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Comparison of definitive-intent finely fractionated and palliative-intent coarsely fractionated radiotherapy as adjuvant treatment of feline microscopic injection-site sarcoma

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Abstract

Objectives The aim of this retrospective, bi-institutional study was to evaluate the progression-free interval in a cohort of cats with postoperative microscopic injection-site sarcoma (ISS) treated with two different radiotherapy protocols.

Methods Included in the study were cats with ISSs undergoing macroscopic surgical removal and subsequent electron beam radiotherapy treatment with either a finely fractionated protocol (48 or 52.8 Gy over 4 weeks delivered in 12 or 16 fractions) or a coarsely fractionated protocol (36 Gy over 3 weeks administered in six fractions). Medical records were reviewed and follow-up information was collected. The Kaplan–Meier method and log-rank test were used to compare the progression-free interval (PFI) between the two protocols and to test the influence of many clinical variables.

Results Fifty-nine cats were included; 38 underwent a finely fractionated protocol and 21 a coarsely fractionated protocol. PFI was not significantly different between the two groups. Overall PFI was 2000 days (2000 vs 540 days; $P = 0.449$). When only first-occurrence cases were included, median PFI was significantly longer in the finely fractionated group compared with the coarsely fractionated group (1430 vs 540 days; $P = 0.007$). In cats that underwent multiple surgeries PFI was not different between protocols (233 vs 395 days; $P = 0.353$).

Conclusions and relevance Cats with primarily occurring ISSs appear to benefit from postoperative finely fractionated radiotherapy. The same benefit was not evident in cats that underwent multiple surgeries and we think a coarsely fractionated protocol would be indicated in these cases.

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Introduction

In the multimodal approach to feline injection-site sarcoma (ISS), radiation therapy (RT) is indicated after surgery to reduce the risk of local recurrence and increase progression-free interval (PFI).[1–3]

Many different postoperative approaches have been proposed, including curative, palliative intent and stereotactic RT; however, the comparison of RT protocols in cats with microscopic disease has been underinvestigated.[1–7] The choice of the most convenient treatment after surgery has important implications in terms of clinical benefit and the owner's finances.

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According to different studies, median PFI ranges between 5.7 and 22.0 months when cats receive RT following surgical excision.[2,4,5] Hypotheses to explain this wide range include different delivered total doses and radiation techniques, and the use of adjuvant chemotherapy.

Palliative RT seems to play a role, especially in cats without macroscopic disease. In a group of cats with macroscopic and microscopic disease receiving four fractions of 8 Gy each, median PFI was 10 months and median survival time (ST) 24 months.[7] Intriguingly, in those cats treated with such a palliative-intent protocol without gross disease, PFI increased to 20 months, suggesting that the benefit of a more hypofractionated protocol could be maximised if used in the microscopic setting.[7] In the same study, the number of previous surgeries was significantly associated with a shorter ST, whereas in another study this factor did not influence prognosis.[8]

The aim of this retrospective, bi-institutional study was to evaluate the PFI in a cohort of cats with microscopic ISSs treated with finely fractionated (definitive intent) or with six treatments of 6 Gy coarsely fractionated (palliative intent) electron beam RT in a cohort of cats with microscopic ISSs. The second aim was to test the influence of other potential prognostic factors (sex, age, anatomical location, size before surgery, number of surgeries, status of surgical margins, interval between surgery and RT, adjuvant medical therapy) on PFI. It was hypothesised that the 6 × 6 Gy coarsely fractionated palliative-intent RT would be as efficacious as a more finely fractionated definitive-intent RT protocol in terms of local tumour control.

Materials and methods

Case selection

The databases of the Veterinary Oncology Centre, Sasso Marconi, Italy, and the Vetsuisse Faculty, University of Zurich, Switzerland, were reviewed to identify client-owned cats with histologically confirmed ISSs at a previous site of injection that underwent surgical removal and subsequent RT treatment (2009–2014). Medical records and histology reports were retrospectively reviewed to retrieve demographic information (breed, sex, age), tumour characteristics (anatomical location, largest diameter measured by calliper from physical examination or imaging studies, histological grade, status of surgical margins) and clinical data (first occurrence or relapse, number of surgeries, interval between surgery and RT, results of clinical staging). Stage was established with the modified tumour, node and metastasis (TNM) staging system.[9] Surgical margins were defined as infiltrated if cancer cells were found at the edge of the removed tissue; if the distance between the outer edge of the removed tissue and the edge of the cancer was thicker than 2 mm, the margins were defined as clean; if this distance was less than 2 mm, the margins were defined as clean but close. Cats for which follow-up was not available were excluded from the study.

