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Transversus Abdominis Plane (TAP) and intercostal blocks in dogs undergoing total mastectomy: a retrospective analysis of survival and perioperative complication rates

Diploma Thesis

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Abstract

Transverse abdominis plane (TAP) block is an underutilized method of local anesthesia in veterinary medicine as compared to human medicine which has shown its potential and the various advantages over general anesthesia. TAP block seems attractive to be utilized in mastectomy in canines since it numbs the pain in the area affected of the surgical intervention. There is only a scarce body of literature available that used TAP in canines, mostly restricted to cadaver studies. The aim of this study is to evaluate the potential of TAP in canine mastectomy as means of anesthesia in comparison to general anesthesia. This study is designed as retrospective evaluation of the available data of the veterinary university in Vienna from 10 years. A total of 249 dogs could be identified, 82 showed sufficient data to be further processed. Overall, the TAP group showed less complications as compared to the general anesthesia group without local anesthesia; however, both showed a rather high incidence of mild adverse reactions such as arrythmia, bradycardia or hypothermia. Both groups showed an excellent long-term survival and a low relapse/neoplasia rate indicating that both methods are well suited for anesthesia in a mastectomy setting. Based on the results of this restrospective study, it seems attractive to use TAP for canine mastectomy, yet further prospective studies on larger cohorts with more standardization of the technique are needed to show the potential benefit of this method.

Kurzzusammenfassung

Der transverse abdominis (plane) block (TAP) ist ein Verfahren zur Lokalanästhesie, welches in der Veterinärmedizin jedoch nur relativ selten zum Einsatz kommt. In der Humanmedizin jedoch ist es ein häufig verwendetes und verbreitetes Verfahren. Der TAP Block scheint insbesondere bei Mastektomien ein attraktives Verfahren zu sein, da dieses Verfahren in der gewünschten Region den Schmerz stillt. In der Literatur finden sich jedoch nur wenige Arbeiten zum TAP Block bei Hunden und diese wurden häufig an Kadavern durchgeführt, um die theoretischen Grundlagen zu zeigen. In dieser Arbeit soll das Potential des TAP Block Verfahrens bei Mastektomien von Hunden aufgezeigt werden. Es handelt sich um eine retrospective Studie mit Daten der Veterinärmedizinischen Universtiät Wien (Vetmeduni Vienna) über einen Zeitraum von 10 Jahren. Es wurden 249 Mastektomien, die bei Hunden durchgeführt wurden, im TIS gefunden. Von diesen wurden 82 Patienten ausgewählt, da ausreichend Daten vorlagen. In dieser Studie wurde gezeigt, dass die TAP Gruppe im Vergleich zur Kontrollgruppe weniger Komplikationen zeigte. Jedoch muss beachtet warden, dass trotz allem beide Verfahren mit einer hohen Rate an geringgradigen Komplikationen verbunden waren. Dazu zählten eine Bradykardie, eine Arrythmie und eine Hypothermie. Langzeit follow-up Daten zeigen bei beiden Verfahren eine sehr geringe Anzahl an Rezidiven bzw. Neoplasien. Daher können beide Methoden als adäquat eingestuft werden. Basierend auf diesen Ergebnissen sollten prospektive, standardisierte Studien durchgeführt warden, um das TAP Verfahren weiter zu validieren und in Zukunft eventuell als Standardverfahren einzuführen.

Abbreviations

ACP - Acepromazine

CMT - Canine mammary tumor

DNA - Deoxyribonucleic acid

OHE - Ovariohysterectomy

TAP - Transversus abdominis plane

TIS - Database of the veterinary medicine university of Vienna

TNM - Tumor, lymph node, metastasis

US - Ultrasound

WHO - World Health Organization

Content

1. Introduction

Mastectomy is the surgical removal of breast tissue, most often performed due to cancerous changes within the tissue to relieve pain, stop spreading of tumor cells (metastasis) and to avoid tumor-related complications. Total mastectomy is routinely performed in dogs suffering from mammary tumors. These dogs are often of old age and thus are already likely to have comorbidities. Therefore, they need special care and have a higher anesthetic morbidity and mortality (Nakagawa et al. 2007). Thus, a balanced anesthesia regime is necessary to prevent any severe side effects and complications. Regional anesthesia respresents an alternative to general anesthesia. The use of regional anesthesia may improve the outcome of surgery by reducing the number of general anesthetics and analgesics required (Kettner et al. 2011). Inadequate perioperative analgesic coverage during abdominal surgery could be associated with longer periods of hospitalization, poor surgical outcomes and increased consumption of analgesics, which can lead to drug toxicity (Kehlet and Dahl, 1993). Despite a common ground on how to use anesthesia in mastectomy surgery in dogs, there is still a variation due to personal preference, breed and age of the dogs as well as situation-dependent decisions. Thus, prospective comparisons of different anesthesia approaches are difficult to perform and might also be harmful in certain situations in which the method would not fit well to the situation. Tosituation. To our knowledge, there is not much literature dealing with this topic.

The aim of this diploma thesis therefore was to compare the intra-, postoperative and long-term outcome of female dogs undergoing total mastectomy due to mammary tumor that received additional to the general anesthesia a Transversus Abdominis Plane (TAP) and intercostal blocks or that received systemically administered analgesia only. It was hypothesized that dogs undergoing elective total mastectomy receiving a TAP and intercostal blocks have less perioperative complications and a better long-term outcome (i.e. one year survival) compared to dogs only receiving systemic analgesia.

2. Literature overview

2.1. Canine mammaries

The mammary glands are modified apocrine sweat glands, which are only found in mammals. They consist of ducts forming a network surrounded by fibrovascular and adipose tissues. The development of this gland is unique in the sense that the final developmental steps are not being fulfilled unless the animal becomes pregnant. During pregnancy, a proliferation of the tissue occurs as well as milk-producing acini and secretion of milk.

Dogs have five pairs of mammary glands, although there have been also reports of four or six pairs. They start near the axillary region and extend backwards until the groin (inguinal region). Canines have two thoracic, two abdominal and one inguinal pair of mammaries (Silver, 1966). One side of five glands (either left or right) is denoted as mammary chain (Figure 1). It is also common that dogs only have nine glands, i.e., an asymmetric distribution of the mammary glands. The normal glands feel soft and pliant. In a healthy state, there are no firm lumps to feel.

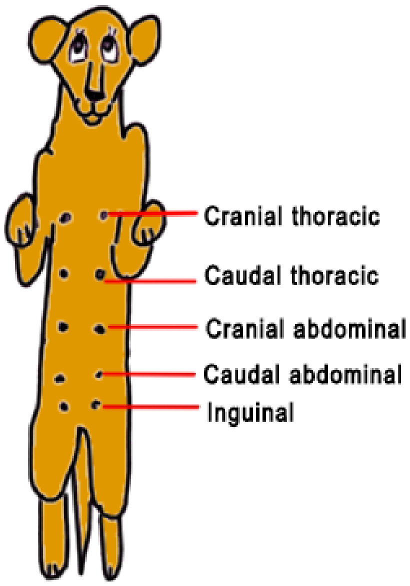

Figure 1: Location of the five mammary glands of canines (Mar Vista Animal Medical Center, 2021)

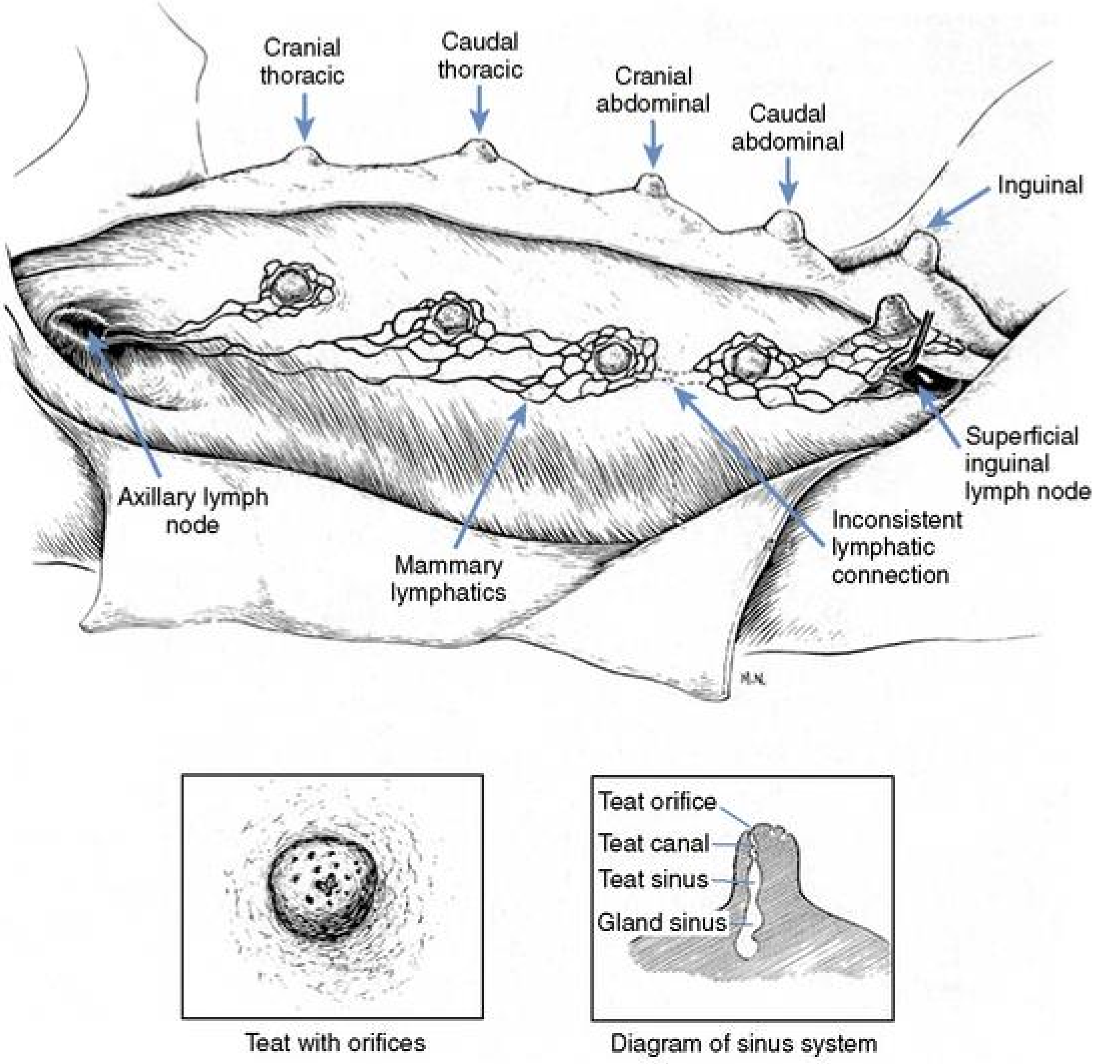

Figure 2: Schematic drawing of canine mammaries, in this example from a dog suffering from mastitis (Evans & GC., 1993)

The development starts already in the embryonal phase when two ventral linear thickenings of the ectoderm can be visualized. This also called „ridges“ or „milk lines“ extend from the axillary to the inguinal region. The cells migrate along these lines, forming a placode, ultimately developing mammary glands.

