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Invited Review

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

M. Martano*, S. Iussich, E. Morello, P. Buracco

Department of Veterinary Sciences, University of Turin, 10095 Grugliasco, Italy

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ABSTRACT

Canine oral fibrosarcoma (oFSA) is a malignant, infiltrating, mesenchymal tumour affecting the oral cavity primarily of medium to large middle aged dogs. The diagnosis often is made late in the course of the disease, due to the frequent caudal location of the tumour, and histopathology is not always sufficient to discriminate undifferentiated oFSA from other poorly differentiated malignant mesenchymal tumours occurring at the same site, especially in small biopsy samples. The literature exclusively relating to oFSA is limited and outcome data following treatment are difficult to compare. The purpose of this article is to provide an overview of the literature spanning the last 30 years, specifically with regard to different treatment modalities in their relation to prognosis of canine oFSA. Overall, the survival rate for dogs with oFSA has improved in recent years (overall survival 247–743 days, compared to 30–540 days in papers published before 2000), probably due to better surgical planning. The major concern in clinical management of canine oFSA is the high local rate of recurrence (up to 57%), whereas metastasis occurs late in about 10–14% of affected dogs. Wide surgical excision is the mainstay of treatment. Initially, the tumour was considered to be radioresistant, but a combination of surgery and radiotherapy seems to be the most promising treatment modality at present. Despite a histopathological diagnosis of a low-grade tumour, an aggressive treatment approach is always warranted to cure oFSA, but the ability to control local disease still represents the major challenge.

Introduction

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

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

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

* Corresponding author.
E-mail address: marina.martano@unito.it (M. Martano).

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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) described a 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 3–13 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 metastasis, except for one dog which already had lymph node involvement; metastases to the lymph nodes or lungs subsequently developed in 12–20% of cases. Since then, this tumour entity has been widely recognised and it is now understood that the treatment should not differ from the standard treatment for dogs with higher grade oFSAs.

Establishing a diagnosis

Clinical staging

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

Fine needle aspiration of any enlarged lymph node should be performed for clinical staging. However, lymphadenectomy and histology should be considered to reliably determine lymph node status. Fine needle aspiration of the primary mass is often unrewarding, because of the difficulty in collecting a sufficient

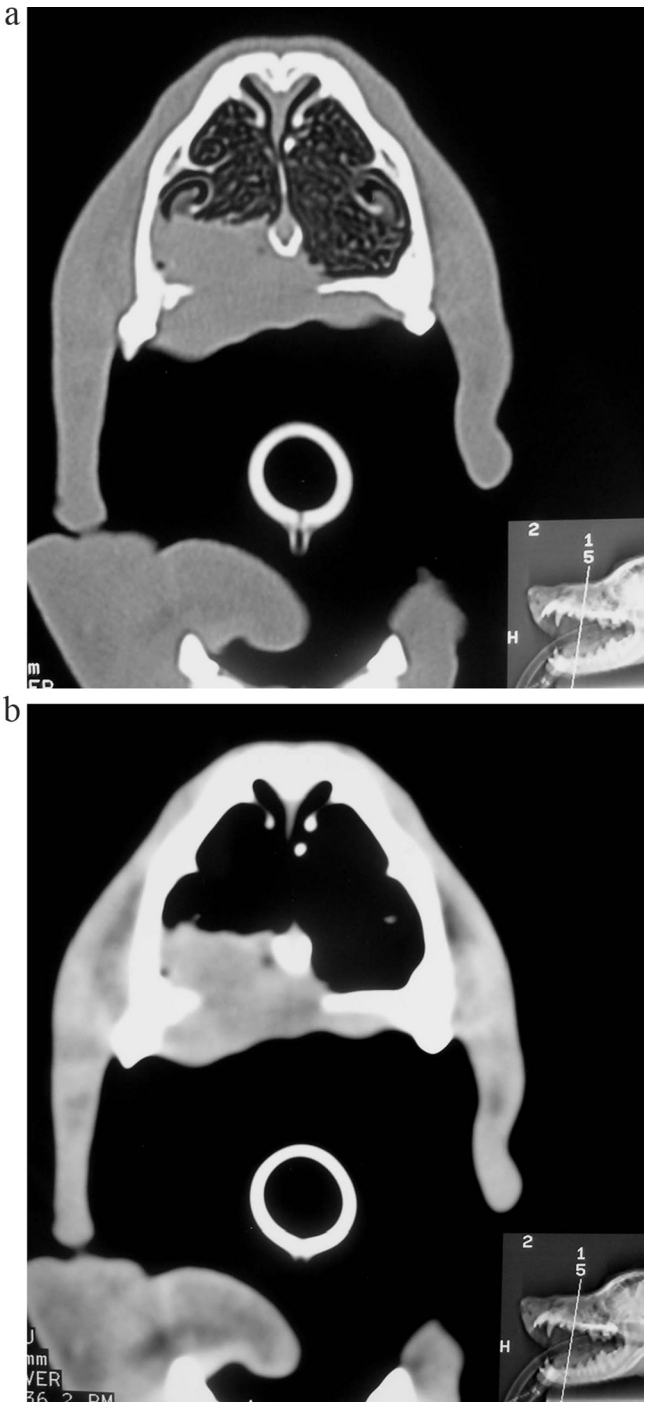

Fig. 1. Computed tomography (CT) images of an oral mass diagnosed as fibrosarcoma. (a) Post contrast scan showing bone involvement of the maxilla and invasion into the nasal cavity. (b) Soft tissue involvement in the same dog. In this case, surgery was not performed since the owners refused neoadjuvant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

number of cells for interpretive analysis by cytology, due to the intrinsic characteristics of mesenchymal tumours, and because of concurrent local inflammation and necrosis. An incisional biopsy of the primary mass is mandatory to achieve a diagnosis (Harvey, 1980; Richardson et al., 1983; Hoyt and Withrow, 1984; Vestraete, 2005). However, some authors argue that, since malignant histological type strongly influences survival, but has minimal impact on the surgical plan, it may be left up to the clinician to propose whether or not to perform an incisional biopsy. This choice is based on the owner's