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Research Article

Survivorship Endpoints in Pet Dogs with Naturally Occurring Cancer as Models for Human Cancer

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Abstract

Pet dogs with cancer have been valuable models for human cancer drug development (Comparative Oncology). Despite strong similarities, the false perception that survivorship in veterinary cancer patients does not exist creates a challenge in translation of efficacy signals, from dog studies to humans, and constrains innovation in veterinary oncology. Until now veterinary oncology has been unique in its focus on the median when reporting patient outcomes. This narrow perspective has created a misperception regarding a more aggressive biology of many canine cancers and a lack of clarity in translation of preclinical signs of activity from dog studies to drug development decisions in humans. Using splenic hemangiosarcoma as an example, we sought to open a discussion on survivorship in veterinary oncology and shift focus away from the median. Data from 53 dogs that underwent splenectomy and adjuvant doxorubicin for stage I or II splenic hemangiosarcoma were aggregated from three published studies. Both quantitative statistical models and qualitative descriptions of survivorship were then applied to this unified dataset. The one- and two-year survival rates were both 11.8% (95% CI [4.8 to 22.3]). Given the expected lifespan of this cohort of dogs, this was suggestive of hemangiosarcoma survivorship of approximately 12% with existing treatment standards in one of the most aggressive canine cancers that is a translational model for the highly aggressive human angiosarcoma. Quantitative statistical models of survivorship were not feasible due to insufficient cohort size suggesting the need for adjustments to the conduct and design of veterinary cancer studies.

Keywords: Angiosarcoma; Chemotherapy; Comparative oncology; Doxorubicin; Hemangiosarcoma; Spleen

Abbreviations: CI: Confidence Interval; ANOVA: Analysis of Variance; MTD: Maximally Tolerated Dose; MTP-PE: Muramyl Tripeptide Phosphyatidyl Ethanolamine; PK: Pharmacokinetic; PD: Pharmacodynamic, EMA: European Medicines Agency; FDA: Food and Drug Administration

Introduction

The inclusion of dogs in the development of new cancer drugs has been recognized as a way in which to answer necessary drug development questions that cannot be effectively asked or answered in human clinical trials or conventional preclinical models [1]. Indeed, the recognized failure of the cancer drug development path to deliver effective new cancer drugs to human patients may be the result of an inability to effectively answer these currently unanswered drug development questions. Hemangiosarcoma is an aggressive canine neoplasm of the endothelial lineage that has been considered to be a relevant model for human angiosarcoma [2,3]. Despite the fact that these endothelial-derived cancers in each species can develop in several organs, the primary difference between the canine and human endothelial cancers is the high prevalence of the canine cancer in visceral locations, most commonly the spleen, and the high prevalence of the human cancer for the skin. Splenic hemangiosarcoma accounts for 50-65% of all canine hemangiosarcoma; however, the heart, skin and subcutis, and liver are often affected. Metastasis is frequent and is believed to occur either hematogenously or via direct implantation of cancer cells within the peritoneum after intra-abdominal tumor rupture. The liver, omentum and lungs are the most frequent sites of metastasis [4]. Median survival times of 19-86 days have been reported with splenectomy alone [5-7]. Adjuvant chemotherapy is believed to be helpful. Doxorubicin is the most widely utilized adjuvant therapy, often as a single agent, in combination, or sequentially with other agents [8-17]. The reported median outcomes are challenging to interpret through a human oncology lens since median survival in most human cancers is not routinely assessed or valued. Angiosarcoma survivorship of approximately 40% is often used as a description of outcome in this aggressive human cancer [18-20].

Emblematic of the field of veterinary oncology, outcomes for dogs with hemangiosarcoma have disproportionately focused on median survival and median progression-free survival. In human oncology studies, the 5-year survival rate from initial diagnosis is often used as a guideline for survivorship [21].

