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Canine oral fibrosarcoma: Changes in prognosis over the last 30 years?

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1685558> since 2019-01-03T12:52:26Z

Published version:

DOI:10.1016/j.tvjl.2018.09.005

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1 **Review**

2

3 **Canine oral fibrosarcoma: Changes in prognosis over the last 30 years?**

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15 **Abstract**

16 Canine oral fibrosarcoma (oFSA) is a malignant, infiltrating, mesenchymal tumour affecting
17 the oral cavity primarily of medium to large middle aged dogs. The diagnosis often is made late in
18 the course of the disease, due to the frequent caudal location of the tumour, and histopathology is
19 not always sufficient to discriminate undifferentiated oFSA from other poorly differentiated
20 malignant mesenchymal tumours occurring at the same site, especially in small biopsy samples. The
21 literature exclusively relating to oFSA is limited and outcome data following treatment are difficult
22 to compare. The purpose of this article is to provide an overview of the literature spanning the last
23 30 years, specifically with regard to different treatment modalities in their relation to prognosis of
24 canine oFSA.

25
26 Overall, the survival rate for dogs with oFSA has improved in recent years (overall survival
27 247 to 743 days, as opposed to 30 - 540 days in papers published before 2000), probably due to
28 better surgical planning. The major concern in clinical management of canine oFSA is the high
29 local rate of recurrence (up to 57%), whereas metastasis occurs late in about 10-14% of affected
30 dogs. Wide surgical excision is the mainstay of treatment. Initially, the tumour was considered to be
31 radioresistant, but the combination of surgery and radiotherapy seems to be the most promising
32 treatment modality at present. Despite a histopathological diagnosis of a low grade tumour, an
33 aggressive treatment approach is always warranted to cure oFSA, but the ability to control local
34 disease still represents the major challenge.

35
36 *Keywords:* Canine oral fibrosarcoma; En bloc excision; Local recurrence; Prognosis; Radiotherapy

37 **Introduction**

38 Oral tumours represent 6-7% of all canine malignancies and, among these, oral fibrosarcoma
39 (oFSA) accounts for 8-25%, being the third most common malignant neoplasm of the oral cavity in
40 dogs (Liptak and Withrow, 2013). The median age of dogs with oFSA at diagnosis is 8 years, which
41 is slightly younger than dogs diagnosed with malignant melanoma and squamous cell carcinoma of
42 the oral cavity (Liptak and Withrow, 2013). Dogs under 5 years of age at diagnosis are also reported
43 (Todoroff and Brodey, 1979; Hoyt and Withrow, 1984). Medium to large breed dogs (> 20 kg)
44 seem to be more commonly affected. There is no sex predilection, although male dogs are over-
45 represented in some studies (Todoroff and Brodey, 1979; Hoyt and Withrow, 1984). Golden
46 retrievers are over-represented, especially in cases with a variant of the tumour characterised by an
47 aggressive biological behaviour, known as ‘high-low’ oFSA, despite more benign histological
48 features (Ciekot et al., 1994).

49
50 Undifferentiated forms of oFSA may be difficult to distinguish histologically from other
51 poorly differentiated malignant mesenchymal tumours affecting the oral cavity. In these cases,
52 immunohistochemistry (IHC) may be needed to achieve the final diagnosis, even though few
53 specific markers are available (Boy et al., 2005; Smedley et al., 2011; Munday et al., 2017; Ramos-
54 Vara and Borst, 2017).

55
56 Most of the literature on oral tumours in dogs encompasses different histotypes and different
57 treatment modalities; therefore, direct comparisons amongst papers are difficult to conduct. There
58 are relatively few articles that focus exclusively on the treatment of canine oFSA and a more than
59 10 year gap is evident between articles published in the 1990s and recent years (Thrall, 1981;
60 Creasey and Thrall, 1982; Ciekot et al., 1994; Poirier et al., 2006; Frazier et al., 2012; Gardner et
61 al., 2015; Milovancev et al., 2016). The aim of this paper is to review the literature relating to
62 canine oFSA published within the past 30 years, focusing on the changes in treatment, prognosis

and on the improvements made during this time span. Personal experience is also presented briefly (see Appendix: Supplementary Table 1).

Clinical presentation of dogs with oral fibrosarcoma

Oral FSAs in dogs usually appear as firm, pink to red, swellings or masses, frequently involving the gingiva of the maxilla, and the hard and soft palate; the underlying bone can be invaded in up to 72% of cases. As the tumour progresses, ulceration of the mass may occur, as well as facial deformity (Liptak and Withrow, 2013). Clinical signs may be minimal initially and owners may notice the problem only late in the course of the disease, especially for more caudally located tumours. In addition to facial swelling, other clinical signs may be drooling of blood-tinged saliva, when ulceration is present, and, less often, foul odour or difficulty in prehending food.

‘High-low’ oral fibrosarcoma

The growth rate of oFSA can be variable, depending on the histological grade. Ciekot et al. (1994) first described a unique subtype of FSA known as ‘histologically low grade, yet biologically high grade, fibrosarcoma’ (‘high-low’ FSA), which is characterised by a histologically low grade diagnosis despite a high grade clinical behaviour. Twenty-five dogs with ‘high-low’ oFSA were included in that study, with a range of 3 to 13 years of age (median 8 years). There was an almost even distribution among sexes, but a higher frequency (52%) in Golden retrievers. Sixteen tumours occurred in the maxilla. On histological examination, all specimens were characterised by *‘haphazard proliferation of fibrous connective tissue with moderately low to low cellularity, abundant collagenous stroma, minimal nuclear pleomorphism, low mitotic rate, and poor demarcation from surrounding tissue. Invasion of the fibrous tissue into surrounding muscle and bone’* was sometimes evident. Some of the cases had been diagnosed previously as nodular fasciitis. The treatment of these dogs included variable combinations of radical surgery, radiation, chemotherapy and hyperthermia. The initial staging was negative for lung or lymph node

89 metastasis, except for one dog that already had lymph node involvement; metastases to lung or
90 lymph node subsequently developed in 12-20% of cases, respectively. Since then, this tumour entity
91 has been widely recognised and it is now understood that the treatment should not differ from the
92 standard for dogs with higher grade oFSAs.

