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A five-year cohort study on testicular tumors from a population-based canine cancer registry in central Italy (Umbria)

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1 A FIVE-YEAR EPIDEMIOLOGICAL SURVEY ON TESTICULAR TUMORS IN A
2 POPULATION-BASED CANINE CANCER REGISTRY IN CENTRAL ITALY (UMBRIA)

3
4 **Abstract**

5 Canine testicular tumors account for about 90% of tumors affecting the male genitalia. Seminomas
6 (SEM), Sertoli cell tumors (SCT), and interstitial cell tumors (ICT) are the most common histological
7 diagnoses, but their incidence shows high variability among studies. The aim of this study is to report
8 the results, acquired in five years from the population-based Umbria Canine Cancer Registry, on
9 testicular tumors.

10 From 2014 to 2018, 388 testicular tumors (on 1969 total male tumors) were diagnosed. The median
11 incidence was 35 cases/100,000 dogs, with a prevalence of 19,7%. Most tumors were diagnosed as
12 ICT (50%), with fewer SEMs and SCTs (29% and 17%, respectively). Only 3% of tumors were
13 mixed germ cell–sex cord-stromal tumors (MGC-SCST). Ten percent of cases had multiple tumors
14 in the same testicle, with the combination SEM-ICT being prevalent (69.2%). Tumors in
15 cryptorchid testes were 5.9% of the total, mostly SCT (60.9%). Mean age at diagnosis was
16 10.7 ± 2.7 , with similar values for different types of tumor. The most represented breeds were
17 Golden Retriever, Bulldog, and West Highland White Terrier, whereas a decreased risk was
18 observed in Pugs, Poodles, Italian segugio, Boxer and Italian cane corso breeds. A value of <0.3 cm
19 (major diameter) of lesions at the moment of trimming was associated with a final histological
20 diagnosis of tumor.

21 Canine Cancer Registries, if provided with reliable data on the total population, can offer solid
22 information on incidence and prevalence of different types of tumors in specific territories,
23 contributing to the supervision of its inhabitants' health.

24
25 **Key words:** Canine Cancer Registry; testicular neoplasms; incidence; risk factors; dogs.

26 **Background**

27 Testicular tumors are common in dogs, representing about 90% of all tumors diagnosed on male
28 genitalia. (Liao et al., 2009; Nødtvedt et al., 2011) Different epidemiological studies revealed that
29 testicular cancer in dogs is the fourth most common site, after cutaneous, mammary and oral tumors.
30 (Vascellari et al., 2009), being the second most common anatomic site of tumor development in intact
31 males (Liao et al., 2009; Merlo et al., 2008).

32 Canine testicular tumors can arise either from sex-cords stroma (Sertoli cell tumor and interstitial
33 cells tumor, also known as “Leydig cell tumor”), or from germ cells (seminoma, embryonal
34 carcinoma, and teratoma). Mixed tumors, such as mixed germ cell–sex stromal cell tumors (MGC-
35 SCST) and gonadoblastomas, are instead characterized by a mixture of different types of tumor cells.
36 (Meuten, n.d.)

37 Sertoli cell tumor (SCT) originates from Sertoli cells of seminiferous tubules. Macroscopically, these
38 tumors are firm, whitish and usually well demarcated within the testicular parenchyma. Neoplastic
39 cells are arranged in islands or tubules and supported by abundant mature fibrous tissue. These tumors
40 can be utterly categorized into intratubular or diffuse form. (Kennedy P.C., 1998; Meuten, n.d.) These
41 tumors are the most common in cryptorchid testes and are dogs with inguinal hernias are reported to
42 bear a higher tumor risk. (Hayes et al., 1985; Hayes and Pendergrass, 1976). Interstitial cell tumors
43 (ICT) derive from interstitial Leydig cells. Macroscopically, they usually protrude from the cut
44 surface and are yellow/brown in color. Histologically, ICT occur in three main patterns: solid-diffuse,
45 cystic-vascular and pseudoadenomatous. Seminoma (SEM), instead, originates from testicular germ
46 cells. These tumors can be also further classified into the intratubular type, the early stage of tumor
47 development, that can progress into the diffuse type, characterized by large, nodular aggregates,
48 separated by fibrous septa and blood vessels. (Kennedy P.C., 1998; Maxie, 2016; Meuten, n.d.)

