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Endoscopic laser debulking of nasal tumors in dogs after curative intent radiotherapy
–
a descriptive feasibility study.

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1. General introduction

The aim of this study is to describe and evaluate a novel endoscopic laser debulking treatment plan, evaluating technical feasibility, complications, and clinical outcome of nasosinal neoplasia in dogs. This introduction will cover the normal sinonasal anatomy, types of neoplasia, clinical and pathological behavior of the tumor, diagnosis, current treatment modalities and reasoning behind possible novel treatment options.

1.1 The anatomy of the sinonasal area

The nose consists in a broad sense of the external nose, the paranasal sinuses, and the paired nasal cavities.[1] Dorsally the nose is formed by the nasal bones, laterally by the maxillae and the palatine processes of the incisive bones and ventrally by the maxillae and the palatine bones. The cribriform plate of the ethmoid bone restricts the nose caudally, separating nasal cavity from the brain. Ventrally the nasal cavity connects with the nasopharynx and dorsally with the frontal sinuses, which are caudally bordered by the calvarium. The nose is divided into the left and right nasal cavities by the median septum; the rostral continuation of the crista galli of the ethmoid bone. The ethmoid bone consists of hyaline cartilage of which the caudal part ossifies with age.[2]

The muzzle is formed by the rostral portion of the mandible and maxilla and the apex of the nose.[2] Each species and also each dog breed has a different form, size and nature of the muzzle and nostrils. The area around the nostrils of dogs is sharply demarcated from the unmodified skin and hairless.[1,2] The nasal plane, or planum nasale, is divided by the philtrum, a median groove which continues ventrally to divide the upper lip.[1,2] Dogs always have a moistened nasal plane created by an abundant secretion of the glands of the nasal mucosa. The secretion is mainly produced by the lateral nasal glands which are situated within the maxillary recess (recessus maxillaris) and some smaller glands in the mucosa.[1,2]

The nasal cartilages support the external nares. Attached to the rostral end of the nasal septum are the lateral nasal cartilages from which they extend ventrally and dorsally; cartilage nasi lateralis dorsalis and cartilage nasi lateralis ventralis. The nasal cartilages thereby determine the opening and the form of the nostrils. The ventral and dorsal nasal cartilages are connected with each other.[2] The nasal vestibule is the cranial end of the nasal cavity; the part where the nostrils surround the nasal vestibule and come in contact with the nasal mucosa, creating a sharply defined line at which several ducts may open.[1,2] For example the nasal puncta of the nasolacrimal duct is located caudally of the vestibule, and in dogs the smaller and less distinct openings of the serous lateral nasal glands also secrete in this region.[2]

As earlier described, the nasal cavity is divided by the nasal septum into a left and right side. The nasal cavity (cava nasi) start at the nostrils and runs down to the cribriform plate of the ethmoid bone. The interior of the nasal cavity consist of nasal conchae (conchae nasals): cartilaginous or ossified scrolls that are covered with nasal mucosa. The complex conchae provides a wider surface of the respiratory area, in combination with the higher number of olfactory receptor cells this makes that dogs have an excellent olfactory sense. Under the mucosa various anastomosing vessels form the vascular plexii. The nasal cavity is connected through the choanae caudoventrally with the nasopharynx.[2]

The conchae that is the longest and extends the furthest into the nasal cavity is the endoturbinate I. It also forms the osseous base of the concha nasalis dorsalis. Surrounding the first endoturbinate is the endoturbinate II forming the bony part of the

concha nasalis media. The second to fourth endoturbinates are very well developed in dogs. In contrast to the dorsal and middle concha, the ventral nasal concha, also known as the concha nasalis ventralis, is part of the maxilla.[2]
The conchae divide the nasal cavity in different air-containing spaces and clefts, creating three nasal meatuses:

- Dorsal nasal meatus (meatus nasi dorsalis): the passage between the dorsal nasal concha and the roof of the nasal cavity, leading to the furthest part in the cavity. Presents air to the olfactory mucosa.
- Middle nasal meatus (meatus nasi medius): between the ventral and dorsal nasal conchae. Communicates with the paranasal sinuses.
- Ventral nasal meatus (meatus nasi ventralis): the area created between the floor of the nasal cavity and the ventral nasal conchae. This is the principal pathway for air flowing into to nose and to the pharynx.

The longitudinal area on each side of the nasal septum is called the common nasal meatus (meatus nasi communis), communicating with all the other nasal meatuses.[2]

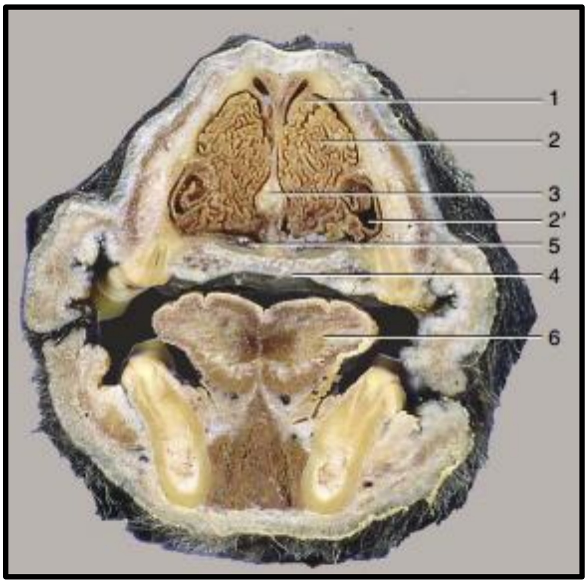

Fig. 1: Transverse section of the canine head at the level of P2.
1. dorsal concha, 2. ventral concha. 2' recess of ventral concha. 3. nasal septum. 4. hard palate. 5. venous plexus in nasal mucosa. 6. tongue. (from Dyce, 2010)

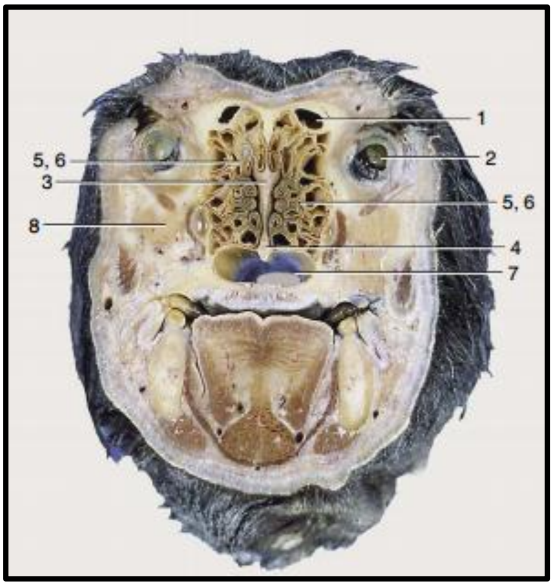

Fig. 2: Transverse section of the canine head at the level of the eyeball.
1. frontal sinus, 2. eyeball, 3. ethmoid bone, 4. vomer, 5&6. ethmoidal conchae, 7. choana, 8. zygomatic gland. (from Dyce, 2010)

The nasal mucosa merged with the underlying periosteum varies in thickness, for example some areas ventrally are thicker. Mucosal thickness varies with the degree of vascular congestion, during congestion of the vessels they greatly obstructed the airflow, creating the stuffiness that's also seen during a cold.[1]
Other functions of the nasal cavity, apart from olfaction, is warming, humidifying and cleansing the incoming air respectively by passing over the very vascular mucosa, by serous nasal secretion and vaporization of the tears, and by contact with the secretion of

many scattered mucous glands. The secretions of the mucous glands create a layer on the nasal mucosa, trapping droplets and particles that come in contact with it. The cilia of the epithelium move this layer towards the pharynx were it can be swallowed.[1]

Paranasal sinuses are air-filled cavities between the internal and external lamina of the skull bones. The following paranasal sinuses (sinus paranasales) can be found in the dog: sinus maxillaris, sinus frontalis, sinus platinus and sinus sphenoidalis.[2]