During the puberty phase, the further development is triggered by the production and release of estrogens from the ovary. This causes cell proliferation at the ducts forming terminal end buds.

Then, in pregnancy, growth occurs (i.e., lengthening) of the ductal system due to a rise of progesterone levels. In the ducts also alveoli (the secreting units of the glands) are being formed under the influence of prolactin. Postpartum a regression phase occurs, which takes about 40 days. In pseudopregnancy of canines the same changes occur inside the mammary gland, yet with less alveolar secretion (Sorenmo, Rasotto, Zappulli, & Goldschmidt, 2011).

2.2. Mammary neoplasia

Mammary carcinomas are the most common malignancies in intact female dogs (V.M. Kristiansen et al. 2016). Mammary tumors constitute about half of all tumors in bitches and approximately half of the canine mammary tumors (CMT) are malignant (Patricio Rivera et al. 2009). The major factor associated with the development of mammary gland tumors in the dog is hormonal influence (C. Andrew Novosad, DVM, 2003) A study focusing on the incidence of canine mammary tumors found tumors in approximately 0.05% of females that were spayed before their first heat cycle. This figure increased to 8% or 26% when the animals were spayed after their first or second heat, respectively (Yaritza Salas et al. 2015). This shows that dogs that are undergoing an early sterilization have a decreased risk for developing mammary tumors.

The most common mammary gland tumor in the dog is a benign fibroadenoma (Moulton JE, et al 1970). The fibroadenoma is a neoplastic mass that consists of tubules lined by cuboidal or columnar cells, with nuclei that are round and uniform (Goldschmidt et al, 2011)

The majority of the malignant tumors are comprised of epithelial tumors or carcinomas. Mammary tumors may have one cell type present, which is considered simple, or both secretory and ductular cells, which is considered complex. (C. Andrew Novosad, DVM, 2003) The term 'inflammatory mammary carcinoma' has been used to describe a poorly differ- entailed carcinoma with widespread dermal lymphatic obstruction. (Susaneck S J, Allen TA, Hoopes J, et al, 1983) Inflammatory carcinomas are associated with a high rate of nodal and widespread metastasis at the time of diagnosis. (C. Andrew Novosad, DVM, 2003)

2.3. Risk factors

The two main risk factors of developing mammary neoplasia in dogs are age and hormones, the latter being heavily influenced by the time of spaying as described previously. However, there are also additional factors tobe considered including the breed and diet as well as the weight of dogs.

2.3.1. Age

Similar to humans, age is the one of the most important risk factors to consider when it comes to develop mammary carcinomas in dogs. At the age of 8 years the risk starts to drastically increase with a linear increase by age. This was confirmed in several studies, including. (Dorn, Taylor, Schneider, Hibbard, & Klauber, 1968) (Taylor, et al., 1976). It is of note that there is an influence of the natural life span of the breed, meaning that the age of onset can vary depending on the expected lifespan. Furthermore, younger dogs are more likely to develop benign neoplasms, while older dogs are more likely to develop malignant disease. This was confirmed by a study showing that the average age for benign neoplasms was 8.5 years while malignant developments occurred at an average age of 9.5 years (Sorenmo, et al., 2009). The mammary tumor specifically is rare to occur in dogs under 5 years of age, with the exception of external hormone application (e.g., progestins) (Schneider R. , 1970).

2.3.2. Hormones

Exposure to hormones, especially early in life is an important cause of mammary neoplasms. It has been shown that the risk for developing mammary tumors in dogs increases drastically during the first heat cycles. It has been shown that dogs who have ovariohysterectomy (OHE) before the first cycle only have a 0.5% risk while the first estrus increases the risk to 8% and the second to 26% (Schneider, Dorn, & Taylor, 1969). It is discussed controversially if there is a benefit of a later OHE. The publication of Schneider et. al., 1969 did not find any positive effects after the second estrus, later studies however showed some protection, e.g.,OHE between the fourth and sixth estrus still provided some protection (Taylor, et al., 1976). These studies show a dose dependency of female hormones in the development of mammary neoplasms in dogs, i.e., no exposure (before the first estrus) shows the smallest risk while the risk increases with exposure. Interestingly, this shows that the foundation is laid in young age of dogs, but the development of carcinomas occurs slowly and only becomes important later in life (see above). The same effects as described in the natural exposure to hormones hold true in cohorts which received exogeneous doses of progestins and estrogens, which will increase the risk of mammary tumor development (Selman, van Garderen, Mol, & van der Ingh, 1995) (Concannon, Spraker, Casey, & Hansel, 1981). These studies found a more frequent as well as an earlier tumor development. Dogs who were exposed to progestin developed a higher rate of benign tumors while a combination of progestins and estrogens lead to an increase in malignant tumors (Sorenmo, et al., 2009). The same has been observed in privately owned canines, e.g., when administering medication to delay/prevent the estrus, progestin-treated dogs had a significantly increased risk of developing mammary tumors with an odds ratio 2.3 as compared to nonexposed dogs (Stovring, Moe, & Glattre, 1997).

2.3.3. Breed

Mammary carcinomas can occur in every breed of dogs. The description of the likelihood which breeds are most affected is difficult since miniature breeds are overrepresented in epidemiological studies. There is however a body of literature suggesting that certain breeds are at higher risk of developing mammary tumors which are listed in Table 1 (Sorenmo, et al., 2009).

Table 1: List of canine breeds at higher risk of developing mammary tumors (Sorenmo, et al., 2009)

English Springer Spaniel	Toy Poodle
Brittany	Maltese
Cocker Spaniel	Chihuahua
English Setter	Beagle
Pointer	Dachshund
Afghan Hound	West Highland White Terrier
German Shepherd Dog	Yorkshire Terrier
Miniature Poodle	Bichon Frise

Since studies show that certain breeds are at higher risk, there is likely a genetic component, which has not yet been fully understood. Furthermore, individual lines of breeds might also be of different risk, e.g., a study conducted on Beagles showed an increased risk of developing neoplasms in one line while the other line showed a decreased risk (Schafer, et al., 1998).

2.3.4. Diet/Obesity

According to specific studies on diet, body composition and the risk of mammary tumors, the weight of the dog in young age seems to play a role in developing mammary tumors. This was shown in a study that concluded that thin dogs which were thin at the age of 9-12 months show a lower risk of developing mammary tumors compared to a control group (Sonnenschein, Glickman, Goldschmidt, & McKee, 1991).

In the same study obesity within one year of the tumor diagnosis as well as a high fat diet did not significantly increase the risk. A more recent study confirmed these findings as the authors found a correlation between obesity at one year of age and development of mammary tumors (Perez Alenza, Rutteman, & Pena, 1998). These studies show that the most important timepoint of setting the risk for tumor development later in life is the first year of age rather than obesity and a high fat diet later in life. This is also consistent with the previously mentioned findings of dogs being exposed to hormones in their early life.

It can be hypothesized that there are the same effects in canines as compared to humans when it comes to obesity and hormones, i.e., postmenopausal women are at higher breast cancer risk after the menopause due to circulating free estrogen and increased local estrogen production. These mechanisms seem to be similar in canines, showing that the effect is strongest in their early life when the hormonal effects on the tissue are most damaging (Sorenmo, Rasotto, Zappulli, & Goldschmidt, 2011).

2.4. Clinical presentation

Typically, dogs present with multiple tumors rather than one. This has been shown in a prospective study in privately owned dogs focusing on canine mammary tumors showing that almost 70% of all dogs had more than one tumor (Sorenmo, et al., 2009). Most often, the two caudal pairs of glands are affected while the axillary glands are less likely to be involved, at least in the first occurrence of neoplasms (Taylor, et al., 1976). The tumors themselves are relatively easy to detect by clinical examination since they appear as one (or multiple) palpable masses in the glands. The findings of course depend on the tumor size and stage, i.e., they can be small or large, freely movable or fixed or ulcerated.

When the mammary chains are being palpated during the physical exam, multiple smaller tumors are likely to be found along the chains. These can be of various histopathologist. Enlargement of the benign tumors tending towards malignancy with increasing size has been observed (Sorenmo, et al., 2009). Such findings show that canine tumors have a histopathological continuum transitioning from benign to malign over time. It has also been found that dogs with a history of benign tumors are more likely to develop malignant carcinoma later (Bender, Dorn, & Schneider, 1984) (Sorenmo, et al., 2009). Such findings show that the theory of canine mammary tumors develop dynamically. Clinically, they might present as separate entities, but from an etiological standpoint, they are related. The lymph nodes can be enlarged, but might not be. Most often, there are no systemic signs of illness in dogs, except for the inflammatory carcinoma which is accompanied with extensive invasion of the lymph nodes and a strong inflammatory response.

