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ORIGINAL ARTICLE

Epidemiology of canine cutaneous round cell tumours on the canary archipelago in Spain

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Abstract

In this study we undertook a comprehensive analysis of a Pet Tumour Registry of the Canary Archipelago (PTR-CA) in Spain to investigate the epidemiology of canine cutaneous round cell tumours. From a database of 2526 tumours collected from 2003 to 2020, we conducted a longitudinal analysis of the main trends in diagnosis, age, multiplicity and anatomical distribution as well as a case–control study comparing these cases with the contemporaneous canine population of the Canary Archipelago to analyse breed distribution. In line with former studies, we found histiocytomas mostly affect young dogs (2, IQR 1–5) and mast cell tumours affect middle-to-old dogs (8, IQR 6–10) with grade 1 affecting at younger ages (6.5, IQR 6–8) than both grade 2 (8, IQR 6–10 years) and grade 3 (9, IQR 7–11). Histiocytomas and plasmacytomas showed a similar anatomical distribution appearing mainly on the face, head and neck regions while mast cell tumours occur mainly on limbs and trunk. Higher risk for mast cell tumours and histiocytomas were found for Bulldog-related breeds such as Boxer ($OR_{MCT} = 23.61$, CI95%: 19.12–29.15, $OR_{HCT} = 10.17$, CI95%: 6.60–15.67), Boston Terrier (OR_{MCT} 19.47, CI95%: 7.73–49.05, OR_{HCT} 32.61, CI95%: 11.81–90.07) and Pug (OR_{MCT} 8.10, CI95%: 5.92–11.07, OR_{HCT} 7.87, CI95%: 4.66–13.28) while Chihuahua dogs showed significantly less risk (OR_{MCT} 0.18, CI95%: 0.09–0.33, OR_{HCT} 0.41, CI95%: 0.21–0.78). Notably, the Canarian Mastiff, a local breed, had a low risk of suffering from a mast cell tumour which raises the question of whether this relates to a genetic peculiarity of this breed or some husbandry and environmental factor.

KEYWORDS
breed, cancer, cutaneous neoplasia, epidemiology, histiocytoma, mastocytoma, mast cell tumour, neoplasia, pathology report, plasmacytoma, round cell, skin tumour, tumour, veterinary

1 | INTRODUCTION

Skin tumours alongside mammary tumours are the most frequently diagnosed cancers of the canine population.[1–10] The cutaneous round cell tumour (CRCT) group commonly includes canine cutaneous histiocytoma (HCT), cutaneous lymphoma (LYM), plasmacytoma (PLA) and mast cell tumours (MCT). Less commonly reported round cell histotypes include transmissible

venereal tumour, histiocytic sarcoma melanoma and neuroendocrine tumours.[11]

Previous studies conducted on several countries such as the United States,[12,13] Denmark,[14] Romania,[15] Switzerland,[16] Portugal,[17] Korea[18] and Japan[19] have described the epidemiology of several canine skin tumours including MCT and, to a lesser extent, HCT and PLA. Additionally, other studies in the United States,[20–23] the United Kingdom,[24–26] Italy,[27] Poland,[28,29] Portugal,[30] Austria,[31] Croatia[32] and Australia[33,34] have focused specifically on different aspects of MCT epidemiology such as the association of breeds, age or anatomical distribution and the presence of simultaneous MCT. In the case of PLA, five studies from the United States[35–39] and one conducted on The Netherlands[40] have covered different aspects of its epidemiology in dogs. However, less attention has been paid to HCT with just one single specific study.[41]

Nonetheless, with the exception of the Norwegian Canine Cancer Project,[2] the Swiss canine cancer registry[8,16] and the study of Villamil et al,[12] all studies analysed samples of less than 600 MCT, less than 300 HCT and less than 100 cases of PLA.

The main paper of the Swiss canine cancer registry[8] covered a period from 1955 to 2008. The same group subsequently published a paper focused on skin tumours which covered a 5-year period from 2008 to 2013.[16] The Villamil et al study[12] also analysed data obtained from a larger period of time (1964 to 2002) but an important limitation reported by the authors was that the method of diagnosis was not always reported so tumour diagnosis could represent anything from a histologic diagnosis to a clinical impression.

Mochizuki et al[23] included a larger sample of MCT and the SAVSNET tumour registry[9] included larger samples of MCT, HCT and PLA but neither provided a denominator suitable for assessment of the risk for MCT, HCT and PLA in the whole population.

This study aims to enrich the existing literature with a new epidemiology paper conducted in Spain, where no study of similar characteristics has been conducted so far, in order to obtain a clear depiction of the epidemiology of these CRCT in the Spanish region of the Canary Archipelago.

The aims of this study were to: (a) evaluate the frequency of CRCT in the whole collection of tumours diagnosed by the Anatomical Pathology Diagnostic Service (APDS) of the Faculty of Veterinary Sciences of the ULPGC as well as the main trends followed by this CRCT over the study period; (b) analyse age at diagnosis of the different tumour histotypes and its relation with grade in the case of MCT; (c) assess anatomical distribution of the different tumour histotypes; (d) analyse the presence of simultaneous MCT; (e) analyse the relation of the different breeds and different grades of MCT; (f) analyse variable 'breed' adjusted by sex and island as a risk factor for MCT; (g) analyse variable 'breed' adjusted by sex and island as a risk factor for HCT; (h) analyse variable 'sex' adjusted by island as a risk factor for PLA.

2 | METHODS

2.1 | Study design and description of the study populations

The focus of this study is MCT, HCT, and PLA. LYM and other less frequently diagnosed CRCT cases were excluded as the numbers of these groups were not considered large enough to conduct an appropriate analysis of these histotypes.

The study case definition was: any tumour from a dog with a histopathological diagnosis (light microscopy examination of samples processed by the haematoxylin and eosin protocol) of a MCT, HCT or PLA affecting the skin and / or subcutis of a dog. For MCT, cases in which toluidine blue and Giemsa stains were required to make a diagnosis were included. Both cutaneous and subcutaneous MCT were included in the study although no differentiation was made between them. Tumours without a confirmed diagnosis by the histological examination process previously described (for instance those requiring immunohistochemistry to be confirmed) were excluded. Similarly, reports with a diagnosis of MCT, HCT or PLA obtained by cytological interpretation or affecting locations different from the skin and/or subcutis were excluded.

