REVIEW

Treatment of nasal tumours in dogs: a review

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Nasal tumours are common neoplasms in dogs and often represent a diagnostic and therapeutic challenge due to their confined location within the nasal cavities. The main goal of this review is to extract the most relevant information from a wide and often confusing evidence-based medicine on the treatment of canine nasal tumours and conclude with current recommendations. This report highlights the different therapeutic modalities available and describes their technical aspects, interests and limitations. Megavoltage radiotherapy, as the most recent treatment and standard of care, is particularly examined, especially the different types of radiotherapy units, the main protocols used and their advantages and limits. Newer and non-conventional treatments are also discussed.

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INTRODUCTION

Nasal and paranasal sinus tumours are relatively common neoplasms in dogs, accounting for approximately 1 to 2% of all cancers (Madewell *et al.* 1976) and 70% of chronic nasal diseases in this species (Finck *et al.* 2015). Other causes of chronic nasal discharge include fungal rhinitis (aspergillosis), chronic rhinitis (an inflammatory/allergic condition) and foreign bodies. Two thirds of nasal tumours are carcinomas, most commonly adenocarcinomas, although squamous cell carcinomas (SCC), undifferentiated carcinomas and transitional carcinomas are also reported. A third are sarcomas, most commonly chondrosarcomas, fibrosarcomas, osteosarcomas and undifferentiated/anaplastic sarcomas (Buchholz *et al.* 2009, Mason *et al.* 2013, Sones *et al.* 2013, Kubicek *et al.* 2016). Extranodal lymphoma can also affect the nasal cavity and, rarely, other tumours such as melanoma, mast cell tumour, angiofibroma and esthesioneuroblastoma (Burgess *et al.* 2011, George *et al.* 2016, Davies *et al.* 2017, Gumpel *et al.* 2017).

Dogs of dolichocephalic breeds are predominantly affected, in particular the golden retriever, Labrador, German shepherd dog and English springer spaniel (Mellanby *et al.* 2002, Yoon *et al.* 2008). However, any breed can be affected. There is no clear sex predilection, although a few studies have suggested a slight male predominance (Correa *et al.* 2003). The mean and median age of dogs at the time of diagnosis is 10 years but dogs of all ages can be affected, and nasal tumours have been reported in dogs as young as 1 year old (Sones *et al.* 2013). Aetiology is unknown, although one study supported a link between pollutants, in particular cigarette smoke and nasal tumours in dogs (Reif *et al.* 1998).

Clinical signs commonly seen in dogs with nasal neoplasia include epistaxis, nasal discharge, sneezing, stertor or signs of nasal obstruction, epiphora, nasal congestion and dyspnoea (Avner *et al.* 2008, Mason *et al.* 2013, Finck *et al.* 2014). Signs may progress from unilateral to bilateral. Cases with advanced disease may also present with facial deformity, exophthalmos and neurological signs such as seizures and behavioural changes (Northrup *et al.* 2001, Weeden & Degner 2016). Most nasal diseases share similar clinical signs and further diagnostic tests are required to reach a definitive diagnosis, although history and clinical signs can help to determine the most likely diagnosis (Table 1) (Ladue *et al.* 1999, Russo *et al.* 1999, Avner *et al.* 2008, Gieger *et al.* 2008, Lux *et al.* 2017).

Historically, radiography of the nasal cavities was the diagnostic imaging modality of choice and was also used for radiotherapy (RT) planning, but this has been largely replaced by computed tomography (CT) or magnetic resonance imaging (MRI) (Gieger *et al.* 2008, Agthe *et al.* 2009, Drees *et al.* 2009, Cohn 2014, Lux *et al.* 2017). Radiographic, CT and MRI features of nasal tumours have been extensively described in the literature and are summarised in Table 1. CT is superior to radiography for both diagnosis and staging, and is required for RT planning in most centres. MRI is more sensitive for identifying cerebral involvement (Drees *et al.* 2009). Imaging findings cannot differentiate types of nasal tumours, although nasal chondrosarcoma may show more specific imaging features (Jania *et al.* 2019). Therefore, rhinoscopy-guided or blind nasal biopsies are used to obtain a histological diagnosis. Two to three samples are often necessary

Table 1. Typical clinical signs and imaging findings in dogs with nasal tumour, sinonasal aspergillosis, chronic lymphoplasmocytic rhinitis and nasal foreign body