93

94 **Establishing a diagnosis**

95 *Clinical staging*

96 As for any malignant tumour, the first step is to establish a clear diagnosis, to evaluate the
97 extent of local tumour infiltration and to screen for local and distant metastases (clinical staging).
98 Staging includes thorough physical examination of the oral cavity and regional lymph nodes, three-
99 view thoracic radiographs, and complete pre-anaesthetic blood and heart evaluation. Since
100 computed tomography (CT) is now widely available, it is usually preferred over radiography to
101 evaluate the extent of infiltration of the primary tumour in the skull; CT also allows evaluation of
102 adjacent bone invasion (Fig. 1 a, b), assists in surgical planning, and thoracic CT is more sensitive
103 than radiographs in detecting lung metastasis (Ghirelli et al., 2013). Moreover, CT allows
104 evaluation of local non-palpable lymph nodes, such as the medial retropharyngeal and parotid
105 lymph nodes. However, a recent study contradicts this statement, showing that this diagnostic tool
106 demonstrates poor sensitivity in the detection of lymph node metastasis from tumours of canine
107 head, particularly for micrometastasis (Skinner et al., 2018). Magnetic resonance imaging (MRI)
108 may also be used for staging purposes, as it is superior in evaluation of soft tissue involvement
109 compared to CT (Vestraete, 2005; Johnson et al., 2016).

110

111 Fine needle aspiration of any enlarged lymph node should be performed for clinical staging.
112 However, lymphadenectomy and histology should be considered to reliably determine lymph node
113 status. Fine needle aspiration of the primary mass is often unrewarding, because of the difficulty in
114 collecting a sufficient number of cells for interpretive analysis by cytology, due to the intrinsic

115 characteristics of mesenchymal tumours, and because of concurrent local inflammation and
116 necrosis. An incisional biopsy of the primary mass is mandatory to achieve diagnosis (Harvey,
117 1980; Richardson et al., 1983; Hoyt and Withrow, 1984; Vestraete, 2005). However, some authors
118 argue that, since malignant histological type strongly influences survival, but has a minimal impact
119 on the surgical plan, it may be left up to the clinician to propose whether or not to perform an
120 incisional biopsy. This choice is based on the owner's decision whether or not to treat depending on
121 the prognosis, or on cases where there is doubt regarding the malignancy of the lesion or when
122 treatment modalities other than surgery are preferred (Birchard and Carothers, 1990; Berg, 1998;
123 Liptak and Lascelles, 2012).

124

125 When performing an incisional biopsy of the primary mass, care should be taken to gain
126 access to the lesion from the oral cavity instead through the skin, to avoid dissemination of the
127 tumour. Accurate site and size of biopsy are also important, since necrosis and inflammation, which
128 usually accompany tumour growth, could lead to false negative results. In some cases, multiple
129 biopsies may be needed, since the diagnosis of oral fibrosarcoma is not always easy to reach and
130 histopathology may not be sufficient. Incisional biopsies should not adversely affect the definitive
131 surgical procedure; therefore, central sampling should be preferred over sampling the periphery of
132 the tumour.

133

134 *Histopathology*

135 Many articles on histological classification of canine cutaneous and subcutaneous soft tissue
136 sarcomas have been published (Avallone et al., 2007; McSporran 2009; Tamburini et al., 2010;
137 Dennis et al., 2011; Zornhagen et al., 2014; Milovancev et al., 2015). However, few studies have
138 focussed specifically on sarcomas located in the oral cavity, since these are traditionally considered
139 to be a separate entity, characterised by a more local malignant biological behaviour compared to
140 soft tissue sarcomas at other sites (Kuntz et al., 1997; Dennis et al., 2011; Bray, 2016).

141

142 Histologically, oFSAs are composed of '*moderately to poorly differentiated large spindle-*
143 *shaped cells that are arranged in interlacing bundles separated by small amounts of collagenous*
144 *matrix*' (Munday et al., 2017). Less cellular differentiation and the presence of more frequent
145 mitotic figures and necrosis, together with an infiltrative growth pattern, allow differentiation from
146 fibroma. The distinction from odontogenic tumours is usually straightforward, unless odontogenic
147 epithelium is not present; in this case, the location of the mass away from the dental arcade may
148 help in the diagnosis. Oral osteosarcoma can be diagnosed when osteoid deposition, recognised as
149 homogeneous eosinophilic extracellular material within the neoplasm, is evident (Munday et al.,
150 2017).

151

152 Biopsy samples from oFSAs containing overlying and adjacent epithelium may increase the
153 ability to differentiating this entity from oral spindleoid amelanotic melanocytic tumours, since the
154 sensitivity of the specific melanocytic markers used by IHC may be low if intraepithelial nests of
155 neoplastic cells (one of the criteria commonly used to identify melanocytic tumours) cannot be
156 detected. This variant of oral melanoma may be difficult to differentiate from other spindle cell
157 tumours of the oral cavity on the basis of histopathology alone. IHC with a panel of specific anti-
158 melanocytic antibodies, including anti-melanoma antibody (PNL2), melan-A, tyrosinase-related
159 protein (TRP)-1 and TRP-2, was considered of aid in establishing a diagnosis (Smedley et al., 2011;
160 Munday et al., 2017); other monoclonal antibodies such as anti-melanoma gp100 (S-100) and the
161 Human Melanoma Black 45 (HMB45) may complete the panel for melanocytic tumours detection
162 in dogs. IHC should be performed in cases in which histopathology alone is inconclusive, such as in
163 poorly differentiated tumours; for example, positive immunostaining for myocyte markers, such as
164 anti-actin and anti-desmin, may help in differentiating poorly differentiated oFSA from tumours of
165 muscle origin, such as leiomyosarcoma (Boy et al., 2005), rhabdomyosarcoma and myoepithelial or
166 myofibroblastic tumours. Fibrosarcomas usually also exhibit negative immunostaining for cluster of

167 differentiation (CD) 31, anti-von Willebrand's factor antibody (factor VIII-associated antigen) and
168 CD34, as opposed to tumours of endothelial origin (haemangiosarcomas, lymphangiosarcomas)
169 (Ramos-Vara and Borst, 2017).

