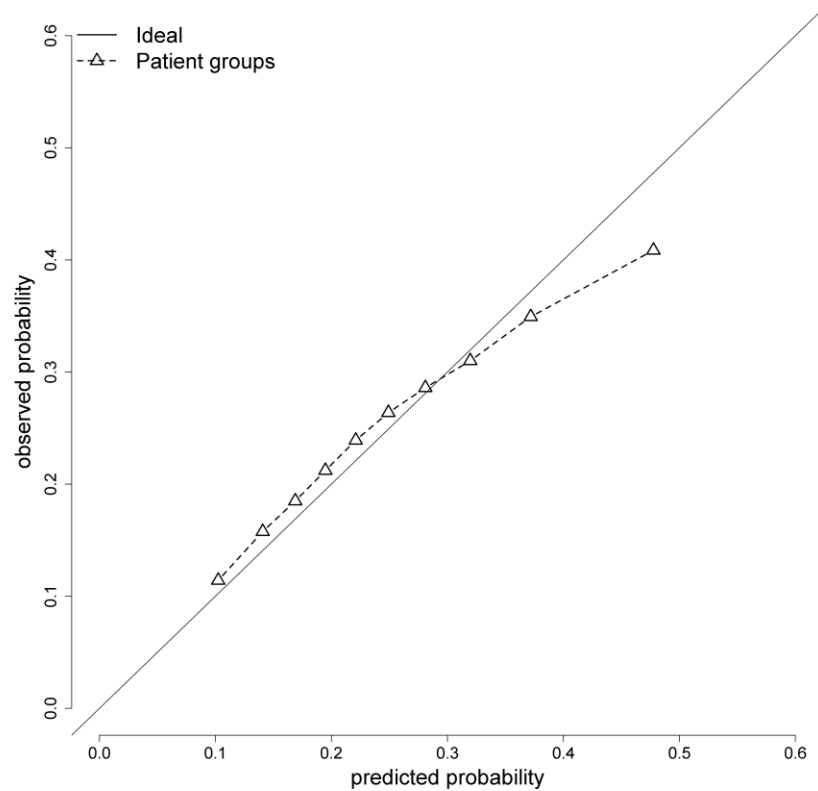


Appendix

Appendix figure A. Calibration plot comparing predicted probabilities to observed probabilities in deciles of patients. For 5-month mortality in dogs with osteosarcoma.



This figure is based on data of 1295 subjects. As described in the main text, missing values were imputed and results were internally validated by bootstrap resampling. 100 imputed datasets were created and per imputed datasets 100 bootstrapped samples were created.

Appendix table A. Characteristics of studies included in the IPDMA on the effect of chemotherapy compared to no chemotherapy in canine's with osteosarcoma treated with amputation.

Study	Published?	Design	Number of subjects	Surgery	Radiation therapy	Characteristics recorded											
						Carboplatin	Cisplatin	Doxorubicin	Doxorubicin combination	Age	Weight	Gender	Neutered	SALP	Breed	Location	Chemotherapy
Amsellem	No	NR	36	Amputation	No	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bacon	No	NR	145	Amputation	No	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Kirpensteijn (Kirpensteijn et al., 2002)	Yes	NR	90	Amputation	No			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Kow (Kow et al., 2008)	Yes	NR	63	Amputation	No	✓		✓	✓	✓		✓		✓	✓	✓	✓
Maritato	No	NR	66	Amputation	No	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓

NR = Non Randomized study.

Appendix table B. Imputed baseline characteristics of dogs treated with carboplatin versus no chemotherapy in dogs surgically treated for osteosarcoma.