As a result of the combination of highly varied longevity for veterinary patients, based on species, age and size, coupled with variable cancer-associated clinical outcomes, it is unlikely that a consistent time benchmark of survivorship (i.e. 5 year survival) can be applied to all veterinary oncology patients. We expect that time benchmarks for rates of survivorship will need to be proposed, verified, and then utilized for each individual veterinary cancer diagnosis. Until now, veterinary oncology is often viewed as only delivering palliative outcomes to patients and has avoided the possibility of survivorship goals [22]. This perceived focus on palliative outcomes has constrained progress in veterinary oncology and has made the translation of therapeutic results from dog studies to desired drug development decisions in humans challenging. A change in perspective in veterinary oncology is needed to both clarify the translation of therapeutic results from dogs to humans and improve outcomes to pet owners. The consequence of reporting survivorship in veterinary oncology will be a new recognition that veterinary oncology is not only a palliative effort and will be the beginning of defining new baselines upon which innovators may deliver meaningful impacts to outcome both to advance care in veterinary oncology and deliver meaningful translational data from comparative oncology studies. This new and needed perspective on survivorship endpoints will further compliment the field of comparative oncology and the recognized valued attributes that have made translation studies of new therapeutics from pet dogs with cancer to the human so compelling. By better aligning therapeutic activity endpoints, we may be able to better inform translation decision-making as part of a comparative oncology approach to human cancer drug development.

As part of our broader interest to bring awareness of survivorship endpoints to veterinary oncology, the purpose of our study was to begin to define survivorship in a population of dogs with stage I or II splenic hemangiosarcoma treated with adjuvant doxorubicin-based chemotherapy regimens. Based on a qualitative assessment of the plateau at the right side of the Kaplan-Meier survival analysis of our assembled cohort and our judgements of the non-hemangiosarcoma-associated longevity of the typical patient, we now qualitatively propose that dogs that live to one year after splenectomy are unlikely to have subsequent cancer recurrence and likely represent a survivorship cohort of approximately 12% with existing therapy. Through this work we hope to expand awareness of survivorship and survivorship analysis in veterinary oncology and begin to better align our goals with treatment approaches that are common in human oncology.

Materials and Methods

Based on the hypothesis that survivorship exists but has been ignored in veterinary oncology we sought to define survivorship in a retrospective analysis of canine splenic hemangiosarcoma. Canine hemangiosarcoma is one of the most aggressive veterinary cancers and has been used as a model for human translation [2,3]. If survivorship can be described in this veterinary cancer, then

survivorship should be definable in most veterinary cancers.

A retrospective literature search was performed using Medline (PubMed) for studies published between January 2012 and March 2020 of histologically diagnosed splenic hemangiosarcoma in which dogs received a doxorubicin-based chemotherapy regimen after splenectomy. Manuscripts were selected and reviewed that included canine hemangiosarcoma stage I and II patients that were treated with splenectomy followed by a conventional doxorubicin-based adjuvant regimen (30mg/m^2 every 14-21 days for at least three cycles), included a Kaplan-Meier survival curve, and where authors were willing to provide raw outcome data for re-analysis. The information obtained from each author group included tumor stage, number of doses of doxorubicin, dosage of doxorubicin, any other drugs administered, survival time, age, and sex. Stage I was defined as hemangiosarcoma confined to the spleen (non-ruptured) and stage II as splenic hemangiosarcoma that had ruptured +/- local lymph node metastasis. Survival time was calculated from the date of surgery to the date of death due to any cause.

Statistical Methods

All statistical analyses were performed using Stata statistical software (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

Prior to pooling data from the independent studies, demographic characteristics (age and sex), disease characteristics (stage of disease), treatment received (number of doses of doxorubicin) and overall survival were compared among the studies. Continuous variables (age and number of doses of doxorubicin) were compared using one-way analysis of variance (ANOVA); categorical variables (sex, stage of disease) were compared using Fisher's exact tests. Pairwise multiple comparisons were performed using Sidak adjustments for multiple hypothesis testing if the global p-value was less than 0.05. Univariate Kaplan-Meier overall survival curves were constructed for each study and compared using a logrank test.

The data from the independent studies were then pooled and a composite Kaplan-Meier curve was constructed. The median overall survival and estimates of overall survival probabilities at 3, 6, 9, 12 and 24 months, with 95% confidence intervals (CIs) for the percentiles of survival time were constructed using a robust nonparametric method due to Brookmeyer and Crowley [23]. Univariate Cox proportional hazards models were constructed to assess the possible influence of signal, disease characteristics, and treatment received on overall survival.