Data for this work was obtained from the diagnostic pathology reports from the APDS of the Faculty of Veterinary Sciences of the ULPGC[42] during the study period 2003 to 2020 as well as from the Canary registry of animal identification (ZOOCAN), a centralized web-based registry, managed by the Regional College of Veterinary Surgeons, in which veterinary practitioners are legally required to register all companion animals under their care.[43]

This study was structured in two parts for which different subsets of data were used as explained below.

In the first part, a longitudinal analysis of the relative proportions of the different CRCT within the case cohort was carried out. For each tumour type, the breed, age at diagnosis and anatomical distribution was evaluated and compared.

Additionally, for MCT, we studied the distribution and trend of multiplicity (dogs with more than one simultaneously diagnosed MCT) as well as the different MCT grades reported according to Patnaik's 3-tier histopathological approach.[44] In particular, we analysed the distribution of MCT of different grades on different breeds, for which we only considered those breeds with, at least, two cases of grade 1 MCT or grade 3 MCT or both. HCT and PLA were not analysed for multiple tumours given the small number of cases.

Specifically, this part of the study included a total of 2526 CRCT distributed as shown in Table 2.

The second part of the study consisted of a case–control study where we compared a selection of dogs with a diagnosis of, at least, one the three aforementioned histotypes (MCT case group, HCT case group and PLA case group) with a reference population (control group) obtained from ZOOCAN with the goal of evaluating the effect of the variables breed, sex and island as risk factors for these

TABLE 1 Number of cases and controls by the year of birth. For the case–control study, dogs were selected by year of birth. Different periods (in bold) were chosen for the analysis of the different histotypes in order to obtain a larger number of controls than cases as well as to have at least 10 cases by histotype, except for Plasmacytoma (PLA), on a yearly basis. In this sense, Mast cell tumours (MCT) were analysed in dogs born on the period 2000–2015, Histiocytoma (HCT) in dogs within the period 2000–2018 and Plasmacytoma (PLA) were studied on dogs born between 2000 and 2012. Note that this is not the number of tumours diagnosed but the number of dogs born in these years that developed any of these tumours later in life

Year of birth	Dogs from the control group	Dogs with an HCT	Dogs with a MCT	Dogs with a PLA
2000	191	10	66	6
2001	201	13	59	6
2002	326	12	53	4
2003	491	26	46	8
2004	660	29	68	6
2005	1101	35	68	4
2006	1723	36	78	11
2007	2652	40	79	12
2008	4148	43	90	6
2009	7371	46	86	5
2010	21 873	61	78	6
2011	34 560	44	63	7
2012	33 830	35	46	9
2013	34 447	32	43	3
2014	34 801	27	26	2
2015	35 249	10	11	2
2016	35 009	23	4	0
2017	32 400	12	2	0
2018	30 221	12	2	0
Total	311 254	546	968	97

TABLE 2 Relative proportions of the different cutaneous round cell tumours diagnosed over the study period 2003–2020

Histological type	*n*	Proportion (CI95%)	OR per year (CI95%)[a]	Trend test *p*-value
Histiocytoma	668	26.44% (24.73%; 28.21%)	0.94 [0.93, 0.96]	<0.0001
Mast cell tumour	1712	67.78% (65.91%; 69.60%)	1.05 [1.03, 1.06]	<0.0001
Plasmacytoma	146	5.78% (4.90%; 6.76%)	1.03 [1.00, 1.07]	0.0841

[a]An OR >1 means an increasing frequency of diagnosis while a value of OR <1 implies a decreasing frequency. OR with a CI95% including one means a stable tendency with no significant changes either downwards or upwards.

histotypes. Crossbreed dogs were the base category for breed analysis while female dogs and the island of Gran Canaria were the ones used for analysing sex and island as risk factors.

In order to facilitate a comparison that reduced age related bias, dogs in the control group were selected in such a way that their birth years were in the same range as the birth years of the cases.

Additionally, as can be seen in Table 1, we chose a study period for this part of the study ranging from 2000 to 2018 given that dogs born later (in 2019 onwards) were considered to be at low risk from any of the histotypes under study (MCT, HCT or PLA). Taking into consideration prior literature regarding the age at diagnosis of each tumour we used slightly different study periods for each tumour type. The precise study periods were chosen based on having at least 10 cases for the HCT group and the MCT group as well as breeds with at least four cases for either MCT and HCT. On the PLA case group, we included years with at least 4 cases given that the study for this histotype was limited to the sex as a risk factor. Therefore, the study period for the MCT, HCT and PLA cases groups run from 2000 to 2015, 2000 to 2018 and 2000 to 2012, respectively.

It should be emphasized that Table 1 shows number of dogs by year of birth instead of number of tumours by year of diagnosis. For instance, in 2005, there were 1101 dogs from the control group born that year as well as 35, 68 and 4 dogs born also in 2005 that ended up suffering from an HCT, a MCT or a PLA, respectively, later in life.

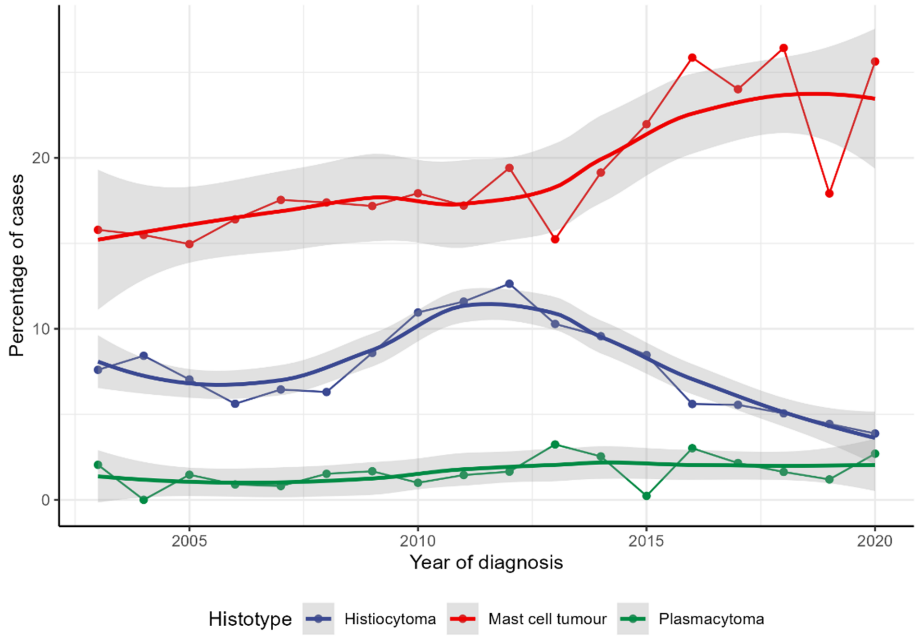

FIGURE 1 Percentage of the different histotypes with respect to the total number of tumours over the study period.