Variables	No chemotherapy N = 100.00	Carboplatin N = 43.34
5 month mortality N (%)	36.98(37%)	6.21(14%)
Age (years) mean(sd)	9.64(2.87)	8.50(2.55)
Weight (kg) mean(sd)	36.04(19.63)	28.83(21.90)
Male gender N (%)	58.00(58%)	27.78(64%)
Neutered N (%)	89.00(89%)	37.73(87%)
High SALP N (%)	61.56(62%)	11.87(27%)
Breed		
Other N (%)	36.00(36%)	23.56(55%)
Rottweiler N (%)	8.00(8%)	4.37(10%)
Golden Retriever N (%)	7.00(7%)	0.21(0%)
Labrador Retriever N (%)	9.00(9%)	2.24(5%)
Greyhound N (%)	5.00(5%)	2.00(5%)
Doberman N (%)	4.00(4%)	3.00(7%)
Mixed N (%)	31.00(31%)	7.96(18%)
Tumor location		
Other N (%)	42.38(42%)	13.72(32%)
Prox. Humerus N (%)	19.74(20%)	9.68(22%)
Dist. Femur or Prox. Tibia N (%)	22.74(23%)	4.96(11%)
Dist. Radius N (%)	15.14(15%)	14.98(35%)
Logit(5 month mortality risk) mean (sd)	-0.42(0.51)	-0.74(0.48)
5 month mortality risk median (Q1; Q3)	0.39(0.32; 0.49)	0.31(.27; 0.39)

Results are presented as means over all 100 imputed dataset. Serum alkaline phosphatase (SALP); N equals the mean number of subjects, sd equals the mean standard deviation, Q1 and Q3 the mean first and second quartile. These dogs were originally included in studies by Amsellem, Bacon, Kow and Maritato.

Appendix table C. Imputed baseline characteristics of dogs treated with cisplatin versus no chemotherapy in dogs surgically treated for osteosarcoma.

Variables	No chemotherapy N = 43.00	Cisplatin N = 34.93
5 month mortality N (%)	19.99(44%)	12.00(34%)
Age (years) mean (sd)	9.74(2.44)	8.72(2.85)
Weight (kg) mean (sd)	36.74(15.20)	32.81(11.44)
Male gender N (%)	24.00(56%)	17.95(51%)
Neutered N (%)	39.00(91%)	32.50(93%)
High SALP N (%)	28.73(67%)	21.22(61%)
Breed		
Other N (%)	12.00(28%)	11.31(32%)
Rottweiler N (%)	6.00(14%)	0(0%)
Golden Retriever N (%)	3.00(7%)	7.16(2%)
Labrador Retriever N (%)	4.00(9%)	3.00(9%)
Greyhound N (%)	1.00(2%)	2.00(6%)
Doberman N (%)	3.00(7%)	1.00(3%)
Mixed N (%)	14(33%)	10.46(30%)
Tumor location		
Other N(%)	15.00(35%)	21.17(61%)
Prox. Humerus N (%)	14.00(33%)	2.14(6%)
Dist. Femur or Prox. Tibia N (%)	7.00(16%)	7.31(21%)
Dist. Radius N (%)	7.00(16%)	4.31(12%)
Logit(5 month mortality risk) mean (sd)	-0.34(0.43)	-0.57(0.43)
5 month mortality risk median (Q1; Q3)	0.41(0.34; 0.50)	0.35(0.30; 0.40)

Results are presented as means over all 100 imputed dataset. Serum alkaline phosphatase (SALP); N equals the mean number of subjects, sd equals the mean standard deviation, Q1 and Q3 the mean first and second quartile. These dogs were originally included in a study by Bacon.

Appendix table D. Imputed baseline characteristics of dogs treated with doxorubicin versus no chemotherapy in dogs surgically treated for osteosarcoma.

Variables	No chemotherapy N = 88.00	Doxorubicin N = 77.59
5 month mortality N (%)	32.98(37%)	14.57(19%)
Age (years) mean (sd)	9.65(2.80)	9.49(2.50)
Weight (kg) mean (sd)	39.60(18.17)	34.16(13.84)
Male gender N (%)	53.00(60%)	39.92(51%)
Neutered N (%)	80.00(91%)	71.72(92%)
High SALP N (%)	57.16(65%)	27.92(36%)
Breed		
Other N (%)	29.00(33%)	22.77(29%)
Rottweiler N (%)	8.00(9%)	10.72(14%)
Golden Retriever N (%)	7.00(8%)	10.32(13%)
Labrador Retriever N (%)	9.00(10%)	3.36(4%)
Greyhound N (%)	5.00(6%)	10.00(13%)
Doberman N (%)	4.00(5%)	1.00(1%)
Mixed N (%)	26.00(30%)	19.42(25%)
Tumor location		
Other N (%)	37.38(42%)	24.34(31%)
Prox. Humerus N (%)	17.17(20%)	18.88(24%)
Dist. Femur or Prox. Tibia N (%)	18.74(21%)	21.81(28%)
Dist. Radius N (%)	14.14(16%)	12.56(16%)
Logit(5 month mortality risk) mean (sd)	-0.35(0.48)	-0.53(0.44)
5 month mortality risk median (Q1; Q3)	0.41(0.34; 0.50)	0.37(0.31; 0.44)