Exploratory analyses were performed to determine if a subset of patients could be identified that might be survivors of their disease. Specifically, mixture cure models as implemented in Stata module strix [17], non-mixture cure models as implemented in Stata module strix [24], and split population mixture models as implemented in Stata module spsurv were constructed [25]. Subsequently a qualitative approach to define survivorship was employed through visual assessment of the start of the right-side plateau of the aggregated Kaplan Meier survival data.

Results

The Medline search of canine splenic hemangiosarcoma manuscripts identified three published studies that satisfied the rigorous manuscript eligibility criteria. A total of 53 dogs from these studies met this study's inclusion criteria: 10 from Study 1, 22 from Study 2, 21 from Study 3 [9,13,17]. Demographic and disease characteristics, number of doses of doxorubicin received, and survival status of dogs from the three studies are summarized in Table 1. Stage of disease was similar across the 3 studies ($p = 0.56$). The number of doses of doxorubicin administered differed among the studies ($p = 0.0035$). Pairwise comparisons after Sidak adjustment for multiple hypothesis testing indicated that dogs in Study 2 received significantly more doses of doxorubicin (mean 5.1) than dogs in Study 3 (mean 3.6); neither of the other two pairwise comparisons were statistically significant. Despite some differences noted for age and doses of doxorubicin, there were no statistically significant differences among the studies with respect to overall survival from surgery (logrank p-value = 0.76), which justified pooling of the 3 studies for subsequent analyses. Survival status irrespective of time of death was consistent across studies ($p = 1.000$); however, cause of death differed among studies ($p = 0.007$). Pairwise comparisons after Sidak adjustment for multiple hypothesis testing indicated that significantly more dogs were reported to have died due to progressive hemangiosarcoma in Study 2 (90.0%) than in Study 3 (63.2%), although this is confounded by the fact that 6 dogs in Study 3 died due to unknown causes. Since cause of death was unknown for some dogs, subsequent survival analyses were performed using overall survival.

Variable	Study 1 N = 10	Study 2 N = 22	Study 3 N = 21	Total N = 53	p-value
Sex					
F	NA	1 (4.5%)	0 (0%)	1 (2.3%	
FS	NA	11 (50.0%)	9 (42.3%)	20 (46.5%)	
M	NA	1 (4.5%)	1 (4.8%)	2 (4.7%)	0.90‡
MC	NA	9 (40.9%)	10 (47.6%)	19 (44.2%)	
MI	NA	0 (0%)	1 (4.8%)	1 (2.3%)	
Age					
Mean ± SD Median (range)	NA NA	9.5 ± 1.9 10 (3, 13)	11.1 ± 1.7 11.5 (8, 15)	10.3 ± 2.0 10 (5, 15)	0.0065§
Stage					
1	3 (30.0%)	5 (22.7%)	3 (14.3%)	11 (20.8%)	0.56‡
2	7 (70.0%)	17 (77.3%)	18 (85.7%)	42 (79.2%)	
Doses of doxorubicin					
1	0 (0%)	1 (4.6%)	3 (14.3%)	4 (7.5%)	
2	0 (0%)	0 (0%)	4 (19.0%)	4 (7.5%)	
3	1 (10.0%)	0 (0%)	2 (9.5%)	3 (5.7%)	
4	2 (20.0%)	6 (27.3%)	2 (9.5%)	10 (18.9%)	
5	7 (70.0%)	3 (13.6%)	9 (42.9%)	19 (35.8%)	
6	0 (0%)	12 (54.5%)	1 (4.9%)	13 (24.5%)	
Mean ± SD Median (range)	4.6 ± 0.7 5 (3, 5)	5.1 ± 1.3 6 (1, 6)	3.6 ±10.7 4 (1, 6)	4.6 ± 0.7 5 (1, 6)	0.0035§
Survival status					
Alive	0 (0%)	2 (9.1%)	2 (9.5%)	4 (7.5%)	1.000‡
Dead	10 (100%)	20 (90.9%)	19 (90.5%)	49 (92.5%)	
Cause of death					
Progressive hemangiosarcoma	7 (70.0%)	18 (90.0%)	12 (63.2%)	37 (75.5%)	
Unrelated cause	3 (30.0%)	2 (10.0%)	1 (5.3%)	6 (12.2%)	0.007‡
Unknown cause	0 (0%)	0 (0%)	6 (31.6%)	6 (12.2%)	
Maximum follow-up (months)	49.48	39.79	27.24	49.48	

† Kahn SA, et al. [6]; Matsuyama A, et al. [10]; Wendelburg KM, et al. [14]
‡ p-value from Fisher's exact test
§ p-value from one-way analysis of variance

Table 1: Assembly of Comprehensive Hemangiosarcoma Cohort from 3 Past Published Studies †.

