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Mast cell tumours in the Golden Retriever Lifetime Study: a cohort study assessing frequency, clinical features and survival

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Abstract

Background The Golden Retriever Lifetime Study (GRLS) is a prospective cohort of dogs within the contiguous United States, designed to investigate health of Golden Retrievers, with cancer as a research focus. Mast cell tumour (MCT) represents the most common skin malignancy in dogs. This is the first exploration of MCT epidemiology within the GRLS cohort, and the first epidemiologic report specific to MCT in the Golden Retriever breed.

Methods MCT frequency was reported as proportion of the cohort, and incidence rate for first lifetime diagnosis. A lifetable was produced to assess incidence risk per year of age. The anatomical location, tissue origin and histopathologic grade of MCTs themselves were reported descriptively. Dogs with multiple MCT presentations or metastasis were further explored. Survival was compared between dogs with MCT and the remaining cohort, followed by a stratified analysis of time from first MCT diagnosis to death using Kaplan-Meier curves and the log-rank test.

Results Within the cohort of 3,044 dogs, 164 (5.39%) dogs were diagnosed with 234 MCTs, corresponding to an incidence rate of 5.58 per 1,000 dog years at risk (95% confidence interval (95% CI): 4.76–6.51). Median overall lifespan was 11.68 years (95% CI: 11.25–12.33) in dogs diagnosed with MCT and 11.75 years (95% CI: 11.61–11.98) within the remaining cohort - with no statistically significant difference observed (log-rank test, $p = 0.54$). Regarding histologic grade, 47 of 234 tumours (20.09%) met the GRLS high-grade definition (with either Kiupel high or Patnaik grade 3 characteristics). *De novo* tumours were diagnosed in 26 dogs (15.85%), local recurrence occurred in 8 dogs (4.88%) and metastasis in 16 dogs (9.76%). Median survival time from first MCT diagnosis was 1,367 days (95% CI: 1200–1870) with only 11.59% ($n = 19$) having MCT recorded as cause of death. After stratification, survival was statistically significantly decreased in MCT cases where there was presence of local recurrence, presence of metastasis, or high histopathological grade (log-rank test, $p < 0.05$).

Conclusions This epidemiological study reports age-specific frequency, clinical features and prognostic factors for Golden Retrievers with MCT. In this cohort, the lifespan of dogs with MCT diagnosis was not statistically significantly different from the remaining cohort.

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Keywords Mast cell, Tumour, Mastocytoma, Golden retriever, Epidemiology, Cancer, Canine, Survival

Background

Mast cell tumours (MCTs) are the most common cutaneous malignancy in dogs, representing 16–21% of skin neoplasias [1–4]. MCTs usually present as integumentary masses, either cutaneous or subcutaneous, and less often occur at other mucosal, muscle and visceral sites including oral cavity, intestines and spleen [5]. Canine MCT display a broad spectrum of clinical behaviours, ranging from low-grade lesions that may be cured by surgical excision, to highly malignant tumours with inflammation and ulceration at the primary site. Metastasis may affect the lymph nodes, and visceral organs, the liver and spleen [5]. Paraneoplastic effects, instigated by release of mast cell derived inflammatory mediators including heparin, histamine and proteases, can cause pruritus, bruising, skin oedema and gastrointestinal signs [6]. Given these potential sequelae, efforts have been made to analyse factors which can aid treatment decisions and prognostication in these patients [7]. Histological grading systems proposed by Patnaik and Kiupel have been shown to be consistently prognostic [8, 9], and are optimised when applied synergistically [10]. A range of histological and molecular prognosticators are reported in the literature including, but not limited to, mitotic count, margin status, *c-kit* mutation in exon 11, Ki67 and KIT staining pattern [11–17]. Clinical factors reported to be associated with prognosis include tumour size (> 3 cm), anatomical location, and erythema, ulceration and pruritus of the mass [13, 18–23].

Breed is postulated to be associated with prognosis, with Pugs and Boxers generally developing low-grade MCTs whilst Shar-peis tend to develop high grade [4, 24, 25]. Golden Retrievers have consistently been identified as a breed at increased risk of MCTs [25–30]. Germline risk factors for MCT have been explored in Golden Retrievers [31, 32], with a mutation of G Protein Subunit Alpha I2 (GNAI2) and hyaluronidase genes identified as risk factors for MCT development within Golden Retrievers in the United States (US) specifically. However, the associated clinical features of MCT within a US Golden Retriever cohort have not previously been reported.

The Golden Retriever Lifetime Study (GRLS) is a prospective cohort study of Golden Retrievers in the United States (US), managed and funded by the nonprofit Morris Animal Foundation [33]. Cancer is a major GRLS focus with primary endpoints of interest including haemangiosarcoma, lymphoma, osteosarcoma and high-grade MCT [34]. The GRLS “high-grade” study definition of MCT is based on pre-existing Patnaik and Kiupel histological grading systems [8, 9]. The Patnaik system assigns

grades P1 (low), P2 (intermediate), P3 (high) based on cellular features and tissue morphology [8] while the Kiupel system includes KL (low) and KH (high) that were introduced based on more quantifiable features aiming to improve pathologist agreement [9]. For the purpose of the GRLS study, MCT which were graded either Patnaik grade 3, or Kiupel high (P3, P3KH, P2KH, KH) were considered high grade.

Currently there is limited prognostic information published for low-grade tumours, or cases managed in a general practitioner setting. The GRLS longitudinal canine health study aims to provide information on breed-specific disease features and prognosis within US Golden Retrievers presenting to general practitioners. The objectives were to report the incidence, clinical and histological features and survival of MCT in GRLS, investigating prognostic factors for this cohort. GRLS provides unique insight, allowing study of prognosis for affected dogs, and comparison to their unaffected peers within the cohort. The study hypothesised that lifespan would be decreased in dogs diagnosed with MCT when compared to the remaining cohort. It was hypothesised that cases with high histologic grade would have decreased survival when compared to dogs only diagnosed with low-grade tumours. Likewise, dogs with confirmed metastasis were hypothesised to have decreased survival.

Methods

Study population

Between June 2012 and April 2015, 3,044 Golden Retrievers with three-generation pedigree, aged six months to two years, were enrolled to GRLS. Enrolment was balanced by sex and stratified for roughly equal recruitment across five geographical regions (Midwest, Mountain, Northeast, Pacific, South, detailed elsewhere [33]). Dogs with prior malignancy were excluded. Informed consent was given by dog owners and veterinarians for collection of medical records and biological samples. Full enrolment and cohort details are described elsewhere [33–35].

Annual observational data collected included: owner questionnaire, veterinarian questionnaire performed after annual veterinarian visit, and biological samples (including whole blood, serum, urine, faeces, hair and toenails). Inputs from the annual questionnaires were managed by the Morris Animal Foundation study team who collate results to an anonymised online secure data portal [36]. Neoplasia diagnosis was via veterinarian submission of a biopsy kit connected to the GRLS diagnostic laboratory account. Two blinded veterinary pathologists reviewed histopathological samples [33]. When malignant neoplasia was confirmed, a malignancy-related

questionnaire was completed by the attending study veterinarian. At end of life of all dogs, postmortem examination was encouraged, in addition to a submitted veterinarian report on cause of death. Clinical records were collated posthumously. Population characteristics were extracted and formatted from the datasets detailed in Additional file (1). Exploratory analyses of risk factors for diagnosis (methods and results) are presented in Additional file (2). These analyses did not demonstrate consistent biological or dose-response patterns and were underpowered to reliably assess rarer exposures. As such, the findings are presented as exploratory and should be interpreted cautiously.