Procedures

Cats were treated under general anaesthesia with electron beam radiation delivered using a 6 megavolt linear accelerator (Clinac DMX or Clinac iX; Varian), equipped with an 80 leaf multi-leaf collimator. Treatment planning was performed by hand calculation and designed with the aim of maximal sparing of adjacent spinal cord, lung and abdominal organs. Field size and beam energy were set to include the surgical scar and a minimum of 3 cm of lateral and deep surrounding tissue, unless a demarcation by a change of compartment was present or depth was prevented by the presence of a very sensitive organ, such as spinal cord. Radiographs and/or ultrasound were used to measure the distance from organs (spinal cord, lung, abdominal organs) or CT study was used to better define the suspected area of microscopic infiltration and the distance from organs at risk. If CT was used, a total body examination was performed with the helical technique, with a slice thickness of 1.25 mm, acquired before and after intravenous administration of contrast medium (ioversol; Optiray 300 mg/ml [Covidien]).

Cats were irradiated with a single electron field with an energy range of 6–12 megavolts. Two RT protocols were used: a finely fractionated definitive-intent protocol, consisting of a prescribed total dose of 48 (Vetsuisse Faculty) or 52.8 Gy (Veterinary Oncology Centre) delivered in 12 fractions of 4 Gy or 16 fractions of 3.3 Gy over 4 weeks, or the 6 × 6 coarsely fractionated palliative-intent protocol with a total dose of 36 Gy administered in six bi-weekly fractions of 6 Gy over 3 weeks. Protocols were chosen based on general animal health and owner preferences. Source surface distance was 100 cm. A bolus of tissue-equivalent material of 0.5–1.5 cm depth was used to improve dose distribution uniformity to the surface. Bolus thickness was decided depending on the energy used, serving either the purpose of increasing surface dose and/or limiting depth of dose penetration.

The 90% isodose line was chosen to encompass the target volume and for dose normalisation.[10]

Treatment toxicity was evaluated during and 3 weeks after RT, and graded based on the Veterinary Radiation Therapy Oncology Group Criteria.[11] Monthly clinical re-checks were suggested either at the primary treatment centre or at the referring veterinarian's practice.

Follow-up information was obtained by medical record review or by telephone communication with the referring veterinarian and owner if the cat was not evaluated at the primary RT centre. Thoracic radiographs were performed at the 3 month interval and whenever clinically indicated.

PFI was calculated for each cat and defined as the interval (days) between the first radiation fraction and the onset of local recurrence or development of distant metastasis. Cats developing further ISS-related disease were recorded as events. The remaining cats were censored to the date of death or to the last follow-up (if death had not occurred).

Statistical analysis

Differences in the demographic and clinical features between cats receiving the two protocols were evaluated with the Mann–Whitney U-test and Fisher's exact test.

The Kaplan–Meier method and the log-rank test were used to compare PFI between the two protocols. Additionally, other variables were tested for prognostic significance, including institutions, demographic information, anatomical location, tumour diameter, number of surgeries, time between first surgery and RT, time between last surgery and RT, margins status and chemotherapy administration.

Data were analysed with commercial software (SPSS Statistics version 19 [IBM] and Prism version 5.0 [GraphPad]); P values ⩽0.05 were considered significant.

Results

Fifty-nine cats were included; 39 (66.1%) were treated at the Veterinary Oncology Centre and 20 (33.9%) at the Vetsuisse Faculty. Median age was 10 years (range 5–15.7 years). There were 37 spayed females (62.7%) and 22 castrated males (37.3%). There were 54 (91.5%) European Shorthair cats, three Norwegian Forest Cats, one Siamese and one British Shorthair.

The most common location of the surgical scar was the trunk (n = 50; 84.7%): 23 of these (39.0%) were in the interscapular region, 21 (35.6%) were located in other parts of the thoracic wall and six (10.2%) in the abdominal wall. In nine cats (15.2%), the proximal limbs were involved. Median tumour diameter before surgery was 3 cm (range 0.3–11 cm). All cats had only one RT treatment. Thirty-four (57.6%) cats had only one surgery, whereas 25 (42.4%) cats underwent two (n = 22) or more than two (n = 3) surgical procedures before RT. The median interval between the single/first surgery and RT was 41 days (range 10–1825 days); the median interval between the single/last surgery and RT was 25 days (range 10–180 days).

