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Complete List of Authors:	Berlato, Davide; The Animal Health Trust, Oncology Unit Murphy, Sue; The Animal Health Trust, Oncology Unit Laberke, Silja; The Animal Health Trust, Oncology Unit Verganti, Sara; The Animal Health Trust, Oncology Unit

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Abstract:	Objectives. The main aim of the study is to establish response, disease-free interval, and overall survival of cats with nasal planum squamous cell carcinoma treated with Sr90 plesiotherapy. A secondary aim is to determine whether a fractionated protocol is more effective than a single-dose protocol in terms of response, disease-free interval and overall survival. The third aim is to evaluate whether we can identify prognostic factors that can influence overall survival. Methods. Retrospective study including cats with a diagnosis of nasal planum squamous cell carcinoma treated with Sr90 plesiotherapy in a single institution. Results. Seventy-four cats are included in the study. Thirty-two were treated with a fractionated protocol and 42 with a single-dose treatment. Sr90 plesiotherapy was able to induce complete response in 74% of cats with nasal planum squamous cell carcinoma. The median disease-free interval was 780 days (95%C.I. 383–1177) with 17% of cats experiencing local recurrence. The OS for all cats was 1039 days (95%C.I. 55–1528). The disease-free interval of cats treated with the fractionated Sr90 was significantly longer compared to the single-dose treatment, while response and overall survival were not statistically different. Other prognostic factors that influenced the overall survival were early stage disease, absence of concurrent problems and complete response to the treatment. Acute and long-term toxicity associated with the treatment were minimal and the aesthetic outcome was pleasing in almost all cases. Conclusions and relevance. Strontium plesiotherapy is a safe and effective treatment of nasal planum squamous cell carcinoma in cats.

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Authors:

Berlato, D., Oncology Unit, Animal Health Trust, Newmarket, United Kingdom

Murphy, S., Oncology Unit, Animal Health Trust, Newmarket, United Kingdom

Laberke, S., Oncology Unit, Animal Health Trust, Newmarket, United Kingdom

Verganti S., Oncology Unit, Animal Health Trust, Newmarket, United Kingdom

Corresponding author:

Berlato, D.

DipECVIM-CA(Onc) MSc(Clin Onc) PhD

Email: davide.berlato@aht.org.uk

Address: Animal Health Trust, Oncology Unit, Lanwades Park, Kentford, Newmarket, Suffolk, CB8 7UU, United Kingdom

Telephone: +44 01638 552700

Abstract

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Methods. Retrospective study including cats with a diagnosis of nasal planum squamous cell carcinoma treated with Sr90 plesiotherapy in a single institution.

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Conclusions and relevance. Strontium plesiotherapy is a safe and effective treatment of nasal planum squamous cell carcinoma in cats.

Introduction

Squamous cell carcinoma (SCC) is one of the most common malignant skin tumours in cats and accounts for between 15 and 25% of cutaneous tumours in this species.[1,2] Solar exposure is important in its development and SCCs of this aetiology are seen almost exclusively in non-pigmented areas of the head, such as nasal planum, eyelids and pinnae, with white cats or coloured cats with white areas being at greater risk.[3,4]

The stage of cutaneous SCC (T-stage) is defined by the depth of invasion and by the size of the lesion (Table 1).[5] Feline cutaneous SCCs are relatively slow to metastatise and are reported to spread to the draining lymph nodes and the lungs.[4]

Strontium plesiotherapy (Sr90) is an effective treatment of early stage nasal planum SCC in cats (Tis, T1 and T2), while it is considered ineffective for advanced stage SCC (T3 and T4).[4] At the moment there are two radiation protocols published in the veterinary literature. The first consists of a total dose of 200Gy administered in 5 fractions on an alternate day basis[6]; the second of a total dose between 97-195Gy administered in a single treatment.[7] Both protocols are reported to induce complete remission in ~85% of cats. For cases that achieve complete remission, recurrence was not reported with the fractionated protocol and we would expect a low recurrence rate, while local recurrence was reported in 20% of cats treated with a single fraction.[6,7]

The aim of this retrospective study is to establish response, disease-free interval (DFI), and overall survival (OS) of a large cohort of cats with nasal planum SCC treated with Sr90. A secondary aim is to determine whether the fractionated

protocol (5-Sr) is more effective than the single-dose protocol (1-Sr) in terms of response, DFI and OS. Finally, we would like to evaluate whether we can identify prognostic factors that influenced the OS.

