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

6 **Abstract**

7 Localized histiocytic sarcoma may occur as a primary lesion in periarticular
8 tissues of large appendicular joints. Treatment options for the primary lesion
9 include radical surgical excision, radiation therapy (RT), or both, in
10 combination with chemotherapy for potential systemic metastases. In an
11 effort to better characterize the time to progression (TTP) following surgical
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
15 PAHS cases undergoing surgery (predominantly limb amputation) or RT
16 followed by systemic chemotherapy. Of ~~4950~~ dogs, 34 underwent RT and ~~156~~
17 underwent surgery. All dogs received adjuvant chemotherapy. There was no
18 statistically significant difference in TTP or overall survival between groups. The
19 median TTP was ~~336299~~ days for the operated dogs and ~~2170~~ days for the
20 irradiated dogs ($P = 0.1 1775). The median overall survival time was 398 days
21 for the operated dogs and ~~2405~~ days for the irradiated dogs ($P = 0.1 4205). On
22 multivariable analysis, the variables significantly associated with an increased
23 risk of both tumor progression and tumor-related death were regional lymph
24 node and distant metastasis at admission. Survival and local control rates
25 following RT may be comparable to radical resection. These data may better$$

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

28

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

30

31 **Introduction**

32

33 Localized histiocytic sarcoma arises from myeloid dendritic antigen-
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
36 affected.¹ It is described as a single primary lesion with or without locoregional
37 lymph node metastasis.¹ Certain breeds, such as Bernese mountain dogs,
38 Rottweiler, Flat coated retrievers, Golden retrievers and miniature schnauzer
39 are genetically predisposed.²⁻⁵

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

50 Histiocytic sarcoma is reported to be radiosensitive.¹ 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
69 the cells (spindle, round, and multinucleated cells) on histopathology. At the
70 discretion of the pathologist, the diagnosis of PAHS was confirmed by
71 immunohistochemistry (CD18 and/or IBA-1).²

72 To be included in the study, dogs had to undergo clinical staging (consisting
73 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
77 of symptoms, site of disease, manner of diagnosis (histopathology +/-
78 immunohistochemistry), type of imaging, [bone lysis \(yes/no\)](#), lymph node
79 involvement (yes/no), distant metastasis (yes/no), administration of steroids
80 (yes/no), local treatment (surgery/ RT), systemic treatment (drugs, dosage
81 and number of cycles), treatment-related toxicity, time to progression (TTP),
82 overall survival (OS), and cause of death.

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

86

87 **Treatment and follow-up**

88 Dogs treated with surgery underwent limb amputation or wide local excision.
89 For RT, neither protocols or techniques, nor target- or organ-at-risk contouring
90 practices were standardized. RT data collected included absorbed dose,
91 tumor volumes, type of treatment planning, delivery, fractionation protocol
92 and total physical dose, where available.

93 The recommendation for type of systemic chemotherapy was based on the
94 judgment of the clinicians managing the cases and on owners' preferences.

95 Treatment-related adverse events were recorded according to the Veterinary
96 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
111 no new lesions, stable disease (SD) was defined between <30% and >20%
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

121 as mean \pm SD in case of normal distribution, or as median with a range in case
122 of non-normal distribution.

123 The distribution of demographic features and possible outcome variables
124 between operated and irradiated dogs were assessed with Fisher's exact
125 test or χ^2 test. The considered variables included breed, sex, age, body
126 weight, duration of symptoms, tumor site, [presence of bone lysis](#), presence of
127 regional nodal and distant metastases at admission and pre-treatment with
128 steroids. For age, weight and duration of symptoms, the median was used as
129 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
134 closure were censored. OS was calculated from the first day of treatment to
135 the date of death or to the date of last known alive as defined by follow-up
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.](#)

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

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

145 evaluated variables included treatment received (surgery vs. RT) 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 Forty-nine dogs were included in the study: 34 (69.4%) were treated with
160 RT and 15 (30.6%) were treated with surgery.