In 31 (52.5%) cats, surgical margins were infiltrated, in 18 (30.5%) cases clean and in 10 (16.9%) cases clean but close. Histological grade was available for 19 cases (32.2%). There were six (31.6%) grade 1, eight (42.1%) grade 2 and five (26.3%) grade 3 tumours.

Clinical staging was performed in 35 cases (59.3%) by CT and in 24 (40.6%) cases by thoracic radiographs and abdominal ultrasound. No suspected or confirmed metastatic lesions were detected.

Thirty-eight (64.4%) cats were treated with a finely fractionated definitive-intent RT protocol and 21 (35.6%) received the 6 × 6 Gy coarsely fractionated palliative-intent protocol.

Demographic features and potential prognostic variables were homogeneously distributed between the two treatment groups, with the exception of anatomical location: tumours located on the limbs were more frequent in the 6 × 6 Gy hypofractionated group than in the definitive-intent group (Table 1).

Twelve cats (20.3%) received adjuvant medical therapy: four cats were in the 6 × 6 Gy hypofractionated group and eight in the definitive-intent group. Ten cats were treated with doxorubicin and carboplatin at standard doses, whereas two cats received masitinib.

Acute side effects were observed in five (8.5%) cats treated with the definitive-intent protocol, including grade 1 toxicity in four cats (erythema, dry desquamation) and grade 2 toxicity in two cats (patchy, moist dermatitis). The administration of medical treatment did not increase the incidence of acute side effects. No acute side effects were observed in cats receiving the 6 × 6 Gy hypofractionated protocol. Late side effects included grade 1 leukotrichia in all cases.

At the end of the study, 25 (42.4%) cats were still alive, and 34 had died because of local recurrence (n = 13; 22.0%), tumour-unrelated causes (n = 13; 22.0%) or for an unknown reason (n = 8; 13.6%).

Neither thoracic nodules compatible with metastatic disease nor evidence of lung fibrosis was documented by thoracic radiographs in the follow-up period.

In 21 (35.6%) cats, the ISS recurred, with an overall 1 year recurrence rate of 25.4% and a 2 year recurrence rate of 32.2%. When stratifying cases based on the RT protocol, the recurrence rate between the two protocols was balanced, with 13 (34.2%) cats in the definitive-intent group and eight (38.1%) cats in the 6 × 6Gy hypofractionated group experiencing recurrent disease (P = 0.783).

Cats were monitored for a median follow-up time of 471 days (interquartile range 172–1077 days). Overall median PFI was 2000 days (95% confidence interval [CI] 373–3627), with no significant difference between the definitive-intent and 6 × 6 Gy hypofractionated groups (P = 0.449). When only first-occurrence cases were included, median PFI was significantly longer in the finely fractionated group (1430 days; 95% CI 62–2797) compared with the 6 × 6 Gy coarsely fractionated group (540 days; 95% CI 256–824) (P = 0.007). Conversely, in cats receiving multiple surgeries before RT, PFI did not change according to the protocol (P = 0.353), with a median PFI of 233 days (95% CI 36–430) in the definitive-intent group and 395 days (95% CI 120–1276) in the 6 × 6 Gy hypofractionated group (Table 2; Figures 1 and 2). Among the other variables tested for prognostic significance (institution, demographic information, anatomical location, tumour

Table 1 Demographic and clinical features of 59 cats with microscopic injection-site sarcoma receiving a definitive-intent or a 6 × 6 Gy hypofractionated radiotherapy protocol

Variable	Definitive-intent protocol (16 × 3 Gy daily; n = 38)	Hypofractionated protocol (6 × 6 Gy twice weekly; n = 21)	*P* value
Breed			0.336
DSH/DLH	36	18	
Purebred	2	3	
Sex			0.780
Male	15	7	
Female	23	14	
Median (range) age (years)	9 (5–14)	11 (6–15.7)	0.126
Tumour anatomical location			0.007*
Trunk	36	14	
Limbs	2	7	
Median (range) tumour diameter (cm)	2.35 (0.5–11)	3 (0.3–10)	0.114
Multiple surgeries			0.999
No (first occurrence)	22	12	
Yes	16	9	
Median (range) interval between first surgery and RT (days)	36 (10–832)	45 (10–1825)	0.396
Median (range) interval between last surgery and RT (days)	21 (10–180)	30 (10–60)	0.648
Surgical margins status			0.075
Clean	15	3	
Clean but close/infiltrated	23	18	
Chemotherapy			0.999
No	30	17	
Yes	8	4	
Acute RT side effects			
No	33	21	0.150
Yes	5	0	

