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Outcome comparison between radiation therapy and surgery as primary treatment for dogs with periarticular histiocytic sarcoma: An Italian Society of Veterinary Oncology study

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Outcome comparison between radiation therapy and surgery as primary treatment for dogs with periarticular histiocytic sarcoma: a xxx study

4

5

6 Abstract

7 Localized histiocytic sarcoma may occur as a primary lesion in periarticular tissues of large appendicular joints. Treatment options for the primary lesion 8 include radical surgical excision, radiation therapy (RT), or both, in 9 10 combination with chemotherapy for potential systemic metastases. In an effort to better characterize the time to progression (TTP) following surgical 11 12 versus non-surgical approaches for periarticular histiocytic sarcoma (PAHS), a 13 contemporary European population of affected dogs were was 14 retrospectively surveyed. Medical records were queried for newly-diagnosed PAHS cases undergoing surgery (predominantly limb amputation) or RT 15 followed by systemic chemotherapy. Of 4950 dogs, 34 underwent RT and 156 16 17 underwent surgery. All dogs received adjuvant chemotherapy. There was no 18 statistically significant difference in TTP or overall survival between groups. The median TTP was 336299 days for the operated dogs and 2170 days for the 19 20 irradiated dogs (P = 0.11775). The median overall survival time was 398 days 21 for the operated dogs and 2405 days for the irradiated dogs (P = 0.14205). On 22 multivariable analysis, the variables significantly associated with an increased 23 risk of both tumor progression and tumor-related death were regional lymph node and distant metastasis at admission. Survival and local control rates 24 following RT may be comparable to radical resection. These data may better 25

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26 inform shared decision-making processes between multidisciplinary care27 providers and owners.

28

29 Keywords: radiotherapy, amputation, histiocytic disorder, joint, canine

30

31 Introduction

32

Localized histiocytic sarcoma arises from myeloid dendritic antigen-33 34 presenting cells and occurs as a primary lesion in periarticular tissues of large 35 appendicular joints, with the stifle, elbow, and shoulder most commonly affected.¹ It is described as a single primary lesion with or without locoregional 36 lymph node metastasis.¹ Certain breeds, such as Bernese mountain dogs, 37 38 Rottweiler, Flat coated retrievers, Golden retrievers and miniature schnauzer are genetically predisposed.2-5 39 Periarticular histiocytic sarcoma (PAHS) is reported to develop at previously 40

41 diseased appendicular joints.³⁻⁶ Radiographically, lesions are characterized 42 by destructive bony changes spanning the affected joint, in conjunction with a periarticular soft tissue mass.⁷ According to one study, PAHS has a better 43 prognosis than other localized visceral histiocytic sarcomas, and should be 44 treated by surgical excision, radiation therapy (RT), or both, in combination 45 46 with chemotherapy.⁸ Complete tumor removal whilst preserving a functional 47 limb is generally impossible due to the proximity of articular and neurovascular structures, therefore limb amputation is typically required to achieve 48 49 adequate local tumor control.

50	Histocytic sarcoma is reported to be radiosensitive." Thus, RT presents an
51	alternative local treatment modality to achieve primary tumor control with
52	functional limb preservation.
53	However, whether RT achieves similar local control and survival outcomes to
54	radical resection remains to be determined.
55	The aim of this retrospective, multi-center study was to compare the survival
56	outcomes of dogs with PAHS treated with surgery or RT, in combination with
57	adjuvant systemic chemotherapy. It was hypothesized that the two treatment
58	modalities would provide similar outcome.
59	
60	
61	Material and methods
62	
63	Inclusion and exclusion criteria
64	This study was designed by xxx. Medical records were reviewed to identify
65	dogs with a histologically (+/- immunohistochemistry) confirmed PAHS. PAHS
66	was defined as a sarcoma in which part of the tumor was superficial to the
67	joint, and which was overlying the epiphysis or metaphysis of the bone. The
68	diagnosis of PAHS was confirmed based on the pleomorphic morphology of