Material and Methods

Case Selection

The database of a single institution was searched for cats treated with Sr90 between 1992 and 2017. Cats were included in the study if there was a histological diagnosis of nasal planum SCC. Information collected for each cat includes signalment (breed, age, and gender), concurrent diseases, clinical stage, staging investigations, protocol used (5-Sr or 1-Sr, total dose, number of treatment fields) and toxicity (acute and late using the VRTOG criteria[8]).

Procedures

The strontium applicator has a 0.7cm^2 active area and is attached to a hand-held probe with a Perspex guard. All cats received Sr90 under general anaesthesia in a designated 'Radiation controlled area'. All treatments were administered by an oncologist and consisted in the application of a variable number of overlapping fields to cover the entire lesion with margins of at least 2mm around the tumour. The total dose prescribed and the fractionation (5-Sr or 1-Sr) depended on the clinical judgement of the oncologist in charge of the case or on the owner's preference. The 5-Sr was delivered in 5 fractions on a Monday-Wednesday-Friday schedule (total dose range 200–260Gy), while the 1-Sr was delivered in a single treatment (total dose range 85–140Gy). The duration of exposure to deliver the prescribed dose was calculated on the day of the first treatment using an internally

developed electronic spreadsheet taking into account the source decay over the time. The dose reported is the dose delivered to the surface, while the dose at 2mm depth is ~30% of the surface dose.

Statistical analysis

The outcome measures evaluated are response, DFI and OS. The response assessment (complete response [CR], partial response [PR], stable disease [SD] or progressive disease [PD]) is based on RECIST criteria[9] and evaluated 6 to 8 weeks after treatment. When the owner could not come to the hospital for a revisit, the response was assessed with a digital image sent via email. DFI was defined as the period from date of the first Sr90 until date of recurrence (local in the nasal planum within or without the radiation field, loco-regional to the draining lymph nodes, or systemic metastasis), and OS was defined as the period from date of the first Sr90 until death from any cause. When the exact date of an event was unknown (for example a cat died in Nov 2015) we approximated the date to the first day of the month. If partial or incomplete information were available from our records, we contacted the referring veterinary practice for an update. Cats without follow-up after the first Sr90 were excluded.

Chi-square or Fisher's exact was used to compare categorical variables. T-Test was used to assess normal continuous variables. Survival analysis (Kaplan Meier [KM] and Log-Rank) was used to compare outcomes of the two different protocols (5-Sr and 1-Sr) and to evaluate other prognostic factors. The following categories were used for the statistical analyses: age (divided in quartiles), gender (male neutered, male entire and female neutered), concurrent diseases (present or

absent), T-stage (early stage [Tis, T1 and T2]; late stage [T3 and T4]), total dose (<135 Gy or ≥135 Gy [135 Gy was the median dose]), the number of treatment fields (<3 or ≥3 [3 was the median number of fields]), recurrence for cats that achieved CR (occurred or did not occur) and response to the first Sr90 (CR, PR, PD). Factors with a $p<0.10$ were included in the Cox Multivariate Regression analysis. Results of the statistical tests were considered significant for a $p<0.05$.

Commercial software was used for the statistical analysis (IBM SPSS Statistic for Windows, Version 21.0, Armonk, NY, US).

Results

Patients

One-hundred-and-twenty-three cats treated with Sr90 between 1992 and 2017 were found in our database (Figure 1). Seventy-four cats were included in the study and their mean and median age was 11.5 and 11.1 years, respectively (range 3.1–20.1). There were 49 neutered males, 22 neutered females, and 1 entire male. Sixty-six cats were domestic short hair, 5 domestic long hair, and 1 ragdoll. Sixty-four cats (86%) had a coloured coat with white areas or white coat, while 4 had solid colour (5%) and hair colour was unknown for 6 cats.