For inclusion in the current study, diagnoses of MCT (MCT events) were identified in the GRLS “Study Endpoints” dataset (Additional file 1). This included veterinarian-led diagnoses received by questionnaire submission, and postmortem diagnoses. Whilst veterinarian questionnaire submissions qualified for inclusion as MCT events, cytology and histology reports were requested by the study team if not accessible through the GRLS diagnostic laboratory account. Data censor date was 31/05/2025. Data were analysed in Excel and R [37, 38] using packages ggplot2, survminer, survival, tidyverse and powerSurvEpi. MCT cases were defined as dogs who had received at least one available-lifetime MCT diagnosis, whilst the remainder of the cohort who were not diagnosed with MCT were non-cases. Dogs could be withdrawn at any point during the study and were classified as “inactive” if no study components (samples/questionnaires) were submitted for three consecutive years.

Frequency

Based on a previously reported MCT frequency in a mixed breed population [39], an a priori sample size calculation based on an expected MCT frequency of 1% with a precision of $\pm 0.05\%$, a finite population of 3,044 and 95% confidence, estimated a required sample size of 2,985. To estimate the incidence rate of diagnosis with first MCT, “dog years at risk” (DYAR) were calculated for each study dog. For non-cases, DYAR were time from birth to death or censoring; for MCT cases, DYAR were time from birth to first MCT diagnosis. Incidence rate was calculated by dividing the number of MCT cases by the total DYAR, with a Poisson distribution-based confidence interval calculated [40].

A lifetable was constructed using each year of age as one-year intervals [40]. Dogs either remained without MCT, were diagnosed (outcome), or removed from the denominator (died/alive without MCT diagnosis within each interval). Based on the assumption that withdrawals occurred uniformly throughout the interval (mid-interval assumption [41]), half of the number of withdrawn/inactive dogs were subtracted from the effective denominator

for the interval. Annual incidence risk and cumulative percentage of dogs remaining without MCT were calculated. Confidence intervals were generated via bootstrapping [42, 43].

MCT case descriptives

The “Study endpoints” dataset recorded details of endpoint diagnoses (haemangiosarcoma, lymphoma, osteosarcoma, MCT), meaning a single dog could have multiple events. MCT events were extracted and cleaned, ensuring uniform formatting where multiple tumour locations were documented at a single date point. Within the “Study endpoints” dataset, tissue origin of the MCT were categorised as cutaneous, subcutaneous or “Other”. Dogs who developed integumentary MCT at multiple distinct anatomical sites were classed as having *de novo* tumours, with an event logged for each, whether these were diagnosed at the same or differing dates. The “Study Endpoints” dataset also flagged MCT events which represented local recurrence at the same site. For the purpose of this study, recurrence of a mass was identified by The Morris Animal Foundation study team based on consistent submitted location both in textual format and as logged on an anatomical map. Anatomical MCT locations from histopathology reports or malignancy questionnaires were grouped to axilla, conjunctiva, external genitalia/perineal (including tail), head/neck, inguinal, limb, muzzle, torso, liver/spleen or lymph node, along with a broad grouping of “other” if the primary tumour was non-integumentary or the location could not be classified (Additional file 3). Histopathological grades using Patnaik and Kiupel grading systems were extracted, with “Unavailable” used when a histopathological grade was not given. MCT events within each grade were split as to whether the MCT was cutaneous or subcutaneous.

For dogs with multiple tumours (*de novo* or local recurrence), time interval between masses was calculated. Median, inter-quartile range (IQR) and range for time from first MCT to *de novo* tumour was calculated, and median time to progression from MCT to local recurrence was calculated. Where metastatic MCT events were recorded, method of diagnosis and site were reported. Median, IQR and range for time from first recorded MCT to metastasis was calculated.

Survival

Censor date was set as 31/05/2025. Age at death (or at censor date if alive) was calculated. The Kaplan-Meier estimator was used to assess time from birth to death (lifespan) with 95% confidence intervals calculated, stratified by MCT cases versus non-cases. For MCT cases, “Malignancy and cause of death” dataset was used to identify dogs with MCT listed as their cause of death, based on postmortem or veterinarian questionnaire.

Kaplan-Meier curves were generated from the date of first MCT diagnosis to death, for two outcomes: (1) MCT-related mortality, with censoring for deaths due to other causes, dogs still alive (as of 31/05/2025), withdrawn, or inactive; and (2) all-cause mortality, with censoring for dogs still alive or at their withdrawal or inactive date. Kaplan-Meier curves were stratified by variables: cutaneous/subcutaneous/other, low/high-grade/other grouping and binary outcomes for development of *de novo* MCT, local recurrence and metastasis. Group differences were assessed using the log-rank test, with statistical significance set at 5%. Overall survival proportions (all-cause mortality) at 1-, 2- and 5-years were calculated. To assign a singular cutaneous/subcutaneous/other tumour location to each dog (including those with multiple MCT events), category was based on all MCTs (excluding metastatic sites): dogs with cutaneous only or subcutaneous only were assigned accordingly, whereas those with both subcutaneous/cutaneous or primary non-integumentary sites were grouped as “Other.” Dogs

ever diagnosed with a high-grade tumour were assigned this grouping and the analysis of survival concerning histopathological grade was performed from the date of first high-grade diagnosis.

Results

Population characteristics

The population demographics of the entire cohort ($n=3044$) and then the proportion of each category represented by MCT cases ($n=164$) is shown in Table 1, with further information on the data extraction process in Additional file 1. Cohort median bodyweight was 31.80 kg (inter-quartile range (IQR): 28.32–35.51, range: 18.51–56.15) and median height to withers was 58.42 cm (IQR: 55.88–60.06, range: 43.81–86.36). Median body condition score was 5/9 (IQR: 5–6, range: 3–9). Among MCT cases, median age at first diagnosis was 8.06 years (IQR: 6.11–9.56, range: 1.26–13.03) whereas non-cases had median endpoint (death, inactive, withdrawn) of

Table 1 Golden Retriever Lifetime Study population demographics

Variable	Category	Cohort number (%)	Number of cases with mast cell tumour and percentage within category (%)
Sex	Female	1504 (49.41%)	88 (5.85%)
	Male	1540 (50.59%)	76 (4.94%)
Neuter	Entire	602 (19.77%)	19 (3.16%)
	Neutered	2442 (80.22%)	145 (5.93%)
Age at neuter	Entire	602 (19.77%)	19 (3.16%)
	≤ 6 months	427 (14.03%)	17 (3.98%)
	6 > 12 months	821 (26.97%)	54 (6.58%)
	12 > 24 months	546 (17.94%)	40 (7.33%)
	> 24 months	633 (20.83%)	32 (5.05%)
Height	Date unavailable	15 (0.49%)	2 (13.33%)
	≤ 55 cm	335 (11.01%)	21 (6.27%)
	55–60 cm	961 (31.57%)	54 (5.62%)
	> 60 cm	699 (22.96%)	52 (7.44%)
	Unavailable	1049 (34.46%)	37 (3.53%)
Bodyweight	≤ 25.00 kg	216 (7.10%)	12 (5.56%)
	25.01–30.00 kg	821 (26.97%)	39 (4.75%)
	30.01–35.00 kg	981 (32.23%)	70 (7.14%)
	> 35.00 kg	791 (25.99%)	41 (5.18%)
	Unavailable	235 (7.72%)	2 (0.85%)
Body Condition Score (1–9)	1–3	5 (0.16%)	0
	4/5	1383 (57.29%)	88 (11.61%)
	6/7	697 (22.90%)	55 (15.27%)
	8/9	71 (2.33%)	5 (13.81%)
	Unavailable	888 (29.17%)	16 (1.80%)
US Region	Midwest	449 (14.75%)	21 (4.68%)
	Mountain	266 (8.74%)	24 (9.02%)
	Northeast	373 (12.25%)	21 (5.63%)
	Pacific	292 (9.59%)	15 (5.14%)
	South	643 (21.12%)	35 (5.44%)
	Unavailable	1021 (33.54%)	48 (4.70%)

Population demographics of dogs enrolled in the Golden Retriever Lifetime Study. Category frequencies for the entire cohort ($n=3044$) and mast cell tumour cases ($n=164$) are shown. The dataset source and formatting are detailed in Additional file 1

10.92 years (IQR: 8.37–11.94, range: 0.74–14.90). Risk factor exploration is detailed in Additional file 2.