- the cells (spindle, round, and multinucleated cells) on histopathology. At the
 discretion of the pathologist, the diagnosis of PAHS was confirmed by
 immunohistochemistry (CD18 and/or IBA-1).²
- To be included in the study, dogs had to undergo clinical staging (consisting
 of three-view thoracic radiographs and abdominal ultrasound and/or total

74 body CT [TBCT]), surgery or radiation therapy, combined with systemic 75 treatment, and had to have at least 4 weeks follow-up to assess response. 76 Additional data necessary for inclusion were signalment, symptoms, duration of symptoms, site of disease, manner of diagnosis (histopathology +/-77 immunohistochemistry), type of imaging, bone lysis (yes/no), lymph node 78 79 involvement (yes/no), distant metastasis (yes/no), administration of steroids 80 (yes/no), local treatment (surgery/ RT), systemic treatment (drugs, dosage and number of cycles), treatment-related toxicity, time to progression (TTP), 81 82 overall survival (OS), and cause of death.

In an effort to exclude dogs with the disseminated form of histiocytic sarcoma,
dogs were not included in the study if lameness or periarticular swelling
occurred after the diagnosis of visceral histiocytic sarcoma.

86

87 Treatment and follow-up

Dogs treated with surgery underwent limb amputation or wide local excision.
For RT, neither protocols or techniques, nor target- or organ-at-risk contouring
practices were standardized. RT data collected included absorbed dose,
tumor volumes, type of treatment planning, delivery, fractionation protocol
and total physical dose, where available.
The recommendation for type of systemic chemotherapy was based on the

judgment of the clinicians managing the cases and on owners' preferences.
Treatment-related adverse events were recorded according to the Veterinary
Cooperative Oncology Group (VCOG) guidelines.⁹

97 Monthly clinical re-checks were suggested either at the primary oncology 98 center or at the referring veterinarian. Follow-up information was obtained by 99 medical record review or by telephone communication with the referring 100 veterinarian and/or owner if the dog was not evaluated at the primary 101 oncology center. Thoracic radiographs and abdominal ultrasound were 102 performed at 3-month intervals and whenever clinically indicated.

103 Response data were based on the Veterinary Cooperative Oncology 104 Group's RECIST criteria for solid tumors assessed by physical examination and 105 measurements using calipers or imaging, dependent on tumor location and 106 owners' compliance.¹⁰ Surgically treated dogs were monitored for recurrence 107 or metastatic development, not for disease response. Conversely, in the gross 108 disease setting (irradiated dogs), complete response (CR) was defined as 109 resolution of all clinical and/or imaging-based evidence of disease, partial 110 response (PR) was defined as at least 30% decrease in tumor diameter with no new lesions, stable disease (SD) was defined between <30% and >20% 111 112 difference in tumor diameter with no new lesions, and progressive disease 113 (PD) was defined as greater than 20% increase in tumor diameter or the 114 development of new lesions. Overall response rate (ORR) was defined as CR 115 + PR.

116

117 Statistical analysis

118 Descriptive statistics were used in the analysis of dogs and tumor 119 characteristics. When appropriate, data sets were tested for normality by use 120 of the D'Agostino and Pearson omnibus normality test. Values were expressed as mean ± SD in case of normal distribution, or as median with a range in case
of non-normal distribution.

The distribution of demographic features and possible outcome variables between operated and irradiated dogs where assessed with Fisher's exact test or χ^2 test. The considered variables included breed, sex, age, body weight, duration of symptoms, tumor site, presence of bone lysis, presence of regional nodal and distant metastases at admission and pre-treatment with steroids. For age, weight and duration of symptoms, the median was used as the cut-off value.

130 TTP was calculated from the first day of treatment (either surgery or RT) to the 131 date of first-documented tumor progression (local or distant). Additionally, 132 time to progression of known lesions and time to development of new lesions 133 were separately assessed. Dogs not progressing or alive at data-analysis closure were censored. OS was calculated from the first day of treatment to 134 the date of death or to the date of last known alive as defined by follow-up 135 136 conversations with owner if death did not occur. All dogs that were dead at 137 the end of the study were recorded as events.