Tumour staging and concurrent problems

Local stage was evaluated in all cats. The SCC was staged as *in situ* (Tis) in 9 (12%), T1 in 17 (23%), T2 in 42 (57%), T3 in 4 (5%), and T4 in 2 cats (3%). There was a significant difference in the distribution of stages between the two treatment groups (Pearson Chi-square; p=0.018); 1-Sr had more TIS and T1 compared to 5-Sr (50% vs. 16%). All cats had pre-anaesthetic blood tests. Other investigations to

evaluate local invasion, local and distant spread, or concurrent problems were performed in 44 cats (59%). Local invasion was evaluated in 5 cats (computed-tomography [CT] of the head), local spread in 12 cats (lymph node cytology), thoracic imaging was performed in 45 cats (38 thoracic radiographs, 5 thoracic CT, and 2 echocardiography), and abdominal imaging in 9 cats (7 abdominal radiographs and 2 abdominal ultrasound). None of the cats presented with local or distant metastases. Twenty-three cats (31%) had concurrent problems including 8 with heart murmur and/or cardiac disease, 5 with SCC affecting either pinnae or eyelids, 4 with chronic kidney disease and hyperthyroidism, 3 with chronic kidney disease, 1 with hyperthyroidism, 1 with epilepsy and 1 with pancreatic carcinoma. Four cats with concurrent problems were treated with 5-Sr and 19 with 1-Sr. There was a significant statistical difference in the distribution of concurrent diseases between the two treatments groups (X^2; p=0.003).

Treatment

Thirty-two cats (43%) were treated with a 5-Sr and 42 (57%) with the 1-Sr. Mean and median dose for 5-Sr was 233Gy and 235Gy, respectively (range 200–260Gy), while mean and median for 1-Sr was 120Gy (range 85–140Gy). There was a significant statistical difference between the mean total dose of the two treatment groups (T-test; p<0.001). For the overall population mean and median number of treatment fields was 2.7 and 3.0, respectively, and there was no statistical difference between 5-Sr and 1-Sr (T-test; p=0.30).

Response, recurrence rate and DFI

After treatment with Sr90, 55 (74%) tumours achieved CR, 16 (22%) PR, and 3 (4%) PD. There was a significant association between the T-stage before Sr90 and response (X^2; p=0.002). CR was achieved in 89% of cats with Tis, 94% of T1, 68% of T2, 50% of T3 and 0% of T4. Of cats that received 5-Sr, 23 (72%) achieved CR, 8 (25%) PR and 1 (3%) PD, while of cats that received 1-Sr, 32 (76%) achieved CR, 8 (19%) PR and 2 (5%) PD. There was no significant statistical difference in the response between 5-Sr and 1-Sr (X^2; p=0.79).

Of the 55 cats achieving CR, the overall DFI was 780 days (95%C.I. 383–1177). The DFI was significantly longer in cats that received 5-Sr (1966 days [95%C.I. 413–3518]) compared to 1-Sr (248 days [95%C.I. 0–911]) (Log-Rank; p=0.004; Figure 2). Recurrence occurred in the nasal planum in 17 (31%) cats and it was within the radiation field in 4 cats, marginal to the field in 2 cats, and outside the radiation field in 5 cats. Among cats that experienced recurrence, 6 received 5-Sr and 11 1-Sr. There was no significant difference in recurrence rate between the two protocols (X^2; p=0.74). The median time of recurrence was 251 days (95%C.I. 48–454) and there was no significant difference in time to recurrence between 5-Sr and 1-Sr (Log-Rank; p=0.41). The distribution of the total dose between SCC that recurred and that did not recur was not statistically different (Mann-Whitney-U-test; p=0.34). After recurrence, 12 cats received a second Sr90 (all 1-Sr) and then 4 cats went on to receive further treatment (2 nosectomies, 1 external-beam radiotherapy and 1 topical imiquimod). The median survival of these 17 cats after recurrence was 974 days (95%C.I. 367–1581).

Of the 16 cats achieving PR after Sr90, 6 cats received a second Sr90 treatment (all 1-Sr), while 2 were treated with external-beam radiotherapy. After the second Sr90, 3 cats went on to receive further treatment (1 nosectomy, 1 external-beam radiotherapy and 1 third treatment of Sr90). The median survival of these 16 cats after the first Sr90 was 435 days (95%C.I. 166–704).