DLH = domestic longhair; DSH = domestic shorthair; RT = radiation therapy
*$P<0.05$

Table 2 Recurrence rates and progression-free interval (PFI) in 59 cats with microscopic injection-site sarcoma receiving a definitive-intent or a 6 × 6 Gy hypofractionated radiotherapy protocol, stratified according to the number of surgeries

	Definitive-intent protocol (16 × 3 Gy daily; n = 38)	6 × 6 Gy hypofractionated protocol (6 × 6 Gy twice weekly; n = 21)	*P* value
Total (n = 59)			
Recurrence rate (%)	34.2	38.1	0.783
Median (95% CI) PFI (days)	2000 (1178–2821)	540 (297–783)	0.449
First occurrence (n = 34)			
Recurrence rate (%)	13.6	33.3	0.211
Median (95% CI) PFI (days)	1430 (62–2797)	540 (256–824)	0.007*
Multiple surgeries (n = 25)			
Recurrence rate (%)	62.5	44.4	0.434
Median (95% CI) PFI (days)	233 (36–430)	395 (120–1276)	0.353

CI = confidence interval
*$P<0.05$

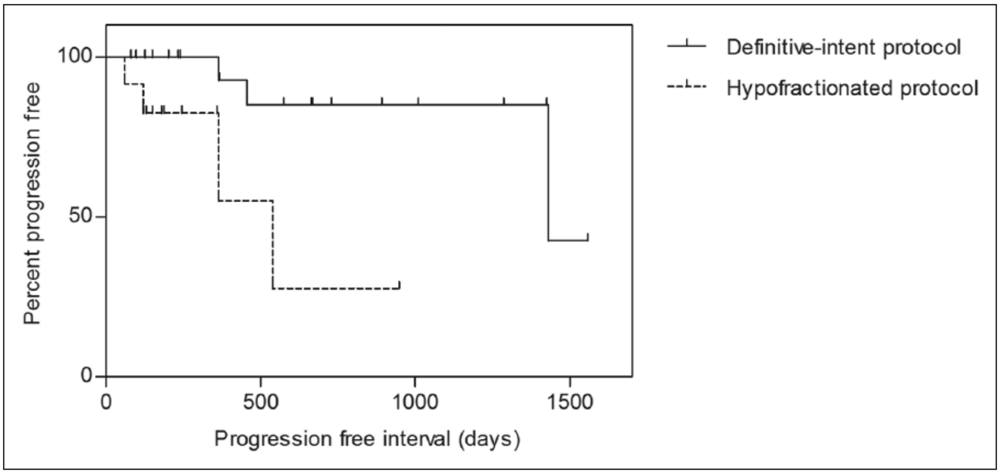

Figure 1 Progression-free interval (PFI) for first-occurrence cases treated with definitive-intent (solid line) and 6 × 6 Gy hypofractionated (dashed line) protocol. PFI is statistically different in the two groups ($P = 0.007$)

