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Occurrence of mast cell tumors in intact and neutered dogs  
Literature review

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## **1. Abstract**

Mast cell tumors are the most common cutaneous tumors in dogs and their etiology remains incompletely understood. Concurrently, sterilization is one of the most frequently conducted surgical procedure on the reproductive system of dogs. Several studies have explored the potential link between the risk of development of mast cell tumors and sterilization. The purpose of this thesis was to offer a comprehensive overview about the occurrence of mast cell tumors in sterilized and intact dogs, and to analyze the results of the conducted studies, while giving an overview of their hypotheses, methodologies, and findings, as well as their limitations and the conclusions researchers have drawn from them. Through an extensive review of English-language publications, journal articles, and scientific books, we examined a wide range of hypotheses put forth by researchers. The hypotheses made by researchers ranged from the protective effect of sexual hormones, over socioeconomic perspectives to the increased occurrence of mast cell tumors in a higher age, which is more frequently reached by sterilized dogs. The results of these studies revealed statistically significant findings that indicate an association between sterilization and the development of mast cell tumors in dogs. Furthermore, certain breeds demonstrate varying susceptibility to this association. Researchers have drawn valuable conclusions from these results, suggesting that future research should build upon this foundation. Addressing the limitations faced during these studies and refining study designs would contribute further to a more comprehensive understanding of this complex relationship.

### **1.1 Absztrakt**

A hízósejtes daganat az egyik leggyakrabban előforduló bőrdaganat típus kutyáknál, kialakulásának oka pontosan ma még nem teljesen tisztázott. Ezzel párhuzamosan az ivartalanítás az egyik leggyakrabban végzett sebészeti beavatkozás a kutyák reprodukív rendszerén. Számos tanulmány vizsgálta a hízósejtes daganatok kialakulásának kockázata és az ivartalanítás közötti lehetséges kapcsolatot. A disszertáció célja az volt, hogy átfogó áttekintést nyújtson a hízósejtes daganatok előfordulásáról ivartalanított és intakt kutyákban, és elemezze az elvégzett vizsgálatok eredményeit, áttekintést adva a lehetséges hipotézisekről, a kutatások módszertanáról, eredményeiről, valamint ismertesse az elvégzett kutatások korlátait, és a kutatók következtetéseit. Az angol nyelvű publikációk,

folyóiratcikkek és tudományos könyvek széleskörű áttekintésén keresztül a kutatók által felállított hipotézisek széles skáláját vizsgáltuk meg. A kutatók hipotézisei a nemi hormonok védő hatásától, a társadalmi-gazdasági perspektívákon át a hízósejtes daganatok magasabb életkorban bekövetkező fokozott előfordulásáig terjedtek, amit az ivartalanított kutyák gyakrabban érnek el. E vizsgálatok eredményei statisztikailag szignifikáns eredményeket tártak fel, amelyek összefüggésre utaltak az ivartalanítás és a hízósejtes daganatok kialakulása között kutyákban. Ezenkívül bizonyos fajták eltérő fogékonyságot mutattak ezzel összefüggésben. A kutatók értékes következtetéseket vontak le ezekből az eredményekből, amelyek arra utaltak, hogy a jövőbeni kutatásoknak erre az alapra kell építeniük. A vizsgálatok során tapasztalt korlátok felismerése és a kutatási tervek finomítása hozzájárulna e bonyolult kapcsolat átfogóbb megértéséhez.

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## **2. Introduction**

Sterilization, performed on both male and female dogs, is one of the most frequently conducted surgeries involving the reproductive system. In many countries, including the United States of America (where over 80% of owned dogs are castrated), and numerous European countries, the primary reason for castration is pet population control[1, 2]. While this motive is certainly valid, it is essential to consider the associated risks and benefits when deciding to perform gonadectomy on a dog.

Risks include short-term dangers, such as surgical and anesthesia complications, as well as long-term health implications, including but not limited to behavioral changes, potential incontinence, and an increased risk of developing neoplasias[3, 4]. While previous literature indicates that the risk of certain types of cancer is elevated in castrated dogs, there are other neoplasias for which the risk is decreased or absent due to the removal of the affected organ during gonadectomy.