Three cats developed progressive disease after Sr90; the survival after Sr90 was 63, 65, and 290 days. The cat that lived longer was treated with external-beam radiotherapy as rescue treatment.

Overall survival and prognostic factors

During the follow-up period, 47 (64%) cats died and 27 (36%) were still alive at the time of data collection. The median OS of the 74 cats included in the study was 1039 days (95%C.I. 55–1528). Cats treated with 5-Sr had an OS of 1293 days (95%C.I. 491–2095) and cats treated with 1-Sr of 678 days (95%C.I. 338–1018). There was no difference in survival between the two protocols (Log-Rank; p=0.07; Figure 2).

Among the prognostic factors evaluated with the Log-Rank, age (p=0.11), gender (p=0.29), number of treatment fields (p=0.33) and recurrence for cats that achieved CR (p=0.24) were not significantly impacting on the OS, while T-stage (p<0.001), presence of concurrent diseases (p=0.001), total dose (p=0.01), and response to the first Sr90 (p<0.001) were significant. Results are summarised in Table 2 and Figure 3.

The multivariate analysis (Table 3) confirmed the significance of the T-stage (p<0.001), the presence of concurrent diseases (p=0.003) and the response to the

first Sr90 ($p<0.001$), while the total dose lost its significance ($p=0.10$). The risk associated with individual factors was high for concurrent disease (HR 3.72) and response to the first Sr90 (HR for PR 4.76; HR for PD 8.66), and low for the T-stage at presentation (HR for advanced stage 0.08).

Toxicity and aesthetic outcome

The acute toxicity was described in 19 cases. The dermatitis was classified as mild (VRTOG grade 1) in 15 cats, moderate (VRTOG grade 2) in 1 cat, and severe (VRTOG grade 3) in 3 cats. Long-term side effects were consistent with alopecia in all cases. Three cats developed epidermal hyperplasia and hyperkeratosis confirmed on histopathology. The cosmetic outcome was described by the attending clinician in 21 cats and judged as excellent or very good in 18 cats or pleasing with a mild deformation of the cartilage in 3 cats (Figure 4).

Discussion

Signalment and hair colour of cats included in this study was similar to previous literature.[6,7,10,11] The SCC was at an early local stage in the majority of cats (92%) and advanced in few cases (8%). Staging for systemic disease was not complete in all cats, but in none of the cases we found evidence of local or distant metastasis at presentation.[10] Concurrent problems were present in 31% of cats and this is similar to what has been reported.[7]

The main aim of this retrospective study was to establish response and outcomes of cats with nasal planum SCC treated with two different protocols of Sr90. We found that Sr90 is able to induce CR in 76% of cats. The DFI for cats that achieved CR was 780 days and was significantly longer with 5-Sr compared to 1-Sr.

These results are similar to a previous study describing the use of a fractionated protocol; after the first Sr90, CR was achieved in 73% of cats and the DFI was 652 days.[6] A higher response rate and DFI was seen in a study describing a single-dose protocol,[7] in which CR was achieved in 88% of cats and the DFI was 1710 days. The better response rate could be explained with the inclusion of cats with advanced disease and a lower percentage of cats with SCC *in situ* in our study. The difference in DFI was also conspicuous considering that the DFI of cats treated with 1-Sr in our study was only 248 days. The main reason for such disparity lies within the different definition of DFI: in our study we defined DFI as the time between the first Sr90 and the occurrence of another nasal planum SCC (within or outside the radiation field), while in Hammond's study they only considered SCC recurring within the radiation field as recurrence. In our opinion, the definition of DFI we adopted is more representative of the progression of the disease accounting for the '*field carcinogenesis*' and provides more relevant information about the chances of another SCC occurring.

From previous studies, we were expecting a low recurrence rate with 5-Sr[6], and a high recurrence rate with 1-Sr[7]. The overall recurrence rate in this study was 31%, but we could not demonstrate a significant difference between 5-Sr and 1-Sr (~~8.1~~26% versus ~~14.1~~34%, respectively). Interestingly, tumour recurrence did not significantly influence OS and cats lived a long time after recurrence even if additional treatment was not pursued.

