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Which dogs with appendicular osteosarcoma benefit most from chemotherapy after surgery? Results from an individual patient data meta-analysis

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ABSTRACT

Osteosarcoma (OS) is a malignant tumor of mesenchymal origin that produces osteoid. Given that the prognosis can vary considerably between dogs, we aimed to explore whether treatment could be tailored towards patient subgroups, characterized by their predicted risk of mortality. For the current study, a subset of five nonrandomized studies (400 subjects of whom 88 were dead at 5 months follow-up) was used from a previously published 20 study individual patient data meta-analysis. Missing data was dependent on observed variables and was imputed to correct for this dependency. Based on a previously published multivariable prognostic model, the 5-month mortality risk was predicted. Subsequently, in surgically treated dogs, using a logistic regression model with a random intercept for a study indicator, we explored whether chemotherapy effectiveness depended on predicted 5-month mortality risk. After adjustment for potential confounders the main effect of any chemotherapy was 0.48 (odds ratio) (95%CI 0.30; 0.78). Testing for chemotherapy by predicted 5-month mortality risk interaction revealed that the effects of any chemotherapy decreased with increasing predicted risk; interaction OR 3.41 (1.07; 10.84). Results from individually comparing carboplatin, cisplatin, doxorubicin and doxorubicin combination therapy to no chemotherapy, were similar in magnitude and direction. These results indicate that the main treatment effects of chemotherapy do not necessarily apply to all patients.

1. Introduction

Osteosarcoma (OS) is a malignant tumor of mesenchymal origin that produces osteoid. In dogs, OS most frequently occurs in large and giant breeds (Cooley and Waters, 1997; McNeill et al., 2007; Norrdin et al., 1989; Ru et al., 1998; Spodnick et al., 1992). Dogs that are treated with amputation have a median survival time of five months, with the majority succumbing to metastatic disease (Brodey and Abt, 1976; Straw and Withrow, 1996). Clinical studies have shown that on average survival in OS dogs can be extended by administrating chemotherapy (Bailey et al., 2003; Chun et al., 2005, 2000; Straw et al., 1991; Vail et al., 2002).

After performing an aggregated meta-analysis (Boerman et al., 2012), a prognostic model for mortality in surgically treated canine osteosarcoma patients was developed using a 20 study individual patient data meta-analysis (IPDMA) (Schmidt et al., 2013). Such a prognostic model can be used to predict a dog's risk of early mortality (Moons et al., 2012). This offers the possibility to identify subgroups of dogs according to their baseline prognosis and target treatment to patients most likely to benefit. This can poten-

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tially prevent dogs from unnecessarily receiving treatment, which is relevant in terms of both costs and quality of life.

In the current paper, using a five study subset of our previously published IPDMA (Schmidt et al., 2013), chemotherapy effects were individualized by determining whether dogs with a different 5-month mortality predicted risk, reacted differently to chemotherapy treatment. Specifically, using an adapted version of the previously published prediction model (Schmidt et al., 2013), we first predicted a dog's 5-month mortality risk based on age, weight, gender neuter status, serum alkaline phosphatase (SALP) level, breed, and tumor location at time of surgery. Subsequently we evaluated what the effect was of "any chemotherapy" compared to no chemotherapy on the 5-month mortality incidence and if this effect differed between dogs with different predicted 5-month mortality risks. These estimates were compared for consistency to compound specific estimates for carboplatin, cisplatin, doxorubicin and doxorubicin combination therapy (the available groups of chemotherapy).

2. Materials and methods

The effects of the different chemotherapeutics compared to no chemotherapy were determined using individual patient data (IPD). These IPD were used previously in an IPD meta-analysis (IPDMA) combining data of 20 studies to determine prognostic factors for early mortality in dogs with osteosarcoma (Schmidt et al., 2013). A detailed description of the data accrual can be found in the original publication (a review protocol is unavailable). Briefly, studies were collected via the Veterinary Society of Surgical Oncology (VSSO). In January 2012, a call for collaboration was sent out to VSSO members and other veterinary oncologic researchers. Data was deemed eligible if baseline patient characteristics of OS dogs and time to event (death or metastasis) were recorded. To reduce the possibility of publication bias (Easterbrook et al., 1991), published and unpublished studies were both eligible. All dogs in these studies were diagnosed with osteosarcoma. For the present analysis, dogs were excluded if they did not receive surgery; due to euthanasia ($n = 197$), who received limb-sparing surgery ($n = 41$), who received an infrequently used chemotherapeutic protocol ($n = 13$) or who received radiation therapy ($n = 11$). Note that the exclusion of the 41 dogs (collected in 3 studies) treated with limb-sparing surgery is contrary to the original publication, and given the small number does not markedly influence our results. Additionally, the study by Sottnik et al. (2010) only collected data on metastasis, not mortality, and was excluded. Data was available from 1295 dogs collected in 16 studies.