Diagnosis	Typical signalment/ history	Typical clinical signs	Typical radiographic findings	Typical CT findings	Typical MRI findings
Neoplasia	Older dogs Chronic, unilateral (can progress to bilateral) progressive signs	Stertor Unilateral (then bilateral), mucoid, mucopurulent or sanguineous nasal discharge Nasal obstruction Facial deformity/asymmetry Sneezing/reverse sneezing Epistaxis Exopthalmia Seizures/neurological signs (Burk 1992, Tasker *et al*. 1999, Lefebvre *et al*. 2005, Rassnick *et al*. 2006)	Increased soft tissue density throughout nasal cavity (often most marked caudally) with loss of the nasal turbinates Lysis of facial bones and/or the cribiform plate Soft tissue opacity in the ipsilateral frontal sinus Invasion of contralateral nasal cavity, nasopharynx and/or retrobulbar space (Gibbs *et al*. 1979, Sullivan *et al*. 1987, Thrall *et al*. 1989, Park *et al*. 1992, Morris *et al*. 1996, Russo *et al*. 1999, Tasker *et al*. 1999, Petite & Dennis 2006, Meler *et al*. 2008)	Soft tissue attenuating mass with moderate to strong contrast enhancement and lysis of the nasal turbinates. "Popcorn" mineralisation in chondrosarcoma Lysis of facial bones and/or the cribiform plate Fluid accumulation within the nasal cavity and frontal sinus Invasion of contralateral nasal cavity, nasopharynx, retrobulbar space, cranial cavity and/or subcutis (Thrall *et al*. 1989, Park *et al*. 1992, Codner *et al*. 1993, Adams *et al*. 1998, Saunders *et al*. 2003, Lefebvre *et al*. 2005, Rassnick *et al*. 2006, Kondo *et al*. 2008, Buchholz *et al*. 2009, Drees *et al*. 2009, Jania *et al*. 2019)	T2w and T1w hyperintense (to muscle) mass within the nasal cavity with mild to moderate contrast enhancement and lysis of the nasal turbinates Lysis of facial bones and/or the cribiform plate Fluid accumulation within the nasal cavity and frontal sinus Invasion of contralateral nasal cavity, nasopharynx, retrobulbar space, cranial cavity and/or subcutis (Avner *et al*. 2008, Miles *et al*. 2008, Drees *et al*. 2009, Lux *et al*. 2017)
Aspergillosis	All ages Chronic, unilateral (can progress to bilateral) progressive signs	Sneezing Unilateral progressing to bilateral mucoid/muco-purulent nasal discharge, often copious Epistaxis (mild–severe) Rhinarial depigmentation and ulceration (Burk 1992, Tasker *et al*. 1999, Lefebvre *et al*. 2005)	Increased radiolucency with mucosal thickening and loss of the nasal turbinates in (mid) nasal cavity Unilateral or bilateral Soft tissue opacity within the frontal sinus No or mild punctuate osteolysis of the facial bones (Gibbs *et al*. 1979, Sullivan *et al*. 1986, Tasker *et al*. 1999, Saunders & Van Bree 2003, Saunders *et al*. 2004, Meler *et al*. 2008)	Thickening and increased contrast enhancement of the nasal mucosa and loss of nasal turbinates giving a cavitated appearance Unilateral or bilateral Fluid accumulation and mucosal thickening within the frontal sinus No or mild punctuate osteolysis of the facial bones, sometimes hyperostosis of the frontal bone (Burk 1992, Saunders *et al*. 2002, Saunders *et al*. 2003, Saunders & Van Bree 2003, Saunders *et al*. 2004, Lefebvre *et al*. 2005)	Thickening and T1w hyperintensity of the nasal mucosa, loss of nasal turbinates giving a cavitated appearance Unilateral or bilateral Fluid accumulation and mucosal thickening within the frontal sinus No or mild osteolysis of the facial bones, sometimes hyperostosis of the frontal bone (Saunders *et al*. 2004, Miles *et al*. 2008, Furtado *et al*. 2014)
(Chronic) Inflammatory (lymphoplasmocytic) Rhinitis (can occur concurrently with Neoplasia or Aspergillosis)	Young adults Chronic, sometimes seasonal	Serous bilateral mucoid-mucopurulent nasal discharge-nasal discharge Epistaxis less common Possible obstruction/partial obstruction to nasal airflow secondary to mucus accumulation (Burk 1992, Windsor *et al*. 2004)	Diffuse increased soft tissue opacity (mild to moderate) within the nasal cavities and mild loss of visualisation of nasal turbinates Bilateral and often symmetrical No bone lysis (Gibbs *et al*. 1979, Tasker *et al*. 1999, Russo *et al*. 1999, Windsor *et al*. 2004, Meler *et al*. 2008)	Fluid accumulation (small to moderate amount) within the nasal cavities with no or minimal lysis of nasal turbinates Bilateral and symmetrical No bone lysis (Saunders *et al*. 2003, Windsor *et al*. 2004, Lefebvre *et al*. 2005)	Fluid accumulation (small to moderate amount) within the nasal cavities with no or minimal lysis of nasal turbinates, T1w hypointensity of the nasal mucosa Bilateral and symmetrical No bone lysis (Miles *et al*. 2008, Furtado *et al*. 2014)
Foreign body	Short history Sudden onset sneezing	Acute onset sneezing/reverse sneezing (may be paroxysmal) Unilateral discharge of varying types (Tasker *et al*. 1999)	Focal, sometimes patchy increased soft tissue opacity and loss of visualisation of nasal turbinates Unilateral Sometimes visualisation of a radio-opaque foreign body (Gibbs *et al*. 1979, Tasker *et al*. 1999)	Variably visible foreign body, with focal accumulation of soft tissue attenuating material and focal lysis of nasal turbinates Unilateral Focal facial bone lysis (Saunders *et al*. 2003, Saunders & Van Bree 2003, Jones & Ober 2007)	Specific features not reported in the literature yet likely similar to the CT findings. Foreign bodies are classically T1w and T2w hypointense and surrounded with fluid

to obtain a diagnostic sample as larger tumours often contain necrotic and/or inflammatory areas (Harris *et al*. 2014).

The relationship between tumour stage and prognosis is controversial, at least in part due to lack of consistency in approach and contradictory findings from small number studies (Gibbs *et al*. 1979, Morris *et al*. 1996, Henry *et al*. 1998, Mason *et al*. 2013, Mayer *et al*. 2019). Most studies report an association between CT stage at presentation and overall survival, with worse outcomes if there is CT evidence of cribriform plate involvement or extension into the brain (Kondo *et al*. 2008, Adams *et al*. 2009, Mason *et al*. 2013, Woodruff *et al*. 2018, Mayer *et al*. 2019). Similarly, the presence of lymph nodes and pulmonary metastasis has been variably associated with prognosis in the literature (Gibbs *et al*. 1979, Langova *et al*. 2004, Kubicek *et al*. 2016). It is now largely accepted that more advanced CT-based stages are associated with a poorer prognosis. The most commonly used CT staging system is shown in Fig 1 (Adams *et al*. 2009). The presence of facial deformity, dyspnoea, epistaxis and lack of improvement of clinical signs following RT have also been associated with a negative prognosis, but inconsistently (Ladue *et al*. 1999, Northrup *et al*. 2001, Gieger *et al*. 2008).

The relationship between histological diagnosis and prognosis is unclear. Most studies have not demonstrated any difference in prognosis between tumour types when treated with RT, although the cohorts tend to be small and the studies underpowered to detect subtle differences (Adams *et al*. 1998, Mellanby *et al*. 2002, Kondo *et al*. 2008, Lawrence *et al*. 2010). Sarcomas, especially chondrosarcomas, treated with RT have been associated with a better prognosis than carcinomas (Sones *et al*. 2013, Glasser *et al*. 2014), while osteosarcoma has been associated with a poor prognosis in one study (Kubicek *et al*. 2016). Conversly, sarcomas have been reported to have a lower volume reduction following RT compared to carcinomas, while their median survival times (MST) were similar when RT was followed by surgery (Morgan *et al*. 2018). Carcinomas other than adenocarcinomas (*i.e*. SCC, undifferentiated/anaplastic carcinomas) have been associated with a poorer prognosis (Gibbs *et al*. 1979, Woodruff *et al*. 2019).

Many different treatments have been used to try to cure or temporarily improve the quality of life of dogs with nasal tumours. Most therapies focus on treatment of the local disease. Historically, rhinotomy and tumour excision was the only widely available treatment, but this was associated with high morbidity/mortality and poor survival, and since the 1990s (Lana *et al*. 2004), RT has become the standard of care.

Different chemotherapeutic agents have also been used, either as single agents, or in combination with surgery or RT, often with disappointing results (Laing & Binnington 1988, Langova *et al*. 2004, De Vos *et al*. 2012, London *et al*. 2012, Woodruff *et al*. 2019). Less commonly reported treatments include cryotherapy, electrochemotherapy or photodynamic therapy (PDT) (Lucroy *et al*. 2003, Murphy *et al*. 2011, Suzuki *et al*. 2017).

Comparing the efficiency of treatments using the available literature is challenging. Many retrospective studies are hampered by case selection bias. Although there are many RT studies, these use different RT protocols and machines, and different radiation planning and delivery techniques and different statistical methods. The impact of different combinations of treatments further confuses matters, and in surgical papers, the skills/techniques of surgeons are varied. This review pulls together the available information for the different treatment options.

