4. Results

4.1. Signalment

Seventy-three dogs of the following breeds: Mixed breed (20) Golden Retriever (13), Labrador (10) Husky (3), Sheltie (2), Rhodesian Ridgeback (2), Cocker Spaniel (2) Australian Cattle Dog (1), Basset Hound (1), Beagle (1), Belgian Malanois (1), Bernese Mountain Dog (1), Border Collie (1), Boxer (1), Dalmatian (1), Doberman (1), German Shepherd Dog (1), Great Dane (1), Jack Russell Terrier (1), Malamute (1), Manchester Terrier (1), Miniature Schnauzer (1), Samoyed (1), Springer Spaniel (1), Tibetan Terrier (1), Weimeraner (1), Wheaton Terrier (1), and Whippet (1) were irradiated for 74 soft-tissue sarcomas.

Patients averaged 8.7 years of age (median 9, range 1.4-16.0 years) at the time radiation therapy was initiated. The average weight was 29 kg with a median of 30 kg and a range of 7 to 54 kg. Slightly more female dogs (53%) were treated than male dogs (47%) with the vast majority of all dogs either spayed or neutered (Table 7).

4.2. Tumor Presentation

The limbs were the most common site of sarcoma origin, accounting for 35 tumors, followed by the trunk (n=19), oral structures (n=17) and non-oral sarcoma of the head and neck (n=3). The proximal extremity (n=7) was less frequently affected than the distal extremity (n=28). Of the 35 tumors of the limbs, 25 were located in the front limb and 10 were located in the rear limb. The thigh accounted for five tumors of the proximal extremity and the upper arm gave rise to two tumors. Oral tumors were distributed as follows: maxilla (n=9), hard palate (n=4), lip (n=2) and soft palate (n=2).

Median age did not vary greatly according to location, with the exception of the head where the three dogs were of younger mean and median age (Figure 1).

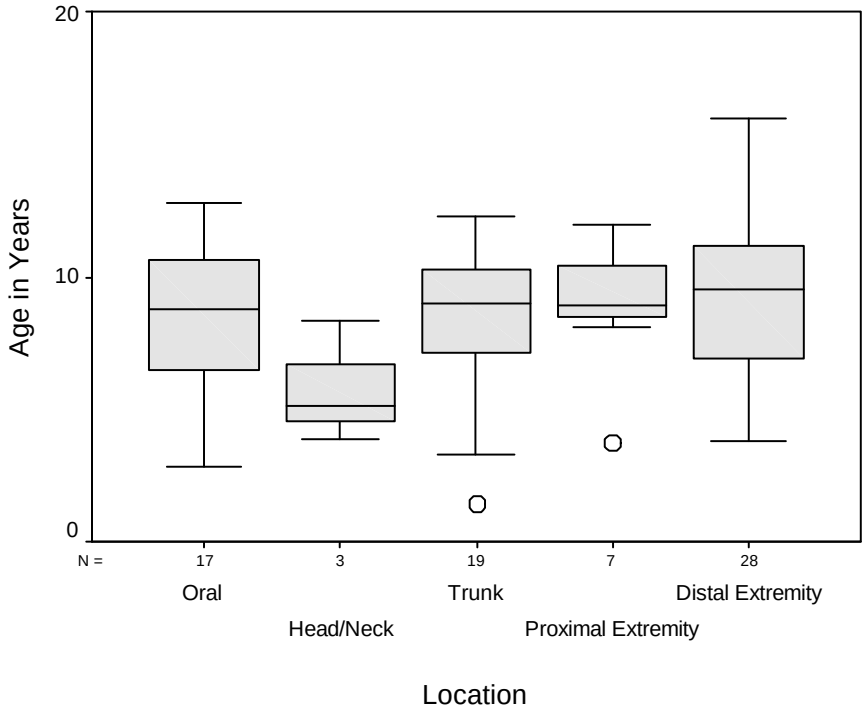


Figure 1 Distribution of age according to anatomic location.

Sex did not greatly influence anatomic distribution of tumors, which was similar between males and females with the exceptions of the distal extremity that was overrepresented in female dogs and the proximal extremity which was overrepresented in male dogs (Table 7).

Sex	Location										Total	
	Oral cavity		Head/Neck		Trunk		Prox Extrem		Dis Extrem.			
	n=	%	n=	%	n=	%	n=	%	n=	%	Count	%
Female, Spayed	8	10.8%	2	1.4%	8	10.8%	2	2.80%	16	21.6%	**36**	**48.6%**
Female, Intact	0	0.0%	0	0.0%	1	1.4%	0	0.00%	2	2.8%	**3**	**4.1%**
Male, Neutered	7	9.5%	1	1.4%%	10	13.5%	4	5.40%	7	9.4%	**29**	**39.2%**
Male, Intact	2	2.7%	0	0.0%	0	0.00%	1	1.4.%	3	4.1%	**6**	**8.1%**
Total	17	24.4%	3	4.2%	19	25.7%	7	9.6%	28	37.9%	**74**	**100%**

Table 7 Anatomic distribution based on sex (one neutered male presented with two tumors of the trunk).

FSA (n=29, 39%) was the most common tumor type followed by HPC (n=20, 27%) and MPNST (n=10, 14%). Fifteen tumors (20%) that were either rare or defied homogenous description were grouped together as “Misc” for the purposes of analysis. The “Misc” group consisted of tumors of the following histotypes: undifferentiated sarcoma/spindle cell sarcoma of undetermined origin (n=8), malignant fibrous histiocytoma (MFH) (n=3), liposarcoma (n=1), infiltrative lipoma (n=1), lymphangiosarcoma (n=1), and tendon sheath tumor (n=1).

Females were more commonly afflicted with MPNST (n=8, 75%) and HPC (n=12, 60%), than male dogs (MPNST n=2, 25%; HPC n=8, 40%) while males more commonly presented with FSA (n=18, 62%) than did female dogs (n=11, 38%). Misc tumors were similarly distributed among male (n=7, 47%) and female dogs (n=8, 53%).

The HPC group contained dogs with the oldest mean age, 10.1 years (median 10 years), followed by FSA with a mean age of 8.1 years (median 9 years), MPNST (mean 8.9, median 9.4 years) and Misc (mean 8.5 years, median 7.4 years). The oldest dog in the study (16 years) belonged to the HPC group while the youngest dog in the study was 1.4 years of age with an infiltrative lipoma (Misc tumor). Box and whisker plots of age distribution according to tumor type are given in Figure 2.

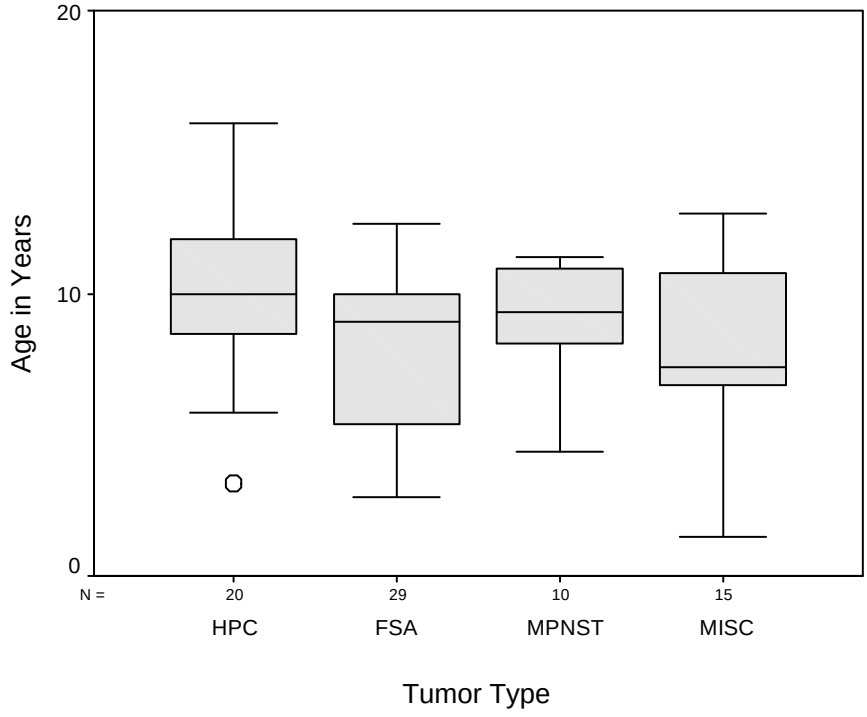
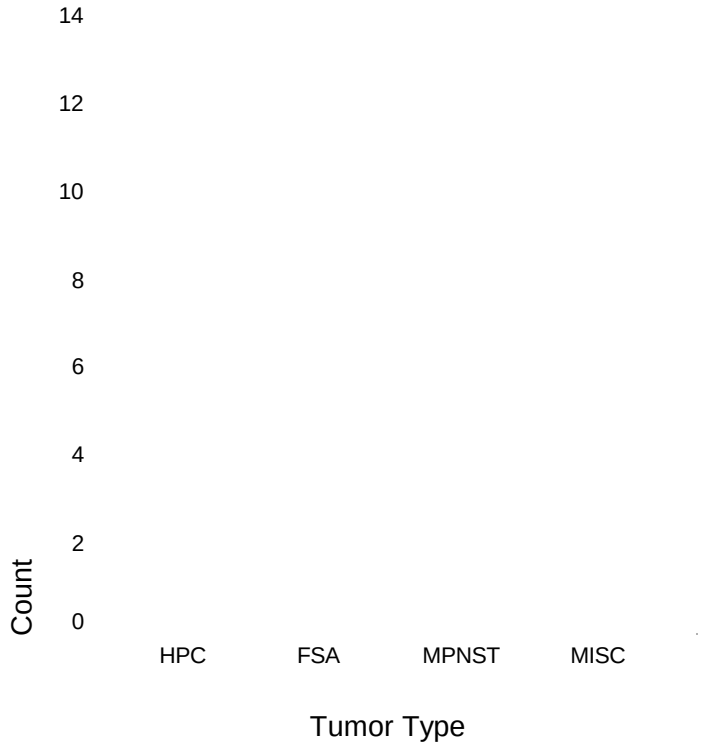
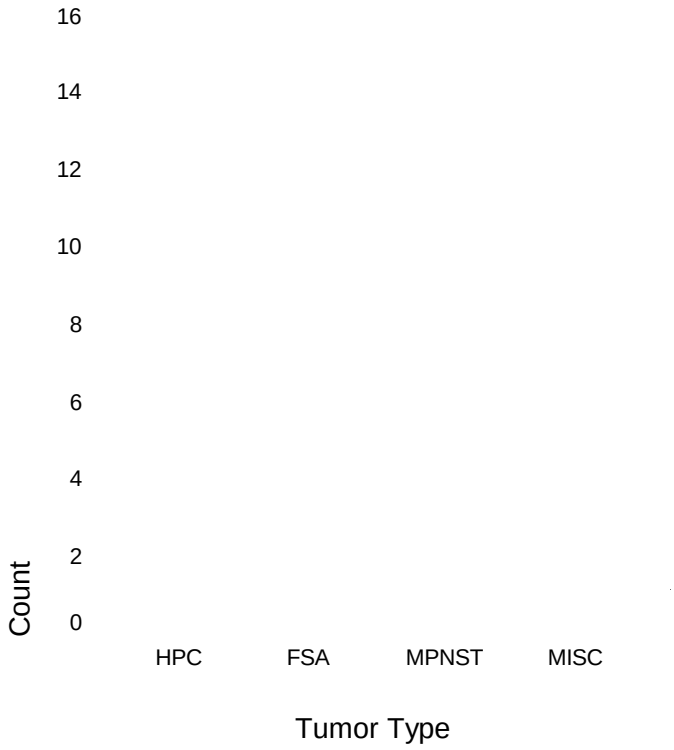
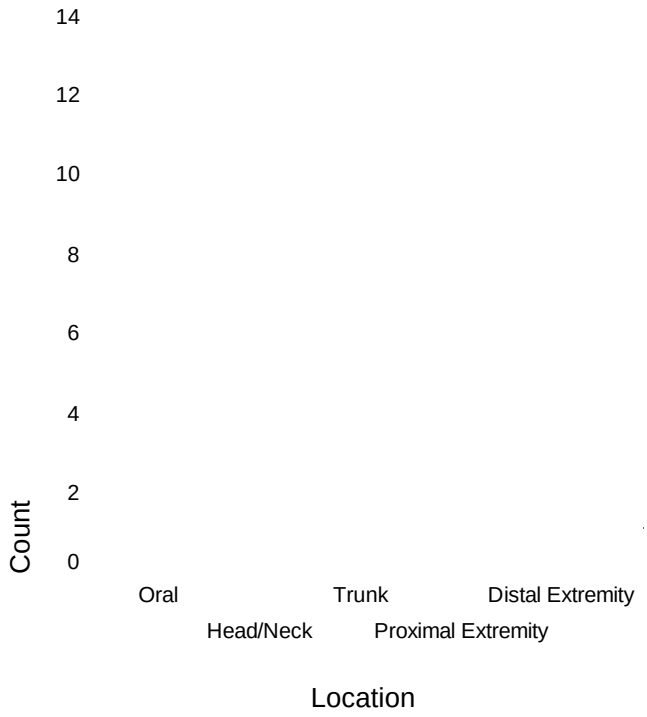