The dogs suffer from extensive involvement of the mammary glands suffering from swelling, pain edema and co-moieties are anorexia, illness and overall weakness. In these dogs, surgery is likely not possible and survival is poor (Perez Alenza, Tabanera, & Pena, 2001).

2.5. Diagnosis of mammary neoplasia

During examination, a thorough history and a complete physical exam that includes careful palpation of the mammary glands needs to be performed in all dogs with suspected mammary gland tumors. This includes not only palpation of the gland that is suspected, but the entire mammary chain since tumors are likely not to be solitary. Since most dogs are middle- to old age, they might have concurrent illnesses and require additional treatment due to concomitant health issues. Dogs who are suffering solely from a neoplasm however are likely to be healthy and fit systemically with few exceptions like inflammatory carcinomas. Before considering any form of definitive therapy, it is important to clinically evaluate the patient with a thorough physical examination. A complete blood cell count, serum chemistry profile, and urinalysis should be obtained before anesthesia. Thoracic radiographs, including ventrodorsal as well as right and left lateral views should be performed to evaluate potential metastasis. An abdominal ultrasound should be performed if abnormalities are noted on physical examination or if blood-work abnormalities exist. A coagulation profile is indicated if an inflammatory mammary carcinoma is suspected due to the high association with disseminated intravascular coagulation (Susaneck, Allen, Hoopes, Withrow, & Macy, 1983). All palpable tumors need to be excised, noted regarding their location, size and they should be sent for histopathological examination.

Mammary carcinoma is staged using the tumor, lymph node, metastasis (TNM) system, meaning that the information about tumor size, lymph node involvement and possible metastasis needs to be recorded. The tumor size describes the node with the largest diameter. The lymph node involvement includes description of being palpable or clinically enlarged and if possible, cytological evaluation should be performed, the latter being considered efficient in evaluation of metastatic disease (Langenbach, McManus, Hendrick, Shofer, & Sorenmo, 2001). If the first lymph node turns out to be cytological negative, no further assessment might be needed. For evaluation of metastatic disease, X-ray of the thorax is the gold standard for staging, since the lungs are most often affected (Fidler & Brodey, 1967). However, additional tests like ultrasound, radiography of the skeleton or other imaging like nuclear medicine can be indicated when further metastases are being suspected.

Table 2: Staging systems for Canine Mammary Tumors (Sorenmo, Rasotto, Zappulli, & Goldschmidt, 2011)

Table 2. Staging Systems for Canine Mammary Tumors

Original WHO Staging System[57]				Modified WHO[77 a]			
Stage I	$T_{1a,b,c}$	N_0	M_0	Stage I	T_1	N_0	M_0
Stage II	T_0	N_1	M_0	Stage II	T_2	N_0	M_0
	$T_{1a,b,c}$	N_1	M_0				
	$T_{2a,b,c}$	N_0 or N_{1a}	M_0				
Stage III	$T_{3a,b,c}$	$_{Any}N$	M_0	Stage III	T_3	N_0	M_0
	$_{Any}T$	$_{Any}N_b$	M_0				
Stage IV	$_{Any}T$	$_{Any}N$	M_1	Stage IV	$_{Any}T$	N_1	M_0
No stage V				Stage V	$_{Any}T$	$_{Any}N$	M_1

Abbreviations

Original WHO Staging System	Modified WHO
T: primary tumor (a, not fixed; b, fixed to skin; c, fixed to muscle)	T: primary tumor
T_0: No evidence of tumor	
T_1: <3 cm maximum diameter (a, b, c)	T_1: <3 cm maximum diameter
T_2: 3–5 cm maximum diameter (a, b, c)	T_2: 3–5 cm maximum diameter
T_3: >5 cm maximum diameter (a, b, c)	T_3: >5 cm maximum diameter
T_4: any T, inflammatory carcinoma	
N: regional lymph node status (a, not fixed; b, fixed)	N: regional lymph node status
Assessed by clinical exam or histopathology	Assessed by histology or cytology
N_0: no metastasis	N_0: no metastasis
N_1: metastasis ipsilateral lymph node(a, b)	N_1: metastasis
N_2: metastasis bilateral lymph nodes (a, b)	
M: distant metastasis	M: distant metastasis
M_0: No distant metastasis	M_0: No distant metastasis
M_1: Distant metastasis detected	M_1: Distant metastasis detected

[a] Excluding inflammatory carcinoma.

From the clinical and imaging evaluation, the dogs receive a clinical stage. Currently, there are two staging systems in use, the original and the modified World Health Organization (WHO) system (Owens, 1980) (Rutteman, Withrow, & MacEwen, Tumors of the mammary gland, 2001). Both systems are shown in Table 2.

Such staging systems have various benefits including easier communication between different sites, providing records for research and evaluation of treatment response, prognostic information and also helps to distinguish whether treatment has a curing or a palliative approach. The mammary carcinoma TNM staging for canines however has not yet been validated regarding its prognostic significance since there have been no prospective studies conducted. Still, results from several large retrospective studies that identify TNM and WHO stage as prognostic factors are consistent, i.e., more aggressive tumors grow faster than less aggressive types. Furthermore, they are most often larger and thus more likely to have metastatic subclones. Therefore, these staging systems are still an attractive option for prognostic significance andguide to vetsin their treatment decision (Sorenmo, Rasotto, Zappulli, & Goldschmidt, 2011).

2.6. Prognostic factors

The main prognostic factors to be considered are tumor size, stage and lymph node involvement which are described here.

2.6.1. Tumor size

Tumor size is -as categorized in the TNM classification- an important prognostic factor. In the staging systems, there is a distinction between three sizes, i.e., T1: <3 cm, T2: 3–5 cm, and T3: >5 cm (Owens, 1980) (Rutteman, Withrow, & MacEwen, Tumors of the mammary gland, 2001). Most studies use these size categories to evaluate prognostic factors. While the classification is widely accepted, a general consensus of the critical size of the tumor to change for the worse could not be reached, i.e., there is no consensus whether three or four or five centimeter in diameter worsen prognosis. A study found that dogs with tumors of T1 size had a statistically significant lower recurrence rate while T2 and T3 tumors did not appear to have a drastic difference (Kurzman & Gilbertson, 1986). A study from Philibert et. al., 2003 looking at the survival rate also found a significantly better outcome for T1 tumors compared to T2 and larger while the study from Yamagami et. al. showed comparable results for T1 and T2 and only T3 was significantly different (worse) and finally the study from Cang et. al. found that five centimeter is the turning point to have a worse outcome (Philibert, et al., 2003) (Yamagami, Kobayashi, & Takahashi, 1996) (Chang, Chang, Chang, & Wong, 2005). The work of Misdorp and Hart claimed that size is a prognostic factor only when it comes to complex carcinomas while Hellmen et. al. and Shofer et. al. did not find any correlation between tumor size and prognosis (Misdorp & Hart, Prognostic factors in canine mammary cancer, 1976) (Hellemen, Bergstrom, & Holmberg, 1993) (Shofer, Sonnenschein, Goldschmidt, Laster, & Glickman, 1989).

Although there is conflicting evidence in the literature, size as prognostic factor is generally accepted in the clinical routine and most studies support that the categorization of size is in fact an important prognostic factor. Naturally, considering only the tumor size is not reflecting overall prognosis and survival and other parameters need to be factored in as well.

2.6.2. Lymph node status

Lymph node status I s a binary classification. The lymph nodes are either categorized as “N0”, which means no metastasis or as N1 being metastasis confirmed by histopathology or cytology. In the two classification systems, a positive lymph node is treated differently. In the modified system, N1 is classified as stage IV disease, while in the original system, the classification also includes lymph node side (and unilaterality/bilaterality) as well as being fixed or not. This information is used to classify between stage II or III (Kurzman & Gilbertson, 1986) (Rutteman, Withrow, & MacEwen, Tumors of the mammary gland, 2001). Again, lymph node status has been shown with conflicting results regarding its prognosis, some studies show its prognostic value, while others don't (Misdorp, Else, Hellmen, & Lipscomb, 1999) (Misdorp & Hart, Prognostic factors in canine mammary cancer, 1976). These findings might be the result of retrospective evaluation of studies since the surgical procedures, follow-up time, histopathological evaluation, end points, remission duration, time to progression and other factors have not been standardized and did not distinguish between tumor types, which also play a big role in the prognosis of canine mammary tumors and in the potential of spreading along the lymph drainage.

2.6.3. Tumor stage

Tumor stage describes the overall stage according to the classification systems; thus, this description already includes size and lymph node status. The staging systems as base for studies has been studied regarding its prognostic significance. Yamagai found significant differences between stages one, three and four (stage two could not be evaluated due to a too small sample size at that time) when considering the original staging system of the WHO (Yamagami, Kobayashi, & Takahashi, 1996). In studies evaluating the modified system, Chang et. al. found statistical differences between stages one, two and three in comparison with stages four and five (Chang, Chang, Chang, & Wong, 2005). In the study of Philibert, stage one dogs were shown to have a longer overall survival compared to the higher classifications (Philibert, et al., 2003). Again, such studies suffer from limitations regarding a lack of standardization.

2.7. Treatment of mammary tumors

There are multiple options to treat mammary tumors in canines, most are well studied and have proven to be efficient.