Among the 53 dogs in the pooled dataset, 26 received doxorubicin alone and 21 received doxorubicin and metronomic cyclophosphamide. The remaining 6 dogs received: maximally tolerated doses (MTD) of cyclophosphamide along with doxorubicin (n = 2); MTD cyclophosphamide, doxorubicin, vincristine, and metronomic cyclophosphamide (n = 1); ifosfomide concurrently with doxorubicin (n = 1); doxorubicin followed by vincristine and cyclophosphamide (n = 1); cisplatin after doxorubicin (n = 1). When the dogs were grouped into those who received doxorubicin alone, those who received doxorubicin and metronomic cyclophosphamide, or those who received other treatment regimens, there were no statistically significant differences in overall survival (logrank p-value = 0.59).

Univariate Cox proportional hazards models were constructed for age, stage of disease and doses of doxorubicin to determine if these variables were associated with overall survival from time of surgery in the pooled dataset (Table 2). Age was not significantly related to overall survival after surgery (p = 0.77). As expected, dogs with Stage 2 disease had shorter survival than dogs with Stage 1 disease (hazard ratio [HR] = 1.80; 95% CI [0.87 to 3.75]), although this increase was not statistically significant (p = 0.12). When number of doses of doxorubicin administered was analyzed as a continuous variable, increased numbers of doses were associated with improved survival (HR = 0.70; p = 0.001). There, however, is an inherent bias in this statistic as dogs who live longer are able to receive more doses. When the number of doses of doxorubicin administered was dichotomized to < 3 vs. ≥ 3, the HR was 0.50 which was not statistically significant (p = 0.12).

The univariate Kaplan-Meier overall survival curve for the pooled dataset is displayed in Figure 1. The median overall survival time from surgery was 5.0 months with an approximate 95% CI of 4.2 to 5.9 months. However, several other statistics can be derived from this survival curve that might be more informative and reflective of the existence of the hypothesized survivorship cohort (Table 3). Indeed, the 12-month and 24-month overall survival rates were both 11.8% (95% CI: 4.8% to 22.3%) since no dogs died between 10 and 26 months, and qualitatively suggested a plateau in survivorship at 12 months. The maximum follow-up of dogs that were still alive was 49.48 months (Table 1). This suggests that there may be a subset of dogs who can be considered as "survivors". However, since there were only six dogs who survived beyond 10 months (11.8% of the total population), even qualitative assessments of survivorship are challenging and will require validation. Cause of death was attributed to progressive hemangiosarcoma for one dog, an unrelated cause for two dogs, and an unknown cause for one dog. Despite the small numbers of dogs and deaths in this portion of the survival curve, analyses were performed to assess the use of potential cure models. Initial attempts to create mixture cure models and non-mixture cure models failed to converge to a useful model. However, a split population mixture model produced an estimated probability, c, of never failing = 0.0122 with standard error 0.0252 (p = 0.31 for testing the null hypothesis that c = 0). Therefore, we cannot reject the hypothesis that a subset of this population of this assembled cohort includes survivors of their disease. Nonetheless larger studies are needed to create useful quantitative models of survivorship. Using a qualitative assessment of the Kaplan Meier survival curve for this cohort of 53 dogs with splenic hemangiosarcoma, treated with splenectomy and doxorubicin-based adjuvant therapy, we propose that dogs that live at least one year after splenectomy are unlikely to have subsequent cancer recurrence and may be described as survivors.

Variable	N	Deaths	HR	95% CI	p-value†
Age (continuous)	43	39	1.02	0.88 to 1.19	0.77
Stage (2 vs. 1)	53	49	1.80	0.87 to 3.75	0.12
Doses of doxorubicin (continuous)	53	49	0.70	0.57 to 0.87	0.001
Doses of doxorubicin (≥ 3 vs. < 3)	53	49	0.50	0.21 to 1.20	0.12
HR = hazard ratio; CI = confidence interval †p-value from Wald test					

Table 2: Univariate Cox Proportional Hazards Models.