Figure 2 Age distribution according to tumor type.

The MPNST group (n=10) represented the group with the heaviest mean weight, 33 kg (median 34.5 kg), followed by Misc (mean 30.1 median 30) and FSA (mean 30 kg, median 31 kg). Dogs with HPC had the lightest mean weight (26 kg, median 27.5 kg). Hemangiopericytoma was most common in the distal limb and absent from the oral cavity and head. FSA was the most common tumor of the oral cavity. Other tumors enjoyed a uniform anatomical distribution as shown in Figure 3.




16
14
12
10
8
6
4
2
0
Count
HPC
FSA
MPNST
MISC
Tumor Type


14
12
10
8
6
4
2
0
Count
Oral
Head/Neck
Trunk
Proximal Extremity
Distal Extremity
Location

sites prior to presentation for the STS that received RT. Three dogs developed STS at other sites after the completion of radiation.

4.4. Radiation

Median field size was 78.5 cm^2, with an average field size of 138 cm^2. The area eliminated by the use of blocks was not eliminated for the purposes of calculation. Sixty fields were treated with photons and electrons were used in 14 cases. The 14 fields that were treated with electrons averaged 317 cm^2 (median 225 cm^2) and photon fields averaged 96 cm^2 with a median of 65 cm^2. A difference between electron and photon field sizes was clearly demonstrated on statistical evaluation ($P<0.001$, Mann-Whitney). Sixty radiations fields were constructed to treat residual disease and based on a surgical scar. Fourteen radiation fields were based on macroscopic disease. Mean and median photon field sizes were larger if macroscopic disease was present at the time of irradiation (mean 143 cm^2, median 96 cm^2) compared to field sizes based solely on the surgical scar (mean 83 cm^2, median 60 cm^2); statistical comparison between the groups resulted in a P-value of 0.074 (Mann-Whitney). A clear difference in field-size was not apparent ($P=0.32$, Mann-Whitney) in dogs that received photon radiation following surgical treatment from a referral center (mean 73 cm^2, median 55 cm^2) compared to surgery undertaken by a primary care veterinarian (mean 90 cm^2, median 67 cm^2). Mean photon field sizes were larger (96 cm^2, median 63 cm^2) if multiple surgeries were undertaken prior to RT compared to RT following the first excision attempt (77 cm^2, median 56 cm^2), but a statistical difference was not obvious ($P=0.56$, Mann-Whitney).

4.5. Toxicity

Moist desquamation was seen in 53 of 67 patients treated with a definitive radiation protocol. Early radiation effects required corticosteroids in 28 cases to decrease inflammation, 18 cases necessitated topical medication and 11 animals received systemic antibiotics. Twenty-one dogs developed transient lameness in the peri- or post RT period. Two dogs shed dewclaws and sloughing of the carpal pad occurred in one dog. Acute toxicity limited treatment in one dog that received low

dose doxorubicin as a radiosensitizer. Increased ocular discharge was noticed five months following radiation therapy in one dog that was diagnosed with radiation induced scarring of the nasolacrimal duct. Less severe late complications such as alopecia or dermal fibrosis were not consistently evaluated and are not included, however such reactions were frequent. Two animals had an eye included in the radiation field, but died before effects were expected and did not develop ocular lesions.

Major radiation reactions included radiation-induced sarcoma of the treatment field. Two dogs developed oral osteosarcoma (OSA). One dog that developed OSA of the mucous membranes 142 days after completing radiation therapy had received 48 Gy of radiation at another institution five-years earlier. Although radiation fields were not identical, some overlapping of the previous radiation field was encountered. Another dog developed OSA of the hard palate 1,392 days after the completion of RT. Both reactions resulted in death. A dog with a low-grade MPNST that was treated with electron irradiation developed a high-grade anaplastic sarcoma in the radiation field 1,197 days post RT. Although a recurrence of the original tumor cannot be excluded, the difference in tumor morphology suggests a radiation induced soft-tissue sarcoma.

Doxorubicin was administered to nine dogs and was generally well tolerated. One dog required hospitalization for neutropenia. Cardiotoxicity was not seen in any dog; no animal that received doxorubicin died of cardiac related illness.

4.6. Overall Survival

Median overall survival was estimated at 1,049 days. Of the 73 dogs studied, 31 were dead at the end of the study and 42 dogs were alive and censored. The survival curve is shown in Figure 6. One-hundred and eighty day survival intervals were calculated based on the Kaplan-Meier curve (Table 8). Of the 31 dogs that died during the course of the study, causes of death included: STS related causes (17), other cancer related conditions (5) cardiac disease (3), euthanasia related to “old age”(3), CNS disease (1), megaesophagus (1) and renal failure (1).

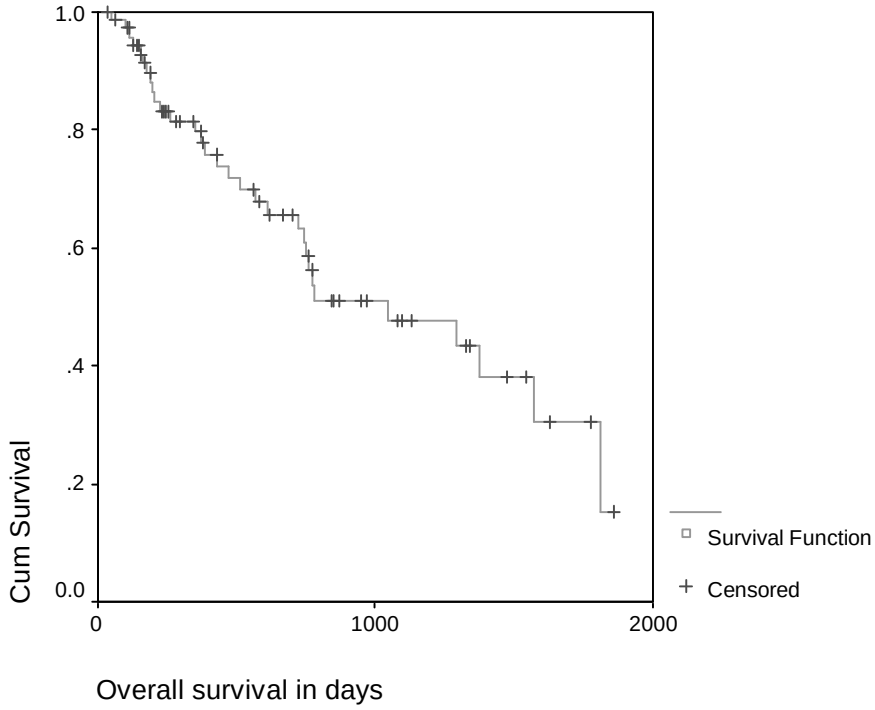


Figure 6 Overall survival of all 73 dogs that received RT.

Interval Post RT	Percentage Alive
180	89.7%
360	79.6%
540	69.8%
720	63.3%
900	51.1%
1080	47.7%

Table 8 Overall survival at180-day intervals

4.7. Survival

Seventeen (23.3%) of the animals studied had died of tumor related causes at the conclusion of the study period. A Kaplan-Meier survival curve was generated

for all 73 animals included in this study (Figure 7) and 180-day survival intervals were calculated (Table 9). Mean survival was estimated at 1,356 days, median survival was not reached. Of the 17 animals that died due to tumor related causes six dogs died of recurrent disease, three dogs died of metastatic disease, and eight dogs that were not treated with surgery died of local tumor progression.