161 There were 20 (40.8%) Flat-coated retrievers, 8 (16.3%) Bernese mountain dogs,
162 4 (8.2%) mixed breed dogs, 3 (6.1%) Golden retriever, 2
163 (4.1%) Rhodesian ridgeback, 2 (4.1%) Rottweiler, and one (2%) each of the
164 following: Border collie, Bloodhound, Corgi, old English sheepdog, Harzer
165 fuchs, Poodle, Australian shepherd, Tibetan spaniel, Labrador retriever, and
166 American Staffordshire bull terrier.

167 There were 254 (4950%) female dogs (1920 of which were spayed) and 25
168 (510%) males (9 of which were castrated). The median age was 8 years

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

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 28 (57.1%) 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
183 (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 was revealed in 35 (71.4%) cases.
189 Eight dogs undergoing lymphadenectomy as part of their surgical procedure
190 had histopathological confirmation of nodal metastatic disease; overall, there
191 were no false positive or false negative results when comparing cytology with
192 histology.

193 Table 1 summarizes the demographic, tumor and treatment characteristics of
194 both surgery and radiation therapy groups. There was good balance
195 between groups regarding demographic features and possible outcome
196 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
214 computer-assisted using dedicated planning software was used in 12 (35.3%)
215 patients (n=32, 2 missing). All patients were treated under a short general
216 anesthesia. Positioning and verification thereof were accomplished

217 according to the individual institutions' routines. [In all 5 3DCRT-plans the](#)
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 plans were 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 \(2.9%\).](#)

228 Most dogs (32/34) were treated with a palliative-intent hypofractionated
229 radiation protocol delivered once or twice weekly and received ≤ 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) [and a median of 6 Gy](#).

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 \(range, 1 to](#)
238 [107\).](#)

239 Thirty-one (91.3%) dogs received post-radiation lomustine at [a median](#)
240 [dosage of 80 mg/m² \(range, 70 to 90\) every 21 days](#)~~standard dosage~~

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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
245 bone marrow (BM) toxicity, 4 had hepatic toxicity, 1 dog had gastrointestinal
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
248 one episode of grade 3 hepatic toxicity and one episode of grade 5
249 neutropenia (Table 3).

250 All _____ operated dogs _____ underwent 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 to 105).

257 ~~Thirteen-Thirteen~~ (86.7~~1~~%) dogs received adjuvant lomustine at ~~standard~~
258 ~~dosage~~ 80 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~~
260 ~~epirubicin,~~ one (6.7~~3~~%) dog was treated with doxorubicin (1 cycle) and one
261 (6.7~~3~~%) dog with vincristine (4 cycles). ~~Nine-Eight~~ (53~~6~~.3~~2~~%) dogs experienced
262 adverse events: ~~23~~ dogs experienced BM toxicity, 2 dogs had hepatic toxicity,
263 1 dog had BM and GI toxicity, 1 dog had hepatic and BM toxicity, 1 dog had
264 GI toxicity, and 1 dog experienced haemorrhagic cystitis. There were 2

265 episodes of ~~grade 3 and~~ grade 4 BM toxicity, ~~respectively, one episode of~~
266 ~~grade 4 GI toxicity and~~ 1 episode of grade 4 hepatic toxicity and 1 episode
267 of grade 3 BM toxicity (Table 3).

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,
281 185-419) 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 0.117).

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% CI, 183-613) for the
287 operated dogs and 240 days (95% CI, 210-270) for the irradiated dogs
288 (difference not significant, $P = 0.142$; Figure 1).

289 The only variables significantly associated with an increased risk of overall
290 disease progression and death were regional lymph node and distant
291 metastases at patient admission (Tables 4 and 5). On multivariable survival
292 analysis, both variables retained prognostic significance (Table 6).

293

294

295 When specifically considering distant metastases, 8 (50%) operated dogs and
296 29 (85.3%) irradiated dogs developed metastatic lesions or the pre-existing
297 metastases progressed.

298 The overall median follow up time was 217 days (range, 29-1406). Forty dogs
299 (75% of the operated and 76.5% of the irradiated dogs) experienced tumor
300 progression. At the end of the study, the same 40 dogs had died for cancer-
301 related causes. The median TTP was 299 days (95% CI, 183-415) for the
302 operated dogs and 210 days (95% CI, 179-241) for the irradiated dogs
303 (difference not significant, P = 0.201).

