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Multimodular Approach to the Treatment of Canine Nasal Tumours

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1 Introduction

Nasal and paranasal sinus tumours are relatively frequent neoplasms in dogs, constituting approximately 1 to 2% of all cancer cases in this species and representing 70% of chronic nasal conditions among canines. [1, 2]

The significance of this study lies in the growing need for effective and humane approaches to address the challenges posed by nasal tumours in dogs. These tumours not only impact the nasal and paranasal structures but often extend to affect critical areas, such as the cribriform plate and the brain, necessitating a holistic and multimodal approach to diagnosis and treatment.

The journey through this thesis will encompass the evolution of diagnostic tools, including advanced imaging techniques, histopathological examination, and grading systems, as well as the development of therapeutic modalities such as radiation therapy, chemotherapy, and surgical interventions.

The structure of this thesis unfolds in 2 major parts: the first deals with the knowledge accumulated in the scientific literature, while the second offers a valuable retrospective perspective derived from a substantial dataset, which was collected during the past 25 years, from 1997 to 2023 at the University of Veterinary Medicine Budapest.

Numerous publications in the literature about the occurrence, diagnosis, staging, therapeutic options and prognosis of nasal tumours in dogs were discussed. Unfortunately, these all conclude in similar unfavourable results, due to the localisation, biological behaviour or late diagnosis of the disease. Nowadays radiation therapy is considered the gold standard for dogs suffering from nasal tumours, but unfortunately its use is limited due to the need for general anaesthesia and the high costs involved in this therapy. [1]

The second, retrospective part of this work, involved dogs diagnosed with nasal tumours, which were able to meet the for the study required criteria. These criteria could be found in 151 dogs and included the clinical and/or histopathological or cytological diagnosis of canine nasal tumours.

In essence, the mission of this thesis is to explore the horizons of a multimodular approach in canine nasal tumour treatment. By bridging the gap between scientific knowledge and practical application, it aims to enhance the well-being of dogs suffering from these challenging conditions and, in turn, offer a better future for both dogs and the veterinarians dedicated to their care.

2 Literature review

2.1 Anatomy

2.1.1 Anatomy of the nasal cavity

The nose (*nasus*) can be divided into the external (*nasus externus*) and the internal nose (*nasal internus*) or also nasal cavity (*cavum nasi*). The former including the cartilages of the nose (*cartilagines nasi*) and the latter one is associated with the nose's conchae, which consist of laminae originating from the lateral and dorsal walls of the nasal cavity.

The most rostral part of the nose is called apex nasi. The whole plane end of it with the nostrils (*nares*) is known as the nasal plane (*planum nasi*). Rostral a cartilaginous part is found, followed by a bony part located further caudally. [3]

Most of the nasal cavity is divided into two nasal cavities (*cava nasi*) by the nasal septum (*septum nasi*), which starts rostrally at the nostrils and extends through the nose until the conchae. It is composed of three parts, starting rostral to caudal, there is a cartilaginous part, separated by the membranous nasal septum and most caudal, the bony component known as osseous septum is located. [3]

The nasal cavities themselves start at the nostrils, followed by the nasal vestibules at the beginning of the cava nasi and end with the nasal conchae and the air passages in between the conchae, which are considered as meatus. The conchae as well as the meatuses can additionally be divided into different parts according to their location. There are dorsal-, ventral-, medial- and ethmoidal conchae, the latter one shapes the ethmoidal labyrinth (*labyrinthus ethmoidalis*). Furthermore, the airspaces in between the conchae, the meatuses, are like mentioned before separated into the dorsal-, middle- and ventral nasal meatus within each nasal cavity. The "end" of the nasal cavity or rather the border between nasal and cranial cavity is formed by the transverse cribriform plate (*lamina cribrosa*). [3]

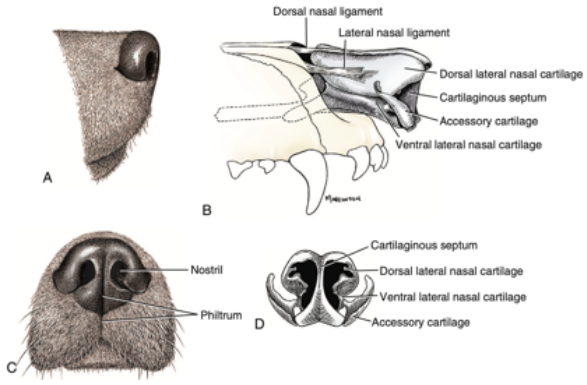

Figure 3. External nose and nasal cartilages [3]

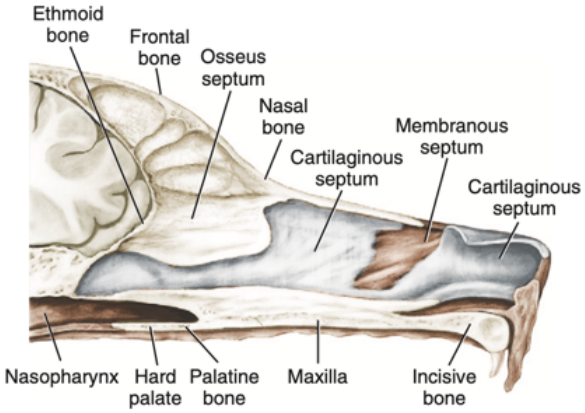

Figure 4. Sagittal section of the nasal cavity [3]

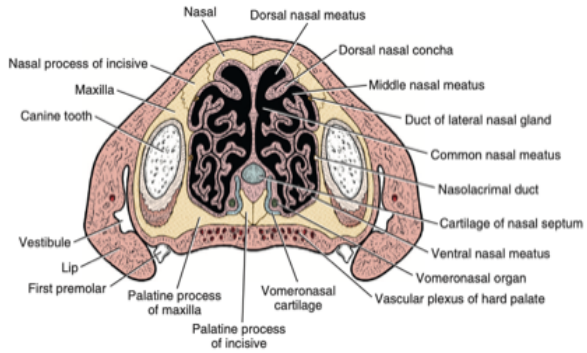

Figure 2. Transverse section of the nasal cavities

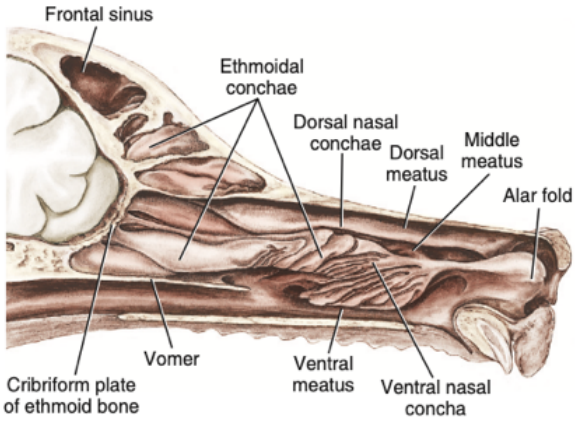

Figure 1. Sagittal section of the nasal cavity with conchae [3]

2.1.2 Anatomy of the paranasal sinuses of the nose

The paranasal sinuses of dogs include three sinuses restricted by different facial bones on each side of the skull, including the maxillary recess (*recessus maxillaris*), the frontal sinus (*sinus frontalis*) and the sphenoid sinus (*sinus sphenoidalis*). In comparison with other animals in dogs there is no sinus but a recess of the maxilla because it is not completely enclosed by the maxilla, but rather has two small, narrowed openings above the P4 and caudal of it above the last molar tooth. The borders of the maxillary recess are given through the medially located ethmoid bone and the lateral border provided by maxillary, palatine and lacrimal bones.

The frontal sinus primarily resides between the outer and inner tables of the frontal bone and exhibits greater size variation compared to other cranial cavities. It can be segmented into lateral,

medial, and rostral components. The largest segment of the frontal sinus is the lateral portion, which substantially occupies the space beneath the zygomatic process of the frontal bone and opens into the nasal cavity in form of the nasofrontal opening (*aperatura sinus frontalis*). In contrast, the medial compartment, separated by a bone flap, is relatively smaller and may be lacking in certain brachycephalic dogs. The rostral segment represents the smallest portion. Located inside the presphenoid bone, the previously mentioned sphenoid sinus can be found, almost completely filled with endoturbinate IV.

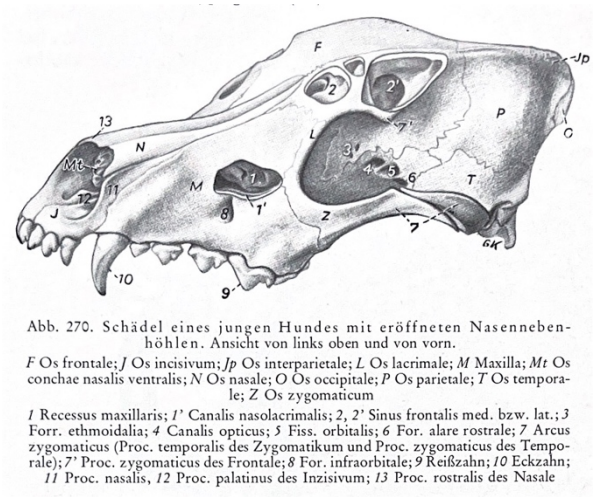

Abb. 270. Schädel eines jungen Hundes mit eröffneten Nasennebenhöhlen. Ansicht von links oben und von vorn.

F Os frontale; *J* Os incisivum; *Jp* Os interparietale; *L* Os lacrimale; *M* Maxilla; *Mt* Os conchae nasalis ventralis; *N* Os nasale; *O* Os occipitale; *P* Os parietale; *T* Os temporale; *Z* Os zygomaticum

1 Recessus maxillaris; *1'* Canalis nasolacrimalis; *2*, *2'* Sinus frontalis med. bzw. lat.; *3* Forr. ethmoidalia; *4* Canalis opticus; *5* Fiss. orbitalis; *6* For. alare rostrale; *7* Arcus zygomaticus (Proc. temporalis des Zygomatikum und Proc. zygomaticus des Temporale); *7'* Proc. zygomaticus des Frontale; *8* For. infraorbitale; *9* Reißzahn; *10* Eckzahn; *11* Proc. nasalis, *12* Proc. palatinus des Inzisivum; *13* Proc. rostralis des Nasale

Figure 5. Skull of a young dog with opened paranasal sinuses [4]

2.2 Incidence and Pathology

According to an article in the veterinary scientific journal “Topics in Companion Animal Medicine”, among all canine neoplasms nasal tumours have a rather rare appearance of less than 2 %. [4] These neoplasms can arise from various tissue types, most commonly affected tissues include bones, connective tissue and epithelial tissue, hence the most frequently occurring nasal tumours are sarcomas and carcinomas. The majority of canine nasal tumours reported, in fact two thirds of them, are carcinomas, most commonly adenocarcinomas, followed by sarcomas, which compromises one third. In both tumour types the tendency to metastasize is low, and the rate of metastasis in adenocarcinomas it is slightly higher than in sarcomas. [1] For instance in 40% of 285 cases treated with radiation therapy metastatic lesions beyond the tumour could be found according to an article of Malinowski. Most of these mentioned metastases were located in the lymph nodes or lungs. [5] In another article by Kondo et al. that these canine nasal tumours are considered to be locally invasive and difficult to cure, due to their tendency to invade the oral cavity, orbit and brain. [6]

Prevalences regarding the age, breed and sex of the affected animal can be seen. As some may expect, older dogs are at greater risk for getting a nasal tumour, compared to younger dogs.

Although it is still possible that even in dogs below six months of age nasal tumours appear, the biggest threat of falling ill is between the period from the 10th to the 13th year of a dog's life. [7]
The potential of getting a nasal tumour is of course given in any dog breed, although there is some, long-nosed, doliocephalic breeds which are affected more commonly. These dog breeds include for example the English Springer, Golden Retriever, Labrador and German Shepherd dog. [1]
There are varying opinions in different studies regarding the correlation between the sex of the dogs and the appearance of nasal neoplasia, but they suggest no or only a slightly more common appearance in male dogs. [8]

2.3 Clinical symptoms

"Clinical signs are referable to a slowly and insidiously expanding space-occupying mass in the sinonasal region with attendant invasion and destruction of adjacent structures, and associated loss of function. The most common signs is unilateral or bilateral nasal discharge, which is commonly mucopurulent and may be bloodstained." [7]
Signs of nasal tumours do not differ from other nasal disorders in most of the cases, they overlap significantly with other disorders like nasal foreign bodies. Among others sneezing, stertor, epistaxis or signs of nasal obstruction, epiphora, nasal congestion and dyspnoea. [1]
In more severe and advanced forms of nasal neoplasia, the dog's face may appear deformed, or exophthalmos may appear. In some cases, neurological signs, including seizures, changes of behaviour, circling, visual impairment, as well as ataxia may occur to mention a few. An invasion of the tumour into the cranial vault and brain may be linked to the previously mentioned neurological symptoms. [7]
Nevertheless, it cannot be dismissed that the examples of clinical signs above do not represent a definitive diagnosis for a nasal tumour, but they are rather to be regarded as a differential diagnosis of various nasal and or respiratory disorders. The differential diagnosis may include rhinitis, for instance due to an infectious bacterial or fungal background, foreign body impaction or osteomyelitis. [7]

2.4 Diagnostics

A history of a slowly, progressive development is characteristic for nasal tumours, so by the time of reaching a definite diagnosis the tumour usually has already existed for an average of three months. Therefore, not only the clinical signs are used to diagnose the diseased dog, but also the support of different diagnostic imaging methods. To finalize the diagnosis histopathological biopsy and examination is required. [9]

2.4.1 Physical Examination and Blood Work

Like in any case of nasal diseases, in order to rule out other systemic diseases, it is necessary to perform a complete physical check-up to rule out other systemic diseases, before performing further diagnostic procedures. This should include various laboratory examinations of the animal's blood, such as a complete blood count (CBC), a serum biochemistry profile and an evaluation of the clotting factors. Besides that, special attention should of course be paid to the previously mentioned typical clinical signs, as well as to the eyes. These also have to be inspected carefully, to see if there are any kind of bleedings visible. [5]

2.4.2 Diagnostic Imaging

In case of an intranasal disease diagnostic imaging is considered as a key element, because it enables the veterinarian to get a picture of the soft tissue and bony structures of the diseased animal's nasal cavity and sinus system, as these cannot be seen during physical examination. [10]

2.4.2.1 Radiography

In the past the imaging method of preference was radiography due to the fact that it was mostly available. [1] To be able to get a meaningful impression of the nasal cavity and sinus system, it is necessary to take a minimum of four x-rays, including a lateral, ventrodorsal, intraoral and frontal sinus or skyline view. The complexity of the canine nose with its overlying bony structures, makes this previously commonly used diagnostic tool unreliable, as the outcome of the images are often considered to be not sensitive enough to be able to recognize a difference between the radiographic picture of a dog suffering from inflammatory or fungal rhinitis or nasal neoplasia. [11] However nowadays it has been superseded in most cases by more modern imaging techniques like computed tomography (CT) or magnetic resonance imaging (MRI). [1]

2.4.2.2 Sinonasal Endoscopy

The visual exploration of the nasal cavity with its chambers as well as the assessment of the oral cavity and caudal nasopharynx via a rigid or flexible endoscope or an otoscopic cone, refers to the term rhinoscopy. Its wide range of possible applications include the search and removal of possible foreign bodies, the examination of the nasal mucosa for any kind of changes like inflammations or mass lesions and the facilitation of gathering nasal samples for histopathological analysis and culturing. [10]

Haemorrhages are possible complications of rhinoscopy, it may falsify or change further imaging studies and therefore sinonasal endoscopy should be performed only after other diagnostic imagines like radiography. [8] Possible disadvantages of rhinoscopy include that not all areas of the nasal cavity can be examined, as lots of the small recesses cannot be reached with the endoscope. Another possible limitation concerns discharge or mucous interfering with the rhinoscope, disabling appropriate examination and diagnosis. [10]

2.4.2.3 Computed Tomography (CT) and Magnetic Resonance Therapy (MRT)

To define the extent of suspected nasal neoplasia, as well as for biopsy taking and the planning of possible treatment, cross-sectional imaging, more precisely computed tomography (CT) and magnetic resonance imaging (MRI) are used. [12]

The invasion of the nasal cavity by soft tissue attenuating material, possibly extending further into the frontal sinus or the involvement of bony destruction of the turbinates or nasal septum, are considered as CT-based characteristics of canine nasal tumours. [12] According to Malinowski in "*Canine and Feline Nasal Neoplasia*", published 2006 in the *Clinical Techniques in Small Animal Practice* journal, computed tomography is supposedly the optimal tool for the assessment of the degree of bone involvement and the extension of the neoplasm in general. CT enables a better, more detailed view of the nasal cavity and paranasal sinuses, it can recreate the desired dorsal and sagittal areas, which enables a more advanced picture of the nose compared to conventional radiographs. The later ones have the disadvantage that some tumour/fluid-to-air interfaces are not visible on the image. [5]

MRI has an increasing availability nowadays and is generally known to have a better cross-sectional contrast resolution when it comes to soft tissues. Therefore it can be used to have a

better picture of the localization and extension of the nasal tumour mass internally and externally to the nasal cavity. [12]

To conclude this brief comparison of these both cross-sectional imaging modalities, CT is generally preferred for the examination of bony structures, especially the cribriforme plate of the ethmoid bone, while MRI on the other hand is more commonly applied for soft tissue imaging and allows a better view of possible cerebral abnormalities. According to the study "Comparison of computed tomography and magnetic resonance imaging for the evaluation of canine intranasal neoplasia" by Drees et al. both diagnostic methods performed similarly in evaluating intranasal tumours in dogs, however, computed tomography may be more effective in detecting bone lysis and mucosal thickening, while magnetic resonance imaging may be better at detecting small amounts of fluid in the nasal cavity. Thus, when putting aside the tumour's possible extent into the cranial cavity, no big advantage could be found in either CT or MRI. The study's final conclusion was that at least from a clinically relevant point of view, nothing important could be turned to good account by using MRI instead of CT, which usually turns out to be a satisfactory diagnostic and staging tool in canine nasal tumours. [12]

Table 1. Comparison of imaging techniques for dogs with nasal disease [12]

	Skull Radiographs	CT	MRI
Availability	Readily available	Moderate availability	Least available
General anesthesia	Required	Anesthesia or sedation	Required
Cost	Least expensive	Moderately expensive	Most expensive
Show cribriform plate integrity	Poor	Excellent	Excellent
Ability to discriminate between tissue and mucus	Poor	Excellent (with contrast)	Excellent
Sensitivity to detect soft tissue changes	Poor to moderate	Good	Excellent
Sensitivity to detect bony changes (lysis or hyperostosis)	Moderate	Excellent	Good
Ability to evaluate sinuses	Moderate	Excellent	Good to excellent

Cohn created a comparative table, which compromises a brief but good overview of the three different imaging procedures mentioned previously. [13]

2.4.3 Other Diagnostic Tools

Finally, yet importantly are the cytological and histological examination methods.