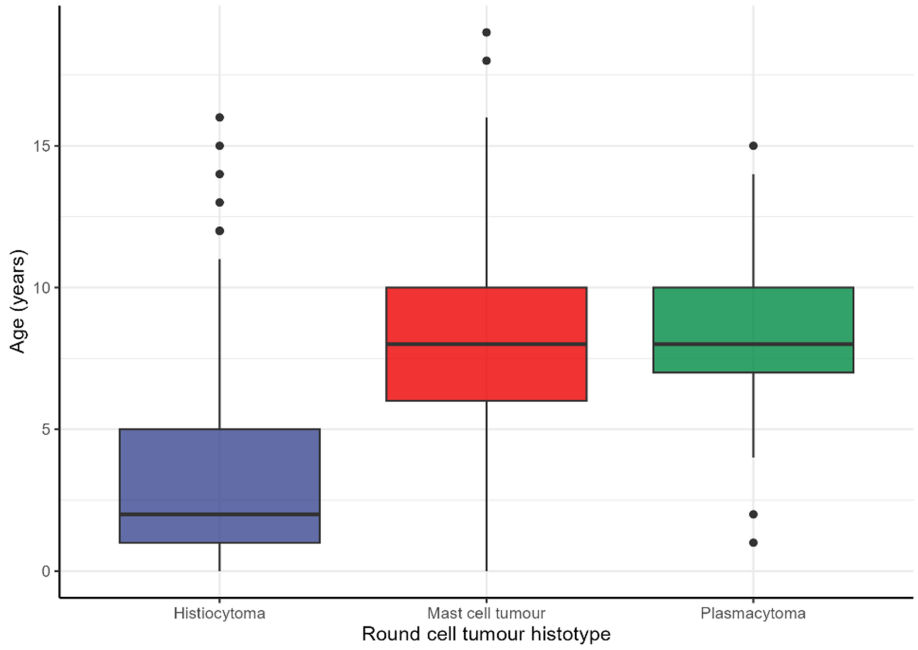

FIGURE 2 Median (IQR) of age by histotype. Median (IQR) was 2^{1-5} for Histiocytoma, 8^{6-10} for Mast cell tumour and 8^{7-10} for Plasmacytoma. Differences between these ages were significant (Kruskal-Wallis test Chi square = 753.4, $p < 0.001$, df = 2), and post hoc pairwise multiple comparisons showed that the age at diagnosis for Histiocytoma was significantly lower than that of Mast cell tumour and Plasmacytoma (Conover test $p < 0.001$ in both cases). Between Mast cell tumour and Plasmacytoma there was no significant difference ($p = 0.478$).

Also, for this reason, numbers on the three right columns in Table 1 tend to descend as the year of birth gets close to 2018 given that, the younger the animal, the less is the chance of being affected by a tumour.

Concerning the area under study, the Canary Archipelago is an Autonomous Community in Spain located in the Atlantic Ocean about 1500 km southwest of the mainland. There are eight islands with a total population in 2021 of 2.172.944 people[45] with 80% of people living in the islands of Gran Canaria and Tenerife where the two main metropolitan areas, Las Palmas de Gran Canaria and Santa Cruz de Tenerife are located.

2.2 | Statistical analysis

Both exploratory and statistical analysis were performed with the R Language and Environment for Statistical Computing, version 4.1.2.[46] Categorical variables were summarized as numbers and percentages; age was expressed as median and interquartile range. The Cochran-Armitage trend test was used for assessing the presence of increasing or decreasing trend in proportions. Increase (or decrease) of odds-ratio per year with its 95% confidence interval was reported to assess the magnitude of the trend. Association in contingency tables was also assessed by chi-squared test.

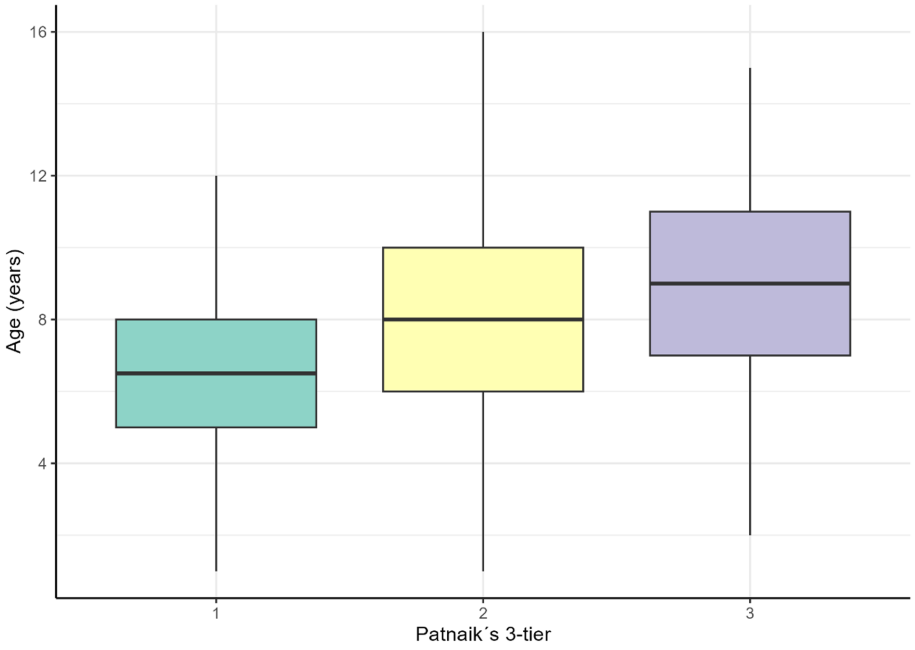

FIGURE 3 Median (IQR) of age by Patnaik's 3-tier histopathological approach. Median (IQR) was 6.5[5–8] for Grade 1, 8[6–10] for Grade 2 and 9[7–11] for Grade 3. Differences between these ages were significant (Kruskal-Wallis test Chi square = 21.4, $p < 0.001$, df = 2), and Conover post hoc pairwise multiple comparisons resulted in significant differences between all groups ($p = 0.0004$ for grade 2 vs. grade 1, $p < 0.0001$ for grade 3 vs. grade 1 and $p = 0.0097$ for grade 3 vs. grade 2).