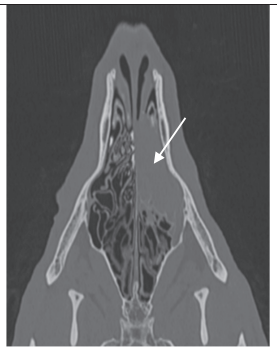
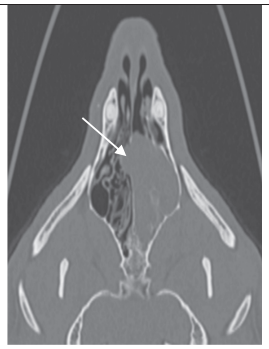
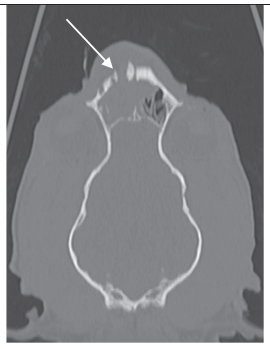
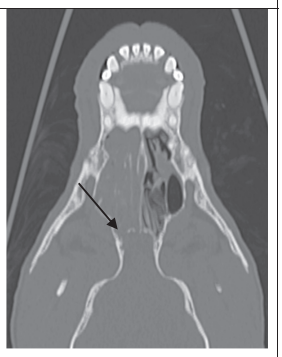
CT stage	T1	T2	T3	T4
Description	Tumour confined to one nasal passage with no bone involvement beyond turbinates	Any bone involvement beyond turbinates with no evidence of orbital, subcutaneous, submucosal involvement	Orbital, subcutaneous, submucosal or nasopharyngeal involvement	Tumour causing lysis of the cribiform plate
Example	 Tumour confined to one nasal cavity	 Tumour extension through the nasal septum	 Tumour extension through the maxillary bone within the subcutis	 Tumour extension through the cribriform plate within the cranial cavity

FIG 1. Modified Adams CT staging system for canine nasal tumours (Adams *et al*. 2009) and examples

RADIATION THERAPY FOR NASAL TUMOURS

In humans, RT is the mainstay of treatment for nasopharyngeal cancer (The Royal College of Radiologists 2016). Standard protocols for nasopharyngeal carcinoma deliver a total dose of 65 to 70 Gy, daily fractionated over 6 to 7 weeks, but hyperfractionated RT treatment (twice a day or more) has been associated with a better outcome (Baujat *et al.* 2010). The total dose administered has also been shown to be significantly associated with the prognosis in multivariate analysis and a total dose superior or equal to 70 Gy has been associated with a better outcome (Wang 1989, Ali & Al-sarraf 2000). However, this cannot be extrapolated directly to dogs as the tumours have a different histogenesis.

The requirement for general anaesthesia and costs involved in RT in dogs limit fractionation. Nevertheless, RT is currently the gold standard for treatment of nasal tumours in dogs. Multiple studies have shown efficacy, as a sole treatment or in association with surgery or chemotherapy, though the inherent variability in these studies [different machines, different RT protocols and planning, different staging systems, different patient cohorts (tumour types and concurrent treatments) and different statistical analysis], makes direct comparison difficult.

Brief history of radiotherapy

In both humans and veterinary medicine, radiation sources have evolved with time and are summarised in Fig 2. They include intranasal 192 Iridium brachytherapy devices, Cobalt 60 machines and linear accelerators, with different radiation types such as electron therapy, proton therapy and orthovoltage or megavoltage X-rays (Thompson *et al.* 1992, Northrup *et al.* 2001, Mellanby *et al.* 2002, Correa *et al.* 2003, Buchholz *et al.* 2009, Mayer-Stankeová *et al.* 2009, Maruo *et al.* 2015). Brachytherapy relies on insertion of radioactive implants (192 Iridium) directly into the tissue to treat and has been seldom used for the treatment of canine nasal tumours (Thompson *et al.* 1992). As regards external beam RT (or teletherapy), orthovoltage (200 to 500 kV) and supervoltage X-rays (500 to 1000 kV) were the most common types of radiation used in the first half of the 20th century but had limited penetration within tissues and were associated with high absorbed dose to the superficial structures and bones. The second half of the 20th century saw the development of megavoltage radiation (1 to 25 MV), first produced using Cobalt 60 units, then by linear accelerators. Since the 1990s, megavoltage X-rays produced by linear accelerators have become the most commonly used radiation both in humans and small animals (Connell & Hellman 2009, Martins 2018). 3D conformal RT, delivering computer-planned treatments using linear accelerators, provides much better dose distribution, and has been the standard of care for many years. Over the last few decades, technological advances in RT have mainly focused on improving treatment planning and radiation delivery, with the development of intensity-modulated radiation therapy (IMRT), stereotactic radiation therapy (SRT), stereotactic radiosurgery (SRS), helical tomotherapy and volumetric modulated arc therapy (VMAT). Finally, intense medical research has focused on improving RT protocols to optimise efficacy while limiting radiation toxicity (Connell & Hellman 2009). The main types and characteristics of external beam RT are presented in Fig 2.

Radiation toxicity

Radiation toxicity is one of the major drawbacks of RT, and all RT protocols have been associated with early (less than 3 months after treatment) and late (more than 3 months after treatment) toxicity (Thrall *et al.* 1993, Gieger *et al.* 2008, Belshaw *et al.* 2011, Fujiwara *et al.* 2013, Sones *et al.* 2013, George *et al.* 2016) although these are inconsistently evaluated and recorded in the veterinary literature, and most of the evidence base is retrospective studies. Grading of adverse events has been described by the Veterinary Radiation Therapy Oncology Group (Appendix S1) (Ladue & Klein 2001). Briefly, the most common radiation toxicity affects the skin, eyes, ocular and oral mucosa and less commonly brain. Early toxicities include mucositis, erythema, desquamation, conjunctivitis and ocular ulceration; late toxicities include alopecia,

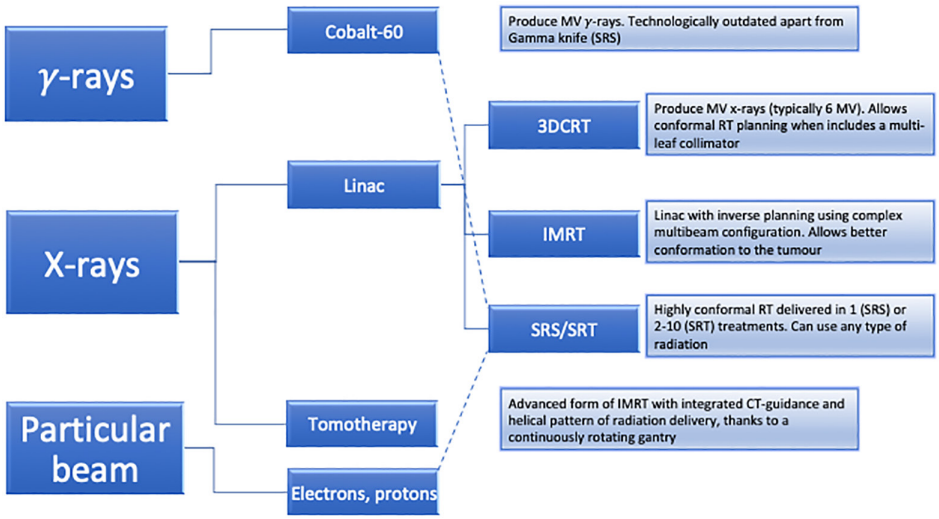


FIG 2. Main types of external beam radiotherapy (RT) units and planning systems. 3DCRT: 3D conformal RT, MV: megavoltage, IMRT: intensity-modulated RT, SRS: stereotactic radiosurgery, SRT: stereotactic RT

skin and soft tissue fibrosis, leukotrichia, keratoconjunctivitis sicca, uveitis and lens changes. Ischaemic necrosis of bone or brain is possible but infrequent with adequate planning.