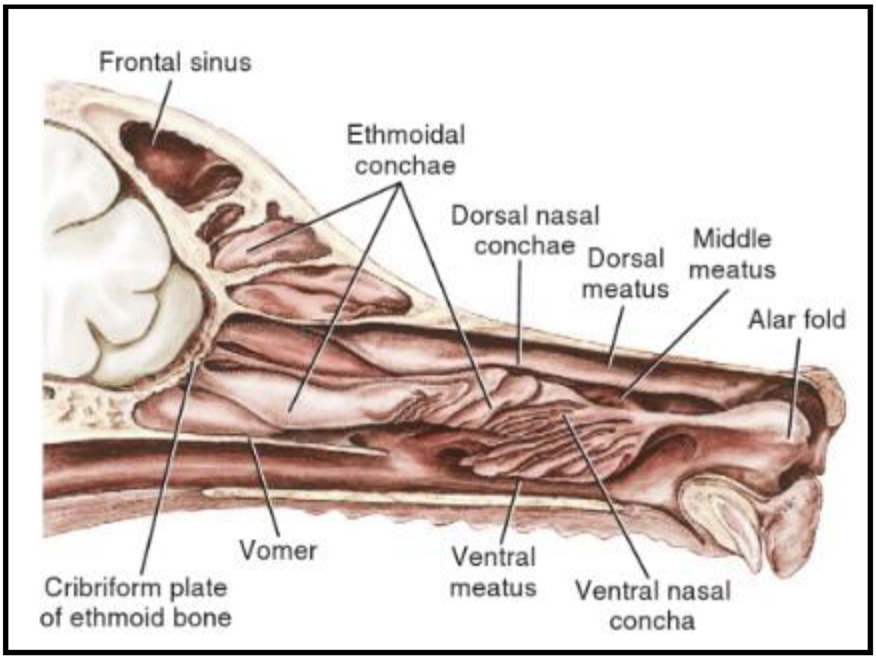

Fig. 3: Sagittal section, showing the conchae.[28]

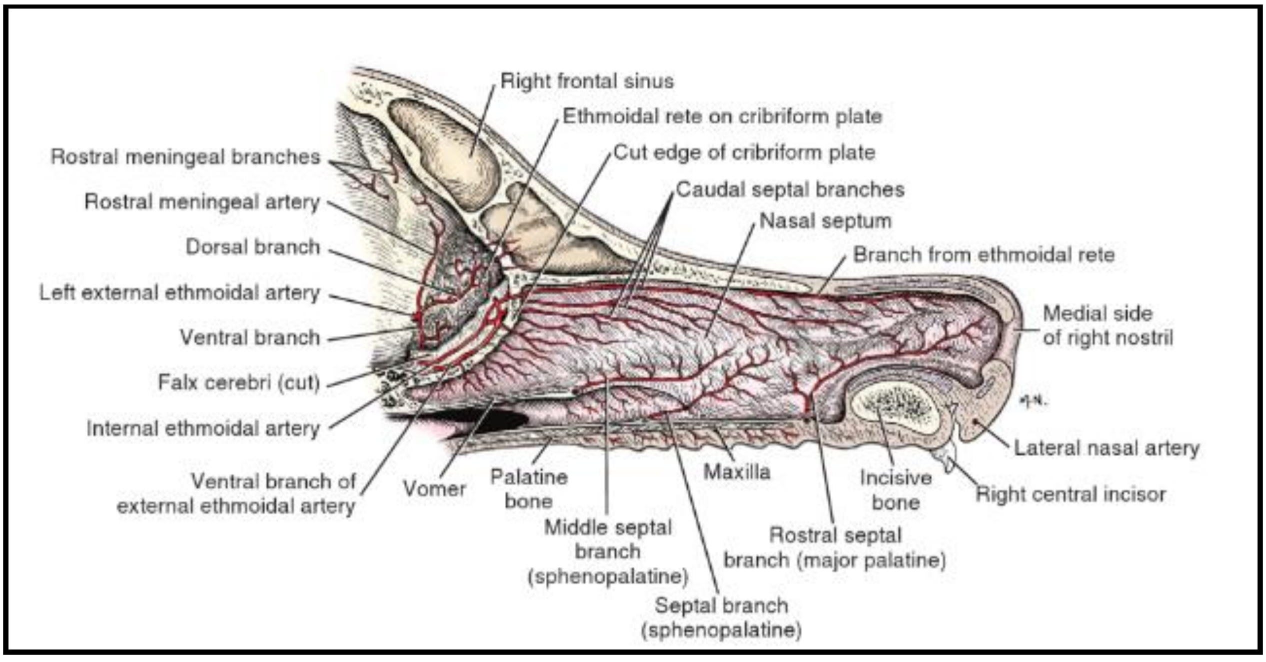

Fig. 4: Sagittal section, showing arteries of the nasal septum.[28]

1.2 Nasal tumors in dogs

Tumors of the nasal cavity and paranasal sinuses make up approximately 1% of all the neoplasms that occur in dogs.[3,4,10,11,14] Tumors in the nasal cavity are most often found in middle-aged and older dogs (over 10 years), but may occasionally occur in younger dogs.[3,4,5,10,13,14] Males have a slightly higher chance to develop nasal tumors compared to females.[3,10,13] Medium sized and large breeds are more commonly affected compared to the smaller breeds.[3,10]
There are speculations that dolichocephalic breeds (for example collie-like dogs) have a higher chance of developing a nasal tumor compared to other dogs, and brachycephalic breeds seem to have a lower risk.[3,4,6,10,14] A study of Reif *et al.* (1998) associated exposure to environmental tobacco with an increased risk of development of a nasal tumor, using a group of 103 dogs diagnosed with a nasal tumor versus a control group of 378 dogs with different tumors. Unfortunately this was not confirmed in a subsequent study of Bukowski *et al.* (1998), where 129 cases were investigated versus a control group of 176 cases, concluding that tobacco smoke was not a risk factor and was suggestive of a nonsignificant, mildly protective effect at the lower exposure. Results are therefore inconclusive. However in the same study of Bukowski *et al.* (1998), it became clear that indoor exposure to fossil fuel combustion products, produced by coal or kerosene heaters, has proven to contribute to the suggested environmental risk in developing this cancer.

Fig. 5: Longitudinal section of the head of a dog.
Showing a large pale tumor mass replacing all the nasal structures: nasal chondrosarcoma.[7]

1.2.1 Pathology and natural behavior of the tumor tissue

Primary tumors of the respiratory tract can originate from the epithelium or the supporting surrounding structures. These epithelial and mesenchymal neoplasms are regularly seen in the upper respiratory tract.[7,8] Unfortunately nasal tumors in dogs are malignant in approximately 80% of cases,[7,14] with most being of epithelial origin.[11] Despite the malignant nature of these tumors, they rarely metastasize.[7,13] If the tumor does metastasize, most common sites are the regional lymph nodes and the lungs. Less common sites include bones, kidneys, liver, skin and brain.[3,10,13] The tumors are

characterized by progressive invasion of the surrounding tissue and bone structures, which causes the most problems.[3,8,14] Most common nasal tumors that occur in dogs are adenocarcinomas, squamous cell carcinomas, and undifferentiated carcinomas.[3,5,8,14] This group of malignant epithelial tumors represents almost two-third of the intranasal tumors, while the sarcomas (such as a fibrosarcoma, chondrosarcoma, osteosarcoma, and undifferentiated sarcoma) fill in the rest of the remaining cancers.[3,10,14] Benign tumors that may occur are adenomas, fibromas, papillomas and transmissible venereal tumors.[5] Less frequent tumors are chondrosarcoma, osteosarcoma, lymphosarcoma and primary venereal tumors.[8]
A number of immunohistochemical studies tried to find an association between a possible molecular mechanism and the nasosinal tumorgenesis in dogs. The study of Gamblin *et al.* (1997), using a single polyclonal antihuman antibody, showed that in nearly 60% of tested nasal adenocarcinomas, nuclear p53 accumulation was detected. This suggests that an overexpression of a mutated p53 tumor suppressor protein may play a role. Expression of cyclooxygenase-2 has been detected in most nasosinal epithelial tumors sampled, and in normal paratumoral respiratory epithelium and stromal tissue, to varying degrees.[15,16]

1.2.2 Histologic classification of sinonasal neoplasms

	Origin			
	Epithelial	**Nonepithelial Skeletal**	**Nonepithelial Soft tissue**	**Miscellaneous**
Type of tumor	Squamous cell carcinoma: nonkeratinizing/ keratinizing	Chondrosarcoma	Lymphosarcoma	Adenocarcinoid
		Osteosarcoma	Fibrosarcoma	Esthesio-neuroblastoma
			Hemangiosacro ma	Carcinoid
			Muscular origin	Melanoma
			Fibrous histiocytoma	
			Malignant nerve sheath	

Table 1 : based on the study of Patnaik A.K.[29,13]