TABLE 3 Anatomical distribution of Mast cell tumours, Histiocytomas and Plasmacytomas. Anatomical distribution of Mast cell tumours, Histiocytomas and Plasmacytomas. Firstly, an overall analysis of the frequency distribution of histotypes between the different anatomical regions showed significant differences between them (chi-squared = 344.7, df = 10, $p < 0.0001$). Secondly, multiple comparison post-hoc chi-squared analysis revealed that differences between the anatomical distributions of HCT and PLA were not significant ($p = 0.38$), but both distributions differed significantly from that of MCT ($p < 0.0001$)

Location	Mast cell tumour	Histiocytoma	Plasmacytoma
Limbs	602 (36.4%)	205 (31.8%)	41 (28.9%)
Trunk	632 (38.2%)	148 (22.9%)	26 (18.3%)
Face, head and neck	221 (13.3%)	282 (43.7%)	68 (47.9%)
Perianal and scrotum region	177 (10.7%)	4 (0.6%)	2 (1.4%)
Tail	24 (1.4%)	6 (0.9%)	5 (3.5%)

Post-hoc chi-square tests with Bonferroni adjustment were used for pairwise comparisons when significant differences were detected between groups. Shapiro–Wilk test was used for testing normality. Kruskal-Wallis test was used for testing if age was equally distributed in several groups. Multiple post-hoc comparisons after Kruskal-Wallis test were performed using Conover-test. Logistic regression analysis was used to evaluate the association of dog breed with the risk of MCT and HCT, adjusted by island and sex, and odds ratios with 95% confidence intervals were reported. For PLA, logistic regression was used to analyse sex, adjusted by island, as a risk factor. In all tests, p-values lower than 0.05 were considered as statistically significant.

TABLE 4 Anatomical distribution of Mast cell tumours by grade according to Patnaik's 3-tier histopathological approach. An overall analysis of the frequency distribution of the different grades of Mast cell tumour between the different anatomical regions showed no significant differences between them (chi-squared = 14.60, df = 10, $p = 0.14$)

Location	Grade 1	Grade 2	Grade 3
Trunk	25 (54.3%)	452 (38.8%)	52 (37.7%)
Limbs	9 (19.6%)	423 (36.3%)	41 (29.7%)
Face, head and neck	8 (17.4%)	151 (13.0%)	25 (18.1%)
Perianal and scrotum region	4 (8.7%)	119 (10.2%)	19 (13.8%)
Tail	0 (0.0%)	19 (1.6%)	1 (0.7%)

3 | RESULTS

3.1 | Results from the longitudinal study

(a) Cutaneous round cell tumour distribution and evolution over the study period

Over the study period 2003–2020, 2526 CRCT, diagnosed by histology, were analysed. The whole tumour histotypes (MCT, PLA, HCT), distributed as shown in Table 2, comprised for 28.83% of all skin and subcutis tumours diagnosed by the APDS over the same period.

Table 2 shows the tendencies to the changes in the relative proportion of MCT, HCT and PLA diagnosed over the study period. For HCT, we found a significant downward tendency (OR <1, p-value <0.0001) while, for MCT, the tendency was also significant but upward (OR >1, p-value <0.0001). No significant trend (p-value = 0.084) was detected for PLA.

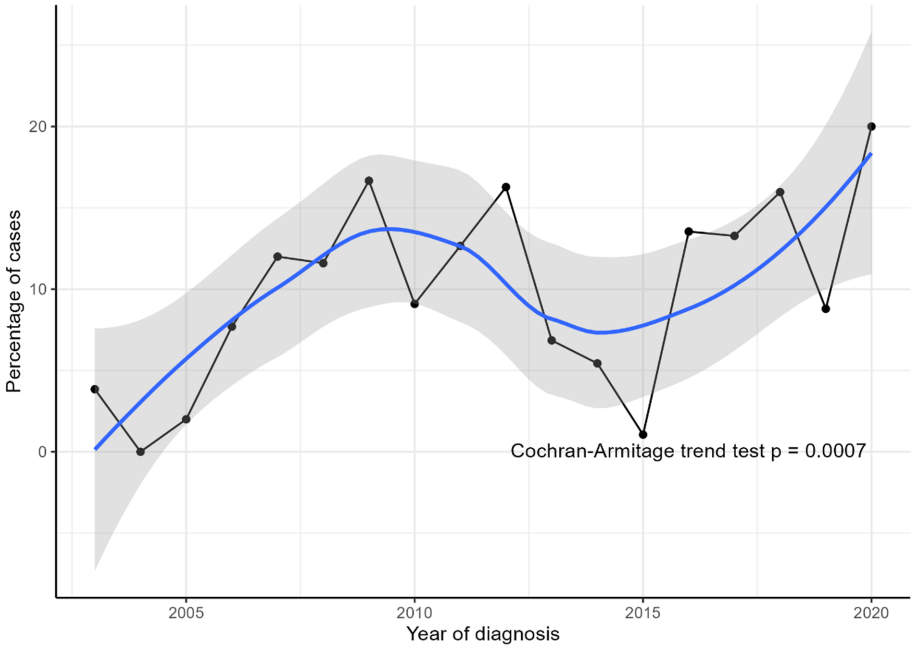

FIGURE 4 Percentage of dogs with multiple simultaneously diagnosed Mast cell tumours.

The relative proportions of each histotype (MCT, HCT and PLA) was compared with the whole collections of tumours diagnosed every year on the APDS. The tendency for MCT went from 15.9% in 2003 to 25.9% in 2020. On the contrary, diagnosis of HCT followed a downward tendency of −3.72% (from 7.6% to 3.9%). Finally, the difference for PLA went from 2.1% in 2003 to 2.7% in 2020. It should be noted that the relative proportions shown in Table 2 were related to the total of skin and subcutis tumours different from MCT, HCT and PLA while the relative proportions shown in Figure 1 were calculated over all the different kinds of tumours (not only skin and subcutis tumours) diagnosed on the APDS over the study period.

Concerning the different grades of MCT, this information was available on 1394 reports from which 47 (3.4%) were described as grade 1, 1206 (86.5%) as grade 2 and 141 (10.1%) as grade 3.

(b) Age at diagnosis

As shown in Figure 2, MCT and PLA were diagnosed at 8-year-old dogs (IQR 6–10 and 7–10 respectively) while HCT were diagnosed at younger ages (2, IQR 1–5). Significant differences were detected (Kruskal-Wallis test Chi square = 753.4, $p < 0.001$, df = 2) and post-hoc Conover test was applied for pairwise multiple comparisons resulting in significant differences between MCT and HCT ($p < 0.001$), and between PLA and HCT ($p < 0.001$) but with no significant differences between MCT and PLA ($p = 0.478$).

