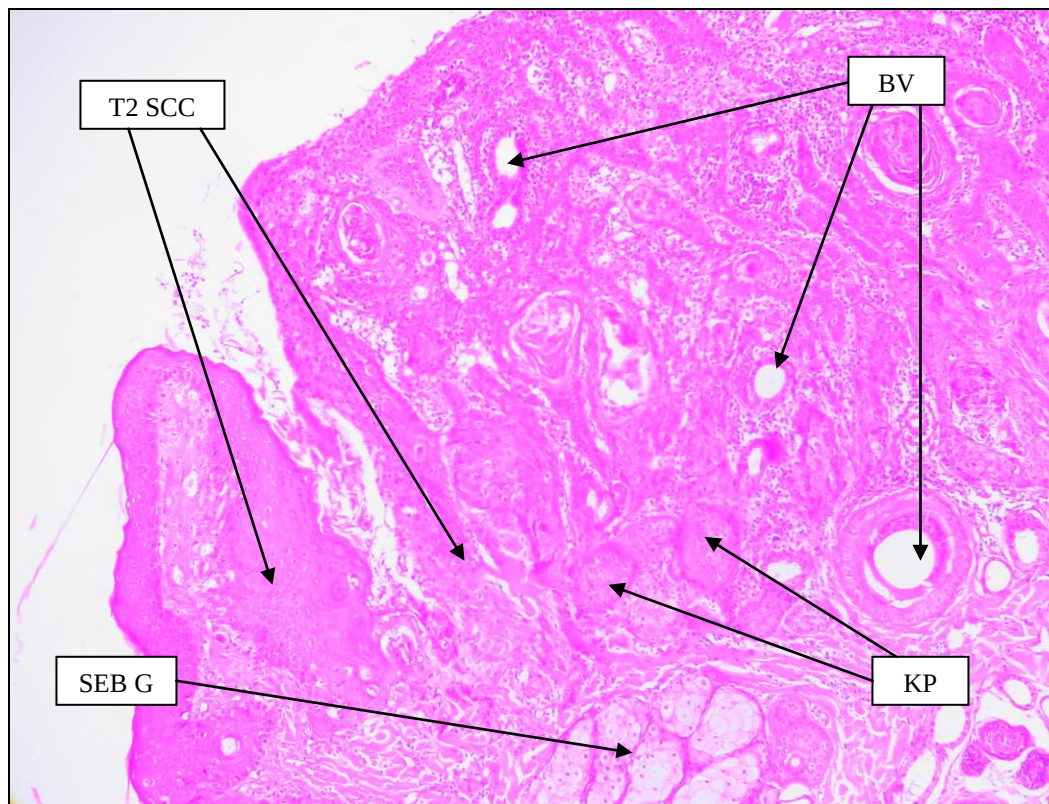
Figure 3.8 Well-differentiated squamous cell carcinoma (X 400)

Clinically the nasal planum would have the appearance of a T1 tumour that is shown in the text as Figure 2.1 on page 33.

3.4.2 The histopathology of the intermediate (T2 and T3) squamous cell carcinoma

Two typical sections of an intermediate infiltrating squamous cell carcinoma (Figure 3.9 on page 55 and Figure 3.10 on page 56) are shown arising from a carcinoma of the epidermis. There is neo-vascularisation and early keratin

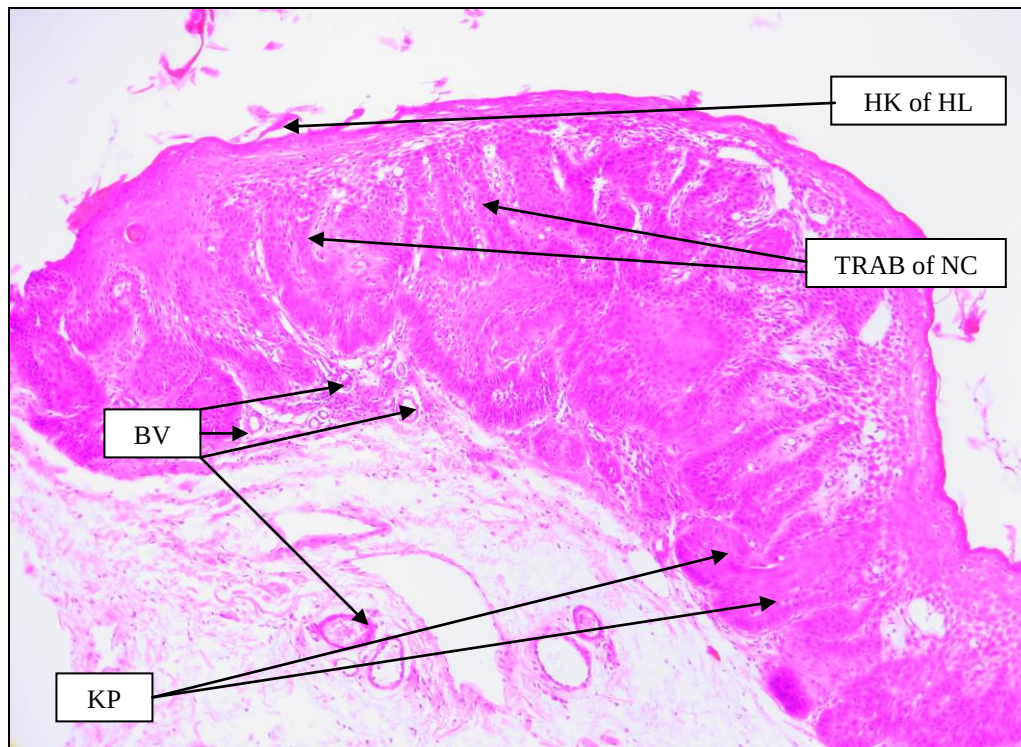
pearl formation in addition to those changes already shown in Figure 3.7 and Figure 3.8. It is interesting to note that the sebaceous glands can still be distinguished in Figure 3.9 but not in Figure 3.10 and that the hyperkeratosis has disappeared in Figure 3.9 and is greatly diminished in Figure 3.10.