1.2.3 Clinical symptoms

Symptoms that a dog with a nasal tumors shows are mainly determined by the local invasiveness of the tumor.[5] One of the most common symptoms is nasal discharge ranging from serous, mucoid, mucopurulent to hemorrhagic (epistaxis).[3,5,8,13,14] One or both nostrils can be involved, often showing increased discharge with bilateral involvement.[5] In most animals the nasal discharge starts unilateral and progresses to bilateral.[5] Other symptoms that are seen are dyspnea[3,8,9,13],sneezing[3,5,8,13,14], stertorous breathing[3,14], nasal stridor[8,14], reversed sneezing[9], epiphora[3,9,10,14] and a reduced or absent air flow at one of the nasal passages[5, 14]. Facial and oral deformities can be caused by damage to the bone or soft tissue structures of the sinonasale structures.[3,12]

Neurological signs can be seen if the tumor grows towards the cranial vault.[3,5,10,14] However, absence of neurological symptoms does not imply absence of cerebral involvement such as invasion of tumor tissue in the brain.[3,5] Growth into the orbit or retrobulbar space can result in exopthalmos or an inability to retropulse the eye.[3] Neurological symptoms such as seizures, behavioral changes, abnormal mental state and ocular abnormalities are rarely seen as the primary clinical sign.[3,5] Weight loss and anorexia can coexist with respiratory symptoms, but are often absent.[3] The clinical signs in a dog with a nasal tumor show significant overlap with clinical signs for sinonasal aspergillosis, nasal foreign bodies and chronic rhinitis.[11]

Fig. 6: Dog with a nasal adenocarcinoma: nasal deformation and epistaxis.[27]

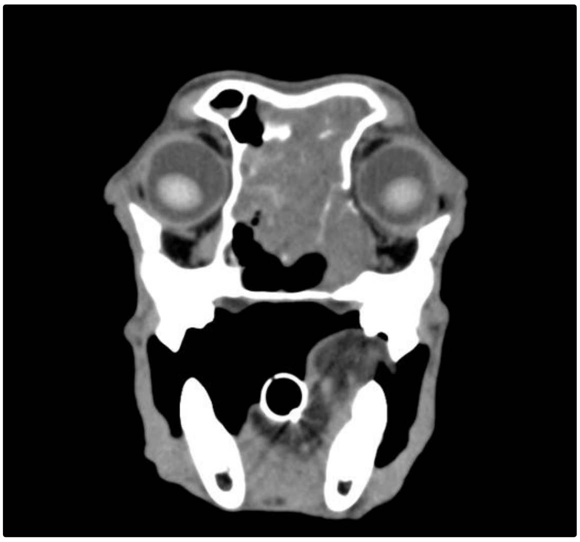

Fig. 7: CT-scan of a dog involved in the study, Epagneul Breton, where tumor growth in both nasal cavities and into the left orbita is seen.

1.2.4 Diagnosis

On average, a dogs shows clinical signs for three months before a diagnosis is made.[3] Clinical signs such as an intermittent nasal discharge and/or epistaxis usually directs towards a suspicion of a neoplasm.[10] A diagnosis is based on clinical symptoms and can be confirmed by imaging of the nasal cavity and frontal sinuses, using a CT-scan or MRI, or by a rhinoscopy.[5] A definitive diagnosis can be made by sending in a biopsy for histopathologic examination, usually providing a conclusion of the type of tumor.[3,5,8,10] According to Harris *et al.* (2014) there are no differences in confirmation of neoplasia between biopsies taken blind, at rhinoscopy or imaging-guided.[11] Sometimes a fine needle aspiration can provide a conclusive result as well.[5] Ruling out a coagulation disorder prior to biopsy can be wise, because some bleeding during the procedure can happen, but is not necessary.[3]
Radiographic imagining is important to make an estimation of the extensiveness of the tumor by determining which tissues or bone structures are affected.[3,5] The most sensitive techniques for imaging of nasal tumors are CT and MRI scans, which are more sensitive than radiography.[3,5,10] A nasal neoplasm is often accompanied by an inflammatory response of the nasal mucosa, sometimes leading to a secondary bacterial or fungal infection.[5] In some cases all the signals point in the direction of a tumor but no

final diagnosis can be made. With persistent signs it is advised to repeat imaging, rhinoscopy, and biopsy in one to three months.[5]

1.3 Treatment and estimated survival time of nasal tumors

Nowadays there are a lot of different treatment options for the therapy of nasal tumors in dogs. Unfortunately a full recovery is still hard to accomplish; most animals die during the treatment or are euthanized due to the severity of the clinical signs. The estimated survival times of the different treatment options are very variable. Often different treatment options are used together, thus providing a new treatment protocol.

Irradiation that uses high-energy megavoltage (MeV) equipment (cobalt source or linear accelerator) as sole therapy for dogs with nasosinal tumors has become the treatment of choice in practice: the golden standard. No surgical intervention takes place before or after the irradiation. Doses from 40 to 54 Gray (Gy) are usually administered in 10 to 18 treatments.[3] Although irradiation using a linear accelerator is the golden standard complete remission is not achieved in most cases and most tumors will only reduce in size. Furthermore, regrowth of the tumor occurs within a year after the irradiation in most dogs. Euthanasia is inevitable in these cases. Overall mean survival time for dogs treated with radiotherapy ranges from eight to 14 months, irrespective of histological diagnosis.[10]

Other interventions that are used are a surgical therapy, chemotherapy or a combination of surgery and radiation. Cryosurgery and immunotherapy are not the therapies of choice for managing a nasal tumor as they have not been shown to improve survival times.[10]

The absence of irradiation therapy results in a poor prognosis for dogs, the mean survival time after surgery, chemotherapy or absence of treatment is three to six months. [10] Median survival for dogs with a nasal carcinoma and no treatment is 95 days (95% confidence interval, 73 till 113 days).[3] Prognosis for dogs with epistaxis is worse than dogs without epistaxis (median survival time is 88 days versus 224 days).[3] Euthanasia is often suggested to dogs with constant epistaxis, constant nasal discharge or neurological symptoms.[5]

In the table 2 a summary is given of the average survival time of dogs with a defined nasal tumor or carcinoma, comparing untreated dogs to dogs treated with different therapies.

Treatment	Number of animals	Median survival time	Study	Year	Survival for longer than a year?
Untreated with epistaxis	139	88 days	Rassnick et al.	2006	no
Untreated without epistaxis	139	224 days	Rassnick et al.	2006	yes, some
Untreated independent clinical signs	139	95 days	Rassnick et al.	2006	-
Treatment: megavoltage irradiation with or without prior surgical treatment	77 64	13 months	Theon et al. & Henry et al.	1993 1998	1 year = 55-60 % 2 year = 25-45%
Treatment: megavoltage irradiation followed by surgical debulking	53	47.7 months	Adams et al.	2005	2 year = 69 % 3 year = 58 %
Treatment: megavoltage irradiation without surgical debulking	53	19.7 months	Adams et al.	2005	2 year = 44 % 3 year = 24 %
Treatment: orthovoltage irradiation after surgical debulking	70	16.5 months	Evans et al.	1989	1 year = 54% 2 year = 43 %
Treatment: orthovoltage irradiation and surgery	42	7 months	Northrup et al.	2001	1 year = 37% 2 year = 17 %
Treatment: surgical removal (via rhinotomy)	15	9 months (unilateral 11 months bilateral 3 months)	Laing & Binnington et al.	1988	No, and transnasal curettage or rhinotomy had no survival advantage
Treatment: chemotherapy with cisplatin	11	20 weeks	Hahn et al.	1992	No, and only a response rate of 27%
Treatment: combination chemotherapy cisplatin with irradiation	13	Median 474-580 days	Lana et al.	1997	Yes
Treatment: Antivascular photodynamic therapy, using BPD-MA, followed by local irradiation with visible light.	14, of which 7 had a nasal tumor	-	Osaki et al.	2009	1 year = 57 %

Table 2: Different treatment options for dogs diagnosed with a nasal carcinoma/tumor compared to the survival time.[17-26]

1.4 Research goal

Is there another option for dogs for which the golden standard therapy is not enough? The cases where the tumor does shrink but does not go in complete remission? Or the cases where the tumor grows back in a couple of weeks, months or after a year? These tumor cells usually are not very radiation-sensitive anymore, so the tumor will probably not respond to another round of radiation therapy. Radiation therapy followed by surgery is an option, as described earlier on, but this treatment is invasive without guarantee of an extended lifespan. Because of the invasiveness and the effect on the dogs most owners choose to stop the treatment when radiation therapy is not sufficient anymore. For these dogs the divisions Oncology and Surgery at the Faculty of Veterinary Medicine of companion animals at the University of Utrecht have come up with a new treatment: radiation therapy followed by endoscopic laser debulking. The aim of this study is to describe and evaluate the novel endoscopic laser debulking technique in respect of technical feasibility, complications, and clinical outcome.

Hypothesis
We expect that endoscopic laser debulking of post-radiation residual nasal tumor is feasible on an out-patient basis, without major complications, with comparable or improved clinical outcome compared to published results of post-radiation surgery by invasive rhinotomy.