Survival plots were generated according to the Kaplan-Meier product-limit Survival plots were generated according to the Kaplan-Meier product-limit method and were compared using the log-rank test. Survival estimates were presented as medians with the corresponding 95% confidence intervals (95% Cls).

The influence of potential prognostic variables on tumor progression and OS
was investigated with univariable Coxs' regression analyses. Additional

145	evaluated variables included treatment received (surgery vs. R1) and
146	treatment-related toxicity (present/absent). Factors with a P value < 0.1 on
147	univariable analysis were further tested for independence in a multivariable
148	Cox proportional hazard model.
149	Data were analyzed by use of commercial software programs (SPSS Statistics
150	v.25, IBM, Armonk, New York, and Prism v.8.0, GraphPad, San Diego,
151	California). P-values <0.05 were considered significant.
152	
153	Cell Line Validation Statement
154	No cell lines were used in the current study.
155	
156	
157	Results
158	
159	<u>Forty-nine</u> dogs were included in the study: 34 (69.4%) were treated with
160	RT and 15 (30.6%) were treated with surgery.
161	
101	There were 20 (40 <u>.8</u> %) Flat-coated retrievers, 8 (16 <u>.3</u> %) Bernese mountain dogs,
162	There were 20 (40.8%) Flat-coated retrievers, 8 (16.3%) Bernese mountain dogs,4 (8.2%) mixed breed dogs, 3 (6.1%) Golden retriever, 2
162 163	There were 20 (40.8%) Flat-coated retrievers, 8 (16.3%) Bernese mountain dogs, 4 (8.2%) mixed breed dogs, 3 (6.1%) Golden retriever, 2 (4.1%) Rhodesian ridgeback, 2 (4.1%) Rottweiler, and one (2%) each of the
162 163 164	There were 20 (40.8%) Flat-coated retrievers, 8 (16.3%) Bernese mountain dogs, 4 (8.2%) mixed breed dogs, 3 (6.1%) Golden retriever, 2 (4.1%) Rhodesian ridgeback, 2 (4.1%) Rottweiler, and one (2%) each of the following: <u>Border collie</u> , Bloodhound, Corgi, old English sheepdog, Harzer
162 163 164 165	There were 20 (40,8%) Flat-coated retrievers, 8 (16,3%) Bernese mountain dogs, 4 (8,2%) mixed breed dogs, 3 (6,1%) Golden retriever, 2 (4,1%) Rhodesian ridgeback, 2 (4,1%) Rottweiler, and one (2%) each of the following: <u>Border collie</u> , Bloodhound, Corgi, old English sheepdog, Harzer fuchs, Poodle, Australian shepherd, Tibetan spaniel, Labrador retriever, and
161 162 163 164 165 166	There were 20 (40,8%) Flat-coated retrievers, 8 (16,3%) Bernese mountain dogs, 4 (8,2%) mixed breed dogs, 3 (6,1%) Golden retriever, 2 (4,1%) Rhodesian ridgeback, 2 (4,1%) Rottweiler, and one (2%) each of the following: <u>Border collie</u> , Bloodhound, Corgi, old English sheepdog, Harzer fuchs, Poodle, Australian shepherd, Tibetan spaniel, Labrador retriever, and American <u>S</u> taffordshire bull terrier.
161 162 163 164 165 166 167	There were 20 (40.3%) Flat-coated retrievers, 8 (16.3%) Bernese mountain dogs, 4 (8.2%) mixed breed dogs, 3 (6.1%) Golden retriever, 2 (4.1%) Rhodesian ridgeback, 2 (4.1%) Rottweiler, and one (2%) each of the following: <u>Border collie</u> , Bloodhound, Corgi, old English sheepdog, Harzer fuchs, Poodle, Australian shepherd, Tibetan spaniel, Labrador retriever, and American <u>S</u> taffordshire bull terrier. There were 254 (4950%) female dogs (1920 of which were spayed) and 25

(range, 4 to 14 years) and the median weight was 33.2 kg (range, 5.5 to 61kg).