304 The median OS was 398 days (95% CI, 220-575) for the operated dogs and 245
305 days (95% CI, 215-276) for the irradiated dogs (difference not significant, P =
306 0.105; Figure 1). On univariable analysis, the variables significantly associated
307 with an increased risk of both tumor progression and tumor-related death
308 were regional lymph node and distant metastasis at patient admission (Table
309 4). On multivariable analysis, both variables retained prognostic significance
310 (Table 5).

311

312

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313 **Discussion**

314

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

318 The choice of local control modality in optimizing TTP, OS, and limb function in
319 dogs with PAHS has not received substantial scientific attention. To our
320 knowledge, this is the first study that directly compared survival outcome of
321 dogs with PAHS treated with surgery or RT, with adjuvant systemic
322 chemotherapy, and our results documented that TTP and OS after surgery
323 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.

335 While surgery is usually quoted to be a definitive-intent treatment, RT is mostly
336 referred to as palliative. The outcome between the two treatments has not

337 been different in the dataset presented herein (TTP and OS). This
338 nomenclature is hence somewhat arbitrary, as most of the dogs (40/50; 80%)
339 indeed died from disease progression within a relatively short time.

340

341 Dogs with PAHS with and without skeletal lesions due to histiocytic sarcoma
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
344 dogs with a post-mortem examination had evidence of metastatic spread.⁷
345 In dogs with radiographically detected bone involvement only, soft tissue
346 masses adjacent bone lesions became apparent at postmortem
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
356 disease (personal communication). Radiation therapy provides not only rapid
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
360 therapeutically (e.g. with known metastasis) or prophylactically. In light of the

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

366 Interestingly, [8/12](#) patients ([67%](#)) treated with conformal radiation
367 techniques such as 3DCRT or IMRT (and hence 3-dimensional imaging)
368 achieved CR. High response rates have also been described before, with
369 [13/19](#) dogs ([68%](#)) achieving CR shortly after treatment with palliative-intent
370 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
382 ~~[In our case series, a lower rate of metastatic progression was observed in the](#)~~
383 ~~[surgery group compared with the irradiated group \(50% versus 85.3%,](#)~~
384 ~~[respectively\).](#)~~ The presence of nodal or distant metastasis was a negative

385 prognostic factor in the current study, and this is in line with the published
386 literature.¹ The local control achievable with limb amputation also
387 immediately removes a reservoir of neoplastic cells, thereby possibly
388 preventing new metastatic lesions to occur. Surprisingly, in 11 dogs with PAHS
389 treated with definitive-intent surgery (e.g. had no measurable disease), 8/11
390 of which also received chemotherapy, median TTP was short as well, with [a](#)
391 [median of](#) 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

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

413

414 The limitations of this study relate to its retrospective nature with its inherent
415 biases and to the small population. Even though groups were in part well-
416 balanced regarding possible prognostic variables, two thirds of dogs were
417 irradiated and only one third underwent surgery, which will preclude from our
418 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

426 (especially CTV, and PTV) was not carefully performed and without 3D
427 imaging a substantial risk of underestimating tumor volumes (and lymph
428 nodes) remains. Delineation of tumor targets (especially CTV, and PTV) was

429 not commonly done. Additionally, without careful treatment planning, under-
430 dosage could also result from insufficient dose build-up at soft-tissue-air

431 interfaces such as the surface area. Even if the treatments are prescribed in a

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
435 recommend that treatment planners adhere to strict contouring and
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
441 remission. The true remission rate may be higher or lower because follow-up
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
446 confirmation.

447 While it is true that ideally all cases should be tested by means of
448 immunohistochemistry to confirm the diagnosis, this may not always be
449 mandatory. In the current series, any effort was made to exclude cases
450 lacking the characteristic features of HS, including sheets of large,
451 pleomorphic, mononuclear, and multinucleated giant cells, showing marked
452 cytological atypia and bizarre mitotic figures.

453 In conclusion, according to our data, compared with surgery, RT provided
454 similar local control and OS and good tolerability in dogs with PAHS also
455 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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533 Figure 1. Kaplan-Meier survival plots for [49](#) dogs with PAHS. There was no
534 difference in OS among operated and irradiated dogs.