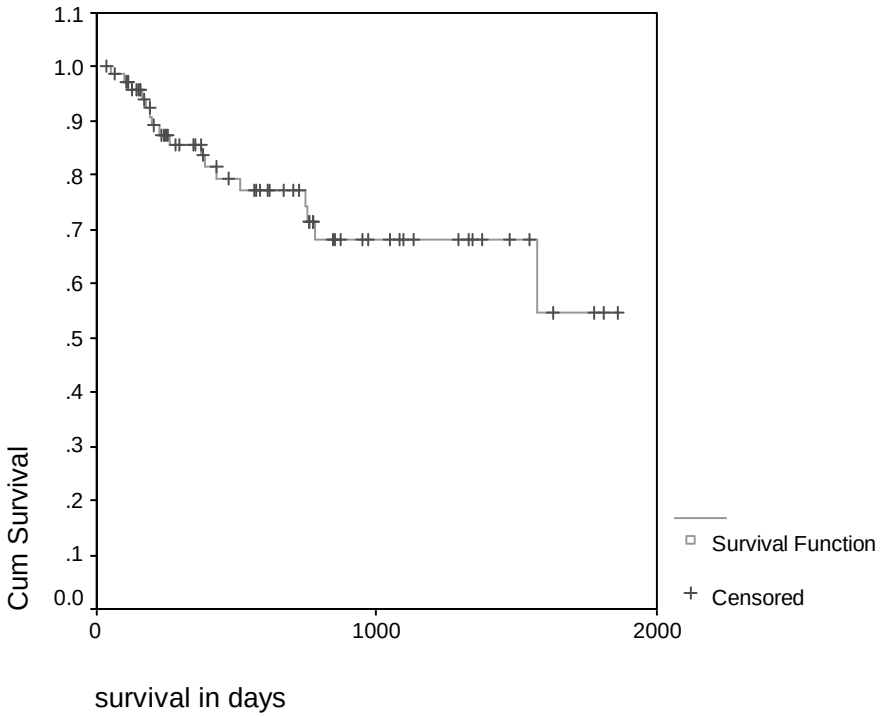


Figure 7 Kaplan-Meier survival curve of all 73 dogs studied.

Of the dogs with non-resected disease, four were treated with a definitive protocol, and four with a hypofractionated protocol. One additional dog that received palliative RT died due to tumor related causes, but the exact date of death was unknown and was considered lost to follow-up and censored at the last known contact.

Interval Post RT (day)	Percentage that did not die to Tumor related cause.
180	92.5
360	85.7
540	77.2
720	77.2
900	68.1
1080	68.1

Table 9 Survival at 180-day intervals of all dogs studied.

4.8. DFI

At the time of radiation therapy, 59 dogs (with 60 tumors) had undergone incomplete excision and were treated for microscopic disease. Ten of the tumors were orally located and 50 tumors were of non-oral location. The remaining 14 cases were excluded from DFI calculations. During the study period, 11 recurrent events were recorded and 49 treatment fields were censored. Kaplan-Meier analysis revealed a median DFI estimate of 1,420 days and median DFI was not reached (Figure 8). The percentage of tumors that had not recurred was calculated at 180-day intervals (Table 10). Seven recurrences occurred with non-oral sarcoma and four recurrences occurred in the oral cavity.

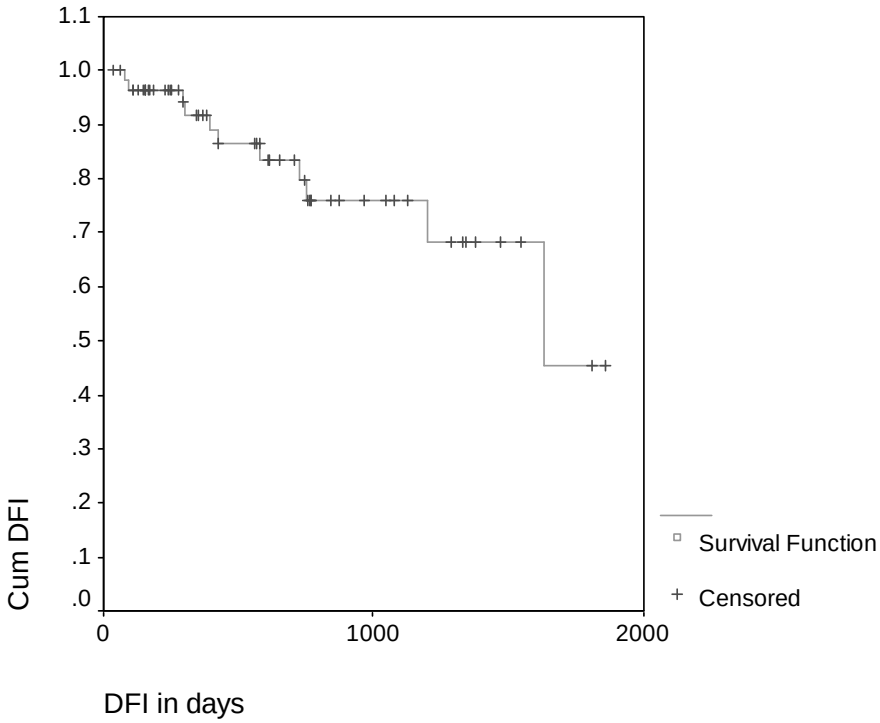


Figure 8 Kaplan-Meier DFI curve of 60 dogs that underwent excision prior to RT.

Interval Post-RT (days)	Percentage without local recurrence.
180	96.6%
360	91.8%
540	86.4%
720	83.3%
900	75.9%
1080	75.9%

Table 10 DFI of all dogs at 180-day intervals.

4.9. Metastasis

No animal that received doxorubicin died of metastatic disease. Four dogs with high-grade tumors did not receive adjuvant doxorubicin, two of those dogs

developed metastases. Metastasis was detected in four of 73 dogs (5.5%), two of which were confirmed to be of spindle cell origin on biopsy. The two confirmed cases included a dog with a liposarcoma that developed abdominal spindle cell metastases in the omentum and pancreas and was euthanised 172 days after radiation treatment was completed and a dog with a high-grade FSA that developed pulmonary metastasis 740 days after the completion of radiation treatment.

Two unconfirmed cases included a Golden Retriever with an oral sarcoma and radiographic evidence of a thoracic mass prior to treatment that resulted in euthanasia 52 days after the completion of RT but did not under go biopsy or necropsy of the thoracic lesion. In another dog, a nodular pulmonary pattern was detected on radiographic examination. Additional radiographic studies detected a pelvic mass with a radiographic appearance consistent with osteosarcoma; however, spindle cell metastasis could not be definitively excluded. Euthanasia was conducted 762 days after RT was completed. Based on clinical data, death was not considered to be a result of STS metastasis for the purposes of survival analysis. Three cases were considered to be of STS origin (4.1%).

4.10. Recurrence and Survival

Survival was examined in the sixty dogs that underwent surgery prior to radiation based on the development of recurrence. Survival of the eleven dogs that experienced recurrence was compared to survival of forty-nine dogs that did not develop recurrence. Survival of both groups was plotted with the Kaplan-Meier method (Figure 9).

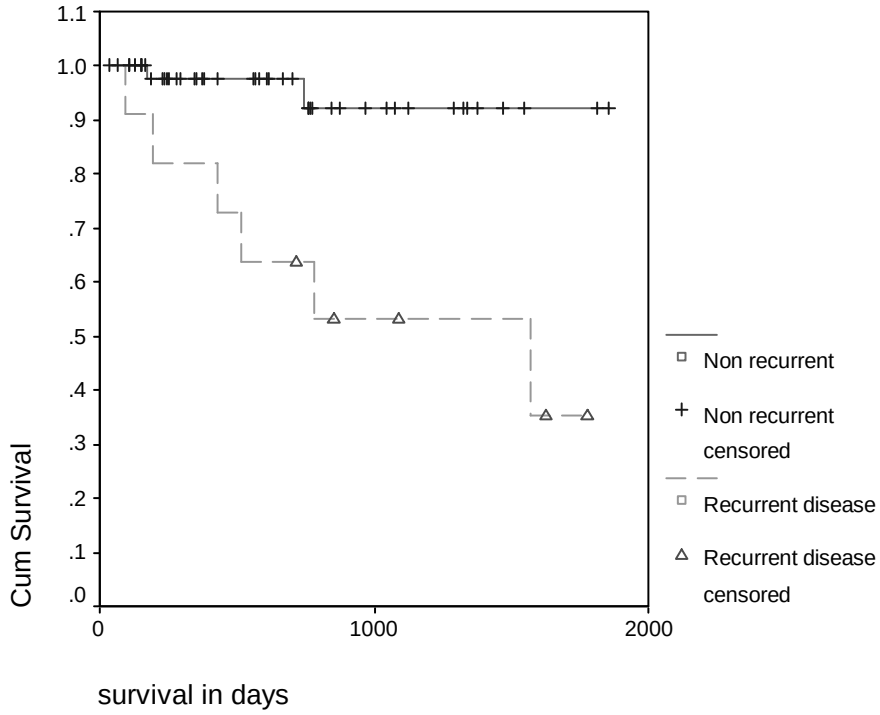


Figure 9 Survival of all sixty dogs that underwent resection prior to surgery. Dogs are grouped according to recurrence of disease.

Log-rank analysis (P=0.021) revealed a survival disadvantage for dogs with recurrent disease (median 1,572 days) compared to dogs that did not develop recurrent disease (median survival not reached).

4.11. Oral vs. Non-Oral Location

Seventeen dogs were treated for oral sarcoma, 14 received a definitive protocol and three received a palliative protocol. Nine dogs underwent surgery prior to radiation treatment and seven dogs were treated for measurable disease. Fifty-seven dogs were treated for non-oral sarcoma, 51 dogs with 52 tumors were treated for residual disease (51 with a definitive protocol, and one with a hypo-fractionated protocol). Five dogs were treated for measurable disease (three with a definitive protocol and two with a hypofractionated protocol).

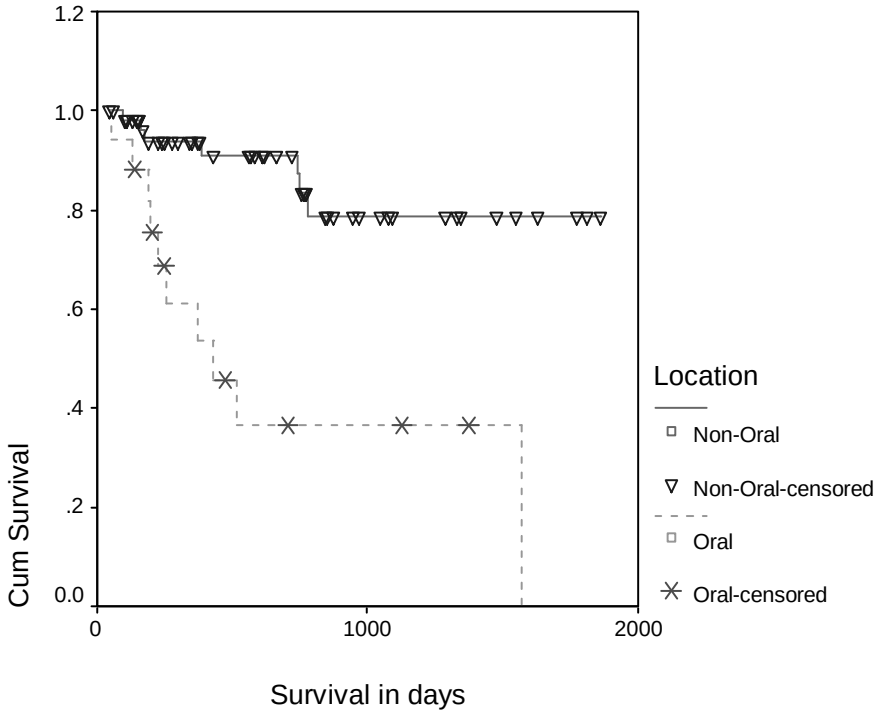


Figure 10 Kaplan-Meier analysis undertaken according to location. Oral locations were grouped together and non-oral locations were grouped together.