170

171 **Treatment**

172 Since 1980, amongst articles on canine malignant oral tumours, only very few focus on oFSA
173 exclusively or include a high number of cases, except for some in which the number of dogs with
174 oFSA exceeds 20 (Todoroff and Brodey, 1979; Ciekot et al., 1994; Théon et al., 1997; Poirier et al.,
175 2006; Frazier et al., 2012; Gardner et al., 2015; Sarowitz et al., 2017). Moreover, most of these
176 articles include dogs that have received a variety of different treatment modalities, and the
177 diagnostic approach was not uniform, thus making comparisons difficult.

178

179 Oral FSA in dogs is characterised by a high rate of recurrence, which can occur in up to 57%
180 of cases (Todoroff and Brodey, 1979; Salisbury et al., 1986; Kosovsky et al., 1991; Schwarz et al.,
181 1991 a, b; Wallace et al., 1992; Lascelles et al., 2003; Frazier et al., 2012; Sarowitz et al., 2017). In
182 contrast, distant metastases are less common, being detected in 0-35% of cases (Todoroff and
183 Brodey, 1979; Salisbury and Lantz, 1988; Wallace et al., 1992; Ciekot et al., 1994; Poirier et al.,
184 2006; Frazier et al., 2012; Sarowitz et al., 2017). Therefore, the major challenge in treatment is
185 achieving local control. En bloc excision plays an important role in accomplishing this goal, but
186 multimodality treatment, primarily combining surgery and radiation therapy, is the mainstay of
187 treatment (Hoyt and Withrow, 1984; Emms, 1987; Kosovsky et al., 1991; White, 1991; Wallace et
188 al., 1992; Ciekot et al., 1994; Burk, 1996; Berg, 1998; Gardner et al., 2015; Sarowitz et al., 2017).

189

190 *Surgery*

191 Mandibulectomy and maxillectomy have become the routine methods for treating canine oral
192 malignancies, with good clinical and functional outcome (Withrow and Holmberg, 1983; Bradley et

193 al., 1984; White et al., 1985; Emms and Harvey, 1986; Salisbury et al., 1986; Salisbury and Lantz,
194 1988; Birchard and Carothers, 1990; Kosovsky et al., 1991; Schwarz et al., 1991 a, b; White, 1991;
195 Wallace et al., 1992; Fox et al., 1997; Lascelles et al., 2003, 2004; Vestraete, 2005; Sarowitz et al.,
196 2017). However, for oral malignancies, including oFSA, there is still debate about how to determine
197 the safest surgical margins to limit local recurrence. CT or MRI evaluation of the primary lesion is
198 helpful in determining such margins, mainly for caudally located tumours. Most authors report that
199 at least 1 cm of macroscopically normal soft tissue or bone surrounding the tumour should be
200 removed (Bradley et al., 1984; Hoyt and Withrow, 1984; Emms and Harvey, 1986; Kosovski et al.,
201 1991; Wallace et al., 1993; Berg, 1998; Frazier et al., 2012); whenever possible, a margin of 2-3 cm
202 is preferable, but this may not be always possible to achieve (Liptak and Lascelles, 2012; Sarowitz
203 et al., 2017).

204

205 Information about the completeness of surgical excision is reported in some publications
206 (Schwarz et al., 1991a, b; Ciekot et al., 1994; Forrest et al., 2000; Lascelles et al., 2003, 2004;
207 Frazier et al., 2012; Gardner et al., 2015; Sarowitz et al., 2017). In larger studies, the proportion of
208 dogs in which tumours could be removed with clean margins was never higher than 71% (Schwarz
209 et al., 1991a). Technical limitations in margin evaluation still remain a challenge, despite
210 improvements made in this field over the past few years and the growing awareness of surgeons to
211 correctly prepare the tissue sample for the pathologist (Milovancev et al., 2017). The role of the
212 tumour microenvironment in promoting tumour invasion and metastasis, as well as the concept of
213 tumour heterogeneity, may help to explain the recurrence of ‘completely excised’ neoplasms
214 (Milovancev and Russell, 2017).

215

216 *Radiotherapy*

217 In earlier studies, oFSA was considered a radioresistant tumour (Todoroff and Brodey, 1979;
218 Harvey, 1980; Thrall, 1981; Richardson et al., 1983; Harvey, 1985; Emms, 1987; Vestraete, 2005).

219 This was probably due to the limitations that came with orthovoltage radiation machines (Todoroff
220 and Brodey, 1979; Thrall, 1981; Brewer and Turrel, 1982; Creasey and Thrall, 1982). The
221 combination of orthovoltage radiation with the radiosensitiser misonidazole did not seem to
222 improve the outcome and was associated with side effects (Creasey and Thrall, 1982).
223 Hyperthermia has also been used together with orthovoltage radiotherapy (Brewer and Turrel, 1982;
224 Schwarz et al., 1991a, b), but this combination is now rarely used, due to the difficulty in
225 administering heating and the availability of more advanced radiotherapy machines.

226
227 With the advent of megavoltage equipment, in fact, both the incidence and severity of side
228 effects, and the overall results of treatment have improved considerably (Hoyt and Withrow, 1984;
229 Burk, 1996; Théon et al., 1997; Berg, 1998; Dhaliwal et al., 1998; Forrest, 2000; Lascelles et al.,
230 2004; Poirier et al., 2006; Frazier et al., 2012; Gardner et al., 2015). Costs remain the major issue of
231 this treatment modality, especially in some European countries. A high dose of radiation, > 50 Gy,
232 is considered necessary to overcome radioresistance (Poirier et al., 2006).

233
234 Radiotherapy alone, with a curative or palliative intent, may be useful for the treatment of
235 canine oFSA, producing similar results to those of surgery alone. In a study conducted by Poirier et
236 al. (2006) on macroscopic oral lesions, the overall times to progression and overall survival were
237 205 and 310 days, respectively; this is not substantially different from what has been achieved
238 through surgery alone (Lascelles et al., 2004; Sarowitz et al., 2017). Similar results were reported
239 by Gardner et al. (2015) in a smaller group of dogs.

