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

Abstract

Localized histiocytic sarcoma may occur as a primary lesion in periarticular tissues of large appendicular joints. Treatment options for the primary lesion include radical surgical excision, radiation therapy (RT), or both, in combination with chemotherapy for potential systemic metastases. In an effort to better characterize the time to progression (TTP) following surgical versus non-surgical approaches for periarticular histiocytic sarcoma (PAHS), a contemporary European population of affected dogs ~~were~~ was retrospectively surveyed. Medical records were queried for newly-diagnosed PAHS cases undergoing surgery (predominantly limb amputation) or RT followed by systemic chemotherapy. Of 49~~50~~ dogs, 34 underwent RT and 15~~6~~ underwent surgery. All dogs received adjuvant chemotherapy. There was no statistically significant difference in TTP or overall survival between groups. The median TTP was 336~~299~~ days for the operated dogs and 217~~0~~ days for the irradiated dogs (*P* = 0.1177~~5~~). The median overall survival time was 398 days for the operated dogs and 240~~5~~ days for the irradiated dogs (*P* = 0.1420~~5~~5). On multivariable analysis, the variables significantly associated with an increased risk of both tumor progression and tumor-related death were regional lymph node and distant metastasis at admission. Survival and local control rates following RT may be comparable to radical resection. These data may better

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

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

Introduction

Localized histiocytic sarcoma arises from myeloid dendritic antigen-presenting cells and occurs as a primary lesion in periarticular tissues of large appendicular joints, with the stifle, elbow, and shoulder most commonly affected.[1] It is described as a single primary lesion with or without locoregional lymph node metastasis.[1] Certain breeds, such as Bernese mountain dogs, Rottweiler, Flat coated retrievers, Golden retrievers and miniature schnauzer are genetically predisposed.[2-5]

Periarticular histiocytic sarcoma (PAHS) is reported to develop at previously diseased appendicular joints.[3-6] Radiographically, lesions are characterized 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 prognosis than other localized visceral histiocytic sarcomas, and should be treated by surgical excision, radiation therapy (RT), or both, in combination with chemotherapy.[8] Complete tumor removal whilst preserving a functional limb is generally impossible due to the proximity of articular and neurovascular structures, therefore limb amputation is typically required to achieve adequate local tumor control.

Histiocytic sarcoma is reported to be radiosensitive.[1] Thus, RT presents an alternative local treatment modality to achieve primary tumor control with functional limb preservation.

However, whether RT achieves similar local control and survival outcomes to radical resection remains to be determined.

The aim of this retrospective, multi-center study was to compare the survival outcomes of dogs with PAHS treated with surgery or RT, in combination with adjuvant systemic chemotherapy. It was hypothesized that the two treatment modalities would provide similar outcome.

Material and methods

Inclusion and exclusion criteria

This study was designed by xxx. Medical records were reviewed to identify dogs with a histologically (+/- immunohistochemistry) confirmed PAHS. PAHS was defined as a sarcoma in which part of the tumor was superficial to the joint, and which was overlying the epiphysis or metaphysis of the bone. The 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

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

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]

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

Response data were based on the Veterinary Cooperative Oncology Group's RECIST criteria for solid tumors assessed by physical examination and measurements using calipers or imaging, dependent on tumor location and owners' compliance.[10] Surgically treated dogs were monitored for recurrence or metastatic development, not for disease response. Conversely, in the gross disease setting (irradiated dogs), complete response (CR) was defined as resolution of all clinical and/or imaging-based evidence of disease, partial 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% difference in tumor diameter with no new lesions, and progressive disease (PD) was defined as greater than 20% increase in tumor diameter or the development of new lesions. Overall response rate (ORR) was defined as CR + PR.

Statistical analysis

Descriptive statistics were used in the analysis of dogs and tumor characteristics. When appropriate, data sets were tested for normality by use 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 $\chi 2$ 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.

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

Survival plots were generated according to the Kaplan-Meier product-limit

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method and were compared using the log-rank test. Survival estimates were presented as medians with the corresponding 95% confidence intervals (95% CIs).

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

evaluated variables included treatment received (surgery vs. RT) and treatment-related toxicity (present/absent). Factors with a *P* value < 0.1 on univariable analysis were further tested for independence in a multivariable Cox proportional hazard model.