Frequency

Within the cohort of 3,044 enrolled dogs, 164 (5.38%) dogs were diagnosed with MCT. The total dog-years at risk of unaffected dogs, plus years to first MCT diagnosis, was 29,366.73 years, giving an incidence rate for first MCT of 5.58 per 1,000 DYAR (95% CI: 4.76–6.51). A lifetable was created, showing incidence risk by year of age for dogs in the cohort, the censored cases show dogs recorded as inactive/withdrawn (Table 2).

The lifetable showed a peak annual incidence risk of 1.39% for Golden Retrievers > 8–9 years of age.

Clinical and histological features

Across the 164 MCT cases, there were 234 MCT events. Tissue origins of the MCT were cutaneous ($n=165/234$, 70.51%), subcutaneous ($n=39/234$, 16.67%) and other ($n=30/234$, 12.82%). Within “other”, eighteen were metastatic entries, six were mucosal or visceral, four entries involved tumours of the digit which were not classified as either cutaneous/subcutaneous, and there were a further two unknown entries. On an individual dog level, 14/164 (8.54%) MCT cases had both cutaneous and subcutaneous tumours.

Histopathological grading with either the Patnaik or Kiupel system, or both, was reported for 165/165 (100%) and 28/39 (71.79%) cutaneous and subcutaneous MCT events respectively. The most frequently assigned histopathological grade was P2KL (Fig. 1). Overall, 47 MCT

events (20.09%) met the high-grade GRLS study definition (P2KH, P3KH, KH) and 157 MCT events were low grade (P1, KL, P1KL, P2KL). Of the MCT events where grade was “Unavailable” ($n=30$, 12.82%) were the ungraded subcutaneous tumours ($n=11$, 4.70%), events logging MCT metastasis ($n=16$, 6.84%) and non-integumentary sites ($n=3$, 1.28%).

The most common tumour locations were torso ($n=69$, 29.48%), limb ($n=54$, 23.07%), and head/neck ($n=29$, 12.39%). The anatomical locations of the 234 MCT events, categorised based on the GRLS study definition of high/low grade are shown in Fig. 2.

Follow-up and recurrence

Median available follow-up for MCT cases was 948 days (IQR: 352.25–1768.25, range: 0–3791). Most dogs ($n=138$, 84.15%) had a solitary MCT whilst 26 dogs (15.85%) developed *de novo* MCT at discrete sites (Fig. 3). Overall median number of MCT was 1 (range: 1–5). The dogs with multiple MCT had: 2 masses ($n=13$), 3 masses ($n=6$), 4 masses ($n=4$), and 5 masses ($n=3$) documented. During the study, 8 dogs (4.88%) had reported local recurrence. Of the recurrences, 2/8 (25.00%) were P2KL (low), recurring at the digit and torso. The other recurrences were classified as high-grade and were P2KH ($n=1$, 12.50%) and P3KH ($n=5$, 62.50%). Six dogs (3.64%) had both *de novo* tumours at novel locations and same-site recurrence during the study period. Median time from first MCT to a subsequent *de novo* MCT diagnosis was 368 days (IQR: 49–736, range: 0–1938). Median

Table 2 Actuarial lifetable to show age of first mast cell tumour (MCT) diagnosis

Age interval (years)	Total at risk	Outcome: MCT	Reached study end	Withdrawn/inactive	Effective denominator	One-year incidence risk (95% CI)	Cumulative probability without outcome (95% CI)
(0,1]	3044	0	1	0	3044	0.00% (CI:0.00–0.20%)	100.0% (CI:99.8–100.0%)
(1,2]	3043	2	46	40	3023	0.07% (CI:0.00–0.41%)	99.9% (CI:99.4–100.0%)
(2,3]	2995	4	102	87	2951.5	0.14% (CI:0.00–0.62%)	99.8% (CI:98.8–100.0%)
(3,4]	2889	6	105	88	2845	0.21% (CI:0.07–0.85%)	99.6% (CI:98.1–99.9%)
(4,5]	2778	12	94	67	2744.5	0.44% (CI:0.07–0.90%)	99.2% (CI:97.1–99.8%)
(5,6]	2672	14	102	59	2642.5	0.53% (CI:0.14–1.29%)	98.6% (CI:96.2–99.7%)
(6,7]	2556	23	90	39	2536.5	0.91% (CI:0.22–1.37%)	97.7% (CI:95.2–99.4%)
(7,8]	2443	18	124	37	2424.5	0.74% (CI:0.24–1.45%)	97.0% (CI:94.1–99.0%)
(8,9]	2301	32	172	13	2294.5	1.39% (CI:0.26–1.54%)	95.7% (CI:93.1–98.3%)
(9,10]	2097	20	277	14	2090	0.95% (CI:0.15–1.81%)	93.8% (CI:91.8–97.5%)
(10,11]	1800	17	402	27	1786.5	0.94% (CI:0.55–1.44%)	93.9% (CI:90.2–96.7%)
(11,12]	1381	11	701	38	1362	0.81% (CI:0.00–2.93%)	93.1% (CI:88.3–95.9%)
(12,13]	669	3	464	20	659	0.46% (CI:0.00–4.71%)	92.7% (CI:84.7–95.6%)
(13,14]	202	2	179	7	198.5	1.01% (CI:0.00–3.81%)	91.7% (CI:79.2–95.5%)

Actuarial life table showing time to development of first mast cell tumour (MCT) by year of age among 3,044 dogs enrolled in the Golden Retriever Lifetime Study (GRLS). The total at risk represents the Golden Retrievers remaining in the study population in the year interval. Outcome is development of first MCT. Study end is those dogs who died or are currently alive within the interval. Those withdrawn/inactive within the interval shown contribute /2 to the effective denominator. Incidence risk for each interval and the cumulative probability of remaining free of MCT are presented alongside 95% confidence intervals (CI) calculated via bootstrapping