2.7.1. Surgery

Surgical resection is the current gold standard therapy for mammary gland tumors in dogs and considered to be the single most effective therapy method to attain local tumor control with the exception of inflammatory carcinoma or presence of distant metastases (Papazoglou, Basdani, Rabidi, Patsikas, & Karayiannopoulou, 2014). This is opposite to the strategy in humans, where a therapy is desired that keeps the breast tissue intact and mastectomy is to avoided as good as possible (which is possible in around 70% of cases) using chemo- and radiation therapy (Jakesz, Gebhard, Gnant, & Taucher, 1999). There are multiple options of surgical tumor removal in dogs, which include radical mastectomy, regional mastectomy and nodulectomy (lupectomy), which are described in more detail later.

As long as the type of surgical resection in dogs seems not to affect survival, surgery is aiming at complete tumor removal with clean histological margins using the simplest technique (Papazoglou, Basdani, Rabidi, Patsikas, & Karayiannopoulou, 2014). Tumors with a T1 classification can also be lumpectomy curative treated using surgical removal while those with higher stages and metastasis benefit from additional treatments in conjunction with surgery (Sorenmo K. , 2003).

Lumpectomy or nodulectomy

In this technique, only the nodule (visible tumor) is removed alongside a rim (as small as possible) of the healthy tissue. Lumpectomy or nodulectomy describes mainly the removal of benign and small (< 0.5-1cm diameter) and firm, non-adherent or fixed to the skin nodules [1-3,5]. Lumpectomy is performed the following way:

Incising the skin as close as possible over the nodule, which can be grasped and separated from the surrounding parenchyma. In larger lumps (> 2cm) an elliptical incision should be performed. Then, using mosquito hemostats or scissors, the lump (or nodule) is being removed. Additionally, biopsy can be performed using this technique.

The technique is mainly used for benign masses, since in malignant tumors, such a surgery is most often accompanied with tumor recurrence and thus should be avoided in such cases (Papazoglou, Basdani, Rabidi, Patsikas, & Karayiannopoulou, 2014).

Simple or single mastectomy

This method describes the mastectomy of a single mammary gland, which is indicated in larger tumors having a central location, which are fixed to the skin or the underlying tissue. (Papazoglou, Basdani, Rabidi, Patsikas, & Karayiannopoulou, 2014). In this method, an elliptical incision has to be performed due to the larger extent of the nodule and the rim of healthy tissue should be at least 2cm. Additionally, the muscle fascia and/or the underlying muscle of the abdominal wall should be also excised en block.

Regional mastectomy

This method is indicated when large mammary tumors are located not only in one, but in multiple consecutive glands or between two glands. The reasoning behind this is that two glands share the same venous and lymphatic drainage pathway and thus they should be removed together. Thus, either glands 1-3 or 3-5 are being resected en block alongside their ipsilateral lymph nodes. The lymph nodes are being excised mainly for staging purposes, i.e., the presence of a positive lymph node will affect the further therapy strategy (Papazoglou, Basdani, Rabidi, Patsikas, & Karayiannopoulou, 2014).

Unilateral Mastectomy

This describes the method of removing glands 1-5 of a chain as a unit en block. Unilateral mastectomy is indicated when tumors occur in multiple glands of the respective chain, since it is in most cases easier to remove the entire chain rather than multiple individual mastectomies. Furthermore, two single chain mastectomies (in the end: radical mastectomy) are being performed when multiple tumors can be palpated in both chains. The two surgeries however will be performed with a 4-6 week break in between. The decision often lies within the breed of dogs, since flat chested animals can undergo a bilateral mastectomy easier than those which are deep-chested (Papazoglou, Basdani, Rabidi, Patsikas, & Karayiannopoulou, 2014).

Sometimes, unilateral mastectomy is favored to prevent recurrence and/or development of new malignant growth, especially in young dogs with benign, atypic lesions (Gilbertson, Kurzman, Zachrau, Hurvitz, & Black, 1983).The prophylactic removal of both chains (i.e., radical mastectomy) is not recommended since the impact of the procedure is large for the dog, thus regular re-examinations and regular follow-up exams are recommended to have the chance to early intervene surgically, when any new lesion forms (Polton, 2009).

It was shown that more than half of dogs with regional mastectomy (58%) of a benign tumor developed a new tumor in the ipsilateral mammary chain. These tumors were malignant in 74% of cases. Even more so, when the initial tumor was already malignant, these dogs are even more likely to develop a new malignant growth ipsilateral. Thus, unilateral mastectomy can be considered as the method of choice and the safer approach to prevent recurrent surgery (Stratmann, Failing, Richter, & Wehrend, 2008).

What kind of surgery is recommended by Papazoglou is shown in Table 3.

Table 3: Recommended surgical strategy depending on the size and extent of the mammary tumor (Papazoglou, Basdani, Rabidi, Patsikas, & Karayiannopoulou, 2014)

Tumor location	**Type of surgical excision**
Single benign tumor <0.5-1 cm	Lumpectomy or nodulectomy
Multiple benign or malignant tumors <0.5-1 cm in one or both chains	Unilateral/ regional mastectomy-staged or concurrent bilateral mastectomies
Multiple large tumors in one or both chains	Regional/unilateral mastectomy-staged or concurrent bilateral mastectomies
Single large tumor in one gland	Regional or unilateral mastectomy
Single large tumor with central location in one gland with distinct anatomic boundaries	Simple mastectomy/regional or unilateral mastectomy
Malignant tumor adhered to underlying tissues	Regional or unilateral mastectomy incorporating muscle/fascia
Tumor/tumors in adjacent glands or between glands	Regional or unilateral mastectomy
Tumors located in or between glands 1, 2 and 3	Regional mastectomy of glands 1-3 ± axillary node removal or unilateral mastectomy
Tumors located in or between glands 3, 4 and 5	Regional mastectomy 3-5 + inguinal node removal or unilateral mastectomy

Complications of Mastectomy

There are multiple complications that can be associated with mastectomy in bitches. These include seroma formation which is common and associated with not adequate dead space elimination which has been shown to improve by placing active drainages (Papazoglou, et al., 2006). Furthermore, incision dehiscence which can be seen both uni- or bilateral especially in the inguinal region is common. Additional complications include infections of the wound, ischemic necrosis, edema (especially in the hind legs) which was shown to be irreducible in some cases, being attributed to lymphatic obstruction by neoplastic cells following mastectomy incision and self-mutilation (Papazoglou, Basdani, Rabidi, Patsikas, & Karayiannopoulou, 2014).

Surgery technique

Mastectomy is being performed using an elliptical incision into the skin and the subcutaneous tissue around the mammary glands that are involved. Furthermore, 1-2cm margins of healthy tissue are removed in all directions, i.e., down the pectoral muscle and the abdominal oblique fascia or the rectal fascia. The ventral border is (if possible) the ventral midline. Then, to remove the skin, the skin is elevated cranially and traction applied caudally. When the underlying muscle or fascia is not involved in the tumor, then only gentle traction is used to strip the mammary chain from the tissues. If the glands 1 and 2 are involved, sharp and blot dissection however has to be likely performed, while glands 3-5 are blot loosely adherent and thus easier to be dissected. Is the tumor fixed or if there is an invasion, then the plane of dissection has to be directed towards the next muscle (or fascia), Large vessels are closed using electrosurgery to prevent excessive bleeding and hemorrhage. Wound lavage using saline solution should be performed during excision (Papazoglou, Basdani, Rabidi, Patsikas, & Karayiannopoulou, 2014).

After mastectomy, the wound has to be closed. This part is considered to be the most challenging part of the surgery (Papazoglou, Basdani, Rabidi, Patsikas, & Karayiannopoulou, 2014). This can be performed using various techniques. Dead space elimination as well as the management of the tension along the incision are important issues when it comes to closure of the mastectomy wound (Papazoglou, et al., 2006). The closing can be performed by absorbable sutures, by simple interrupted or cruciate sutures using filament or staples and active or passive drains (Papazoglou, et al., 2006). There is also the option to use skin only closure techniques, which is accomplished by inserting an active suction drain while closing the skin using widely placed tension relieving sutures.

All dogs undergoing surgery (mastectomy) should receive analgesia, using meloxicam or ketamine, both pre-emptive and followed by a few hours' long infusion. Active drains remain in place for 1-3 days after surgery and bandage changes should be also performed regularly. Sutures are being removed around 10 days after surgery (Papazoglou, Basdani, Rabidi, Patsikas, & Karayiannopoulou, 2014).

2.7.2. Chemotherapy

Chemotherapy is -in contrast to humans- not a primary method of tumor therapy. However, in some cases, e.g., irroperable tumors or as adjuvant measure, chemotherapy plays a role in the treatment of tumors. Various studies have been conducted on using chemotherapies in dogs, yet there are no distinct results regarding prophylactic chemotherapy after surgical intervention. Thus, the following descriptions of chemotherapy are based on examples of the literature and sorted by the medication being used in the respective studies.

5-Fluorouracil

5-Fluorouracil is a pyrimidine analogue. Damage to the cells occurs in two ways, namely by blocking of the enzymes Thymidylatsynthetasis and Uracilphosphatasis. Thus, DNA production is hampered and uracile cannot be embedded into the RNA. The use of 5-

Fluorouracil is often recommended and in a prospective study from 2001 by Karayannopoulou, combination of chemotherapy and surgery, a benefit of the combination therapy could be shown, precisely dogs with both treatments had a median survival of 24 months, while the control group only showed a median survival of 6 months (Brown, 1983) (Gorman, 1991) (Karayannopoulou, Kaldrymidou, Constantinidis, & Dessiris, 2001). As limitation however, it should be noted that the study only consisted of 8 dogs per group.

Cisplatin

Cisplatin is a cycle-unspecific chemotherapeutic. It works by binding to adenin, guanin and purin to prevent any further cell proliferation (Gorman, 1991). Therapies were conducted using 60mg/m² for 28 days in dogs. The use of cisplatin has shown to improve recurrence free time and overall survival as compared to using other single therapy options (Gorman, 1991).