In addition to addressing neoplastic diseases, castration also eliminates other frequently occurring disorders. For instance, it significantly reduces the occurrence of conditions like pyometra, often observed in older, intact female dogs, pseudopregnancy or unintended pregnancies[5].

This work aims to examine existing scientific literature concerning the relationship between castration and the development of mast cell tumors.

Mast cell tumors are the most common cutaneous tumors in dogs[6] and their treatment can be challenging, depending on their histologic grading and the clinical status of the patient. Needless to say, their development should be prevented, when possible, but to achieve prevention it is crucial to understand the etiology of the disease.

Existing literature on mast cell tumors, as well as other types of cancer, like lymphoma, transitional cell carcinoma, hemangiosarcoma, or osteosarcoma, indicates a correlation between an increased risk of neoplasia development and castration[2, 7–9].

Certainly, numerous factors contribute to the development of neoplasias, including genetics, environmental risk factors, age, breed, gender, and diet. Furthermore, the castration status and age at castration play crucial roles.

This complexity underscores the challenge of understanding the etiology of mast cell tumors and necessitates extensive research to comprehensively grasp the topic and contextualize the gathered knowledge. The more knowledge is available, the better veterinarians can provide

well-founded advice to owners making a decision regarding castration for their dog and the better we can work towards preventing the development of mast cell tumors.

### **3. Literature review**

#### **3.1 Mast cell tumors**

Mastocytomas, also known as mast cell tumors, are malignant neoplasias that derive from mast cells and can be found locally in the skin or systemically in the viscera of dogs, cats, and other animals. Due to the bioactive substances in their granules, mast cells play various roles in the body, including wound healing, antiparasitic activity, and the induction of innate immune responses [6]. However, these bioactive substances may also worsen the condition of patients with mast cell tumors after degranulation occurs, for example, due to mechanical manipulation during examination.

##### **3.1.1 Appearance**

The appearance of mast cell tumors may vary, as their shape can be papular, nodular, or pendunculated. The skin at the site of lesion may be erythematous, hyperpigmented or flesh-colored and can be alopecic or sometimes ulcerated. The size of mast cell tumors ranges from a few millimeters to a few centimeters. In most cases, they appear as solitary tumors, preferably on the trunk, the perineum, the limbs or on the head and neck, but sometimes multiple tumors develop simultaneously. Multiple lesions can be seen independently from each other or when the disease progresses [10].

Some locations can indicate a more aggressive behavior of the mast cell tumor, such as the nail bed, the preputial region, the scrotum, and the nasal plane [11].

Dermal or subcutaneous edema can be observed in the affected area in some instances. This can be due to the hyperhistaminemia that occurs after degranulation of mast cells [11].

There are also systemic forms of mast cell tumors, such as the visceral form where an infiltration of the abdominal lymph nodes, the spleen and the liver can be observed. In case of disseminated mastocytosis the bone marrow is involved and when mast cells proliferate uncontrollably in the bone marrow it is called mast cell leukemia. Mastocythemia is a form of systemic infiltration, where mast cells are found in the peripheral blood [11].

### 3.1.2 Secondary clinical signs

Paraneoplastic syndrome is observed in about 50% of patients as a result of mast cell degranulation.

The granules in mast cells contain various substances, including histamine, heparin, and proteolytic enzymes. Degranulation can occur due to mechanical manipulation during the physical examination of the patient and can cause the formation of Darier's sign with symptoms such as erythema, edema, and papule formation.

Other common secondary clinical signs from hyperhistaminemia include gastrointestinal complications such as ulceration of the stomach and less frequently the duodenum. Histamine stimulates the parietal cells, which leads to increased gastric acid production and gastric motility. Histamine may also damage vascular endothelium and release fibrolysin, causing necrosis of the stomach mucosa and intravascular thrombosis. In case of advanced disease, the massive histamine release can seldomly lead to circulatory collapse.

Heparin, on the other hand, can cause coagulopathies, resulting in local bleeding, anemia, hematochezia, or melena. In very severe cases, it may lead to intestinal perforation and therefore peritonitis and sepsis.

A postoperative delay in wound healing can occur after the release of vasoactive amines and proteolytic enzymes from the mast cell granules. [6, 11]

### 3.1.3 Incidence

Although mast cell tumors are more commonly observed in older dogs, with the mean age ranging from 8 to 9 years, they can also occur in very young dogs. One study researching different cutaneous neoplasias in dogs under one year of age found mast cell tumors in dogs as young as two months[12]. Another article described a case of a 4-week-old boxer with a mast cell tumor on the ventro-cranial abdomen[13].

