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Chemotherapy effectiveness and mortality prediction in surgically treated osteosarcoma dogs: A validation study

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ABSTRACT

Canine osteosarcoma is the most common bone cancer, and an important cause of mortality and morbidity, in large purebred dogs. Previously we constructed two multivariable models to predict a dog's 5-month or 1-year mortality risk after surgical treatment for osteosarcoma. According to the 5-month model, dogs with a relatively low risk of 5-month mortality benefited most from additional chemotherapy treatment. In the present study, we externally validated these results using an independent cohort study of 794 dogs. External performance of our prediction models showed some disagreement between observed and predicted risk, mean difference: −0.11 (95% confidence interval [95% CI]-0.29; 0.08) for 5-month risk and 0.25 (95%CI 0.10; 0.40) for 1-year mortality risk. After updating the intercept, agreement improved: −0.0004 (95%CI-0.16; 0.16) and −0.002 (95%CI-0.15; 0.15). The chemotherapy by predicted mortality risk interaction (*P*-value = 0.01) showed that the chemotherapy compared to no chemotherapy effectiveness was modified by 5-month mortality risk: dogs with a relatively lower risk of mortality benefited most from additional chemotherapy. Chemotherapy effectiveness on 1-year mortality was not significantly modified by predicted risk (*P*-value = 0.28). In conclusion, this external validation study confirmed that our multivariable risk prediction models can predict a patient's mortality risk and that dogs with a relatively lower risk of 5-month mortality seem to benefit most from chemotherapy.

1. Introduction

Surgically treated dogs with appendicular osteosarcoma (OS), a malignant tumor of mesenchymal origin that produces osteoid, have a median survival time of 5 months (Brodey and Abt, 1976; Cooley and Waters, 1997; McNeill et al., 2007; Norrdin et al., 1989; Ru et al., 1998; Spodnick et al., 1992; Straw and Withrow, 1996). For the average patient, previous studies have shown that additional chemotherapy can extend median survival beyond these 5 months (Bailey et al., 2003; Chun et al., 2000, 2005; Straw et al., 1991; Vail et al., 2002).

Recently, using an Individual Patient Data Meta-Analysis (IPDMA), we constructed a multivariable prediction tool, predicting a dog's risk of mortality at 5 months and 1 year after receiving surgical treatment for OS (Schmidt et al., 2013). This tool predicts mortality risk based on a patient's age, weight, gender, neuter status, serum alkaline phosphatase (SALP) level, breed, and tumor location. In a nested study, we explored whether chemotherapy effectiveness differed between dogs with a different predicted risk (i.e., subgroup analysis; Schmidt et al., 2015). Results showed that chemotherapy (compared to no chemotherapy) was most effective in dogs with a relatively low predicted risk. This implies that perhaps dogs with a lower predicted risk of mortality should be

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preferentially treated with additional chemotherapy. Combining information on a dog's mortality risk with a personalized estimate of treatment effect can aid veterinary professionals to better tailor treatment to a dog's needs, which is relevant in terms of extending survival, decreasing healthcare costs, and increasing quality of life.

In the present study, we validate these finding using an independent cohort study collected at the Flint Animal Cancer Center at Colorado State University (Selmic et al., 2014). Specifically, we first applied our previously developed "original" prediction model to these external data and determined model performance. Second, we validated the differential chemotherapy effectiveness between dogs with different baseline mortality risks.

2. Materials and methods

The external validation of the prediction models and the chemotherapy subgroup-specific effects were evaluated using a subset of the Colorado State University cohort study (Selmic et al., 2014); data were collected based on a retrospectively review of electronic medical records. For the current analyses, dogs were eligible if they received surgical treatment (amputation or limb-spare) for OS. Because of the relatively rare occurrence, 49 dog receiving cisplatin/carboplatin, cisplatin or any other kind of (combination) chemotherapy were excluded. Patients were also excluded if they received radiation therapy ($n = 133$), had a zero or negative follow-up time ($n = 15$, measured from date of surgery to date of last contact), had an erroneous date of metastasis (after the date of death, $n = 9$), there was confirmed or a suspicion of metastasis at baseline ($n = 16$), received pamidronate ($n = 9$) or were small purebred dogs ($n = 5$). Exclusion criteria were identical to our discovery paper (Schmidt et al., 2015), with the slight difference that (to prevent small exposure categories) dogs with cisplatin or doxorubicin combination therapy, or small pure bred dogs, were excluded. Data were collected based on medical records, hence routine (scintigraphy based) staging information was not always available. Additionally, we emphasize that sample size was determined in an opportunistic manner, without formal sample size calculations; because of the retrospective nature of this cohort, this did not impact patient safety.