Cyclophosphamid and Melphalan

Cyclophosphamid and Melphalan are alcylating compounds that interact with the cells in all phases. Cyclosphamid is recommended to be used with a dosage of 50mg/m² for 3-5 days per week while melphalan should be given as 1,5mg/m² 3-10 days orally. There is however no specific data on recurrence rates or survival in mammary tumors (Brewer & Theilen, 1985).

Vincristin and Vinblastin

Both compounds are plant alkaloids. They hinder mitosis during the metaphase of cell proliferation. In higher doses, they even cause strand breaks and translocalisations. As single therapy, Vinplastin is used at doses of 2,0-2,5 mg/m² for 7 days. Vincristin on the other hand is only recommended in combination with other chemotherapy medication (Dobson & Gorman, 1993)

Methotrexat

Methotrexat is an analogue of folic acid. It binds much higher to Dihydrofolatreduktasis compared to the natural occurring Dihydrofolic acid. Following, the ^{1}C metabolism is blocked (Crow, 1986).

Doxorubicin and Cyclophosphamid

Doxorubicin at 30 mg/m² in combination with Cyclophosphamid at 50mg/m², the first daily and the second all 3 days, both for 21 days has been successfully used in mamma carcinomas and showed remission of the tumor (Brown, 1983).

2.7.3. Hormonal Therapy

Around half of mammary carcinomas in bitches show estrogen receptors (Rutteman, Misdorp, Blankenstein, & van den Brom, 1988) (Sartin, Barnes, Kwapien, & LG., 1992). Therefore, anti-estrogen substances such as tamoxifen bind to these receptors without oestradiol effects. It could come to side effects such as swelling of the vulva, vaginal discharge, changes in behavior similar to the heat, cystitis, hair loss, bleeding, endometritis and incontinence (Rutteman, Misdorp, Blankenstein, & van den Brom, 1988). While hormonal therapy is widely used in humans, there is still debate whether it is useful in dogs or not. The effectivity as antitumoral therapy seems low and is currently not recommended (Macewen & Withrow, 1996). There are however results that showed the use of tamoxifen dosed at 0,42 mg/kg (orally) had a positive effect on the adeno carcinoma of the mammary glands (Oglivie & Moore, 1996).

Further options to influence the hormonal status are ovarian ablation or aromatase inhibitors. This has been successfully used in humans. These kinds of endocrine therapies might also have a benefit in canines, yet there is a lack of studies in these specialized methods and therefore the ovariohysterectomy still remains the most important type of endocrine therapy for bitches (Cassalli, et al., 2014).

2.7.4. Radiation Therapy

Radiotherapy is not a routine treatment in dogs' mammary carcinomas. Therefore, there are currently only limited available studies about the efficiency and efficacy of this kind of treatment available. Reasons are manifold. There is the issue of movement of the dogs during radiotherapy and also the cost and expenditure involved. Some results however have been obtained (Macewen & Withrow, 1996). One example are bitches with adeno carcinoma who underwent radiotherapy with a dose of 40 Gray in total and another study that showed recurrent free survival of over one year (Karayanopoulou, Kaldrimidou, & Dessiris, 1989) (Mauldin & Maleo, 1995). A palliative approach is also possible and is being used in inoperable and inflamed carcinomas (Gorman, 1991) (Withrow & Macewen, 1996).

2.7.5. Immune Therapy

Immune therapy, precisely immune stimulators have been studied in terms of efficiency in canine mammary carcinoma. Formalin fixed bacterial vaccines showed stimulation of macrophages and phagocytes in the organism (Hayes & Mooney, 1985). Furthermore, a combination of serratia macescens and streptococcus pyogenes seem to have a stimulating effect on macrophages and T-cells (Macewen E. , 1995). Also, Levamisol and bacterial vaccines made from Bacillus Callmette-Guerin only showed mild positive effects in canine mammary tumors as compared to surgical removal alone (Rutten, et al., 1990). Another promising stimulator was Muramyl tripeptide-phosphatidyl-ethanolamine covered by liposomes, which is a bacterial cell wall unit having macrophage and monocyte stimulating effects, yet this has not yet shown antitumorous effects (Teske & Ruttemann, 1992).

2.8. Anesthetic management

Anesthetic management is crucial for the success of therapy, especially when using surgical intervention. Naturally, anesthesia must numb the pain and suppress any kind of movement of the canine in order to operate. However, the depth should be as little as possible to allow for quick recovery as well as to reduce the risk of complications or even death. Since dogs developing cancer are likely to be old, special care must be taken to keep these dogs with already lower overall health status safe. In general, two types of anesthesia can be distinguished, these are the regional and general anesthesia, meaning that either only part of the dogs' body is numbed or the dog is entirely in a sleeping state respectively. In this thesis, locoregional anesthesia was the main focus, thus general anesthesia should be described only superficial.

2.8.1. General anesthesia

General anesthesia describes the application of sedatives and analgesics to bring the dog into a sleeping state without consciousness. The advantages of this method are a complete undisturbed surgical procedure with the dog not reacting to any kind of stimulus. Disadvantageous however is the higher invasiveness, potential anesthesiologic complications and even long-term risks. There are discussions about the risk of anesthesia promoting relapse in certain kinds of cancer (Faroni, et al., 2021) (Karayannopoulou, et al., 2022). Overall, general anesthesia might even not be necessary in many surgical procedures, since they are likely performed quickly. This also holds true for canine mammary carcinoma.

2.8.2. Locoregional anesthesia

Local/Locoregional or regional anesthesia describes the use of an aesthetic agents to decrease sensation in a specific part of the body, e.g., a single limb. By using this method, it is possible to perform surgery in an awake state and allows patients to breathe on their own without external machines. Furthermore, patient transition is performed much quicker, i.e., there is less preparatory work to be performed and discharge of the patients is quicker as well due to the shorter postoperative recovery time. Local anesthetics which hare being used for regional anesthesia work by inhibiting the impulse depolarization through a blockade of the sodium channels in the affected/desired region. Around 20% of all anesthetic procedures are being performed as regional anesthesia (Bonnet, de Montblanc, & Houhou, 2001). Spinal anesthesiais most commonly used and well known in the preoperative setting. Also well-known is the epidural anesthesia in laboring women. Regional anesthesia is mainly usedin limb and eye surgery procedures and also for minimum invasive surgeries. The risk of regional anesthesia is -compared to general anesthesia- very low, complications such as peripheral nerve damage or hematoma at the injection site are the most common side-effects.

The use of regional anesthesia has recently been associated with improvements in long-term survival in women who underwent breast cancer surgery since an aesthetic is said to modulate the inflammatory and immune response associated with the trauma caused by surgery, thus reducing opioid and general anesthetic consumption and promoting cancer cells' death (Pérez-González, Cuéllar-Guzmán, Soliz, & Cata, 2017). There is no data comparing the anesthetic approaches in canines as there is for women, but the overall expectation is that the results will be similar in dogs.

Overall, local anesthesia can be considered as a safe method, yet there are potential adverse reactions that can occur. These can be subdivided into systemic and local reactions.

Serious side effects can occur secondary to rapid intravenous bolus injections of too high doses of the local anesthetic drugs. Generally, these medications are not injected at a high rate and not even into the blood stream (with the exception of lidocaine), but accidental puncture of the veins can occur. To avoid accidental injections, aspiration should always be performed to determine if the needle is placed correctly. In humans, the incidence of this occurring is 1–7.5 in 10,000 (Auroy, et al., 2002). For canines, no data is available.Using lidocaine, at concentrations, inhibitory neuron depression can cause muscle fasciculations, visual disturbance, weakness and cause cerebral excitation, even seizures. At higher concentrations (i.e., overdose), profound depression of the central nervous system can occur, leading to respiratory failure, coma and even death. Other adverse effects of local anesthetics can include anaphylaxis. This condition is however very rare and primarily associated with ester-type drugs (Grubb & Lobprise, 2020).

2.8.3. Local anesthetics

In this section an overview of commonly used local anesthetic agents is provided. The medications are separated into Amid type and Ester type. The first consisting of Lidocaine, Bupivacaine and Ropivacaine and the latter of Procaine and Tetracaine.

Lidocaine, Bupivacaine and Ropivacaine are chemically referred to as aminoethyl amides. Their mechanism is based on the inhibition of voltage-gated sodium channels. This causes a stabilization of the membrane and thus slows the depolarization and repolarization of the membrane. These types have successfully shown their use in minor surgical procedures such as incisions, dental procedures and biopsies. Usually, they are admitted as a single infection locally into the lesion (or area of the procedure), but it is also possible to use them as infusion for pain management in the postoperative phase. Since local anesthesia have different durations, the short acting versions are often combined with epinephrine in order to decrease the absorption rate and thus the duration of action is being prolonged. Side effects are rare and mostly occur due to the dosage of the medication and most often result from systemic administration. Symptoms include tinnitus, twitching, drowsiness, dizziness, nausea, vomiting and constipation. In higher doses also cardiac depression and ventricular arrythmias can occur (National Institute of Diabetes and Digestive and Kidney Diseases, 2012).

The ester type an aesthetic Procaine was popular in the early 20th century being used for infiltration and spinal blocks, but was later superseded by lidocaine. This was mainly attributed to low potency, slow onset and a short duration of the medication. Furthermore, allergies were reported (Suzuki, Gerner, & Lirk, 2019).

Tetracaine, also an ester type, has a slow-onset, is potent and is intermediate/long acting. When Tetracaine is administered together with a vasoconstricting drug such as epinephrine, even longer durations can be achieved. Tetracaine however is said to be quite toxic and neurotoxicity has been reported in high doses in animal models which can lead to cauda equina syndrome.This medication is mainly used topical but sometimes also for spinal anesthesia. It is highly soluble in lipid and a large amount can be absorbed when it's used in the mucous membrane or in wounded skin (Suzuki, Gerner, & Lirk, 2019).