2. Materials and Methods

2.1 Demographics

The study was carried out in nine dogs of different breeds, size, sex, and age. The animals entered the study through the Department of Clinical Sciences of Companion Animals at the Faculty of Veterinary Medicine in Utrecht. Some of the dogs were diagnosed with a nasal tumor at their own veterinary clinic and were redirected to the Faculty of Veterinary Medicine in Utrecht for further treatment. Other owners made an appointment at the Faculty without a referral of their own clinic because of the severity of the clinical signs their dogs were showing. The dogs were selected for this study based on the following criteria: diagnosed with a nasal tumor through histology of a biopsy or strongly suspected of a nasal tumor after a CT-scan or rhinoscopy at the University Clinic for Companion Animals.
During this study we had access to the history of the dogs. All dogs had one or more clinical examination at the division Oncology or Surgery prior to the treatment, including multiple control examinations during and after treatments. All dogs had a CT scan made prior to the irradiation and endoscopic laser debulking and most dogs (8/9) had a second CT-scan made after the irradiation and endoscopic laser debulking. Also with two dogs was decided to make a control MRI instead of a second CT-scan after the radiation therapy. We had access to the histopathological reports and histological diagnosis. All this data, collected from the system Vetware, was used for this study: history of the dogs, clinical examination reports, policlinical reports, radiological reports, histopathological reports and surgical reports.

2.2 Pre- and post-treatment survey's

Furthermore, surveys for the owners of the dogs were drawn up, of which the results were used alongside the data collected from Vetware. Owners of patients which were treated at the Department of Clinical Sciences of Companion Animals were called personally to administer the survey orally, information of all owners was obtained. These surveys included questionnaires, with questions about previous clinical signs and the presence or absence of current symptoms. Topics such as pain, well-being and satisfaction of the owner were also incorporated in the survey.

2.3 Treatment protocol

In week one a CT-scan was made of the patient. Radiation therapy was then started. Twelve weeks after the last irradiation a new CT-scan was planned to evaluate the tumor residues or complete remission of the tumor. If residual or recurrent tumor mass was visible on CT, the first session of the surgical removal of tumor tissue took place through rhinoscopy laser tumor ablation: a combination of contact mode laser dissection and vaporization of tissue through an endoscopic (rhinoscopic) approach. A control rhinoscopy took place six to eight weeks after the first rhinoscopic laser tumor ablation session for evaluation. If residual tumor mass was still visible a second rhinoscopic laser tumor ablation session took place during this rhinoscopy (7/9 dogs). At 12 weeks two of the nine dogs received a third rhinoscopy with a possible third laser ablation. One dog was scheduled for a fourth rhinoscopy with laser ablation. It is advisable to at least perform a rhinoscopy, following initial laser debulking if tumor regrowth is seen, every three to six months after the previous session.

The treatment plan consisted of a combination of radiation therapy, curative setting, 17x in doses of 40 to 54 Gy, followed by minimal invasive surgical debulking of the remaining tumor parts by means of endoscopic laser surgery. The surgical debulking by means of endoscopic laser surgery and the rhinoscopy were performed under general anesthesia. During the rhinoscopy new biopsy specimens could be collected which were fixed in a 7% buffered formalin solution and were sent in for histological research.

T-1	• Diagnosis nasal tumor
	  • By histological report
	  • By CT-scan

T0	• CT planning for radiation therapy (RT) and curative intent radiation therapy

T1	• CT evaluation residual disease
	  • 12 weeks post last RT session
	  • 1st session removal of residual tumor through rhinoscopy laser tumor ablation

T2	• Controlled rhinoscopy
	  • 6 to 8 weeks after the first rhinoscopic laser tumor ablation session
	  • if necessary 2nd rhinoscopic laser tumor ablation session

T3	• Controlled rhinoscopy
	  • Every 3 to 6 months after previous rhinoscopic session
	  • if necessary repeat rhinoscopic laser tumor ablation session

Table 3: Treatment protocol for nasal tumors at the Faculty of Veterinary Medicine in Utrecht.

After the radiation therapy a variety of medicines were prescribed to the dogs; all nine dogs received painkillers and six dogs also received antibiotics after the radiation treatment. The painkillers were different nonsteroidal anti-inflammatory drugs such as Carprodyl® (carprofen), Rimadyl® (carprofen), Metacam® (meloxicam) or Carporal® (carprofen) of which one type was prescribed to each dog. All dogs also received Tramadol in case the pain the dogs were showing was very severe, these could be combined with the current pain medication providing a synergistic effect. As for the antibiotics, five dogs received Synulox® (amoxicillin and clavulanic acid) and one dog received Doxoral® (doxycycline).

With the radiological, clinical and surgical reports an analysis was made of factors such as tumor response, relapse, complications, blood loss, clinical signs (clinical effect and morbidity), endurance, survival time, and possible influencing factors such as tumor type, initial tumor volume, and invasion in surrounding tissues. Radiologic side effects were taken into account, for example most dogs underwent one or more ophthalmological examinations. A distinction was made between tumor associated side-effects, radiation side-effects and side-effect caused by endoscopic laser debulking of the tumor.

The end stage for the dogs was reached when the dog died of a natural death or when it was decided to euthanize the dog because its quality of life was severely compromised.

The result were processed through Excel and statistical analysis in SPSS Statistics 22, using the Kaplan-Meier method. Excel is also used to calculate the mean, median and standard deviation.

Fig. 8: Rhinoscopic laser tumor ablation session.

Fig. 9: Rhinoscopic laser tumor ablation session performed by surgeon S.A. van Nimwegen.

3. Results

3.1 General

Of the nine dogs included in this study, in the period from 2013 to 2016, four were female (45%) and five were male (55%), two males (22%) and three females (34%) were castrated. The group existed of one cross-breed dog and a variety of purebred dogs: Border Collie, Epagneul Breton, French Bulldog, Labrador, Norwegian Elkhound, Saluki, Vizsla, and Weimaraner. Seven were a mesocephalic breed, one was a dolichocephalic breed and one was a brachiocephalic breed. The mean weight of the dogs was 26.6 kilogram (range: 11.2-41.5 kilogram)
The median weight of the dogs was 27.6 kilogram (standard deviation:9,94 kilogram). The mean age of the dogs at the first visit at the Faculty of Veterinary Medicine was nine years and two weeks (range: 6-14 years). The median age of the dogs was nine years (standard deviation: 2 years and 3 months).

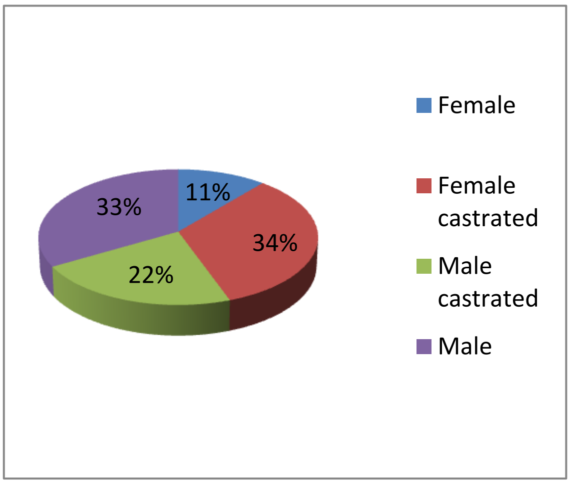

Fig. 10: Overview of the 9 female and male dogs treated in the period of 2013-2016

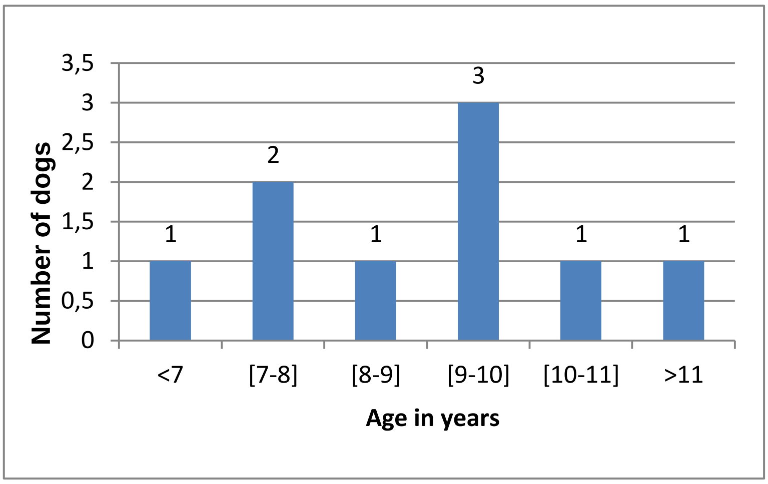

Fig. 11: Age of the 9 dogs at the beginning of the treatment plan expressed in years.