Statistic	Estimate	95% CI
25th percentile	3.4 months	2.2 to 4.2 months
50th percentile (median)	5.0 months	4.2 to 5.9 months
75th percentile	6.8 months	6.8 to 9.7 months
3-month overall survival rate	80.8%	67.3 to 89.2%
6-month overall survival rate	33.5%	21.1 to 46.5%
9-month overall survival rate	17.8%	8.8 to 29.3%
12-month overall survival rate	11.8%	4.8 to 22.3%
24-month overall survival rate	11.8%	4.8 to 22.3%
HR = hazard ratio; CI = confidence interval		

Table 3: Statistics from Kaplan-Meier Overall Survival Curve.

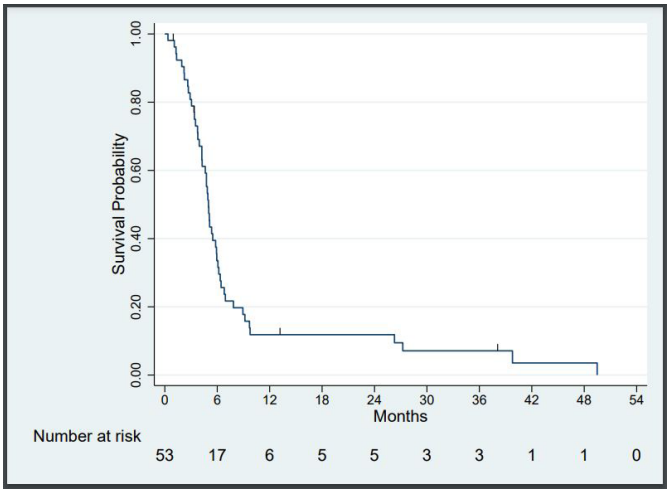

Figure 1: A comprehensive Kaplan-Meier survival analysis reveals a plateau in survivorship after 12 months. The univariate Kaplan-Meier overall survival curve for the pooled dataset of 53 dogs reveals a median overall survival time from surgery was 5.0 months. However, the 12-month and 24-month overall survival rates were both 11.8% (95% CI: 4.8% to 22.3%) since no dogs died between 10 and 26 months, and qualitatively suggests a plateau in survivorship at 12 months.

Discussion

We have compiled data from three distinct published studies in an effort to begin a perspective change in veterinary and comparative oncology that recognizes survivorship as a potential outcome. Outcomes of survivorship for dogs with stage I or II splenic hemangiosarcoma treated with a doxorubicin-based regimen after splenectomy were defined and now supports the fact that the field of veterinary oncology does deliver survivorship as a possible outcome for a cancer patient. Specifically, in this population, 1-year and 2-year survival rates with corresponding confidence intervals suggest a rate of survivorship of approximately 12%. We believe this rate of survivorship can serve as a useful benchmark upon which further improvements in survivorship can be measured through the conduct of veterinary and comparative oncology clinical trials of novel therapeutics. We believe that improvements in these survivorship endpoints will better inform translational decision-making from these canine trials to the human and accelerate innovation within veterinary oncology.

The field of comparative oncology has often described the inclusion of pet dogs with naturally occurring cancer in the human cancer drug development path. These research studies have allowed essential human cancer drug development questions to be answered that are challenging to answer in human clinical trials or conventional preclinical cancer models. By answering these questions many predict that the failures in human cancer drug development can be improved. The successful translation of data from naturally occurring pet dog studies to human cancer drug development is based on the high similarity between specific cancers in dogs and humans at the histologic, genomic, biological, and drug-response levels. Furthermore, the ability to rapidly assess drug, Pk/PD, tolerability, and efficacy in the same individual animal creates important opportunities to optimize human drug development studies [26]. A challenge in the translation of data from dogs to humans is the unique reliance of veterinary oncology to use median outcome measures as the endpoint assessment in research studies involving pet dogs. Ideally such efficacy endpoints would include parallel endpoints to human trials and prioritize survivorship. Such parallel terminology and approach would simplify translation across species.