Concerning age and MCT grade, Figure 3 shows that grade 1 MCT were diagnosed at younger ages (6.5, IQR 6–8) than both grade 2 (8, IQR 6–10 years) and grade 3 (9, IQR 7–11) MCT.

These differences were statistically significant (Kruskal-Wallis test Chi square = 21.4, $p = 0.000023$, df = 2) and post-hoc Conover test was applied for pairwise multiple comparisons resulting in significant differences between all groups ($p = 0.0004$ for grade 2 vs grade 1, $p < 0.0001$ for grade 3 vs grade 1 and $p = 0.0097$ for grade 3 vs grade 2).

TABLE 5 Breed distribution of different Mast cell tumours grades according to Patnaik's 3-tier histopathological approach. For this analysis, only breeds with at least two cases of Grade 1 or Grade 3 Mast cell tumour or both were included

Breed	Grade 1	Grade 2	Grade 3
Crossbreed	14 (3.1%)	381 (84.7%)	55 (12.2%)
Boxer	14 (6.2%)	198 (87.6%)	14 (6.2%)
French Bulldog	3 (2.2%)	122 (89.7%)	11 (8.1%)
Pug	2 (3.1%)	60 (92.3%)	3 (4.6%)
Labrador Retriever	4 (6.8%)	53 (89.8%)	2 (3.4%)
Yorkshire Terrier	1 (2.3%)	35 (79.5%)	8 (18.2%)
Staffordshire Bull Terrier	1 (2.3%)	39 (90.7%)	3 (7.0%)
Shar-Pei	1 (2.6%)	27 (71.1%)	10 (26.3%)
Bull Terrier	1 (5.3%)	15 (78.9%)	3 (15.8%)
Canarian Mastiff	0 (0.0%)	14 (82.4%)	3 (17.6%)
Rottweiler	0 (0.0%)	6 (66.7%)	3 (33.3%)
Total	41 (3.7%)	950 (85.9%)	115 (10.4%)

(c) Anatomical distribution of the different tumour histotypes

The three types of tumours histotypes showed different frequency distributions across the anatomical locations considered (Table 3, chi-squared = 344.69, df = 10, $p < 0.0001$) and the multiple comparison post-hoc chi-squared analysis revealed that the differences between the anatomical distributions of HCT and PLA were not significant ($p = 0.38$), but both distributions were significantly different from that of MCT ($p < 0.0001$). Table 3 shows that the highest proportion

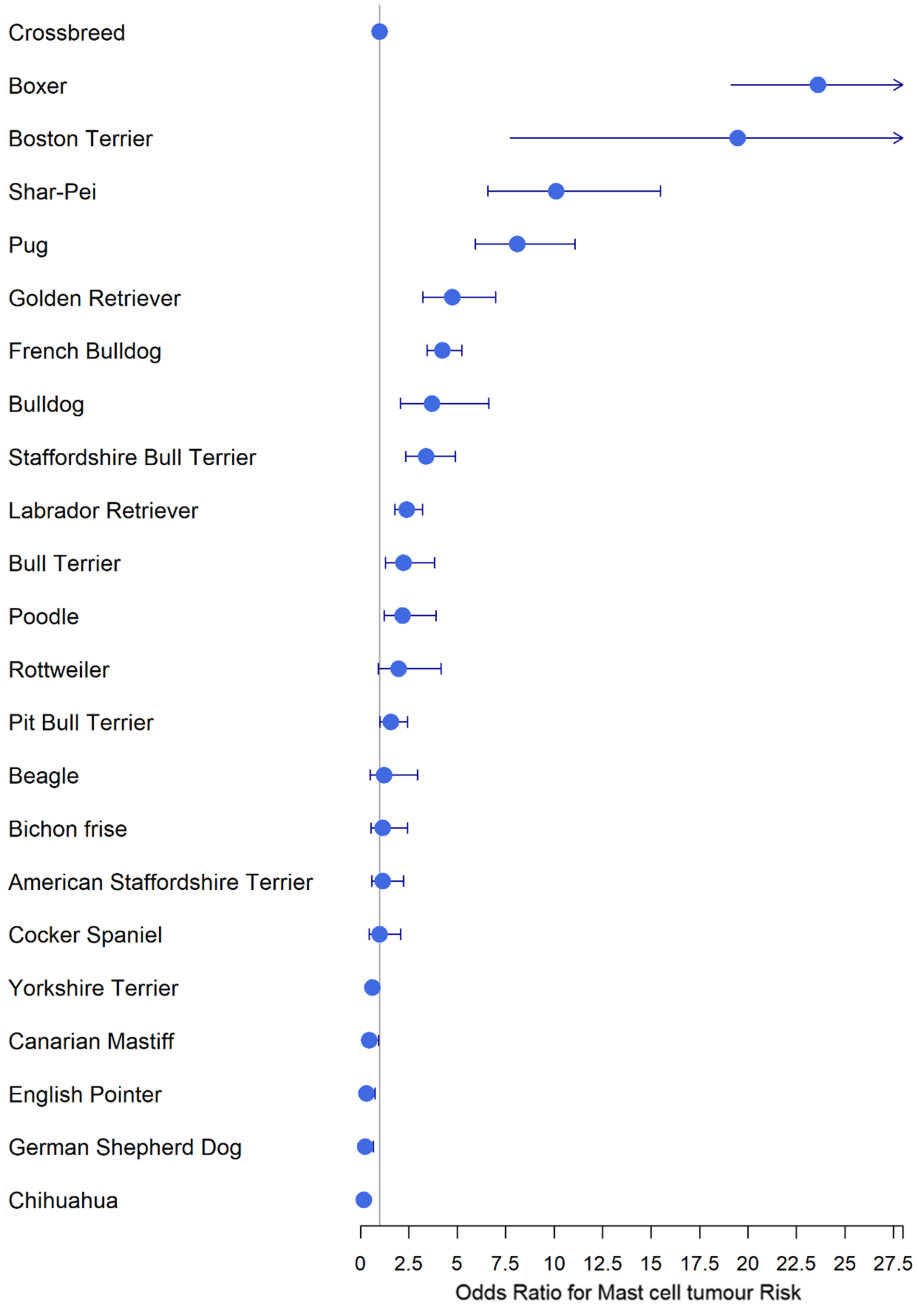

FIGURE 5 Odds Ratios (± 95% confidence intervals) for Mast cell tumour risk by dog breed when compared with crossbreed dogs (baseline), adjusted by island and sex.

of HCT and PLA (43.7% and 47.9% respectively) occurs on the face, head and neck regions, compared to only 13.3% of MCT. MCTs, in turn, occur more frequently than HCT and PLA on the limbs, trunk and perianal and scrotum regions.