240
241 In general, when a curative intent radiation protocol is attempted, a total dose of 40-60 Gy is
242 administered in daily fractions of 3-4.2 Gy, on a Monday through Friday schedule, both in a
243 macroscopic (Poirier et al., 2006) or adjuvant setting (Forrest et al., 2000; Gardner et al., 2015). For
244 palliative purposes, coarsely fractionated protocols, consisting of the administration of a total dose

245 of 24-30 Gy, delivered in three fractions of 8 Gy each or five fractions of 6 Gy each, have been
246 proposed (Poirier et al., 2006). Nonetheless, oral FSA seems to be less sensitive to radiation when
247 compared to the same histotype growing at other sites (Forrest et al., 2000).

248

249 Within the past 15 years, the use of CT scanning for both the early detection of lung
250 metastasis and for surgical planning has almost completely replaced the need for radiographs.
251 Despite this, the recurrence rate still is as high as 54% (Sarowitz et al., 2017) to 57% (Lascelles et
252 al., 2003) when surgery is the sole treatment modality. In the authors' experience of a small case
253 series of 13 oFSAs treated by surgery alone, the recurrence rate was 30.7%, and clean surgical
254 margins could be obtained in 10/13 (76.9%) cases, most of which had CT performed as part of the
255 surgical planning. The median disease-free interval was 317 days and median overall survival was
256 not reached (see Appendix: Supplementary Table 1). A recently published article using the same
257 treatment modality in eight dogs reported a median survival of 249 days and a median progression-
258 free survival of 138 days (Gardner et al. 2015). The combination of surgery and adjuvant
259 megavoltage radiotherapy leads to an improvement of tumour control (recurrence rate 24.1%) and
260 median overall survival (743 days), as reported by Frazier et al. (2012).

261

262 *Chemotherapy and targeted therapy*

263 Although chemotherapy has been used as adjuvant treatment for oFSA (Emms et al., 1986;
264 Schwarz et al., 1991 a, b; Ciekot et al., 1994; Gardner et al., 2015), its role is still unclear and has
265 not been investigated in detail. As for most sarcomas, oFSA is considered to be chemoresistant
266 (Harvey, 1985). However, the most commonly administered drug in association with surgery and/or
267 radiation is doxorubicin. Recently, the effect of two tyrosine kinase inhibitors (TKI), imatinib and
268 masitinib, on canine oFSA cells and tissue samples was investigated, based on the premise that
269 some canine oFSA samples and two canine oFSA cell lines expressed platelet-derived growth factor
270 receptors (PDGFRs)- α and β (Milovancev et al., 2016). A mild inhibitory effect of both TKIs was

271 observed in vitro, but at a concentration too high to be used in a clinical setting. The addition of
272 doxorubicin in the cell culture slightly potentiated the action of the TKIs. This finding is worth
273 further investigation in order to use these drugs as adjuvant cytotoxic drugs. A recent publication on
274 dogs affected by malignant tumours showed that the combination of doxorubicin (at a slightly
275 reduced dose) and toceranib appears to be safe (Pellin et al., 2017). Oral FSAs were not included in
276 the study, but it might be worth investigating such a combination in this type of tumour.

277

278 In two studies, vascular endothelial growth factor (VEGF) plasma concentrations were
279 measured in dogs with various malignant and benign tumours, including oFSA (Wergin and Kaser-
280 Hotz, 2004; Sobczynska-Rak et al., 2014). In both studies, VEGF concentrations were lower in FSA
281 compared to other malignant tumours, such as oral melanoma and squamous cell carcinoma;
282 however, in the study of Wergin and Kaser-Hotz (2004) the location of the fibrosarcoma was not
283 stated and it is not clear whether oFSA was included.

284

285 There are no published data on the use of metronomic chemotherapy for palliative treatment
286 of canine oFSA. This approach is based on the '*oral administration of chemotherapy at relatively*
287 *low, minimally toxic doses, on a frequent or continuous schedule of treatment, with no extended*
288 *drug-free breaks*' (Gaspar et al., 2018). The more commonly used drugs are different combinations
289 of cyclophosphamide, chlorambucil and lomustine, together with thalidomide, metformin,
290 piroxicam or other anti-cyclooxygenases (COX) agents, in order to stimulate the host immune
291 system, modify tumour microenvironment and act against tumour neoangiogenesis.

292 The promising results obtained in dogs affected by soft tissue sarcomas at sites other than the
293 oral cavity may encourage the use of metronomic chemotherapy for oFSA (Emslie et al., 2008;
294 Burton et al., 2011). In particular, the disease-free interval of dogs with incompletely resected soft
295 tissue sarcomas of the trunk and extremities was significantly longer when metronomic
296 chemotherapy was administered (Emslie et al., 2008).

297

298 The effects of electrochemogene therapy with a combination of bleomycin and interleukin
299 (IL)-12 on different histotypes of spontaneous canine tumours were reported by Reed et al. (2010).
300 This technique is based on the ability to increase cell permeability and allow movement of
301 molecules into cells by the application of a series of square-wave electrical pulses (electroporation)
302 to the tumour mass. This may be applied to both gene and drug therapy. In the study conducted by
303 Reed et al. (2010) one inoperable oFSA was included, and an initial partial response was seen
304 before progressive disease developed. The authors concluded that this tumour type might be
305 partially responsive to this treatment, with mild side effects; therefore, this technique may be
306 worthy of further investigation, mainly for non-resectable cases.

307

308 **Prognosis**

309 Local tumour control still represents the main challenge in canine oFSA. Literature beyond
310 the year 2000 was chosen for evaluating prognosis of oFSA. Most of the articles published after that
311 time included CT scanning as part of clinical staging, compared to previous reports where thoracic
312 and skull radiographs were performed most frequently for clinical staging purposes. Including more
313 advanced imaging modalities should have improved the ability to better plan the surgical excision.
314 Nonetheless, the incidence of local recurrence has not improved as much as expected.