Key: BV - blood vessels, KP - keratin pearls, HK of HL- hyperkeratosis of the horny layer (greatly diminished), T2 SCC - Grade T2 squamous cell carcinoma

Figure 3.9 Intermediate squamous cell carcinoma (X 100)

Clinically these tumours are painful and tend to bleed easily when bumped, when the cat eats or grooms itself. This happens because the protective squamous layer is either no longer present or greatly diminished in thickness and there is an abundance of blood vessels in and around the tumour tissue.



Key: BV - blood vessels, KP - keratin pearls, TRAB of NC - trabeculae of neoplastic cells, HK of HL - hyperkeratosis of the horny layer (greatly diminished)

Figure 3.10 Intermediate squamous cell carcinoma, (X 100)

3.4.3 The poorly-differentiated (T3 and T4) squamous cell carcinomas

The following sections in Figure 3.11, Figure 3.12 and Figure 3.13 show the extreme damage that is caused to the integrity of the epidermis, dermis and cartilage of the nasal turbinates by the squamous cell carcinoma. Usually the healthy unbroken junction between the cartilage and the dermis is clinically easy to appreciate when visually grading tumours (Figure 2.1 on page 33). However, when this junction is disturbed the nasal turbinates become visible and resulting carcinoma will be graded a T4 (Figure 2.1).

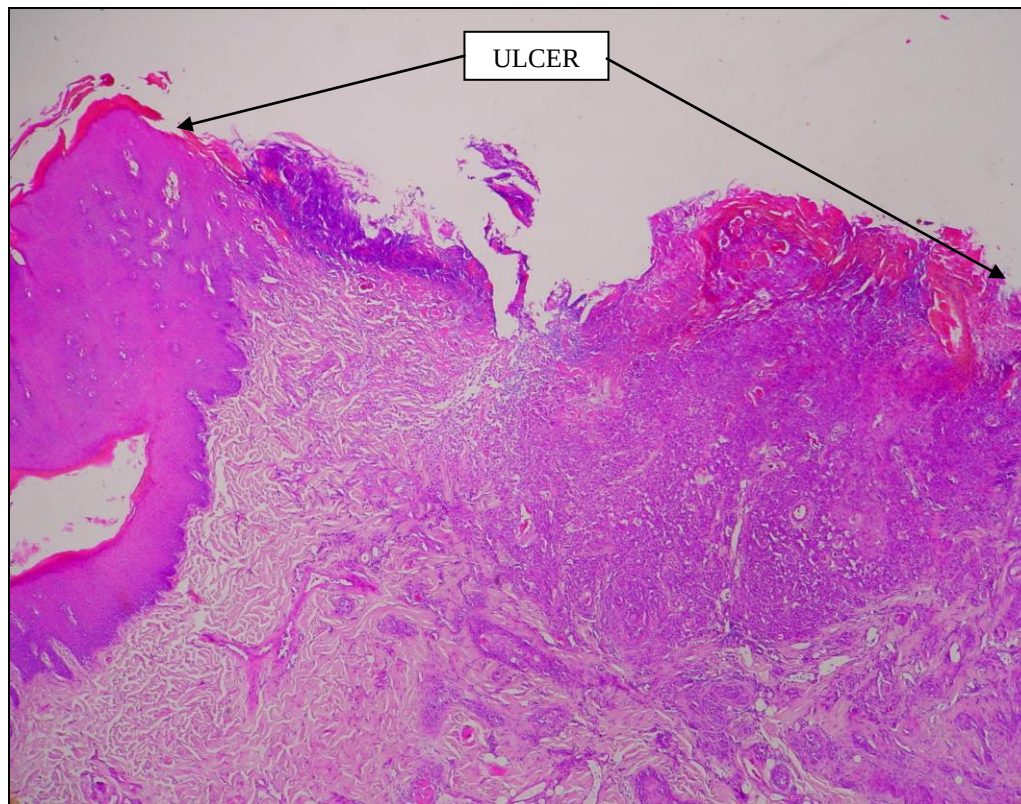
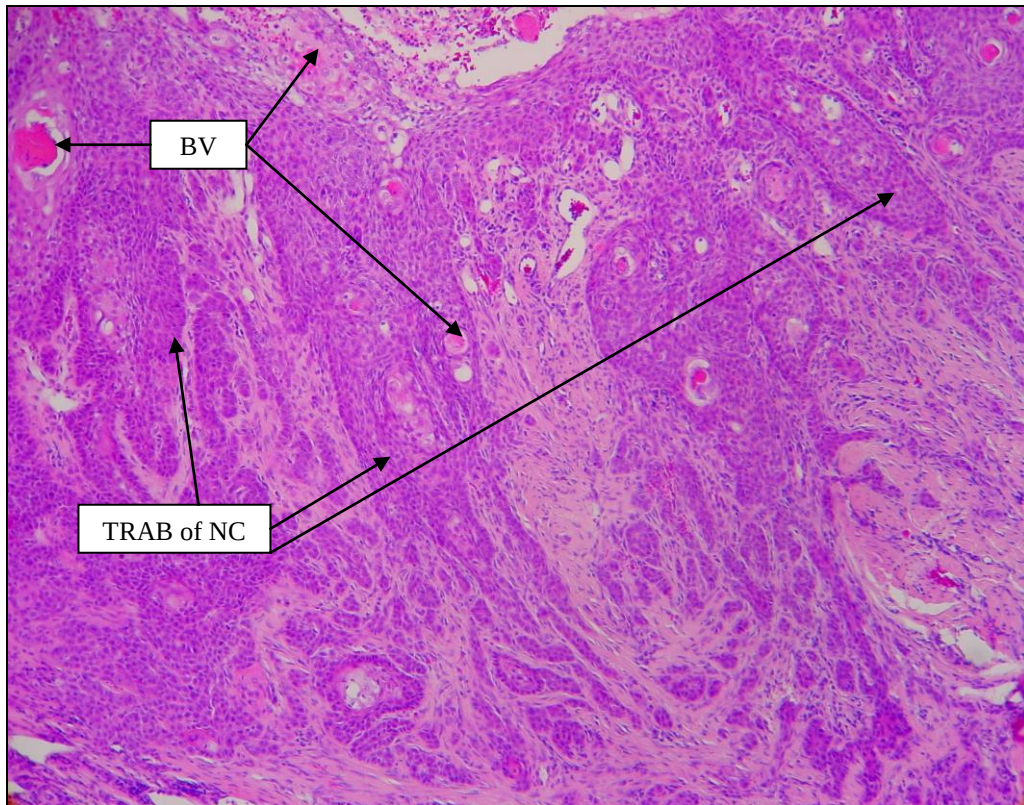


Figure 3.11 Poorly-differentiated squamous cell carcinoma, (X 40).