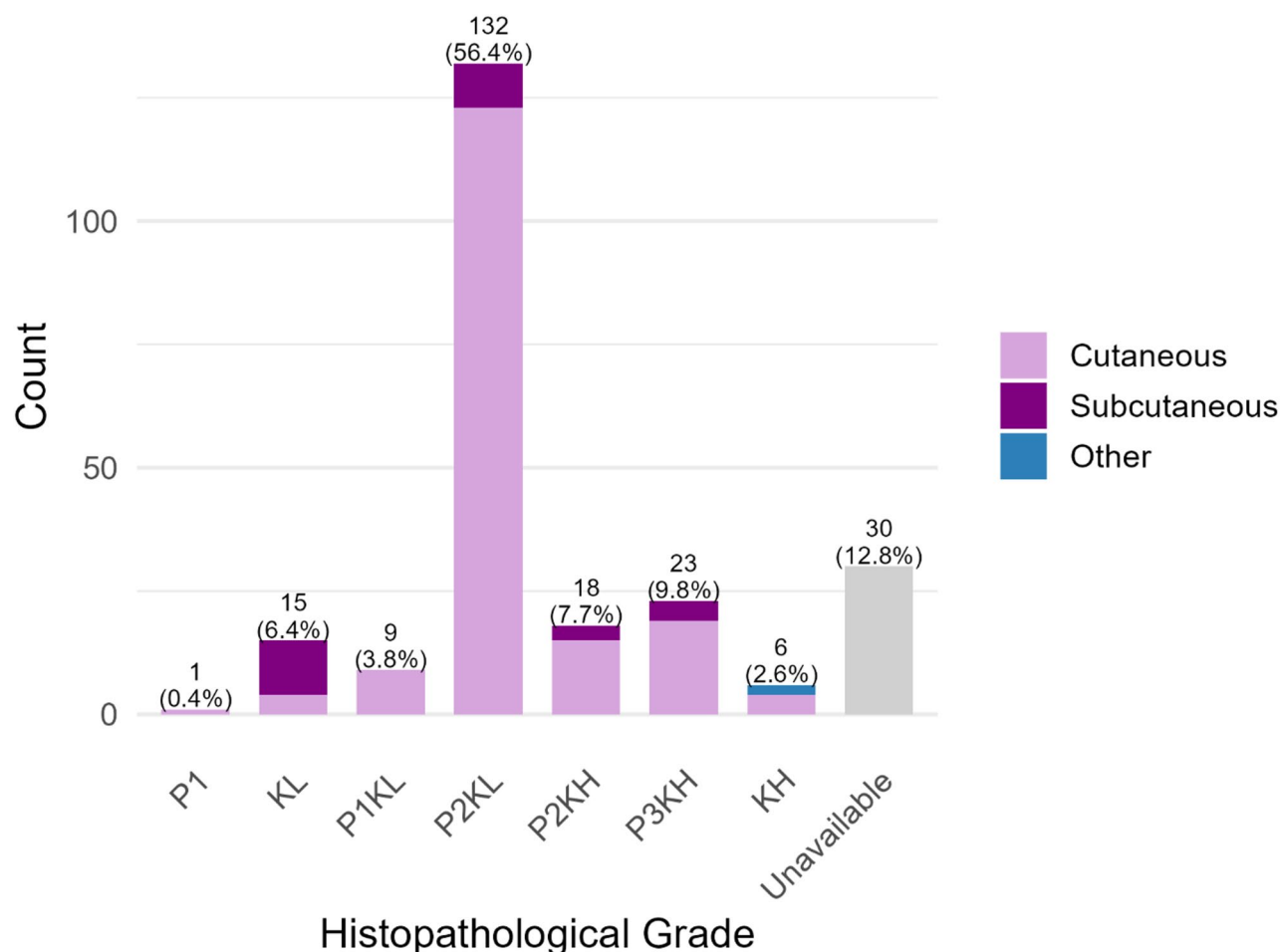


Fig. 1 The histopathological grade of identified mast cell tumour events ($n = 234$). P denotes the Patnaik grade (1–3) and K denotes Kiupel (L–low/H–high). Lighter colour denotes cutaneous tumours and darker for subcutaneous. “Unavailable” was used when a grade was not given and included 11 subcutaneous tumours and 19 other entries which were not typed

progression time from diagnosis to local recurrence was 273 days (IQR: 192.3–383, range: 34–620).

Of the 16/164 (9.76%) MCT cases with documented metastasis, 8/16 (50.00%) had nodal metastasis, 4/16 (25.00%) had distant metastasis, and 4/16 (25.00%) had both lymph node and distant metastasis (Table 3). Two dogs had postmortem confirmed pulmonary metastasis alongside hepatic/splenic metastasis. Of the dogs with metastasis, 2/16 (12.50%) had a prior subcutaneous tumour, 8/16 (50.00%) had a prior cutaneous MCT and for 6/16 (37.50%) MCT were mucosal or visceral. All GRLS dogs with metastatic MCT had at least one high grade tumour; however, for dogs with overt or occult multiple tumours, the primary lesion responsible for metastasis could not be definitively identified. Median time from first MCT diagnosis to metastasis was 38.50 days (IQR: 0–400.50, range: 0–1315).

Survival

Median lifespan for the 164 MCT cases was 11.68 years (95% CI: 11.25–12.33) and 11.75 years (95% CI: 11.61–11.98) for the non-cases. MCT cases and non-cases were not statistically significantly different in lifespan ($p = 0.54$) (Fig. 4).

Of the 164 MCT cases, enrolment status on 31/05/2025 was alive ($n = 69$, 42.07%), deceased ($n = 91$, 55.48%), inactive ($n = 2$, 1.22%) and withdrawn ($n = 2$, 1.22%). Median survival time from first MCT diagnosis to death for all-cause mortality was 1,367 days (95% CI: 1200–1870) and for MCT-related mortality was not reached, as only 19 dogs (11.59%) succumbed to MCT-related death. Post-mortem confirmation was available for 11/19 (57.89%) of these dogs. Survival probabilities for all-cause mortality at 1, 2 and 5 years after first MCT diagnosis were: 81.7% (95% CI: 75.9–88.0), 70.0% (95% CI: 63.1–77.7) and 40.6% (95% CI: 32.8–50.3) respectively. Of the dogs with MCT-related mortality, 17/19 dogs (89.47%) had at least one