After the collection of samples for a cytological exam, the samples get stained prior to the examination. Among others they are examined for the occurance of possible tumour cells, inflammatory cells or any kind of pathogenic structure. [9]

Different methods of sample collection may be used to obtain an appropriate sample. The diagnostic accuracy can differ depending on which sample collection technique has been used. For instance, the performance of a nasal lavage results in a lower number of collected cells and therefore less sensitivity, compared to samples taken by means of brush cytology or impression smear. As Aupperle et al. state in their article, brush cytology resulted in the most accurate outcome of diagnosis, in 86% of the examined cases it was possible to correctly differentiate between nasal rhinitis and nasal neoplasia by cytological examination. [9]
In the journal "Tierärztliche Praxis Kleintiere/Heimtiere", the accuracy of a histopathological and bacterial examination to reach a definite diagnosis in case of nasal discharge in dogs was examined. Within the study mentioned it was possible to figure out that a bacterial culture of the affected dogs' nasal discharge is not enough to provide a diagnosis, but rhinoscopy together with CT and biopsy is recommended in case of dogs with nasal discharge. [14] It is without question that in order to get a final diagnosis of dogs diseased with nasal cancer, a histopathological exam is needed. [13, 14] For the performance of an histological exam the obtainment of a tissue sample is required. [9] Within the research of this work it was shown that it is of high importance how the tissue sample is collected prior to the histopathological examination. It is highly recommended to collect tissue biopsies by means of an endoscope, to be able to see and properly meet the desired intranasal tissue. Blind biopsies should be avoided if possible, because of the common risk of receiving a false-negative result when accidentally collecting inflammatory tissues from neighboring structures and not the suspected neoplasm itself. [14]

2.5 Staging

In the years between 1940-1952 a system for the objective description of primary tumours' anatomical extent, the involvement of regional lymph nodes, as well as the appearance of distant metastasis, was developed by Pierre Denoix. This system is called the TNM-System, in which T is used to determine the size of the primary tumour, N examines changes in the reginal lymph nodes and M provides informations on the possible presence of distant metastases. This system, originally intended for and still used by human malignant tumours, was adapted to domestic animals by the World Health Organization (WHO) in 1980 and formed the foundation to classify tumours, and therefore make neoplastic diseases comparable and reproducible. [15]

In the past the WHO staging system was based on radiographic findings but was later overruled by the usage of computed tomography (CT) and magnetic resonance therapy (MRT). In dogs suffering from sinonasal tumours the possibility of a further classification can be considered, to indicate the neoplasm's extend and degree of bony erosion, this system is referred to Theon Modified Staging System. [16] [17]

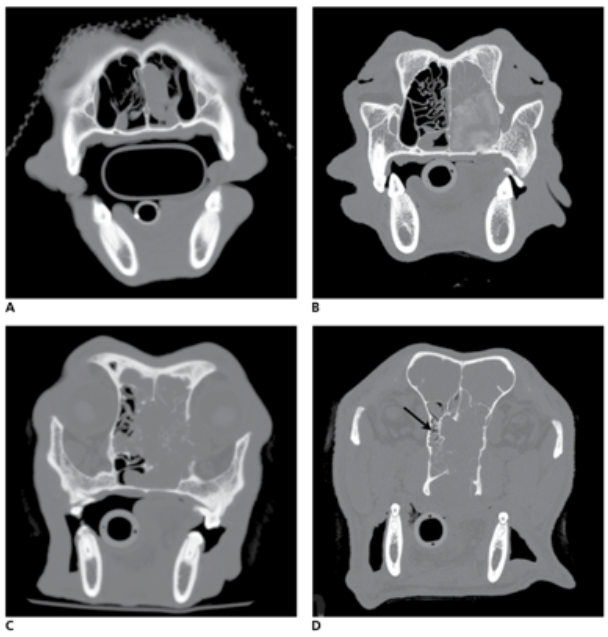

Figure 6. Examples of CT staging of nasal tumours from four dogs A: Stage 1, B: Stage2, C: Stage3, D: Stage 4 [4]

Theon's modified system consists of 2 stages, where stage 1 is considered less severe because this stage describes nasal tumours which have not invaded the frontal sinus yet but are confined to the nasal passage. Compared to this stage 2 shows a more severe form of neoplasm, in this case a bilateral invasion into the frontal sinuses and additionally an erosion of bones of the nasal passage. [17]

Nowadays Modified Adams Clinical Staging Methods for sinonasal tumours is considered the most relevant and commonly used method according to Vail et al. [2] It is based on computed tomography and is used to describe the local tumour extension in four clinical stages. Stage 1 includes the involvement of one nasal passage, paranasal sinus or frontal sinus, without the bone involvement beyond turbinates, whereas in stage 4 tumours which cause lysis of the cribriform plate are found. [2] In accordance with Adams et al. the significance of association between the disease free survival (DFS) and the staging system improved slightly when combining the Modified Adams Staging System with examination of the histologic type of nasal tumour. [18]

Table 2. Modified Adams Staging System for Canine Nasal Tumours [7, 19]

Stage 1	Confined to one nasal passage, paranasal sinus or frontal sinus, with no bone involvement beyond turbinates
Stage 2	Any bony involvement (beyond turbinates), but with no evidence of orbit/subcutaneous/submucosal mass
Stage 3	Orbit involved or nasopharyngeal or subcutaneous or submucosal mass
Stage 4	Tumour causing lysis of the cribriform plate

2.6 Multimodular therapy approaches

Nowadays a variety of treatment modalities for nasal tumours has been reported, with the goal to cure the affected dogs or improve the quality of their further life. Earlier, surgery in particular rhinotomy and excision of the tumour was considered as standard treatment, due to the fact that is was widely available. Nowadays it has been replaced widely with radiotherapy. Other treatment options include chemotherapy with different agents or less popular ones like cryotherapy, electrochemotherapy or photodynamic therapy. [1]

Occasionally cases of dogs with nasal neoplasm can be detected, in which the clinical signs can be temporarily alleviated by different symptomatic treatments like antibiotics, steroids or non-steroidal anti-inflammatory drugs. [2]

Despite this not insignificant choice of various treatments, the longterm prognosis of dogs diagnosed with nasal neoplasia remains poor and the median survival time (MST) of patients not treated is three to six months. Alternating treatments and combinations of treatments result different median survival times or disease free periods. [19]

The treatment of sinonasal carcinomas and sarcomas in form or surgical excision, radiation therapy, chemotherapy or other therapeutic approaches, are directed mainly towards the local disease control, which usually manifests at a critical location close to the brain and eyes. Depending on the chosen therapy option differences in the median survival time can be observed. [2]

Among other therapies, photodynamic therapy, cryoablation or immunotherapy may be used in case of canine nasal tumours. According to the book “Small Animal Clinical Oncology” these do not live up to their expectations or their results are too preliminary to determine clear results. [2]

2.6.1 Surgical Therapy

In the past the main treatment method and only widely available one was considered to be surgery, more precisely rhinotomy and tumour excision. Unfortunately, surgery alone, was linked to a rather poor survival rate and high morbidity. [1]

Therefore, contemporary practice no longer relies on surgical therapy as the sole treatment approach. Instead, it is primarily employed for obtaining biopsy samples from the nasal cavity. [20]

Rhinotomy, a surgical procedure, may be utilized to alleviate obstructions and thereby alleviate clinical symptoms in certain dogs. [21] Nonetheless when it comes to benign tumours, surgery should be included in the treatment. In case of malignant neoplasms, surgery on its own is not recommended and will not result in an increased survival time, in some cases it may even result in the opposite, it is possible that it may even shorten the survival time. [22]

The surgical approach of the nasal cavity is mainly done with the indication to collect samples for a biopsy and for surgical debulking. Rhinotomy may be done via a dorsal, ventral or lateral approach to the nasal cavity with the lateral approach being used the least common, due to the fact that it only allows to access the nasal vestibule. [20]

Both surgeries, dorsal and ventral rhinotomy, are done under general anaesthesia and in order to avoid the possible inhalation of blood or excretions during the surgery, the dogs' pharynxes are packed with tissues. Additionally, the dogs are intubated as well and during the act of extubation, it is recommended to have to cuff of the intubation tube slightly inflated, so that accumulated blood and excretions get removed while extubating the animals.

Dorsal rhinotomy is considered the surgical gold standard in dogs. It is done with the dog in ventral recumbency by making a midline skin incision on the dorsum nasi extending caudally from the nasal planum. Dependent on the desired area of the nose to be explored, the incision either ends at the height of the nasal canthus of the eyes or may be continued further caudally and to an imaginary line, which connects the zygomatic processes of the frontal bones. To be able to explore the underlying bone it is necessary to deepen the incision into the subcutaneous tissue and

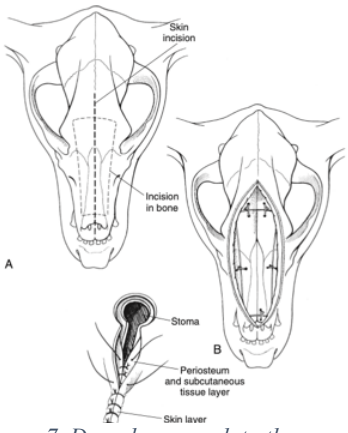

Figure 7. Dorsal approach to the nasal cavity [22]

periosteum and continue by making a unilateral or bilateral bone flap by the use of an osteotome or an oscillating saw. Determined by the intention of the surgery and the extension of the tumour, the turbinates are removed or not. In case of a curative intent, they are removed, if only a simple biopsy is taken it may not be necessary to remove them. To achieve better visibility of the nasal cavity and frontal sinuses, it is important to flush it with sterile saline solution and remove all possible blood clots and debris. [20] Afterwards everything can be inspected and possible tumour debulking can be done. For possible bleedings, cauterization devices, cold sterile saline solution and/or digital pressure is used. When everything is completed, biopsy taken and tumour debulked, the bone flap, the periosteum and the subcutaneous tissue sutured with absorbable suture material, while the skin is sutured with non-absorbable material. [20, 21]

In the matter of ventral rhinotomy, the surgery begins with the dog in dorsal recumbency, so that the ventral side of the nose is accessible and by fixation of the mandible dorsally the mouth is kept wide open. This approach is used to visualize the nasal cavities with nasopharynx and the rostral part of the frontal sinuses. Advantages of this approach can be seen in the fact that it reaches a better cosmetic outcome and the risk of developing a subcutaneous emphysema is limited, while disadvantages include the limited visibility of the frontal sinuses and the risk of the formation of an oronasal fistula. [20] To reach the nasal cavity again a midline incision in the hard palate is made, extended caudally through the soft palate if necessary and the mucoperiosteum is elevated and lifted laterally towards the alveolar ridge. During this step it is necessary to take care of the palatine foramen, as they are the origin of palatine nerves and vessels, which must be spared. Now the nasal cavity is accessible for exploration, biopsy samples can be taken, and any abnormal or tumourous tissue may be removed. Possible haemorrhages are controlled as mentioned above, although in case of this approach it should be avoided to use cautery. In the end of the surgery, the incision is closed in three layers, first the soft palate's nasal mucosa, followed by the submucosa-periosteum of the hard palate and finally the oral mucosa of hard and soft palates. [20, 21]

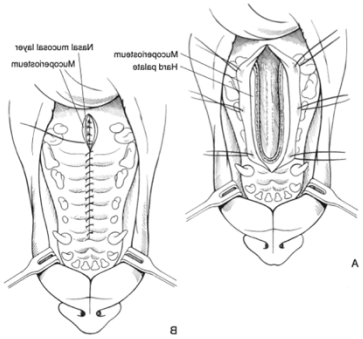

Figure 8. Ventral approach to the nasal cavity [22]

2.6.2 Radiotherapy

Radiation therapy (RT) is considered as the most effective sole way of controlling canine nasal tumours. [2] Despite the poor long-term prognosis of these tumours, when speaking of sole therapies, radiation appears to have the longest median survival time. According to the "Oncology Corner" journal, where multiple articles were compared, in radiotherapy the longest median survival times (MST) of 12 to 16 months have been reported, compared to cases where no treatment, surgery, chemotherapy, immunotherapy or cryosurgery has been performed. In the later scenarios the MSTs only reached 3 to 6 months, due to the increasing appearance of severe adverse effects and the owners tendencies to euthanize their pets. [17]

Depending on the type of tumour, radiology may be used as a single therapy option or in combination with for example surgery. It can be used with either curative or palliative intention. Additionally the neoplasm's type and location is determining the pre-, intra- or postoperatively use of radiotherapy. [23]

Radiation therapy is a treatment method that uses high-energy radiation to kill cancer cells and shrink tumours. [24] More precisely its mechanism of action, hence the principles of radiation biology is based on ionizing radiation, which is used to kill cells by damaging molecules in cells, especially desoxyribonucleic acid (DNA), resulting in the death of the cells attacked. [25]

To allow for reoxygenation of tumour cells and subsequent killing of more tumour cells, the total radiation dose is often administered as a number of smaller doses or fractions. However, the known big issue with radiation therapy is that it can also attack healthy tissue, so it's crucial to examine the animal's suitability for it before beginning treatment. [24]

In veterinary medicine, teletherapy, which is the administration of radiation via the use of an external beam, is considered to be the most frequently used radiation therapy method. This external beam RT is further divided according to the energy of the photon, into orthovoltage and megavoltage, with megavoltage being most commonly used among the external beam RTs, due to its advanced tissue-penetrating capabilities compared to orthovoltage therapy. Megavoltage may result in an average photon energy greater than 1 million electron volts (1 MeV) and its radiation is received from linear accelerators or cobalt machines. [25]

Prior to the start of radiation therapy, a protocol needs to be developed for the specific patient and it can differ based on type of tumour, stage of tumour and the facility of the treatment.