171 Intermittent to progressive lameness was present in 45 (91.8%) dogs; in 11 of 172 them swelling of the affected joint was observed. The median duration of 173 lameness was 60 days (range, 15 to 730 days). In 4 (8.2%) dogs, a non-painful 174 mass around the involved joint was noticed. One (2%) dog was confirmed to 175 have had previous joint disease in the tumor-affected joint. The diseased joints 176 were the elbow (n=21; 42.9%), stifle (n=12; 24.5%), shoulder (n=11; 22.4%), hip 177 (n=2; 4.1%), tarsus (n=2; 4.1%), and carpus (n=1; 2%). All cases were 178 diagnosed by histopathology; CD18 and/or IBA-1 were used to confirm the 179 diagnosis in 2<u>8</u> (5<u>7.1</u>%) dogs.

180 For staging work-up, 38 (77.6%) dogs underwent total body CT scan, while 181 11 (22.4%) dogs had bone radiographs, thoracic radiographs and abdominal 182 ultrasound performed. Based on imaging, 35 (71.5%) dogs had bone lysis, 13 83 (26.5%) dogs had no abnormalities detected, and the information was not 184 available for one (2%) dog. Distant metastasis was documented in 12 (24.5%) 185 dogs: spleen (n=6), lungs (n=3), lung and skin (n=1), lung and spleen (n=1), 186 spleen and liver (n=1) based on imaging and cytological evaluation. 187 Regional lymph node cytological evaluation was obtained in all dogs; 188 metastatic involvement <u>was revealed in</u> 3<u>5</u> (7<u>1.4</u>%) cases. 189 Eight dogs undergoing lymphadenectomy as part of their surgical procedure .90 had histopathological confirmation of nodal metastatic disease; overall, there

191 were no false positive or false negative results when comparing cytology with

192 <u>histology.</u>

Table 1 summarizes the demographic, tumor and treatment characteristics of
both surgery and radiation therapy groups. There was good balance
between groups regarding demographic features and possible outcome
variables (Table 1).

197

198 Treatment and toxicity

199 Among the 34 dogs that were irradiated, 4 (11.8%) received pre-treatment 200 steroids. Protocols were chosen based on general animal health and owner 201 preferences. Radiation was delivered with either a cobalt-60 teletherapy 202 machine, or 6MV linear accelerators equipped with multi-leaf-collimators, 203 using photons and 2-dimensional manual planning (n=19), 3-dimensional 204 conformal radiation therapy (3DCRT) (n=5) or intensity-modulated radiation 205 therapy (IMRT), (n=7). One patient was treated with electrons (18MeV), also 206 manually planned. In 2 patients radiation dose information was missing. 207 Animals were treated at 5 different institutions: 9 patients were treated with 208 cobalt-60, 6 patients on an Elekta Synergy, Elekta Instrument AB Stockholm 209 (xxx); 5 patients were treated on a Clinac DMX, Varian Medical Systems, Palo 210 Alto, USA (xxx); 10 patients on a Clinac iX, Varian Medical Systems, Palo Alto, 211 USA (xxx), 2 patients on a Clinac 2100, Varian Medical Systems, Palo Alto, USA 212 (xxx) and 2 patients on a Primus, Siemens (xxx). 213 Treatment planning was performed manually in 20 (58.8%) patients, and

computer-assisted using dedicated planning software was used in 12 (35.3%)
patients (n=32, 2 missing). All patients were treated under a short general
anesthesia. Positioning and verification thereof were accomplished