Treatment planning

In order to create a standard 3D conformal RT plan (3DCRT), the basic steps are acquiring a CT scan of the patient (although a volumetric MRI scan can also be used), delineating target volumes (tumour and "margins") and organs at risk (OARs, normal tissues at risk of damage), and creating the treatment plan in planning software. In conventional 3DCRT treatment planning, the computer calculates dose from a plan that is manually optimised by the (human) planner making adjustments to try to minimise dose to OARs while ensuring adequate and homogeneous dosing of the tumour, within tight constraints. This involves the planner choosing the number and direction of beams, applying multileaf collimator (MLC) to a margin around the tumour and adjusting these manually, and selecting dynamic wedges and appropriate beam weightings (Fig 3). In contrast, IMRT relies on inverse planning, where software computes the spatial information to produce a more complex beam configuration (Lawrence *et al.* 2010). Essentially, the planner generates the desired distribution, and the computer then calculates a group of beam intensities that will produce, as closely as possible, the desired dose distribution. This allows the radiation dose to conform more precisely to the three-dimensional shape of the tumour by modulating or controlling the intensity of the radiation beam in multiple small volumes, using very many "beamlets" with different MLC configurations (and a heterogeneous dose for each beam) to achieve more precise conformation and to control precisely the dose delivered to different volumes within the treated volume.

Treatment dose and fractionation

Definitive RT treatment allows administration of a larger dose while limiting late radiation toxicity, and theoretically limiting tumour repopulation and/or repair (Connell & Hellman 2009, Nolan & Dobson 2018). Definitive protocols in dogs are most commonly daily-fractionated or administered on a Monday, Wednesday and Friday (MWF) basis. MST from a number of studies using definitive treatment are summarised in Table 2, and range from 350 to 650 days (Thrall *et al.* 1993, Morris *et al.* 1994, Mason *et al.* 2013, Sones *et al.* 2013, Tan-Coleman *et al.* 2013, Glasser *et al.* 2014). Older studies (before 1995), studies with fewer than 10 dogs, and those evaluating multimodality treatments have been excluded. The impact of the precise fractionation on outcome is unclear: Sones *et al.* (2013) reported that dogs with intranasal sarcomas receiving daily fractions had a significantly longer MST than dogs receiving a MWF protocol (Sones *et al.* 2013). To the authors' knowledge, this finding was not repeated in any similar study. Interestingly, an older study using a Cobalt source to treat 115 dogs found that MST was longer for dogs treated with three or more fractions per week (compared to less frequently) and at least 37 Gy in total (Yoon *et al.* 2008).

Due to the problem of adverse effects, palliative (hypofractionated) protocols are used to improve the dog's quality of life while minimising acute radiation toxicity and increasing survival time (compared to non-treated dogs) (Rassnick *et al.* 2006). These protocols are often used in advanced disease, or for practical and financial reasons. In patients with advanced disease, minimising acute toxicity when life expectancy is short is important. Hypofractionation makes it possible for normal cells to repair and repopulate between treatments, and this minimises acute toxicity.

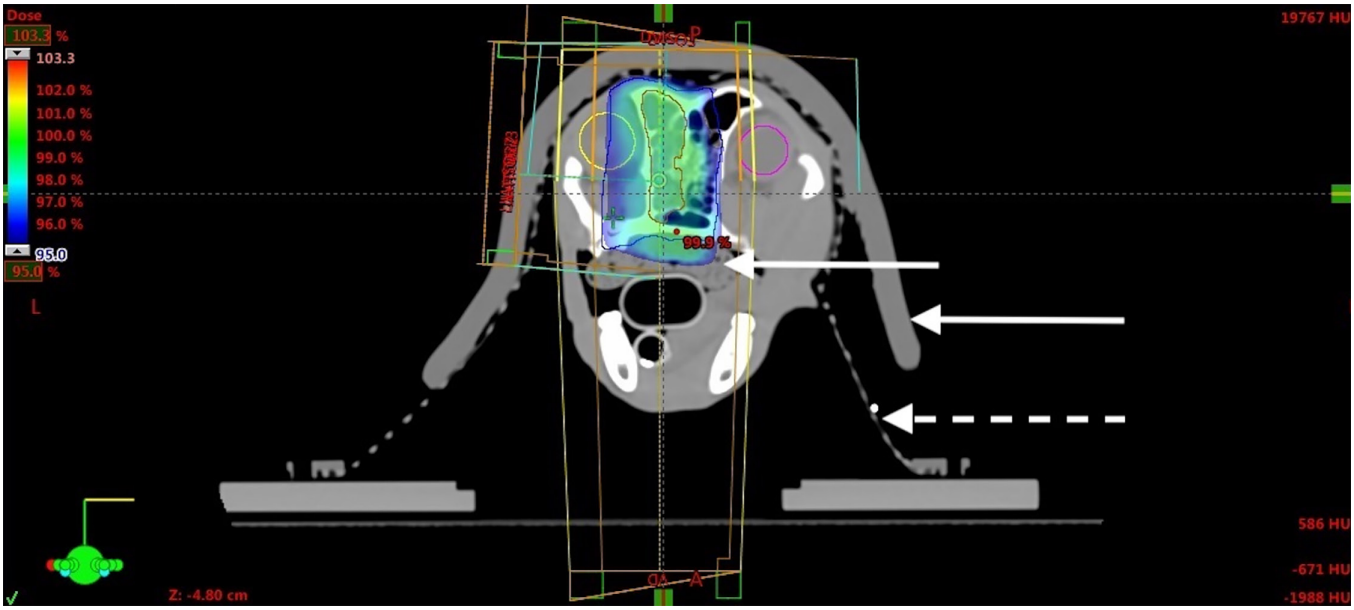


FIG 3. Three-dimensional conformal radiation therapy planning using Eclipse™, for treatment of a nasal carcinoma in a 3-year-old female neutered Staffordshire Bull Terrier. The dog is anaesthetised and immobilised using a mouldable pillow and thermoplastic mask (dashed arrow). Bolus material (white arrows) has been placed over the thermoplastic mask and in the oral cavity to improve dose distribution. The colourwash shows dose above 95%. The gross tumour volume is outlined in red and the planned treatment volume in blue, the left eye in yellow and the right eye in purple, with the brain outlined in cyan