Additionally the protocol is adjusted to its intention, so whether the RT's purpose is to standard or palliative radiation therapy. [24]

"The radiation dose is the absorbed doseof energy deposited in the tissue". [24] This measurement is quantified in grays (Gy), with one gray corresponding to the absorption of 1 joule of energy per kilogram of tissue (1 joule/kg). In case of standard radiation therapy the delivery of a smaller dosage per fraction is used, but for a usually longer and/or more frequent application and therefore a larger total dose compared to the palliative usage of RT. Hence when considering the article "Veterinary Radiation Therapy: Review and Current State of the Art", a full course of radiation therapy consists of the delivery of 2,25 to 3,2 Gy/fraction, administered daily on a Monday to Friday schedule and 16 to 25 treatments, which results in a final total dose of 48 to 63 Gy. [24] Other important points about the RT is that the animal is anaesthetized during the treatment and it is necessary to determine its actual localization of animal and treatment field, which is then tested with a localization film. [24]

Acute and late radiation side effects can be observed. Primarily acute effects appear in fast proliferating tissues, like the oropharyngeal or nasal mucosa or the skin, while late effects tend to occur in nerves and bones, in tissues where no more mitosis happens. [17]

During the course of radiation therapy and sometimes even weeks after the end of the therapy, acute side effects with varying degrees affect the animals. These include for example oral mucositis, conjunctivitis, keratoconjunctivitis sicca and skin erythema and desquamation.

Late radiation side effects are seen months to years after treatment and it also affects mainly normal tissues, that were included in the treatment field, like the eyes and the skin. [17, 24] No bone, nor nerval late side effects could be found during this research for late radiation side effects.

The pain connected to the previously mentioned side effects, may be relieved by the usage of oral medications and oral rinses, including for example nonsteroidal anti-inflammatory drugs or opioids. [17]

2.6.3 Chemotherapy

Chemotherapy is mostly used in combination with other therapy modalities, as an adjunct to local therapy like radiation, nevertheless it is used as a sole agent in the treatment of canine nasal tumours as well. [1] The effects of cytotoxic drugs may include partial (PR) or complete

remission (CR), decreased in the tumour sizes and possible extension of lifespan (OS) in some cases. [26]

Nowadays there is the possibility of systemic, as well as local or locoregional chemotherapy. The traditional chemotherapeutic method, systemic intravenous drug delivery works on the principle of a diffusion gradient, the movement of chemotherapy drugs through a process of simple diffusion, moving from the intravascular into the surrounding tissue or interstitial spaces. On the other hand, ways of local chemotherapy administration have been developed, without the need of the agent to infiltrate the whole vascular system. One example of this method, a solution which enables the increase of efficacy of dose chemotherapy delivery, is to infuse the vessels directly, which supplying the neoplasm directly. [27]

2.6.3.1 Systemic chemotherapy

Tumours and their draining lymph nodes are situated in the interstitial or extravascular space. Malignant cells tend to disseminate into different body parts. Therefore, it is important that the chemotherapeutic agents is able to traverse the vascular endothelium and consequently reach all possible body parts where tumour cells might spread.

Systemic chemotherapy for nasal cancer in dogs may be administered via different ways, including orally, subcutaneously, intramuscularly or intravenously. [26] The goal is to reach enough chemotherapeutic concentration to destroy malignant cells and minimize harmful side effects on adjacent tissues. This means that the relative mass of the affected organ compared with the total body mass has to be taken into consideration when figuring out the effective concentration of the usable chemotherapy. Additionally this limitation of concentration results therefore also in an extended period of time needed for the treatment itself and especially the evaluation of its effectiveness, so that it may be changed immediately if necessary. [27]

The most commonly used cytotoxic agent used in the treatment of solid tumours in dogs is considered to be Carboplatin, but also other drugs like Doxorubicin, Carboplatin, Cisplatin, Mitoxantrone, Fluorouracil Cyclophosphamide or even L-phenylalanine mustard are used. [1]

The main weakness of systemic chemotherapy is that the agent cannot decide where it causes a direct effect, it travels through the entire body and therefore it may result in various side effects. Therapy discontinuation, therapy reduction or even premature death may be the consequence.

Intravenous chemotherapy administration may attack the bone marrow and lead to lympholysis, with the final outcome of an impairment of the body's natural immunological response. [27]
In general, the combination of different chemotherapeutic agents is a common practice nowadays and results in an increased tumouricidal effect of the combined agents to treat a given malignancy. More sustained remission and an increase of the survival times may be caused by the fact that the development of drug resistant clones is delayed or decreased by multichemotherapy. [28]
Chemotherapeutic agents usually have a narrow therapeutic index even in low doses and are therefore in the need of very careful handling, as even the occupational exposure of the personnel administering the therapy can lead to side effects like headache or nausea. This is why it is very important that all possible safety measures during the administration of chemotherapy must be taken to protect everyone included in the cytotoxic drug administration, including especially the personnel administering agent and the owners of the affected animal. Equipment used for chemotherapy administration should not be reused. Excretes, more precisely the urine and faeces of the patient should be properly disposed for the next 24 to 48h after chemotherapy. [28]
Safety measures during the administration include approved masks, gowns and gloves. Additionally, there are closed systems available for the administration of cytotoxic drugs, which reduce the risk of aerosolization. Prior to the start of the therapy, a protocol for the administration should be made, including the way of administration, the general and side effects and other important pieces of information like emergency procedures should a spill occur. The majority of chemotherapies is given intravenously, so it is crucial that the vein catheter is well-placed in a new leg, where no damage to the veins has occurred during the recent use of it or the attempt of "fishing" for the vein. This is due to the fact that any kind of previous use of the vein or damage during the attempt of inserting the vein catheter can result in microtears and possible paravenous tissue damage or destruction even. [26]

2.6.3.2 Local chemotherapy

The term "local chemotherapy" refers to the delivery of chemotherapeutic agents directly to the tumour or its surrounding tissues, rather than administering the agent through the whole body via the bloodstream. [27, 29] The big advantage of is that higher concentrations of the drug can reach the tumour, while the exposure of the normal tissue is minimized. [27] In other words under local

chemotherapy the major limitation of most systemic chemotherapeutic agents, the lack of tissue specificity, is avoided by using a local approach without burdening the whole body. [29] Different solutions have been developed to increase the efficacy of dose chemotherapy delivery to the targeted neoplastic tissue, including intra-arterial, intraperitoneal, intratumoural or intravenous. [27, 29]

The article “Novel Application for Electrochemotherapy: Immersion of Nasal Cavity in Dog” published in 2017 introduces the application of electrochemotherapy. This treatment method is considered as a local cancer treatment, mainly used in cutaneous and subcutaneous tumours. Within Suzuki et al.’s study electrochemotherapy was used as an adjuvant therapy tool to surgery to treat and eliminate intranasal tumours. [30]

To amplify the contact and conductivity between the plate electrodes and the residual tumour, it was necessary to immerse the nasal cavity in liquid and bleomycin prior to the application of the electric field. The electric pulses passing through the target tissue were based on electroporation and electropermeabilization of cellular membranes.[30] Moreover a different but similar option of the usage of electrochemotherapy was described in another research article, by which a minimally invasive device, a single needle electrode (SiNE), was introduced to deliver an appropriate electric field. [31] The outcome of it was an increase of membrane permeability, which made it possible for molecules, DNA and drugs to enter the cells. [30, 31] In the end it could be proven that the novel electrochemotherapy application was successful on the elimination of nasal tumours and the main difficulties found were that the surgery was limited due to the complex anatomy and possible residual tumours in the bone cavity. [30]

Another method of local chemotherapy is isolated limb infusion (ILI) or isolated limb perfusion (ILP). [32] ILI or ILP is typically performed under general anaesthesia, during which angiographic catheters are positioned above the knee or elbow of the extremity to be treated and a proximal tourniquet is inflated. This is followed by the infusion of the chemotherapeutic agent, which is circulated approximately 20 minutes through the limb. [33] This is another method used for the local delivery of cytotoxic drugs in a high concentration without systemic side effects. [32] In both studies found during this research Melphalan was used for ILI or ILP. [32, 33]

A different article by Lane et al. examined different variants of chemotherapeutic drug delivery with its challenges, including the direct arterial delivery, drug eluting particles, stop flow techniques, isolated hepatic infusion and implantable multicatheter access systems. [27]
It states for example that hepatic arterial infusion (HAI) for secondary colorectal cancer belongs among the best studied areas of regional chemotherapy infusion. Within this treatment modality the arteries supplying the neoplasm get implanted either percutaneously with an indwelling arterial hepatic catheter connected to an infusion reservoir containing the chemotherapy or via a transcutaneous implantation of a catheter into the gastroduodenal artery which in this case is connected to pump delivering chemotherapy over a period of time. [27]
TACE, Transcatheter arterial chemoembolization was also introduced in this article, as a system which uses drug eluting embolic particles, mixed with chemotherapy to be administered into the main arteries supplying the tumour, to reach a higher intratumour drug concentration. Similar to TACE is the DC Bead drug delivery embolization system, during which mostly hydrophilic, nonreabsorbable hydrogels combined with cytotoxic agents like Doxorubicin are used. Despite the great advantage of this method of chemotherapy delivery, here too disadvantages limiting its current use could be found. These include occlusion of normal tissue with secondary ischaemia or the possibility of developing pulmonary embolisms or infarcts due to unintended migration of embolic particles into the systemic circulation. [27]
Furthermore, stop flow techniques were introduced within Lane et al.'s work. This technique of locoregional chemotherapy delivery is based on the cessation of the blood flow supplying the tumourous tissue. It can be executed via the use of balloon catheters positioned for example within the aorta above the celiac axis and within the vena cava above the hepatic veins to interrupt the blood flow and thereby generating a artificially closed circulation for perfusion of the liver and other adjacent tissues. Unfortunately, also this method of locoregional chemotherapy is not commonly used, because even here shortcomings were found, which include for instance the unintentionally escape of chemotherapeutic agents into the venous circulation during the deflation of the balloons used. [27]

Hence, all in all in the examples the approaches of local chemotherapy described in the article mentioned above, lots of adverse effects could be found. Despite that it is believed that local use of chemotherapy is a promising method to improve the effectiveness of chemotherapy delivery. [27]

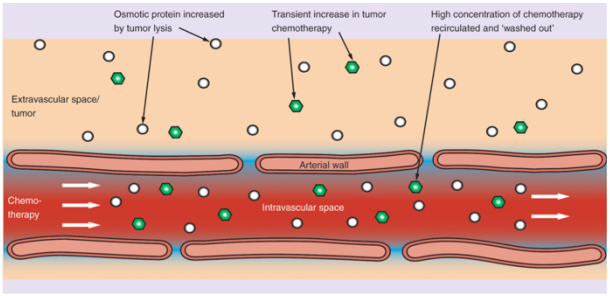

Figure 10. Intra-arterial chemotherapy at the tumour vascular interface [28]

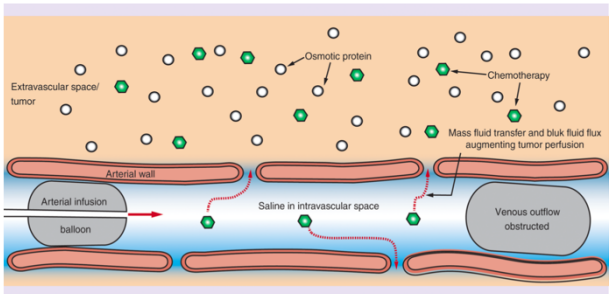

Figure 10. Mechansms of vascular isolation and mass fluid transfer [28]

Magnetic drug targeting (MDT) is another option of the local chemotherapy administration. By using this rather new method it is possible to increase the drug dose administered into the region of the tumour via the use of magnetic nanoparticles. To increase the therapeutic agent administered in the tumour, the agent is focused from outside of the patient's body by the use of an external magnetic field. More precisely a chemotherapeutic agent, Mitoxantrone, is bound to ferrofluids, this magnetic, drug-loaded fluid is administered into an artery close to the tumour and then put into the desired position via the power of an external magnetic field. This pilot study yielded a favourable outcome, showcasing the effectiveness of a single MDT treatment with a reduced chemotherapeutic dose in comparison to systemic administration. This approach led to a notable reduction in tumour size and vascularization, while also being notably free from observable adverse effects. [34]

The main point of criticism was that a comprehensive knowledge of the tumour's vascularization is necessary, to provide the foundation for the nanoparticles to be distributed evenly within the neoplastic tissue. [34]

These are just a few of the possibilities nowadays when thinking about techniques to avoid the burden of systemic chemotherapy, by the usage of methods of local or locoregional chemotherapeutic delivery.

2.6.3.3 Piroxicam

According to Borzacchiello et al. “Cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) are known to play a role in the carcinomas of many human and animal primary epithelial tumours.” Cyclooxygenase (COX) is an enzyme, which is responsible for the catalyzation of arachidonic acid into prostaglandin (PG). [35] Nonsteroidal anti-inflammatory drugs (NSAIDs) work on the basis of targeting COX enzymes. Reports state that COX-2 compared to COX-1 enzyme does not appear to be in normal healthy tissue, but is rather induced by cytokines, growth factors, oncogenes and tumour promotors. On the contrary, COX-1 enzyme can be found in normal tissues. It is responsible for the catalysis of prostaglandin, which is an important part of the normal physiology of several organs. One can conclude from this previously given information, that an overexpression of COX-2 enzyme, is connected with neoplastic growth. [35] In Borzachiello et al.’s study the COX-1 and COX-2 expression was examined in canine nasal tumours. In almost all tested neoplastic specimens of the canine nasal carcinomas COX-2 enzymes were overexpressed. COX-1 could be found only in a few of the neoplastic specimens and in addition the expression was considered to be only weak in most of them. [35]
This knowledge makes the inhibition of the COX-2 enzymes an interesting and important target for chemotherapeutic use of COX-2 inhibitors. [36] Although the exact mechanism of NSAIDs on carcinomas is not well prescribed and understood, they are commonly used within anticancer treatment. [37] Unlike other NSAIDs, Piroxicam does not appear to have an apoptotic effect on neoplastic cells, it is still used in the cancer treatment due to its inhibitory effect on tumour cell proliferation. [37, 38]
Within the course of this work no study could be found, in which Piroxicam was used as a sole treatment or in a Piroxicam only control group. The use of Piroxicam was found only in connection with other chemotherapeutic agents, like Carboplatin or Piroxicam. [39]

2.6.4 Combination of different therapies

Close collaboration between different scientific disciplines is an essential part for the successful treatment of oncologic patients. The treatment method is required to be adapted to various factors, including the type of tumour, its biological behavior and clinical stage. In addition, patient-, family-, and treatment-related factors must be considered when choosing and planning cancer therapy. The latest mentioned, consists among others on the specific indication, whether

the treatment is supposed to act curative or palliative. For instance, surgery and radiotherapy are used rather curative as locally invasive treatment options, even though they may also be used palliative. Compared to this, chemotherapy is not considered as a curative, but palliative therapy. When thinking of the treatment-related factors to be considered when choosing the right treatment, the decision whether single or multiple treatment modalities should be chosen, as in some cases greater success may be achieved by the combination of two or more therapy methods. [40]

Radiation therapy is like mentioned above, the standard curative or palliative treatment of canine nasal tumours. [1] According to a study by Adams et al. surgery in combination with megavoltage radiation therapy is considered to have a better treatment outcome, when surgery is performed at the right timing. According to the study, dogs treated with radiation therapy before further surgical debulking is done, results in a better outcome. Early reoccurrence of nasal tumours was observed to be eliminated or delayed. [41]

Another combined therapy module found during the research of this thesis was the treatment via slow-release Cisplatin in combination with radiation therapy for canine nasal tumours, which was examined within the course of a study by Lana et al. [42] In human medicine the combination of radiation with chemotherapy has already shown promising results. The idea of connecting these two treatment modalities is based on the thought of the usage of drugs acting as radiation sensitizers or enhancing the desired cell death. During the course of the study, radiation was delivered together with Cisplatin as the radiosensitizing agent used. Cisplatin was administered using a so called open-cell polyactic acid product (OPLA-Pt), a slow-release system to deliver Cisplatin. In conclusion the combination therapy resulted in consistent or even improved survival in comparison with previously published protocols. [42]

A viable combined treatment strategy was additionally described in the study “Canine intranasal tumours treated with alternating Carboplatin and Doxorubicin in conjunction with oral Piroxicam: 29 cases”, in which an alternating chemotherapy protocol was used with adjunctive Piroxicam. The alternating agents used were Carboplatin and Doxorubicin and the outcome of the study was that the tested protocol was well-tolerated by the dogs, which makes the mentioned combination a viable treatment option for canine intranasal tumours. [39]

Other combinations of therapies could be found within the research of this paper, however they will not be discussed further here.