There are further Ester type anesthetics such as Chloropropane, Cocaine and Benzocaine, but these are not used in the frequency as the described medications.

2.8.4. Intercostal Block

An intercoastal block is a type of local anesthesia which acts on intercostalnerves to enable pain control that results from injuries and surgeries on the chest area (Trebacz, Trebacz, Jurka, & Galanty, 2011). In order to reach analgesia of a given area, at least two intercostal nerves before and after the place of the injury should be performed. There are however potential complications that can occur, which include: lack (or insufficient) anesthesia, pneumothorax, laceration of intercostal vessels or injury of thoracal organs (Trebacz, Trebacz, Jurka, & Galanty, 2011).

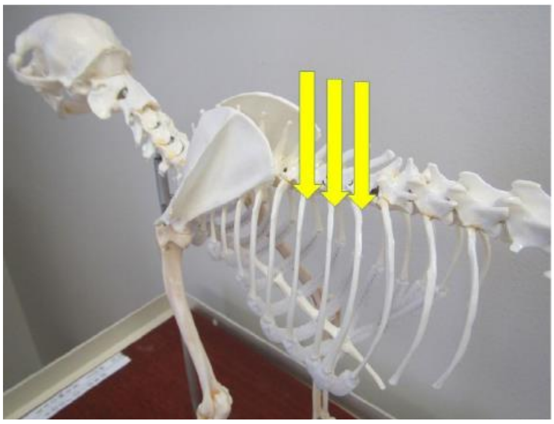

Figure 3: Landmarks for the intercostal block on a dog skeleton. The injection site is indicated by the arrows (Grubb & Lobprise, 2020)

Technique:

The needle needs to be inserted into the skin and the muscle layers caudal to the proximal portion of the ribs (i.e., as close as possible to the spinal column). The needle needs to be placed 2-3 ribs caudal as well as 2-3 cranial of the area that should be desensitized (Grubb & Lobprise, 2020).

2.8.5. Transversus abdominis plane block

The technique of the ultrasound (US) guided TAP block is a method to provide perioperative analgesia to the abdominal wall and is used in veterinary medicine only recently (Schroeder, Schroeder, & Johnson, Transversus abdominis plane block for exploratory laparotomy in a Canadian lynx (Lynx canadensis)., 2010). The reasoning behind this method is to reduce the administration of systemic analgetic agents when dogs undergo surgery of the abdominal wall (Portela, Romano, & Briganti, Retrospective clinical evaluation of ultrasound guided transverse abdominis plane block in dogs undergoing mastectomy., 2014).

Traditionally, if local anesthetic was required in veterinary medicine, an epidural anesthesia was performed. This is done by inserting the needle into the skin of the midline lumbar region (7th lumbar and 1st sacral vertebra) and instilling a local anesthetic. This spreads out in the tissue and determines how much of the area is blocked. Generally, the spread is more cranial and thus provides abdominal block. There are however various risks associated with this traditional method, including bacterial infections, hypotension since the autonomic nerval system is being blocked, potential intravenous administration of the anesthetic due to the venous sinuses in the epidural space, delayed urinary retention and delayed respiratory depression. Additionally, there are various contraindications including coagulopathy, septicemia, an abnormally shaped pelvic region and skin infections. Generally, the (TAP block) is described as a technique of blocking the abdominal wall. This is achieved by injecting a local anesthetic agent between the muscle fascia of abdominal internal oblique and transverse abdominal muscles and it is combined with the use of an ultrasound probe (Taylor, et al., 2013). In human medicine, TAPblock has been used often and is sufficiently reported in the literature for the use in a large variety of surgicalprocedures. In veterinary medicine, however, TAP block techniqueshave only been little reported.The TAP block is subdivided into two subblocks. The first is the subcostal TAP block, which includes blocking the spinal nerves of T10, T11, T12, T13 and the Mid abdominal TAP Block which blocks T13, L1 and L2. Thus, the subcostal TAP block will be performed in cranial mastectomy, while the Mid abdominal block in caudal mastectomy. In cases of total mastectomy, both methods are combined.Anatomically, the abdominal wall of canines is made up of various muscles, including the obliquus externus abdominis peripheral, the obliquus internus abdominis in the middle and the transversus abdominis at the inner side. Between the obliquus internus abdominis and the transversus abdominis muscles, a fascial plane denoted as transversus abdominis plane is located (see Figure 4) (Castañeda-Herrera, Buriticá-Gaviria, & Echeverry-Bonilla, 2017). The TAP block consisted of two separate injections of 0,3-0,35 mL/kg of bupivacaine 0,25%, one in the caudal abdominal region, cranial to the iliac crest, and a second injection just caudal to the last rib (Portela, Verdier, & Otero, Regional anesthetic techniques for the pelvic limb and abdominal wall in small animals: A review of the literature and technique description, 2018).

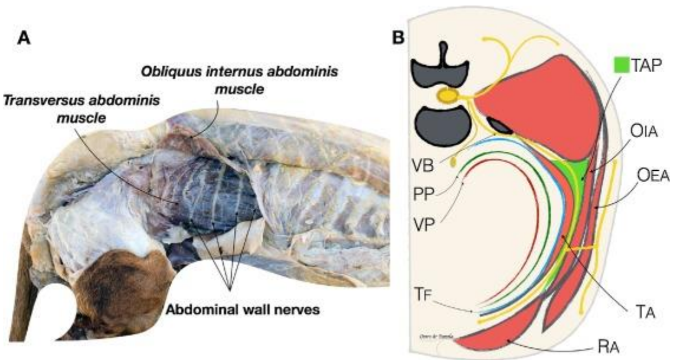

Figure 4: Abdominal wall dissection in a dog showing the abdominal wall nerves after resecting and flipping the obliquus internus muscle (Portela, Verdier, & Otero, Regional

anesthetic techniques for the pelvic limb and abdominal wall in small animals: A review of the literature and technique description, 2018)

The degree of the motoric or sensorics blockade is dependent on the nerve being blocked as well as the anesthetic agent that is being used and how local this can be administered to the desired nerve. To determine the location, anatomical landmarks are crucial, which can and should be double-checked using US or electrical nerve stimulations. In the abdominal wall, all nerves involved are sensory nerves, thus electrical stimulations are not appropriate as no other reaction can and will be observed. Thus, US and anatomical landmarks are the appropriate choices in TAP. The literature body on the use of TAP in canines is mainly limited to cadaver studies.

There seems to be an effect of the volume of the agent administered in TAP. This was evaluated by Bruggnik et. al. who evaluated the influence of the volume of the drug on the coverage of the nerve roots of the abdominal wall using methylene blue solution. The results showed a statistically significant root coverage with increasing volume from 0,25 ml/kg, 0,5 ml/kg, 0,75ml/kg and 1 ml/kg. The 1 ml/kg showed the highest coverage which was four dermatomes. The smallest volume (0,25 ml/kg) still blocked three dermatomes. Despite the study being conducted in Beagle cadavers, the results seem to be comparable in live tissues (Bruggink, KM, Baker-Herman, & Schroeder, 2012). Interestingly, in two no dye was found even after 24 hours waiting period, presumably due to intraperitoneal injection which is also a known complication in TAP.

Another group used iodinated agents and performed a computed tomography to visualize the spread of a TAP injection using this contrast material. They found that there was no significant difference in the volume of the injection, but also a high number of intraperitoneal spreads. This study however might be limited since X-Ray contrast agents have a comparably high viscosity which could hamper the spread in the tissue, especially in cadavers since the lack of body heat does not contribute to an easy spread of the solution (Zoff, Laborda-Vidal, Mortier, Amengual, & Rioja, 2017).

Although there is a large body of literature that shows clear evidence of the effectiveness of the TAP block in human patients, there have been no prospective studies undertaken in canines and even more so not in alive animals. The only available sources are regarding the spread of local anesthesia and these must be interpreted with extreme caution since there might be either an over- or and underestimation of the spread and effectiveness of the local anesthetics (Bruggink, KM, Baker-Herman, & Schroeder, 2012) (Zoff, Laborda-Vidal, Mortier, Amengual, & Rioja, 2017).

3. Material and Methods

3.1. Study cohort / Eligibility criteria

The study cohort included all female canines that underwent mastectomy, both partial and total which were listed in the database system of the Vetmeduni Vienna. No restrictions regarding age, breed, size (weight) or other factors have been set.

The electronic medical record data base (TIS) of the Vetmeduni Vienna was scanned for canine mastectomies between 2009-2019. Search criteria used were "total mastectomy" and canines who did not receive any secondary or further surgery were included, dogs with an additional ovariohysterectomy were excluded from further processing. The obtained data was used to categorize the records in two groups, one received general anesthesia only while the second also received TAP Block/intercostal block. Other patients, which underwent surgery using other regional/local anesthesia mthods such as quadratus lumborum block were excluded. In the next step, the data was separated regarding the medication they received and screened for complications. Finally, the data was checked for completeness of data. With the available data these two groups were compared in terms of perioperative complications (e.g. bradycardia, hypothermia, hypotension, arrythmia, hypercapnia, apnea, painting) as well as postoperative (i.e. short-term) complications such as local inflammatory reaction, death, pain and bleeding. Long-term outcome defiend with one year postoperatively, included the parameter death/alive, reoccurens of neoplasia and metastases.

In case of missing survival information, the owners of the pets were contacted via phone to check whether the animal was still alive.

3.2. Ethical considerations

Due to the retrospective nature, no ethics committee vote was needed for the conduction of this study.