In Figure 3.11 there is a deep ulcer through the epidermis and the dermis with resulting inflammation and crust formation. Around the ulcer there is some degree of hyperkeratosis of the horny layer visible. The sub-epithelial tissue contains numerous proliferating cords and nests of malignant neoplastic cells originating from the overlying epithelium. A few indistinct attempts at keratin pearl formation are seen and the basement membrane has been breached. No sebaceous glands are visible.

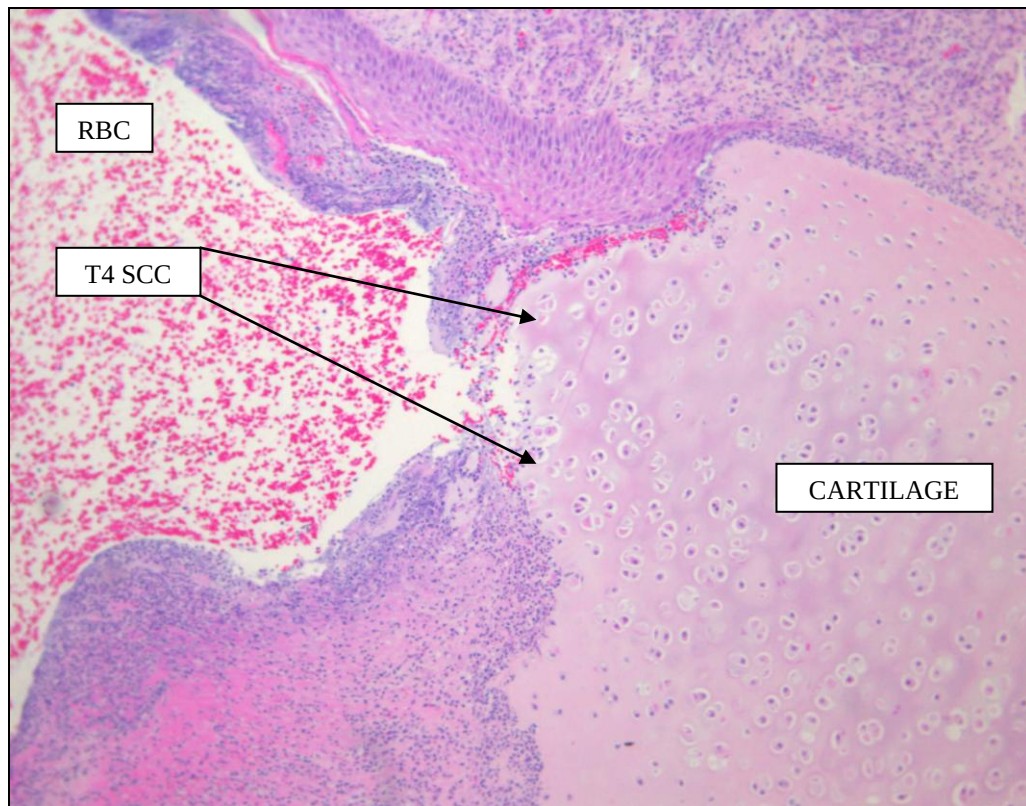
When examining this section it becomes obvious why the area from which the biopsy is taken is would influence the histological grading of the squamous cell tumour.



Key: BV - blood vessels, TRAB of NC - trabeculae of neoplastic cells

Figure 3.12 Poorly-differentiated squamous cell carcinoma (X 100)

The neoplastic tissue is highly invasive. Numerous blood vessels can be seen together with trabeculae of neoplastic cells penetrating the dermis.



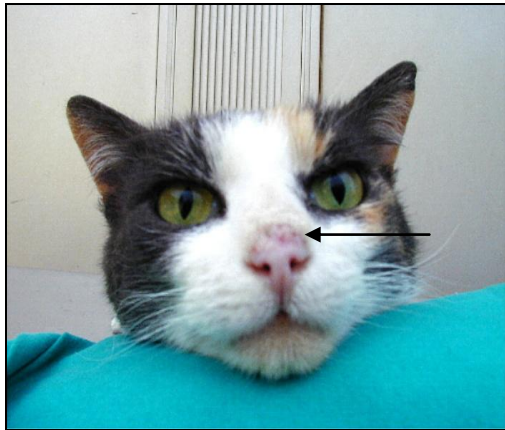
Key: T4 SCC - Poorly-differentiated squamous cell carcinoma, RBC – erythrocytes

Figure 3.13 Poorly differentiated squamous cell carcinoma (X 40).

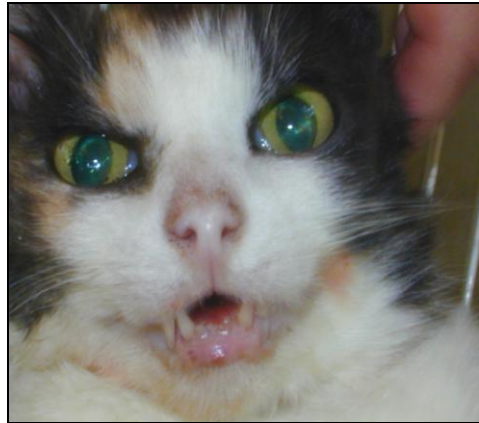
This section shows the poorly differentiated tumour (Grade T4) invading the nasal cartilage. The basement membrane has been breached and the tumour has spread from the epidermis, to the dermis and is invading the cartilage. The normal architecture of the junction between the dermis and the cartilage as seen in (Figure 1.5 on page 12) has been destroyed by the tumour.