217	according to the individual institutions' routines. In all 5 3DCRT-plans the
l 218	recommendations for specifying dose and volumes were adhered to as
219	proposed by Keyerleber et al. (2012), and in the ICRU reports 50 and 62 and
220	for the 7 IMRT plans, recommendations of for 3DCRT and ICRU report 83 and
221	Rohrer Bley et al. (2019) for IMRT planswere followed. 11-15
222	The remaining 20 plans were hand-calculated.
223	The target volumes and relative absorbed doses are shown in Table 2.
224	Lymph nodes were irradiated in 22/34 cases (64.7%). The reason for lymph
225	node irradiation was stated to be prophylactic in 4 patients (11.8%),
226	therapeutic (e.g. with known macrometastasis) in 17 dogs (50%) and both,
227	therapeutic and prophylactic in one dog (2.9%).
1 228	Most dogs (32/34) were treated with a palliative-intent hypofractionated
229	radiation protocol delivered once or twice weekly and received \leq 36.0 Gy of
230	total dose. Total doses ranged from 16.0 to 51.2 Gy, with a mean total dose of
231	31.6 Gy (± 6.5) and a median of 30 Gy. Fraction numbers ranged from 2 to 16
232	with a mean of 5.9 (± 3.3) and a median of 5 fractions. Fraction sizes ranged
233	from 3.0 to 8.0 Gy, with a mean of 6.0 Gy (± 1.5 <u>) and a median of 6 Gy</u> .
234	Treatment was well-tolerated in all dogs. Thirty-one (91.2%) dogs experienced
235	a clinical improvement of their lameness during RT, 2 (5.9%) dogs remained
236	stable and 1 (2.9%) dog had a worsening of its symptoms.
237	Chemotherapy was started after a median of 14 days after RT (range, 1 to
238	<u>107).</u>

- 239 Thirty-one (91.3%) dogs received post-radiation lomustine at a median
- dosage of 80 mg/m² (range, 70 to 90) every 21 daysstandard dosage 240

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241 (median, 5 cycles; range, 1 to 8 cycles); one (2.9%) dog was treated with an 242 investigational drug (TRIN2755)¹⁶, one (2.9%) received doxorubicin (4 cycles) 243 and one (2.9%) received carboplatin and cyclophosphamide (4 cycles). 244 Eleven (32.4%) dogs experienced adverse events: 4 of 34 dogs experienced bone marrow (BM) toxicity, 4 had hepatic toxicity, 1 dog had gastrointestinal 245 246 (GI) and hepatic toxicity, 1 dog had BM and GI toxicity, and 1 dog 247 experienced fever. All adverse events were graded 1-2 with the exception of one episode of grade 3 hepatic toxicity and one episode of grade 5 248 249 neutropenia (Table 3).

250 All dogs____underwent _operated limb amputation. 251 None of these dogs received pre-treatment steroids. The procedure was well-252 None of these dogs 253 received pre-treatment steroids. The procedure was well-tolerated in all dogs, 254 with no reported complications. 255 Chemotherapy was started after a median of 14 days after surgery (range, 13

256 <u>to 105).</u>

257 Thirteen_Thirteen (86.71.1%) dogs received adjuvant lomustine at standard 258 dosage80 mg/m² (range, 70 to 90) every 21 days - (median, 6 cycles; range, 1 259 to 6 cycles); one (6.3%) dog received 4 cycles of alternating lomustine and epirubicin, one (6.73%) dog was treated with doxorubicin (1 cycle) and one 260 261 (6.73%) dog with vincristine (4 cycles). Nine Eight (536.32%) dogs experienced **2**62 adverse events: 23 dogs experienced BM toxicity, 2 dogs had hepatic toxicity, 1 dog had BM and GI toxicity, 1 dog had hepatic and BM toxicity, 1 dog had 263 264 GI toxicity, and 1 dog experienced haemorrhagic cystitis. There were 2