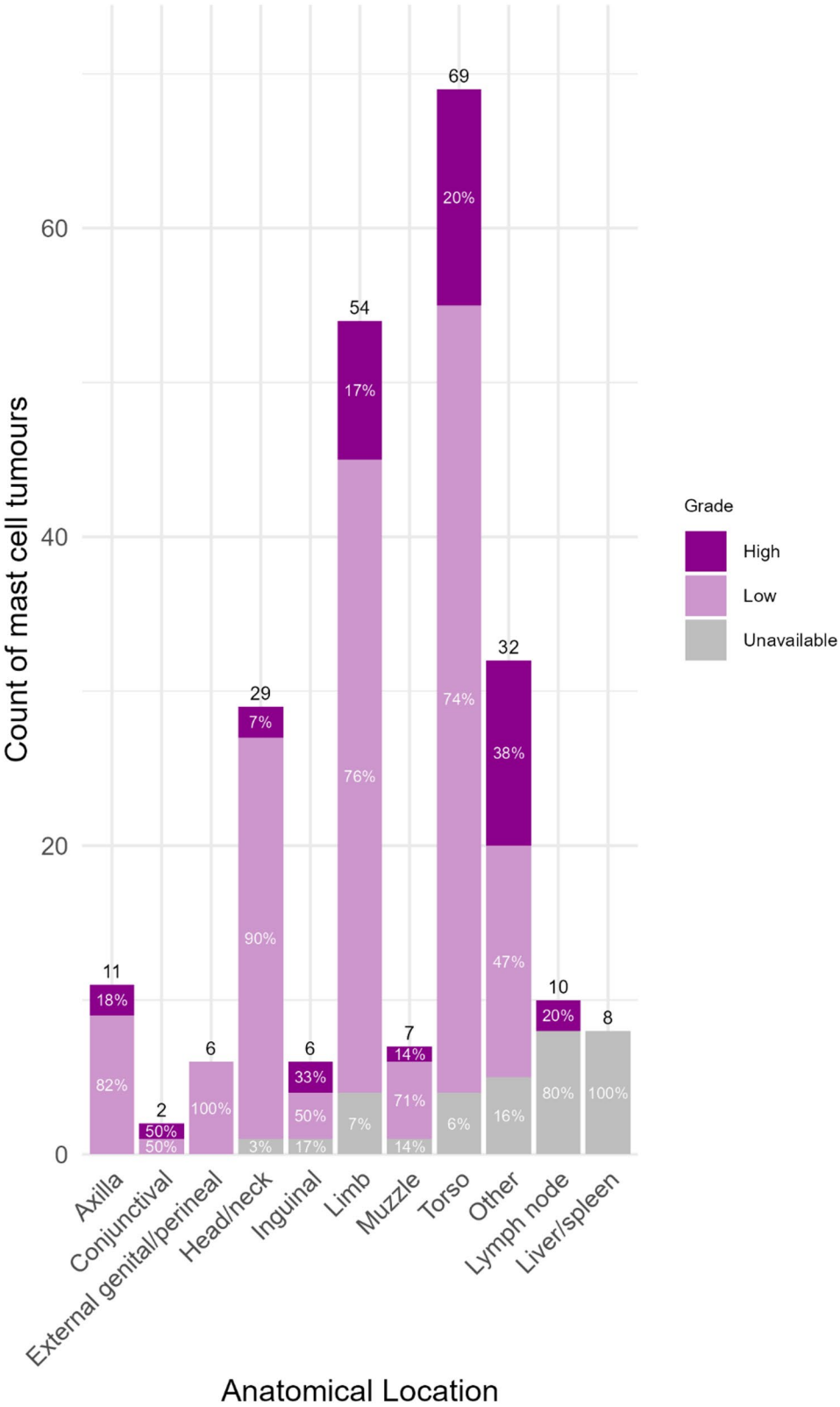


Fig. 2 Low/high-grade distribution across anatomical locations for mast cell tumour events ($n=234$) diagnosed in Golden Retriever Lifetime Study. The totals in black show number of mast cell tumours at the location, white % is proportion of high/low/unavailable at each site. (P1, KL, P1KL, P2KL as low; P2KH, P3KH and KH as high). Other was used for where anatomical location was unrecorded/miscellaneous (Additional file 3)

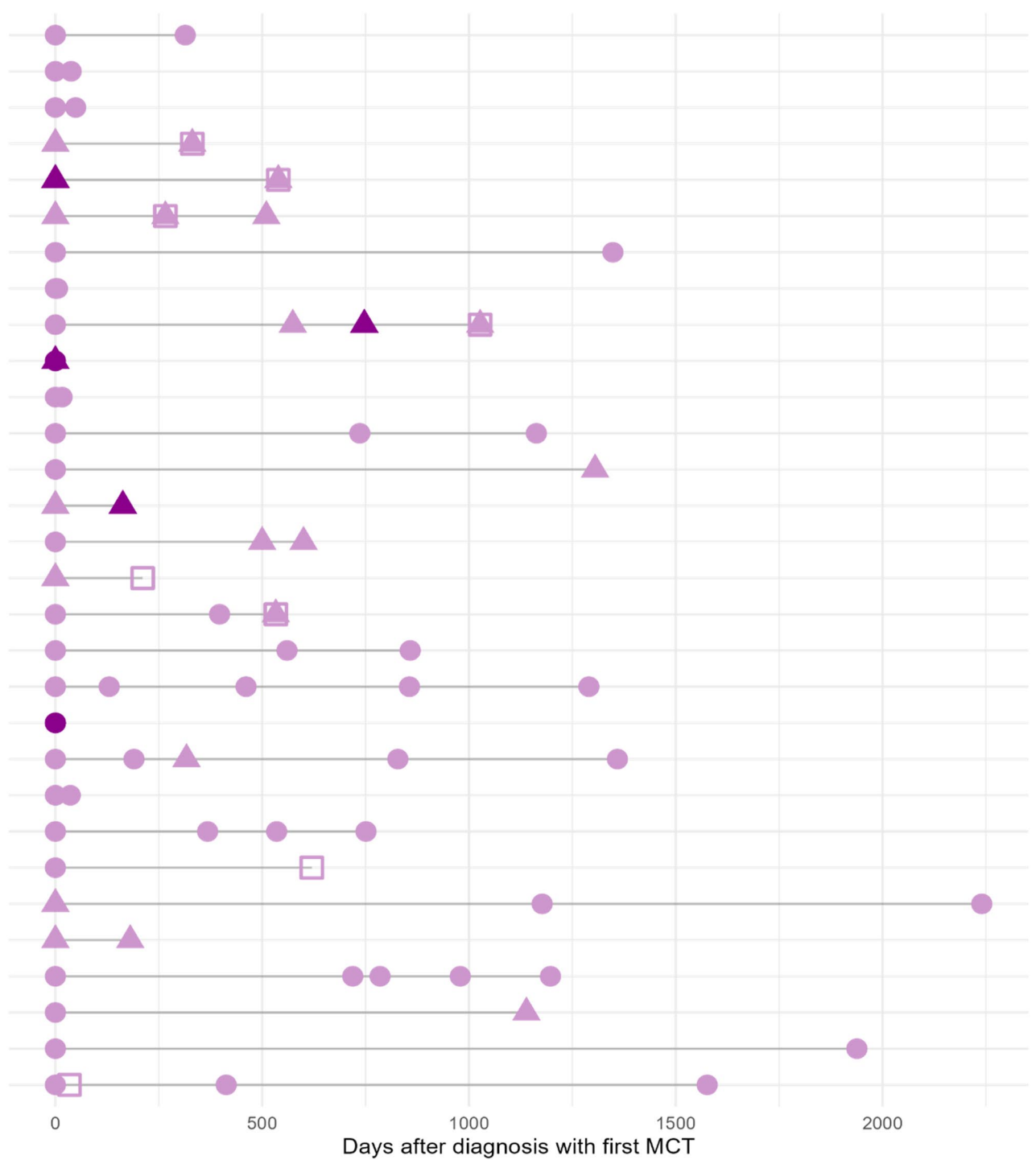


Fig. 3 Timeline of the mast cell tumour (MCT) diagnoses in dogs with recurrent or multiple tumours. Metastases not included. Each dog ($n=30$) has a timeline with each MCT represented by a circle for low grade (P1KL, P1, KL, P2KL) or triangle if high grade (P2KH, P3, P3KH, KH). Square outline indicates local recurrence. Darker purple indicated multiple simultaneous sites on the same date

Table 3 Documented metastatic sites

Dog	Metastasis location:	Diagnostic method
1	Kidney, spleen	PM
2	L prescapular LN	Cytology
	Spleen, lungs	PM
3	Ileocolic LN, Liver	PM
4	Liver, spleen	PM
5	L submandibular LN	Cytology
6	Oral, lung, spleen, liver	PM
	Mandibular LN, spleen	Cytology
7	Spleen, liver, kidney	Not documented
8	R prescapular LN	Cytology
9	R inguinal LN	Histopathology
10	Spinal cord, liver, LN	PM
11	R prescapular LN	Histopathology
12	R axillary LN	Cytology
13	L inguinal LN	Histopathology
14	Pancreaticoduodenal LN	Not documented
15	Subcutis and LN	PM
16	Liver and spleen	Cytology

Documented metastatic sites for the 16 dogs within Golden Retriever Lifetime Study (GRLS) with recorded metastatic MCT. Multiple rows are shown per dog if the diagnosis date or method differed. The method of diagnosis is shown. LN=lymph node, PM=postmortem, L=left, R=right

high grade tumour. Within the remaining two dogs, both received P2KL grading on histopathology.