Finally, we evaluated whether there were differences in the anatomical distribution of MCT by grade but none were identified (chi-squared = 14.60, df = 10, *p*-value = 0.14), as shown in Table 4.

(d) Multiple MCT

Longitudinal changes in the frequency of dogs being diagnosed with more than one MCT simultaneously evolution is shown in Figure 4. The proportion of animals affected by more than one MCT simultaneously increased markedly over the study period from 3.8% in 2003 to 20% in 2020 (Supplementary Table 1) in such a way that the odds of having multiple MCTs increased by 6% on average each year (OR = 1.062, CI95% [1.03, 1.1])

(e) Breeds and MCT grade

We found an association between breed and MCT grade (*p*-value = 0.0106), but post-hoc pairwise comparisons between breeds were not carried out due to the insufficient number of cases to perform this test.

As shown in Table 5, for grade 3 MCT, Shar-Pei and Rottweilers showed the highest proportion and French Bulldog, Staffordshire Bull Terrier, Boxer and Pug were diagnosed least frequently. Concerning grade 1 MCT, Boxer and Golden Retrievers obtained the highest proportions.

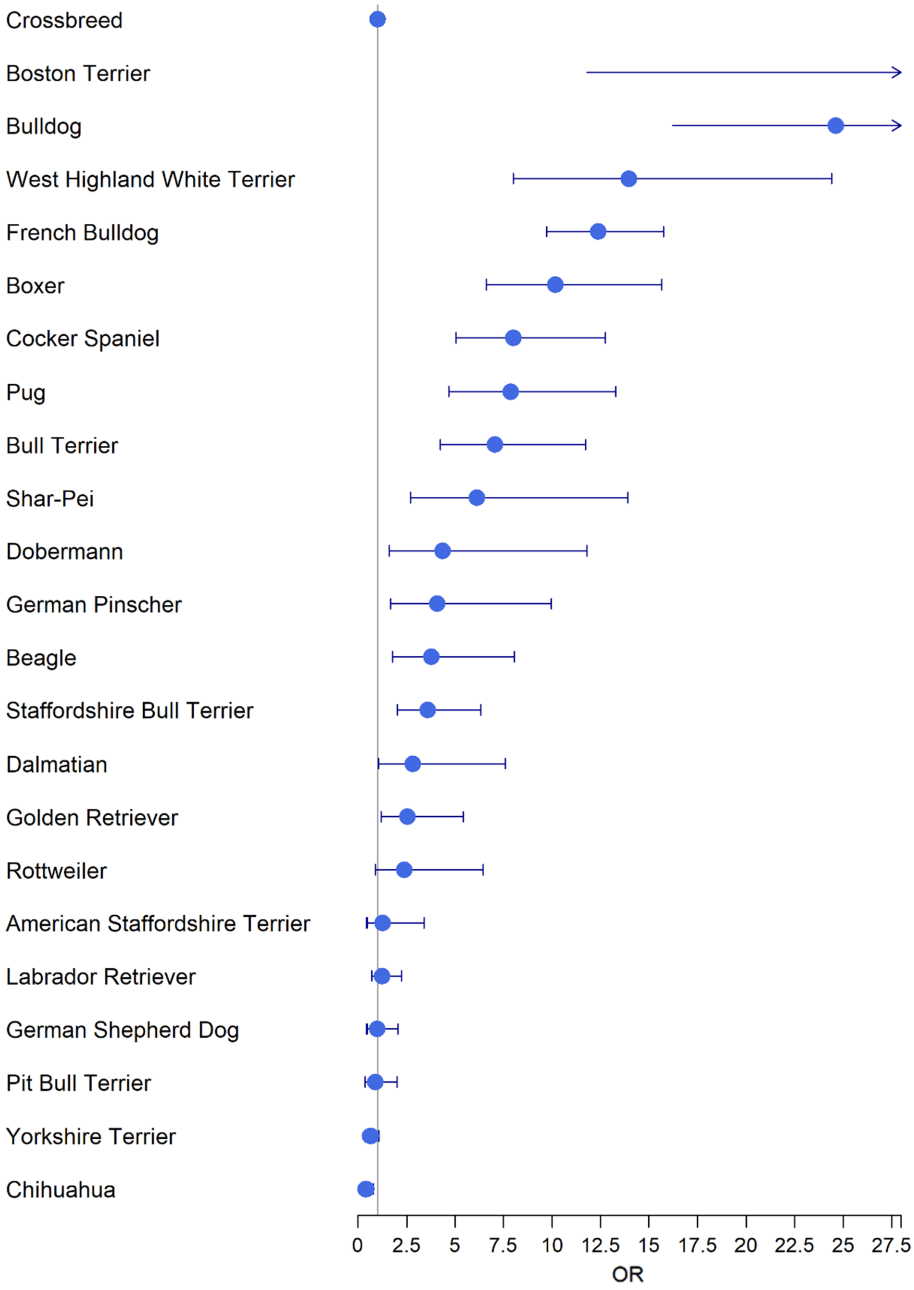

FIGURE 6 Odds Ratios (± 95% confidence intervals) for Histiocytoma risk by dog breed when compared with crossbreed dogs (baseline), adjusted by island and sex.

3.2 | Results from the case–control studies

This section describes the results of the case–control studies. Variable breed adjusted by sex and island was analysed for MCT (Figure 5 and Supplementary Table 2) and HCT (Figure 6 and Supplementary Table 3) cases while only sex, adjusted by island, was analysed for PLA cases (Supplementary Table 4).

Concerning the risk associated with the island upon which the dogs lived, all islands showed a lower risk than Gran Canaria (base category) for MCT. For HCT, the islands of Tenerife, Lanzarote and La Palma showed a lower risk while, for PLA, only the island of Tenerife showed a lower OR than Gran Canaria.