The OS in this study was 1039 days and there was no significant difference between patients receiving 5-Sr and 1-Sr. Cats treated with 5-Sr had an OS of 1293

248 days, which was slightly longer compared to the 780 days in the Goodfellow's
249 study[6], while cats treated with 1-Sr had an OS of 678 days. Unfortunately, the
250 Hammond's study could not be used as comparison because the authors reported
251 the tumour-specific survival (all cats that died for a cause unrelated to the SCC were
252 censored) and not the OS.

253 A secondary aim was to evaluate whether 5-Sr was more effective than 1-Sr.
254 In this study population, the only significant difference between the two treatments
255 groups was the DFI, while response rate and OS were not different. These findings
256 suggest that cats achieving CR after Sr90 enjoyed a longer DFI if they were treated
257 with 5-Sr compared to 1-Sr. However, the OS of cats treated with 5-Sr or 1-Sr was
258 not different implying that the time to recurrence is not impacting on the overall
259 survival time. From this retrospective study is not possible to establish which
260 protocol is superior and a controlled study should be prospectively designed to
261 address this aspect.

262 Our study found few prognostic factors that were significantly associated
263 with the OS in the univariate and multivariate analysis. The first one was T-stage at
264 presentation, which made perfect biological sense considering that the higher the T-
265 stage the deeper the infiltration of the tumour, and given that one of the main
266 limitations of Sr90 is the poor penetration of the β-particles into the tissue. In the
267 multivariate analysis, cats with advanced stage had 8% increased risk to die
268 compared to cats with early stage.
269 The second factor was the presence of concurrent health conditions. It is intuitive
270 that cats with extension of the SCC to other sites or with systemic conditions are

likely to succumb earlier than cats with only the nasal planum SCC. Cats with a concurrent problem were more likely to be treated with 1-Sr because the aim of the treatment was palliative rather than curative-intent. During follow-up time cats with concurrent disease were 3.72 times more likely to die than cats without any other condition.

The third factor was the response to the first Sr90. Cats with CR of the tumour survived longer than cats that had a PR or PD. Cats that achieved PR were 4.76 more at risk of dying than cats that achieved CR; the risk was 8.66 times higher for cats that achieved PD. This prognostic factor was also described in the Hammond's study.[7]

Finally, the total dose, as a categorical variable dichotomised by the median value, was significant in the univariate analysis, but lost its significance in the multivariate analysis. The only explanation we can provide for this finding is that the dose prescribed was in part biased by the judgement of the attending clinician (for example small and superficial tumours were prescribed a lower total dose compared with large and deep tumours; cats with concurrent problems that could not be anaesthetised many times received a higher dose, etc.). This hypothesis is supported by the fact that the total dose administered to cats that experienced recurrence was not statistically different from cats that did not. ~~It is possible that the inconsistencies in dose prescription associated with a retrospective study as well as the relatively low number of cats included in each category biased these results.~~

Acute toxicity after completing Sr90 was described in 19 cats. In the majority of cases the toxicity was mild (79%), but in few cases it was classified as moderate

(5%) or severe (16%). In the authors' experience, the treatment area becomes initially mildly erythematous in the periphery and then a thick scab forms over the neoplastic ulcer. Over the following 4-8 weeks, the scab becomes gradually smaller and then falls off. Given that most nasal planum SCCs present clinically as non-healing ulcers, in some case it is difficult ~~it might be difficult~~ to distinguish between neoplastic ulceration and radiation toxicity and the only way is to evaluate the lesion progression over the time ~~related to the treatment~~. Long-term side effects included alopecia and, in few cases, epidermal hyperplasia and/or hyperkeratosis. The latter presents clinically as scaling dermatitis or as non-healing ulcer and both these presentations can be misinterpreted as recurrence. Thus, a biopsy should always be performed when recurrence is suspected before recommending additional treatment. According to the attending clinician and with all the limitations of retrospective studies, the cosmetic outcome of most patients was pleasing, but occasionally a small deformation of the underlying cartilage remained.

Conclusion

Sr90 is a safe and effective treatment of nasal planum SCC in cats. In this study, 5-Sr90 was associated with a longer DFI compared with 1-Sr, but did not impact response or OS. Other important prognostic factors that affected OS are T-stage at presentation, presence of concurrent diseases and response to the first Sr90.