Table 2. Outcomes for definitive fractionated RT for nasal tumours in dogs

Article	Number of dogs	RT source	Planning	RT Protocol	Adjunctive treatment†	MST‡ (days)
Adams *et al*. 1998	21	Cobalt 60	CT-based	Daily, 10 fractions, 42 Gy	None	428
Adams *et al*. 2005	40	Megavoltage RT, machine not specified	2D computer planning system	Daily, 10 fractions, 42 Gy	None	601 (19.7 months)
Hunley *et al*. 2010	12	6 MV§ linac	IMRT¶	MWF, 18 or 21 fractions, 54 or 63 Gy	5 dogs had chemotherapy	446
Lawrence *et al*. 2010	31	6 MV linac	IMRT	Daily, 10 fractions, 42 Gy	None	420
Mason *et al*. 2013	22	6 MV linac	3D computer planning system	MWF, 12 fractions, 48 Gy	None	427
Sones *et al*. 2013	35	Various linacs	Not specified	Daily, 10 to 20 fractions, 42 to 60 Gy	Few dogs had surgery and/or chemotherapy	641
Sones *et al*. 2013	40	Various linacs	Not specified	MWF, 10 to 12 fractions, 45 to 54 Gy	Few dogs had surgery and/or chemotherapy	347

RT Radiotherapy, MST Median survival times, IMRT Intensity-modulated radiation therapy, MWF Monday, Wednesday and Friday.
†NSAIDs and antibiotics are not included in the adjunctive treatments.
‡MST. When in months are approximated in days by multiplying by a factor 30.5.
§Megavolts.
¶Intensity-modulated radiation therapy.

Although the risk of late radiation toxicity is increased by large fraction size, this is less of a consideration if it is unlikely that the patient will live long enough to develop significant late radiation toxicity. Palliative RT protocols (summarised in Table 3) tend to deliver 32Gy or less in fractions of 5 to 8 Gy once weekly (Mellanby *et al*. 2002, Gieger *et al*. 2008, Buchholz *et al*. 2009, Belshaw *et al*. 2011, Maruo *et al*. 2011, Fujiwara *et al*. 2013, Sones *et al*. 2013, Tan-Coleman *et al*. 2013). The MSTs of dogs treated with palliative RT *versus* definitive RT are generally shorter (median of MSTs in Table 3 is 259 days, compared to 428 days for the fractionated protocols in Table 2).

New perspectives in veterinary radiation therapy

Advances in technology have allowed the development of further techniques, including helical tomotherapy, SRS and SRT. Helical tomotherapy is an advanced form of IMRT with an integrated image guidance (megavoltage CT) that allows administration of a fan beam of radiation while correcting for imprecisions in positioning (Gutiérrez *et al*. 2007). The main advantage of IMRT/helical tomotherapy over conventional RT is a significant reduction of radiation toxicity with equivalent tumour control (Lawrence *et al*. 2010, Glasser *et al*. 2014).

SRS and SRT are based on similar principles of highly targeted, stereotactic treatment and are only available in few referral centres in the United States (Nolan & Gieger 2019). Their difference is in fractionation. While SRT is often hypofractionated (three to five treatments), SRS delivers a single, very high dose of radiation. SRT has been used in a study on 29 dogs with (non-lymphomatous) nasal tumours that received 30 Gy of radiation in 3 daily fractions of 10 Gy. The median survival time was 354 days (Gieger & Nolan 2018). In a second study SRT was used on 28 dogs that received three fractions of 9 or 10 Gy, or a single fraction of 20 Gy (the latter technically represents SRS yet the survival times were not detailed for each protocol). The median survival time was 388 days (Mayer *et al*. 2019). A third study involved 19 dogs received 27 Gy in 3 daily treatments of 9 Gy. The MST was 399 days (Glasser *et al*. 2014). SRS sensu stricto has been reported once in the veterinary literature (Kubicek *et al*. 2016). Fifty-seven dogs with nasal tumours received a single dose of 18.75 to 56 Gy (median 30 Gy): medial survival time was 259 days (8.5 months). It is noteworthy that amongst these dogs, seven had osteosarcoma and had a significantly shorter survival time (3.1 months). As yet, it is unclear if these methodologies can achieve the same results as conventional 3DCRT. In addition, absolute precision is required, as large fractions can result in significant toxicities to normal tissues.

Other types of radiation therapy

Other forms of RT reported in nasal tumours include proton therapy, which relies on the fact that at the end of the proton's track, the radiation dose rapidly falls off to zero (Bragg peak). This allows accurately targeted radiation delivery while sparing healthy tissues. Mayer-Stankeová *et al*. described nine dogs with nasal tumours treated with various protocols (4 days a week, 10 to 17 fractions, 35 to 59.5 Gy) (Mayer-Stankeová *et al*. 2009). The MST was 385 days, similar to conventional RT treatment yet radiation toxicity was generally less severe. A second study used a mathematical model to compare RT planning and probabilities of radiation toxicity between proton and photon therapy (Kaser-Hotz *et al*. 2002), and showed that proton therapy would benefit dogs with tumours with a complex shape as it allowed better conformation. Proton beam linacs have been historically very expensive but more affordable machines are available nowadays. While it is a promising technique, it is unlikely to become wildly available to our veterinary patients in the near future.

Orthovoltage RT is considered inappropriate for nasal tumours, as it uses 200 to 500 kV photons, which cannot penetrate through bone into the nasal cavity and lead to a high absorbed dose to the skin and bone. It has however been used infrequently in the past, often in conjunction with debulking surgery (Thrall & Harvey 1983, Ladue *et al*. 1999, Northrup *et al*. 2001). Northrup *et al*. (2001) evaluated post-operative adjunctive orthovoltage therapy in 42 dogs with nasal tumours that had debulking surgery prior to a "definitive" protocol of RT

Table 3. Outcomes for palliative RT for nasal tumours in dogs

Article	Number of dogs	RT machine	Planning	RT protocol	Adjunctive treatment†	MST‡ (days)
Belshaw *et al*. 2011	42	4 MV¶ linac	CT-based manual planning	Weekly, 4 fractions, 34 to 36 Gy	None	201
Buchholz *et al*. 2009	38	6 MV linac	3D computer planning system	Weekly, 3 to 4 fractions, 24 to 32 Gy or Biweekly, 4 to 5 fractions, 24 to 30 Gy or daily, 10 fractions, 30 Gy	3 dogs had chemotherapy, 3 dogs had a second course of RT, 3 dogs had both	308 (10.1 months)
Fujiwara *et al*. 2013	38	4 MV linac	3D computer planning system	Weekly, 6 to 10 Gy/fractions (median 8), 16.2 to 32.4 Gy (median 32)	7 dogs had surgery, 5 dogs had a second course of RT	512
Gieger *et al*. 2008	48	Linac or Cobalt 60	Various methods	16 to 40 Gy (median 24), 4 to 10 Gy/ fractions (median 8)	11 had a second course of RT	146
Maruo *et al*. 2011	63	4 MV linac	3D computer planning system	Weekly, 4 fractions, 10 to 40 Gy (median 32)	None	197
Mellanby *et al*. 2002	56	4 MV linac	Radiography-based manual planning	Weekly, 4 fractions, 36 Gy	None	212
Sones *et al*. 2013	18	Various linacs	Not specified	4 to 8 fractions, 20 to 36 Gy	Few dogs had surgery and/or chemotherapy	305
Tan-Coleman *et al*. 2013	18	6 MV linac	Various methods	Daily, 5 fractions, 20 Gy	6 dogs had chemotherapy, 6 had a second course of RT	309

RT Radiotherapy, MST Median survival times.
†NSAIDs and antibiotics are not included in the adjunctive treatments.
‡When in months are approximated in days by multiplying by a factor 30.5.
¶Megavolts.