Prognostic factors for survival

Kaplan-Meier curves are shown in Fig. 5. There was a statistically significantly decreased survival time for MCT cases where nodal or distant metastasis was documented, compared to dogs without metastasis, for both MCT-related and all-cause mortality (log-rank, $p < 0.01$). Likewise, MCT cases diagnosed with a high-grade tumour compared to low-grade only, had statistically significantly decreased survival time for both MCT-related and all-cause mortality (log-rank, $p < 0.01$). Presence of local recurrence was statistically significantly associated with MCT-related mortality compared to no recurrence documented (log-rank, $p < 0.01$). For dogs with *de novo* tumours, compared to dogs with one solitary MCT, there was no statistically significant difference in MCT-related mortality (log-rank, $p = 0.40$). All-cause survival probabilities are shown in Table 4.

Discussion

This is the first evaluation of MCT within the GRLS cohort, reporting frequency and clinical features. To the time of analysis, 164 (5.39%) of the cohort of 3044 Golden Retrievers had been diagnosed with MCT, giving an incidence rate of 55.8 per 10,000 DYAR (95% CI: 47.6–65.1). This suggests that Golden Retrievers could be up to ten-times over-represented for MCT given that rates

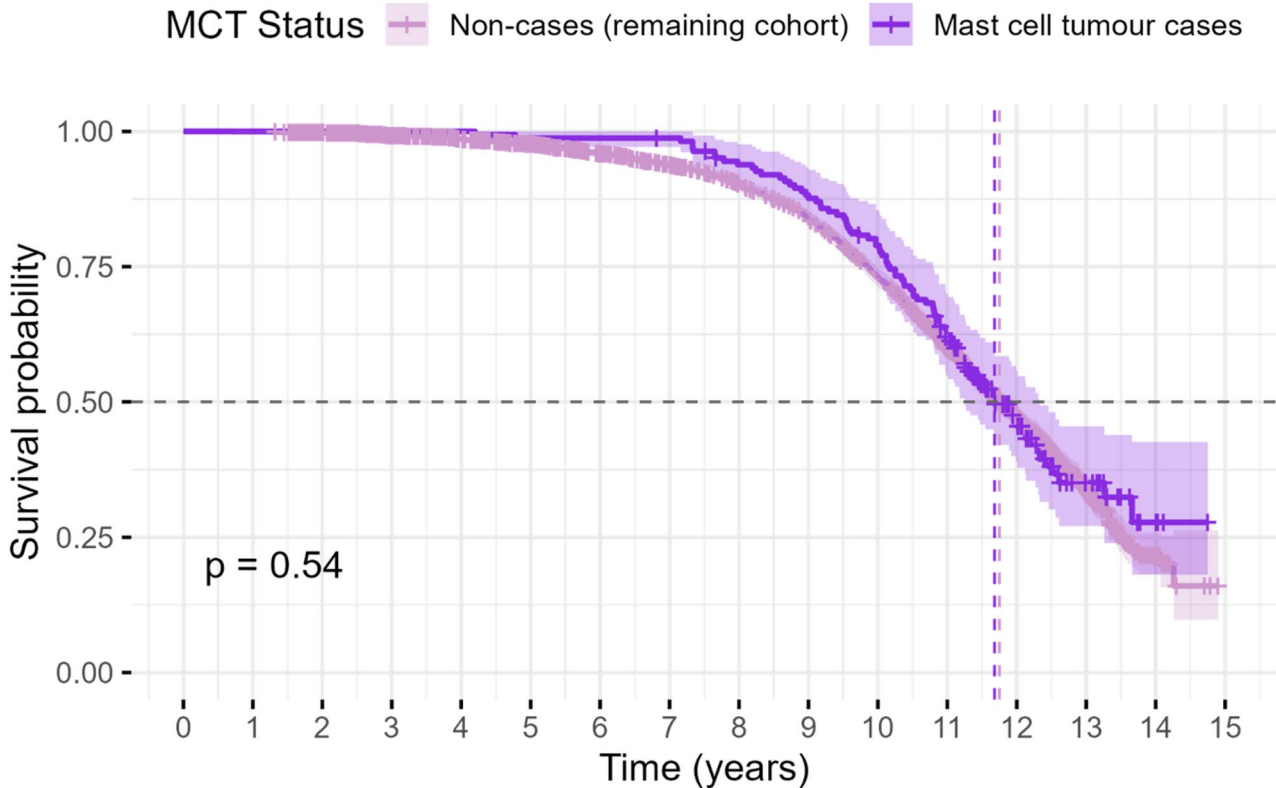


Fig. 4 Kaplan-meier survival curve for dogs in the golden retriever lifetime study ($n = 3044$), stratified by mast cell tumour (MCT) status: MCT cases ($n = 164$, 5.38%) and non-cases ($n = 2880$, 94.61%). A dashed horizontal line marks the median lifespan. Log rank p -value is shown

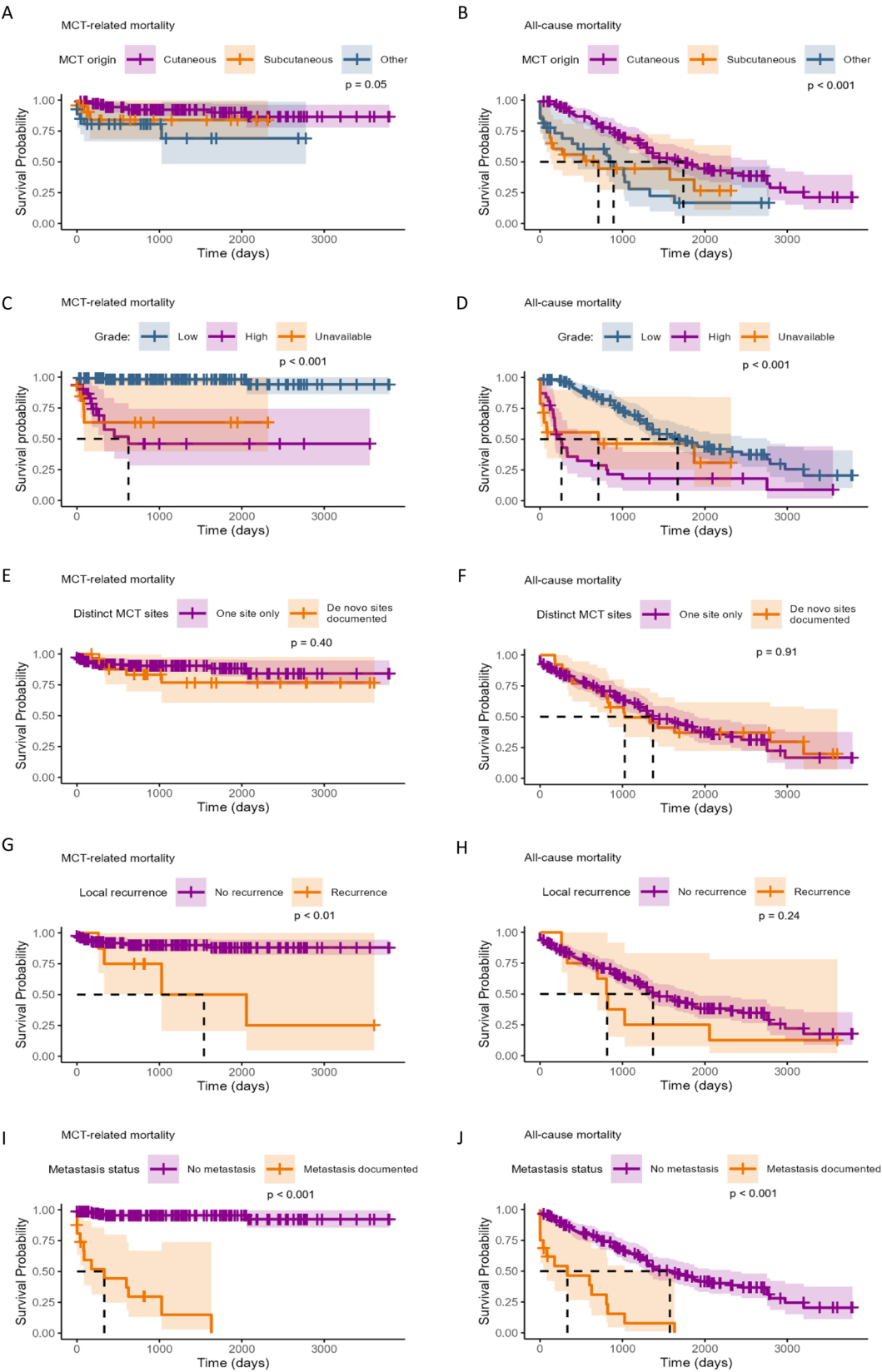


Fig. 5 (See legend on next page.)