Ten of 17 dogs with oral tumors died of sarcoma related causes as did seven of 56 dogs (with 57 tumors) with non-oral tumors. A survival difference was noted on statistical comparison ($p<0.001$, Log-rank). Median survival was not reached for non-oral tumors, but was estimated at 430 days for oral tumors.

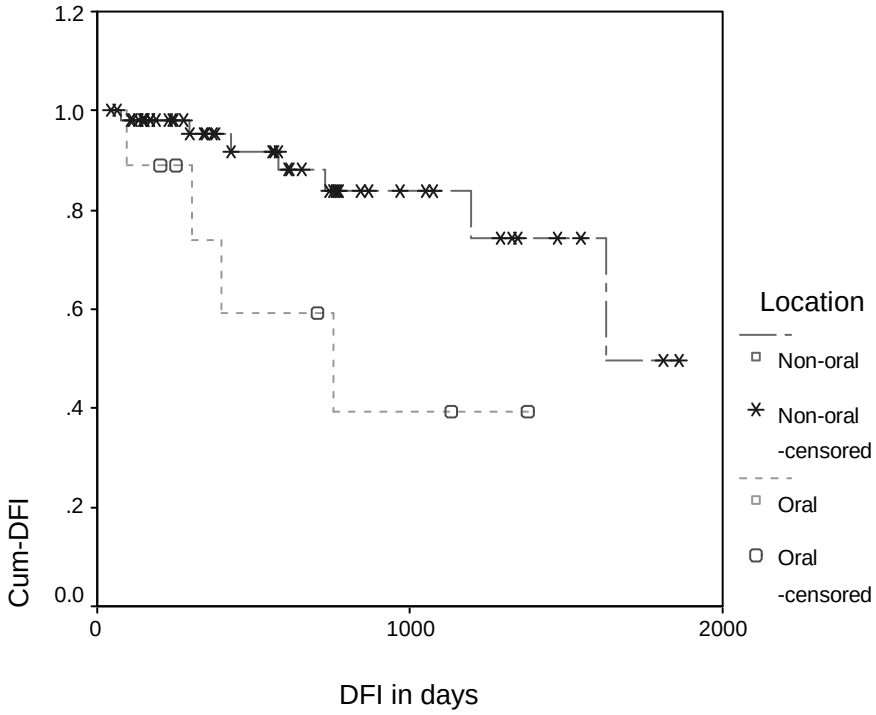


Table 11 Kaplan-Meier analysis of DFI of excised tumors according to location. Tumors are grouped based on oral vs. Non-oral location.

A difference in recurrence was noted between oral and non-oral locations (p=0.0175). Four of nine excised oral tumors recurred compared to seven of 51 excised non-oral tumors; median DFI was 735 days for oral tumors and 1,629 days for non-oral tumors.

4.12. Group I

4.12.1. Dogs Included in Group I

Fifty dogs treated with a definitive protocol of external beam radiation for 51 incompletely excised soft-tissue tumors were included in Group I. Palpable or visible tumors and involvement of the oral cavity served as exclusion criteria. The median follow-up period was 611 days (mean 670) with a range of 47-1,869 days. The median age at the start of radiation therapy was 9 years (mean 8.6, min 3.3, max 13) with a median weight of 29 kg (mean 28 kg, min 7, max 47 kg). Mixed-breed dogs, Labradors and Golden Retrievers were the most common breeds represented (Table 12). Twenty-seven spayed females, three intact females, 17 castrated males, and three intact males were present in Group I.

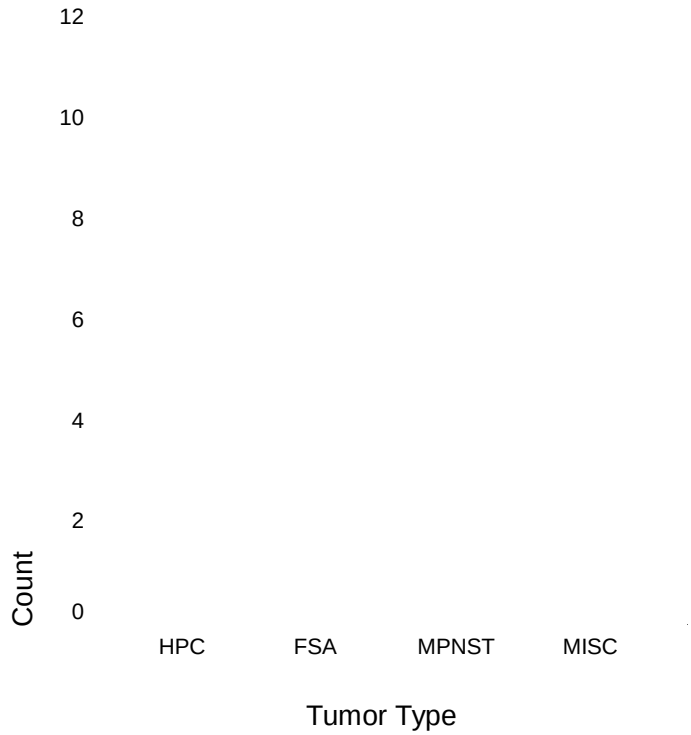
Breed	Number
Mixed Breed	14
Labrador	7
Golden Retriever	6
Cocker Spaniel	2
Husky	2
Rhodesian Ridgeback	3
Sheltie	2
Australian Cattle Dog	1
Basset Hound	1
Beagle	1
Belgian Malinois	1
Border Collie	1
Doberman	1
German Shepherd Dog	1
Great Dane	1
Jack Russel Terrier	1
Manchester Terrier	1
Miniature Schnauzer	1
Samoyed	1
Wheaton Terrier	1
Whippet	1
Total	50

Table 12 Breeds included in Group I

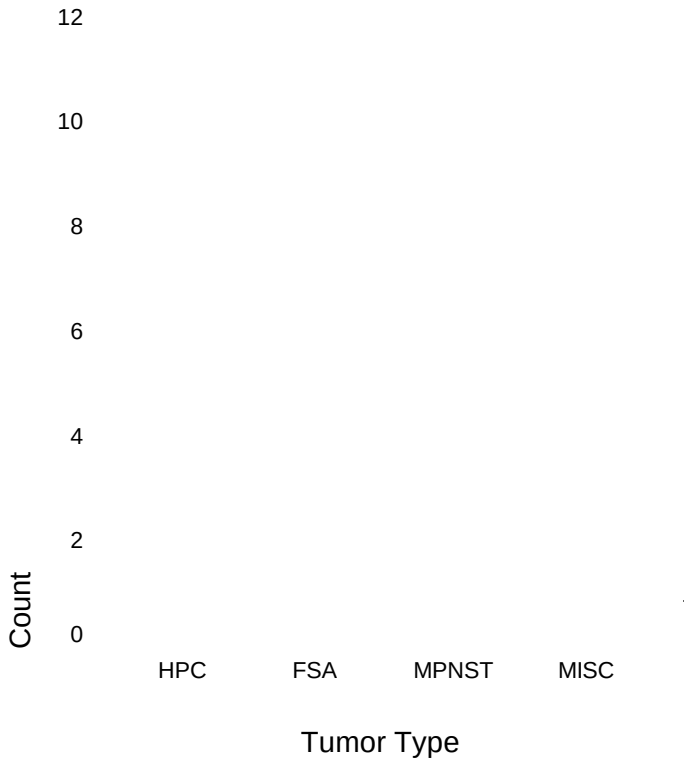
4.12.2. Tumors Included in Group I

Nine MPNST, 16 HPC, and 17 FSA constituted sub-groups large enough to analyze. Two malignant fibrous histiocytomas, one liposarcoma, one lymphangiosarcoma, four undifferentiated sarcoma/spindle cell tumors of undetermined origin and one tendon sheath tumor were grouped together and analyzed as the group “Misc”.

Twenty-five tumors were located in the distal extremity, 16 in the trunk, six in the proximal extremity and three in the head/neck. Hemangiopericytoma was the most common tumor of the distal extremity and FSA was the most common tumor of the trunk (Figure 11).



intermediate-high-grade). The histological distribution according to tumor grade is shown in Figure 12.



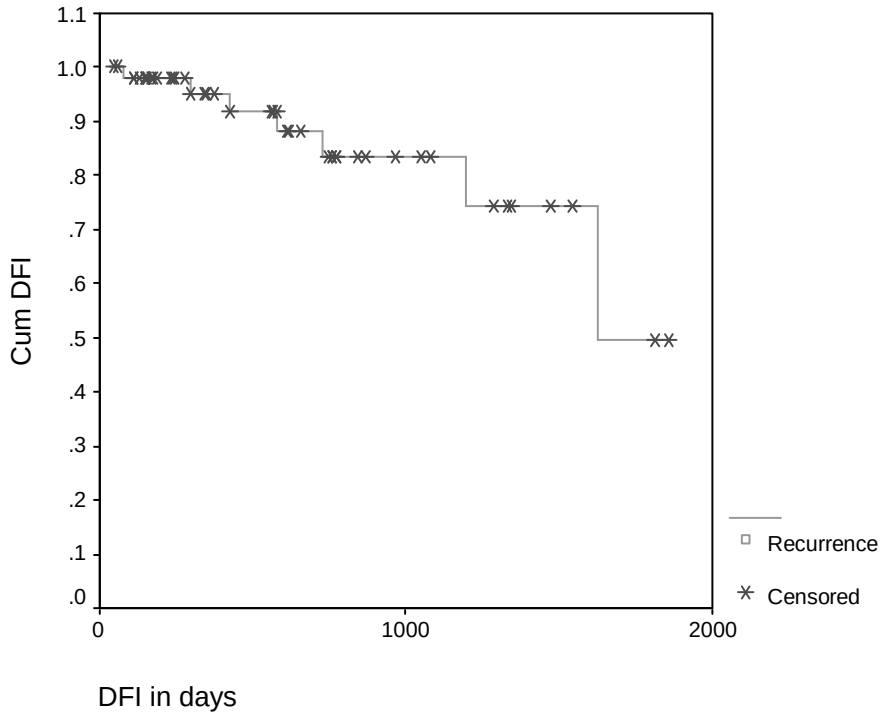


Figure 13 Kaplan-Meier curve based on the DFI of the dogs included in Group I.

Six-month (180-day) disease free interval rates were calculated and are shown in Table 13. Median DFI is estimated at 1,629 days. The last censored value occurred at 1,829 days.