To answer our present questions, does chemotherapy effectiveness differ between dogs with different predicted 5-month mortality risk, we used the 1295 dogs to construct a logistic regression prediction model; predicting mortality at 5 months. Subsequently, from these 1295 dogs (16 studies), studies were selected that included at least five dogs on no chemotherapy and at least five dogs treated with one of the interventions of interest (i.e., carboplatin, cisplatin, doxorubicin or doxorubicin combination therapy). Five nonrandomized studies fulfilled this criterion; of these 5 studies, three were previously published (Amsellem et al., 2014; Kirpensteijn et al., 2002; Kow et al., 2008), the two unpublished studies, by Maritato and Bacon, were based on routine healthcare records. After excluding dogs that received lobaplatin chemotherapy ($n = 27$) 400 subjects remained. Regrettably, none of these 5 studies randomly allocated chemotherapy hence chemotherapy associations are likely confounded; an issue that will be addressed later. We will first briefly describe how the logistic regression prediction model was derived (using the 1295 dogs). Second, we describe in detail how the predicted 5-month mortality risk was calculated for each individual dog, resulting in an individualized prediction. Third, we explain how individualized chemotherapy effect estimates were derived (based on the 400 dogs). Finally, a number of sensitivity analyses are discussed. Note that this study focused on 5-month mortality, because this is regarded as a clinical relevant endpoint (Brodey and Abt, 1976; Spodnick et al., 1992; Straw et al., 1991), however we are not aware of any biological rational other than that it reflects the median survival time after amputation (without further treatment).

2.1. Data analysis: prediction model

Instead of using the Cox's proportional hazards prediction model described in Schmidt et al. (2013), the current analysis uses a logistic regression model with random intercept for study. The reasons for switching to a "simpler" logistic regression model were twofold. First, the logistic model has a time independent intercept (contrary to the baseline hazard in a Cox model) making it easier to introduce our methodology, second, the proportional hazard assumption for the treatment by predicted risk interaction term seemed to be violated, including the null at 1 year (see Manuscript 2 for more detail). The logistic regression prediction model used the previously described 1295 dogs IPDMA and regressed a 5-month mortality indicator on the predictor's gender, neuter status, tumor location (proximal humerus, distal femur or proximal tibia, distal radius, versus other locations), age (years, continuous), weight (kg, continuous), breed (Rottweiler, Golden Retriever, Labrador Retriever, Greyhound, Doberman, mixed breeds, versus other breeds) and serum alkaline phosphatase (SALP, using study specific cut-off values for high and normal SALP levels). Chemotherapy was included as a nuisance variable and was set to zero (no chemotherapy) when predicting the 5-month mortality risk. As in the original publication, all predictors were predefined and no model selection was used (Schmidt et al., 2013). However, linearity of the continuous predictors was assessed by comparing a model (using a likelihood ratio test) with restricted cubic splines (5 knots) to a model forcing linearity. Additionally, restricted cubic spline plots were created to visually inspect linearity. Besides, SALP which was dichotomized, no deviations from linearity were observed (Refer to Table 1 for the derived prediction model based on 1295 dogs with). To prevent overfitting our prediction model (further) no additional model comparisons were performed (Chatfield, 1995). Please see the Appendix for a description of the model performance and Fig. A, a calibration plot comparing predicted versus observed 5-month mortality risk.

In the 1295 dogs about 8% of the data was missing, information on 5-month mortality was missing for 4.2% of the observations and chemotherapy for 2.4% of the observations (see for more details Schmidt et al., 2013). Univariable tests showed that missingness was associated with observed variables (results available from the first author) biasing a complete case analysis (Altman and Bland, 2007; Rubin, 1976). To adjust bias due to missing data, this dependency was taken into account by imputing missing observation using the aregImpute algorithm from the Hmisc package version 3.13-0 (Harrell and Dupont, 2013). The aregImpute algorithm was implemented using 10 burn-in iterations, 100 approximate bootstrap samples and predictive mean matching. To get correct estimates of the standard errors 100 imputed datasets were created (i.e., multiple imputation). Results over all 100 imputed datasets were pooled using Rubin's rules (Little and Rubin, 2002; Marshall et al., 2009).

2.2. Data analysis: predicting 5-month mortality

An individual dogs' risk of 5-month mortality, under no chemotherapy, was predicted using the coefficient presented in

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