3.5 VISUAL RESULTS OF ONE PATIENT FROM EACH GRADE

The following photographs are part of the treatment record. This record keeping makes it easy to show the client the result of the treatment. The pictures are printed in colour and given to the client. This allows the client to continually monitor his or her cat and be aware if tumour re-growth occurs.



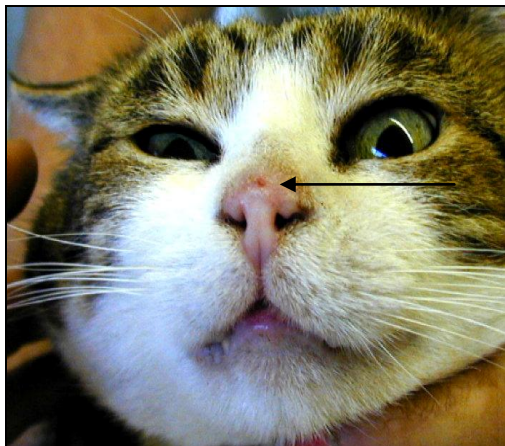
(a) at presentation



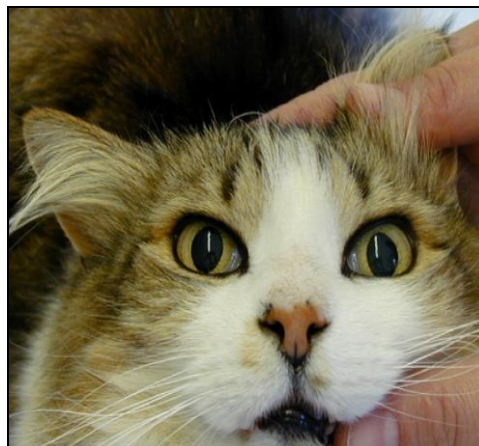
(b) twenty-four months later

The arrow shows the black flecks on the nasal planum

Figure 3.14: Grade T1. The appearance at presentation and the lesion twenty-four months later



(a) at presentation



(b) twenty-four months later

Figure 3.15: Grade T2 The appearance at presentation and the lesion twenty-four months later



(a) at presentation



(b) twenty-four months later

Figure 3.16: Grade T3 The appearance at presentation and the lesion twenty-four months later



(a) at presentation



(b) twenty-four months later there were no survivors

Figure 3.17 Grade T4 The appearance at presentation,

3.6 SIDE EFFECTS OF RADIATION ON THE NASAL PLANUM

There was no evidence of erythema, dry desquamation, pruritus or necrosis. Localised hair loss occurred in a few of the Grade 4 cases but the hair regrew after about six weeks. The late side effects of retinal degeneration and cataract formation were not observed at any time.

3.7 THE COST OF THE TREATMENT ACCORDING TO THE GRADE OF THE TUMOUR

The cost of radiation per treatment at the University during this study (1999-2002) was R75.00, This included the veterinary fee together with the cost of the anaesthetic. It is interesting to note that currently in a private facility the cost is R385.00 per treatment.

Table 3.6 Number and cost of treatments/grade

Tumour Grade	Number of treatments	Cost (1999-2002) University	Current cost at private facility
1	3 (3X2Gy)	R225.00	R1155.00
2	4 (4X2Gy)	R300.00	R1542.00
3	5 (5X3Gy)	R375.00	R1920.00
4	9 (9X3Gy)	R625.00	R3465.00

3.8 THE VIABILITY OF ENVIRONMENTAL CONTROL

The owners were advised to limit their cat's exposure to solar radiation at the initial consultation and reminded of this important aspect regularly. However it was apparent during the monitoring of the study that very few owners followed the recommendation.

On the 'honesty scale' 1-3 (least to best), (pages 50 and 54), only two of the 75 owners scored two, and one owner scored a three. No statistical analysis is possible with such low numbers but for the sake of completion the three cats were tracked. Interestingly, of the two owners who 'tried' (score two on the scale 1-3) to control

their cats exposure to UVB, cat (Grade T1 No. 8) lived for 25 months and died of a non-related cause and cat (Grade T2 No. 1) lived for 36 months and died of a non-related cause. The one owner who did score three has a cat that is now eleven years old, seven years after the initial radiation treatment.

CHAPTER FOUR

DISCUSSION

4.1 INTRODUCTION

Radiation treatment of the squamous cell carcinoma tumour of the nasal planum is dependent on the tumour cells' response to the radiation. The UVB rays' damage to the DNA of the basement membrane cell has been discussed in Chapter One. However it is not known how long it takes before the tumour can be seen clinically. It appears that the condition may develop slowly over months, or even years, but at a certain point the rate of tumour growth becomes exponential. This time is dependent on the cell cycle of the proliferating cells, the fraction of the total tumour cell population that is dividing and the degree of cell loss from the tumour (LaTorre Travis, 1989). Pictures of the two cats (Figure 3.1 and Figure 3.2 on pages 39 and 40) that did not receive any treatment show how fast this exponential growth can be.

Histological examination is an effective method of confirming the presence of the squamous cell carcinoma tumour. However taking a biopsy for grading a tumour has certain drawbacks, these difficulties include the following: the area of the tumour from which the biopsy has been taken, the fact that the tumour would flare up aggressively after the biopsy was taken, the extra expense to the owner and most importantly the unnecessary discomfort to the cat.

Environmental control was practical and possible but it was difficult to convince owners of the benefit, whilst the cost of the radiation therapy was so inexpensive at the subsidised university rate. The fact that the owners were not convinced during this study to limit their cats' exposure to UVB was disappointing, even though as time went by it was evident that the cats could adjust to the environmental control. The new clients were shown pictures of patients that had been environmentally controlled, in comparison to those that had not and this has led to an increase in the environmental control on the part of the owners, resulting in this aspect of the treatment improving. The fact that radiation treatment is now considerably more expensive is an added inducement for environmental control.