Breeds that are predisposed to developing mastocytomas are Boxers, Pugs, Boston Terriers, Labrador and Golden Retrievers, Beagles, Weimaraner and Chinese Shar Pei[10]. Other literature also include English Bulldogs, Cocker Spaniel, Schnauzer, Staffordshire Terrier and Rhodesian Ridgebacks among the predisposed breeds and state, that mixed breeds are most affected by mast cell tumors[6].

In a recent publication, however, German Shepherds, Chihuahuas, Poodles, Yorkshire Terriers and Cocker Spaniels are described as breeds with lower risk of developing mast cell tumors [11].

Estimating the precise incidence of mast cell tumors is challenging because there are no representative population studies in veterinary medicine, as commonly conducted in human medicine[1]. Nardi et al. cite an incidence ranging from 20,9% up to 22,4%. With this incidence, mast cell tumors rank as the second most frequent malignant neoplasia, following mammary tumors [11].

#### 3.1.4 Diagnosis

As in many types of tumors, fine needle aspiration and cytology of the taken sample forms the foundation of the diagnostic investigation of mast cell tumors. The technique achieves a correct diagnosis rate of up to 96%. The samples should be stained with May-Grünwald-Giemsa or Instant Prov staining. The frequently used Diff-Quick staining is not optimal to stain the granules in mast cells.

During cytology, the presence of fine to coarse intracytoplasmic granules that stain basophilic is a characteristic feature of mast cells. However, these granules are often absent in high-grade tumors due to a loss of cell differentiation or spontaneous degranulation.

Cytology can provide crucial information for the upcoming surgery but should not be the only diagnostic tool used for grading.

Additional to the cytological examination of the tumor itself it is advised to investigate the sentinel and/or regional lymph nodes for metastases. It is important to note that false negative results are possible.

Histopathology remains the primary tool for the examination of mast cell tumors, playing a critical role in determining the appropriate therapy and providing a prognosis. While examination of the entire tumor is preferred, incisional biopsies can be valuable in case of cytoreductive therapy. In case of multiple lesions, each nodule should be sent in separately for individual examination.

Nardi et al. proposed to use both the Patnaik et al. and the Kiupel et al. grading system for histopathological grading of mast cell tumors. While the Patnaik et al. system works on a numeric scale from 1 to 3, the Kiupel et al. system divides mast cell tumors into low- and high-grade tumors.

Further diagnostics can be done with immunohistochemistry, with Ki-67 and KIT being the most frequently used markers for this method.

The tyrosine kinase KIT and its ligand SCF (stem cell factor) are responsible for proliferation, differentiation and maturation of mast cells and a mutation in the c-kit gene is



considered to be an explanation for the development of mast cell tumors, as well as a higher risk for recurrence and metastasis. [6, 11]

### 3.1.5 Staging

There are different approaches to staging of mast cell tumors, which include several factors and indicate that estimating a prognosis and determining the appropriate treatment might be more difficult than for other tumors.

While thoracic radiography and abdominal ultrasound are valuable methods for identifying metastases in many cases, they frequently prove insufficient for staging of mast cell tumors. According to Book et al., abdominal ultrasound for metastasis screening of the spleen and liver is only sensitive in 43% and 0% of the cases [14]. Thoracic radiography can be done voluntarily, but it is of lower priority, as the likelihood of lung metastases in case of mast cell tumors is low. These tumors tend to spread to sentinel lymph nodes, skin, spleen, and the liver. The risk of metastasis also depends on the differentiation of the tumor. In case of well differentiated tumors less than 10% will metastasize, while poorly differentiated tumors have a 55-95% chance of spreading to other organs and tissues [11, 15].

According to Hughes et al. CT is not sufficient to detect early stages of metastasis in the liver and spleen. While they were positive in cytological examination, they did not have an abnormal appearance in the CT [16].

As mentioned before in the diagnosis chapter, the examination of sentinel and regional lymph nodes is especially important in case of mast cell tumors. Warland et al. cited, that there was no metastasis to be detected without also finding metastasis in the sentinel lymph nodes [17]. To identify the sentinel lymph nodes, contrast ultrasound can be helpful and has an accuracy of 95% [18].