2.7 Prognosis

In accordance with Wilson at the time of a definite diagnosis, the existence of the tumour is considered to be already 3 months. [7] The overall prognosis of untreated nasal tumours is poor, if the tumour does not get any kind of treatment, a MST of 95 days could be evaluated in a retrospective study of dogs with nasal carcinoma. [43]

Due to a rather aggressive, local disease progression in case of canine nasal cancer the median survival times of patients ranges between 3-6 months, for dogs which received for example chemotherapy, cryosurgery or no treatment. After local, extended progression most dogs will die or be euthanized. [42]

Diverse results can be found in different studies about the factors influencing the prognosis in dogs diagnosed with nasal tumours, including for example the histopathological type of the tumour or the presence of metastases at the time of diagnosis. [44]

The connection between tumour stage and prognosis remains a subject of controversy, primarily because of inconsistencies in the approach and conflicting results from limited studies. Numerous studies have consistently linked the clinical stage determined through CT scans with overall survival, indicating worse outcomes when there's evidence of cribriform plate involvement, brain extension, lymph node involvement, or pulmonary metastasis. Advanced CT-based stages are generally associated with poorer prognoses, using a commonly employed CT staging system, the Modified Adams Staging System. Furthermore, facial deformity, dyspnoea, epistaxis, and an inadequate response to radiation therapy have been sporadically associated with negative prognoses. The relationship between histological diagnosis and prognosis is still unclear, primarily due to limited sample sizes and insufficient statistical power in most studies. Notably, sarcomas, especially chondrosarcomas, tend to have better outcomes when treated with radiation therapy, while osteosarcoma has shown a poorer prognosis in some instances. Sarcomas, however, may experience less reduction in tumour volume following radiation therapy compared to carcinomas, though their median survival times (MST) tend to be similar when radiation therapy is followed by surgery. Carcinomas other than adenocarcinomas, such as SCC and undifferentiated/anaplastic carcinomas, typically carry worse prognoses. [1]

3 Own studies

3.1 Material and Methods

The study was performed on dogs diagnosed with nasal tumours during the last 25 years, from 1997 until 2023 at the University of Veterinary Medicine Budapest (Istvan utca 2, 1078 Budapest) and the Veterinary Haematology and Oncology Clinic – ÁHOK (Bolgárkertész u. 31, 1148 Budapest).

Criteria for dogs to be included in this study were the firm clinical and/or histopathological or cytological diagnosis of canine nasal tumours. All together 151 dogs met these criteria and therefore could be included in the study.

Subjects of the investigation included the distribution of age, sex and breed of the dogs presented with nasal tumours. Additionally, it included the examination of the occurrence, distribution and impact on the survival of each histological category of nasal tumours. It also contains a comparison of the main therapeutic methods used in canine nasal tumours, with a special attention to the use of local chemotherapy. Another goal was to improve the quality of life and time of survival of the patients, by investigating local chemotherapy via the use of absorbing platinum derivatives in gel form.

3.1.1 Nationale and Anamnesis

The average age was 9.71 (± 2,99) years. (Figure 11)

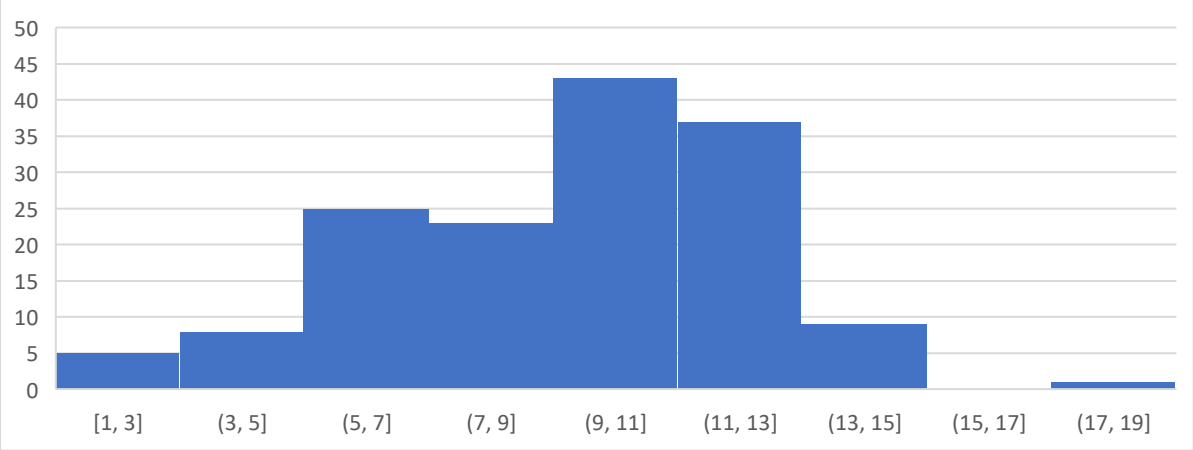

Figure 11. Age distribution of the dogs

There were 82 male (65 castrated) and 69 (55 ovariectomized) female dogs included. Male to female ratio was 1.188. There were several breeds included, although the most frequent was the Mongrels. Table 4 contains the breed distribution. Altogether 41 breeds were represented and among them 55 were dolichocephalic and 6 brachycephalic breeds.

Table 3. Distribution of dog breeds included

Alaskan Malamute	3	Husky	2
American Bulldog	2	Labrador Retriever	5
Beagle	5	Laika	1
Bernese Mountain Dog	1	Miniature Schnauzer	2
Bichon Havanese	4	Mongrel	41
Bobtail	1	Poodle	1
Bolognese Dog	2	Pug	1
Boxer	5	Rhodesian Ridgeback	1
Bull Terrier	2	Rottweiler	5
Bullmastiff Dog	1	Russian Black Terrier	1
Caucasian Shepherd Dog	1	Shetland Dog	1
Cesky Terrier	1	Shih Tzu	1
Cocker Spaniel	5	Smooth Fox Terrier	2
Collie	2	Spitz	2
Dachshund	3	Staffordshire Bull Terrier	2
Dalmatian	1	Transylvanian Hound	1
French Bulldog	3	Weimaraner	1
German Shepherd	14	West Highland White Terrier	1
Giant Schnauzer	4	White Swiss Shepherd Dog	1
Golden Retriever	6	Yorkshire Terrier	2
Hungarian Vizsla	11		

3.1.2 Diagnostics

After the primary examinations, including chest x-ray, complete blood count, clinical biochemistry including the basic panel (total protein, albumin, alanine transaminase, alkaline phosphatase, creatinine, urea, lactic dehydrogenase, total calcium, phosphate), and the acid base panel including blood gases and electrolytes (Na^+, K^+, Ca^{2+}, Cl^-), moreover haemostasis panel (activated thromboplastin time, prothrombin time) endoscopic examination, computed tomography examinations were performed. Mostly during endoscopy tissue samples were taken from the nasal lesions. In some occasions the dogs went for surgical intervention as an option of

therapy, and when they surgeons performed the curatage, they separated samples for histopathology examinations, too. In some cases, endoscopy was not performed due to the advanced disease of the dogs.
During the late 1990s and early 2000s years there were more dogs diagnosed without the use of CT, endoscopy and histopathology examinations. In the late 2000s, close to 2010, when the facilities became more advanced, the owners showed an increase in willingness to proceed and also pay for more accurate diagnostics. For this reason, the use of diagnostic tools increased dramatically.

The clinical signs were all related to epistaxis. The duration of clinical signs before diagnosis ranged between 1 weeks to 6 months. The diagnosis was made by nasal and chest X-ray (n=28; 17.17 %), rhinoscopy (n=112, 68.71%), CT (n=106, 65.03%), histopathology (n=118, 72.39%), cytology (n=32, 19.63%). The frequency of CT and histopathology examinations increased by the time period from 1996 until 2023.

3.1.2.1 Staging

Like previously mentioned above in the literature review part of this work, the staging of dogs or more precisely their tumours, is an essential part of the planning of therapy. The Modified Adams Staging System [Table 5] is the most commonly used system, which describes four clinical stages of local tumour extension. [7, 19] A 5th stage to be used for this study was added to this already existing system to express even more advanced cases with lung involvement.

Table 4. Modified Adams Staging System [7, 19]

Stage 1	Confined to one nasal passage, paranasal sinus or frontal sinus, with no bone involvement beyond turbinates
Stage 2	Any bony involvement (beyond turbinates), but with no evidence of orbit/subcutaneous/submucosal mass
Stage 3	Orbit involved or nasopharyngeal or subcutaneous or submucosal mass
Stage 4	Tumour causing lysis of the cribriform plate
Stage 5	Involvement of lungs – evidence of pulmonary metastasis

According to the staging system the stage distribution of this study is seen at Table 6. Although, there were 45 cases not initially diagnosed by CT, only 36 cases were non specified by stage. In the remaining 9 cases, X-ray images provided information that was consistent with the CT-stages, despite the initial CT scans not clearly indicating the disease stage. This consistency was shown due to the presence of obvious radiographic signs, such as the detection of pulmonary metastasis and/or bone lysis of the cribriform plate.

Table 5. Stage Distribution of Dogs with Nasal Tumours

Stage	Number	Percentage (%)
0	36	23,84
1	23	15,23
2	31	20,53
3	22	14,57
4	34	22,52
5	5	3,31

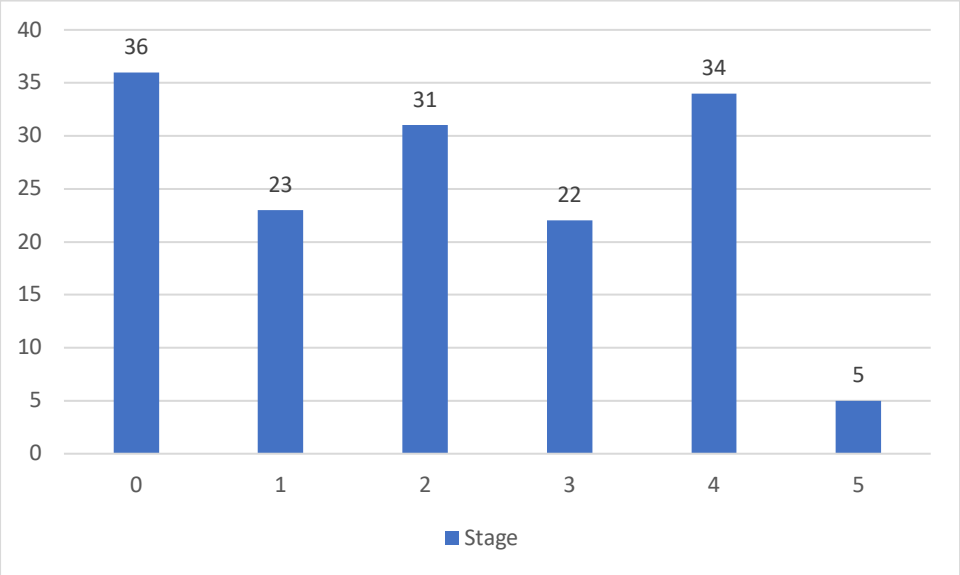

Figure 12. Number of dogs in different stages
Note: "0" = non-specified due to lack of CT-examination

3.1.2.2 Histopathology and Grading

A histopathological examination was performed in the Department of Pathology at the University of Veterinary Medicine Budapest, in some cases immunohistopathology was carried out.

Malignancy was graded according to the degree of differentiation of all tumour types, cellular pleomorphism, and mitotic activity. They are divided into three different grades: well-differentiated (Grade 1), moderately differentiated (Grade 2), and poorly differentiated forms (Grade 3). [45–47]

The histopathological types of the tumour examined were as follows: adenocarcinoma, chondrosarcoma, different types of sarcomas, osteosarcoma, squamous and anaplastic carcinoma, and lymphoma. In some dogs (n=28) histopathology examination was not performed. As mentioned above, within the time period of this study the use of diagnostic tools increased significantly, which includes the histopathological examinations.
The ages of the dogs of the study, matched with the histopathological types of their tumours are listed in Table 7 and in Figure 12.

Table 6. Age matched distribution of histopathological tumour types in 151 dogs with canine nasal tumours

Histopathology	I (0-5 years)	II (5<-10 years)	III (10<-12 years)	IV (12<-20 years)	All
Adenocarcinoma	5	34	32	17	88
Chondrosarcoma	3	7	5	1	16
Lymphoma	1	2	1	1	5
Non-specified	3	13	11	1	28
Soft tissue sarcoma	1	4	2	0	7
Osteosarcoma	0	2	0	0	2
Squamous cell carcinoma	0	2	3	0	5

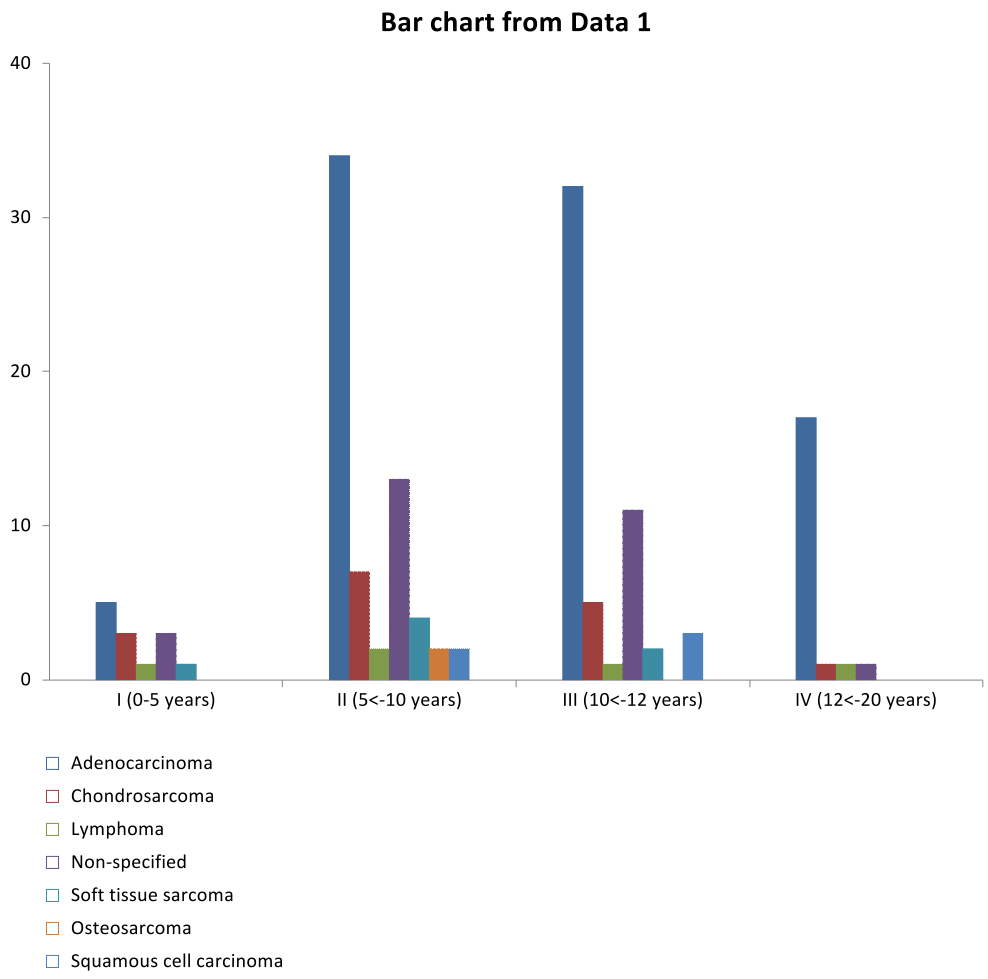

Figure 13. Histopathological types of canine nasal tumours arranged by age groups

The histopathological grades of the 151 cases of canine nasal tumours are listed in Table 8 and Figure 13.