4.2 COMPARISON TO OTHER STUDIES

The aim of every cancer therapy is to permanently remove all the cancer and pre-cancerous cells. However, direct comparison of the previous studies is difficult because of the wide range of treatments, the lack of grading of the subjects and the different defined end points, Clarke (1991), Peaston et al. (1993) and Theon et al. (1995) reported the same difficulty in comparing their work to other studies. However, if no comparison is made, then this study joins most of the other studies in coming to no definite conclusion as to the value of the treatment. It also leaves the veterinarian in practice unable to guide his/her client in the choice of treatments available.

In general, the results of this study compared satisfactorily to the six different therapies (surgery, cryotherapy, hyperthermia, photodynamic therapy,

chemotherapy and various radiation therapies) reviewed in this study in terms of survival. Although this study can only be directly compared to the visually graded studies of Theon et al. (1995) and Magne et al. (1997) the other forms of grading, treatment and results are included for completeness.

4.2.1 Grading of the tumours

Table 1.2 (page 26) summarises the form of therapy, the number of cats in the study and whether or not the cats' tumours were graded.

a) No grading.

Seven of the fifteen studies in Table 1.2 did not record any grading: Atwater et al. (1991), Clarke (1991), Orenberg (1992), Roberts et al. (1991) and Lana et al. (1997) (Lana's study covered surgical, cryotherapy and radiation therapy). On a survival judgment with non-graded tumours, the range of the results for surgery, cryotherapy and cobalt radiation treatment was large.

b) Histological grading.

Three studies were graded into well or poorly differentiated tumours Bostock et al. (1972), Withrow and Straw (1990) and Peaston et al. (1993). Theon et al. (1995) graded histologically into three groups. Three studies dealt with only the well-differentiated tumours: Grier et al. (1980), Evans et al. (1985) and Van Vechten (1993).

c) Visual grading.

The clinical visual appearance of the nasal planum tumour is very important as this is when the owner and the clinician first become aware of the tumour. The

greater the destruction of the normal configuration of the nasal planum, the higher the grading. An adaptation from The World Health Organisation (WHO) (Table 2.2 on page 32) was used to grade the patients. Magne et al. (1997) grouped the patients into three, on size and invasiveness of the tumour. Theon et al. (1995) grouped into four (Note that Theon also graded histologically into three groups). This present study grouped the cats into four grades. Experience from the present study found that use of four grades was both practical and satisfactory.

Table 4.1. Visual grading of three studies; percentage of each grade at presentation

Study	Total no of cats	T1 %	T2 %	T3 %	T4 %
Magne et al. (1997)	61	(T1a) 25%		(T1b) 30%	(T2) 45%
Theon et al. (1995)	90	17%	31%	37%	27%
Crewe (2008)	75	21%	20%	32%	27%



Although Magne et al. (1997) graded the nasal planum lesions into three grades, both T1b and T2 were described as invasive. With these three studies the early presentation T1 was the lowest number (except for T2 in the present study) indicating that the owners only became aware of the disease in the later stages.. This is a problem as all the treatment modalities that have been discussed are more effect at the early stage of the disease.

The two visually graded studies that this study tries to compare results to are Theon et al. (1995) and Magne et al. (1997). They had subtly different end points; Theon et al. (1995) study had a progression-free survival time period (the interval between completion of irradiation and measurable tumour growth or death) and Magne et al. (1997) had a disease-free period. Despite these different end points, the results of these studies at twelve months was comparable (see Table 1.4 on page 27) where Theon et al. (1995) showed T1 was 84% and Magne et al. (1997) (see Table 1.6 page 28) where T1a was 100%. In the present study survival of twelve months, for T1 was 100% (excluding one death from non-related disease at six months) so that these three studies show good correlation on treatment of early stages the nasal carcinomas.

4.2.2 Endpoints of graded studies measured in months

Some studies defined their endpoint as survival; others used progression-free survival time, reduction in the size of the tumour and disease free period. Ten of the fifteen studies referred to in Table 1.6 on page 28 used the 'disease free period' as the end point for their study, making this the most accepted endpoint in this series of therapies. Several of the investigators noted that they did not manage to visually monitor their patients throughout the study period making the study difficult to complete. It should be emphasised that except for straightforward survival all the end points in this series of studies (progression-free survival time, reduction in the size of the tumour and disease free period) are open to human

interpretation of the lesion. The finality of death reduces these difficulties of interpretation. In this present study the criteria was simply, overall survival during a twenty-four month period.

Comparing the current results to these two studies it appears that the visual grading of the patients was reasonably consistent and could possibly be more standardised in the future.

4.2.3 Different modalities of treatment

a) Surgery

The first two studies concluded that this modality was only suitable for well-differentiated tumours. Bostock (1972) reported in his study that the well-differentiated cases had a median survival time of 11 months and the poorly differentiated tumours only a four month median survival time. The result of the Withrow and Straw (1990) study of nine cats showed that six cats were clinically free with a mean of 18 months (range 8-27 months) and local recurrence occurred in three cats with advanced poorly differentiated lesions at one, two and five months.

Lana et al. (1997) reported on 21 cases but without reference to grading and found the disease-free interval to be a median of 60 months. The Lana et al. (1997) study appears to be more successful than the first two studies that have similar results but as the patients were not graded it is difficult to compare. When the results are compared for the early stages of the disease, the present study at

two years gives a survival rate of 100% for T1 and 87% for T2 (excluding those patients that died from non-related causes). This appears to be a better result than those results in the Bostock (1972) and Withrow and Straw (1990) studies at the early stages of the disease. However for the more advanced stages, the studies of Bostock (1972), Withrow and Straw (1990) and this study showed similar results.

This surgical option is both very invasive and disfiguring and does not appear to give better results than radiation as applied in this study. The surgery option in South Africa would cost approximately R3500.00 and therefore the radiation treatment is less expensive and not painful.

b) Cryotherapy

None of the three studies Clarke (1991), Atwater et al. (1991) and Lana et al. (1997) graded their patients. All three reported a high recurrence of the disease and multiple treatments to give any long term control. Although liquid nitrogen is easily available to practices in South Africa this therapy does not have much of a following due to the early recurrence of the disease. Figure 4.1 shows a cat (a) after two treatments during a seven month period and (b) after radiation treatment.

In South Africa each treatment would cost approximately R1500.00.