Days	Disease Free %
180	98 %
360	95 %
540	92 %
720	88 %
900	84 %
1080	84 %.

Table 13 Percentage of disease free animals in Group I at 180-day intervals. Calculations are based on Kaplan-Meier analysis.

-Results-

The seven dogs with recurrent disease included:

a 9-year old Labrador with a psuedo-encapsulated nerve-sheath tumor of the right hip, which ruptured during excision. Ulceration was noted at the surgical site shortly (20 days) after completing radiation therapy. Seventy-seven days post-RT a mass was noted caudal to the radiation field; euthanasia was conducted on request of the owner.

A nine-year-old Husky was treated for a nerve sheath tumor of the right thigh. The tumor returned 293 days after completing radiation therapy. The tumor was subsequently completely excised with no further recurrence.

A Jack Russell Terrier, 13 years old, experienced recurrence of a hemangiopericytoma of the left elbow 425 days after the completion of radiation therapy. Stabilization was achieved with the delivery of hypofractionated protocol consisting of three fractions of 700 cGy until a total dose of 7,000 cGy was achieved. Euthanasia was undertaken ten months later due to complications of oral malignant melanoma.

A 9-year-dog treated for a nerve sheath tumor of the ventral thorax. A 728-day DFI was achieved before the dog presented with a recurrent tumor dorsal to the radiation field that encroached into the axillary region resulting in forelimb lameness. The suggestion of radical excision was declined and the owners elected euthanasia shortly thereafter.

A four-year-old mixed breed with a low-grade nerve sheath tumor at the time of excision, developed recurrence in the radiation field 1,197 days post RT. Complete excision was achieved and evaluated as a high-grade undifferentiated sarcoma. It could not be conclusively concluded if the tumor was recurrent or a radiation induced neoplasia. The dog was alive with no further recurrence 1,777 days after completing radiation therapy.

A Wheaton Terrier, 8.4 years old, with an ungraded MPNST on the dorsum of the nose. On excision, biopsy did not detect bony involvement. Recurrence was noted 580 days following the completion of radiation therapy. The dog was still alive at last contact, 1,092 days after completing radiation treatment.

A nine-year-old Cocker Spaniel with a hemangiopericytoma of the carpal region experienced recurrence inside the RT field 1,629 days after radiation therapy. Complete excision of the recurrent tumor was accomplished.

4.12.4. Survival of Group I

Four deaths were related to STS. Two deaths associated with local recurrence occurred at 95 and 780 days are described above. Two deaths due to metastatic disease occurred at days 172 and 745 post-RT. A 7-year Labrador with a high-grade liposarcoma of carpal region developed abdominal metastases 172 days after RT was completed. Euthanasia was performed shortly after diagnosis. A 10-year-old Samoyed was treated for a high-grade FSA of the ventral cranial thoracic region. Metastatic disease was detected in the thorax 745 days after the completion of radiation therapy. Surgical exploration and biopsy revealed 8x5x3 cm high-grade spindle cell tumor followed by euthanasia shortly thereafter.

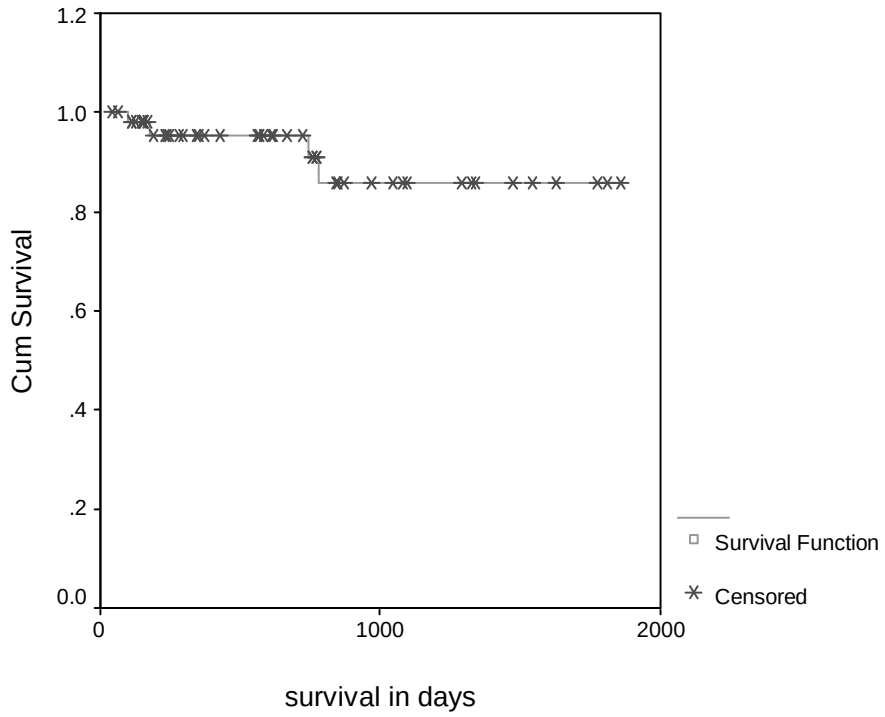


Figure 14 Kaplan-Meier curve of survival for dogs in Group I.

Kaplan-Meier analysis of survival (Figure 14) revealed a 3-year survival rate of 86% (Table 14), median survival was not reached.

Days	Percentage alive
360	95%
720	95%
1080	86%

Table 14 Survival (not dead of tumor related cause) of dogs in Group I reported at 360 day intervals.

4.12.5. Overall Survival of Group I

All animals that died during the course of this study were considered events in overall survival analysis. Of the 50 dogs represented, 15 survival events occurred (30%) and 34 cases were censored (70%). Eight of the fifteen dogs died of cancer related causes, but only four of those were STS related. Causes of death included: cardiac disease (3), “old age” (3), probable metastatic OSA (1), malignant melanoma (1), CNS disease (1), generalized histiocytic malignancy (1) and intestinal carcinoma (1).

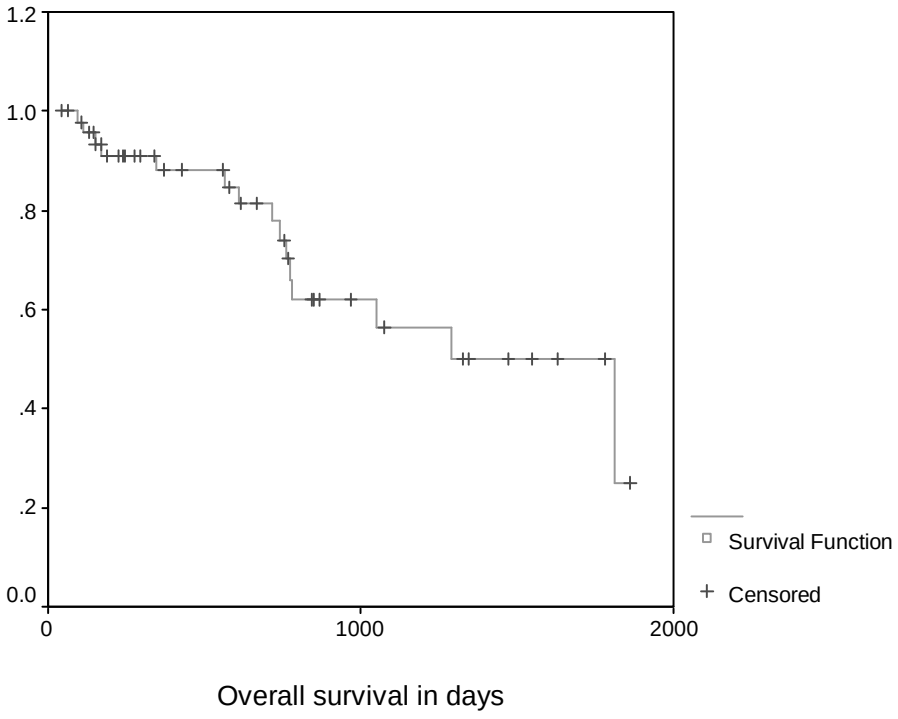


Figure 15 Kaplan-Meier curve based on overall survival of all animals in Group I.

The last event occurred at 1,811 days and the longest censored interval occurred at 1,856 days. A Kaplan-Meier curve was generated (Figure 15) and survival rates recorded at 180-day intervals are shown in

Table 15. Median overall survival is estimated at 1,811 days.

Interval in days	Percentage alive
180	91
360	88
540	88
720	73
900	63
1080	57

Table 15 Overall survival rates calculated at 180 day intervals based on Kaplan-Meier analysis.

4.12.6. Analysis of Prognostic Factors of Group I

4.12.6.1. Local Recurrence

Recurrence was examined based on six factors: histotype, grade, anatomic location, surgical history, field-size and interval between surgery and radiation. Seven tumors recurred following excision and 44 tumors were censored.

Tumor type was assessed for all dogs in Group I. Five malignant peripheral nerve sheath tumors (n=9, 56%) returned as did two hemangiopericytomas (n=16, 12.5%). No fibrosarcomas (n=17, 0%) or Misc tumors (n=9, 0 %) recurred in Group I.

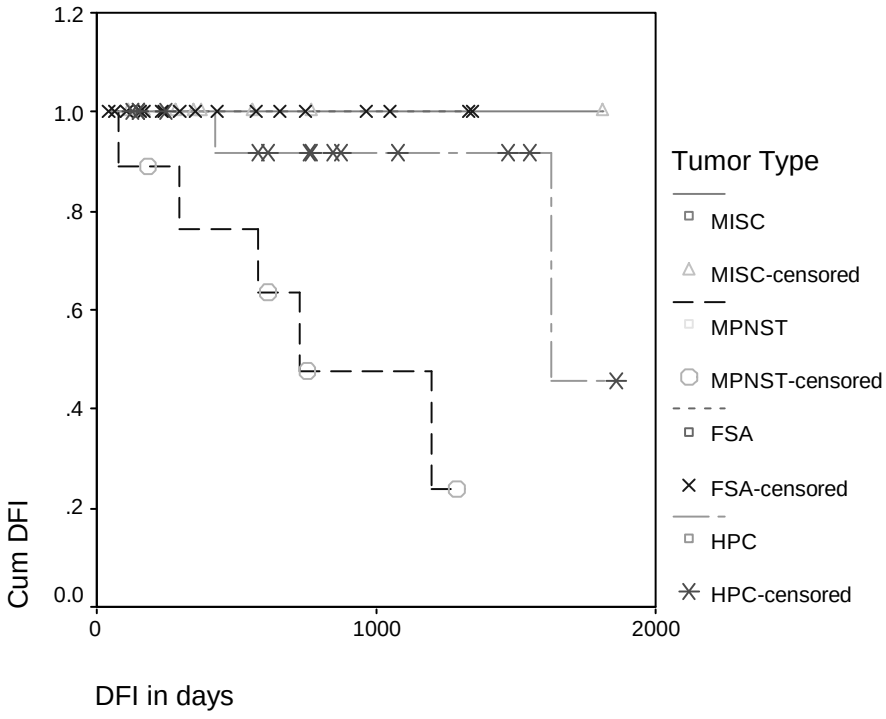


Figure 16 Kaplan-Meier DFI curve generated according to histotype.