An important example of the challenges and consequences of failed translation comes from the development and approval of muramyl tripeptide phosphyatidyl ethanolamine (MTP-PE) in canine osteosarcoma comparative oncology research studies and then in human osteosarcoma approval studies in Europe. In this example research studies in canine osteosarcoma eloquently described improvements in median progression free survival in dogs receiving MTP-PE as an adjuvant to primary tumor surgical resection compared to surgery alone [27]. Subsequent studies further demonstrated the advantage of MTP-PE when combined with chemotherapy compared to adjuvant chemotherapy alone [28]. These data supported the translation of MTP-PE to pediatric osteosarcoma studies, however, the fact that the order and sequence of MTP-PE and chemotherapy influenced the described median outcome improvements in dogs was overlooked in the human translation and not included in the preparation of the human trials. The result of this was more limited survival benefit in humans that was accepted as sufficient for approval of MTP-PE by the European Medicines Agency (EMA) in Europe but not sufficient for the United States Food and Drug Administration (FDA) [29,30]. Reanalysis of survivorship from these human clinical trials have suggested clearer evidence of benefit from MTP-PE [31]. It is reasonable to ask if efficacy signal for various MTP-PE regimens of adjuvant therapy used in dogs would have been better understood and translated to human trial development efforts if the data reported on survivorship as an endpoint rather than merely reporting median outcomes?

Veterinary oncology is unique in its reliance on reporting the median survival and progression free survival and the management and outcomes for dogs with cancer appears distinct from the human experience. By concentrating only on the single measure and ignoring the remainder of the survival curve, we are not depicting a sufficient overview of the treatment outcomes to patient families, and we may be constraining the agenda of innovators in both animal health and human health.

A landmark essay titled “The Median Isn’t the Message” by world-renowned evolutionary biologist, Stephen J. Gould, spotlighted the detrimental effects the previously median-centric approach used in adult oncology, in-part based on his own cancer diagnosis [32]. Initially distraught by the reported median survival time of 8 months for his own diagnosis of abdominal mesothelioma, Gould lamented the fact that a broader perspective of the entire survival curve had not been shared, and specifically that the hope at the right side of the curve was not communicated to him. His comprehension of statistics began a dialog in adult oncology on the topic of survivorship. We now seek to bring this awareness to veterinary oncology.

The 5-year survival rate has been proposed as a time measure of success in human cancers [21]. It is important to consider, that even in aggressive human cancers this rate of survivorship is known, communicated, and used as a benchmark for improvements through innovations. There is no reason why this should not also be the approach for veterinary cancers. Veterinary oncology has always been regarded as a palliative specialty because no one has attempted to approach it as anything more, not because survivorship is impossible. The predominant difference between human and veterinary oncology has long been perceived as a lack of a possible cure, however this is untrue. Veterinary oncology has ignored the right side of the curve, however small it may be.

Hemangiosarcoma is one of the most aggressive cancers in dogs, yet we were able to show that there is a population of survivors of this disease.

In our splenic hemangiosarcoma cohort, the 1-year survival rate was 11.8%, which is consistent with previously published reports, ranging from 9.1 to 29.2% with surgery and anthracycline-based therapy [8,10,12-13,15]. More importantly, the fact that this rate of survivorship was identical at 12 and 24 months provides a rationale to consider survivorship in this cohort being defined at 12 months. Furthermore, our knowledge of the patient cohort and the high risk of non-hemangiosarcoma mortality in this large breed older dog cohort further supports our proposal that 12 months post-surgery may be a reasonable place to define survivorship for stage I and II splenic hemangiosarcoma treated with splenectomy and adjuvant doxorubicin chemotherapy. We understand these results are based on a small number of dogs and we hope this perspective and both qualitative and quantitative approaches will be validated in a larger cohort of patients. Indeed, in this report, we sought to bring attention to to statistical tools that may be useful in the quantitative assessment of veterinary oncology survivorship. Consideration should be given to including these tools in future veterinary oncology studies to create a broader narrative on patient outcomes and survivorship, distinct from the historical median-centric approaches prioritized in veterinary oncology. We hope for our approach to presenting data in the future be more aligned with how human oncology outcomes are described.