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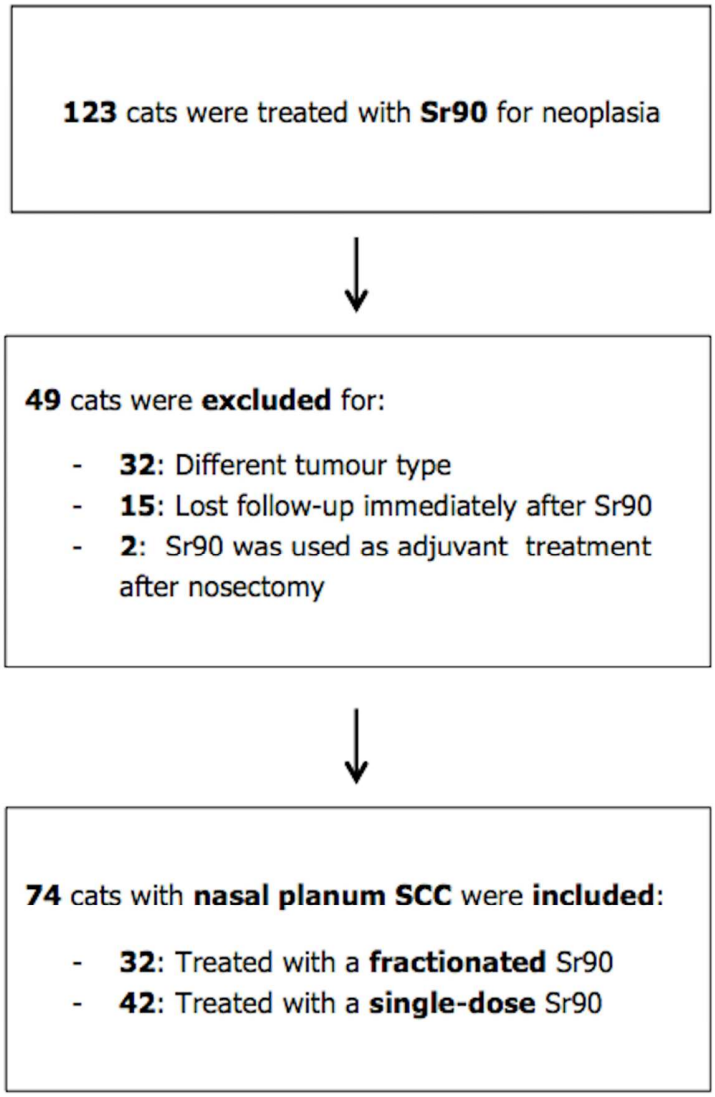

Figure 1. Flow-chart representing the inclusion process of the cases in the present study.