However, as of today it was not possible to establish a single standardized system for staging of mast cell tumors, according to the authors knowledge.

### 3.1.6 Treatment

There are many different possibilities for the therapy of mast cell tumors. Some of the most important ones shall be highlighted in the following chapter.

Surgery remains the most important therapeutic approach, whenever possible. As with other tumors as well, wide margins in lateral and deep orientation are important. The removal of the sentinel and regional lymph nodes is recommended [11].

As in the physical examination, the tumor should not be manipulated profusely during surgery to avoid possible degranulation and the associated secondary symptoms, that were mentioned previously.

There are some additional therapies that can be considered for mast cell tumors. Electrochemotherapy can be used in addition to surgery, if it is not possible to excise the tumor with wide margins, or as a single therapy. The electric impulses increase the access of the chemotherapeutics to the affected area, which enhances the cytotoxic effect [11].

Radiation therapy can be utilized to decrease the size of the tumor prior to surgery, postsurgical to control remaining tumor tissue, or for palliative care of the patient [10, 11]. It is also advised in case of tumors that are located in hard to operate on locations.

In those cases, the intralesional application of *Tigilanol Tiglate* can also be beneficial.

Chemotherapy has variable value according to one author [10], but can be valuable in case of progressed disease, high grade tumors, or before surgery to reduce tumor size [11].

Supportive and/or palliative treatment is done primarily by treating the secondary clinical signs described in the previous chapter.

### 3.1.7 Prognosis

While for low grade tumors that were excised with wide margins surgery is often curative, high-grade tumors can occur again and metastasize often. This underscores the significance of tumor grade in determining the patient's prognosis. Another prognostic factor is the location of the tumor. Lesions situated in the inguinal or perineal area, on the muzzle, or in the oral or nasal cavity have a higher metastasis rate compared to tumors located in other sites [10].

## **3.2 Mast cell tumors and sterilization**

Numerous authors have dedicated their research to understanding how gonadectomy influences the risk of development of various types of neoplasias. Some publications focus on specific tumors, while others concentrate on multiple tumor types simultaneously. Additionally, there is breed-specific literature where scientists have explored the impact of gonadectomy on breeds such as Golden Retrievers, Rottweilers, Labrador Retrievers, and Magyar Vizslas.

While some studies include non-neoplastic diseases and behavioral alterations as well, this thesis specifically concentrates on the connection between castration and mast cell tumors, omitting the previously mentioned topics.

A majority of the authors utilized retrospective study models for their research, drawing their data from large databases, often those of universities. These databases store extensive patient information, that reach back decades and include details like breed, age, body weight, diagnosis, diagnostic methods, castration status, and sometimes age at castration and many more.

One example of such a database is the VMDB (Veterinary medical database, [www.vmdb.org](http://www.vmdb.org)), where 26 North American universities have contributed their records [19]. Other studies sourced their data from a single hospital, such as the record system of the Veterinary Medical Teaching Hospital at University of California, Davis [2].

Large databases as the aforementioned ones provide scientists with useful information, that have been submitted from fellow veterinarians.

Regarding the data used, it is noticeable, that there are some differences in the reviewed publications. While some authors differentiated between neutered and intact patients, others also categorized the neutered group by the age the patients were castrated. Some even considered the time interval between neutering and diagnosis [2, 8, 20–22]. This differentiation is especially important in the context of the hypothesis that sex hormones may have a protective effect against tumor development, making it crucial to understand whether or not the removal of the gonads may have the possibility to have an influence on this matter [2, 8].

Several hypotheses have emerged on the basis of removal of sexual hormone-producing organs and other hormones affecting neoplasia development. Some suggest that sexual hormones have a protective effect against tumor development and progression because they have an influence on development and growth [2, 23].

Another theory suggests that there is increased LH-Receptor expression and higher LH-concentration after gonadectomy, leading to nitric oxide release and induced cell division, resulting in long-term complications, that may be avoided by gonad-sparing sterilization [20, 24].