315

316 *One year survival*

317 The one year survival, regardless of the type of treatment, is reported as 7-76% in studies
318 published before 2000 (Todoroff and Brodey, 1979; Harvey, 1980; Thrall, 1981; Brewer and Turrel,
319 1982; White, 1985; Emms and Harvey, 1986; Kosovsky et al., 1991; White, 1991; Wallace et al.,
320 1992; Théon et al., 1997) compared to 29.4-87.7% for studies published from 2000 to 2017 (Poirier
321 et al., 2006; Frazier et al., 2012; Sarowitz et al., 2017; personal data, see Appendix: Supplementary
322 Table 1). However, when analysing the data by Mann-Whitney *U* test (Prism v5.0, GraphPad

323 Software), a statistically significant difference was not evident between these two periods ($P = 0.23$;
324 Fig. 2).

325

326 *Overall survival time*

327 In contrast, when comparing overall survival time, a statistically significant improvement ($P =$
328 0.035) was found among groups. The overall survival reported before the 2000 was 30-540 days
329 (Todoroff and Brodey, 1979; Harvey, 1980; Thrall, 1981; Brewer and Turrel, 1982; Bradley et al.,
330 1984; Emms et al., 1986; Salisbury et al., 1986; Salisbury and Lantz, 1988; Kosovsky et al., 1991;
331 Schwarz et al., 1991 a, b; Wallace et al., 1992; Fox et al., 1997) compared to 247-743 days reported
332 in later studies (Forrest et al., 2000; Poirier et al., 2006; Ohlerth et al., 2010; Frazier et al., 2012;
333 Gardner et al., 2015; Sarowitz et al., 2017) (Fig. 3). The difference between the one-year and
334 overall survival could be explained in part by the low number of cases in many of the papers
335 considered, that may have influenced this result. The biology of the tumour, that can be sometimes
336 slow-growing, could also influence the time to progression (both in terms of time to recurrence or
337 metastasis), since it may be longer than one year, thus resulting in a statistically different survival
338 only on the long run. A prospective study enrolling an adequate number of cases followed for at
339 least 2 years would be warranted to clarify this issue.

340

341 *Metastasis*

342 The metastatic rate has not changed substantially throughout the years ($P = 0.40$); a range of
343 0-38.4% is reported in earlier publications (Todoroff and Brodey, 1979; Bradley et al., 1984; White
344 et al., 1985; Emms and Harvey, 1986; Salisbury et al., 1986; Salisbury and Lantz, 1988; Kosovsky
345 et al., 1991; Schwarz et al., 1991 a, b; White, 1991; Wallace et al., 1992; Ciekot et al., 1994; Théon
346 et al., 1997), compared to 0-23% more recently (Lascelles et al., 2003, 2004; Poirier et al., 2006;
347 Frazier et al., 2012; Sarowitz et al., 2017; personal data, see Appendix: Supplementary Table 1)
348 (Fig. 4).

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Recurrence

The recurrence rate was 5-87.5% in earlier publications (Todoroff and Brodey, 1979; Harvey et al., 1980; Thrall, 1981; Brewer and Turrel, 1982; Creasey and Thrall, 1982; Withrow and Holmberg, 1983; Bradley et al., 1984; White et al., 1985; Emms and Harvey, 1986; Salisbury et al., 1986; Salisbury and Lantz, 1988; Kosovsky et al., 1991; Schwarz et al., 1991a, b; White, 1991; Wallace et al., 1992; Ciekot et al., 1994; Théon et al., 1997), compared to 24.1-57.1% in more recent reports (Lascelles et al., 2003, 2004; Frazier et al., 2012; Sarowitz et al., 2017; personal data in Supplementary files); these ranges are not significantly different ($P = 0.68$; Fig. 5).

Time to recurrence

Similarly, the time to recurrence has not changed significantly between the two evaluated time periods ($P = 0.26$); before 2000, tumours recurred after 75-1260 days (Todoroff and Brodey, 1979; Harvey, 1980; Thrall, 1981; Brewer and Turrel, 1982; White, 1985; Emms and Harvey, 1986; Kosovsky et al., 1991; White, 1991; Wallace et al., 1992; Théon et al., 1997), whereas the time to recurrence was 145-1368 days in the more recent literature (Forrest et al., 2000; Lascelles et al., 2004; Poirier et al., 2006; Frazier et al., 2012; Gardner et al., 2015; Sarowitz et al., 2017; personal data, see Appendix: Supplementary Table 1).

Prognostic factors

A few authors have evaluated prognostic factors for long-term survival and disease-free interval. Tumour stage, tumour site (more caudally located masses have a worse prognosis), and completeness of surgical excision were reported most frequently (Salisbury and Lantz, 1988; Schwarz et al., 1991 a, b; Wallace et al., 1992; Théon et al., 1997; Gardner et al., 2015; Sarowitz et al., 2017).

375 **Conclusions**

376 Oral FSA is a malignant, infiltrating mesenchymal tumour affecting the oral cavity of middle-
377 aged dogs. The diagnosis is often made late in the course of the disease because of the frequent
378 caudal location of the tumour. Distant metastases are rarely evident at presentation. Although
379 histopathology may be compatible with a low-grade tumour, an aggressive approach is always
380 warranted to obtain local control of this invasive tumour. Within the last 30 years, some
381 improvements have been made in equipment for radiotherapy and in the surgical procedures
382 available, but the prognosis for this tumour is still guarded. Treatment failure is often due to local
383 tumour recurrence that can still occur in up to 54% of cases. A thorough staging based on CT
384 examination and wide/radical surgical excision is fundamental to eradicate the tumour. Adjuvant
385 treatments, such as radiation therapy, are recommended in order to prolong both the disease-free
386 interval and survival time. A rigorous analysis of the published literature is challenging due to small
387 case series and the many different treatment modalities that were included even in the same study;
388 therefore, the data presented here should be considered cautiously. Nevertheless, an improvement in
389 survival has occurred in recent years, and an optimistic view on the possibility to cure this tumour is
390 justified. Prospective studies focusing on oral FSA and investigating the roles of cytotoxic and
391 targeted chemotherapy, as well as radiotherapy, would be needed to clearly address the best
392 treatment options for this tumour in dogs.

393

394 **Conflict of interest statement**

395 None of the authors has any financial or personal relationships that could inappropriately
396 influence or bias the content of the paper.

397

398 **Acknowledgements**

399 The authors wish to express gratitude to Dr Paola Pregel for support in the statistical analysis.

400

401 **Appendix. Supplementary material**

402 Supplementary data associated with this article can be found, in the online version, at doi:

403 ...