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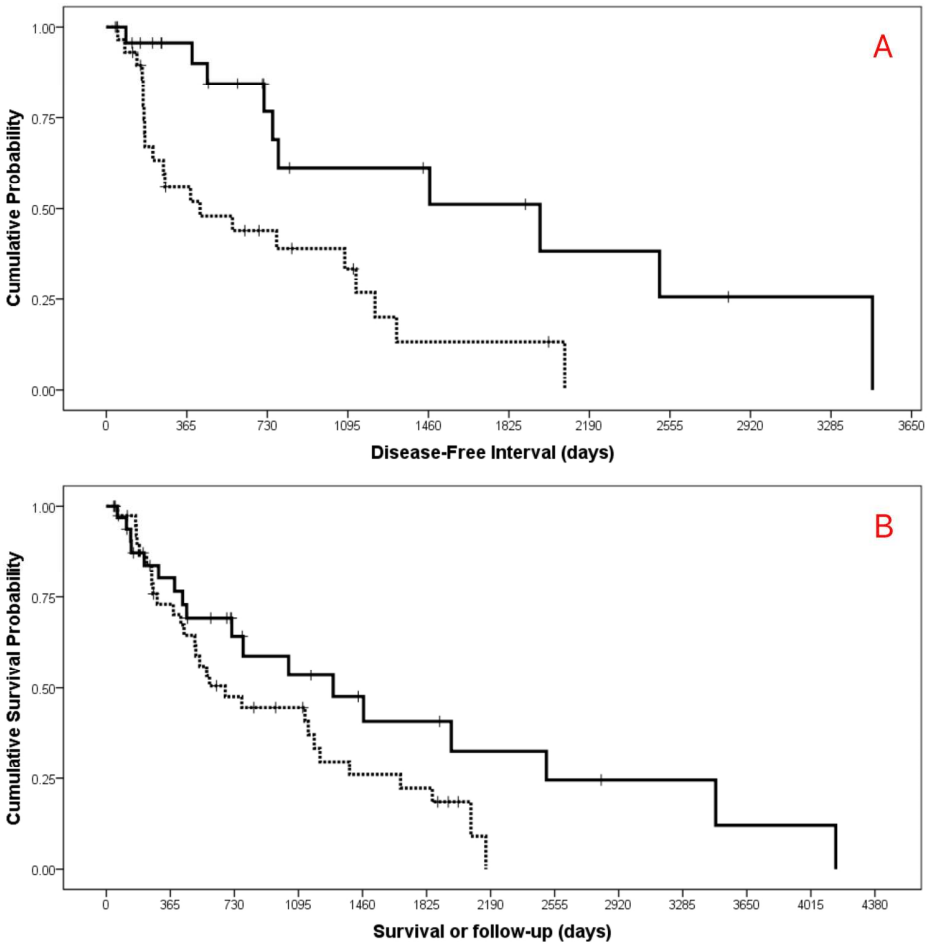

Figure 2. KM survival plots comparing DFI (A) and OS (B) of cats treated with a fractionated (continuous line) or a single-dose Sr90 protocol (dotted line). There was a statistical significant difference in DFI (p=0.004), but not in OS (p=0.07).

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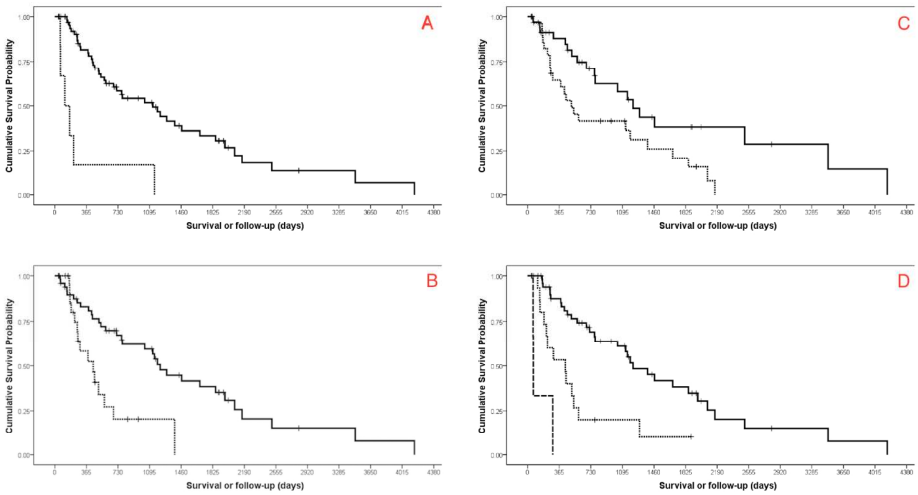

Figure 3. KM survival plots of significant prognostic factors affecting the OS. A- T stage (early stage continuous line; advanced stage dotted line) ($p<0.001$). B- Concurrent diseases (absent continuous line; present dotted line) ($p=0.001$). C- Total dose divided by the median value (≥135 Gy continuous line; <135 Gy dotted line) ($p=0.01$). D- Response to the first Sr90 (CR continuous line; PR dotted line; PD dashed line) ($p<0.001$).