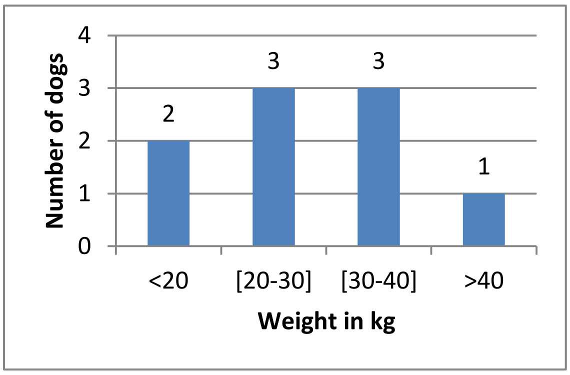

Fig. 12: Overview of the 9 dogs divided into weight classes at offering for the treatment of nasal tumors.

Based upon the histopathological examination, the following diagnoses were made: three cases of adenocarincoma, one transitional carcinoma, one chondrosarcoma, one undifferentiated carcinoma, one malignant tumor of unclear origin, one mesenchymal tumor and one case of which the exact nature was not determined. The localization of the tumor at the beginning of the treatment plan was in three dogs in the right nasal passage and in five dogs in the left nasal passage, one dog had both nasal passages affected. None of the dogs were diagnosed with metastases when the histopathological diagnoses was determined.

The following table presents the baseline characteristics of the patients included in the study.

Dog No.	Breed	Sex[a)]	Age (years) first visit	Body weight (kg)	Tumor site	Tumor type	Tumor stage[b)]	Number of OR's[c)]
1	Crossbred	SF	14	11.2	Right nasal cavity	adenocarincoma	T3N0M0	5
2	Labrador retriever	M	7	36.8	Left nasal cavity	malignant tumor of unclear origin	T3N0M0	2
3	Saluki	CM	10	27.3	Right nasal cavity	adenocarincoma	T4aN0M0	1
4	Norwegian Elkhound	M	8	41.5	Left nasal cavity	chondrosarcoma	T2N0M0	2
5	Vizsla	SF	9	32.0	Left nasal cavity	exact nature was not determined.	T2N0M0	3
6	Border Collie	M	9	22.6	Right nasal cavity & sinus frontalis	Adenocarincom a	T4aN0M0	1
7	Weimaraner	F	6	31.4	Left nasal cavity	transitional carcinoma,	T3N0M0	2
8	Epagneul Breton	CM	9	21.5	Right and left nasal cavity	undifferentiated carcinoma	T4aN0M0	2
9	French Bulldog	SF	7	15.1	Left nasal cavity	Mesenchymal tumor	T2N0M0	2

Table 4: Summary of patient characteristics

a) *M, male; CM, castrated male; F, female; SF, spayed female.*
b) *TNM classification according to the WHO (World Health organization) based on the CT-scans.(Appendix I)*
c) *Number of rhinoscopic operations during the study, with or without endoscopic laser debulking.*

3.2 History and clinical examination prior to treatment

All nine dogs had a history of clinical signs prior to the treatment plan and showed signs of a nasal tumor during the examination, nevertheless the variation in signs between the dogs was wide. Table 5 shows the clinical signs that the dogs showed prior to the treatment plan.

Clinical signs prior treatment	Affected dogs	Non-affected dogs
Decreased airflow	9	0
Mucous discharge	8	1
Epistaxis	6	3
Snoring	6	3
Problems breathing	6	3
Other diseases	5	4
Reversed sneezing	4	5
Change of appearance nose	4	5
Sneezing	4	5
Nasal stridor	3	6
Epiphora	3	6
Decreased endurance	2	7
Damped sinus maxillarus	2	7
Decreased appetite	1	8
Rubbing nose	1	8
Foetor ex ore	1	8
Pharyngeal stridor	1	8

Table 5: Clinical signs prior to treatment plan.

Five dogs had other concurrent diseases, including Cushing's syndrome – one case, cardiological souffle – three cases, discoid lupus erythematosus – one case, bilateral chronic proliferative otitis externa- one case and allergic dermatitis of the toes and ears – one case. Of the five dogs, two dogs were diagnosed with multiple diseases.
One of the dogs had a history of tumors prior to the nasal tumor: a testicular tumor. Which was removed in combination with a castration and no metastases were found.

3.3 History and clinical examination after radiation therapy

After the radiation therapy was finished, according to the treatment plan, the dogs were re-evaluated. All dogs still showed signs caused by the nasal tumor but four dogs had considerably less clinical signs than before. Table 6 shows the clinical signs that the dogs showed after the radiation therapy. The mean age of the dogs while starting the radiation therapy was nine years and two months. The median average was eight years and two months (standard deviation: 2 years and 3 months).

Clinical signs after radiation	Affected dogs	Non-affected dogs
Decreased air flow	7	2
Sneezing	4	5
Other clinical signs unconnected with the nasal tumor	4	5
Difficulty breathing	3	6
Mucous discharge	3	6
Epistaxis	2	7
Reversed sneezing	2	7
Decreased endurance	2	7
Other mass found	2	7
Sensitive nose while touching	1	8
Enlarged lymph nodes	1	8

Change of appearance nose	1	8
Foetor ex ore	1	8
Salivation	1	8
Decreased appetite	1	8

Table 6: Clinical signs after radiation.

Other clinical signs the dogs were showing included one dog with geriatric vestibulair ataxia, which also suffered from trauma caused by a biting incident, one dog with chronic proliferative otitis externa bilateral, this dog also suffered from allergic dermatitis between the toes and ears, one dog with vomiting and diarrhea and one dog with a mass forming rostral on the upper lip (2x3cm).

3.4 Ophthalmological examination

Due to possible side effects of the radiation therapy on the eyes, ophthalmological examinations were provided. Five of the nine dogs paid a visit to the division of ophthalmology at the Faculty of Veterinary Medicine for a consult. Three dogs visited for a second time and only one dog visited the department five times in total.

Symptoms found concerning the eyes	Affected dogs	Non-affected dogs	OU[a)]	OD [a)]	OS [a)]
Corneal edema	4	5	2	1	1
Thickened eyelids	2	7	-	-	-
Nuclear sclerosis	2	7	-	-	-
Conjunctivitis	2	7	-	-	-
Mucous discharge from eyes	2	7	-	-	-
Reduced STT[b)]	2	7	-	-	1

Table 7: Symptoms found during the ophthalmological examination concerning the eyes.

a) *OU, oculus uterque; OD, oculus dexter; OS, oculus sinister*
b) *STT, Schirmer tear test*

In the ophthalmic report only two dogs were giving a clinical diagnosis; keratitis and a decreased tear production due to radiation. These dogs received respectively Optimmune-Canis (ciclosporin) two times a day OU combined with CAF eye drops (vitamin A and chloramphenicol) three times a day OU, and Optimmune-Canis three times a day OD.
One dog in this group did not visit the division of ophthalmology, but visited the ENT division for an ear examination and the division for dermatology for a skin problem. Both divisions within the Faculty of Veterinary Medicine at University Utrecht.

3.5 History and clinical examination during and after laser debulking treatment

The mean age of the dogs while starting the endoscopic laser debulking sessions was nine years and six months. The median age of eight years and seven months (standard deviation: 2 years and 4 months). The number of rhinoscopies with possible laser debulking sessions varied between the dogs. One dog had five laser debulking sessions, one dog had three sessions, five dogs had two sessions and two dogs had one session. Providing a total of 21 rhinoscopic laser debulking sessions.

Clinical signs after surgical debulking	Affected dogs	Non-affected dogs
Sneezing	5	4
Epistaxis	5	4
Relapse tumor after radiation	4	5
Other masses known during treatment?	4	5
Mucous discharge	3	6
Reversed sneezing	3	6
Aspergillosis	2	7
Decreased endurance	2	7
Neurological clinical signs	1	8
Decreased appetite	1	8

Table 8: Clinical signs after the endoscopic laser debulking treatment.

During the first rhinoscopy along with laser debulking at the Faculty of Veterinary Medicine in Utrecht the tumor tissue was largely removed in all dogs. Complete removal could not be achieved by various reasons. Reasons for achieving a complete removal was that the tumor cells already reached the ventral or caudoventral lines of the nose and reached the bone, possible leaving some tumor cells in the nose. Other reasons were that they could not remove a part of the tumor that grew into the orbita, or that tissue in the nose started bleeding or the smoke of the laser became too severe, both blocking the sight of the surgeon. Of the nine dogs six dogs had a mild diffuse bleeding during the surgery, two had an arterial bleeding and one had a persistent bleeding. The loss of blood variated between a few drops of blood or blood cloths up to 400 mm. All dogs with blood loss were treated with a gauze drenched in adrenaline to stop the bleeding. Of the dogs with a severe blood loss compared to others hematocrit was measured after the treatment.