Although cure and survivorship are recognized as distinct, for the purpose of this manuscript we applied statistical tools of cure to define survivorship. Over the years, several authors have proposed survival models that include a subset of patients who may be "survivors" and will never experience the primary survival endpoint. Economists tend to refer to these models as split population survival models; biostatisticians tend to refer to these as cure models. The basic assumption is that "cure" or survivorship is said to occur when the mortality (hazard) rate returns to the same level as that expected in the general population. A challenge to constructing these models may be the need to have good estimates of the expected (or background) mortality for each patient cohort. Since the dogs in the three studies tended to be elderly with a heterogeneous mixture of breeds and sizes, it is not intuitively obvious how to obtain these estimates for each patient, beyond the instincts of a clinician. In general, there are two types of models for estimation of a cure fraction: mixture cure models and non-mixture cure models. Taweab and Ibrahim reviewed both types with a focus on estimating the change-point in these models [32,33]. They described the assumptions underlying these models as follows: mixture cure models assume that the whole population is composed of susceptible patients and cured patients, while non-mixture cure models assume that the treatment leaves the patient with a number of cancer cells which may grow slowly over time and produce a detectable recurrence of cancer. Both types of cure models attempt to identify a change-point where the slopes of survival curves are significantly different, and therefore can quantitatively define a survivorship plateau in the Kaplan-Meier curve. Our attempts to identify a subset of dogs that were "survivors/cured" using these statistical approaches were challenging, due to insufficient patient numbers in the proposed survival sub-cohort. Nonetheless, the currently available statistical procedures for creating cure models may become a useful part of veterinary oncology outcome studies. It is understood that these studies but will require larger numbers of patients with longer follow-up. In the absence of this quantitative approach in the splenic hemangiosarcoma cohort assembled here, we propose the use of 12-month survivorship as a benchmark in canine stage I and II splenic hemangiosarcoma as we evolve from the median-centric analysis so-far prioritized by veterinary oncology. We believe that the inclusion of survivorship rates, no matter how small, adds important value to the conversation of treatment options with owners and provides a benchmark for improvement in future prospective studies.

There are several limitations in our study beyond its inherent retrospective design. Validation of our approach in prospective trials is underway. Specifically, in this retrospective cohort, while every dog received doxorubicin-based chemotherapy, the treatment protocols included additional chemotherapeutics. Indeed, 80% of these patients received metronomic cyclophosphamide, which in several previously published studies has not been demonstrated to significantly affect overall survival [8,11,34]. Similarly complicating were the study differences in the use of monitoring diagnostics. Finally, we only had access to the raw data supplied to us by the primary investigators of the manuscripts combined in this study; therefore, we were only able to consistently assess overall survival and not disease-free intervals. That being said, the nature of this disease predicts that in most dogs the time frame between disease progression and death is generally short. Although we combined three separate data sets, the total number of dogs assessed in this study was still relatively small and they were followed for relatively short periods of time. Accordingly, they did not allow us to effectively leverage statistical modeling in support of our continued interest in shifting the veterinary oncology focus from the median alone to discussions of survivorship.

Moving forward, future clinical studies in veterinary oncology should aim to include these statistical models in the design of prospective studies and when reporting outcome data. Larger study populations than what are typically included in median-centric veterinary oncology studies will be necessary for these models to be successful. However, the actual size of studies that compare a therapeutic effect using rates of survivorship as an endpoint may not be substantively different from those that attempt to measure a shift to the right for the median. Furthermore,

follow-up intensity for a survivorship trial may be reduced and less expensive than median-centric trial designs. This again could benefit the field of comparative oncology, as dogs are excellent spontaneous cancer models, not only because of their similar cancers but overall shorter lifespan requiring less follow up time and therefore a quicker road to assess the benefit of novel therapeutics.

As veterinary oncology evolves from its historic addiction to the median, we believe that reasonable time-based rates of survivorship will need to be determined for each veterinary cancer diagnosis. These new perspectives on survivorship will become more valuable benchmarks for incremental improvement by innovators, change the perspective that veterinary oncology is strictly a palliative specialty and aid in advancement of the field of comparative oncology.

Conflict of interest: The authors declare no conflict of interest.

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