404

405 **References**

- 406 Avallone, G., Helmbold, P., Caniatti, M., Stefanello, D., Nayak, R.C., Roccabianca P., 2007. The
407 spectrum of canine cutaneous perivascular wall tumors: Morphologic, phenotypic and clinical
408 characterization. *Veterinary Pathology* 44, 607-620.
- 409
- 410 Berg, J., 1998. Principles of oncologic orofacial surgery. *Clinical Techniques in Small Animal*
411 *Practice* 13, 38-41.
- 412
- 413 Birchard, S., Carothers, M., 1990. Aggressive surgery in the management of oral neoplasia.
414 *Veterinary Clinics of North America: Small Animal Practice* 20, 1117-1140.
- 415
- 416 Boy, S.C., Van Heerden, W.F.P., Steenkamp, G., 2005. Diagnosis and treatment of primary
417 intraoral leiomyosarcomas in four dogs. *Veterinary Record* 156, 510-513.
- 418
- 419 Bradley, R.L., MacEwen, E.G., Loar, A.S., 1984. Mandibular resection for removal of oral tumors
420 in 30 dogs and 6 cats. *Journal of the American Veterinary Medical Association* 184, 460-463.
- 421
- 422 Bray, J.P., 2016. Soft tissue sarcoma in the dog - part 1: A current review. *Journal of Small Animal*
423 *Practice* 57, 510-519.
- 424
- 425 Brewer, W.G. Jr, Turrel, J.M., 1982. Radiotherapy and hyperthermia in the treatment of
426 fibrosarcoma in the dog. *Journal of the American Veterinary Association* 181, 146-150.
- 427
- 428 Burk, R.L., 1996. Radiation therapy in the treatment of oral neoplasia. *Veterinary Clinics of North*
429 *America: Small Animal Practice* 26, 155-163.
- 430
- 431 Burton, J.H., Mitchell, L., Thamm, D.H., Dow, S.W., Biller, B.J., 2011. Low-dose
432 cyclophosphamide selectively decreases regulatory T cells and inhibits angiogenesis in dogs
433 with soft tissue sarcoma. *Journal of Veterinary Internal Medicine* 25, 920-926.
- 434
- 435 Ciekot, P.A., Powers, B.E., Withrow, S.J., Straw, R.C., Ogilvie, G.K., LaRue, S.M., 1994.
436 Histologically low-grade, yet biologically high-grade, fibrosarcomas of the mandible and
437 maxilla in dogs: 25 cases (1982-1991). *Journal of the American Veterinary Medical*
438 *Association* 204, 610-615.
- 439
- 440 Creasey, W.A., Thrall, D.E., 1982. Pharmacokinetic and anti-tumor studies with the radiosensitizer
441 misonidazole in dogs with spontaneous fibrosarcomas. *American Journal of Veterinary*
442 *Research* 43, 1015-1018.
- 443
- 444 Dennis, M.M., McSporran, K.D., Bacon, N.J., Schulman, F.Y., Foster, R.A., Powers, B.E., 2011.
445 Prognostic factors for cutaneous and subcutaneous soft tissue sarcomas in dogs. *Veterinary*
446 *Pathology* 48, 73-84.

447
448 Dhaliwal, R.S., Kitchell, B.E., Manfra Marretta, S., 1998. Oral tumors in dogs and cats. Part II.
449 Prognosis and treatment. *Compendium on Continuing Education* 20, 1109-1119.
450
451 Elmslie, R.E., Glawe, P., Dow, S.W., 2008. Metronomic therapy with cyclophosphamide and
452 piroxicam affectively delays tumor recurrence in dogs with incompletely resected soft tissue
453 sarcomas. *Journal of Veterinary Internal Medicine* 22, 1373-1379.
454
455 Emms, S.G., Harvey, C.E., 1986. Preliminary results of maxillectomy in the dog and cat. *Journal of*
456 *Small Animal Practice* 27, 291-306.
457
458 Emms, S.G., 1987. The management of oral tumours in dogs and cats. *Australian Veterinary*
459 *Journal* 64, 22-25.
460
461 Forrest, L.J., Chun, R., Adams, W.M., Cooley, J., Vail, D.M., 2000. Postoperative radiotherapy for
462 canine soft tissue sarcoma. *Journal of Veterinary Internal Medicine* 14, 578-582.
463
464 Fox, L.E., Geoghegan, S.L., Davis, L.H., Hartzel, J.S., Kubilis, P., Gruber, L.A., 1997. Owner
465 satisfaction with partial mandibulectomy or maxillectomy for treatment of oral tumors in 27
466 dogs. *Journal of the American Animal Hospital Association* 33, 25-31.
467
468 Frazier, S.A., Johns, S.M., Ortega, J., Zwingenberger, A.L., Kent, M.S., Hammond, G.M.,
469 Rodriguez, C.O. Jr, Steffey, M.A., Skorupski, K.A., 2012. Outcome in dogs with surgically
470 resected oral fibrosarcoma (1997-2008). *Veterinary and Comparative Oncology* 10, 33-43.
471
472 Gardner, H., Fidel, J., Haldorson, G., Dernell, W., Wheeler, B., 2015. Canine oral fibrosarcomas: A
473 retrospective analysis of 65 cases (1998-2010). *Veterinary and Comparative Oncology* 13, 40-
474 47.
475
476 Gaspar, T.B., Henriques, J., Marconato, L., Queiroga, F. L., 2018. The use of low-dose metronomic
477 chemotherapy in dogs - insight into a modern cancer field. *Veterinary and Comparative*
478 *Oncology* 1, 2-11.
479
480 Ghirelli, C.O., Villamizar, L.A., Pinto, A.C., 2013. Comparison of standard radiography and
481 computed tomography in 21 dogs with maxillary masses. *Journal of Veterinary Dentistry* 30,
482 72-76.
483
484 Harvey, H.J., 1980. Cryosurgery of oral tumors in dogs and cats. *Veterinary Clinics of North*
485 *America: Small Animal Practice* 10, 821-830.
486
487 Harvey, H.J., 1985. Oral tumors. *Veterinary Clinics of North America: Small Animal Practice* 15,
488 493-500.
489
490 Hoyt, M.F., Withrow, S.J., 1984. Oral malignancy in the dog. *Journal of the American Animal*
491 *Hospital Association* 20, 83-92.
492
493 Johnson, P.J., Elders, R., Pey, P., Dennis, R., 2016. Clinical and magnetic resonance imaging
494 features of inflammatory versus neoplastic medial retropharyngeal lymph node mass lesions
495 in dogs and cats. *Veterinary Radiology and Ultrasound* 17, 24-32.
496