Relapse of tumor post radiation after the endoscopic laser debulking was seen in four cases, one case already was a relapsed tumor prior to starting the radiation therapy. The first tumor of this case was removed surgically through rhinoscopy at another veterinary clinic before coming to Utrecht. In most cases it was not possible to completely remove the tumor during one laser debulking session. Most common reasons for ceasing rhinoscopy laser debulking were severe hemorrhage causing lack of view for the surgeon and difficulty in differentiating tumorous tissue versus normal tissue.

At the end five of the nine dogs were euthanized because the dogs began to show severe clinical signs leading to a severely compromised quality of life. One dog was euthanized due to a series of epileptic seizures which did not respond to treatment. Another dog had a unstoppable bleeding coming from the mouth. One dog was mentally very absent in his last week, had difficulty walking and a weakness in the hind legs. For the last dog it was decided to stop the treatment protocol because the tumor was not responsive anymore, in consultation with the owner. Also the benefits of the treatment protocol for this dog no longer outweighed the disadvantages for the dog. Eventually when the tumor tissue was fully grown back and the difficulty in breathing dominated he was euthanized. The other four dogs were still alive at the end of this study and are still involved in the treatment plan.

3.6 Estimated survival time

For dogs that passed away during the study, that date was used in the statistical analysis. The other four dogs were still alive at the end of the study, on 12-04-2016. These four dogs were censured in the statistical calculations.

3.6.1. Estimated survival time from start of radiation till death or end study

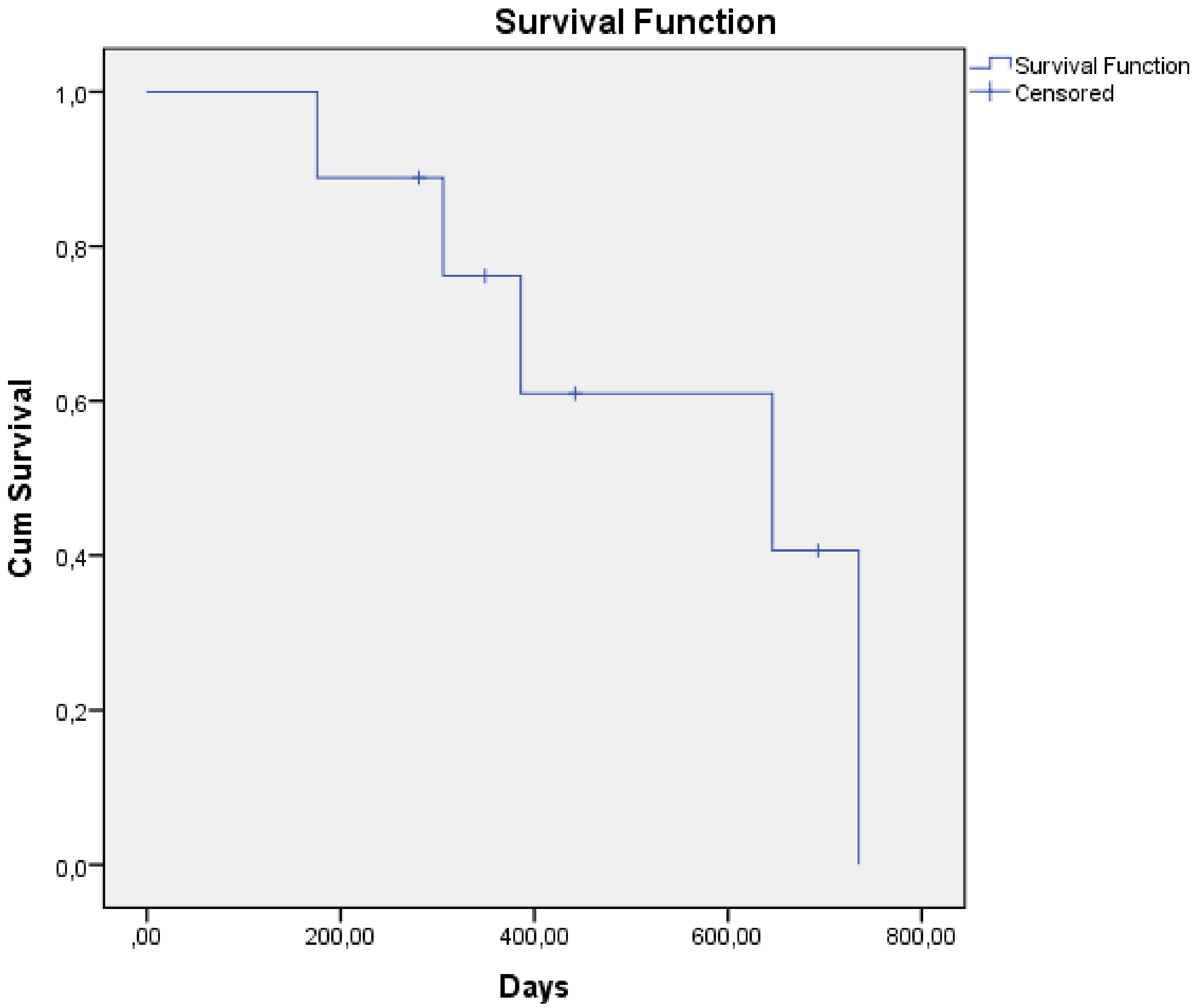

Fig. 13: Estimated survival time in days from start of radiation till dead or end study using Kaplan-Meier method, censuring the dogs alive on 12-04-2016.

The mean survival time of the start of the radiation therapy till death or end of the study is 547,15 days (standard deviation: 83,52 days). The median survival time of the dogs is 646,00 days (standard deviation: 262,26 days).
The mean survival time in months is 18 months (standard deviation: 2,7 months) and the median survival time is 21,3 months (standard deviation: 8,5 months).
(Further tables are listed in appendix II)