(f) MCT: Breed adjusted by sex and island

Twelve breeds had an increased odds of being diagnosed with an MCT compared to crossbreed dogs. In particular, Boxer (OR 23.61, 95% CI 19.12–29.15), Boston Terrier (OR 19.47, 95% CI 7.73–49.05), Shar-Pei (OR 10.09, 95% CI 6.59–15.47), Pug (OR 8.10, 95% CI 5.92–11.07) and Golden Retriever (OR 4.74, 95% CI 3.22–6.98) were the five breeds with the highest OR. On the contrary, only five breeds obtained a significant OR below one. Chihuahua (OR 0.18, 95% CI 0.09–0.33), German Shepherd (OR 0.24, 95% CI 0.09–0.66), English Pointer (OR 0.31, 95% CI 0.13–0.76), Canarian Mastiff (OR 0.45, 95% CI 0.21–0.95) and Yorkshire Terrier (OR 0.61, 95% CI 0.44–0.86).

Male dogs showed lower odds of developing a MCT compared to female dogs (OR 0.81, 95% CI 0.71–0.93).

(g) HCT: Breed adjusted by sex and island

Fourteen breeds had higher odds of being diagnosed with an HCT compared with crossbreed dogs. Higher risk was observed for Boston Terriers (OR 32.61, 95% CI 11.81–90.07), Bulldog (OR 24.6, 95% CI 16.23–37.30), West Highland White Terrier (OR 13.97, 95% CI 8.00–24.40), French Bulldog (OR 12.38, 95% CI 9.71–15.76) and Boxer (OR 10.17, 95% CI 6.60–15.67).

On the contrary, Chihuahua was the only breed showing decreased odds (OR 0.41, 95% CI 0.21–0.78).

Male dogs had higher odds than female dogs (OR 1.27, 95% CI 1.07–1.52).

(h) PLA: Sex adjusted by island

Sex was analysed as a risk factor for developing PLA but no significant differences were observed between male and female dogs (OR 1.50, 95% CI 0.99,2.28).

4 | DISCUSSION

This study describes the epidemiology of a large sample of CRCT (MCT, HCT and PLA) diagnosed on the Canary Island region in Spain from 2003 to 2020 and it is one of the longest studies of this kind within the published literature.

Our results showed a longitudinal increase in the proportion of MCT compared to all tumours as well as a decrease in the proportion of HCT diagnosed over the study period. A plausible reason for these tendencies could be related, at least in part, to a change in the age distribution of the canine population of the Canary Archipelago resulting in a slightly older population. In this sense, neutered rate on the group of dogs suffering from any tumour tripled from 10.3% in 2003 to 32.8% in 2020 (Supplementary Table 5) which would lead to a decrease in new litters and new puppies in the canine population. Additionally, a recent study[46] has shed light over the increasing popularity of importing rescue dogs (overseas adoptions), especially crossbreed young dogs (up to 2 years old) into the UK from different countries like Spain. Consequently, along with a higher neutered rate, the removal of these young animals from the Spanish canine population could be playing a role on the aging of this population favouring an increase in the diagnosis of tumours that more commonly affect middle-to-old dogs such as MCT[6,16,18,23,26,27,29–31] and also a decrease in tumours typically diagnosed in young dogs such as HCT.[6,16–18,41]

Another reason could relate to a better education or the public being more engaged with cancer diagnosis and treatment generally. In this sense, the availability of two specifics drugs for MCT treatment (masitinib and toceranib) since 2009[47,48] could have encouraged veterinary practitioners to diagnose and treat these kinds of tumours more than they used to. Additionally, a better knowledge of HCT behaviour and their tendency to regress spontaneously[49] as well as the high chance of being diagnosed by cytology could be reasons for the downward tendency of HCT diagnosed over the study period.

Concerning age at diagnosis, in our study, MCT were diagnosed on an average age of 8.38 years old which is consistent with former studies[6,16,18,23,26,27,29–31] although one study found average age being older (around 11 years old).[15]

Also, our results analysing differences in age depending on the grade of MCT were similarly consistent with other studies[23,29] in that the proportion of high grade MCT increases with advancing age. In this regard, the previously described aging of the canine population in our region could explain, at least partially, why we obtained smaller proportion of grade 1 MCT (3.4%) and higher ones of grade 2 MCT (86.5%), when compared with previous works[6,14,19,23,30,34] that obtained results ranging from 12.9% to 33.3% for grade 1 and from 33.6% and 76.3% for grade 2. However, our results are in this case consistent with the recent SAVSNET tumour registry[9] which obtained a proportion of grade 1 and 2 MCT of 4.7% and 92.1% respectively.

When it comes to age at diagnosis of HCT, our study also found similar results with prior literature[6,16–18,41] although two studies reported an average age of greater than 5 years,[1511] at diagnosis. Finally, our result for average age for PLA diagnosis was also in line with former publications.[11,35–37,39,40]

Concerning anatomical distribution, our results showed that around 75% of MCT were located evenly on the trunk region and on the limbs while the other 25% were located either on the face, neck and head and on the perianal and scrotum region with similar relative proportions between the different parts of the trunk (thorax and abdomen) but with a clear difference in favour of the hindlimbs vs forelimbs. The reasons for these locational differences are still unknown.

In this sense, in spite of the different ways in which former studies[9,14,16,19,21,27–29,32,33] show results of anatomical distribution for MCT, a general pattern can be observed; most studies found around 30% of MCT affecting both limbs with hindlimbs found to be consistently more frequently affected except in one study from Korea[19] which found extremities to be the first anatomical location with a proportion of 40.9% and another from Italy[27] where only 15.2% of MCT were located on the limbs. Additionally, former studies found MCT to be located on the trunk region with a frequency ranging from 19%[16] to more than 50% of cases[21,29] without a clear difference of any particular region (thorax and abdomen). Finally, all studies showed a frequency of less than 20% for the head-face-neck area although one paper from Austria[32] emphasized than 70% of MCT were located on the trunk and the head.

In our study we did not find strong evidence that any particular anatomical locations are associated with MCT tumours grade. This is discordant with the prior literature which suggests a greater risk of high-grade MCT for the head, inguinal and perigenital areas.[30,33]

When it comes to HCT and PLA, we found more than 40% of cases located on the head-face-neck area, a clear preponderance for abdomen vs thorax and an equal distribution on the hind vs fore limbs. Other studies found HCT[16,18,41] to be located on the head-face-neck area on a frequency ranging from 28.4% to 53% and PLA[19,35,36,38–40]

from 27.8% to 45.6%. Lower frequencies for these tumours on this location were obtained however in a Korean study[19] (18.2 for HCT on the head–neck area) and on the SAVSNET tumour registry[9] (17.8% for HCT and 13.9% for PLA) although up to 45% of the location for these tumours on this database was reported with the generic term ("skin").