(Northrup *et al*. 2001). The MST was 221 days, which is comparable to surgery alone, and only 39% of dogs had a disease-free period. In addition, acute skin toxicity was very high. Similarly, due to limited tissue penetration, electron beam RT has no place in RT of nasal tumours in dogs. However, electrons have been used intra operatively after surgical excision to irradiate the cribriform plate (Maruo *et al*. 2015). Since this technique does not address residual disease in other areas, it is unlikely to be of meaningful benefit, and may increase surgical time and morbidity.

Reirradiation and radiation boost

Recurrence of nasal tumour is the most frequent cause of death in dogs undergoing RT. Several studies have evaluated the use of a dose boost (slightly increasing the dose per fraction or adding an extra fraction on one or more days of treatment) to decrease the incidence of tumour recurrence (Thrall *et al*. 1993, Ladue *et al*. 1999, Gutiérrez *et al*. 2007, Bradshaw *et al*. 2015, Soukup *et al*. 2018). Thrall *et al*. (1993), found a boost technique was associated with unacceptable radiation toxicity and failed to increase the MST (Thrall *et al*. 1993). Consequently, the boost technique has not become established. A more promising method called integrated boosts allows an increase in delivered dose in the centre of the tumour while avoiding healthy tissue: this relies on IMRT (Gutiérrez *et al*. 2007, Bradshaw *et al*. 2015). A recent pilot study in nine dogs used IMRT with an integrated boost, with acceptable side effects (Soukup *et al*. 2018). Clearly boost techniques are most likely to be useful with highly accurate treatment planning and may be incorporated in an IMRT approach.

Reirradiation at recurrence has been described in several studies, summarised in Table 4 (Bommarito *et al*. 2011, Gieger *et al*. 2013, Sones *et al*. 2013, Rancilio *et al*. 2016). Overall, it seems that re-irradiation increased the survival time in dogs with nasal tumours, although progression free intervals were shorter after second irradiation. This is possibly due to lower doses used and/or selection of radiation-resistant subpopulations of tumour cells during the first course of RT. A second course of RT is also associated with a greater risk of significant side effects, particularly late side effects like ischaemic necrosis.

Conclusion on radiotherapy for canine nasal tumours

In summary, RT is currently the gold standard for dogs with nasal tumours. Fractionated (definitive) treatment is associated with a longer MST but palliative treatment requires fewer anaesthetic events and is less expensive and constraining for the owners. Newer treatments such as IMRT, SRS and SRT are associated with fewer side effects with potentially acceptable efficacy, and a significant reduction in the number of treatments. Repeat irradiation is a possible rescue therapy.

SURGICAL TREATMENT OF NASAL TUMOURS

Surgical excision was the main treatment of nasal tumours in dogs for decades, mostly during the second half of the 20th century, alone or in combination with chemotherapy and/or RT (Laing & Binnington 1988, Henry *et al*. 1998). However, high complication rates and short survival were reported, and it is no longer recommended as a standard therapy.

Three surgical approaches to the nasal cavities are described (Weeden & Degner 2016). The dorsal approach allows access to the entire nasal cavities and the frontal sinuses and was most commonly used. Briefly, a dorsal midline incision is made at the level of the nasal cavities and a "lid" osteotomy performed. The

Table 4. Outcomes for palliative re-irradiation for nasal tumours in dogs

Article	Number of dogs	RT machine	Planning	RT Protocol	Adjunctive treatment†	MST‡ (days)
Bommarito *et al*. 2011	9	8 MV¶ linac	3D computer planning system	First course of fractionated RT: 44 to 55 Gy (median 50 Gy), 15 to 20 fractions (median 18) Second course: 23 to 44 Gy (median 36 Gy), 14 to 20 fractions (median 18)	5 dogs had chemotherapy, 1 dog had surgery	927 total time
Gieger *et al*. 2013	37	Various linacs	Various methods	First course of palliative RT: median dose of 24Gy in 3 fractions Second course: median dose of 20Gy	None	453 days from the first treatment and 180 days from the second treatment
Sones *et al*. 2013	8	Linac	Not specified	Various protocols	Not specified	654 total time

RT Radiotherapy, MST Median survival times.
†NSAIDs and antibiotics are not included in the adjunctive treatments.
‡When in months are approximated in days by multiplying by a factor 30.5.
¶Megavolts.

ventral approach allows access to the nasal cavities and nasopharynx, via a central window through the hard palate. Finally, a combined rostrolateral nasal approach allows access to the rostral part of the nasal cavities and nasal septum via a lateral rhinotomy on the side of the mass.

The bulk of the nasal tumour and the nasal turbinates are usually ablated using rongeurs, with extra care not to tear the cribiform plate and accidently penetrate the cranial cavity. Surgery is associated with significant haemorrhage and appropriate haemostasis is required [electrocoagulation, digital pressure or iced saline spiked with epinephrine (1:100,000)] (Maruo *et al*. 2015, Weeden & Degner 2016). Temporary occlusion of the external carotid artery using vascular clamps can decrease haemorrhage and can safely be used for 2 to 3 hours (Hedlund *et al*. 1983).

Complications are frequent, and include extensive subcutaneous emphysema affecting the head (or even the entire body) (Adams *et al*. 2005). Providing a temporary "blow hole" over the dorsal rhinotomy site during the first week after surgery reduces risk. Due to haemorrhage, hypovolaemia or anaemia may develop and require transfusion. Aspiration pneumonia has also been reported. Finally, late complications inherent to extensive turbinectomy include secondary fungal or bacterial rhinitis (Adams *et al*. 2005, Weeden & Degner 2016).

Post-operative care is intensive and includes pain management, antibiotherapy, wound cleaning and removal of blood clots obstructing the nares. Pain and decreased sense of smell can diminish the dog's appetite. Warm and appetising food is recommended. In certain cases, syringe feeding or placement of an oesophageal tube can be necessary (Weeden & Degner 2016).