49 Different studies investigated on the frequency of the different types of testicular cancer in dogs, but
50 often the inclusion/exclusion criteria and the evaluation of the numerator (the total canine population)
51 are differently assessed, therefore providing non-comparable data. (D’Angelo et al., n.d.; Grieco et

52 al., 2008; Hayes and Pendergrass, 1976; Liao et al., 2009) Dated studies report a prevalence of
53 testicular tumors ranging from 0.91% to 5.8% (Cotchin, 1960; Hahn et al., 1992; Reif et al., 1979),
54 while, more recent studies indicated a higher prevalence range (5.4%-27%). (Grieco et al., 2008;
55 Nødtvedt et al., 2011; Ortega-Pacheco et al., 2006; Svara et al., 2014)

56 In Italy, incidence data on canine tumors are still limited. A first study, published in 2008 by Merlo
57 and colleagues, estimated the incidence of canine tumors in the city of Genoa. The incidence rate (IR)
58 of tumors of the genitourinary tract was of 16.7/100.000 dogs, but no further specifications on
59 testicular tumors were included in the study. (Merlo et al., 2008) In a more recent study from Baioni
60 and colleagues, instead, the IR of SEM (66) and SCT (34) were calculated. (Baioni et al., 2017)

61 Testicular tumors are reported to occur most frequently in adult and old dogs, (Liao et al., 2009)
62 differently from humans, where testicular cancer is the most common tumor among young men (15-
63 40 years old). (Chia et al., 2010) Variability in tumor incidence has been described for several dog
64 breeds as well as for ethnic groups in man, suggesting a genetic component to cancer susceptibility.
65 (Maruthappu et al., 2015; Nødtvedt et al., 2011) Cryptorchidism is considered the principal risk
66 factors for primary testicular tumors development in humans. (Cheng et al., 2018) This is true also in
67 canine species, where also inguinal hernia represents a risk factor. (Hayes et al., 1985)

68 In the last decade, the number of Animal Cancer Registries increased all over the world and also in
69 Italy. (Grüntzig et al., 2015; Manuali et al., 2019; Merlo et al., 2008; Tedardi et al., 2015; Vascellari
70 et al., 2009) The Canine Cancer Registry (CCR) of Umbria (central Italy) was created in 2013. This
71 registry includes information on the histological diagnosis of examined canine lesions, together with
72 other data on breed, sex, age, general status, habitat, environment, diet, date of surgical excision, date
73 of tumor diagnosis, tumor stage (TNM), type of sampling, topography (ICD-O codes), anamnesis and
74 owner address with GIS coordinates.

75 The aim of this study is to report the results on canine testicular tumors acquired from the population-
76 based Canine Cancer Registry of Umbria during a period of five year (2014-2018), including data on
77 relative prevalence of each type of tumor

78 **Materials and Methods**

79 *Data source*

80 The data for this study were collected from the web-based platform of the Canine Cancer Registry
81 (CCR) of Umbria (central Italy). This platform is an integral part of the regional canine demographic
82 registry, which allows an affordable calculation of the whole canine population of the area.
83 Histological diagnoses are all performed in a double-blind fashion; whether a discordance occurs
84 among the two pathologists, a third one will intervene in defining the final diagnosis.

85 The evaluation and classification neoplastic lesions are performed according to the WHO's criteria
86 for canine tumors and the topographical and morphological keys set by the International
87 Classification of Diseases for Oncology (ICD-O). (Kennedy P.C., 1998)

88 Information on dogs demography, breed, sex, age, general status (good/preserved/poor), habitat
89 (urban/rural), environment (apartment/garden/mixed/kennel), diet (wet/dry/mixed), date of surgical
90 excision, date of tumor diagnosis, tumor stage (TNM), source (biopsy/surgery/necropsy), topography
91 (ICD-O codes), anamnesis and owner address with GIS coordinates were obtained. (Manuali et al.,
92 2019) For analytical purposes, dogs diagnosed with testicular tumor were divided in three age groups:
93 young (<6 years old), adult (6 to 10 years old) and old dogs (>10 years old). In order to symbolize
94 the geographical distribution of testicular tumors and to create an appropriate map, the Quantum GIS
95 Geographic Information System (<http://qgis.osgeo.org>) was used. Our analysis started from
96 municipalities in which testicular tumors represented $\geq 20\%$ of the total tumors. They were
97 categorized as follow: 20-39%, 40-60% and 100%.