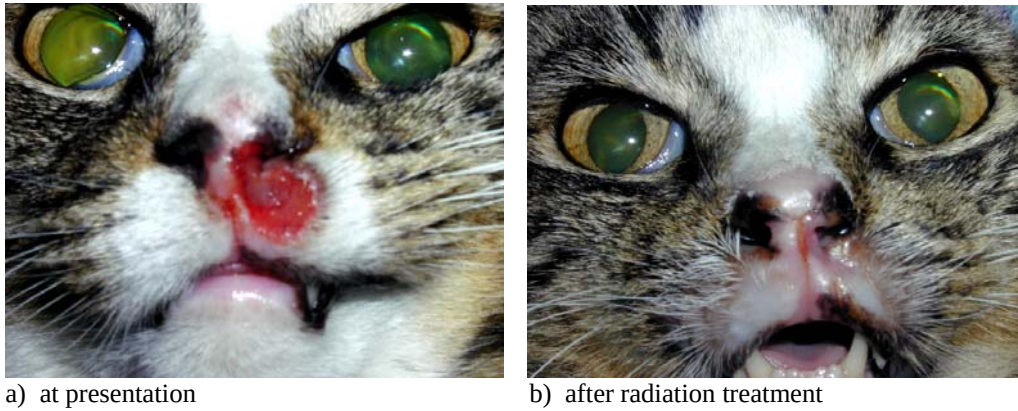


Figure 4.1: (a) Cat after cryotherapy and (b) subsequent radiation therapy

c) Hyperthermia

This technique is difficult and complex. In the study by Greir et al. (1980) the cats were graded with superficial (well-differentiated) lesions. Complete remission was for only two to six months in 68% of the patients. Due to the technical difficulties and the poor results this therapy is not being used in South Africa.

d) Photodynamic therapy

In the three studies, Roberts et al. (1991), Peaston et al. (1993) and Magne et al. (1997) similar results to cryotherapy were again shown, re-emphasizing the benefits of early treatment. Although all the patients in the study by Magne et al. (1997) were histologically confirmed as squamous cell carcinoma, they were also visually graded. The visually graded results gave a similar result to this study, for the grading T1a at 12 months being 100% but only 50% for T1b. The other more advanced grades responded poorly. Complete response rates as well as local control were significantly ($P < 0.05$) related to the severity of the tumour which corresponds well with this study.

e) Chemotherapy

There were two studies in this group. Evans et al. (1985) used cis-retinoic acid in a trial using cats with pre-neoplastic tumours. No reversal of the pre-neoplastic changes occurred. Orenberg et al. (1992) as recorded in Table 1.2 on page 26 and Table 1.5 on page 28 treated one hundred and eighteen cats with a cisplatin collagen-matrix intralesional implant and recorded that 83% of cats had a greater than 50% reduction in tumour size and 64% had complete resolution after six treatments. This treatment is used in South Africa but no recorded trials have been completed here. The cases that have been referred for radiation therapy are those that have not responded and radiation treatment has been requested. The cost for this kind of chemotherapy is between R1000.00-R1500.00 per treatment and usually four to six treatments are given, with a total cost of R4000.00-R6000.00.



a) at presentation



b) after radiation treatment

Figure 4.2: (a) Cat after chemotherapy and (b) subsequent radiation therapy

f) Radiation

(i) Ortho voltage radiation

Theon et al. (1995) used ortho-voltage radiation in a study of ninety cats visually graded T1-T4. Each patient received a total dose of 40 Gy in 4 Gy fractions. In the present study the radiation dose varied with the different tumour grades; for T1 the mean was 5 Gy, T2 was 10 Gy, T3 was 17 Gy and for T4 the mean was 26 Gy.

Theon et al.'s (1995) study showed the total median control was seventeen months and the mean 28 months (see Table 1.4 on page 27) and that the larger tumours adversely affected the results of the treatment. The aforementioned study showed the most beneficial results of all the studies examined. In contrast to Theon et al. (1995) study, the present study used a much lower dose of radiation for all the different tumour grades but was as successful except for T4.

The results being compared are as follows:

- (a) In the current study, the survival results at two years are; T1=75% but it should be noted that the four cats (25%) that died in this group during this period died of non-related causes. The group T2 had a 60% survival but once again four cats (27%) died of non-related causes. See Table 3.5 on page 50 for the cats that survived after the two year period. In the study by Theon et al. (1995) T1 had a result of 84% at twelve months and T2 58% at 60 months. The present study compares very well with Theon's study at the early levels.
- (b) At the higher grade of tumour T3, as reported by Theon et al. (1995) none of the cats survived the five year study period. But the progression survival rate at one year for T3 was 46% with a median of nine months. In the current study at two years, T3 had a median survival of 17 months. In this group the median survival in this study was eight months more than the orthovoltage study even though the total radiation dose was considerably less (17 Gy) and (40 Gy).
- (c) At Grade T4 Theon et al.(1995) had a progression free survival rate of 51% with a median of 22 months at one year. This result is surprising bearing in mind that there was only a 9 month median survival for his T3 group using a total of 40 Gy. The present study showed that at a two year survival the median for T4 was only six months. Theon's result in the T4 group was apparently very much better than in this study.

It is clear that the T3 and T4 tumours in the present study, with their large tumour volume needed a higher total dose of radiation than 26 Gy and maybe even more than the 40 Gy used by Theon et al.(1995). However the toxic radiation dose for nasal planum tissue has not yet been established which makes increasing the radiation dose easier said than done.

Comparison between the study by Theon et al. (1995) and this study is complex but an overall judgement is that both studies show that radiation therapy is a more successful treatment than the other modalities.

At the time of this study orthovoltage radiation was generally not available for veterinary patients in South Africa.

ii) Cobalt Mega voltage radiation

Prof. S. Lana, (2002) (personal communication) a veterinary oncologist at Colorado State University USA, is of the opinion that radiation is certainly a good tool for non- resectable disease but is costly and time-consuming. This statement of Prof. S. Lana is correct, if a total dose of 49 Gy has to be administered. But if the patients are referred at an early stage and a total dose of 10 Gy is needed, radiation would become a more cost effective and less time-consuming form of treatment.

iii) Strontium radiation

Van Vecheten and Theon (1993) in their study described the results of the treatment of twenty-five cats, all with well-differentiated lesions. The irradiation was done with a strontium ophthalmic applicator. This gave a 200 Gy surface dose (2 mm depth) and was given as a single dose. The

effects on the well-differentiated tumours were similar to the results achieved by using ortho-voltage and mega-voltage radiation.