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Fig. 5 Kaplan-Meier survival curves for 164 mast cell tumour (MCT) cases within Golden Retriever Lifetime Study (GRLS) from date of first MCT to death. 95% confidence interval is shaded. Log-rank p-value is shown. Median survival time is dashed line, where reached. **A:** MCT-related mortality stratified by tissue origin (cutaneous/subcutaneous/other). **B:** All-cause mortality stratified by tissue origin (cutaneous/subcutaneous/other). **C:** MCT-related mortality stratified by highest diagnosed histopathologic grade (high/low/unavailable). **D:** All-cause mortality stratified by highest diagnosed histopathologic grade (high/low/unavailable). **E:** MCT-related mortality stratified by whether *de novo* sites were documented. **F:** All-cause mortality stratified by whether *de novo* sites were documented. **G:** MCT-related mortality stratified by local recurrence. **H:** All-cause mortality stratified by local recurrence. **I:** MCT-related mortality stratified by presence of metastasis (nodal/distant/both). **J:** All-cause mortality stratified by presence of metastasis (nodal/distant/both)

of 5.23 MCT (95% CI: 4.90–5.58) per 10,000 DYAR were reported for a population of dogs of multiple breeds in Sweden [44]. Although there may be geographical difference in population frequencies due to genetic clusters or environmental risk factors [31], as well as different study designs, the tenfold higher incidence rate reported for Golden Retrievers in GRLS suggests a genuine and substantial breed predisposition rather than methodological or geographical difference alone. Owners of Golden Retrievers should therefore be vigilant for skin masses and veterinarians should encourage investigating these further.

In GRLS, young dogs were rarely diagnosed with MCT, with 99.1% of the cohort reaching the age of five years without development of MCT. A peak in annual incidence risk of 1.39% (95% CI: 0.95–1.86) was recorded for Golden Retrievers aged > 8–9 years old. This aligns with prior literature reports of median age at diagnosis with MCT of 7.4–9.0 years in populations with multiple breeds [8, 27, 45]. An interesting pattern was seen where incidence risk peaked at > 8–9 years and then decreased between > 9–13 years. This age/diagnosis pattern follows reports from other veterinary cancer studies, where geriatric cancer risk decreases [46, 47], although this could partially reflect a diagnostic bias whereby age may be influencing owner and veterinarian attitudes to investigations and treatments offered and pursued [48]. However, there may also be true biological factors at play. Despite ageing typically being associated with “inflammaging” that includes genetic errors, mutations and oncogenesis, there is a conserved pattern also in humans that neoplasia incidence rates reduce from 90 years old [49]. It has been postulated that cellular senescence, stem cell exhaustion, telomere attrition or a cancer resistant phenotype may be contributory to this decline [50, 51].

In the current study, subcutaneous tumours may have received Patnaik or Kiupel grade, or both, based on the histopathology report. Although both schemes were designed for cutaneous MCT, grade is reported as per the pathologist’s preference and there is evidence for the utility of the Kiupel scheme for subcutaneous tumours also [14, 52]. The majority of MCTs in the current study were classified within the GRLS study low-grade definition (67.09%) compared to high-grade (20.09%); P2KL was the most common. These findings are similar to previous studies which reported proportions of high-grade MCTs from 22.0% to 26.3% [10, 53]. In an Australian study, only

1/27 (3.70%) Golden Retriever MCT were high grade, suggesting the possibility of lower proportion high grade in some populations, although caution should be taken extrapolating from such a small sample size [53]. When compared to all purebred dogs in the US, Golden Retrievers were previously reported as at increased risk of P3 tumours and reduced risk for P1 [25]. The current study does not support that Golden Retrievers are more commonly diagnosed with high-grade MCTs. Better understanding of MCT in the breed will hopefully encourage treatment, which can have an excellent prognosis, in low-grade disease [12].

The anatomical site distribution for MCTs in Golden Retrievers reported in the current study are consistent with available literature for multi-breed populations, with torso and limb sites being most common [54]. Interestingly, although numbers were low, axilla and external genital/perineal tumours within the current study were all low grade - this differs from the literature where both sites are associated with decreased survival [20], although this has been disputed for inguinal and perineal tumours [55]. Patterns of MCT anatomical locations in Golden Retrievers seems to align with distributions reported in mixed breed populations [56].

Golden Retrievers have previously been reported to be at increased risk of developing multiple MCT during their lifetime. In a study following 280 dogs with MCT, Golden Retrievers were shown to be at 3.8 odds compared with crossbreed dogs for developing subsequent MCT > 10 cm from the original tumour, with 44% of Golden Retrievers developing these *de novo* MCTs [13]. In the current study, only 15.85% Golden Retrievers had *de novo* tumours ($n = 26$), which is below the 26.8% reported for a mixed breed population [17], although this result potentially underestimates the full lifetime proportion because the cohort is still ongoing. Local recurrence ($n = 8$, 4.87%) and metastatic rates (both nodal and distant, $n = 16$, 9.76%) within MCT cases in GRLS were low; and none of the dogs diagnosed with metastasis had only low-grade MCT. This finding could influence clinical staging recommendations for Golden Retrievers with low-grade MCT; however, in the absence of standardised staging data, it is unclear whether staging was performed and found to be negative, not performed, or not submitted to GRLS as a MCT event. Pulmonary metastasis, seen in two GRLS dogs in the current study, is considered uncommon [45]; whether this is breed-specific or if

Table 4 Survival probabilities at 1,2 and 5 years for all-cause mortality

Variable	Category	1-year survival % (95% CI)	2-year survival % (95% CI)	5-year survival % (95% CI)	p-value
Sex	Female	81.3 (73.4–90.0)	69.6 (60.2–80.4)	40.5 (30.3–54.1)	0.62
	Male	82.3 (74.0–91.5)	70.5 (60.5–82.0)	40.6 (29.6–55.8)	
Neuter status	Entire	75.0 (58.2–96.6)	70.0 (52.5–93.3)	36.0 (16.7–77.6)	0.72
	Neutered	82.7 (76.6–89.2)	69.9 (62.5–78.2)	41.0 (32.8–51.3)	
MCT tissue origin	Cutaneous	89.9 (84.5–95.8)	77.4 (69.8–85.8)	47.2 (37.9–58.9)	< 0.001
	Subcutaneous	55.9 (38.7–80.7)	44.5 (27.3–72.5)	35.6 (18.5–68.6)	
	Other	69.0 (53.1–89.6)	60.4 (43.8–83.1)	16.8 (6.1–46.0)	
GRLS Grade	High	34.6 (21.1–56.7)	27.7 (15.4–49.6)	17.3 (7.8–38.2)	< 0.001
	Low	94.7 (90.7–98.9)	82.4 (75.5–89.9)	47 (37.5–58.9)	
	Unavailable	55.6 (34.3–89.9)	46.3 (25.4–84.3)	46.3 (25.4–84.3)	
<i>De novo</i> MCTs	Single MCT	82.1 (75.8–88.9)	70.3 (62.7–78.8)	41.5 (32.8–52.5)	0.91
	> 1 MCT diagnosed	80.8 (67.0–97.4)	69.2 (53.6–89.5)	37.1 (22.3–61.8)	
Local recurrence	No recurrence	82.2 (76.3–88.5)	70.5 (63.4–78.4)	41.5 (33.4–51.5)	0.24
	Recurrence	75.0 (50.3–100)	62.5 (36.5–100)	25.0 (7.5–83.0)	
Metastasis	No metastasis	86 (80.4–91.9)	74.5 (67.5–82.2)	45.3 (36.9–55.6)	< 0.001
	Metastasis	42.8 (23.8–76.8)	28.5 (12.6–64.4)	0	