White et al. proposed a different hypothesis, suggesting that pet owners, who are willing to have their pet sterilized might also be more inclined to have tumor biopsies performed [8]. This socio-economic perspective aligns with the critique some authors had about the data source from the large university databases. They argued, that only specific pet owners were

represented in the clientele of referral clinics, such as universities, and could not represent the general population [1, 5].

In a study that compared over 40,000 dogs based on their cause of death, the authors discovered that sterilization had a positive effect on the lifespan of dogs. Sterilized dogs tended to live longer than their intact counterparts [23]. However, they also observed that sterilized dogs were more likely to die from cancer, a disease for which older dogs are predisposed. This led to the hypothesis that sterilized dogs are more frequently diagnosed with cancer than intact dogs because they tend to reach a higher age, and the incidence of cancer increases in the older population.

With diseases like mast cell tumors, as well as other cancer types, whose etiology is multifactorial, it is challenging to differentiate between correlation and causation when examining the results of various studies in the field. Influences, including genetics, environmental factors, diet, and gender, among others, should be considered, though it is not always feasible to do so, mainly due to a lack of data in these areas in the field of veterinary medicine. However, there have been some interesting findings in the reviewed publications, which will be summarized in the upcoming paragraph. As previously mentioned, certain studies focused on specific breeds. It was observed that there was a significant increase in the risk of developing mast cell tumors in sterilized Magyar Vizslas compared to intact ones, irrespective of gender [3]. In Golden Retrievers only the increased risk of sterilized females in comparison to intact females reached significance. The dogs in those studies were grouped by their age at time of castration. The most prominent findings in Golden Retrievers were an increased incidence of mast cell tumors in late spayed female dogs with an incidence of 5,7% compared to 0% in intact female dogs. However, the study did reveal that there were no differences between neutered and intact male dogs [2, 25]. In contrast to that, the differences found between spayed and intact Labrador Retrievers and German Shepherds were not significant [25, 26]. The results of the studies that examined various breeds also indicated that spayed females were at an increased risk for developing mast cell tumors. In a study involving 252 dogs diagnosed with either grade 2 or grade 3 mast cell tumors and 1608 controls, sterilized females were found to be 4.11 times more likely to develop mast cell tumors than their intact counterparts, and this result was statistically significant. Male dogs, on the other hand, were only 1.37 times more likely to develop mast cell tumor. This difference did not reach significance. Interestingly, the same study also observed that intact female dogs were less likely to be diagnosed with mast cell tumors compared to intact males, whereas spayed females had a higher likelihood of diagnosis than neutered males [8].

A study which reviewed the connection of reproductive capability and life span found that some neoplasias were more common in sterilized dogs, including transitional cell carcinoma, osteosarcoma, lymphoma and mast cell tumors, while melanomas and mammary cancer were found less commonly [23].

Overall, the results of the various studies indicate that sterilized dogs are more susceptible to developing mast cell tumors than intact ones. Nevertheless, it is essential to consider the different parameters and put them into perspective, which can be challenging. Breed-specific studies may not be generalizable to the entire dog population, given the variations in the results among breeds. However, they still provide valuable insights into specific breeds, benefiting practicing veterinarians and breeding associations, among others.

These findings can also guide further research aimed at understanding the etiology of mast cell tumors and exploring new treatment approaches.

### **3.3 Other types of tumors and sterilization**

As mentioned in the previous chapter on mast cell tumors in connection with sterilization, several studies encompassed multiple cancer types in their research. This chapter provides a brief summary of the findings to give an overview how the development of other tumors is associated with castration.

The reviewed publications primarily addressed hemangiosarcoma, lymphoma, osteosarcoma, and mammary gland tumors.

Regarding hemangiosarcoma the results varied. In one study that examined Golden Retrievers, a significant increase in the risk of developing hemangiosarcoma was observed only in late-neutered females compared to intact or early-spayed females. No such difference was observed in male dogs. The incidence of hemangiosarcoma in females neutered above 12 months of age exceeded that of intact females or females neutered under 12 months of age by four times. The same study also explored the incidence of lymphosarcomas and found a significant deviation in males neutered under 12 months of age, with a threefold increase in incidence [2].

In Labrador Retrievers there were no significant differences found in the risk of development of lymphosarcoma or hemangiosarcoma regardless of age at gonadectomy, gender, or spay-status. Notably, in contrast to the previous findings concerning hemangiosarcoma in Golden Retrievers, this study did not identify any significant differences between spayed or intact dogs [25].