Results are presented as means over all 100 imputed dataset. Serum alkaline phosphatase (SALP); N equals the mean number of subjects, sd equals the mean standard deviation, Q1 and Q3 the mean first and second quartile. These dogs were originally included in studies by Bacon, Kow and Maritato.

Appendix table E. Imputed baseline characteristics of dogs treated with doxorubicin combination versus no chemotherapy in dogs surgically treated for osteosarcoma.

Variables	No chemotherapy N = 145.00	Doxorubicin combination chemotherapy N = 76.18
5 month mortality N (%)	53.52(37%)	15.55(20%)
Age (years) mean (sd)	9.05(3.01)	8.06(2.85)
Weight (kg) mean (sd)	35.18(18.17)	38.04(15.18)
Male gender N (%)	75.54(52%)	44.39(58%)
Neutered N (%)	110.75(76%)	61.84(81%)
High SALP N (%)	93.70(65%)	28(35%)
Breed		
Other N (%)	62.40(43%)	36.65(48%)
Rottweiler N (%)	14.13(10%)	9.25(12%)
Golden Retriever N (%)	7.12(5%)	5.78(8%)
Labrador Retriever N (%)	13.09(9%)	3.60(5%)
Greyhound N (%)	5.03(3%)	2.35(3%)
Doberman N (%)	6.06(4%)	1.24(2%)
Mixed N (%)	37.17(26%)	17.31(23%)
Tumor location		
Other N (%)	76.71(53%)	24.78(33%)
Prox. Humerus N (%)	19.85(14%)	15.13(20%)
Dist. Femur or Prox. Tibia N (%)	26.98(14%)	18.49(24%)
Dist. Radius N (%)	21.46(15%)	17.78(23%)
Logit(5 month mortality risk) mean (sd)	-0.41(0.47)	-0.53(0.47)
5 month mortality risk median (Q1; Q3)	0.40(0.33; 0.48)	0.37(0.30; 0.44)

Results are presented as means over all 100 imputed dataset. Serum alkaline phosphatase (SALP); N equals the mean number of subjects, sd equals the mean standard deviation, Q1 and Q3 the mean first and second quartile. These dogs were originally included in studies by Amsellem, Bacon, Kirpensteijn, Kow and Maritato.

Appendix table F. Treatment effect estimates of different chemotherapeutics compared to no chemotherapy on 5 month mortality in dogs surgically treated for osteosarcoma.

	Any chemotherapy	Carboplatin	Cisplatin	Doxorubicin	Doxorubicin combination
Crude model					
Treatment effect	0.41 (0.25; 0.68)	0.30 (0.11; 0.82)	0.66 (0.26; 1.67)	0.29 (0.13; 0.64)	0.41 (0.20; 0.85)
Model adjusted for confounders(except breed)					
Treatment effect	0.43 (0.25; 0.72)	0.28 (0.09; 0.87)	0.59 (0.19; 1.84)	0.31 (0.13; 0.71)	0.39 (0.18; 0.87)
Model additionally adjusting for breed					
Treatment effect	0.46 (0.28; 0.75)	0.31 (0.11; 0.89)	0.72 (0.28; 1.88)	0.31 (0.14; 0.69)	0.43 (0.21; 0.88)
Interaction Model adjusted for confounders including breed					
Treatment effect	0.76 (0.38; 1.55)	0.80 (0.11; 5.63)	1.34 (0.33; 5.37)	0.65 (0.23; 1.89)	0.63 (0.24; 1.70)
Interaction effect	3.38 (1.04; 10.96)	4.78 (0.28; 82.31)	3.95 (0.42; 36.91)	6.85 (0.91; 51.39)	2.44 (0.48; 12.34)

Results presented as odds ratios (ORs) and 95 % confidence intervals (95%). All models included a categorical variable indicating study membership.