265	episodes of grade 3 and g rade 4 BM toxicity , respectively , one episode of
266	grade 4 GL toxicity and 1 episode of grade 4 hepatic toxicity and 1 episode
267	of grade 3 BM toxicity (Table 3).
268	
269	Outcome
270	Regarding radiation response, 14 (41.2%) dogs achieved CR, 18 (52.9%)
271	PR, 2 (5.9%) dogs were stable
272	. ORR was 91.2%.
273	Of the 15 dogs treated with surgery, 3 (20%) had progression of pre-existing
274	metastases and 7 (46.7%) developed new metastases. Of the 34 irradiated
275	dogs, 7 (20.6%) had progression of pre-existing metastases and 16 (47%)
276	developed new metastases.
277	The median TTP of known lesions was 336 days for the operated dogs (95% CI,
278	220-452) and 280 days for the operated dogs (95% CI, 171-389) (difference not
279	significant, $P = 0.509$; and the median time to development of new lesions
280	was 336 days (95% CI, 224-448) for the operated dogs and 302 days (95% CI,
281	<u>185-419</u> for the irradiated dogs (difference not significant, $P = 0.509$). Overall,
282	the median TTP was 336 days (95% CI, 209-463) for the operated dogs and 217
283	days (95% CI, 182-252) for the irradiated dogs (difference not significant, $P =$
284	<u>0.117).</u>
285	At the end of the study, 13 operated dogs (86.7%) and 30 irradiated dogs
286	(88.2%) were dead. The median OS was 398 days (95% Cl, 183-613) for the
287	operated dogs and 240 days (95% CI, 210-270) for the irradiated dogs

 $\frac{288}{(difference not significant, P = 0.142; Figure 1).}$

28	39	The only variables significantly associated with an increased risk of overall	
29	9 0	disease progression and death were regional lymph node and distant	
29	91	metastases at patient admission (Tables 4 and 5). On multivariable survival	
29	92	analysis, both variables retained prognostic significance (Table 6).	
29	93		
29	94		
29	95	When specifically considering distant metastases, 8 (50%) operated dogs and	
29	96	29 (85.3%) irradiated dogs developed metastatic lesions or the pre existing	
29	97	metastases progressed.	
29	98	The overall median follow up time was 217 days (range, 29-1406). Forty dogs	ha formattato: Evidenziato
29	99	(75% of the operated and 76.5% of the irradiated dogs) experienced tumor	
3(00	progression. At the end of the study, the same 40 dogs had died for cancer	
3()1	related causes. The median TTP was 299 days (95% Cl, 183 415) for the	
3()2	operated dogs and 210 days (95% CI, 179 241) for the irradiated dogs	
3()3	(difference not significant, P = 0.201).	
3()4	The median OS was 398 days (95% CI, 220-575) for the operated dogs and 245	ha formattato: Evidenziato
3()5	days (95% CI, 215 276) for the irradiated dogs (difference not significant, P =	
3()6	0.105; Figure 1). On univariable analysis, the variables significantly associated	
3()7	with an increased risk of both tumor progression and tumor related death	
3()8	were regional lymph node and distant metastasis at patient admission (Table	
3()9	4). On multivariable analysis, both variables retained prognostic significance	
31	10	(Table 5).	
1 31	11		
_			

313 Discussion

314

The development of treatment strategies for dogs with primary appendicular soft tissue sarcoma has emphasized local control with preservation of limb function, OS, and quality of life.

The choice of local control modality in optimizing TTP, OS, and limb function in dogs with PAHS has not received substantial scientific attention. To our knowledge, this is the first study that directly compared survival outcome of dogs with PAHS treated with surgery or RT, with adjuvant systemic chemotherapy, and our results documented that TTP and OS after surgery were comparable to that after RT.

324 Current treatment options for PAHS consist of radical surgical excision, RT or 325 both, in combination with chemotherapy.⁸ Theoretically, the best treatment is 326 surgery, as it offers the potential to eliminate the entire tumor-bearing joint 327 providing an optimal local tumor control. However, PAHS typically arise in 328 anatomically challenging areas, where a conservative surgery may not 329 guarantee adequate tumor margins and can be associated with major post-330 operative complications and/or high rate of local tumor relapse. A radical 331 surgery can prevent such issues; however, this is not always feasible or 332 recommended depending on the tumor location and especially considering 333 the high rate of regional and distant metastatic disease at presentation, 334 thereby raising the demand for therapeutic alternatives.