The shortest median DFI (Figure 16) was found in the MPNST group (728 days), followed by the HPC group (1,629 days). Median disease free interval could not be estimated for FSA or Misc tumors as all DFI data of both groups was censored. Statistical comparison according to tumor type showed a difference in DFI

between MPNST group and the HPC group (P=0.012) and the FSA group (P=0.012), the difference between the MPNST group and the Misc group (P=0.084) was not as clearly demonstrated.

Disease free interval was examined according to anatomic location. Dogs were placed into one of four groups: head/neck, trunk, proximal extremity and distal extremity groups and DFI curves were compared (Figure 17). The trunk represented the most common location of treatment failure with three recurrences (n=17, 18%) followed by the distal extremity with two recurrences (n=25, 8%), the proximal extremity with one recurrent event (n=6, 17%) and the head/neck with one tumor returning (n=3, 33%).

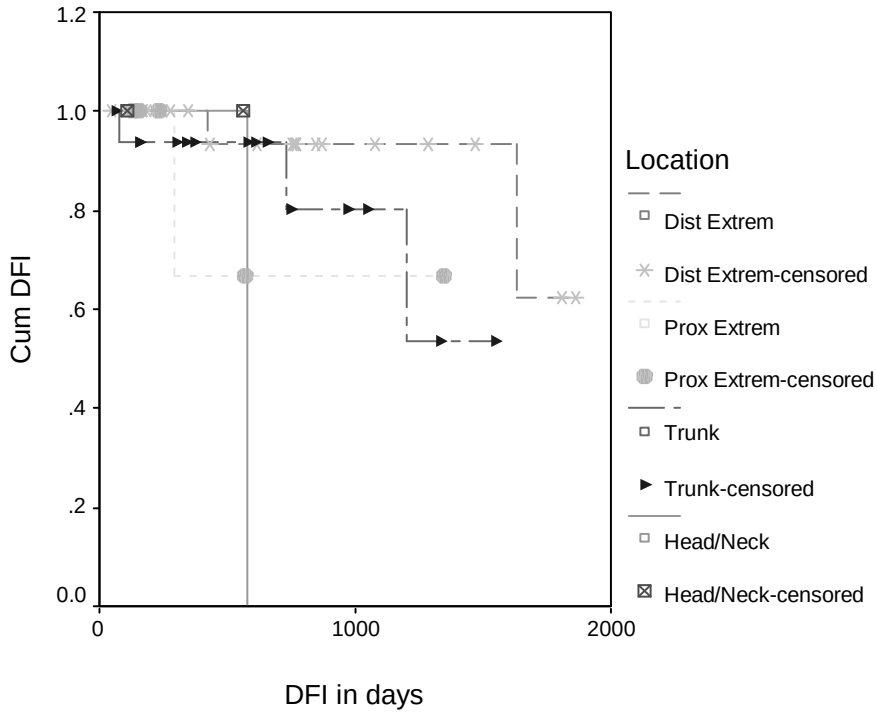


Figure 17 Kaplan-Meier curve of DFI according to anatomic location.

Median DFI was not reached in any location except the head (580 days). Disease free interval was compared with log-rank tests based upon tumor locations. The lowest P-values were found between the head and distal extremity (P=0.049), head and trunk (p=0.12), distal extremity and the trunk (p=0.13), and distal extremity and the proximal extremity (P=0.14).

Six high-grade, 14 intermediate-grade and 11 low-grade tumors were represented in Group I. Nineteen of 51 tumors were ungraded and excluded from

statistical analysis. Mean follow-up period differed between groups, with Grade I tumors having the longest follow up period (919 days) followed by Ungraded (812 days), Grade III (712 days) and Grade II (245 days). No recurrences were noted with high-grade tumors (n=6, 0%) and DFI estimates are not available due to the lack of recurrence.

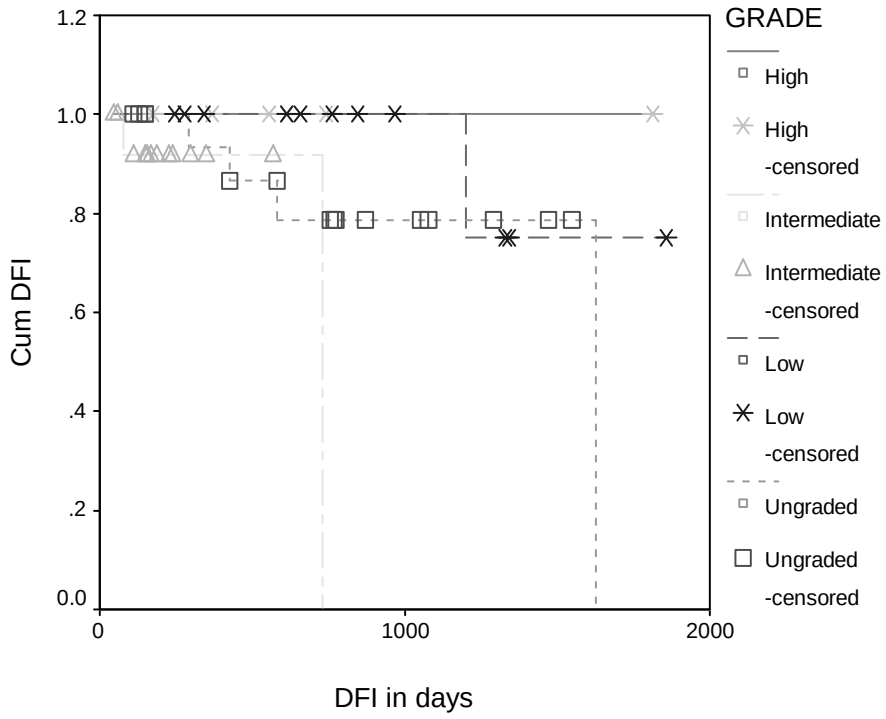


Figure 18 Kaplan-Meier curve of DFI according to histological grade.

Two intermediate-grade tumors (n=14, 14%) recurred at days 77 and 728; median DFI was estimated at 728 days for intermediate-grade tumors. One low-grade tumor (n=11,9%) recurred at day 1,197; median DFI was not reached for the group Grade I. Four ungraded tumors (n=19, 21%) recurred with a median DFI estimate of 1,629 days (Figure 18). The greatest difference in occurred between the groups Grade I and Grade II (p=0.022).

Eighteen surgeries were conducted by primary veterinarians; 32 surgeries were conducted by referral surgeons. Of the seven recurrences, six occurred in cases that were removed by referral surgeon. Sixteen dogs in Group I experienced multiple surgeries and 34 dogs with 35 tumors had only one surgery prior to initiation of radiation therapy. Four recurrences were noted in the group that underwent a single surgery prior to radiation treatment, three recurrences were recorded in dogs that

underwent more than one surgical procedure. All recurrences in dogs that underwent multiple surgeries occurred before any recurrence in dogs that was treated after a single surgery.

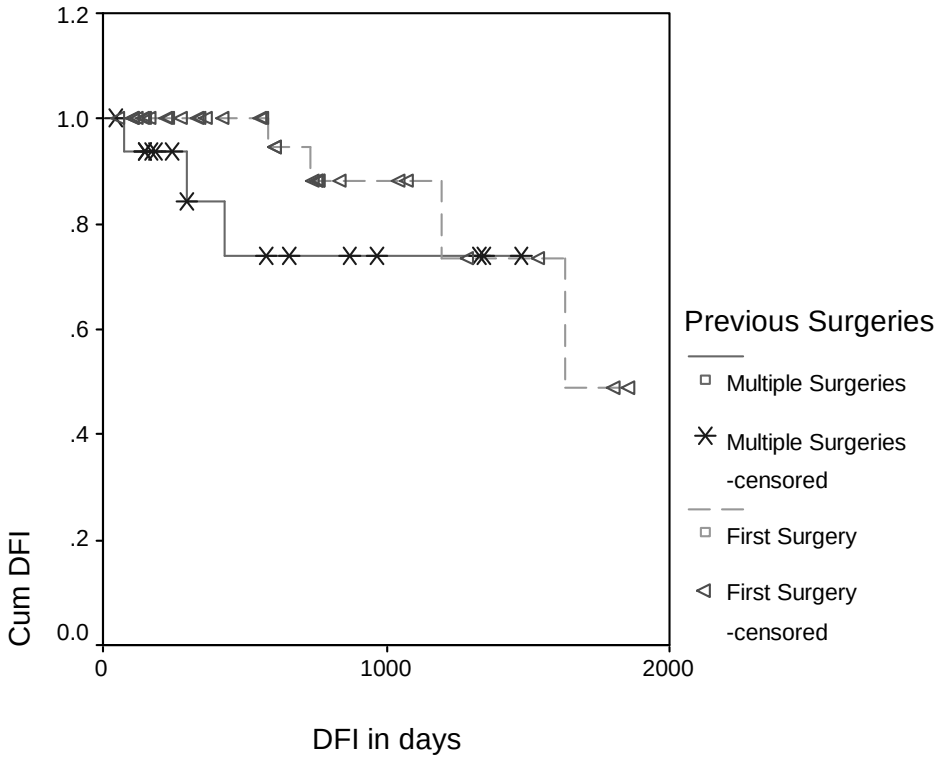


Figure 19 Kaplan-Meier curve of DFI according to a history of multiple surgeries. Dogs with more that one attempt at surgical excision are grouped together and plotted. Dogs that received RT following a single attempt at excision comprise the "first surgery" group.

Statistical comparison between the groups did not demonstrate a clear difference in DFI (P=0.25, Log-Rank). Median survival was estimated at 1,629 days for dogs that underwent a single surgery; median survival was not reached for the group that experienced multiple surgeries prior to receiving RT (Figure 19).

Twelve dogs in Group I were treated with electrons and thirty-nine dogs received treatment with photons. Of the seven tumors that returned, two occurred in dogs treated with electrons while five occurred in dogs that received photon therapy. Five tumors were noted to recur inside the boundaries of the RT field, and two occurred outside the RT field. Photon field-size averaged 88 cm^2 with a median of 61 cm^2 and a range of 24-437cm^2. The mean field size of dogs treated with photons that developed recurrence (70 cm^2) was smaller than the mean field size of dogs that did

not develop recurrent disease (91 cm^2). A Mann-Whitney test did not reveal an obvious difference in mean field-size between the two groups (P=0.29). The DFI of dogs with a treatment area over 75 cm^2 (n=16) was compared to fields under 75 cm^2 (n=22) in size (Figure 20).