The in the previous chapter mentioned study that examined Magyar Vizslas, also investigated the risk of developing hemangiosarcoma and lymphoma. They found a ninefold increase in the risk of hemangiosarcoma in spayed females Vizslas compared to intact females. The dogs in this study were categorized by their age at castration, with early-neutered dogs castrated at under 12 months of age and the late-neutered group consisted of dogs spayed at over 12 months of age. In case of female dogs, the increase in the risk of developing hemangiosarcoma reached significance in both groups. However, in male dogs only those spayed at over 12 months of age had a significant increase in risk compared to intact dogs. The significance was not reached when combining the two age groups.

The authors did not differentiate by gender in case of lymphoma, but they did find a significantly higher risk for neutered dogs compared to intact ones. The increase was 4.3 times higher when combining all groups for age at gonadectomy [3].

Another intriguing finding emerged from authors who investigated the risk of non-Hodgkin's lymphoma in dogs and humans. They hypothesized that the risk of developing lymphoma was lower for intact female dogs, given that this disease also exhibits a lower incidence in women than in men. The study's results aligned with the hypothesis. They discovered that intact female dogs had a reduced risk of developing lymphoma compared to the general population. Furthermore, this difference between males and females was nearly equalized once the female dogs were sterilized [27].

Research on Rottweilers revealed that their risk to develop osteosarcomas was significantly affected by the age at which they were gonadectomized. The authors noted that for each additional month of being sexually intact, there was a 1.4% decrease in the risk of developing osteosarcoma. Furthermore, their results indicated that castrated males had a 3.8 times higher risk, while the risk of developing osteosarcoma in females was increased 3.1 times compared to intact Rottweilers.

In case of mammary gland tumors, authors had differing opinions. A systematic review on the topic of the influence of gonadectomy on mammary cancer argued that the evidence from previous studies was weak. This was because they did not consider factors such as the age at gonadectomy, the time interval between castration and diagnosis, and the administration of ovarian steroid derivatives [28].

The mentioned previous studies found that when female dogs were spayed before their first estrus, the risk for developing mammary gland cancer is almost completely eliminated. However, the risk increases with each estrus cycle the dog undergoes. The lifetime risk for a female dog spayed before the first estrus is 0,5%, while the risk increases to up to 26%

after the second cycle [29]. Several authors who reviewed the initial studies argued that the evidence was not weak, but that any limitations were due to the circumstances of available veterinary research and the veterinary literature in general [1, 5].

In conclusion, these studies provide valuable insights for making informed decisions about dog castration and serve as a foundation for further research on the etiology and biologic behavior of various tumor types.

#### **4. Objectives and questions**

The purpose of this thesis was to consolidate the knowledge from relevant publications regarding the difference in mast cell tumor development between sterilized and intact dogs. For this purpose, we gathered information not only on the incidence of mast cell tumors in neutered and intact dogs but also included details on treatment approaches, exploration of etiology, and the limitations encountered. Our objective was to create a practical summary that can benefit practitioners, dog owners, and other interested parties.

As mentioned earlier, the objectives and hypotheses explored in the reviewed literature encompassed various research areas.

Authors primarily sought to contribute their acquired knowledge to elucidate the etiology of mast cell tumors, at least to some extent. Investigating the extent to which sterilization may cause, rather than merely correlate with, the development of mast cell tumors was another focal point in this field of research. Additionally, developing new approaches for the treatment of mast cell tumors and applying the acquired knowledge to facilitate decisions regarding when and whether to neuter were common objectives in numerous publications.

This chapter aims to provide a summary of the objectives, questions, and hypotheses presented in the reviewed literature. With the intention of achieving this, literature focusing on mast cell tumors and other cancer types was reviewed.

##### **4.1 Objectives of the reviewed publications**

Determining the incidence and risk factors of the development of mast cell tumors took a major part in the aims of various studies. Authors anticipated to apply the obtained findings on clinical work and further improve early recognition and possible prevention of mast cell tumors [30].

Breed-specific studies, for instance, focused on popular pet breeds, breeds essential in public services such as military or police dogs, or breeds significant as service dogs aiding individuals with diverse disabilities and medical conditions [2, 25, 26].