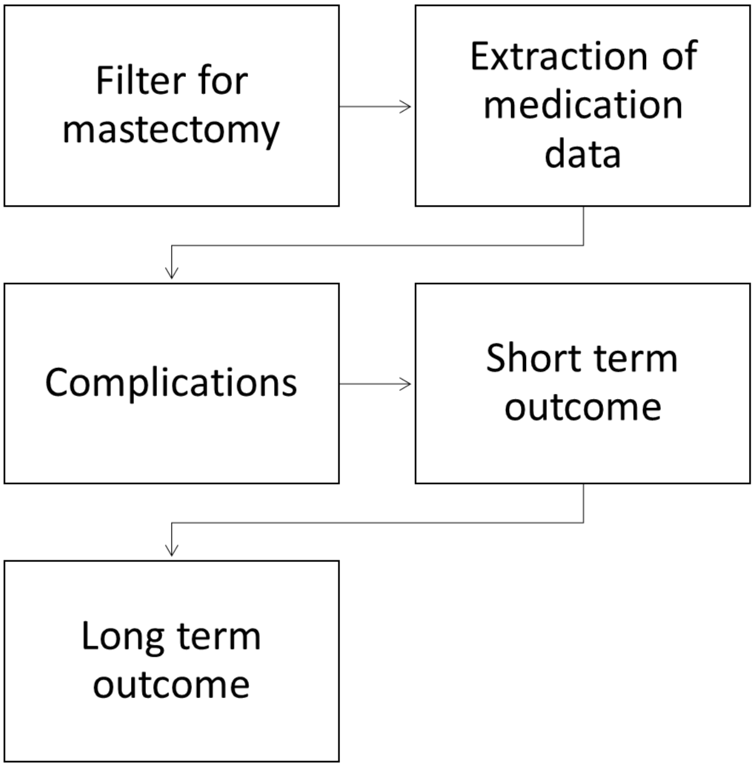

Figure 5: Flow chart of the data extraction process. From the original 249 identified mastectomies, 82 had sufficient data to be finally evaluated.

3.3. Descriptive analysis

To get an overview about the number of mastectomies, the medication used, complications, short- and long-term outcome the data is presented in a descriptive way with mean and Standard deviation (SD) and summarized in tables.

4. Results

Between 2009 and 2019, 249 mastectomies were identified. Eightytwo cases fulfilled all inclusion criteria to be further processed to compare the two methods.

4.1. General overview of the data

The breeds were well mixed and included bitches of various sizes and weight. A list is shown in Table 4.

Table 4: Breeds included in the analysis (8 records did not state the breed)

Breed	Number	Breed	Number	Breed	Number
American Cocker Spaniel	1	English Cocker	1	Mixed Breed	19
American Staffordshire Terrier	2	Bernese mountain dog	1	Newfundland Mix	1
Australian Cattle Dog	1	Epagneul Breton	2	Parson Russell Terrier	1
Australian Shepherd	1	Erdélyi Kopó	1	Pinscher	1
Beagle	3	Eurasian	1	Pitbull-Bullmastiff	1
Border Terrier	1	French Bulldog	1	Poodle	2
Boxer	4	Golden Retriever	2	Shepherd	1
Cavalier King Charles Spaniel	1	Gordon Setter	2	Schnauzer Dog	1
Chihuaua	1	Hannoveranian	1	Siberian Husky	1
Chinese Crested	1	Jack Russel Terrier	1	Pointed dog	1
Cocker Spaniel	2	Labrador Mix	1	Staffordshire-Bullterrier	1
Dachshund Longhaired	2	Labrador	2	Tibetian Terrier	2
Dachshund-Pinscher-Mix	1	Lakeland Terrier	1	Welsh Terrier	2
German Sheperd	1	Malinois	1	Yorkshire Terrier	5
English Bulldog	1	Maltese	1	Miniature Pinsher	1

4.1.1. Premedication

Premedication varied between the dogs and the medications used are shown in Table 5. The dogs received mainly methadone or a combination of methadone and Acepromazine.

Table 5: List of received premedication

Medication	Number	Medication	Number
Ketamine/Metadone/Midazolam	3	Butorphanol/Ketamine/Midazolam	1
Ketamine/Medetomidine/Methadone	5	ACP/Butorphanol	2
ACP/Morphine/Dexmedethomidine	1	Butorphanol/Dexmedetomidine	1
ACP	3	Methadone	10
ACP/Dexmedetomidine/Metadone	2	Butorphanol/Medetomidine	1
Dexmedetomidine/Metadone	2	Butorphanol/Midazolam	2
Medetomidine/Midazolam/Ketamine	2	Medetomidine/Methadone	5
ACP/Methadone	35	Methadone/Midazolam	7

4.1.2. Anesthesia

Anesthesia was induced mainly using ketamine or propofol or a mix of these two. The used medications are shown in Table 6.

Table 6: Medication used for inducing anesthesia

Medication	Number	Medication	Number
Propofol/Ketamine	4	Propofol	62
Midazolam/Aflaxalone	9	Propofol/Midazolam	7

To maintain anesthesia, mainly isoflurane or Isoflurane/Fentanyl was used (Table 7).

Table 7: Medication used during anesthesia.

Medication	Number	Medication	Number
Isoflurane/Ketamine	2	Isoflurane/Dexmedetomidine	1
Isoflurane	29	Isoflurane/Remifentanil/Ketamine	1
Isoflurane/Ketamine/Liocaine	4	Isoflurane/Fentanyl/Propofol	1
Isoflurane/Fentanyl/Medetomidine	4	Isoflurane/Remifentanil	1
Sevoflurane/Fentanyl	1	Isoflurane/Fentanyl/Ketamine	7
Isoflurane/Fentanyl	31		

4.1.3. Complications

Complications mainly included arrythmia, in combination with AV-blocks or bradycardia, loss of orientation and panic during the wake-up process, hypotension, hypothermia ventilation issues such as hypercapnia.

Table 8: Complications during surgery

Complication	Number	Complication	Number
Arrythmia with AV block	9	Technical issues	1
Arrythmia with bradycardia	28	Hypothermia	36
Arrythmia: other	5	Ventilation issues	9
Wake-up complications	5	Euthanasia	1
Hypotension	16	Premedication	7
Anesthesia complications	9		

4.1.4. TAP vs general anesthesia

In the TAP group, 25 animals were included, 20 received Bupivacaine, four Ropivacaine and one received Lidocaine, respectively. The local anesthetic used for the intercoastal block varied between the animals. An overview is shown in Table 9.

In the Bupivacaine group, 16 received Ropivacaine as intercoastal block, wile 4 received nothing. In the Ropivacaine group, 3 received Ropivacaine for TAP and intercoastal block, 1 received Dexmedotomidine additional to Ropivacaine.

The canine that received Lidocaine for TAP also received Lidocaine for the intercoastal block.

Table 9: Number of animals receiving TAP and intercoastal block with the respective medication.

TAP	number	Intercoastal block	number
Bupivacaine	20	Ropivacaine	16
		None	4
Ropivacaine	4	Ropivacaine	3
		Ropivacaine/Dexmedetomidine	1
Lidocaine	1	Lidocaine	1

In the general anesthesia group, 57 animals were included. 48 received propofol as induction, 6 received Propofol and Midazolam and 3 Propofol and Ketamine.

Table 10: Number of animals receiving general anesthesia only

Anesthetic	number	Maintenance	Number
Propofol	48	Isoflurane/Ketamine	2
		Isoflurane	12
		Sevoflurane/Fentanyl	1
		Isoflurane/Fentanyl	26
		Isoflurane/Remifentanil/Ketamine	1
		Isoflurane/Fentanyl/Propofol	1
		Isoflurane/Fentanyl/Ketamine	5
Propofol/Midazolam	7	Isoflurane	4
		Isoflurane/Remifentanil	2
		Isoflurane/Fentanyl/Ketamine	1
Propofol/Ketamine	3	Isoflurane	1
		Isoflurane/Fentanyl	2

In the Propofol group, 26 received Isoflurane /Fentanyl for maintenance 26, followed by Isoflurane in 12 dogs, 5 received Isoflurane/Fentanyl/Ketamine, 2 received Isoflurane/Ketamine, 1 Sevoflurane/Fentanyl and 1 Isoflurane/Fentanyl/Propofol.

In the Propofol/Midazolam group, 4 received Isoflurane as maintenance, 2 received Isoflurane/Remifentanil, and 1 received Isoflurane/Fentanyl/Ketamine.

In the Propofol/Ketamine group, 2 received Isoflurane/Fentanyl and 1 received Isoflurane for maintenance.

Regarding complications, the groups varied. Overall, each method had complications (except TAP using Lidocaine, but only one animal was included in this group). A closer look into the complications is shown in Table 11 for the TAP group and in Table 12 for the general anesthesia group.

Table 11: Number of complications in the TAP group

TAP	Intraoperative complications / Number		Postoperative (short-term) complications / Number		1 year (long-term) follow-up / Number	
Ropivacaine n= 4	None	2	One	4	None	3
	Hypothermia	1			Neoplasm	1
	Bradycardia	1				
Bupivacain n=20	None	9	One	5	Neoplasm	3
	Bradycardia	3	None	10	Metastasis	1
	Hypothermia	5	Exudate	1		
	Painting	2	Pain	2		
	Hypotension	6	Bleeding	1		
	Arrythmia	1				
	Waking up	1				
Lidocaine n = 1	Hypothermia	1	One	1		

Complications occurred in all of the dogs that were included in this study. These occurred mainly intraoperative and postoperative (short term). Long-term complications (1 year) were low and mainly neoplasms, i.e. they are likely not directly correlated with the type of anesthesia used.