Table 7. Grade distribution of different histopathology types of canine nasal tumours

Histopathology	Adeno-carcinoma	Chondro-sarcoma	Lymphoma	Osteo-sarcoma	Soft tissue sarcoma	Squamous cell carcinoma	Non-specified
Grade 0	15	3	0	0	3	0	28
Grade 1	31	6	0	1	3	2	0
Grade 2	17	2	5	1	1	0	0
Grade 3	25	5	0	0	0	3	0
All	88	16	5	2	7	5	28

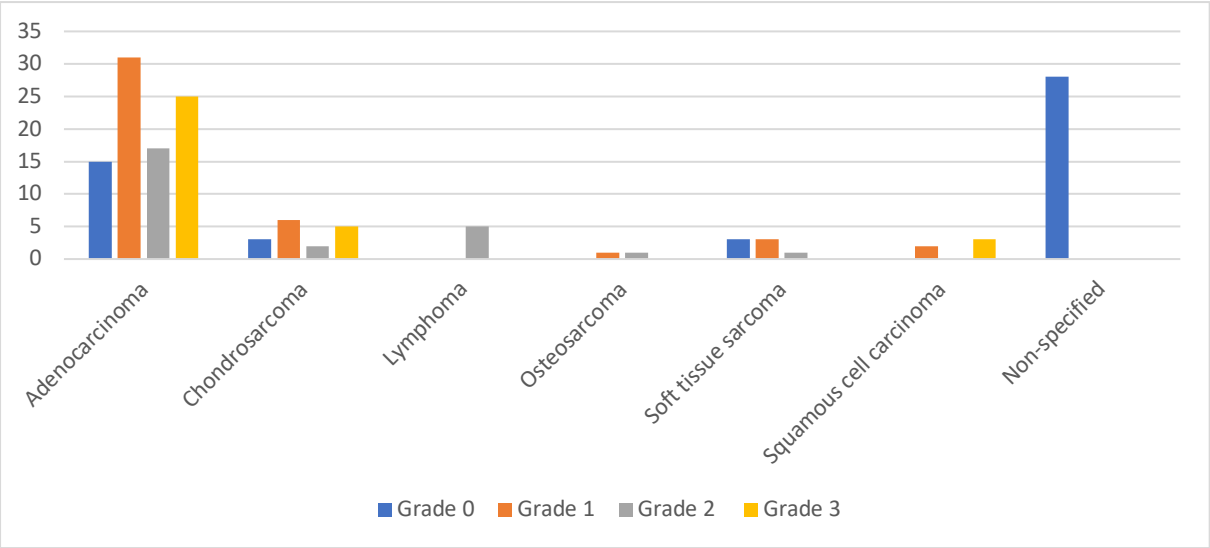

Figure 14. Grade distribution of different histopathological types of canine nasal tumours

3.1.3 Therapeutical approaches

The dogs presented with canine nasal tumours were treated via the following options:

- Surgery – by rhinotomy and curettage,
- Gel formulated Carboplatin and/or Cisplatin local administration,
- Non-gel formatted Carboplatin and/or Cisplatin local administration,
- Prednisolone,
- Meloxicam, Robenacoxib, Carprofen, Ketoprofen, Celecoxib, Piroxicam, Firocoxib,
- Systemic, intravenous Doxorubicin,
- Metronomic, peroral Chlorambucil,
- peroral Lomustin,
- peroral Toceranib,
- peroral Cyclophosphamide,
- radiation therapy.

3.1.3.1 Anti-inflammatory therapy

After endoscopical examination, the dogs were treated with Prednisolone for 1 to 8 weeks with a starting dose of 1 mg/kg bw SID in the morning, combined with Famotidine 1 mg/kg bw BID or Pantoprazole in 1 mg/kg bw BID. The dose of the Prednisolone was reduced after 2 weeks of treatment to 0,5 mg/kg bw SID in the morning.

Among non-steroidal anti-inflammatory drugs, Firocoxib was give in 5 mg/kg bw SID, Meloxicam in 0.1 mg/kg bw SID, 1 mg/kg bw SID, Piroxicam was given in 0.3 mg/kg bw SID. Robenacoxib was used at registered dosages, like 2 mg/kg subcutaneously SID and 1–4 mg/kg orally SID, Ketoprofen was used in 2 mg/kg s.c. or i.m. SID and it was repeated for up to 3 consecutive days, moreover, this drug was used perorally in 0.25 mg/kg SID for up to 30 days, Carprofen was used in 4mg/kg SID in treated dogs.
As mentioned above, in the case of the usage of Prednisolone, H2-receptor blockers or protone pump inhibitors were concomitantly used with NSAIDs.

3.1.3.2 Chemotherapy

3.1.3.2.1 Systemic Chemotherapy

In some patients oral chemotherapy was used for the treatment, due to the histological type or advanced tumour stage. The medications used during this study can be seen in Table 9 to Table 12. Toceranib was used in some clinical cases, with a dosage ranging between 2,7 to 3,5 mg/kg bw every other day. Chlorambucil was used as well with a dosage of 2 mg/m^2 every day together with NSAIDs.

3.1.3.2.2 Local Chemotherapy (Table 9, Table 11)

During the mid 2000s Carboplatin was applied locally into the nose, by puncturing the frontal sinus with a dose of 1/3 of the iv dose (100 mg/square m^2). The first dog, “Tara” a husky, was treated with this therapy on the 26th of January 2008. Tara’s CT revealed fluid in the frontal sinus, which indicated the tumour’s spread towards the cribriform plate and the brain.
Tara and the other dogs which were included in the study at this time, were anaesthetized and intubated with a tracheal tube. Followed by the application of different methods to seal off the nasal and oral passages, which included the closure of the soft palate with intraoral compress cotton gauze and the manual closure of the nostrils using gloves and masque.
Later on, the goal was to find an alternative option, therefore slow-release gel (0.7 % porcine gelatin, G2500, Sigma-Aldrich, Gelatin from porcine skin, © 2023 Merck KGaA, Darmstadt, Germany) combined with Carboplatin, for local treatment of these tumours, was applied, to gain better survival results than surgery and/or chemotherapy.

The first step was a cytoreductive surgery performed via dorsal or ventral rhinotomy. Already during surgical intervention, the first session of chemotherapy was done. Carboplatin gel was administered into the nasal cavities and paranasal sinuses by using Foley catheters. These were inserted antegradelly through the nostrils and retrogradely, by retroflexing the catheter over the soft palate and the frontal sinuses were treated by puncturing of the skull. The dose of Carboplatin was 100-150 mg/m^2, depending on the size of the nasal cavity (brachycephalic vs. dolichocephalic) avoiding leakage of chemotherapy solution with high hydrostatic pressure.

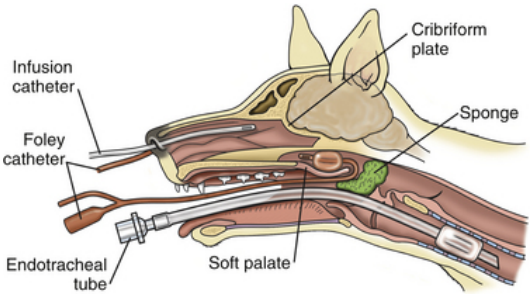

Figure 15. Position of the Foley Catheters [48]

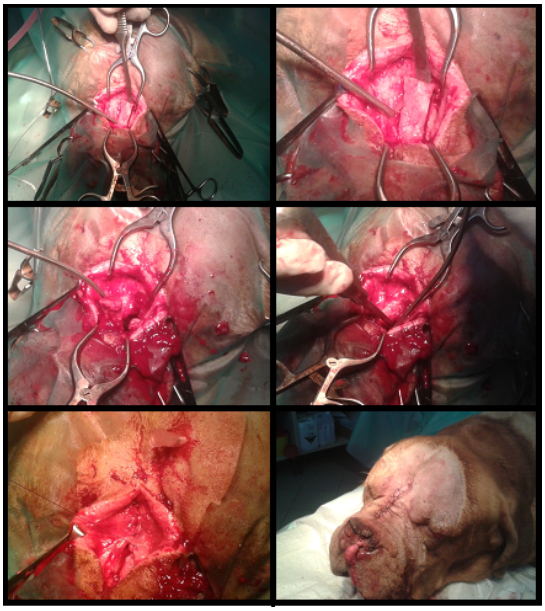
Figure 16. Operation and puncture of the frontal sinus

After the treatment, the dogs were kept in a closed place (kennel), separated from the environment, in order to avoid contamination of their environment during the wake-up process, as the dogs frequently showed sneezing. Interestingly, the dogs' sneezing did not exceed 2 to 3 episodes. The place of captivity was carefully cleaned afterwards via the usage of NaOH solution.

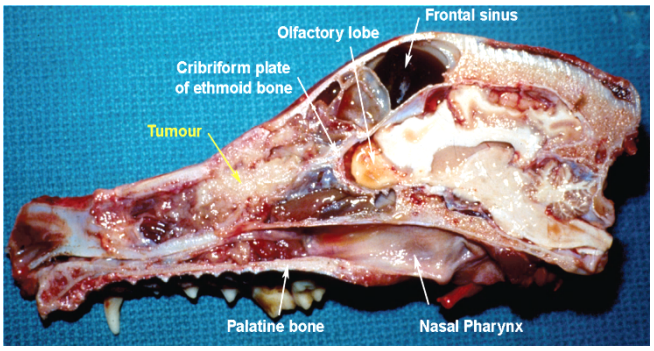

Figure 18. Frontal sinus and nasal cavity by morphological, pathological examination (cross section of the scull)

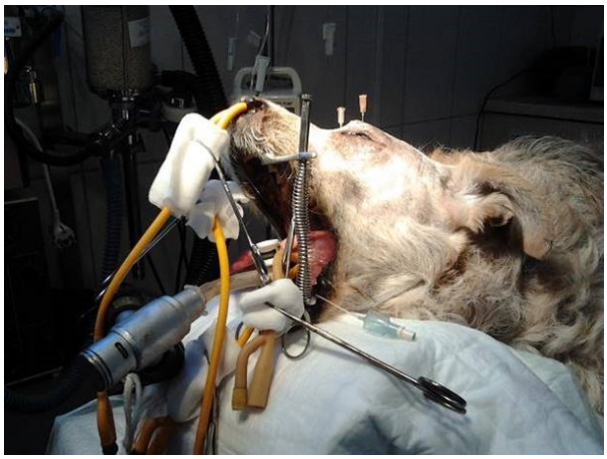

Figure 18. Local chemotherapy administration by puncturing the frontal sinus

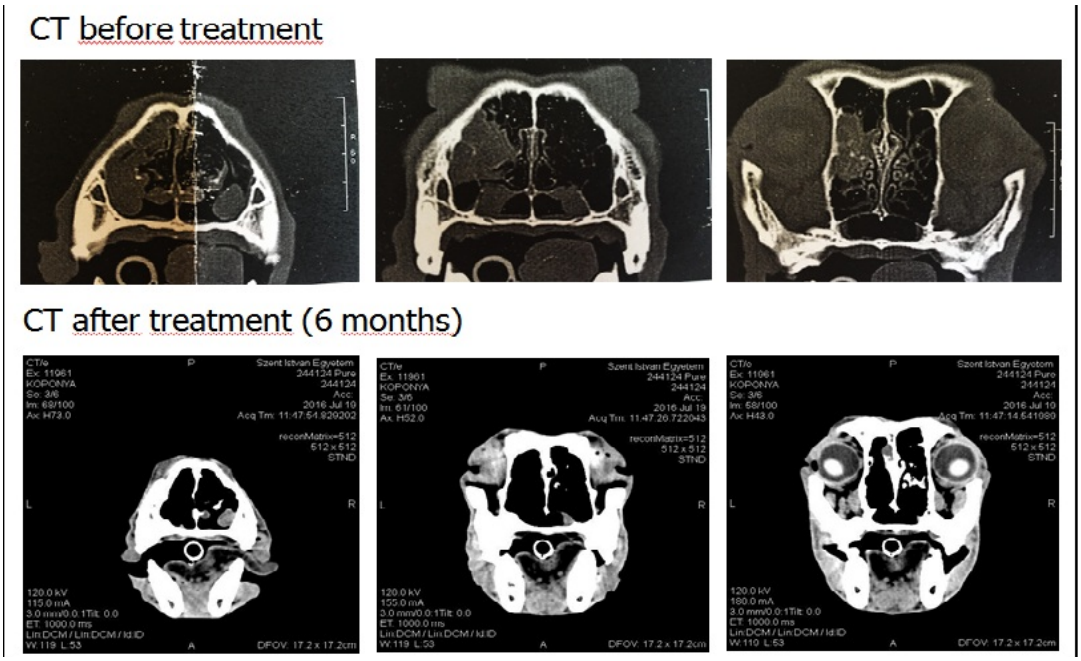

Figure 19. CT-comparison of a dog before and after the treatment
The dog second row shows the scull of a dog which was cured in the end ("Püre", mixbreed, 9th March 2015)

3.1.3.3 Radiation Therapy

Applied equipment was Varian Truebeam 2.0 linear accelerator. It provides digital, arc-based treatments (RapidArc, stereotaxy). CT can be taken before and during treatment: image guided treatments (IGRT). It is intensity modulated RT (IMRT).

3.1.3.3.1 Course of Treatment

Because the nature of the X-rays used in CT examinations is the same as in radiation therapy with applied ionizing rays, therefore it was obtained from the tissue absorption obtained during the CT examination. The information can be used in the preparation of the radiation therapy plan. Different tumours have different radiation sensitivities, as well as the radiation exposure of tissues different. The type of radiation, the area to be irradiated, can be determined according to the location and type of the tumour, volume, the total dose of radiotherapy and the dose delivered at one time. Irradiation does not hurt, cannot be seen or heard, and occasionally lasts a few minutes. The treatment after, the patient does not become "radiant", radioactive. After positioning and before treatment, CT scans (CBCT) are taken to see if does everything exactly match the data specified in the irradiation plan. These checks serve the purpose that each treatment during planning be done in a specified manner.

In general anesthesia: iv. after propofol (6mg/kg body weight) induction, intubation, then anesthesia maintenance using isoflurane (2 vol%)-oxygen (1-2 vol%) gas mixture.

The dogs with advanced tumours received higher doses as 51–57 Gy in 17–19 fractions over 22–24 days once or twice. Dogs with less advanced tumours and after surgery received 42 Gy in 10 fractions over 11 days.

3.1.3.4 Surgical Therapy

Within the study of the 151 cases, 60 dogs were operated by rostral and/or ventral rhinotomy and curettage. 91 dogs were not treated by surgical intervention due to the tumour's progressiveness or the owner's special request. The average of occasions of nasal rhinotomy was 1,35 (from 1 to 5 occasions).

The tables below (Table 9-12) represent the distribution of the different treatment modalities used, with or without the involvement of surgery.

Table 8. Operated dogs (interventional therapies)

	Gel formulated Carboplatin or Cisplatin	Average number of gel formulated therapy	Non-gel formulated local Carboplatin or Cisplatin therapy	Average number of non-gel formulated local Carboplatin or Cisplatin therapy	Radiation therapy	Average number of radiation therapy
Number of dogs	34,00	203,00	8,00	33,00	2,00	7,00
Mean %	56,67	5,97	13,33	4,13	3,33	3,5

Table 9. Operated dogs (non-interventional therapies)

	Prednisolone	Other NSAIDs *	Piroxicam	Firocoxib	Systemic, iv. Chemotherapy (Doxorubicin or Carboplatin)	Lomustin	Toceranib	Metronomic Chlorambucil	Doxorubicin	Cyclophosphamide
Number of dogs	4,00	8,00	19,00	8,00	0,00	1,00	0,00	8,00	3,00	4,00
Mean %	6,67	13,33	31,67	13,33		1,67		13,33	5,00	6,67

* Meloxycam, Robenacoxib, Carprofen, Celecoxib

Table 10. Non-operated dogs (interventional therapies)

	Gel formulated Carboplatin or Cisplatin	Average number of gel formulated therapy	Non-gel formulated local Carboplatin or Cisplatin therapy	Average number of non-gel formulated local Carboplatin or Cisplatin therapy	Radiation therapy	Average number of radiation therapy
Number of dogs	1,00	1,00	11,00	44,00	7,00	13,00
Mean %	1,10	1,00	12,09	4,00	7,69	1,86

Table 11. Non-operated dogs (non-interventional therapies)

	Prednisolone	Other NSAIDs *	Piroxicam	Firocoxib	Systemic, iv. Chemotherapy (Doxorubicin or Carboplatin)	Lomustin	Toceranib	Metronomic Chlorambucil	Doxorubicin	Cyclophosphamide
Number of dogs	9,00	9,00	10,00	30,00	6,00	0,00	5,00	25,00	1,00	0,00
Mean %	9,89	9,89	10,99	32,97	6,59	0,00	5,49	27,47	1,10	0,00

* Meloxycam, Robenacoxib, Carprofen, Celecoxib

3.2 Results

3.2.1 Nationale and Anamnesis

A non-significant difference regarding the survival rate of the different genders could be found. Males lived longer, their mean survival time was (95% Cl) 382.586721 (286.358068 to 478.815374), compared to female dogs with a mean survival time of (95% Cl) 289.813318 (225.583116 to 354.04352).

Contrary to this, the median survival time of female dogs was 256 days and in male dogs it was 262 days. Log rank (Peto) test revealed the following: Chi-square for equivalence of death rates = 2.33262 P = 0.1267.

Depending on the age group, the following life expectancies were measured after the treatment of the dogs. (Table 13, Table 14) The differences were non-significant. . Results of the Log-rank (Peto) test: Chi-square for equivalence of death rates = 4.755528 P = 0.1906; Chi-square for trend = 0.508828 P = 0.4756.