3.6.2. Estimated survival time from start of endoscopic laser debulking till death or end study

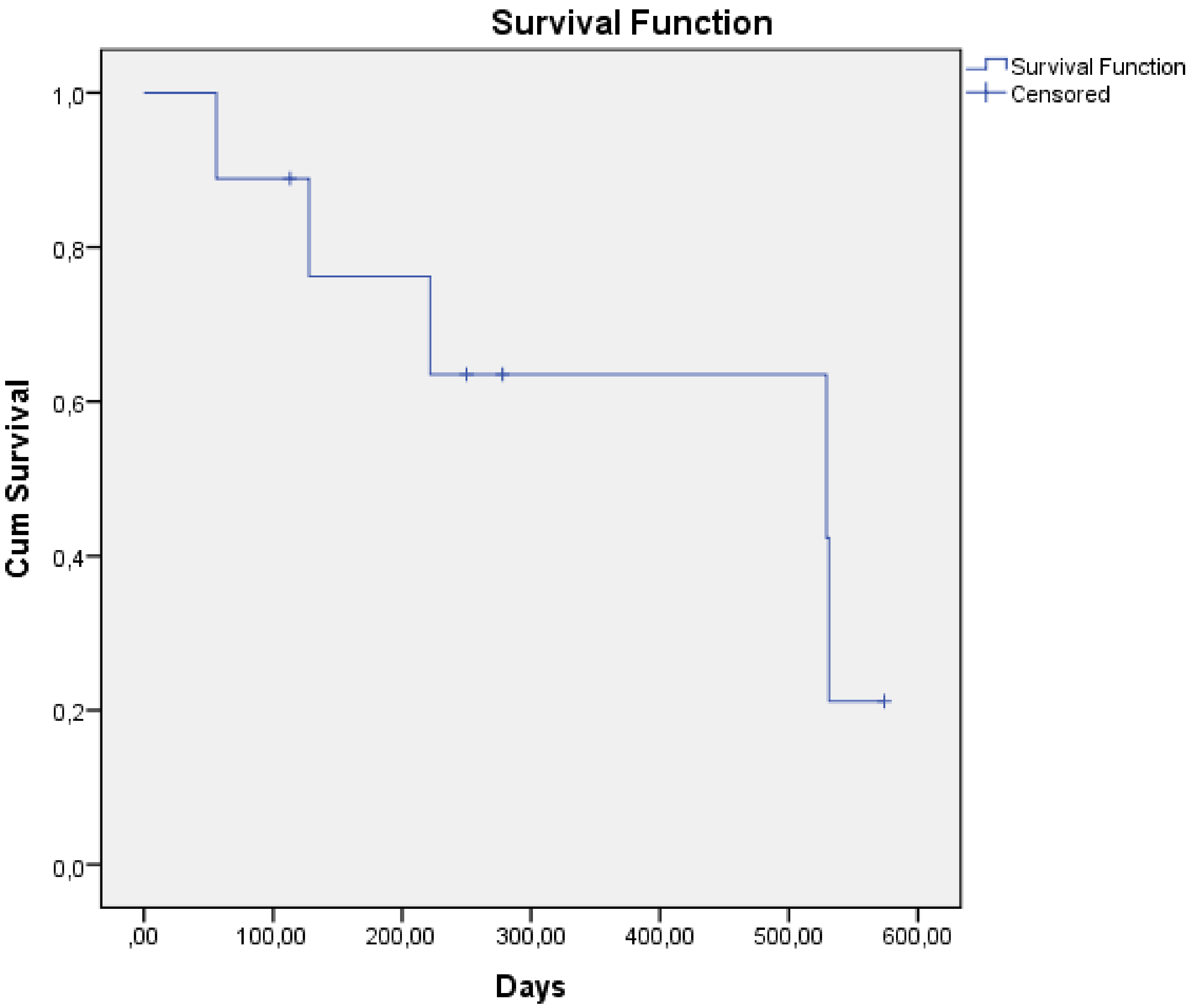

Fig. 14: Estimated survival time in days from start of endoscopic laser debulking till dead or end study using Kaplan-Meier method, censuring the dogs alive on 12-04-2016.

The mean survival time of the start of the endoscopic laser debulking sessions till death or end of the study is 396,49 days (standard deviation: 69,91 days). The median survival time of the dogs is 529,00 days (standard deviation: 299,35 days).
The mean survival time in months is 13 months (standard deviation: 2,3 months) and the median survival time is 17,4 months (standard deviation: 9,8 months).
(Further tables are listed in appendix II)

3.7 Owners response

During the telephone contact with the owners questions were asked to the owners, concerning their own view on the dog's life.

Signs of pain
According to the owners none of the dogs showed signs of pain or signs that the owner could interpret as pain at the beginning of the treatment. Most owners also scored their pets during the radiation and endoscopic laser debulking treatments negative on signals for pain, except for one owner, who strongly agreed that their dog was showing signs of pain after the radiation therapy. The same owner described the period of pain after the treatments as very long, two owners described this period as short and six owners said a period of pain was not present. Eight owners did not agree with the theorem "the recovery of my dog took a long time", and one owners agreed.

Treatment protocol
In the following table the theorems presented to the owners during the survey are listed with the corresponding results.

Theorems answered by owners	strongly agree	agree	neutral	disagree	yes	no
My dog has had a good life	7	2	0	0	-	-
I'm satisfied with the treatment carried out by the university clinic for companion animals in Utrecht	9	0	0	0	-	-
I'm satisfied with the result which has been achieved for my dog after the treatment	6	1	1	1	-	-
Would you consider the treatment afterwards or recommend it to another?	-	-	-	-	8	1[a)]

Table 9: Theorems of the survey with corresponding answers of owners

[a)]*The explanation giving by the owners for the answer no was that their dog was strong, in their eyes, and could handle the treatment, but they were afraid of the effect of this treatment on weaker dogs. Therefore they were sceptic of recommending it to other owners. Also the uncertainty of the couple of months won after the treatment in comparison with the costs played a part in their answer.*

Further comments of owners are listed in appendix III.

4. Discussion

The aim of this study is to describe and evaluate the novel endoscopic laser debulking technique in respect of technical feasibility, complications, and clinical outcome.

Since this is a pilot study on an experimental treatment modality, the group examined is relatively small. The group, consisting of nine dogs, was dependent on dogs presented with nasal tumors at the Faculty of Veterinary Medicine in Utrecht. Unfortunately between 2013 and 2016 not more than nine dogs entered this program: a limitation for this study. However, the clinical relevance and novelty of this study, replacing an invasive surgical approach by a novel, minimally invasive and repeatable outpatient treatment for debulking of residual tumor mass, is considered high. For a more well-founded study a bigger group of patients is necessary.
No specific standards concerning breed, age, weight or sex were met during the inclusion of patients in this study. The broad group of patients makes a good comparison between the animals more difficult. Other factors, linked to the breed, age, weight or sex of the dogs, could have had an effect on the outcome of this study. Remarkable was the number of diseases the dogs were diagnosed with, next to the nasal tumor in this study.
Most diagnoses were made at the Faculty of Veterinary Medicine in Utrecht but some dogs were diagnosed with a tumor by veterinarians in Belgium or the Netherlands that were not linked to the University clinic. In this study we trusted on the expertise of fellow colleagues, assuming that the diagnosis made was correct.

The data collected in Vetware throughout the years 2013 and 2016 is written down by different persons, so some variation is seen. This is not of great importance for the conclusions made by this study concerning the clinical signs of the dogs due to the fact that the owners were also called. Therefore the clinical signs written down in Vetware could be checked with the clinical signs the owners encountered during the different stages of treatment.
Interpretation of the questions by the owners is different per person. Some persons will answer a moral question with a more negative answer than others depending on their own view on their dog's life. With only nine owners this is also a small group to base reliable conclusions on. But it is a good parameter to see how the owners experienced the treatment protocol and how the dogs responded with regard to animal welfare. A point that was brought forward by some owners were the costs of the treatment, which were high in some eyes, in comparison to the unpredictable time the dogs still had to live after treatment.

For a more reliable conclusion a control group is needed, comparing dogs treated with endoscopic laser debulking and dogs untreated with endoscopic laser debulking after both undergoing radiation therapy. Ethically this is not achievable because all patients in this study are pets and not laboratory animals. Not providing proper care and therapy or withholding treatment for pets as a veterinarian is against the "Code for the Veterinarian" set up by the Koninklijke Nederlandse Maatschappij voor Diergeneeskunde (KNMVD). Furthermore the dogs that underwent radiation therapy and were eligible for this study, were dogs whose tumors did not go in complete remission or where tumor relapse was found. Comparing these dogs with dogs that only underwent radiation therapy at the Faculty of Veterinary medicine in Utrecht, a possible control group, would not give a right conclusion. The tumors in these dogs were responsive and disappeared (almost) completely and no tumor relapse was seen or known at the Faculty of Veterinary Medicine in Utrecht. These dogs were not seen back on the clinic, so also no data in Vetware existed of these dogs after the treatment.

Most dogs had a second CT-scan made after the radiation therapy. This provides a reliable image of the tumor prior to the endoscopic laser debulking sessions which could function as an initial value for the size of the tumor. Unfortunately, in some dogs, no CT-scan after radiation was made, which makes it harder to draw conclusions based on the effect of the endoscopic laser debulking and comparison between animals in the study. Another limitation of this study is that not all dogs underwent the same amount of endoscopic laser debulking sessions, creating a wide spread of endoscopic laser debulking sessions per dog. Based on the clinical signs the dogs were showing not all dogs had to come back for a third, fourth or fifth rhinoscopy with possible laser debulking. Dogs that were almost complaint free, or where no fast regrowth of the tumor was seen, needed less endoscopic laser debulking sessions. With some dogs this was also due to the fact that the clinical signs were so severe, further treatment would not be in best interest for the dog. Therefore no further endoscopic laser debulking sessions were performed. In these cases it was decided to euthanize the dog. Five dogs were euthanized during this study and four dogs are still alive at the end of the study and involved in the treatment plan.

When we compare literature with the results of this study we see a good confirmation of the different data. In literature, males tend to have a slightly higher chance of developing a nasal tumor. While this study did show more male dogs (five) than female dogs (four), the number of dogs used in this study is too low to confirm this predisposition.[3,10,13]
Seven dogs were of a mesocephalic breed, one was of a brachiocephalic breed and only one was a dolichocephalic breed. Literature speculates that dolichocephalic breeds tend to have a higher risk in developing nasal tumors compared to others dogs, but results from this study do not confirm this. On the other hand literature states that brachycephalic breeds seem to have a lower risk, as is seen in our study with only one brachycephalic dog.[3,4,6,10,14] Still the group of dogs in this study is too small to draw reliable conclusions. None of the dogs entering this study were of a small breed, four dogs were of a medium breed and five dogs were of a large breed. Literature concluded that medium and large breeds are more commonly affected compared to smaller breeds, as seen in this study. [3,10] Only two dogs were older than 10 years during the first diagnosis and visit to the Faculty of Veterinary Medicine in Utrecht, the other dogs were all middle-aged. This confirms the statement that nasal tumors are most often found in middle-aged and older dogs (over 10 years). [3,4,5,10,13,14] Histopathological findings in this study concluded that an adenocarcinoma was the most common tumor found in this study, and that most tumors were of malignant origin. Literature states that tumors in dogs are often malignant[7,14], and the most common nasal tumors that occur in dogs are adenocarcinomas as is seen in this study.[3,5,8,14] Nasal tumors rarely metastasize [7,13]: in this study none of the dogs were diagnosed with metastases at the beginning of or during the study.