Survival probabilities at 1,2 and 5 years for all-cause mortality in 164 dogs diagnosed with mast cell tumour (MCT) in Golden Retriever Lifetime Study. Stratified by demographic variables and MCT features explored for association with prognosis. Calculated via Kaplan-Meier estimator with 95% confidence intervals (CI) presented. Log-rank p value for all-cause mortality presented

pulmonary metastasis rates need re-evaluation is an area for future study, thoracic metastasis of MCT has been previously documented [57, 58].

The median survival time from birth to death of 11.68 years for MCT was not statistically significantly different compared to 11.75 years for the non-cases, failing to support the study hypothesis. This suggests that for many Golden Retrievers, a MCT diagnosis is not life-limiting. Golden Retrievers experienced prolonged survival with a 40.6% overall five-year survival after first diagnosis with MCT. This is reassuring for owners, particularly when considering median age of diagnosis was eight years. Aligning with the available literature and the study hypothesis, presence of metastasis, and high histological grade were associated with decreased survival [12, 13, 21]. Development of *de novo* tumours was not associated with a statistically significant difference in survival ($p = 0.40$). The proportion of dogs with MCT-related mortality ($n = 19$, 11.59%) was too low for robust multivariable modelling of prognostic factors. Previous estimates of MCT-related mortality include 17.2%, 25.9% and 30.8% based on total populations of 163, 137 and 149 dogs respectively [10, 12, 59]. Given that post-mortem was encouraged for enrolled dogs, the lower rate of MCT-related mortality in the current study compared to previous work was unexpected. However, this lower MCT-related mortality may reflect advances in treatment, or potentially earlier, proactive intervention given that clients whose dogs are enrolled in GRLS are likely to be highly engaged in their dogs' healthcare. The prolonged survival seen after MCT diagnosis (median survival time: 1367 days) indicates that extended survival is

achievable in many dogs and promotes consideration of treatment.

The GRLS cohort provides a unique insight into MCT cases presenting to general practitioners. Many previous studies are based on insurance claim submissions with selection bias for the insured subset of the wider dog population [60]. Insurance claims tend to capture diagnosis frequency but less often capture details on treatment, sequelae and cause of death [39]. Studies from pathology laboratory data tend to stratify to high-risk subgroups, limiting generalisability [14, 61]. Referral cases also tend to represent more complex cases, less generalisable to overall populations [22, 62]. However, the current study had limitations. Recruitment to the cohort used word of mouth and snowball sampling methods that may have introduced some selection bias. However, a randomised sample strategy of the population could have led to higher non-response/drop out [63]. Recruited dogs were required to show three generations of pedigree, so they do not necessarily represent the broader Golden Retriever population in the US, limiting generalisability. Additionally, inbreeding depression previously shown in the cohort may be increasing rate of neoplasia [64].

Enrolment into GRLS ended in 2015. At the time of the current analysis, the youngest enrolled dog was 10.7 years. The MCT probability beyond this age may still be variable (some lag for data submission and processing also possible). Clinical notes were unavailable for many dogs, meaning treatment was not explored and consequently the prognostic impact of treatment, which is established in MCT [7], is not explored in this analysis. Staging methods were not standardised, limiting comparability between individual cases, but this heterogeneity

in management may better reflect the situation in clinical practice. However, if dogs did not undergo staging, then the metastatic rates presented in the current study may be an underestimation. That being said, none of the cases with only low-grade tumours had metastasis identified in the current study, supporting that extensive staging has a low diagnostic yield in dogs with low grade tumours [65]. The number of MCT cases was too low for prognostic factors to be assessed using a multivariable regression approach such as Cox proportional hazards modelling.

Participating owners were highly motivated and consenting to regular veterinary attendance, potentially associated with a more proactive approach to masses. Consequently diagnostic rates in the current study may be higher than for the wider Golden Retriever population where socioeconomic factors and access to veterinary care may constrain the likelihood of receiving a MCT diagnosis [66]. The increased diagnostic rates in the current analysis were compounded by a partial cost subsidy for histopathology, which introduces incentive-caused bias. However, this element of the study design may also have led to more thorough investigation of masses, more definitive diagnoses and more accurate estimation of frequency, albeit one less generalisable to frequency of diagnoses in wider populations.

On the other hand, underreporting is also possible. For dogs where the dedicated laboratory submission process was not followed, diagnoses would be dependent on owner or study veterinarian reporting via questionnaire. Likewise, dogs with prior diagnoses with multiple low-grade tumours, may not have every additional mass investigated or logged with GRLS. The questionnaires are relatively laborious to complete and therefore questionnaire fatigue and recall bias could affect accuracy and completeness of data.

The GRLS cohort design has allowed presentation of age-specific MCT incidence, incidence rate and longitudinal tracking of dogs with multiple tumours. This study demonstrated a high prevalence of low-grade tumours and a fair to good long-term prognosis with similar life expectancies between MCT cases to dogs without a diagnosis of MCT. Low recurrence and metastatic rates are reported. This supports that the diagnosis of MCT in this breed is not necessarily associated with more aggressive tumour behaviour, and this justifies prompt and appropriate management, supporting the health of Golden Retrievers diagnosed with MCT.

Abbreviations

DYAR	Dog years at risk
GRLS	Golden Retriever Lifetime Study
IQR	Interquartile range
KL/KH	Kiupel grading of mast cell tumour - low/high
LN	Lymph node
MCT(s)	Mast cell tumour(s)

P1-3	Patnaik grading of mast cell tumour P1 - low, P2 - intermediate, P3 - high
PM	Postmortem
US	United States
95% CI	95% confidence interval

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

ZS, CT, DCB, AG, DON were responsible for the conception and design. JL/BS were responsible for collation of the datasets. ZS carried out the analysis and drafting the manuscript. All authors were involved in editing the manuscript and gave approval of the published version. Corresponding author: ZS.

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Data availability

The dataset(s) supporting the conclusions of this article is(are) available in the Bette M. Morris Data Commons & Biorepository, <http://datacommons.morrisanimalfoundation.org/> (36)

Declarations

Ethics approval and consent to participate

Informed consent was given by dog owners and veterinarians for collection of medical records and biological samples with overall study approval by the Morris Animal Foundation Welfare Advisory board, described in full elsewhere [33]. Ethical approval was granted by the Royal Veterinary College Social Science Research Ethical Review Board (URN SR2023-0175) for the use of GRLS data for this study.

Consent for publication

All authors have approved the manuscript for submission, and we can confirm the manuscript has not been published or submitted elsewhere.

Competing interests

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