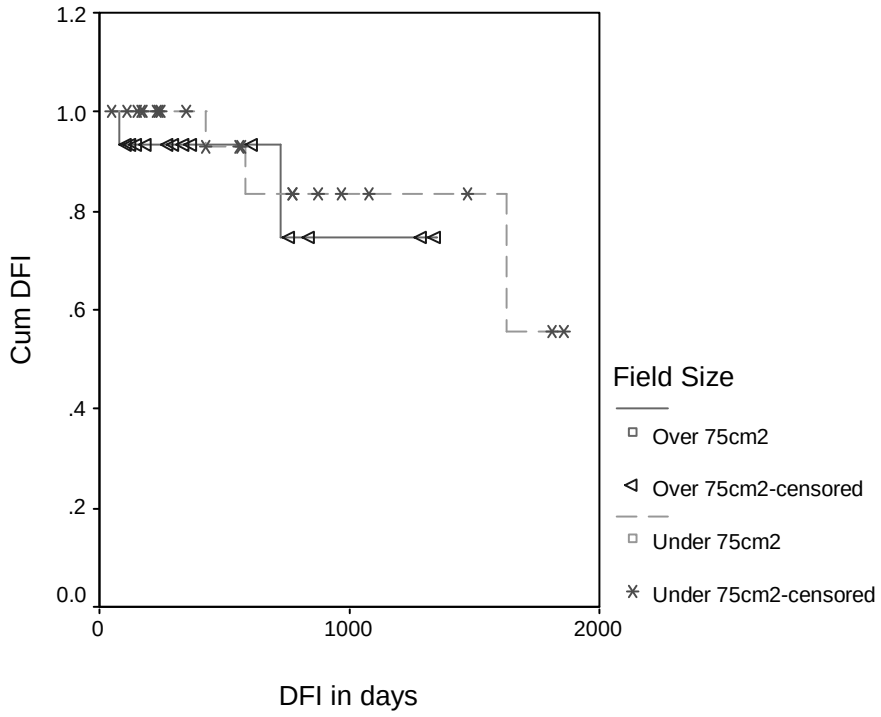


Figure 20Kaplan-Meier curve of DFI according to field-size (electrons excluded). Field sizes over 75 cm^2 are compared to fields under 75 cm^2.

Information concerning field-size was unavailable in one dog. Three tumors returned in the under 75 cm^2 group and two tumors returned in the over 75 cm^2 group. Comparison of DFI curves did not reveal a difference between groups (P=0.55). Median survival was not reached in either group.

The surgery to radiation interval was calculated from the date of the last surgery to the delivery of the first fraction of radiation. The Sx-RT ranged from 14-117 days (median 40, mean 46 days). Dogs that developed recurrence had a slightly longer mean Sx-RT interval (43 days), than did dogs that were recurrence free (47 days), although a difference in mean rank was not demonstrated (P=0.60, Mann-Whitney). The seven dogs that experienced sarcoma return had Sx-RTs of 18, 21, 22, 23, 60, 67 and 117 days.

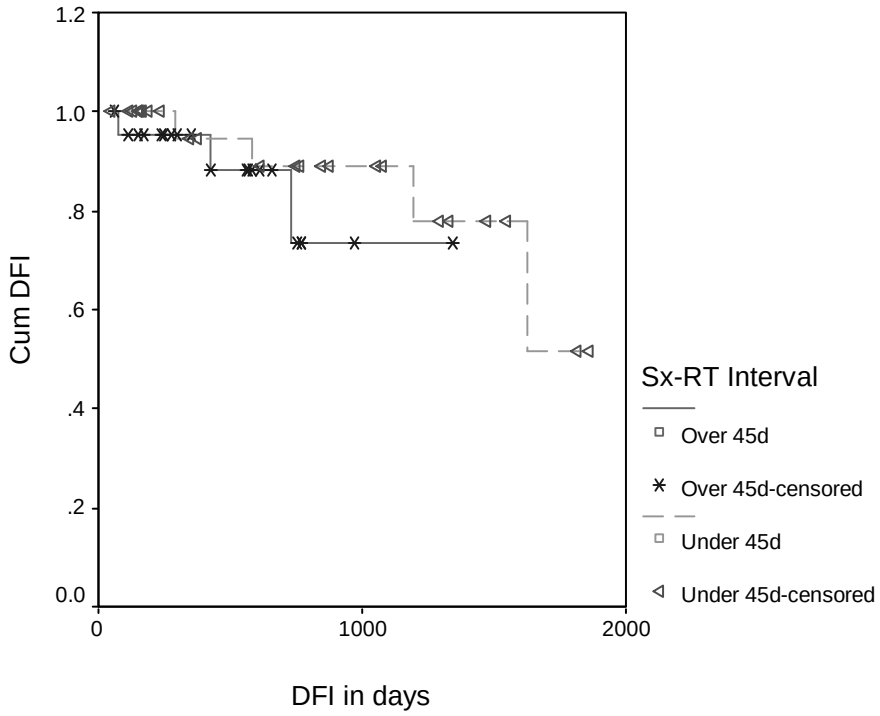


Figure 21 Kaplan-Meier curve of DFI according to Sx-RT interval. Dogs with a Sx-RT over 45 days are compared to dogs with a Sx-RT under 45 days.

Twenty-three dogs had a Sx-RT over 45 days and 28 dogs had a Sx-RT under 45 days. A difference in DFI between the two groups could not be documented (P=0.41, Log-Rank). Median survival was not reached in either group.

The results of statistical comparisons performed for the examination of factors that influence DFI are shown in Table 16.

The mean follow-up period, number of recurrences, number of survival events, median DFI and Median survival are compared pair-wise based on the three factors grade, type and location. The combination tumor type and grade is shown in Table 18, tumor grade and tumor location is described in Table 19 while Table 20 depicts the factor pair type and location.

Histotype			
	Histotypes compared		**P-Value**
	MPNST	MISC	0.084
	MPNST	FSA	0.012
	MPNST	HPC	0.012
	FSA	HPC	0.41
	FSA	Misc	N/A
	HPC	Misc	0.39
Anatomic Location			
	Locations compared		**P-Value**
	Distal Extremity	Proximal Extremity	0.14
	Distal Extremity	Trunk	0.13
	Distal Extremity	Head/Neck	0.049
	Proximal Extremity	Trunk	0.84
	Proximal Extremity	Head/Neck	0.88
	Trunk	Head/Neck	0.12
Tumor Grade			
	Grades compared		**P-Value**
	Grade III	Grade II	0.13
	Grade III	Grade I	0.61
	Grade II	Grade I	0.022
	Surgical History		**P-Value**
	One surgery	Multiple surgeries	0.25
	Field Size		**P-Value**
	Under 75 cm^2	Over 75cm^2	0.55
	Sx-RT		P-Value
	Under 45 days	Over 45 days	0.41

Table 16 Results of statistical analysis (Log-rank) of the examination of factors possibly influencing DFI in Group I are shown. N/A denotes that all data in both groups was censored and comparisons were not possible.

4.12.6.2. Survival

Four dogs died of tumor related causes (8%). Two died of causes related to local recurrence and two died of metastasis. Radiation toxicity did not lead to death in any dog in Group I. Tumor type, tumor location and grade were examined as factors influencing survival. All statistical results are shown in Table 17.

Two dogs in the MPNST group (n=9, 22%) died of local recurrence (median survival not reached). Pulmonary metastasis occurred in one dog with FSA (n=17, 5.9%) and abdominal metastasis occurred in one dog from the Misc group, (liposarcoma, n=9, 11%). Hemangiopericytoma did not result in the death of any dog. Median survival was not reached in any group (Figure 22).

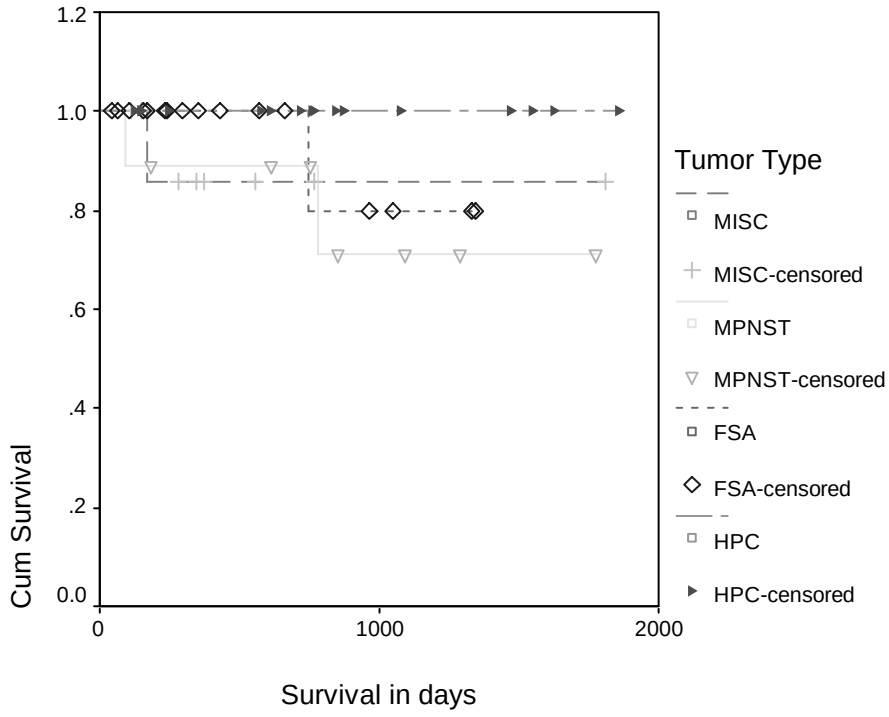


Figure 22 Kaplan-Meier analysis of survival according to histotype.

Log-rank comparison between groups documented the greatest difference between the MPNST and HPC groups (P=0.075), followed by the combinations HPC–Misc (P=0.17) and HPC–FSA (P=0.18).

No survival events occurred in dogs with ungraded tumors (n=19, 0%) or low-grade tumors (n=12, 0%); median survival could not be estimated in either group due to lack of deaths due to tumor related causes. Of the six dogs with high-grade tumors, two of those (33%) developed metastasis. No dog with a high-grade tumor died of recurrent disease. Median survival is estimated at 745 days for the group of six dogs with Grade III disease. Two dogs with intermediate-grade tumors (n=14, 14%) died due to local recurrence with a median survival estimate of 780 days. Mean follow-up period differed between grades with intermediate-grade tumors having a shorter follow-up period (245 days) compared to low (919 days) and high-grade (712 days) tumors. Log-rank tests showed differences in survival between grades I and II (P=0.026) and I and III (P=0.022).