By concentrating on these particular breeds, their aim was to assist attending veterinarians, owners, and caregivers of these dogs in making informed decisions regarding when and whether to neuter their dogs and bringing awareness to potential predisposing factors for mast cell tumors.

Another goal of the breed-specific studies was to support breeders and kennel clubs of the given breed in identifying suitable breeding pairs and determining diseases that the breed is predisposed for. This information can be particularly valuable for establishing standardized breeding examinations and providing guidance to prospective dog owners when considering adoption or purchase of a dog of that breed [3].

#### **4.2 Hypotheses regarding the etiology of mast cell tumors**

De la Riva et al. proposed the hypothesis concerning microsatellite instability and the protective effect of estrogen against this mechanism. They argued that estrogen inhibits the activation of cancer cells, particularly those that are positive for microsatellite instability, a mechanism found in human colon cancer. With the removal of estrogen-producing organs and the subsequent decrease in estrogen concentration, this protective effect diminishes, potentially activating cancer cells and elevating the risk of developing colon cancer in humans. Adopting this hypothesis to veterinary medicine, the authors suggested that neutering before the first estrus cycle might not lead to an increase in the risk of developing mast cell tumors or hemangiosarcoma, since the sensitization of cells with neoplastic potential has not yet occurred.

The authors maintained that the findings in their study supported this hypothesis, as they observed a 5,7% incidence of mast cell tumors in female dogs spayed after 1 year of age, compared to the 0% incidence in intact females.

According to the authors, the increase in incidence in late-spayed females could be attributed to the missing protective effect of estrogen after sterilization, leading to the activation of potential cancer cells, that are susceptible to microsatellite instability.

As this study was breed specific including solely Golden Retrievers further research with other breeds or mixed breed dogs is needed to verify the hypothesis. The authors suggested



that factors such as gender, gonadal hormone influences, and age at gonadectomy should be taken into account for future research [2].

White et al. presented three distinct hypotheses in the discussion section of their publication. The first closely aligns with the approach from de la Riva et al., suggesting that sexual hormones may have a potential protective effect against the development of certain types of tumors, including mast cell tumors. They support their argument by noting a study that reported the presence of estrogen and progesterone receptors in mast cell tumors. However, they also acknowledge that researchers conducting another study were not successful in finding estrogen receptors in these tumors. White et al. conclude that further research is necessary, and that their study can offer the required preliminary data.

Their second hypothesis introduces a socioeconomic perspective, proposing that pet owners, who are willing to have their pet sterilized might also be more inclined to have tumor biopsies performed. This theory corresponds with the often-cited limitations of studies using large databases from referral hospitals, that are second or third in line of patient care and only represent those patients owned by people that are willing and able to provide extensive diagnostics and treatment for their pets.

Their third and final hypothesis suggests that sterilization is not the direct cause of the increased risk of mast cell tumor development but rather serves a “surrogate marker”. As previously demonstrated, spaying increases the risk of obesity, while on the other hand obesity is a known predisposing factor for the development of mast cell tumors [8].

This could also be related to the findings of Hoffmann et al., who noted that sterilized dogs tend to live longer than intact ones. The researchers hypothesized that due to the longer life span of castrated dogs, the occurrence of diseases, that are more commonly seen in older individuals, increases in this population.

Another hypothesis proposed by the same research team explains the etiology of tumors that are occurring at a higher rate in dogs spayed before experiencing puberty with reduced estrogen signaling, which may lead to an increased height compared to intact dogs. They support this argument with a current study in human medicine, which found increased growth to be a predisposing factor for the development of cancer [23].

### **4.3 Hypotheses regarding the treatment of mast cell tumors**

In a study that examined the presence of estrogen and progesterone receptors in mast cell tumors of dogs, researchers hypothesized that due to the growth inhibition and death of

certain cells caused by steroids, endocrine treatment might be a successful approach in the treatment of mast cell tumors. They emphasized that further research needs to be pursued to validate the hypothesis or determine whether steroids, like sexual hormones, only play a minor role in the progression of mast cell tumors [31].