All symptoms shown by the dogs in this study were symptoms which were also discussed in different studies concerning dogs with nasal tumors. The two most common symptoms this group of dogs showed were mucous discharge and epistaxis, two symptoms that literature also linked as most expressed due to a nasal tumor.

Furthermore all dogs experienced a lack of or a decreased airflow through one or both nasal cavities, as found in literature.[3,5,8,9,10,11,12,13,14] After radiation therapy, the dogs in this study still showed clinical signs (most of them only minimally) but the overall number of clinical signs decreased after treatment. Furthermore, all owners made clear during the survey that a great positive change was seen after the radiation therapy; dogs were able to breathe more, increasing the airflow, and overall showing less clinical signs than before. One dog had a very sensitive nose and mouth area after the radiation, this could be an effect of the radiation therapy. This hypersensitivity in the mouth and nose region resulted in a painful recovery and expressions of pain after touching this region during recovery. Because of the pain in this specific area difficulties with eating were seen. This period was marked by the owner as a short period of reduction of welfare for the dog. Two out of nine dogs had a decreased tear production, an effect commonly seen after radiation therapy; still a relatively small number. Four out of nine dogs were diagnosed with corneal edema, but no specific connection between the radiation therapy or the laser debulking sessions and this clinical sign was found in the literature. No other big negative effects were seen with the dogs after the radiation therapy.

Comparing our median survival time of 646 days or 21.3 months, calculated using the Kaplan-Meier method, with other studies showed positive results. Multiple studies had worse results despite various treatment plans. One study showed that dogs with untreated nasal tumors had a median survival time of 95 days, a more positive outcome was seen in dogs that did not show clinical signs (224 days).[17] Radiation treatment with or without a prior surgical treatment provided a median survival time of 13 months in one study.[18,19] Megavoltage irradiation alone as treatment was linked to a median survival time of 19.7 months in one study.[20] Orthovoltage irradiation after surgical debulking and orthovoltage irradiation with surgery provided respectively a median survival time of 16 months and 7 months.[21,22] Chemotherapy with cisplatin alone did not provide a good median survival time (140 days) but combined with irradiation therapy a median of 474-580 days of survival was seen.[24,25] Surgical removal by means of a rhinotomy gave a median survival time of 9 months, with a more positive outcome of 11 months when the tumor was unilateral.[23] All these studies showed a worse survival time compared to the results of our treatment protocol. An important thing to note as well is that all studies showed that irradiation therapy alone or in combination with another treatment is a necessary part of a treatment plan to increase the survival rate and time of a dog with a nasal tumor. A study that exceeded our median survival time was the study of Adams *et al.* (2005). In this study the dogs were treated with megavoltage irradiation therapy followed by surgical debulking, resulting in a median survival time of 47.7 months.[20]

What applies for all the results found in this study is that they are not reliable due to the small number of patients involved in this study. Therefore a comparison of these results with results of new studies on the same subject with a bigger group of animals would be helpful for making reliable conclusions in the future. In the future a control group would be helpful. This could be formed by the dogs of the owners for which the complete treatment plan is too expensive. These dogs can be evaluated after undergoing the same radiation therapy as the dogs in the treatment group before endoscopic laser debulking. Clinical signs, tumor growth, estimated survival rate and time and other factors of these dogs can be compared to the dogs in the treatment group.

5. Conclusion

This is the first long term study done on the treatment of nasal tumors in dogs with radiation therapy followed by one or multiple rhinoscopic laser tumor ablation sessions. In other words, this is the first time results about clinical signs of the dogs, treatment, prognoses and estimated survival time with this technique is written down in a report.
With the results of this study we can conclude that endoscopic laser debulking of post-radiation nasal tumors is feasible on an outpatient basis with minimal surgery-related morbidity, fast recovery, and results in adequate removal of tumor tissue with accompanying decrease in clinical signs. Because this is the first study of its kind, it is hard to compare the results of the study with other studies because not one investigates the same technique. It requires further investigation in the future to evaluate this technique on the long term with a bigger group of animals and control group. More studies in the future can determine if this treatment protocol can be the new golden standard to treat dogs with nasal tumors.

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Appendix I

The TNM classification for cancers of the head and neck in the nasal cavity and paranasal sinuses is provided below, along with anatomic staging.[a)]

Nasal cavity and ethmoid sinus:	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor restricted to any 1 subsite, with or without bony invasion
T2	Tumor invading 2 subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	Moderately advanced local disease Tumor invades any of the following: anterior orbital contents, skin of the nose or cheek, minimal extension to the anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Very advanced local disease Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus
Regional lymph nodes (N)	
NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node ≤ 3 cm in greatest dimension
N2	Metastasis in a single ipsilateral lymph node > 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node > 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension
N3	Metastasis in a lymph node > 6 cm in greatest dimension
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

a. *National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers. V 1.2015.*

Appendix II

Tables of the Kaplan-Meier method analysis in SPSS Statistics 22

Means and Medians for Survival Time

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
547,149	83,523	383,444	710,855	646,000	262,260	131,970	1160,030

a. Estimation is limited to the largest survival time if it is censored.

Table 10: Mean and Median survival table of time in days from start of radiation till dead or end study.

Means and Medians for Survival Time

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
18,004	2,740	12,633	23,375	21,230	8,534	4,504	37,956

a. Estimation is limited to the largest survival time if it is censored.

Table 11: Mean and Median survival table of time in months from start of radiation till dead or end study.

Survival Table

			Cumulative Proportion Surviving at the Time			
	Time	Status	Estimate	Std. Error	N of Cumulative Events	N of Remaining Cases
1	176,000	1	,889	,105	1	8
2	281,000	0	.	.	1	7
3	306,000	1	,762	,148	2	6
4	349,000	0	.	.	2	5
5	386,000	1	,610	,181	3	4
6	442,000	0	.	.	3	3
7	646,000	1	,406	,205	4	2
8	693,000	0	.	.	4	1
9	735,000	1	,000	,000	5	0

Table 12: Survival table of time in days from start of radiation till dead or end study.

Case Processing Summary

		Censored	
Total N	N of Events	N	Percent
9	5	4	44,4%

Table 13: Case processing summary of time in days from start of radiation till dead or end study.

Means and Medians for Survival Time

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
396,487	69,909	259,466	533,507	529,000	299,352	,000	1115,729

a. Estimation is limited to the largest survival time if it is censored.

Table 14: Mean and Median survival table of time in days from start of endoscopic laser debulking session till dead or end study.

Means and Medians for Survival Time

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
13,045	2,290	8,557	17,534	17,400	9,848	,000	36,703

a. Estimation is limited to the largest survival time if it is censored.

Table 15: Mean and Median survival table of time in months from start of endoscopic laser debulking session till dead or end study.

Survival Table

	Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
			Estimate	Std. Error		
1	56,000	1	,889	,105	1	8
2	113,000	0	.	.	1	7
3	128,000	1	,762	,148	2	6
4	222,000	1	,635	,169	3	5
5	250,000	0	.	.	3	4
6	278,000	0	.	.	3	3
7	529,000	1	,423	,206	4	2
8	531,000	1	,212	,182	5	1
9	574,000	0	.	.	5	0

Table 16: Survival table of time in days from start of endoscopic laser debulking session till dead or end study.

Case Processing Summary

Total N	N of Events	Censored	
		N	Percent
9	5	4	44,4%

Table 17: Case processing summary of time in days from start of endoscopic laser debulking session till dead or end study.

Appendix III

Comments of the owners regarding the survey
Comments variated between the owners. Summarizing the positive points, they were satisfied with the care the dogs received at the clinic and with the team of professionals providing this care. They were also satisfied with the communication, contact, explanations and time taken for this of the students and specialists at the clinic. They were seeing this technic as a helpful tool in the future.
The negative comments summarized brought forward that the price was an issue for multiple owners. Their main concern about this was that they could pay this, but what about the owners who did not had the money to help their dog. Other comments were that is was a shame that the treatment only was provided in the Netherlands and not somewhere else, for example in Belgium. One owner had some problem with the administrative processing after the treatments , but other owners did not encounter this problem.