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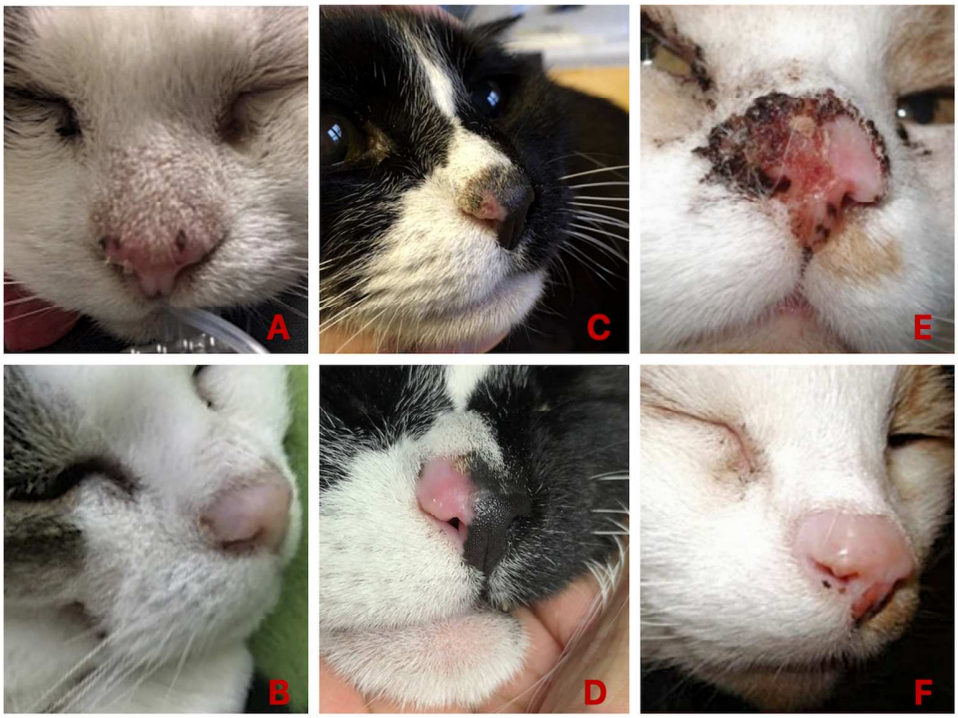

Figure 4. Three cats with nasal planum SCC before and after Sr90 plesiotherapy. A and B – Complete response of two small superficial SCC (Stage Tis). C and D – Complete response of an early stage SCC (Stage T1). E and F – Partial response of an advanced SCC (Stage T3). The nasal philtrum was treated with a second Sr90 treatment.

112x84mm (300 x 300 DPI)

WHO classification of feline tumours of epidermal origin	
T_{is}	Preinvasive carcinoma
T_0	No evidence of tumour
T_1	Tumour <2cm maximum diameter, superficial, or exophytic
T_2	Tumour 2-5cm maximum diameter, or with minimal invasion irrespective of the size
T_3	Tumour >5cm maximum diameter, or with invasion of the subcutis irrespective of the size
T_4	Tumour invading other structures such as fascia, muscle, bone, or cartilage

Variable	*Category*	*No. of cats*	*No. of events*	*MST in days (95% C.I.)*	*P value*
T Stage	Early (Tis, T1 and T2)	68	41	1132 (633 – 1631)	< 0.001
	Advanced (T3 and T4)	6	6	115 (0 – 242)	
Concurrent diseases	Absent	51	32	1218 (1004 – 1432)	0.001
	Present	23	15	443 (222 – 664)	
Total dose	≥ 135 Gy	34	19	1218 (864 – 1572)	0.01
	< 135 Gy	33	23	505 (302 – 708)	
Response	CR	55	31	1218 (886 – 1550)	< 0.001
	PR	16	13	435 (166 – 704)	
	PD	3	4	65 (62 – 68)	

Variable	*Category*	*Multivariate analysis HR (95% C.I.)*	*P value*
T Stage	Early	ref.	< 0.001
	Advanced	0.08 (0.02 – 0.30)	
Concurrent diseases	Absent	ref.	0.003
	Present	3.72 (1.58 – 8.76)	
Total dose	≥ 135 Gy	ref.	0.10
	< 135 Gy	2.43 (0.83 – 7.14)	
Response	CR	ref.	< 0.001
	PR	4.76 (2.14 – 10.59)	
	PD	8.66 (2.19 – 34.29)	
Protocol	Fractionated	ref.	0.53
	Single-dose	0.70 (0.22 – 2.19)	