This therapy is only suitable for superficial lesions. If these machines are readily available for use by veterinarians, the convenience of using only one treatment makes this method effective and probably relatively inexpensive.

This further emphasizes the need for early diagnosis and treatment.

4.3 THE STATISTICAL ANALYSIS OF THE DATA OF THIS STUDY

Bear in mind that as already stated, statistically these are small sample sizes. However in comparing the results to the other visually graded squamous cell carcinoma tumour studies Magne et al. (1997) and Theon et al. (1995) similarities do occur with the visual grading, radiation doses and the consequent results.

4.3.1 The ratio of male to female cats

In the current study this variable showed no statistically significant effect on the rate of survival. Overall there were 18% more females than males in the study. All the cats in the study had been sterilized. The comparable studies did not report on results relating to the different sexes.

4.3.2 The age and tumour levels of the patients

In the present study the variable for age showed no statistically significant effect on the rate of survival. The total range of the affected cats was between 3-23 years, which is large. The mean age for the tumour levels is T1=10.1 y, T2 =10.4 y, T3=10.4 y and T4=12.8 y.

The median age for the total number of cats was 10 years and the mean 10.96 years. This shows good correlation. It was worrying to see that the mean age of grade T1 was 10.8 years and yet the range was 4 to 18 years. This disease has clinically always been regarded as a disease of old cats. To find the range included cats as young as four years old being diagnosed with squamous cell carcinoma of the nasal planum is important as it means that early prevention and recognition of the disease becomes imperative.

In group T4 there was once again a 3 year old cat. The mean age of the group was one year older than the total mean. Statistically this does not have any significance. However, it might be explained by the fact that the owners had ignored the early symptoms or just accepted that their older cats had a non-treatable disease, or that the veterinarians had been trying to treat the lesion unsuccessfully with a variety of treatments.

The age of the cat when presented for radiation treatment is of no importance as cats of twelve years and older with grades T2 and T3 tumours were successfully treated. Previous authors have not correlated age, tumour grade and treatment outcome.

4.3.3 Comparison of the mean radiation dose required for the treatment of the different grades of tumour

Although the mean total radiation dose (Gy) per grade was not statistically significant for survival, using Cox regression, a trend did appear. It showed that the higher the tumour grade, the more radiation was needed to have a therapeutic effect on the tumour. Although this fact might have been expected, the reality is that the other studies using radiation, Theon et al. (1995) and Lana et al. (1997), used a uniform dose of 40 Gy and 49 Gy respectively for all tumours regardless of size and aggression.

During the present series none of the cats showed any discomfort or pain during the radiation therapy. There was a loss of hair, with the cats having a high total radiation treatment, with regrowth over 2 month period, but there was still no evidence of pain or discomfort. This is in contrast to Theon (1995) who used higher doses and reported skin and membrane lesions. None of the cats treated suffered any signs of skin radiation toxicity, acute or late, and there were no adverse effects due to the anaesthetic agent. These reduced side effects may well be due to use of megavoltage radiation in contrast to orthovoltage radiation.

An example of a cat being treated with a high radiation dose (total 76 Gy) in 3 Gy fractions is recorded in Figure 4.3. In this case the owner/cat bond was extremely strong and the owner refused to take the euthanasia option which her veterinarians thought to be the kindest route. The owner understood that the treatment would be palliative and only if there was really good progress would the treatment be continued. As can be seen the patient did respond and lived for a further nine months free of tumour pain,

able to breathe and eat easily. The patient was euthanased due to chronic kidney failure and the visible signs of squamous cell carcinoma recurrence.

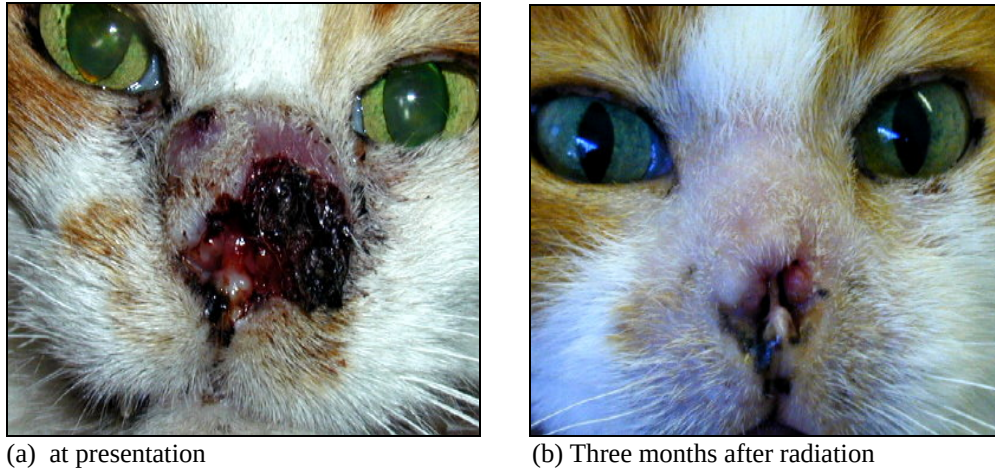


Figure 4.3: Palliative treatment for 18 year old cat

4.4 ENVIRONMENTAL CONTROL OF EXCESSIVE UVB EXPOSURE

Finally, although most studies mentioned that the cause of the squamous cell carcinoma was high UVB exposure, none of the authors of the articles showed much concern with changing the behaviour and environment to protect the vulnerable cat. In this study when the cost of the treatment for T1 and T2 tumours was R225.00 and R300.00, respectively and the cost for T3 and T4 tumours was R375.00 and R625.00, only one client could be persuaded to institute good effective environmental control. It is interesting to observe that now that the costs have risen from R225.00 to R1155.00 to treat a grade T 1 tumour and from R625.00 to R3465.00 for a grade T 4 tumour, approximately 45% of owners are willing to comply with environmental control. These cats are currently being monitored to try and prove the efficacy of this control. A further

factor in the change of attitude of the owners is the heightened awareness of the public to the devastating effects of global warming and increased UVB exposure.