98

99 *Histological evaluation*

100 Testicles were fixed in 10% neutral buffered formalin. Then, lesions were described (colour,
101 consistency and shape). The major diameter of each parenchymal lesion was measured with a caliper
102 and recorded at the moment of trimming after proper fixation in formalin. Representative samples of

103 the tumor were processed for histopathology. Four μm thick sections were cut and routinely stained
104 with hematoxylin and eosin (HE). The diagnosis was determined in a blind fashion by two
105 pathologists, randomly selected among the group that works for the Canine Cancer Registry. Whether
106 the two pathologists do not agree on the diagnosis, a third one is involved in the final diagnosis.

107

108 *Statistical analysis*

109 Statistical analysis was performed with the One-way analysis of variance (ANOVA). The PMR of
110 testicular tumors, compared to the total number of tumors found in male dogs, was calculated
111 according to Dohoo. (Dohoo I, 2009) Only breeds with more than 25 tumors were selected. The PMR
112 was computed by considering the number of testicular tumors in each breed (b_1), the number of all
113 tumors for the breed (n_1), the number of testicular in each other breed (b_0), and the number of tumors
114 in all other breeds. Given these quantities, the PMR is defined as the ratio of (b_1/n_1) and (b_0/n_0).
115 Only breeds with at least 25 tumors were selected and reported, but all breeds are used each time in
116 the computation of the denominator (b_0/n_0). Confidence intervals at the 95% level are reported for
117 each PMR, and standard deviations computed in the logarithmic scale and with a first-order
118 approximation, yielding non-symmetrical limits in the original PMR scale.

119 To establish a trimming cut-off to allow the private practitioner to formulate with more sensitivity a
120 clinical suspicion of testicular tumor, the analysis of the receiver operating characteristic (ROC) curve
121 on the major diameter meastrimming dimension was performed. ROC analysis quantifies the
122 accuracy of diagnostic tests or other evaluation modalities used to discriminate between two states or
123 conditions, which are here referred to as normal and abnormal or control and case. The analysis uses
124 the ROC curve, a graph of the sensitivity versus 1- specificity of the diagnostic test. The sensitivity
125 is the fraction of positive cases that are correctly classified by the diagnostic test, whereas the
126 specificity is the fraction of negative cases that are correctly classified. The cut-off choice typically
127 falls to the value that identifies the highest correctly classified case proportion. The analysis was
128 carried out for all intratubular cancers without distinction between sertoliomas and seminomas.

129

130 **Results**

131 *Incidence and prevalence of testicular tumors in the sample population*

132 Within the CCR, a total of 1969 tumors were diagnosed in male dogs from 2014 to 2018. Among
133 these, 388 (17.16%) had testicular origin and were included in this study.

134 From 2014 to 2018 the annual incidence (IR) of testicular tumors (number of cases/100,000) in the
135 dogs of Umbria was of 12/100,000, 34/100,000, 37/100,000, 46.9/100,000 and 45.8/100,000. Instead,
136 considering all canine male tumors the annual prevalence was 1.7%, 7.3%, 6.7%, 7.3% and 7.9%.
137 The 5 years prevalence was of 19.7% (388 out of a total of 1969) of all registered tumors in male
138 dogs. General status (good/preserved/poor) of the dog, habitat (urban/rural), environment
139 (apartment/garden/mixed/kennel), diet (wet/dry/mixed), and geographical distribution were
140 examined but did not reveal any noteworthy result.

141

142 *Histological diagnosis of testicular tumors*

143 Of the 388 tumors diagnosed, 194 (50%) were ICT, 113 (29%) were SEM, 68 (17%) were SCT, and
144 13 (3%) MCG-SCST. Most of the diagnosed tumors were solitary; only 24 cases (6%) showed more
145 than one testicular tumor, either in the same testis or bilaterally. Unilateral tumors were detected in
146 350 dogs (97.4%), occasionally exhibiting more than one tumor type within the testicular parenchyma
147 (10%). When multiple tumors were diagnosed within the same testis, the combination SEM-ICT was
148 the most frequently observed (69.2%) followed by SCT-ICT (23.1%) and SEM-SCT (10.2%).
149 Tumors in cryptorchid testes were diagnosed in 23 dogs (5.9%); the most represented were SCT
150 (60.9%) and SEM (17.4%).