Table 12. Age distribution of dogs with nasal carcinomma

Group by age period (year)		Frequency	Relative %	Cumulative	Cumulative Relative %
1	0-5	13	8.609272	13	8.609272
2	5<-10	20	13.245033	33	21.854305
3	10<-12	54	35.761589	87	57.615894
4	12<-20	64	42.384106	151	100

Table 13. Age-matched life expectancy of treated dogs with nasal carcinoma

Group by age period (year)		Median survival time (days)
1	112	0-5
2	213	5<-10
3	284	10<-12
4	345	12<-20

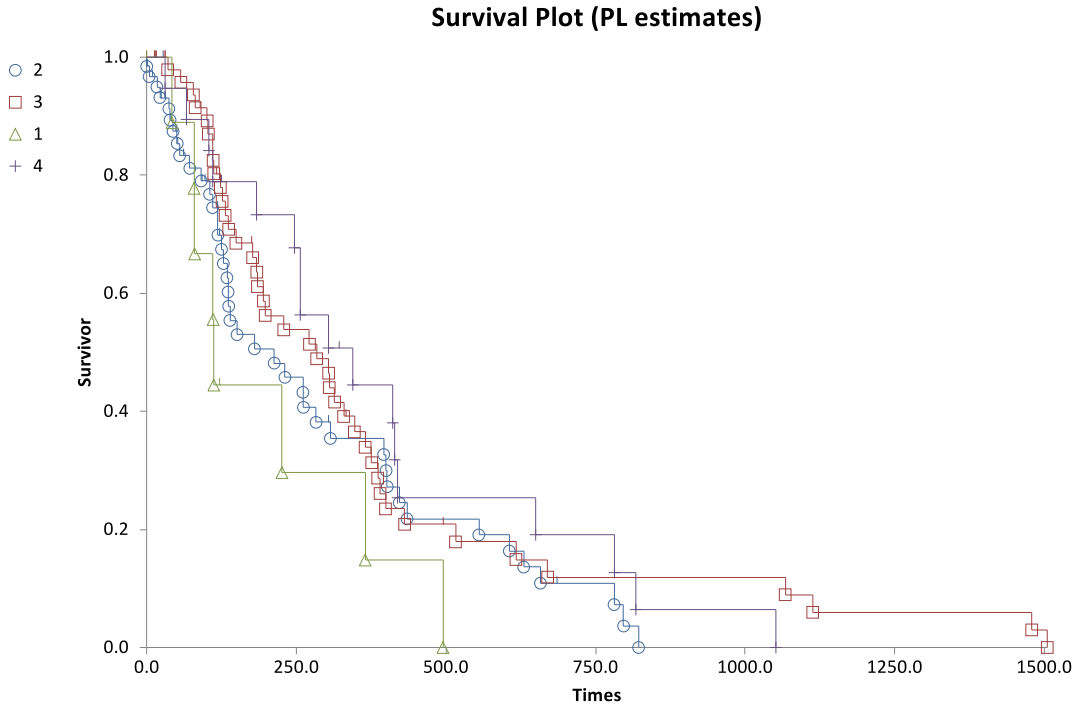

Figure 20. Survival of dogs with different ages expressed by Kapplan-Meier curves
Note: 1: 0-5, 2: 5<-10, 3: 10<-12, 4: 12<-20

3.2.2 Diagnostics

According to the Modified Adam's Staging System the dogs of the study got distributed into different stages. The survival rate of dogs in different stages was significant by the Log rank (Peto) analysis (Tabla xxx, Figure xxx). Chi-square for equivalence of death rates = 19.330954 P = 0.0017; Chi-square for trend = 2.398991 P = 0.1214.

Table 14. Survival data of dogs with nasal tumours belonging to different histopathological types

	Stage 0 (non-specified)	Stage I	Stage II	Stage III	Stage IV	Stage V
Observed deaths	18	28	26	14	28	5
Extent of exposure to risk of death	16.48	16.32	35.924	14.85	16.32	1.99
Relative rate	1.09	1.71	0.64	0.94	1.71	2.51
Median	262	304	396	226	136	110
Mean	303.82	385.24	486.72	370.89	209.61	146.6

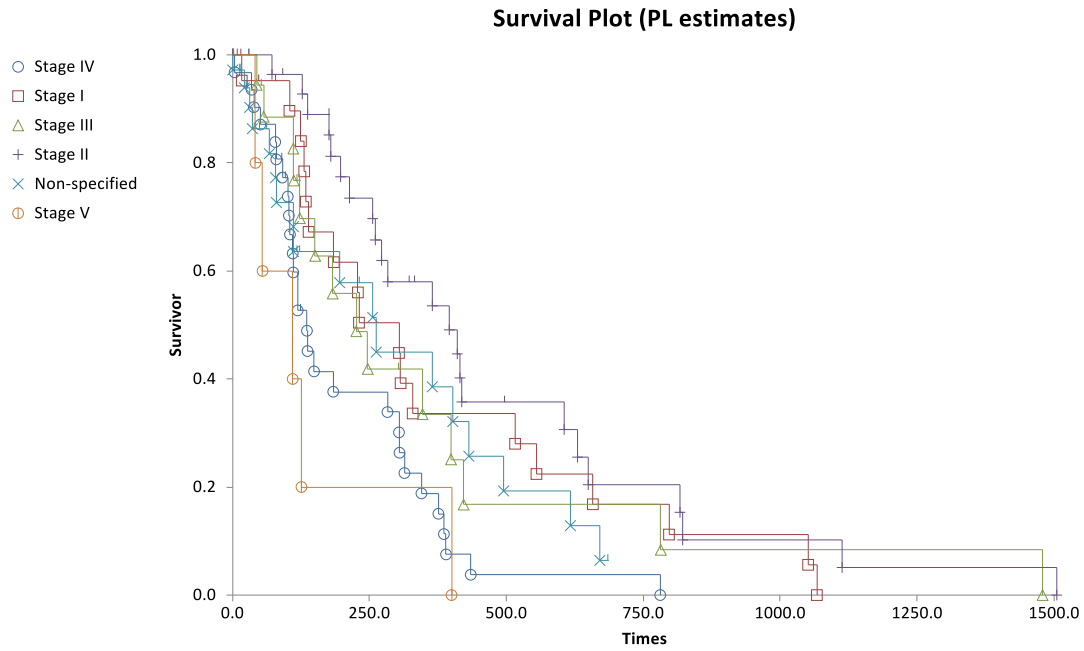

Figure 21. Survival rates of dogs in different stages expressed by Kapplan-Meier curves
Note: Stage "0": non-specified due to the lack of CT-examination

Histopathological the following survival data could be revealed (Table 16, Figure 21). The Log-rank (Peto) test did not reveal significant differences. Chi-square for equivalence of death rates = 5.11616 P = 0.529, Chi-square for trend = 1.819134 P = 0.1774.

Table 15. Survival data of dogs with nasal tumours with different histopathological types

	Adeno-carcinoma (1)	Chondro-sarcoma (2)	Soft tissue sarcoma (3)	Non-specified (4)	Squamous cell carcinoma (5)	Lympho-ma (6)	Osteo-sarcoma (7)
Observed deaths	61	16	2	16	5	4	2
Extent of exposure to risk of death	64.51	16.14	5.36	12.05	4.13	2.54	1.27
Relative rate	0.95	0.99	0.37	1.33	1.21	1.57	1.57
Median	256	213	822	131	283	80	22
Mean	360.3	332.31	704.57	253.85	292	222.5	211

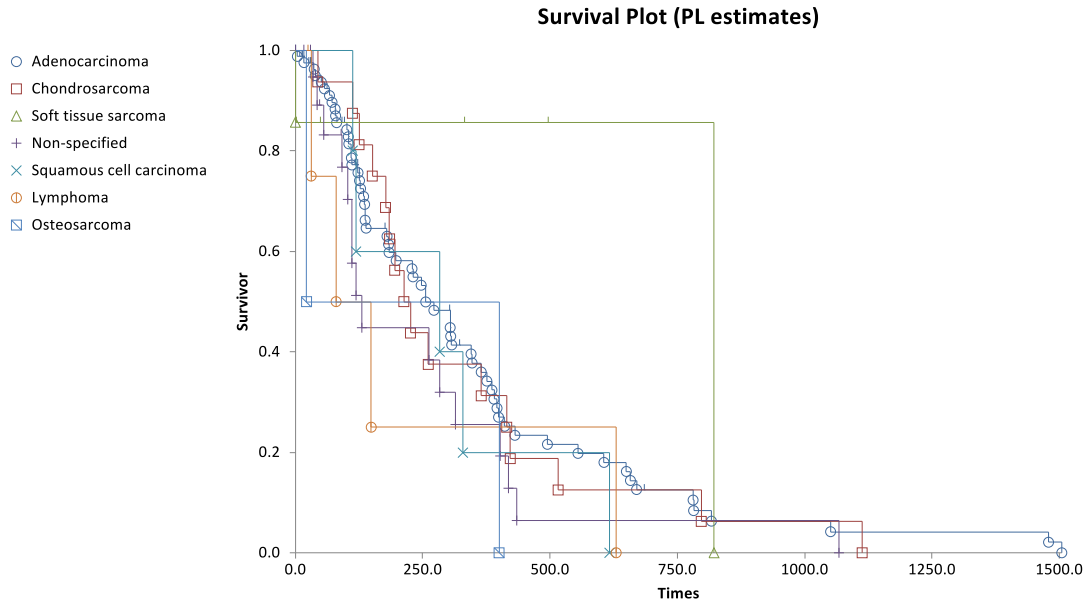

Figure 22. Survival rates in dogs with different histopathology types of nasal tumours expressed by Kapplan-Meier curves

The histological grades of the tumour types were evaluated the same way (Table 17, Figure 22). The data were significantly different by the Log rank (Peto) test as follows: Chi-square for equivalence of death rates = 18.395998 P = 0.0004, Chi-square for trend = 4.457548 P = 0.0347

Table 16. Survival data of dogs with different histological grades of nasal tumours

	Grade 0 (non-specified)	Grade 1	Grade 2	Grade 3
Observed deaths	24	25	22	35

Extent of exposure to risk of death	13.82	18.73	53.75	53.74
Relative rate	1.74	1.33	1.12	0.65
Median	134	365	256	226
Mean	195.12	502.94	302.67	255.62

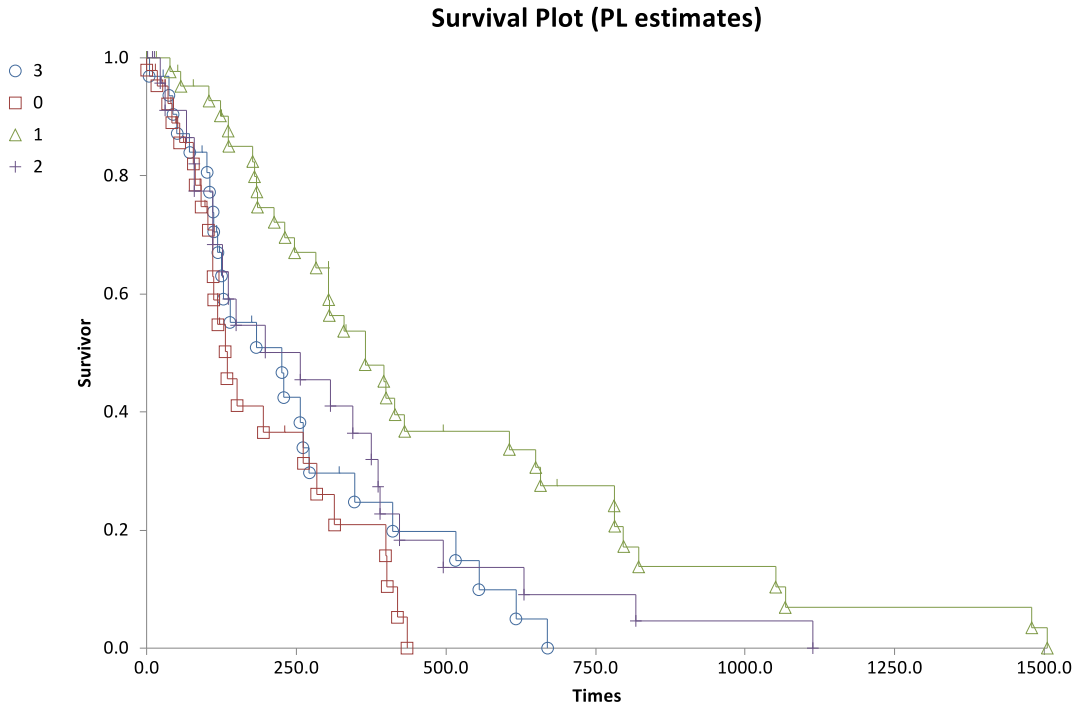

Figure 23. Survival of dogs with different histological grades of nasal tumours expressed by Kapplan-Meier curves
Note: Grade 0 = non-specified due to lack of histopathology or grading

3.2.3 Treatment Outcome

The survival of operated (n=60) (median: 256 days) and non-operated (n=91) (median: 184 days) dogs differed non-significantly (hi-square for equivalence of death rates = 1.362131 P = 0.2432) (Figure 23).

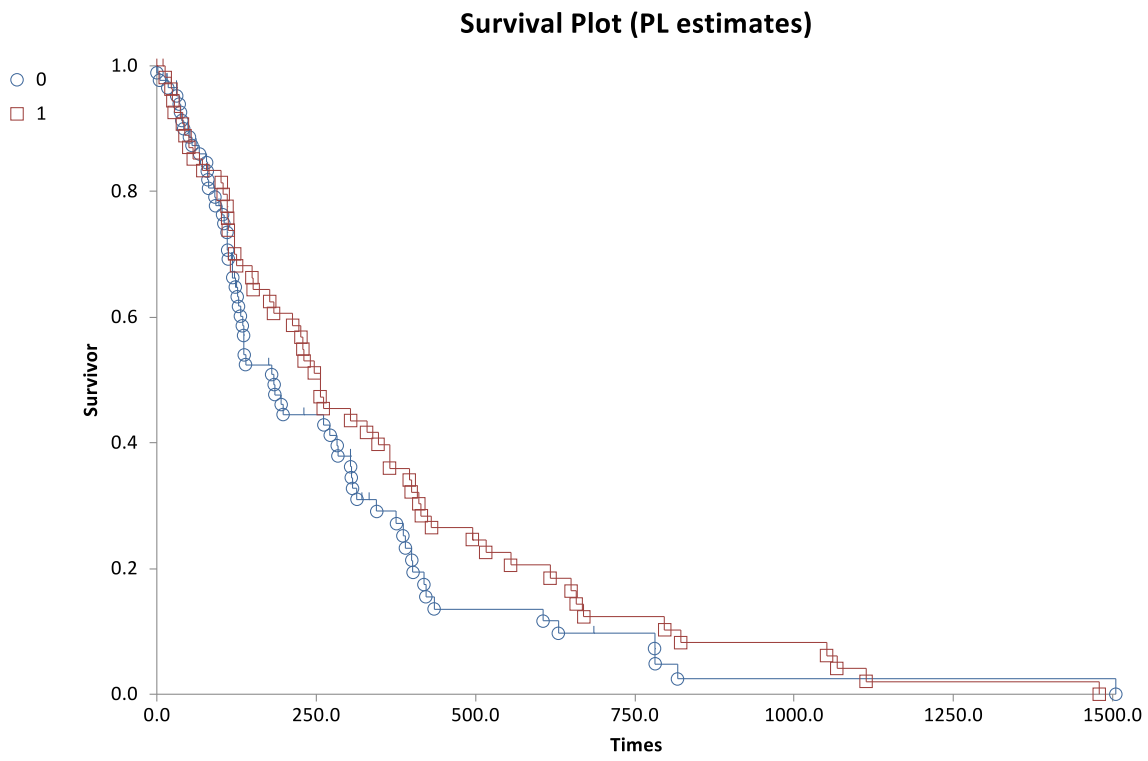

Figure 24. Kapplan-Meier curves to express survival rates of operated and non-operated dogs with nasal tumours

In case of the operated dogs (n=61), the efficacy of the different treatment options, including the following: surgery only, gel formulated Carboplatin, non-gel formulated local Carboplatin, gel formulated Carboplatin, metronomic Chlorambucil and radiation therapy can be seen in the following table and figures (Table 18, Figure 24, Figure 25). The survival data showed significant difference by Log ran (Peto) analysis (Chi-square for equivalence of death rates = 10.406832 P = 0.0341, Chi-square for trend = 7.935278 P = 0.0048).