CHAPTER FIVE

CONCLUSION

As explained in the introduction, the etiology of the nasal planum squamous cell carcinoma is simply, excessive exposure to the B fraction of ultraviolet radiation and the tissues' response to the solar radiation. Although there is now a general awareness of the effect of global warming, there is no hope that in the near future, a thick, protective blanket of ozone will surround the world. Likewise there is little hope that people will stop breeding cats with non-pigmented nasal planums, so where do we go from here? Practical solutions have to be sought.

Recognition of the condition and the various treatments are well recorded. This present study is a refinement of earlier work with radiation and has shown that mega-voltage radiation can play a most effective part in the treatment of actinic induced squamous cell carcinoma of the nasal planum.

In summary this study showed that at two years, different radiation doses used as a survival therapy for the four visually graded levels were very effective at the tumour levels T1 and T2. The treatment was fairly successful at T3 level and only palliative at the T4 level. Initial visual grading of the tumours was statistically highly significant on the survival rate. The age, sex, number of treatments, and the total radiation dose of the patient had no significant effect on the rate of survival using Cox's regression analysis. This means that radiation therapy must be implemented at the earliest opportunity.

The two most difficult challenges for the future are firstly, to educate the veterinarians and the owners to recognise the disease at an early stage and secondly, to obtain access to radiation machines.

It is essential that veterinarians and undergraduates are educated as to the advantage of radiation as an effective treatment for feline nasal planum. This can be by means of congresses, journal articles, web pages, posters, leaflets and informal talks. The owners also have to be informed so that they are aware of the problem and can bring it to the veterinarians' notice at an early stage. This knowledge can be imparted through the media e.g. pet magazines, together with radio and television programmes and information supplied by the veterinarians in their waiting rooms.

As part of this study an Internet search was carried out to ascertain the accessibility of mega voltage radiation facilities to veterinarians for their patients. This search showed that there are two facilities in the United Kingdom, Cambridge University and a private facility in Newmarket. In the United States of America there are forty facilities of which twenty are supported by universities. Canada has a unit attached to the veterinary school and Australia has two units offering radiation therapy. No other countries offering radiation therapy for companion animals could be found. For the many countries that do not have radiation facilities for companion animals the first prize will be early recognition of the tumour and treatment that is available e.g. surgery and cryotherapy with additional environmental control.

In South Africa the Medical School of the University of the Witwatersrand has a cobalt⁶⁰ machine used for animal research that was available for treating dogs and cats. Unfortunately, after this study was completed, the cobalt source was depleted and the university was unable to finance a new source. Fortunately one of the seventeen privately owned mega-voltage radiation facilities in South Africa allowed the use of their linear accelerator for animal radiation outside normal working hours.

Prohibitively high capital and maintenance costs preclude the use of these machines in dedicated veterinary hospitals in South Africa. Only if veterinarians are permitted the use of human facilities will they be able to treat, not only the nasal planum squamous cell tumours but also the other numerous radiosensitive cancers diagnosed in cats and dogs.

Of prime importance with the radiation treatment is the relief of the cats' pain, usually after only two or three treatments. Cats that have been in varying degrees of discomfort begin to respond by eating, grooming, playing and mousing. The owners' joy and the veterinarians' relief at not having to euthanase yet another cat suffering from this destructive tumour brings a realisation of how successful mega-voltage radiation treatment is, despite the time consuming treatments and their expense.

As global warming intensifies and the protective ozone layer diminishes the prevalence of solar induced squamous cell carcinomas will undoubtedly increase. For those areas having a high incidence of feline nasal planum squamous cell carcinoma, a highly desirable situation would be early recognition, visual classification of the tumour and a successful treatment regime.

This study together with the studies undertaken by Theon et al.(1995) and Magne et al. (1997), had good correlation with the grading on visualisation into four groups (least to worst) when the results were compared. Although many different treatments have been tried, the most successful results appear to be radiation of these tumours. Future work should focus on devising a radiation protocol that will achieve the optimal success for each different grade of nasal planum squamous cell carcinoma.

This study has shown that the most practical non invasive solution to squamous cell carcinoma of the nasal planum of cats in the early stages is mega-voltage radiation therapy.

APPENDIX A

University of the Witwatersrand, Johannesburg

7 York Rd, Parktown
2195 South Africa
Tel. (011) 647-1111

INFORMED CONSENT TO TREATMENT

1. I, the undersigned, hereby authorise the veterinarian and staff of the above animal hospital to perform any reasonable treatment, anaesthesia, radiation and surgery they may deem necessary, including and or further or alternative measures as maybe necessary during the course of the Cobalt 60 radiation treatment of my animal.
2. I undertake to keep in daily contact between 9-10am to enable the staff to inform me of the progress, costs incurred and additional treatment involved.
3. I confirm that I am aware of the extent and approximate costs involved, and that I will pay COD on collection of my animal for my animal after each treatment.
4. I acknowledge that I am indebted to the above practice for veterinary treatment, services rendered and expenses incurred therewith and hereby render myself responsible for all costs.
5. I confirm that my animal has a valid vaccination certificate i.e. vaccinated during the previous twelve months.
6. My cat/dog will be brought to the facility in a basket or on a lead.

Name of Owner (person responsible for the account)

.....

Residential

address.....

.....

E-mail

address.....

.....

Telephone number:

HomeWork.....Cell

Signature

.....Date.....

APPENDIX B

CLINICAL DATA SHEET FOR RADIATIONPATIENT

DOG/CAT

NAME of

PET.....

Species.....Breed.....

.....

Sex.....Age.....Weight.....

.....

Referring

Veterinarian.....Dr.....

Practice.....

Telephone.....Email.....

Diagnosis from referring

veterinarian.....

.....

Location.....

Date of relevant history (first noticed, operations etc)

1.....

.....

2.....

.....

3.....

.....

4.....

.....

5.....

SignatureDate

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