Table 12: Number of complications in the general anesthesia group

Anesthetic induction	Maintenance	Intraoperative complications / Number		Postoperative (short term) complications / Number		1 year (long term) follow-up / Number	
Propofol	Isoflurane/Fentanyl	Bradycardia	8	one	20	Dead	2
		Hypothermia	5	none	5	Neoplasia	3
		Apnea	1	Died	1		
		none	12	Pain	1		
		Hypotension	4	Bleeding	3		
		Arrythmia	4				
		Waking up	3				
	Isoflurane	Bradycardia	4	one	18	Dead	1
		Hypothermia	5	Exudate	1	Neoplasia	1
		Hypercapnia	2	Pain	2		
		Painting	2				
		none	11				
		Hypotension	2				
		Arrythmia	1				
		Waking up	3				
	Isoflurane/Fentanyl/Ketamine	Hypothermia	2	one	1	Dead	1
		None	3	none	2		
		Hypotension	1	Pain	1		
	Isolfurane/Ketamine	Hypercapnia	1	one	1		
		Hypotension	1	none	1		
	Isoflurane/Fentanyl/Propofol	Hypercapnia	1	one	1		
Propofol/Midazolam	Isolflurane	Hypothermia	2	one	2		
				none	1		
				pain	1		
		Hypothermia	1	one	1	Dead	1
				none	1		
Propofol/Ketamine	Isoflurane	Arrythmia	1	one	2		
Sum of complications			80		66		9

In the Propofol/Midazolam group, 2 canines had hypothermia during surgery, postoperative, 2 had one and 1 had pain. Finally, in the one-year follow-up 1 died.

In the Propofol only group, several dogs had multiple adverse reactions including 1 with, bradycardia, hypothermia, painting and apnea, 2 with bradycardia and hypothermia, 1 with bradycardia, hypothermia and hypercapnia, 4 with bradycardia and arrythmia, 2 with bradycardia and waking up, 1 with bradycardia, hypotension and arrythmia.

In the Propofol/Ketamine group, 2 canines had no adverse reaction intraoperative, 1 had arrythmia, all 3 had one postoperative and there were no side effects in the long-term follow-up.

5. Discussion

In this retrospective study, the occurrence of adverse perioperative complications as well as the overall survival rate of canines undergoing mastectomy has been evaluated. The aim was to compare the outcomes between the TAP and intercostal block with general anesthesia

TAP is a new method of regional anesthesia, that originated in 2001 in human Applications for abdominal and gynecological surgeries (Ruiz-Tovar, Albrecht, Macfarlane, & Coluzzi, 2019). Thus, it is not as commonly used in veterinary anaesthesia and general anesthesia is still more often used for mastectomy in dogs. The fact that local anesthesia can be considered safer and with less complications for the dogs since it puts less stress on their body, such methods should be comparatively evaluated side-by-side to investigate whether they have an advantage (Sarcon, et al., 2022). To our knowledge, no study comparing TAP and general anesthesia in mastectomy has yet been performed.

In human medicine, there are already multiple papers published and both case-control studies as well as meta-analysis are available about TAP (Ruiz-Tovar, Albrecht, Macfarlane, & Coluzzi, 2019), this is not the case in dogs (McDonnell, et al., 2007) (Ruiz-Tovar, Albrecht, Macfarlane, & Coluzzi, 2019). Even more so, in-vivo studies are scarce and systematically enough to provide any general guideline for its use. TAP block in animals has mainly been described in cadaver studies only. This includes the first report on a Canadian lynx in 2010 (Schroeder, Schroeder, & Johnson, Transversus abdominis plane block for exploratory laparotomy in a Canadian lynx (Lynx canadensis), 2010). Since then, multiple cadaver studies on canines have been performed (Schroeder, Snyder, Tearny, Baker-Herman, & KM., 2011) (Bruggink, KM, Baker-Herman, & Schroeder, 2012) (Drożdżyńska, Monticelli, Neilson, & Viscasillas, 2017).

Multiple complications can be associated with mastectomy in canines. These include seroma formation, incision dehiscence uni- or bilateral, infections of the wound, necrosis and edema

(Papazoglou, Basdani, Rabidi, Patsikas, & Karayiannopoulou, 2014). The present study however focusses on the complications during (or induced by) anesthesia.

In our study, 249 canines who underwent mastectomy were found in the database search which was a fairly good number considering the span of search between 2009 and 2019, i.e., a span of 10 years. The collective was diverse and included various breeds of different sizes and weight. The distribution of total vs. partial mastectomy was around two-thirds vs. one-third respectively. From the entire group, only 82 cases showed sufficiently complete data to be further processed.

In the interoperative setting, 23 animals (out of 25) in the TAP group and 43 in the general anesthesia group (out of 57), had complications. In the postoperative setting, the TAP group constituted 14 out of 25 complications and the other group 48 of 57. Finally, in the one year follow up, 4 neoplasms and 1 metastasis manifestation could be observed in the TAP group and in the general anesthesia group, 5 died, 1 neoplasm and 4 metastases were found. These results show that both groups have a high occurrence of complications, which seem to be highest interoperatively. However, in direct comparison, in the postoperative setting, the TAP group had 75% complications, while the general anesthesia group had 84%.

It was shown that some of the complications did not occur in the TAP group. These include hypercapnia and apnea in the intraoperative phase. Other complications, such as bradycardia, hypotension and arrythmia occurred in both groups, here there seems to be no large effect of the anesthetic agent regarding the occurrence.

It is interesting that there has not been any surgery-complication related death during surgery or postoperatively. Both methods seem to give sufficient safety for the dogs that no life-threatening situations occur which are directly related to the anesthetic type. Neither regarding the method (TAP vs. general anesthesia) nor related to the medication that was? administered.

Furthermore, there is no reported case where TAP failed. This shows that the method is not only possible to be used in a daily routine but appears to be reliable and easy enough to be performed routinely even though it is a comparably unknown and less used technique.

The postoperative occurrence of adverse reactions appears to be higher in the general anesthesia group. This is not surprising, since there is less pain in the TAP group. One animal even died in the postoperative setting in the general anesthesia group.

The neoplasm rate in both groups was low in the one year follow up evaluation, which is a sign that both anesthesia methods are equal when it comes to surgical success. Naturally, the anesthesia is not the main cause for surgical success and also not the direct cause for the occurrence of neoplasm. However, failure in anesthetic management (e.g., too low analgesia, movement, etc.) can render the surgical procedure unsuccessful. Thus, there seems to be no effect of the type of anesthesia when it comes to therapeutic success. The same goes for the metastasis development, since there have been hardly any cases that have been reported.

The overall survival rate after one year is high. Most dogs survived the one-year follow-up period. Of the 5 dead canines, no data is available whether their death was caused by long-term effects of the surgery procedure or if there were other causes involved (or if death occurred natural due to their age).

There is room for improvement in the present study. First, the retrospective nature of the data analysis showed that most of the medical records were not sufficiently prepared for further analysis. Second, the group sizes are different, showing that general anesthesia is still the main method that is being performed in clinical routine care. There is no data available if a planned TAP was cancelled and changed to systemic analgesia or vice versa due to individual reasons. In case of a prospective study, animals could have been randomly selected to undergo one or the other method and avoid such a bias. Furthermore, there has not been a single method or combination of methods (e.g., using one kind of medication for TAP and one for intercoastal block) so that this variation in the use of analgesia is also a large factor that could influence the final result. This is even more prevalent in the general anesthesia group, in which for example 7 groups could be separated in the Propofol group, depending on the analgesia they received during the procedure. This also makes interpretation of the data more complicated. Other risk factors, such as present co-morbidities, allergies etc. have not been considered, mainly due to a lack of the available data.

6. Conclusion

Comparing the two methods of anesthesia showed that both had complications, yet the local anesthesia group seems to have less complications, especially when it comes to more severe ones. The groups studied were rather inhomogeneous consisting of various breeds of different sizes and weight, which is a realistic view of the daily practice. On a more specific note, the TAP group showed less complications compared to general anesthesia. A result which was to be expected given the lower number of drugs and less strain on the body of the canines during anesthetic management. Based on the results from this study, we can assume that locoregional anesthesia using TAP and intercoastal block is a safer procedure and could possibly become the preferred method in canine mastectomy in the future, however care needs to be taken that specific and individual factor could not be established since the data was not prospectively evaluated on a specific cohort and thus the results are not sufficient to provide any general guidance or even guidelines. It should be noted that the type of anesthesia did not have any effect on the success of surgery itself since all the used methods and anesthetic agents provided anesthesia good enough to successfully perform mastectomy. This is also backed by the fact that there were hardly any neoplasms/relapses in the one-year follow up indicating a high success rate. This leads to further questions which should be answered in prospective studies highlighting more points regarding the canines' overall health status, individual needs of certain breeds and a standardization of the TAP method to be used. Furthermore, other surgical interventions using analgesia by TAP and intercoastal block are attractive to be evaluated

7. Summary

In this retrospective study, the occurrence of complications in canines undergoing mastectomy has been evaluated. The aim was to evaluate the rate of complications in by comparing general anesthesia and local anesthesia in dogs. The compared methods were TAP, intercoastal block and general anesthesia. In the literature, the efficient use of TAP in humans has been described, yet there is hardly any data available for canines and if so, most studies have been performed on cadavers showing the spread of local agents after injection and showing potential adverse situations, e.g. intraperitoneal injection. Due to the lack of prospective studies, the use and method of performing TAP mostly relies on the experience of the individual performing the procedure. The study retrospectively gathered data from 10 years of canines undergoing mastectomy (without any additional surgery, e.g. ovariohysterectomies) including all ages, races and weights of canines. The information has been extracted from the local medical records of the veterinary university of Vienna and listed for comparison. Overall, a high number of complications was seen in each group, but most were not severe and could be easily and safely resolved. The locoregional anesthesia group had overall less complications compared to the general anesthesia group. This held true for perioperative and the intraoperative complications. The long-term survival was very high and complications were few in all groups. Due to the retrospective nature of the study, these results cannot be used to draw conclusions about superiority of one method due to the lack of standardization and randomization, yet these results can be used as a base for future prospective and randomized studies in selected groups to evaluate local and general anesthesia in canines in an ordered fashion. Overall, based on the scarce literature available and the results of this study, TAP might be an attractive alternative in canines.

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