Table 17. Results of the different treatment options in operated dogs with nasal tumours

	Surgery only (n=20)	**Non-gel local Carboplatin (n=4)**	**Gel formulated Carboplatin (n=26)**	**Gel formulated Carboplatin + Chlorambucil (n=8)**	**Radiation therapy (n=2)**
Observed deaths	15	4	24	8	1
Extent of exposure to risk of death	7.65	2.76	30.19	9.37	2.02
Relative rate	1.96	1.45	0.79	0.85	0.49

Median	122	183	261	365	670
Mean	188.66	246.5	448.76	421.63	670

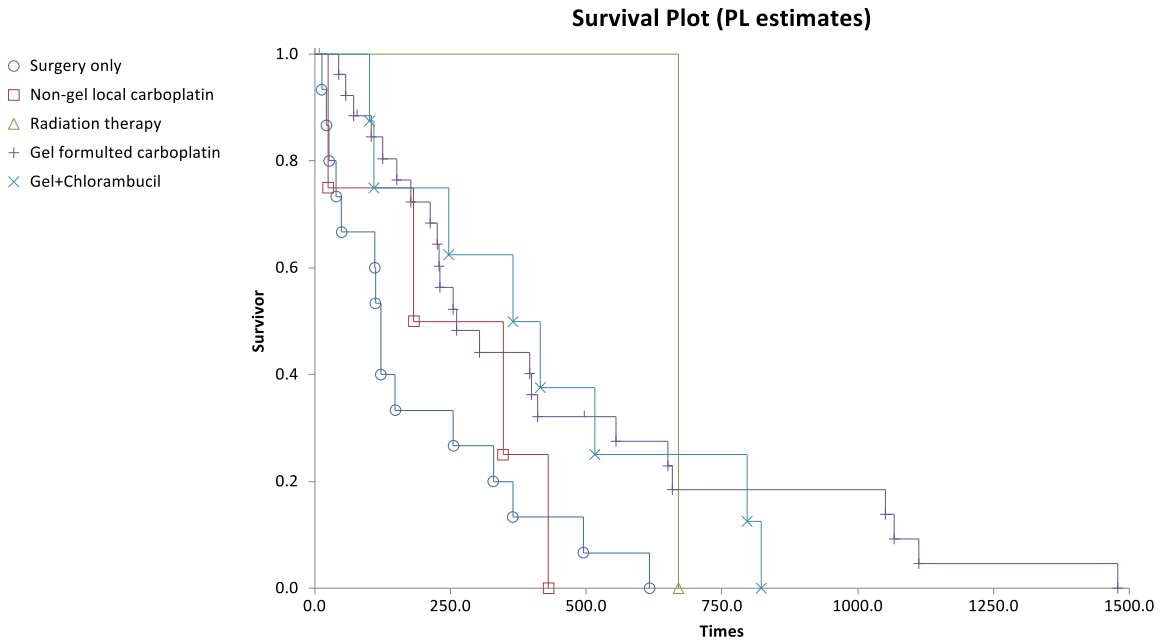

Figure 25. Results of the different treatment options in operated dogs with nasal tumours expressed by Kapplan-Meier curves

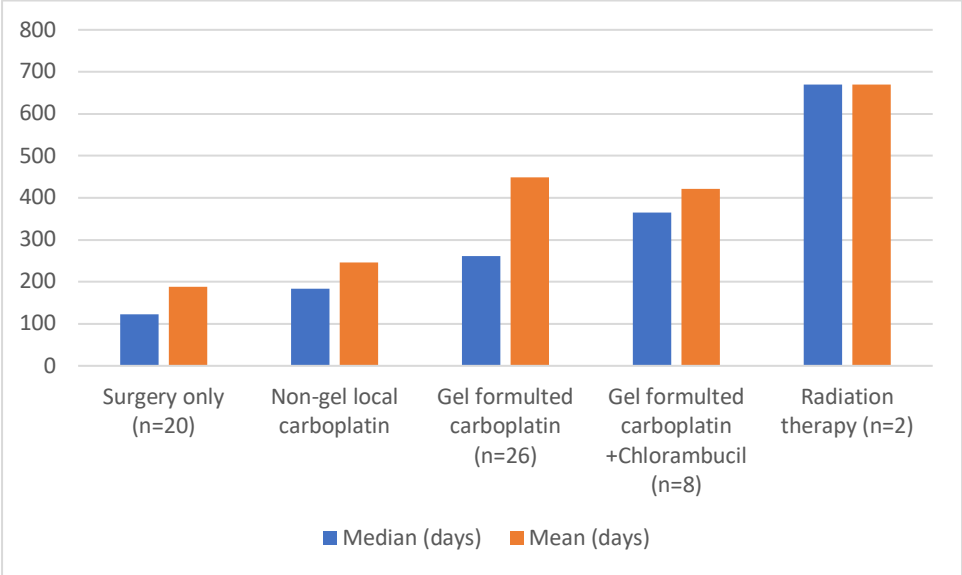

Figure 26. Differences in median and mean survival times in operated dogs with nasal tumours treated with different treatment options

In case of the non-operated dogs (n=90), the efficacy of the different treatment options, including the following: NSAID only, non-gel formulated local Carboplatin, metronomic Chlorambucil, Toceranib, radiation therapy and intravasal chemotherapy (Doxorubicin) can be seen in the following table (Table 19, Figure 26, Figure 27). The survival data showed non-significant difference by Log ran (Peto) analysis (Chi-square for equivalence of death rates = 8.690325 P = 0.1221, Chi-square for trend = 2.718464 P = 0.0992).

Table 18. Results of different treatment options in non-operated dogs with nasal tumours

	NSAID only (n=45)	Non-gel local Carboplatin (n=6)	Chlorambucil (n=22)	Toceranib (n=5)	Intravasal chemotherapy (Doxorubicin) (n=6)	Radiation therapy (n=7)
Observed deaths	21	6	21	4	3	6
Extent of exposure to risk of death	16.69	2.61	26.30	5.95	2.19	7.26
Relative rate	1.26	2.3	0.79	0.67	1.37	0.82
Median	134	81	272	386	128	304
Mean	217.31	129.33	368.68	390.3	126.6	298.5

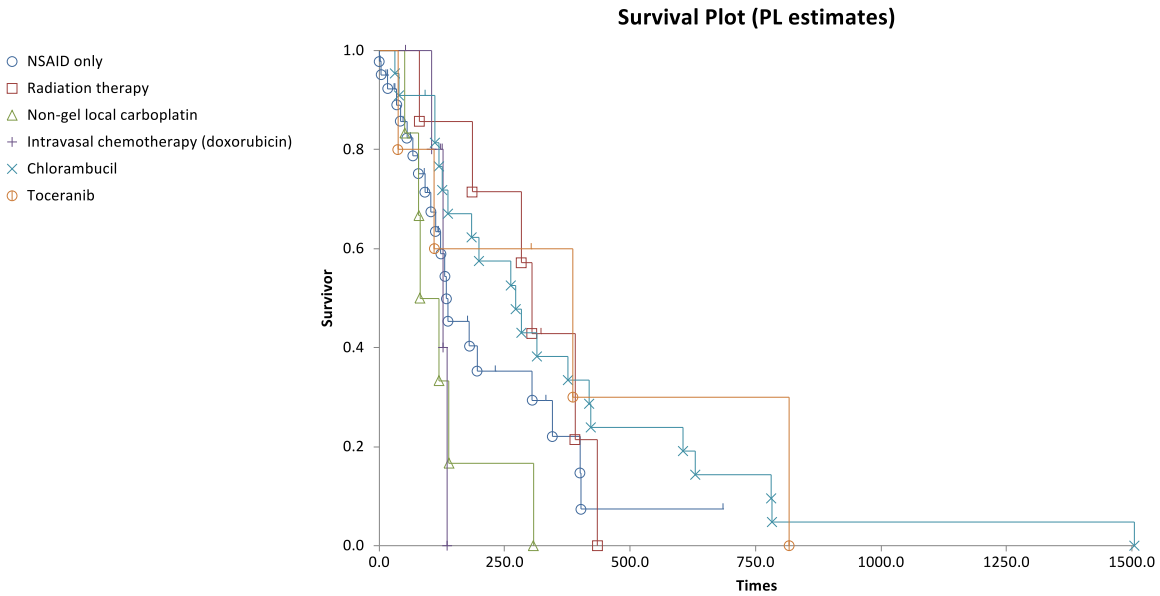

Figure 27. Results of different treatment options in non-operated dogs with nasal tumours expressed by Kapplan-Meier curves

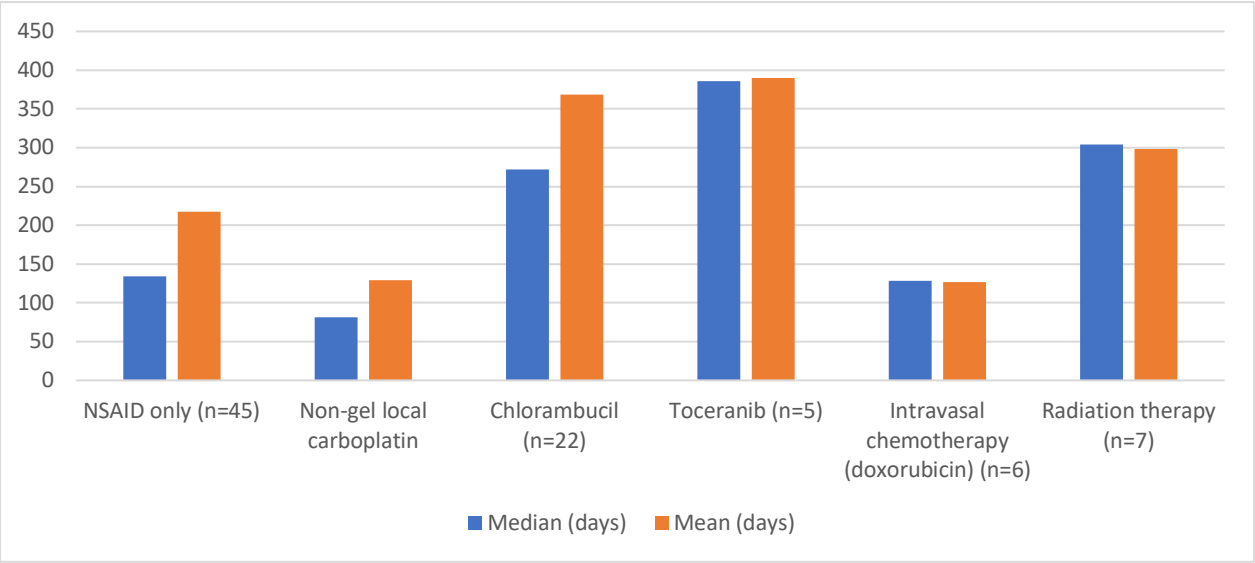

Figure 28. Differences in median and mean survival times in non-operated dogs with nasal tumours treated with different treatment options

The use of anti-inflammatory drugs is essential in tumour therapy. There are several different drugs available for this purpose. The efficacy of the used drugs is listed below. In operated dogs the survival rates were significantly different (Chi-square for equivalence of death rates = 13.011657 P = 0.0112, Chi-square for trend = 0.02158 P = 0.8832) (Table 20, Figure, 28, Figure 29)

Table 19. Efficacy of anti-inflammatory drugs in operated dogs with nasal tumours

	Prednisolone (n=3)	**Other NSAID (n=7)**	**Piroxicam (n=15)**	**Firocoxib (n=8)**	**No-NSAID (n=27)**
Observed deaths	3	6	15	8	20
Extent of exposure to risk of death	2.32	11.88	18.86	8.11	10.82
Relative rate	1.29	0.50	0.79	0.98	1.85
Median	149	670	347	399	122
Mean	292.33	650.71	443.93	365.75	205.23

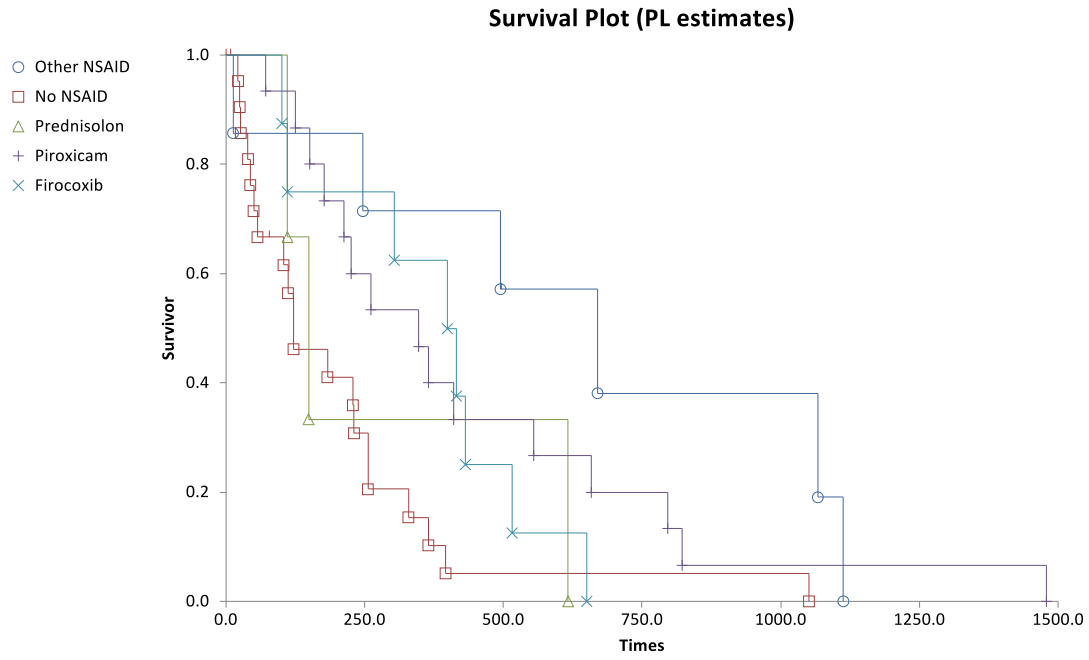

Figure 29. Efficacy of anti-inflammatory drugs in operated dogs with nasal tumours expressed by Kapplan-Meier curves

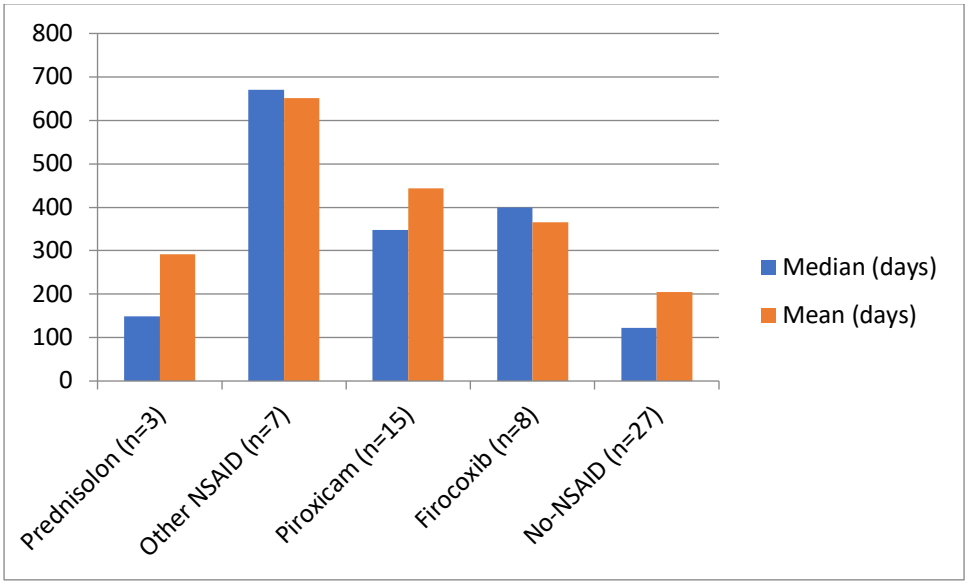

Figure 30. Differences in median and mean survival times in operated dogs with nasal tumours treated with different anti-inflammatory drugs

In non-operated dogs the survival rates were significantly different (Chi-square for equivalence of death rates = 9.944118 P = 0.0414, Chi-square for trend = 0.784831 P = 0.3757) (Table 21, Figure 30, Figure 31).