497 Kosovsky, J.K., Matthiesen, D.T., Marretta, S.M., Patnaik, A.K., 1991. Results of partial
498 mandibulectomy for the treatment of oral tumors in 142 dogs. *Veterinary Surgery* 20, 397-
499 401.
500

501 Kuntz, C.A., Dernell, W.S., Powers, B.E., Devitt, C., Straw, R.C., Withrow, S.J., 1997. Prognostic
502 factors for surgical treatment of soft tissue sarcomas in dogs: 75 cases (1986-1996). *Journal of*
503 *the American Veterinary Medical Association* 211, 1147-1151.
504

505 Lascelles, B.D., Thomson, M.J., Dernell, W.S., Straw, R.C., Lafferty, M., Withrow, S.J., 2003.
506 Combined dorsolateral and intraoral approach for the resection of tumors of the maxilla in the
507 dog. *Journal of the American Veterinary Medical Association* 39, 294-305.
508

509 Lascelles, B.D., Henderson, R.A., Seguin, B., Liptak, J.M., Withrow, S.J., 2004. Bilateral rostral
510 maxillectomy and nasal planectomy for large rostral maxillofacial neoplasms in six dogs and
511 one cat. *Journal of the American Veterinary Medical Association* 40, 137-146.
512

513 Liptak, J.M., Lascelles, D.X., 2012. Oral tumors. In: Kudnig, S.T., Séguin, B. (Eds) *Veterinary*
514 *Surgical Oncology*, 1st Edn. Wiley-Blackwell, West Sussex, UK, pp. 119-178.
515

516 Liptak, J.M., Withrow, S.J., 2013. Cancer of the gastrointestinal tract. In: Withrow, S.J., Vail, D.M.,
517 Page, R.L. (Eds) *Small Animal Clinical Oncology*, 5th Edn. Elsevier, St Louis, Missouri,
518 USA, pp. 318-398.
519

520 McSporran, K.D., 2009. Histologic grade predicts recurrence for marginally excised canine
521 subcutaneous soft tissue sarcomas. *Veterinary Pathology* 46, 928-933.
522

523 Milovancev, M., Hauck, M., Keller, C., Stranahan, L.W., Mansoor, A., Malarkey, D.E., 2015.
524 Comparative pathology of canine soft tissue sarcomas: Possible models of human non-
525 rhabdomyosarcoma soft tissue sarcomas. *Journal of Comparative Pathology* 152, 22-27.
526

527 Milovancev, M., Helfand, S.C., Marley, K., Goodall, C.P., Löhr, C.V., Bracha, S., 2016.
528 Antiproliferative effects of masitinib and imatinib against canine oral fibrosarcoma in vitro.
529 *BMC Veterinary Research* 12, 85.
530

531 Milovancev, M., Russel, D.S., 2017. Surgical margins in the veterinary cancer patient. *Veterinary*
532 *and Comparative Oncology* 15, 1136-1157.
533

534 Milovancev, M.M., Townsend, K.L., Gorman, E., Bracha, S., Curran, K., Russell, D.S., 2017.
535 Shaved margin histopathology and imprint cytology for assessment of excision in canine mast
536 cell tumors and soft tissue sarcomas. *Veterinary Surgery* 46, 879-885.
537

538 Munday, J.S., Löhr, C.V., Kiupel, M., 2017. Tumors of the Alimentary Tract. In: Meuten, D.J. (Ed.)
539 *Tumors in Domestic Animals*, 5th Edn. John Wiley & Sons, New York, USA, pp. 509-511.
540

541 Ohlerth, S., Bley, C.R., Lálúhová, D., Roos, M., Kaser-Hotz, B., 2010. Assessment of changes in
542 vascularity and blood volume in canine sarcomas and squamous cell carcinomas during
543 fractionated radiation therapy using quantified contrast-enhanced power Doppler
544 ultrasonography: A preliminary study. *The Veterinary Journal* 186, 58-63.
545

546 Pellin, M.A., Wouda, R.M., Robinson, K., Tsimbas, K., Kurzman, I.D., Biller, B.J., Vail, D.M.,
547 2017. Safety evaluation of combination doxorubicin and toceranib phosphate (Palladia®) in

548 tumour bearing dogs: A phase I study-finding study. *Veterinary and Comparative Oncology* 3,
549 919-931.

550

551 Poirier, V.J., Rohrer Bley, C., Roos, M., Kaser-Hotz, B., 2006. Efficacy of radiation therapy for the
552 treatment of macroscopic canine oral soft tissue sarcoma. *In vivo* 20, 415-420.

553

554 Ramos-Vara, J.A., Borst, L.B., 2017. Immunohistochemistry: Fundamentals and applications in
555 oncology. In: Meuten, D.J. (Ed.) *Tumors in Domestic Animals*, 5th Edn. John Wiley & Sons,
556 New York, USA, pp. 374-392.

557

558 Reed, S.D., Fulmer, A., Buchholz, J., Zhang, B., Cutrera, J., Shiomitsu, K., Li, S., 2010.
559 Bleomycin/interleukin-12 electrochemogene therapy for treating naturally occurring
560 spontaneous neoplasms in dogs. *Cancer Gene Therapy* 17, 571-578.

561

562 Richardson, R.C., Jones, M.A., Elliott, G.S., 1983. Oral neoplasms in the dog: A diagnostic and
563 therapeutic dilemma. *Compendium on Continuing Education* 5, 441-446.

564

565 Salisbury, S.K., Richardson, D.C., Lantz, G.C., 1986. Partial maxillectomy and premaxillectomy in
566 the treatment of oral neoplasia in the dog and cat. *Veterinary Surgery* 15, 16-26.