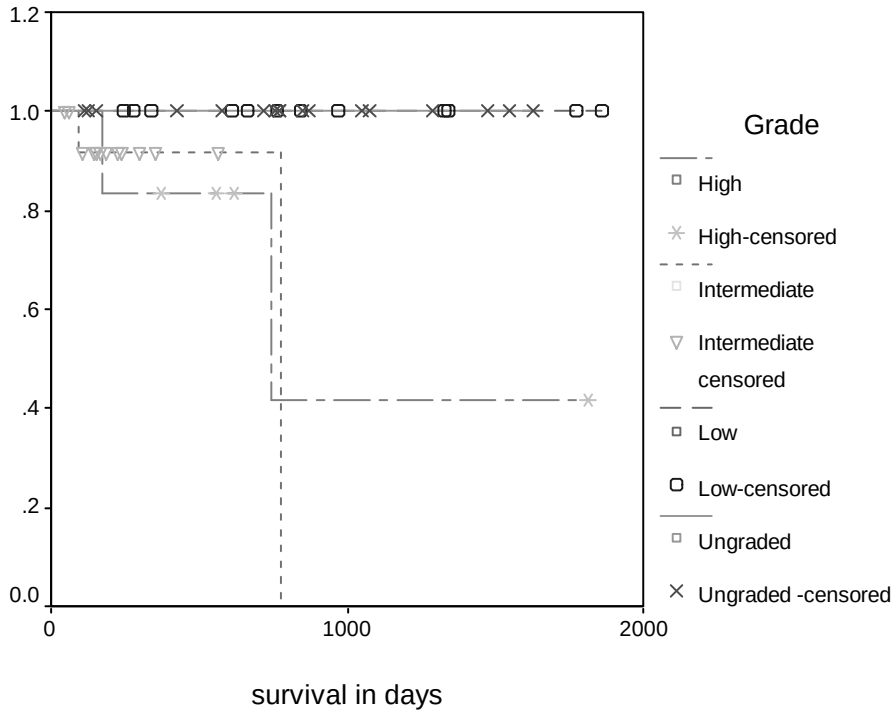


Figure 23 Kaplan-Meier curve of survival according to tumor grade.

Three tumor related deaths occurred in dogs with trunk sarcoma (n=17, 18%), one tumor related death occurred in a dog with a sarcoma of the distal extremity (n=25, 4%). No animal with a proximal extremity tumor (n=6, 0%) or a tumor of the head/neck (n=3, 0%) died of tumor related causes. Survival was compared according to anatomic locations via log-rank tests (Figure 24).

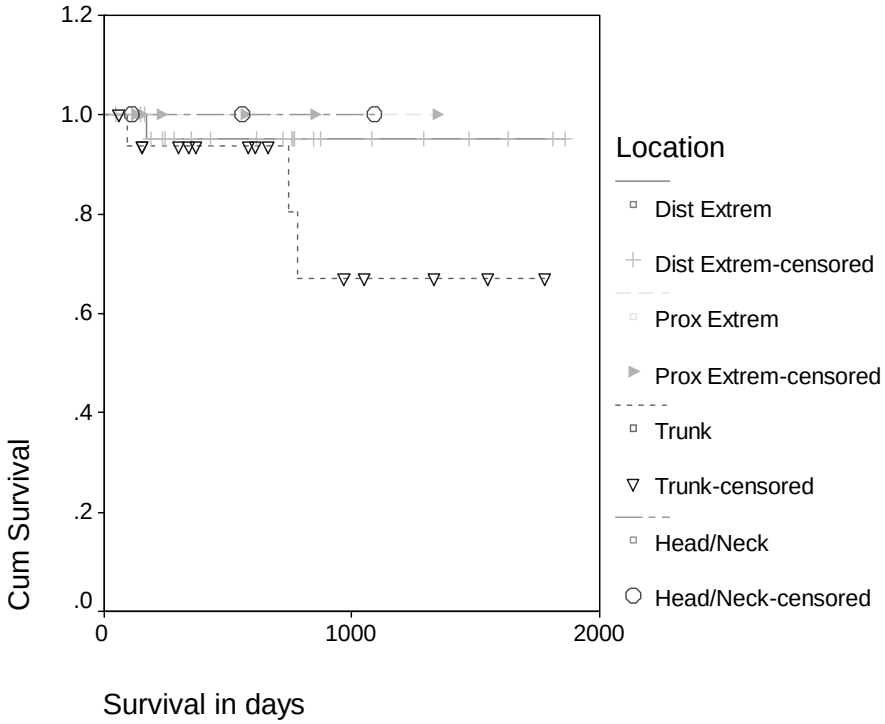


Figure 24 Kaplan-Meier curve of survival according to tumor location (Distal Extrem=Distal extremity, Prox Extrem=Proximal extremity).

Median survival was not reached in any group. A difference in survival according to location was not apparent; the lowest P-value returned was 0.14 (trunk–distal extremity).

Histotype			
	Histotypes compared		**P-Value**
	MPNST	FSA	0.54
	MPNST	HPC	0.075
	MPNST	MISC	0.87
	FSA	HPC	0.18
	FSA	MISC	0.67
	MISC	HPC	0.17
Grade			
	Grades compared		**P-Value**
	Grade I	Grade II	0.026
	Grade I	Grade III	0.022
	Grade II	Grade III	0.56
Anatomic Location			
	Locations compared		**P-Value**
	Distal Extremity	Proximal Extremity	0.66
	Distal Extremity	Trunk	0.14
	Distal Extremity	Head/neck	0.75
	Proximal Extremity	Trunk	0.32
	Proximal Extremity	Head/neck	N/A
	Trunk	Head/neck	0.45

Table 17 Results of statistical analysis (Log-rank) of the examination of factors possibly influencing survival (death related to tumor) in Group I are shown. N/A denotes that all data in both groups was censored and comparisons were not possible.

	Ungraded	Grade I	Grade II	Grade III	Total
HPC					
n=	10	5	1	0	16
Mean follow-up period	894	864	147	N/A	838
Number of recurrences	2	0	0	N/A	2
Median DFI	1629	NR	NR	N/A	1629
Number of deaths	0	0	0	N/A	0
Median survival	NR	NR	NR	N/A	NR
FSA					
n=	2	4	10	1	17
Mean follow-up period	738	1076	221	745	513
Number of recurrences	0	0	0	0	0
Median DFI	NR	NR	NR	NR	NR
Number of deaths	0	0	0	1	1
Median survival	NR	NR	NR	745	NR
MPNST					
n=	4	1	3	1	9
Mean follow-up period	997	1777	353	615	827
Number of recurrences	2	1	2	0	5
Median DFI	580	1197	728	NR	728
Number of deaths	0	0	2	0	2
Median survival	NR	NR	780	NR	NR
MISC					
n=	3	2	0	4	9
Mean follow-up period	344	310	N/A	727	507
Number of recurrences	0	0	0	0	0
Median DFI	NR	NR	N/A	NR	NR
Number of deaths	0		N/A	1	1
Median survival	NR	NR	N/A	NR	NR
Total					
n=	19	12	14	6	51
Mean follow-up period	797	918	244	712	670
Number of recurrences	4	1	2	0	7
Median DFI	1692	NR	728	NR	1629
Number of deaths	0	0	2	1	4
Median survival	NR	NR	780	NR	NR

Table 18 Survival, DFI, distribution and follow-up period according to tumor type and grade. Time interval is in days. NR=not reached, N/A= not applicable, HPC=hemangiopericytoma, FSA= fibrosarcoma, MPNST= Malignant peripheral nerve sheath tumor, MISC=miscellaneous.

	Ungraded	Grade I	Grade II	Grade III	Total
Head					
n=	1	0	1	1	3
Mean follow-up period	1092	N/A	109	558	586
Number of recurrences	1	N/A	0	0	1
Median DFI	580	N/A	NR	NR	580
Number of deaths	0	N/A	0	0	0
Median survival	NR	N/A	NR	NR	NR
Trunk					
n=	5	6	4	2	17
Mean follow-up period	695	948	308	557	677
Number of recurrences	0	1	2	0	3
Median DFI	NR	1197	728	NR	NR
Number of deaths	0	0	2	1	3
Median survival	NR	NR	780	745	NR
Proximal Extremity					
n=	2	1	3	0	6
Mean follow-up period	490	1343	316	N/A	545
Number of recurrences	1	0	0	N/A	0
Median DFI	280	NR	NR	N/A	NR
Number of deaths	0	0	0	N/A	0
Median survival	NR	NR	NR	N/A	NR
Distal Extremity					
n=	11	5	6	2	25
Mean follow-up period	899	797	188	886	704
Number of recurrences	2	0	0	0	2
Median DFI	1629	NR	NR	NR	NR
Number of deaths	0	0	0	1	1
Median survival	NR	NR	NR	745	NR
Total					
n=	19	12	14	6	51
Mean follow-up period	812	918	244	712	670
Number of recurrences	4	1	2	0	7
Median DFI	1629	NR	728	NR	1629
Number of deaths	0	0	2	1	4
Median survival	NR	NR	780	NR	NR

Table 19 Survival, DFI, distribution and follow-up period according to grade and location. Time interval is in days. NR=not reached, N/A= not applicable.

	Head/Neck	Trunk	Pr. Extrem.	Dis. Extrem	Total
HPC					
n=	0	4	1	11	16
Mean follow-up period	N/A	722	129	945	838
Number of recurrences	N/A	0	0	2	2
Median DFI	N/A	NR	NR	1629	1629
Number of deaths	N/A	0	0	0	0
Median survival	N/A	NR	NR	NR	NR
FSA					
n=	1	7	4	5	17
Mean follow-up period	109	730	573	245	513
Number of recurrences	0	0	0	0	0
Median DFI	NR	NR	NR	NR	NR
Number of deaths	0	1	0	0	1
Median survival	NR	NR	NR	NR	NR
MPNST					
n=	1	3	1	4	9
Mean follow-up period	1092	884	293	711	826
Number of recurrences	1	3	1	0	5
Median DFI	580	728	293	NR	728
Number of deaths	1	2	0	0	2
Median survival	NR	780	NR	NR	NR
MISC					
n=	1	3	0	5	8
Mean Follow up period	558	288	N/A	628	507
Number of recurrences	0	0	N/A	1	0
Median DFI	NR	NR	N/A	NR	NR
Number of deaths	0	0	N/A	1	1
Median survival	NR	NR	N/A	NR	NR
Total					
n=	3	17	6	25	51
Mean follow-up period	586	677	545	704	670
Number of recurrences	1	3	0	2	7
Median DFI	580	NR	NR	NR	1629
Number of deaths	0	3	0	1	4
Median survival	NR	NR	NR	NR	NR

Table 20 Survival, DFI, distribution and follow-up period according to tumor type and location. Time interval is in days. NR=not reached, N/A= not applicable, HPC=hemangiopericytoma, FSA= fibrosarcoma, MPNST= Malignant peripheral nerve sheath tumor, MISC=miscellaneous, Prox. Extrem.= proximal extremity, Dis. Extrem.= distal extremity.