Table 20. Efficacy of anti-inflammatory drugs in non-operated dogs with nasal tumours

	Prednisolone (n=7)	Other NSAID (n=8)	Piroxicam (n=9)	Firocoxib (n=30)	No-NSAID (n=36)
Observed deaths	5	5	7	27	
Extent of exposure to risk of death	1.63	4.20	5.63	34.51	15.02
Relative rate	3.07	1.19	1.24	0.78	1.13
Median	55	304	139	284	134
Mean	96.79	226.19	199.5	378.75	237.50

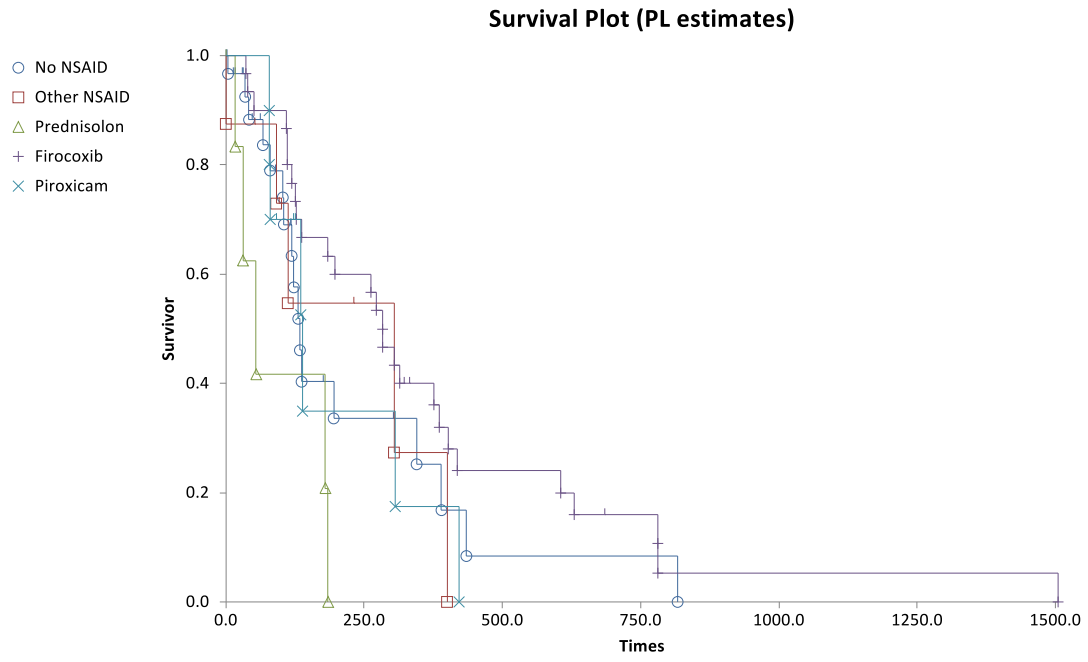

Figure 31. Efficacy of anti-inflammatory drugs in non-operated dogs with nasal tumours expressed by Kapplan-Meier curves

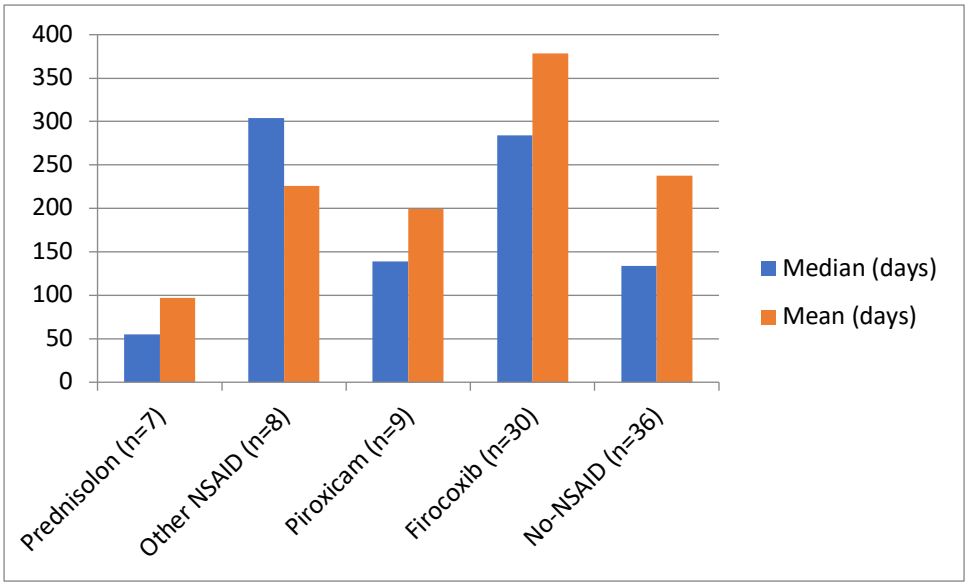

Figure 32. Differences in median and mean survival times in non-operated dogs with nasal tumours treated with different anti-inflammatory drugs

3.2.3.1 Side effects and adverse drug reactions

There were 31 cases reported with grade 2 and 3 side effects. There were 12 local nasal inflammatory processes which required nasal flush and antibiotic therapy. There were 9 cases with 2 to 3 grade diarrhoea, 3 cases with vomiting, 2 cases with grade 3 anorexia, and there were 3 cases with nephropathy, and 2 cases with gastric dilation volvulus syndrome due to sever aerophagia.

3.3 Discussion

In our study we aimed to compare and summarize the experiences in canine nasal tumour therapy during the last 25 years. We in general the patients covered a great number, 151 dog cases. Our general findings agree with the reports, as mentioned that the mean age of dogs at the time of diagnosis is 10 years, and our findings agreed with this statement as the average age was 9.71 (± 2,99) years. [1] Our youngest two cases were 1 year old Hungarian Vizsla and Boxer with adenocarcinoma and chondrosarcoma, respectively. While our oldest case was 19 years old, a Fox Terrier with lymphoma. Nasal tumours have been reported in 1 year old dogs by Sones et al. 2013. [49] Interestingly, the survival times increase by age which means that the younger dogs had more aggressive or less treatable tumours.

According to the reports, there is no gender predilection, but some studies have reported a male predominance which is in accordance with our findings where the male to female ratio was 1.188. [50]

The dolichocephalic breeds are mostly affected, and it was true in our cases with 55 dolichocephalic and 6 brachycephalic breeds. [51] According to some reports the Golden Retriever, Labrador, German Shepherd and English Springer Spaniel are mostly affected [52] we can support these findings, as the most commonly affected breeds in our study are the Mongrels (n=41), then German Shepherd (n=14), Hungarian Vizsla (n=11), Golden Retriever (n=6), Labrador Retriever represented by 5 cases, which was similar to Cocker Spaniels, Boxers, Rottweilers.

Authors have reported that two thirds of nasal tumours are carcinomas, most commonly adenocarcinomas, although squamous cell carcinomas (SCC), undifferentiated carcinomas and transitional carcinomas. We found almost the same with carcinoma, undifferentiated, sarcoma and lymphoma types with 61.6%, 18.5%, 16.6%, 3.3%, respectively. We had similar sarcoma types as mentioned in other reports, such as chondrosarcomas, fibrosarcomas, osteosarcomas and undifferentiated/anaplastic sarcomas. [46, 53] We has extranodal lymphoma which also affected the nasal cavity similar to other reports. [54] Interestingly, we can add to this histopathology type selection that the younger dogs (between 0-5 years of age) does not show this great histopathology type difference, although with an adenocarcinoma predominance (Table 7, Figure 13).

While authors reported that the anaplastic, squamous cell, and undifferentiated carcinoma types showed the least survivals [18], and the sarcoma types the best we added another aspect. According to the grade system we found that the adenocarcinoma and other carcinoma types appear as higher grades more frequently than sarcoma types. As we found 57.5% of carcinoma types appeared as grade 2 and 3 in contrast to the grade 1 cases (42.5%). Although, chondrosarcoma grade 1 was almost the same with grade 2 and 3, but there were more grade 1 case of soft tissue sarcoma than grade 2 or 3 (Table 8, Figure 14). The survival rates clearly show that the examination of tumour tissues for malignancy as grading has a great impact on survival as the differences among survival times were significant according to grades (Table 17.)

Although, we used partly similar staging system to the known 4 tier system reported by Adams et al (2009) [18] and Kondo et al (2008) [6], we added a 5^{th} stage for more advanced cases with

brain and lung involvement. While Kondo et al (2008) [6] found the following distribution for different stages as Stage I:10.59%; Stage II:17.6%; Stage II:31.76%; Stage IV: 40% with high representation of Stage IV. cases, we found a slightly more distributed selection for the frequency of cases in different stages as Non-staged: 23.84%; Stage I: 15.23%; Stage II:20.53%; Stage II:14.57%; Stage IV:22.52%; Stage V:3.31%. according to the original report by Adams at al. (2009) [18] they found the following survival times in days Stage I: 704.55; Stage II: 427, Stage III: 478.85; Stage IV:204.35. It clearly shows that the survival rate is decreasing by the Stage. Our data revealed that the medium survival times were half of the reported periods as follows in days: Stage I: 304; Stage II: 396; Stage III: 226; Stage IV:136; Stage V:110. We could find the same inversely correlating decrease of medium survival time with increased stages, although the survival times were much lower because we could apply radiation therapy in only 9 cases out of 154. In our cases the survival rate of dogs in different stages was significant, although, some authors argue with the real effect of stage on survival at least in part due to lack of consistency in approach and contradictory findings from small number studies. [1]

Treatment options for surgical and non-surgical interventions were found to be controversial as significant finding was not detected, although, the median survival times differed a lot for operated dogs it was 256 and for the non-operated dogs was 91 days, respectively.

Among the operated dogs the survival times showed significant differences among treatment options as Surgery only (n=20), Non-gel local Carboplatin, (n=4), Gel formulated Carboplatin (n=26), Gel formulated Carboplatin + Chlorambucil (n=8) and Radiation therapy (n=2). The best of all was surgery plus radiation therapy with 670 days. It was reported that Stage III cases treated by surgery and radiation tended to survive longer (at least 210 days). [6] Our cases were similar to the before mentioned selection, although, there were some in Stage I and II.

In case of non-operated dogs, the following treatment options were applied: NSAID only (n=45); Non-gel local Carboplatin (n=6); Chlorambucil (n=22); Toceranib (n=5); Intravasal chemotherapy (Doxorubicin) (n=6); Radiation therapy (n=7). The differences were significant. Among these the best option was the Toceranib therapy (medial survival: 390.3 days) and the low dose metronomic Chlorambucil therapy (medial survival: 368.7 days). Interestingly, radiation therapy was the 3rd best option with (medial survival: 298.5 days).

Authors reported that applying Toceranib as primary therapy for stage III and IV nasal tumour cases they found that the median overall survival time was 139 days. [55] Although, our cases

without surgery consisted of some Stage I and II cases, mostly these belonged to stage III, IV and V. It seems that Toceranib is a good option and the inclusion of some dogs with less advanced stages improved our survival rates.

Although, Chlorambucil was reported as a good option for the treatment of nasal lymphoma by some authors [54], later it was suggested that metronomic dosing of this drug might be useful in treating other tumour types, like carcinoma. [56] This consideration was the initiative of us to try a low dose Chlorambucil therapy with different NSAIDs like Firocoxib. It seems that this combination can be also effective in advanced stages, too.

Interestingly there were some reports, about the benefit of gelatin against tumours. [57] They found that porcine skin gelatin administered intraperitoneally prolonged the survival of tumour-bearing mice via activation of peritoneal macrophages and involvement of direct anti-tumour activity of porcine skin gelatin. [57] Other authors concluded that porcine skin (PS) gelatin suppress the proliferation of human tumour cell lines in vitro. They found that antiproliferative activity of PS gelatin might not be attributed to trapping growth factors or autocrine mediators. [58] These findings gave us the idea to combine Carboplatin with porcine skin gelatin toprovide slow-release formula. According to our observations the outcome is quite promising in operated dogs which were treated by gel formulated Carboplatin with a median survival time of 448.76 days. This is the first report of using this option for the treatment of canine nasal tumours.

Platinum based chemotherapy local might provide a good option for the future. Although, authors reported about dogs that received combined radiation and slow release OPLA Cisplatin had longer overall survival times, with a median of 580 days. Those with radiation therapy only had a median survival of 325 days. [59] We believe that the local gel-based platinum as an adjunctive to radiation therapy will provide a good option for the cases in near future.

As we considered that operation with a combination of other therapies could provide benefit in treating nasal tumours other researchers approved similar findings. Local intraoperative intranasal therapy by acridine orange-photodynamic therapy together with radiation therapy was also effective according to authors with a median survival time of 24 months (730 days). [60]

Our findings with intravasal chemotherapy with either Doxorubicin or Carboplatin with piroxicam or prednisolone showed a median survival time as 128 days whereas other authors

used alternating Carboplatin and Doxorubin in conjunction with oral piroxicam. They found that the overall median survival time for dogs in the study was 234 days (range 12-1698 days). [39] Other authors used Carboplatin and Piroxicam combination also with success. [61] Authors agree that combination therapies with chemotherapy drugs and piroxicam or other NSAIDs work better.

The efficacy of different NASIDs was also determined. We found that in operated dogs Robenacoxib, Meloxicam and Carprofen containing "Other NSAID" group showed the best survival (median: 650.71 days), whereas in non-operated dogs "Other NSIADs" showed to be quite useful (median: 304 and mean: 226.19 days), but Firocoxib seemed to be almost as useful with the median of 284 and the mean of 378.75 days.

Neither of the therapy options showed greater side effects, although the dogs were in great care and the owners' compliances were excellent in most of the cases.

4 Summary

Nasal and paranasal sinus tumours are common in dogs, accounting for 1 to 2% of all cancer cases and 70% of chronic nasal conditions. These tumours impact the nasal and paranasal structures and often extend to critical areas like the cribriform plate and the brain, necessitating a holistic and multimodal approach to diagnosis and treatment. This thesis explores the horizons of a multimodular approach in canine nasal tumour treatment, bridging the gap between scientific knowledge and practical application.

The first part of this work covers an overview about canine nasal tumours, including its occurrence, prevalences and its clinical characteristics. It addresses the diverse clinical symptoms, possible diagnostics, staging systems as well as treatment options for this disease.

The goal of the study was to examine 25 years of nasal tumour treatment experience in dogs. The average age of the dogs upon diagnosis, according to the 151 canine cases in the study—the youngest instance was one year old, and the oldest was 19 years old—was 9.71 years. Breeds with dolichocephalic heads, such German Shepherds, Hungarian Vizslas, and Mongrels, have a higher incidence of nasal cancers. Carcinomas were the most prevalent tumour type, followed by lymphomas, sarcomas, and undifferentiated tumours.

According to the study, survival rates differed according to the kind and grade of the tumour, with sarcomas often having lower grades than adenocarcinomas and other carcinomas. Survival was also influenced by the tumours' staging; shorter survival durations were linked to more advanced stages of the malignancies.

Both surgical and non-surgical treatment methods were shown to be contentious. Dogs that had surgery had a median survival period of 256 days; the greatest outcomes were shown in those situations where radiation treatment and surgery were combined. The greatest results were shown with Toceranib therapy and low-dose metronomic Chlorambucil therapy; non-operated dogs had a median survival span of 91 days.

Promising outcomes were seen when Carboplatin and pig skin gelatin were combined in a gel formulation for therapeutic purposes. It was thought that local gel-based platinum combined with radiation treatment would be a possibility in the future.

The research covered several combinations of chemotherapeutic medications and non-steroidal anti-inflammatory medicines (NSAIDs), some of which had promising outcomes. Several

NSAIDs were assessed; in dogs who had surgery, Robenacoxib, Meloxicam, and Carprofen were beneficial, while Firocoxib and other NSAIDs showed potential in non-operated dogs.
Overall, the study found no appreciable adverse effects linked to the available treatment choices, and dog owners' compliance was largely great.

5 List of Abbreviations

BID	“bis in die” = twice a day
Bw	bodyweight
CBC	complete blood count
COX	cyclooxygenase
CR	complete remission
CT	computed tomography
DFS	disease free survival
DNA	desoxyribonucleic acid
HAI	hepatic arterial infusion
ILI	isolated limb infusion
ILP	isolated limb perfusion
I.M.	intramuscular
I.V.	intravenous
MDT	magnetic drug targeting
MRI	magnetic resonance imaging
MRT	magnetic resonance therapy
MST	median survival time
NSAID	non-steroidal anti-inflammatory drug
OS	possible extension of lifespan
PR	partial remission
S.C.	subcutaneous
SCC	squamous cell carcinoma
SID	“semel in die” = once a day
SiNE	single needle electrode
TACE	transcatheter arterial chemoembolization
WHO	world health organisation

6 List of literature references

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7 List of Figures

8 List of Tables

Thesis progress report for veterinary students

Name of student: ……Lea Bodingbauer…….

Neptun code of the student: ……..... HC8NWG.....

Name and title of the supervisor: ……Peter Vajdovich associate professor……

Department:…Clinical Pathology and Oncology……

Thesis title: …
Multimodular Approach to the Treatment of Canine Nasal Tumours.....……...

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	03	18	Discussion of the topic	
2.	2023	04	11	Search for literature	
3.	2023	05	03	Search for veterinary literature	
4.					
5.					

Grade achieved at the end of the first semester: ……5……..

Consultation – 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	09	14	Discussion about the thesis structure	
2.	2023	10	21	Discussion about the first chapters	
3.	2023	11	02	Finalizing the thesis	
4.					
5.					

Grade achieved at the end of the second semester: ……5……..

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

……...
signature of the supervisor

Signature of the student: ……

Signature of the secretary of the department: ……

Date of handing the thesis in ……02… 11……2023…….....