Data were analyzed by use of commercial software programs (SPSS Statistics v.25, IBM, Armonk, New York, and Prism v.8.0, GraphPad, San Diego, California). P-values <0.05 were considered significant.

Cell Line Validation Statement

No cell lines were used in the current study.

Results

Forty-nine dogs were included in the study: 34 (69.4%) were treated with RT and 15 (30.6%) were treated with surgery.

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: Border collie, Bloodhound, Corgi, old English sheepdog, Harzer fuchs, Poodle, Australian shepherd, Tibetan spaniel, Labrador retriever, and American Staffordshire bull terrier.

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

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

Intermittent to progressive lameness was present in 45 (91.8%) dogs; in 11 of them swelling of the affected joint was observed. The median duration of lameness was 60 days (range, 15 to 730 days). In 4 (8.2%) dogs, a non-painful mass around the involved joint was noticed. One (2%) dog was confirmed to have had previous joint disease in the tumor-affected joint. The diseased joints were the elbow (n=21; 42.9%), stifle (n=12; 24.5%), shoulder (n=11; 22.4%), hip (n=2; 4.1%), tarsus (n=2; 4.1%), and carpus (n=1; 2%). All cases were diagnosed by histopathology; CD18 and/or IBA-1 were used to confirm the diagnosis in 28 (57.1%) dogs.

For staging work-up, 38 (77.6%) dogs underwent total body CT scan, while 11 (22.4%) dogs had bone radiographs, thoracic radiographs and abdominal ultrasound performed. Based on imaging, 35 (71.5%) dogs had bone lysis, 13 (26.5%) dogs had no abnormalities detected, and the information was not available for one (2%) dog. Distant metastasis was documented in 12 (24.5%) dogs: spleen (n=6), lungs (n=3), lung and skin (n=1), lung and spleen (n=1), spleen and liver (n=1) based on imaging and cytological evaluation.

Regional lymph node cytological evaluation was obtained in all dogs; metastatic involvement was revealed in 35 (71.4%) cases. Eight dogs undergoing lymphadenectomy as part of their surgical procedure had histopathological confirmation of nodal metastatic disease; overall, there were no false positive or false negative results when comparing cytology with 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

according to the individual institutions' routines. In all 5 3DCRT-plans t~~T~~he recommendations for specifying dose and volumes were adhered to as proposed by Keyerleber et al. (2012), and in the ICRU reports 50 and 62 and for the 7 IMRT plans, recommendations of for 3DCRT and ICRU report 83 and Rohrer Bley et al. (2019) ~~for IMRT plans~~were followed. [11-15]

The remaining 20 plans were hand-calculated.

The target volumes and relative absorbed doses are shown in Table 2.

Lymph nodes were irradiated in 22/34 cases (64.7%). The reason for lymph node irradiation was stated to be prophylactic in 4 patients (11.8%), therapeutic (e.g. with known macrometastasis) in 17 dogs (50%) and both, therapeutic and prophylactic in one dog (2.9%).

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Most dogs (32/34) were treated with a palliative-intent hypofractionated radiation protocol delivered once or twice weekly and received ≤ 36.0 Gy of total dose. Total doses ranged from 16.0 to 51.2 Gy, with a mean total dose of 31.6 Gy (± 6.5) and a median of 30 Gy. Fraction numbers ranged from 2 to 16 with a mean of 5.9 (± 3.3) and a median of 5 fractions. Fraction sizes ranged from 3.0 to 8.0 Gy, with a mean of 6.0 Gy (± 1.5) and a median of 6 Gy.

Treatment was well-tolerated in all dogs. Thirty-one (91.2%) dogs experienced a clinical improvement of their lameness during RT, 2 (5.9%) dogs remained stable and 1 (2.9%) dog had a worsening of its symptoms.

Chemotherapy was started after a median of 14 days after RT (range, 1 to 107).

Thirty-one (91.3%) dogs received post-radiation lomustine at a median dosage of 80 mg/m^2 (range, 70 to 90) every 21 days~~standard dosage~~

(median, 5 cycles; range, 1 to 8 cycles); one (2.9%) dog was treated with an investigational drug (TRIN2755)[16], one (2.9%) received doxorubicin (4 cycles) and one (2.9%) received carboplatin and cyclophosphamide (4 cycles). Eleven (32.4%) dogs experienced adverse events: 4 of 34 dogs experienced bone marrow (BM) toxicity, 4 had hepatic toxicity, 1 dog had gastrointestinal (GI) and hepatic toxicity, 1 dog had BM and GI toxicity, and 1 dog 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 neutropenia (Table 3).