While surgery is usually quoted to be a definitive-intent treatment, RT is mostly referred to as palliative. The outcome between the two treatments has not been different in the dataset presented herein (TTP and OS). This
nomenclature is hence somewhat arbitrary, as most of the dogs (40/50; 80%)
indeed died from disease progression within a relatively short time.

340

Dogs with PAHS with and without skeletal lesions due to histiocytic sarcoma 341 342 were described to have other organ involvement in a majority of cases.^{1,17} In 343 18 patients with PAHS the average survival was 5.3 months and 91% of the 11 dogs with a post-mortem examination had evidence of metastatic spread.7 344 345 In dogs with radiographically detected bone involvement only, soft tissue masses adjacent bone lesions became apparent at postmortem 346 347 examinations.⁷ Hence, it is likely that the soft tissue component is not found or 348 underestimated on radiographic imaging. The extent of disease is crucial for 349 adequate surgical but also RT planning. For appropriate tumor staging and 350 treatment planning of PAHS, we recommend using three-dimensional 351 imaging techniques such as computed tomography (CT) or magnetic 352 resonance imaging (MRI).

353 Histiocytic tumors are believed likely to be highly radiation sensitive, with a very 354 rapid time to regression and pain relief, but this experience is unpublished and 355 a result of unstructured clinical observations in the treatment of macroscopic disease (personal communication). Radiation therapy provides not only rapid 356 357 local pain relief, but also increases survival in patients with PAHS in addition to 358 maintaining or even restoring functionality of the affected limb.^{1,8} In addition, 359 RT can be used to treat the primary site and the locoregional lymph nodes therapeutically (e.g. with known metastasis) or prophylactically. In light of the 360

frequent and early locoregional metastasis, prophylactic irradiation of all locoregional deems sensible. For these advantages, RT has been accepted as a valid choice of treatment for PAHS at many oncology centers, and presents an option for dogs that are not suitable for, or whose owners refuse amputation.

Interestingly, <u>8</u>/12 patients (<u>67</u>%) treated with conformal radiation techniques such as 3DCRT or IMRT (and hence 3-dimensional imaging) achieved CR. High response rates have also been described before, with 13/19 dogs (68%) achieving CR shortly after treatment with palliative-intent protocols.¹

371 Conversely, only 6/20 patients (33%) treated with 2D-RT (parallel opposed 372 fields) or electrons (n=1) achieved CR. This finding corroborates the above 373 stated possibility of underestimating disease after 2D imaging (radiographs) 374 only. Hence, it can be argued that appropriate RT (maybe also using higher 375 doses, definitive-intent protocols) provides similar local control as amputation. 376 The disease metastasizes over time in the majority of cases, stressing the 377 importance of adjuvant chemotherapy. Unfortunately, little is known on the 378 response of PAHS to chemotherapy: response to CCNU could be assessed 379 only in a small number of cases only, and resulted in a temporary CR in 5/12 380 (42%) and PR in 3/12 (25%), respectively.¹

381

In our case series, a lower rate of metastatic progression was observed in the
 surgery group compared with the irradiated group (50% versus 85.3%,
 respectively). The presence of nodal or distant metastasis was a negative

prognostic factor in the current study, and this is in line with the published literature.¹ The local control achievable with limb amputation also immediately removes a reservoir of neoplastic cells, thereby possibly preventing new metastatic lesions to occur. Surprisingly, in 11 dogs with PAHS treated with definitive-intent surgery (e.g. had no measurable disease), 8/11 of which also received chemotherapy, median TTP was short as well, with <u>a</u> <u>median of</u> 162 days (range 56-490 days).

392

393 It must be acknowledged that dogs with metastatic disease at presentation 394 might have been more likely to undergo palliative RT rather than limb 395 amputation. When comparing groups, 56.3% of operated dogs and 62.8% of 396 irradiated dogs had nodal metastasis at admission, whereas 12.5% of 397 operated dogs and 29.4% of irradiated dogs had distant metastasis at 398 admission. Complete remission was obtained in more than one third of 399 irradiated dogs (14/34, 41.2%), which leaves behind a significant 400 proportion of dogs with residual disease that will perpetuate metastatic 401 spread and worsen prognosis. Based on these findings, even if not significant, 402 we would hypothesize that the effect of surgery on local control for PAHS 403 might translate to a parallel improvement in OS. We would also point out that 404 this study has a small patient population, and thus has not been adequately 405 powered to detect differences in OS, thereby potentially limiting our ability to 406 detect a specific survival benefit associated with either of the treatments.