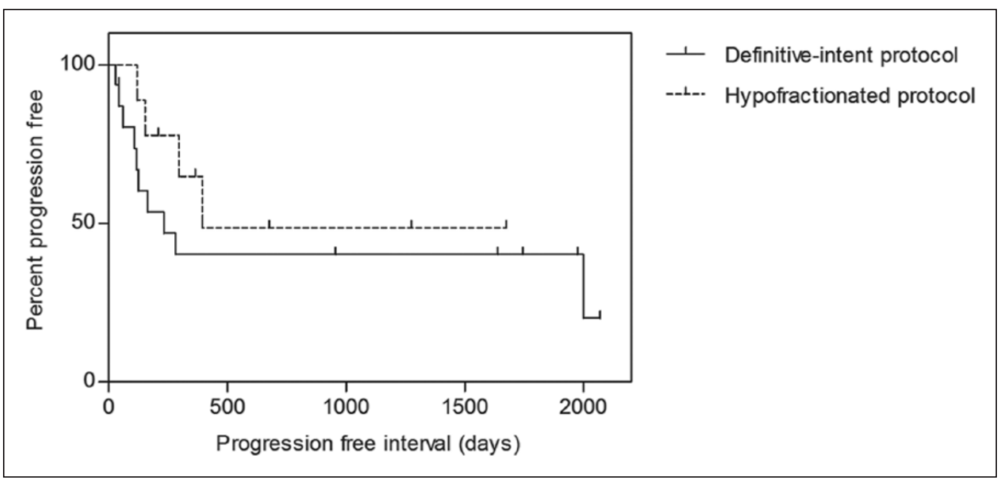

Figure 2 Progression-free interval (PFI) after multiple surgeries. PFI is not statistically different in cats treated with curative (solid line) and curative (dashed line) protocols ($P = 0.353$)

diameter, number of surgeries, time between first surgery and RT, time between last surgery and RT, margins status and chemotherapy administration), only multiple surgeries were significantly associated with shorter PFI (297 days [95% CI 60–534] vs 1430 days [95% CI 170–2690]; $P = 0.033$ [Table 3]).

Discussion

After surgery, further treatment decisions regarding cats with ISSs affects prognosis, and oncologists have the important role of offering the best protocol able to maximise clinical results with minimal side effects and financial impact. In this clinical scenario, clear guidelines on the best RT protocol are lacking. Previous studies have described the role of postoperative RT; however, most of these investigations included cats with both macroscopic and microscopic disease, and did not compare the efficacy of different RT protocols.[1,2,4,5,6,12] Only in the study by Eckstein et al, 27 cats were irradiated with a coarse fractionated protocol of 32 Gy delivered in 4 weekly fractions of 8 Gy, suggesting that a more hypofractionated RT protocol may represent a valid alternative to a definitive-intent RT in the case of microscopic disease.[7]

The present study compares the results of a finely fractionated definitive-intent protocol and a 6 × 6 Gy coarsely fractionated palliative-intent RT protocol, in order to identify possible prognostic variables that could help the oncologist to select the best treatment option in the case of microscopic ISS. Based on our results, the number of previously performed surgeries was the only factor that significantly influenced PFI. First-occurrence cases had a better prognosis if treated with the more intense definitive-intent protocol, with a significantly different PFI compared with the 6 × 6 Gy palliative-intent treatment group (median 47.7 months vs 18.0 months). In agreement with previous studies, the overall PFI was

Table 3 Analysis of variables potentially influencing recurrence rate and progression-free interval (PFI) in 59 cats with microscopic injection-site sarcoma treated by radiation therapy

Variable	Number of cases	Recurrence rate (%)	PFI	
			Median	*P* value
Institution				0.989
Veterinary Oncology Centre	39	30.8	1430	
Vetsuisse Faculty	20	45.0	Not reached	
Breed				0.974
DSH/DLH	54	37.0	2000	
Purebred	5	20.0	Not reached	
Sex				0.539
Male	22	27.3	2000	
Female	37	40.5	1430	
Age (years)†				0.242
<10	29	41.4	1430	
⩾10	30	30.0	2000	
Tumour anatomical location				0.341
Trunk	50	34.0	2000	
Limbs	9	44.4	395	
Tumour diameter (cm)†				0.198
<3	28	28.6	1430	
⩾3	31	38.7	2000	
Multiple surgeries				0.033*
No (first occurrence)	34	20.6	1430	
Yes	25	56.0	297	
Interval between first surgery and RT (days)†				0.549
<41	29	24.1	Not reached	
⩾41	30	40.0	1430	
Interval between last surgery and RT (days)†				0.172
<25	30	40.0	Not reached	
⩾25	29	27.6	2000	
Surgical margins status				0.269
Clean	18	27.8	2000	
Clean but close/infiltrated	41	39.0	Not reached	
Chemotherapy				0.799
No	47	36.2	2000	
Yes	12	33.3	Not reached	