Surgical therapy alone has reported median survival times of 2 to 7 months, and bilateral involvement is a negative prognostic factor (Bradley & Harvey 1973, Henry *et al*. 1998). In one study of 15 dogs, clinical signs resolved in nine dogs post-surgery and persisted in four dogs. The two remaining dogs died post-operatively (Laing & Binnington 1988). Although surgery is considered efficient in improving the quality of life, the median survival times are similar to those of dogs receiving no treatment (MacEwen *et al*. 1977). The studies assessing efficacy of surgical excision on nasal tumours have mostly been carried on at the end of the last century and progress in surgery and anaesthesia may make surgery more viable, but the fundamental problems of inability to achieve adequate local margins and the intensely haemorrhagic nature of the tissue will remain.

Surgical exenteration of nasal tumours has also been used in conjunction with other treatments, including not only RT and chemotherapy but also PDT and electrochemotherapy (Thrall & Harvey 1983, Thompson *et al*. 1992, Thrall *et al*. 1993, Henry *et al*. 1998, Northrup *et al*. 2001, Lucroy *et al*. 2003, Adams *et al*. 2005, Yoon *et al*. 2008, Maruo *et al*. 2015, Bowles *et al*. 2016, Suzuki *et al*. 2017). Two studies failed to show a beneficial effect of surgery on survival time compared to RT alone (Henry *et al*. 1998, Yoon *et al*. 2008), and patients who had RT had the longest survival in one multimodality study (Henry *et al*. 1998). Conversely, two studies found a significant increase in survival time in dogs receiving surgery and RT *versus* RT alone (Morris *et al*. 1994, Adams *et al*. 2005). Four other studies (on 18, 42, 16 and 32 dogs, respectively) showed a MST of 23, 7.4, 15.2 and 14.5 months in dogs treated with surgery and RT, which is similar to reported MST in dogs treated with RT alone (Thrall & Harvey 1983, Northrup *et al*. 2001, Bowles *et al*. 2016, Morgan *et al*. 2018).

Tumour resection has also been combined with PDT and single course electron beam therapy (Maruo *et al*. 2015). Briefly, PDT uses a locally or intravenously administered photosensitizer that, when irradiated with light of a specific wavelength, reacts with oxygen to release reactive singlet oxygen molecules (free radicals). Anti-tumour effects are due to direct cytotoxicity, vascular damage and inflammatory reaction. One study in six dogs treated with surgical resection followed by intra-operative acridine orange PDT reported a MST of 13 months (Maruo *et al*. 2015). Three of these dogs had cribiform plate involvement and also received a single treatment (20 Gy) of intraoperative electron beam RT. Finally, there was a single case report of the use of electrochemotherapy in a dog with intranasal canine transmissible venereal tumour (Suzuki *et al*. 2017). Electrochemotherapy relies on electroporation and electropermeabilisation of cellular membranes under the action of an electric field. Locally administered chemotherapy can better penetrate the cells without the adverse effects associated with systemic chemotherapy. After surgical debulking

the nasal cavities were filled with a solution of bleomycin and an electrical field was applied between two electrodes placed in the nasal cavities. The dog was still alive without recurrence 1 year after the procedure. This technique has not yet been tested on a larger cohort dogs. Clearly, there are safety concerns about local, topical use of bleomycin in this setting.

In summary, surgical resection as the sole treatment of nasal tumours is not recommended, as it does not offer any advantage over more recent treatments, and has significant morbidity and mortality. Several studies suggest that surgical debulking prior to RT might improve prognosis, compared to RT alone, while others refute this. A large scale, randomised prospective study would probably be necessary to answer this question. It may be better to work to improve survival through improving RT by embracing IMRT technology and the possibility of boost technique for definitive intent, with 3D-planned reirradiation likely to be well tolerated.

CHEMOTHERAPY FOR NASAL TUMOURS

Chemotherapy

In humans with nasopharyngeal carcinoma, the classic treatment regimen is based on chemoradiation with or without induction chemotherapy. This is based on the principle that chemotherapy will treat and/or prevent regional and distant metastatic disease while RT treats the primary site. In addition, chemotherapeutic agents can potentiate the effect of RT. In humans, most of these tumours are non-keratinising carcinomas or squamous cell carcinomas, with a relatively high-metastatic potential. However, the metastatic rate in canine nasal tumours is relatively low, and most are adenocarcinomas. In addition, in humans the results of randomised clinical trials and meta-analyses are unfortunately conflicting and a significant number of them fail to demonstrate an increase in survival time with the addition of chemotherapy to RT (Wang 1989, Liu *et al.* 2018).

Despite its apparent lack of efficacy, chemotherapy has been used in many studies evaluating outcome and survival of dogs with nasal tumours (Hahn *et al.* 1992, Henry *et al.* 1998, Lana *et al.* 2004, Langova *et al.* 2004, Tan-Coleman *et al.* 2013, George *et al.* 2016, Woodruff *et al.* 2019). Drugs evaluated for solid tumours include doxorubicin, carboplatin, cisplatin, mitoxantrone, fluorouracil-cyclophosphamide or even L-phenylalanine mustard, but the most popular remains carboplatin. Standard lymphoma protocols have been used for nasal lymphoma, and this is appropriate.

Chemotherapy is most often used as an adjunct to local therapy, but use as a sole treatment has been reported and is summarised in Table 5 (Hahn *et al.* 1992, Langova *et al.* 2004, Woodruff *et al.* 2019). This likely reflects lack of access to RT. The largest study describes 29 dogs with various types of nasal tumour, treated with 1 to 6 cycles of alternating carboplatin (300 mg/m^2) and doxorubicin (30 mg/m^2), given at three-week intervals. Dogs also received daily piroxicam (0.3 mg/Kg), and there was no piroxicam only control group. Overall median survival time for dogs in the study was 234 days (range 12 to 1698 days). Five dogs also received a rescue chemotherapy treatment. Based on clinical signs, three dogs had a complete response, 13 dogs had a partial response, six dogs had stable disease and six dogs had progressive disease (Woodruff *et al.* 2019). Similarly, Hahn *et al.* (1992) evaluated the survival of 11 dogs with nasal adenocarcinoma treated with 2 to 8 cycles of cisplatin at a dosage of 60 mg/m^2 of body surface, given at 3-week intervals. The radiographic response rate was 27% and the median survival time 140 days (20 weeks) (Hahn *et al.* 1992). Langova *et al.* (2004) reported eight dogs with nasal tumours (seven carcinomas and one osteosarcoma) receiving chemotherapy as a sole treatment (Langova *et al.* 2004). All dogs were treated with alternating doses of carboplatin 300 mg/m^2 IV and doxorubicin 30 mg/m^2 IV every 3 weeks for eight doses total. The dogs also received piroxicam at a dose of 0.3 mg/kg by mouth once daily. Again, there was no piroxicam only control group. Complete remission was achieved in four dogs, partial remission occurred in two dogs and two had stable disease, based on CT evaluation: There was resolution of clinical signs after one to two doses of chemotherapy in all dogs. The dogs had remission times ranging from 150 to 960 days: remission times are based on when progression was detected and this was likely when the dog was presented with compatible clinical signs. No progression free intervals or survival times were reported.