For the 794 remaining patients, baseline data were available on age (years), weight (kg), gender (0 female, 1 male), neuter status (0 intact, 1 neutered), high serum alkaline phosphatase (SALP) defined as above 140 IU/dL, continuous monocytes count (10^9cells/L), continuous lymphocyte counts (10^9 cells/L), breed (0 other breed, 1 Rottweiler, 2 Golden Retriever, 3 Labrador Retriever, 4 Greyhound, 5 Doberman, 6 mixed breed) and tumor location (0 other, 1 proximal humerus, 2 distal femur or proximal tibia, 3 distal radius). Additionally, we recorded whether a dog received chemotherapy (0 no chemotherapy, 1 carboplatin or 2 doxorubicin) and if it was alive at 5 months and 1 year (0 alive, 1 dead).

On average, 11% percentage of these variables were missing, the percentage missingness per variable was: 1-year mortality 6.05%, 5-month mortality 2.90%, chemotherapy 27.83%, age 0.13%, weight 0.13%, gender 0.00%, neuter status 0.00%, high SALP 9.57%, monocytes 18.89%, lymphocytes 18.89%, breed 0.00%, and tumor location 1.39%. Univariable analyses showed that missingness was dependent on observed variables (available upon request) indicating that a complete case analysis, excluding missing observations, would be biased (Groenwold et al., 2012; Rubin, 1976). Instead, we used the dependence between the missing observations and observed variables to impute missing values (Rubin, 1976) using the aregImpute algorithm from the Hmisc package version 3.14-5 (Harrell and Dupont, 2013). This algorithm was implemented using 5 burn-in iterations, predictive mean matching and 100 bootstrap samples to determine the (non) linear relationship between the continuous predictor variables and the missing values. To correct for the inherent underestimation of the variance, 15 imputed datasets were created (i.e., multiple imputation) (White and Carlin, 2010); results of the 15 imputed datasets were pooled using Rubin's rules (Little and Rubin, 2002; Marshall et al., 2009).

2.1. Data analysis: prediction model validation

Based on the logistic regression version of our previous derived prediction model (Schmidt et al., 2013), a patient's 5-month and 1-year risk of mortality was calculated by summing the product of their baseline variables and the relevant coefficients (Table 1); please note that because dogs with combination doxorubicin or cisplatin therapy were excluded, the coefficients for these therapies become redundant. Formally, the predicted logit (mortality risk) was calculated using Eq. (1):

$$\text{logit}\,(\text{mortalityrisk}) = \text{logit}\left(\hat{p}_i\right) = \hat{\beta}_0 + \sum_{j=1}^{J} \hat{\beta}_j x_{ij} \quad (1)$$

Where i represent the ith individual and j the jth variable presented in Table 1, $\hat{\beta}_j s$ the natural logarithm of the odds ratio for 5-month mortality and x the variable status after surgical treatment. The predicted logit(1-year mortality risk) was estimated by replacing $\hat{\beta}_j$ by $\hat{\theta}_j$. Finally, the mortality risk was calculated by taking the inverse of the predicted logit (mortality risk), Table 1. Note that for ease of notation, we will often drop the "predicted" from logit (mortality risk), however unless stated otherwise this always refers to an estimate from Eq. (1).

Obviously, these calculations are only relevant for future patients if we can assume the model to be correctly specified (i.e., describe the relationship between the predictors and outcome sufficiently). To evaluate the models predictive performance in this independent validation study we calculated the c-statistic, calibration slope and calibration-in-the-large (Harrell et al., 1996). Calibration was also graphically assessed by plotting the mean observed risk per deciles on the y-axis and the predicted risk on the x-axis (i.e., a graphical representation of the Hosmer–Lemeshow goodness-of-fit test) (Harrell et al., 1996; Steyerberg, 2009; Steyerberg et al., 2010). Please, see Appendix A of Supplementary material for a description of the metrics interpretability.

Besides this simple external validation, the prediction models were corrected for any systematic difference between observed and predicted risk (i.e., calibration-in-the-large $\neq 0$) by re-estimating the intercept in "Update 1" (Moons et al., 2012; Steyerberg, 2009). Such recalibartion can be readily applied in clinical practice using a relatively small number of events (e.g., 30) (Steyerberg, 2009). To aid clinicians in updating the model to their local setting computer code is provided in Appendix A of Supplementary material.

2.1.1. Data analysis: estimating chemotherapy effectiveness

After determining the external performance of our prediction models (predicting 5-month and 1-year mortality risk), we assessed whether the effect of "any chemotherapy" (carboplatin or doxorubicin) compared to no chemotherapy in preventing mortality differed between patients with different predicted risks of mortality. To explore consistency, all analyses are repeated for carboplatin compared to no chemotherapy and doxorubicin compared to no chemotherapy at 5-month and 1-year mortality.

This approach to tailor chemotherapy effects was previously described in detail in Schmidt et al. (2015), which we briefly repeat here. To get an estimate of the risk of mortality if the patient remained untreated with chemotherapy, we re-calculated the logit (mortality risk) by setting (possibly contrary to the fact) the chemotherapy variable to "no chemotherapy" in Eq. (1). Second, to test whether chemotherapy effects differed between patients with