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

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1 **Review**

2

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

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5

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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

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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

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

65

### 66 **Clinical presentation of dogs with oral fibrosarcoma**

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

74

#### 75 *'High-low' oral fibrosarcoma*

76 The growth rate of oFSA can be variable, depending on the histological grade. Ciekot et al.  
77 (1994) first described a unique subtype of FSA known as 'histologically low grade, yet biologically  
78 high grade, fibrosarcoma' ('high-low' FSA), which is characterised by a histologically low grade  
79 diagnosis despite a high grade clinical behaviour. Twenty-five dogs with 'high-low' oFSA were  
80 included in that study, with a range of 3 to 13 years of age (median 8 years). There was an almost  
81 even distribution among sexes, but a higher frequency (52%) in Golden retrievers. Sixteen tumours  
82 occurred in the maxilla. On histological examination, all specimens were characterised by  
83 *'haphazard proliferation of fibrous connective tissue with moderately low to low cellularity,*  
84 *abundant collagenous stroma, minimal nuclear pleomorphism, low mitotic rate, and poor*  
85 *demarcation from surrounding tissue. Invasion of the fibrous tissue into surrounding muscle and*  
86 *bone'* was sometimes evident. Some of the cases had been diagnosed previously as nodular fasciitis.  
87 The treatment of these dogs included variable combinations of radical surgery, radiation,  
88 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; McSporrán 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)- $\alpha$  and  $\beta$  (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).

349

350 *Recurrence*

351           The recurrence rate was 5-87.5% in earlier publications (Todoroff and Brodey, 1979;  
352 Harvey et al., 1980; Thrall, 1981; Brewer and Turrel, 1982; Creasey and Thrall, 1982; Withrow and  
353 Holmberg, 1983; Bradley et al., 1984; White et al., 1985; Emms and Harvey, 1986; Salisbury et al.,  
354 1986; Salisbury and Lantz, 1988; Kosovsky et al., 1991; Schwarz et al., 1991a, b; White, 1991;  
355 Wallace et al., 1992; Ciekot et al., 1994; Théon et al., 1997), compared to 24.1-57.1% in more  
356 recent reports (Lascelles et al., 2003, 2004; Frazier et al., 2012; Sarowitz et al., 2017; personal data  
357 in Supplementary files); these ranges are not significantly different ( $P = 0.68$ ; Fig. 5).

358

359 *Time to recurrence*

360           Similarly, the time to recurrence has not changed significantly between the two evaluated  
361 time periods ( $P = 0.26$ ); before 2000, tumours recurred after 75-1260 days (Todoroff and Brodey,  
362 1979; Harvey, 1980; Thrall, 1981; Brewer and Turrel, 1982; White, 1985; Emms and Harvey, 1986;  
363 Kosovsky et al., 1991; White, 1991; Wallace et al., 1992; Théon et al., 1997), whereas the time to  
364 recurrence was 145-1368 days in the more recent literature (Forrest et al., 2000; Lascelles et al.,  
365 2004; Poirier et al., 2006; Frazier et al., 2012; Gardner et al., 2015; Sarowitz et al., 2017; personal  
366 data, see Appendix: Supplementary Table 1).

367

368 *Prognostic factors*

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

374



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

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400

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401 **Appendix. Supplementary material**

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

403 ...

404

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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 ( $P = 0.26$ ).