We found that the following breeds are pre-disposed to MCT including Bulldog-related breeds such as Boxer, Boston Terrier, Pug, French Bulldog, Staffordshire Bull Terrier, Bull terrier and Bulldog to have the greatest risk of suffering from a MCT when compared with crossbreed dogs along with Retrievers (Golden and Labrador), Shar-Pei and Poodle. These results are consistent with most of literature[12,16,17,19,20,22,23,25–27,29,32] and in line with the hypothesis formulated by a former 1969 study[20] stating that a common ancestry may be behind the predisposition of these breeds when it comes to be affected the MCT.

Low-risk breeds in our study were the Chihuahua, German shepherd, English Pointer and Yorkshire terrier which have been also described previously as low-risk breeds by the same studies.[12,16,19,22,23,25,26,28,30–32]

We also found Canarian Mastiff, a local breed from this region to be a low-risk breed for MCT. Interestingly, a recent study describing the epidemiology of canine mammary tumours on the Canary Archipelago[50] also found local breeds such as the Canary Warren Hound, Majorero and Canarian Mastiff to be low-risk breeds for these kinds of tumours. Reasons for these low-risks-related findings are still unclear due to the lack of studies covering Canary Islands dog breeds. However, at least in part, the high genetic variability found in the Canary Island breeds[51] and their recent origin from mixed ancestral stock could be playing a role in this regard.

Concerning breed and grade of MCT, different studies tend to confirm the fact that certain breeds predisposed for MCT tend to suffer from low-grade MCT while other breeds less frequently affected by this tumour tend to have high-grade MCT. In our case, we found differences on the distribution of the different grades of MCT and the different breeds although our data was not large enough to conduct more in-depth analyses between the particular breeds. However, we found that among our cases of high-grade MCT, Rottweilers and Shar-Pei were the most frequently diagnosed as was the case in three previous studies[23,28,33] while Boxer, and Labrador Retriever were the most frequent breeds among dogs with a low-grade MCT being these observations also consistent with former studies.[17,23,28] In our case, also Canarian Mastiff, a low-risk breed for MCT showed a slightly higher proportion of grade 3 MCT. As pointed out by Mochizuki et al,[23] the discrepancies in proportions of low and high grade among different breeds may indicate that genetic alterations responsible to MCTs may be different from those contributing to aggressive biological behaviour.

We found less risk of males than females developing an MCT. Former studies had mostly found no differences in this regard[15,19,26,27,30,33] while others found higher risk for females.[29]

Regarding breed and risk of HCT, we also found Bulldog-related breeds mentioned previously for MCT and Retrievers plus the addition of West Highland White Terrier (third breed with greater risk), as well as the Cocker, German Pinscher and Beagle to be at greater risk of developing HCT. Chihuahua was the only breed with a lower OR than crossbreeds.

These results for HCT are consistent with other studies[16,17,41] that found Boxer, French Bulldog and English Bulldog to be at a greater risk of suffering from a HCT while Chihuahua was found as the only breed at lower risk than cross-breeds.

We found male dogs to be at a greater risk of HCT which is adds to the discordance in the literature about the relevance of sex to this tumour type.[15,41]

Our results for sex as a factor risk for PLA revealed no differences in risk due to sex for this tumour type, although the only reference to compare with found a greater proportion of males versus female dogs in a sample of 49 dogs suffering from PLA.[36,37]

Finally, when comparing the results obtained in different islands, we saw a lower risk in all islands when compared with Gran Canaria although this is mostly due to an overrepresentation of cases submitted from Gran Canaria to the APDS as explained below.

Some limitations presented in this study should be mentioned. Firstly, concerning the ZOOCAN database, dogs are typically registered in the system on his first visit to the vet but follow-up information (for instance, changes in the neuter status) is usually not recorded. For this reason, the only data provided by ZOOCAN that we considered reliable enough to be used in this study were the variables year of birth and breed of the dogs. Secondly, it should be noted that breed data used for this study was reported by veterinary practitioners (secondary data) so we should expect some degree of uncertainty in the accuracy of breed identification. So, in order to minimize this error, we chose to indicate that a dog belonged to a specific breed when that breed was clearly specified in the report. Any combination of breeds was considered a crossbreed.

Thirdly, as a pathology-based tumour registry,[52] some degree of bias should be expected when a comparison is made between the cancer profile emerging from the APDS and the actual (unknown) one of the canine population. One reason for this is due to a selection bias by veterinary surgeons in such a way that tumours considered more concerning are more likely to be removed and submitted for diagnosis. In this sense, a selection bias in favour of skin tumours over internal tumours is likely given the easy detection by owners or veterinary practitioners. Additionally, socioeconomic factors could play a role in the sense that paying for an anatomopathological analysis may be impractical for less affluent clients. There may also be some effect of socio-economic status and choice of dog breed.

However, it should be noted that the APDS is a diagnostic service integrated in an academic institution, the ULPGC and is an affordable not for profit service aimed at teaching veterinary pathology to students and thus costs are comparatively low.

Additionally, geographic and logistical reasons have created an overrepresentation of cases from the island of Gran Canaria when compared with the other Canary Islands, due to the fact that the APDS is located in the Faculty of Veterinary Sciences in Gran Canaria,

30 min away from the largest city of the Canary Archipelago, Las Palmas de Gran Canaria, providing a clear advantage for cases submitted from this island when compared to the others hindering our options to conduct an island-by-island analysis on this paper due to the lack of uniformity and representativeness of the different islands.

Finally, a pathological diagnosis is somewhat subjective and there is therefore a risk of pathologist bias that should be taken into account.

In conclusion, this study provides the first epidemiological description of the cutaneous round cell tumours that affect canine population on the Canary Archipelago in Spain. Our findings confirm MCT to be one of the most commonly diagnosed tumour affecting middle-to-old dogs and canine cutaneous histiocytomas as the main tumour histotype of young dogs.

Bulldog-related breeds were the most at-risk breeds of developing non-high-grades MCT while others like Shar-Pei were the most affected by high-grade MCT. These breeds were also found be high-risk breeds for HCT while Chihuahua were found to be protected against both MCT and HCT. Specially interesting in our study was to find Canarian Mastiff, a local breed, to be protected against MCT which could suggest some kind of advantage due to the high genetic variability found in the Canary Island dog breeds.

CELL LINE VALIDATION STATEMENT

No cell lines were used in the current study.

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CONFLICT OF INTEREST STATEMENT

A.E. and P.H. are veterinary pathologist at the APDS. The rest of the authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Figshare at https://doi.org/10.6084/m9.figshare.21407595.

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