567

568 Salisbury, S.K., Lantz, G.C., 1988. Long-term results of partial mandibulectomy for treatment of
569 oral tumors in 30 dogs. *Journal of the American Animal Hospital Association* 24, 285-294.

570

571 Sarowitz, B.N., Davis, G.J., Kim, S., 2017. Outcome and prognostic factors following curative-
572 intent surgery for oral tumours in dogs: 234 cases (2004 to 2014). *Journal of Small Animal*
573 *Practice* 58, 146-153.

574

575 Schwarz, P.D., Withrow, S.J., Curtis, C.R., Powers, B.E., Straw, R.C., 1991. Mandibular resection
576 as a treatment for oral cancer in 61 dogs. *Journal of the American Animal Hospital*
577 *Association* 27, 601-610.

578

579 Schwarz, P.D., Withrow, S.J., Curtis, C.R., Powers, B.E., Straw, R.C., 1991. Partial maxillary
580 resection as a treatment for oral cancer in 81 dogs. *Journal of the American Animal Hospital*
581 *Association* 27, 617-624.

582

583 Skinner, O.T., Boston, S.E., Giglio, R.F., Whitley, E.M. Colee, J.C., Porter, E.G., 2018. Diagnostic
584 accuracy of contrast-enhanced computed tomography for assessment of mandibular and
585 medial retropharyngeal lymph node metastasis in dogs with oral and nasal cancer. *Veterinary*
586 *and Comparative Oncology*. July 10, Epub ahead of print.

587

588 Smedley, R.C., Lamoureux, J., Sledge, D.G., Kiupel, M., 2011. Immunohistochemical diagnosis of
589 canine oral amelanotic melanocytic neoplasms. *Veterinary Pathology*, 48, 32-40.

590

591 Sobczynska-Rak, A., Polkowska, I., Silmanowicz, P., 2014. Elevated vascular endothelial growth
592 factors (VEGF) levels in the blood serum of dogs with malignant neoplasms of the oral
593 cavity. *Acta Veterinaria Hungarica* 62, 362-371.

594

595 Tamburini, B.A., Phang, T.L., Fosmire, S.P., Scott, M.C., Trapp, S.C., Duckett, M.M., Robinson,
596 S.R., Slansky, J.E., Sharkey, L.C., Cutter, G.R., et al., 2010. Gene expression profiling
597 identifies inflammation and angiogenesis as distinguishing features of canine
598 hemangiosarcoma. *BMC Cancer* 10, 619.

599

600 Théon, A.P., Rodriguez, C., Madewell, B.R., 1997. Analysis of prognostic factors and patterns of
601 failure in dogs with malignant oral tumors treated with megavoltage irradiation. *Journal of the*
602 *American Veterinary Medical Association* 210, 778-784.

603

604 Thrall, D.E., 1981. Orthovoltage radiotherapy of oral fibrosarcomas in dogs. *Journal of the*
605 *American Veterinary Medicine Association* 179, 159-162.

606

607 Todoroff, R.J., Brodey, R.S., 1979. Oral and pharyngeal neoplasia in the dog: A retrospective
608 survey of 361 cases. *Journal of the American Veterinary Medical Association* 175, 567-571.

609

610 Vestraete, F.J.M., 2005. Mandibulectomy and maxillectomy. *Veterinary Clinics of North America:*
611 *Small Animal Practice* 35, 1009-1039.

612

613 Wallace, J., Matthiesen, D.T., Patnaik, A.K., 1992. Hemimaxillectomy for the treatment of oral
614 tumors in 69 dogs. *Veterinary Surgery* 21, 337-341.

615

616 Wergin, M.C., Kaser-Hotz, B., 2004. Plasma vascular endothelial growth factor (VEGF) measured
617 in seventy dogs with spontaneously occurring tumours. *In Vivo*. 18, 15-20.

618

619 White, R.A.S., Gorman, N.T., Watkins, S.B., Brearley, M.J., 1985. The surgical management of
620 bone-involved oral tumours in the dog. *Journal of Small Animal Practice* 26, 693-708.

621

622 White, R.A.S., 1991. Mandibulectomy and maxillectomy in the dog: Long term survival in 100
623 cases. *Journal of Small Animal Practice* 32, 69-74.

624

625 Withrow, S.J., Holmberg, D.L., 1983. Mandibulectomy in the treatment of oral cancer. *Journal of*
626 *the American Animal Hospital Association* 19, 273-286.

627

628 Zornhagen, K.W., Kristensen, A.T., Hansen, A.E., Oxboel, J., Kjær, A., 2014. Selection of suitable
629 reference genes for normalization of genes of interest in canine soft tissue sarcomas using
630 quantitative real-time polymerase chain reaction. *Veterinary and Comparative Oncology* 13,
631 485-493.

632

633 **Figure legends**

634

635 Fig. 1. Computed tomography (CT) images of an oral mass diagnosed as fibrosarcoma. (a) Post
636 contrast scan showing bone involvement of the maxilla and invasion into the nasal cavity. (b) Soft
637 tissue involvement in the same dog. In this case, surgery was not performed since the owners
638 refused neoadjuvant radiation following surgical debulking.

639

640 Fig. 2. One year survival rate reported by different authors before (7-76%) and after (29.4 - 87.7%)
641 the year 2000. Various combinations of surgery, radiotherapy, hyperthermia, chemotherapy were
642 used in different studies. The difference between the two groups is not statistically different ($P =$
643 0.23).

644

645 Fig. 3. Overall survival reported by different authors before (30-6204 days) and after (247-743
646 days) the year 2000. Different combinations of treatment were used. A significant improvement in
647 survival in recent years was evident ($P = 0.035$).

648

649 Fig. 4. Metastatic rate reported by different authors before (0-38%) and after (0-23%) the year 2000.
650 There was no significant difference between time periods ($P = 0.40$).

651

652 Fig. 5. Median recurrence rate reported before (5-87.5%) and after (24.1-57.1%) the year 2000. A
653 significant improvement in tumour control has not been achieved ($P = 0.68$).

654

655 Fig. 6. Median time to recurrence before (75-1260 days) and after (145- 1368 days) the year 2000.
656 There was no significant difference between time periods ($P = 0.26$).