151

152 *Dogs with testicular tumors*

153 The age of dogs at the moment of the histological diagnosis of a testicular tumor ranged from 1 to 17
154 years (mean age 10.7 ± 2.7 years). Dogs diagnosed with testicular tumor were divided in three age
155 groups: young (<6 years old), adult (6 to 10 years old) and old dogs (>10 years old). Older dogs were
156 the most commonly affected (264/388; 68%) followed by adult dogs (104/388; 26.8%) and young
157 dogs (20/388; 5.2%). The age-group stratification of testicular tumors is detailed in Table 1. Focusing
158 on the histopathological types of tumor distribution and the age of dogs, graphical profiles were
159 described (Figure 1). Specifically, dogs diagnosed with ICT ranged from 1 to 17 years. Most cases
160 were diagnosed in 11-year-old animals (mode), whereas the median age was of 10.8 ± 2.7 . An ICT
161 diagnosis was increasingly more frequent in dogs aged 7 to 11 years. SEMs were diagnosed in dogs
162 aging from 4 to 17 years; this diagnosis was common in dogs of 11 years (mode), with a median of
163 10.6 ± 2.7 . Similarly, SCTs were diagnosed in dogs ranging from 4 to 17 years of age, with a mode of
164 11 years and a median of 10.5 ± 3.0 . Finally, MGCSCT were diagnosed in dogs between 7 and 14
165 years of age, with a mode of 9 years and a median of 10.7 ± 2.5 . Breed-specific differences in risk for
166 testicular tumors development were found in Golden Retriever, Bulldog, West Highland White
167 Terrier, Mixed breed, German Dachshund, Epaneul Breton, German Shepherd, English setter and
168 Jack Russel Terrier (Figure 2). Instead, a decreased risk was observed in Labrador Retriever, Boxer,
169 Shih Tzu and Pugs. Labrador retriever and German Shepherd are the only breeds, among the one
170 selected, to have a computed PMR below one, the threshold corresponding to no protective nor
171 increased-risk effect. The highest observed PMR refers to the Golden Retriever, with a value of 2,21,
172 thus suggesting an increased risk of testicular tumor for the specific breed. When confidence interval
173 is considered, none of the selected breeds have significant difference with respect to the case of no
174 effect $PMR=1$, potentially due to high variability in the data and the limited sample size for inferential
175 purposes.

176

177 *Major diameter of testicular tumors/lesions*

178 The ROC curve analysis (Figure 3) was conducted on 80 ICT, 58 SEM and 22 SCT. Results showed
179 that all tumors that were not detected during trimming were diagnosed as non-tumors (hyperplasia of
180 interstitial cell, small foci of orchitis, etc.). Moreover, lesions detected during trimming but with a
181 major diameter of 0.1 or 0.2 cm were more likely to have a final non-tumor diagnosis (Table 2). This
182 proportion was inverted with lesions with a diameter >0.3 cm, which was assessed as the cutoff value
183 to distinguish non-tumor testicular lesions from neoplastic ones. Table 2 shows the trimming values
184 and the classification based on the histological diagnosis. The sensitivity values, specificity, the
185 proportion of correctly classified cases, and two likelihood values (LR + for positive values and LR-
186 for negative values) for each trimming value are reported in Table 3.

187

188 **Discussion**

189 - Trimming value could be helpful, but it must be remembered that formalin causes shrinking of
190 tissue, therefore the value is, at now, valid only for the pathologist during trimming procedure.

191 - Unilateral tumors were detected in 97.4% of dogs while 10% had more than one testicular tumor
192 either multiple (different tumors in the same testicle), or one type tumor in each testicle as previously
193 reported. (Lipowitz et al., 1973)

194 - In multiple tumors the combination SEM-ICT accounted the 69.2% of cancer cases. Tumors
195 cryptorchid testes represented the 5.9% of cancer cases with a highest frequency of SCT (60.9%).

196

197

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270

271

272 Fig.1. Graphical representation of ICT, MGC-SCST, SCT and SEM histological diagnosis
273 distribution in different ages in dogs.

274 Fig. 2. Probability Morbidity Ratios for breeds with at least 25 tumor cases in the timeframe
275 considered; error bar reported for confidence intervals at 95% level, with a vertical line at 1 denoting
276 a PMR corresponding to absence of protective/increased-risk effect.

277

278 Figure 3: ROC curve

279

280