*$P < 0.05$
†Median used as cut-off value
DSH = domestic shorthair; DLH = domestic longhair; RT = radiation therapy

significantly shorter (median 9.9 months) if cats had already undergone multiple surgeries, thereby confirming that recurrent ISS is more difficult to treat with RT than first-occurrence tumours.[2,7] Notably, after multiple surgeries, the type of RT protocol did not significantly influence PFI, suggesting that a coarsely fractionated RT protocol might be the most convenient choice. Possible explanations may be attributable to the higher vascular damage, tumour-bed hypoxia and increased scar tissues that result after multiple surgeries, possibly influencing the dose–effect response.[13,14] Moreover, if a large area of the body has been involved in disease recurrence, with multiple scars orientated in different directions, there is an increased probability of underestimating the microscopic extent of prior disease, resulting, potentially, in an incomplete field of irradiation, regardless of the protocol. Nevertheless, this second hypothesis seems to be less likely because a high percentage of cats (59.4%) underwent staging CT, which could have helped to more precisely delineate the affected area.[15–17]

Margin status is a well-recognised prognostic factor, and radical surgery has been shown to increase the disease-free interval (DFI) in cats treated with surgery only.[17–19] However, margin status refers to the histopathological evaluation of the excised tissue and the absence of neoplastic cells at the surgical margins is not always predictive of a better prognosis.[20] In a recent study in which a three-dimensional technique was used to evaluate surgical margins, 19% of cases had non-infiltrated margins, yet they recurred.[20] Other studies did not find a correlation between clean surgical margins and PFI if RT was administered in the adjuvant setting.[2,7,8] In our group of cats, margin status did not affect prognosis, regardless of the delivered RT protocol. Therefore, it may be assumed that surgery followed by definitive-intent RT offers the best outcome in the case of first-occurring ISS, regardless of the status of surgical margins. Additionally, in the case of recurrent ISS, palliative-intent RT seems to be a convenient clinical decision and could be offered as an alternative treatment if a second, more radical surgery is not possible or declined by the owner.

The 6 × 6 Gy coarsely fractionated protocol used in this study was delivered in a twice weekly schedule over 3 weeks, with a total dose that was slightly higher (36 Gy vs 32 Gy) and more fractionated (six vs four) than the previously reported protocol of Eckstein et al.[7] The increased fractionation with lower single doses (6 Gy vs 8 Gy) may reduce the risk of late local toxicity, including bone necrosis and radiation-induced tumours.[21,22] This coarsely fractionated protocol was well tolerated without acute toxicity or significant late side effects in any of the treated cats, and only leukotrichia was observed.

Preoperative RT has been previously investigated in cats treated with curative protocols.[1,12] Radiation toxicity was not considered significant; however, postoperative complications were seen in some cases.[1] After 6 × 6 Gy coarsely fractionated RT, the rate of complications might be higher because of increased late toxicity; therefore, further surgical treatment is not recommended.

Adjuvant medical treatment did not influence PFI in either group, and this is in agreement with a previous study, in which surgery followed by adjuvant chemotherapy did not significantly influence DFI and survival time when compared with surgery only.[23] Nevertheless, the small number of cats treated with dose-intense chemotherapy or masitinib may have biased the results in the current study, preventing a difference emerging.

None of the cats in this study developed metastatic disease until the end of the follow-period. Reported metastatic rate in ISSs varies between 10% and 24%, with involvement of the lung, regional lymph nodes, skin or subcutaneous tissue, mediastinum, liver and pelvis.[24] Only thoracic radiographs were repeated in the follow-up period; therefore, it is possible that very small lung nodules and extrathoracic metastases were not identified. However, our population included only cats with microscopic disease treated with postoperative RT and adjuvant medical therapy in 12 cases. Therefore, it is possible that combining treatment strategies results in better metastatic control.

Due to its retrospective nature this study is affected by some limitations. Cats were operated on by different surgeons, and histology samples were examined by various pathologists and commercial laboratories. Histological grade was not available for 32% of cases; therefore, it was not possible to test its prognostic role. Moreover, in the choice of the RT protocol, owners' preferences were taken into account, and it is possible that the presence of infiltrated margins and financial impacts negatively affected the decision for a definitive-intent protocol. Finally, despite a median follow-up time of 471 days, 10 cats were censored before 180 days, as they were the last cases included before data analysis closure; however, they were well balanced between the definitive-intent (n = 6) and palliative-intent protocol (n = 4) groups, so did not influence PFI analysis.

Conclusions

Cats with first-occurring ISSs seem to benefit from postoperative definitive-intent RT. Conversely, for cats having received multiple surgeries, there is apparently no advantage of a definitive-intent over a simpler, 6 × 6 Gy palliative-intent protocol. Therefore, because of its lower costs and time requirements, the latter seems to be a valid alternative in those cases.

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