Even earlier, Henry *et al.* (1998) evaluated 64 dogs with nasal adenocarcinoma that received variable combination of surgery, RT and chemotherapy (Henry *et al.* 1998). Chemotherapy was not associated with a significant increase in survival, although dogs that received fluorouracil-cyclophosphamide chemotherapy had a median survival time longer than other dogs. RT was associated with the best outcomes in this study: dogs that received RT had a significantly longer median survival time (424 days) than dogs that did not (126 days).

George *et al.* (2016) evaluated the efficacy of RT and chemotherapy on canine nasal lymphoma (George *et al.* 2016). In the intermediate to high-grade lymphoma group, cases treated

Table 5. Outcome for chemotherapy (as a sole treatment) for dogs with nasal tumours

Article	Number of dogs	Chemotherapy protocol	MST (days)
Hahn *et al.* 1992	11	2 to 8 cycles of cisplatin 60 g/m^2 IV every 3 weeks	140
Langova *et al.* 2004	8	Alternating doses of carboplatin 300 mg/m^2 IV and doxorubicin 30 mg/m^2 IV every 3 weeks for 8 treatments. Piroxicam 0.3 mg/kg PO once daily	210
Woodruff *et al.* 2019	29	Alternating doses of carboplatin 300 mg/m^2 IV and doxorubicin 30 mg/m^2 IV every 3 weeks for 6 treatments. Piroxicam 0.3 mg/kg PO once daily. Many dogs only received a partial course of chemotherapy and 5 dogs received a rescue protocol	234

MST Median survival times.

with RT ± chemotherapy (11 dogs) had an MST of 455 days and those treated with chemotherapy alone (six dogs) had an MST of 157 days, though chemotherapy was not standardised and some patients received chemotherapy that would not be considered standard of care (chlorambucil-prednisolone), making the data difficult to interpret. In addition, the difference in survival time between these two groups was not statistically significant, likely due to the small number of dogs included.

Some chemotherapy agents (including cisplatin) can act as radiation sensitizers and potentiate cell death. An intramuscular implant of slow-releasing cisplatin was evaluated in 51 dogs, in conjunction with RT (Lana *et al.* 2004). The implant was overall well tolerated (although six had to be removed due to local toxicity) the MST was 474 days, similar to other studies using RT alone.

OTHER MEDICAL THERAPIES

Toceranib, an inhibitor of tyrosine kinases, has recently been evaluated in the treatment of sinonasal tumours in dogs (De Vos *et al.* 2012, London *et al.* 2012). Toceranib was used in seven dogs with nasal tumours at a median dose of 2.7 mg/kg on a Monday–Wednesday–Friday schedule (London *et al.* 2012). Four of these dogs received RT before treatment with toceranib. Two dogs had a follow-up CT and showed complete remission and stable disease, respectively. Three other dogs showed clinical improvement. The median duration of treatment for these five dogs was 18 weeks but no MST was calculated. Most dogs experienced some side effects, mainly gastro-intestinal, but treatment was overall well tolerated. De Vos *et al.* reported a dog with primary frontal sinus squamous cell carcinoma that partially responded to toceranib, with an overall survival time of 237 days (De Vos *et al.* 2012). Although numbers were low, these studies indicate that toceranib can be used and may be beneficial in dogs with nasal tumour. This is consistent with the fact that many canine nasal carcinomas express the vascular endothelial growth factor receptor (VEGFR), a target of this tyrosine kinases inhibitor (Gramer *et al.* 2017).

Non-steroidal anti-inflammatories have been commonly used for the treatment of nasal tumours both for reduction of the inflammatory reaction that often accompanies nasal tumours, but also for anti-COX-2 activity. COX-2 is expressed in 71 to 95% of canine nasal carcinomas (Belshaw *et al.* 2011, Cancedda *et al.* 2015). One study on 24 dogs compared survival and quality of life of dogs treated with either RT and firocoxib (group 1) or RT alone (group 2) (Cancedda *et al.* 2015). There was no difference in MST (group 1335 days; group 2, 244 days). However, the dogs' activity and appetite were significantly improved with the addition of firocoxib to the treatment regimen. The impact of piroxicam on survival in the chemotherapy studies reported above is unknown.

Other treatments of nasal tumours

Electrochemotherapy is rarely used in nasal tumours and has been discussed above. This section will focus on PDT and cryoablation (Lucroy *et al.* 2003, Osaki *et al.* 2009, Murphy *et al.* 2011). For both of these techniques, a major challenge is ensuring adequate dosage of the tumour without the accurate dosimetry applied to RT techniques.

PDT has been briefly discussed in the surgical section. PDT as a sole treatment is reported in three dogs and one cat (Lucroy *et al.* 2003). Most animals in this case series received several courses of PDT and all showed resolution of their clinical signs quickly after the PDT. The only side effect noted was self-limiting, non-painful facial swelling for 24 to 72 hours after treatment. Survival times ranged from 14 weeks to more than 54 weeks (dog still alive at the time of publication).

A second non-conventional treatment, cryoablation, was first reported in the 1980s and required a rhinotomy and surgical debulking followed by spraying or pouring liquid nitrogen into the surgical site. The MST in 12 dogs was only 4.5 months and complications were severe (Withrow 1982). In a recent paper, a transnasal approach has been used, abrogating the need for concurrent surgery (Murphy *et al.* 2011). A high-pressure Argon circulating cryoprobe was placed within the mass under CT-guidance and the volume of tissue treated was monitored by visualisation of a freeze ball using CT, and freeze–thaw cycles induced. Transient mild epiphora was the only side effect noted. On follow-up CT, marked reduction in the size of the tumour was noted and the dog survived for 21 months after cryoablation and died of a cause presumably unrelated to the nasal tumour.

Although only tested on few animals, both these treatments showed some efficacy in the reports. In addition, they were associated with minor acute side effects and no late side effects. PDT and cryoablation lack accurate dosimetry and planning and are unable to treat beyond the nasal cavity. For these reasons, it is unlikely they will replace RT but could represent adjunctive treatments, techniques for short-term palliation or rescue options for recurrent disease. Further research is needed to evaluate their efficacy.

CONCLUSION

The current gold standard in the treatment of canine nasal tumours is RT, whether definitive or palliative. Recent advances in RT machines, techniques, training and 3D planning softwares allow better tumour control while reducing radiation toxicity. Surgery is not currently recommended as a sole or concurrent treatment or prior to RT as morbidity and mortality largely outweigh the potential improvement in the outcome. Chemotherapy alone is of debatable value, with relatively low response rates, but has been used when RT is unavailable. NSAIDs may improve the quality of life of dogs undergoing RT yet there is no proven role in tumour control. There may also be a role for toceranib in a multimodality or palliative approach. Experimental techniques include post-RT exenteration, transnasal PDT and transnasal cryoablation.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Supporting Information

The following supporting information is available for this article:

Appendix S1. Veterinary Radiation Therapy Oncology Group (VRTOG) acute and late radiation.