All operated dogs underwent limb amputation. None of these dogs received pre-treatment steroids. The procedure was well-

None of these dogs received pre-treatment steroids. The procedure was well-tolerated in all dogs, with no reported complications.

Chemotherapy was started after a median of 14 days after surgery (range, 13 to 105).

~~Thirteen~~ Thirteen (8~~6.7~~1~~.1~~%) dogs received adjuvant lomustine at ~~standard dosage~~80 mg/m^2 (range, 70 to 90) every 21 days (median, 6 cycles; range, 1 to 6 cycles); ~~one (6.3%) dog received 4 cycles of alternating lomustine and epirubicin,~~ one (6.7~~3~~%) dog was treated with doxorubicin (1 cycle) and one (6.7~~3~~%) dog with vincristine (4 cycles). ~~Nine~~ Eight (5~~3~~6.3~~2~~%) dogs experienced adverse events: 2~~3~~ 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 GI toxicity, and 1 dog experienced haemorrhagic cystitis. There were 2

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

Outcome

Regarding radiation response, 14 (41.2%) dogs achieved CR, 18 (52.9%) PR, 2 (5.9%) dogs were stable . ORR was 91.2%.

Of the 15 dogs treated with surgery, 3 (20%) had progression of pre-existing metastases and 7 (46.7%) developed new metastases. Of the 34 irradiated dogs, 7 (20.6%) had progression of pre-existing metastases and 16 (47%) developed new metastases.

The median TTP of known lesions was 336 days for the operated dogs (95% CI, 220-452) and 280 days for the operated dogs (95% CI, 171-389) (difference not significant, $P = 0.509$); and the median time to development of new lesions was 336 days (95% CI, 224-448) for the operated dogs and 302 days (95% CI, 185-419) for the irradiated dogs (difference not significant, $P = 0.509$). Overall, the median TTP was 336 days (95% CI, 209-463) for the operated dogs and 217 days (95% CI, 182-252) for the irradiated dogs (difference not significant, $P = 0.117$).

At the end of the study, 13 operated dogs (86.7%) and 30 irradiated dogs (88.2%) were dead. The median OS was 398 days (95% CI, 183-613) for the operated dogs and 240 days (95% CI, 210-270) for the irradiated dogs (difference not significant, $P = 0.142$; Figure 1).

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

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

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

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

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Discussion

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.

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

Dogs with PAHS with and without skeletal lesions due to histiocytic sarcoma were described to have other organ involvement in a majority of cases.[1,17] In 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] In dogs with radiographically detected bone involvement only, soft tissue masses adjacent bone lesions became apparent at postmortem examinations.[7] Hence, it is likely that the soft tissue component is not found or underestimated on radiographic imaging. The extent of disease is crucial for adequate surgical but also RT planning. For appropriate tumor staging and treatment planning of PAHS, we recommend using three-dimensional imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI).

Histiocytic tumors are ~~believed~~ likely to be highly radiation sensitive, with a very rapid time to regression and pain relief, but this experience is unpublished and a result of unstructured clinical observations in the treatment of macroscopic disease (personal communication). Radiation therapy provides not only rapid local pain relief, but also increases survival in patients with PAHS in addition to maintaining or even restoring functionality of the affected limb.[1,8] In addition, 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

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, 8/12 patients (67%) 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]

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

~~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 a median of 162 days (range 56-490 days).

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

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).

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 well-balanced 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.

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

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

Last, only 57% of cases underwent immunohistochemistry for diagnosis confirmation.

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

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local tumor control in dogs with PAHS remains a challenge, and many tumor, patient and institution related factors contribute to the ultimate decision made for each patient. The important observation from our study is that RT offers a comparable clinical outcome to amputation, while preserving articular function. As 74% of the patients died or were euthanized due to metastatic disease, oncologists should focus on improving chemotherapeutic or immunotherapeutic regimen for this disease entity.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgments

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Figure 1. Kaplan-Meier survival plots for 49 dogs with PAHS. There was no difference in OS among operated and irradiated dogs.