407

18

Both treatment strategies were well tolerated; all operated dogs and the majority (88.6%) of irradiated dogs experienced a clinical improvement after local therapy. Undesirable effects were not reported for both surgical treatment (such as re-operation or functional dysfunction) and RT (such as fractures, skin necrosis, functional deficits, and/or serious skin suppurations).

413

The limitations of this study relate to its retrospective nature with its inherent biases and to the small population. Even though groups were in part wellbalanced regarding possible prognostic variables, two thirds of dogs were irradiated and only one third underwent surgery, which will preclude from our precise estimates of treatment effects.

419 Second, the RT and chemotherapy protocols were not standardized. 420 Treatment planning without 3-dimensional diagnostic imaging can lead to an 421 underestimation of tumor size: hence local and even systemic progression 422 could also be due to the under-dosage of the tumor. In our study, CT-based 423 planning was only used in 12/32 cases (37.5%), confirming adequate dose 424 coverage and field size. Twenty dogs were treated with manual treatment 425 planning. Hence, in the majority of cases delineation of tumor targets (especially CTV, and PTV) was not carefully performed and without 3D 426 imaging a substantial risk of underestimating tumor volumes (and lymph 427 428 nodes) remains. Delineation of tumor targets (especially CTV, and PTV) was 429 not commonly done. Additionally, without careful treatment planning, underdosage could also result from insufficient dose build-up at soft-tissue-air 430 interfaces such as the surface area. Even if the treatments are prescribed in a 431

432 "palliative" intent, radiation leads to several months of tumor control and not 433 only symptomatic palliation. Therefore, the choice to use more complex 434 treatment plans could be justified for these patients. In the future we recommend that treatment planners adhere to strict contouring and 435 436 prescription guidelines. These include dose prescription and normalization, as 437 well as standardized CTV delineation and PTV extension according to the 438 institute's technical capabilities.14,15 Most studies, including ours, are limited by 439 a lack of standardized follow-up imaging to assess tumor status. It is unclear to 440 what extent our assessment of "clinical remission" represents a true complete remission. The true remission rate may be higher or lower because follow-up 441 442 imaging in the clinical setting is often only done at the time of recurring clinical 443 signs and is not performed often enough, underestimating earlier remission 444 rate. 445 Last, only 57% of cases underwent immunohistochemistry for diagnosis

While it is true that ideally all cases should be tested by means of
immunohistochemistry to confirm the diagnosis, this may not always be
mandatory. In the current series, any effort was made to exclude cases
lacking the characteristic features of HS, including sheets of large,
pleomorphic, mononuclear, and multinucleated giant cells, showing marked
cytological atypia and bizarre mitotic figures.
In conclusion, according to our data, compared with surgery, RT provided

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confirmation.

454 similar local control and OS and good tolerability in dogs with PAHS also455 receiving systemic chemotherapy. The clinical decision making approach for

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456	local tumor control in dogs with PAHS remains a challenge, and many tumor,
457	patient and institution related factors contribute to the ultimate decision
458	made for each patient. The important observation from our study is that RT
459	offers a comparable clinical outcome to amputation, while preserving
460	articular function. As 74% of the patients died or were euthanized due to
461	metastatic disease, oncologists should focus on improving chemotherapeutic
462	or immunotherapeutic regimen for this disease entity.
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465	Data Availability Statement
466	The data that support the findings of this study are available from the
467	corresponding author upon reasonable request.
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470	Acknowledgments
471	The authors would like to thank xxx
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- Figure 1. Kaplan-Meier survival plots for 49 dogs with PAHS. There was no
- 534 difference in OS among operated and irradiated dogs.