Kutzler et al. put forth the hypothesis that an increase in the expression of LH-Receptors and a subsequent increase in the LH-concentration can be observed after castration. They elaborated that LH-receptors may be responsible for stimulating cell division and nitric oxide release, which may then lead to long-term health complications. During their research Kutzler et al. also revealed that mast cell tumors express LH-receptors and concluded that this may be a mechanism that can be assessed for treatment options with, for example, GnRH-agonists. They targeted the treatment approach to recurrent mast cell tumors and aimed to extend the survival time of affected dogs. Additionally, they proposed that gonad sparing sterilization might be an effective method to extend the health of patients while still preventing reproduction [20].

## **5. Materials and methods**

Publications were obtained through different search engines. The major source of literature was Google Scholar, followed by the National Library of Medicine (“PubMed”) and ResearchGate. Online libraries like the Wiley Online Library were consulted, as well as scientific books and journal articles.

The initial keywords used included “Mast cell tumors”, “sterilization”, “intact”, “canine”, “dog”, “mastocytoma”, “gonadectomy”, “castration”, “spay”, “neuter”, “ovariectomy”, “ovariohysterectomy”, “tumor”, “neoplasia”, among others and various combinations thereof. Furthermore, additional related literature was found through the bibliography of the already reviewed publications.

The literature was then screened for hypotheses, objectives, methods, results, and limitations that were faced during research. The obtained knowledge was summarized to create an overview of the available data.

Subsequently, the author transmitted the gained information from the reviewed literature into this thesis.

## **6. Results**

### **6.1 Mast cell tumors**

In the majority of the reviewed publications, the castration status could at least partially be associated with the incidence or risk of developing mast cell tumors in certain genders and age groups at sterilization.

One of the few studies, where no correlation was found was done by Hart et al., who examined mast cell tumors, among other diseases, in German Shepherds. They discovered that “neutering at any age period was not associated with any evident increase in cancer occurrence above the level of intact males”. The same results came back for the investigation of female dogs. The cancer types examined in this study were mast cell tumors, lymphosarcoma, hemangiosarcoma, and osteosarcoma. For the study they categorized the dogs by age at castration in 4 different groups for each gender. Starting with castration at the age of under 6 months, 6 - 11 months, 1 year (12 - 23 months) and lastly 2 - 8 years. The reason they excluded dogs over the age of 8 years, was that they assumed that the effect of castration would subside and be overshadowed by other factors that are more common in higher ages, such as inflammation.

The results showed a low incidence in mast cell tumors in German Shepherds in general. While 0,44% of the intact males and 1,04% of the females castrated between 2 - 8 years were diagnosed with mast cell tumors, all other groups for age at castration and the intact females had a 0% incidence of these tumors and none of the results reached significance for the difference between spayed and intact dogs [26].

De la Riva et al. researched the incidence of mast cell tumors, hemangiosarcoma and lymphosarcoma in sterilized and intact Golden Retrievers. For this purpose, they differentiated between early-neutered dogs, castrated under one year of age and late-neutered dogs, castrated over one year of age. They also examined the difference between male and female dogs.

They observed a higher occurrence of mast cell tumors in early-neutered female Golden Retrievers, with an incidence of 2,3%. The incidence was even higher at 5,7% in late-neutered females compared to the 0% in intact female dogs. According to their research, the difference between intact female Golden Retrievers and late-neutered females was significant. However, in male Golden Retrievers, there was no difference found between neutered and intact dogs [2]. In contrast, Annette Smith, DVM, who reviewed the role of

neutering in cancer development, wrote that the difference between spayed and intact female Golden Retrievers were not statistically significant [5].

The study conducted by Hart et al. examined long-term health effects of neutering in dogs and for that purpose they compared two popular breeds, the Labrador Retriever, and the Golden Retriever. The dogs were categorized by neuter status and by the age they were neutered. In contrast to de la Riva et al. they chose a narrower range, beginning at under 6 months, followed by 6 - 11 months, above 1 year and 2 - 8 years. Besides the examination of occurrence of different cancers, like lymphosarcoma, hemangiosarcoma and mast cell tumors, they also researched the effect of sterilization on joint disorders.

The data revealed that there was no significant difference in the incidence of mast cell tumors in male Golden Retrievers, regardless of neuter status or age at castration. Males that were castrated before the age of 6 months had an incidence of 3,33%, those neutered between 6 - 11 months had one of 3,23%, followed by 2,5% for males castrated at 1 year of age. Golden Retriever males that were neutered between 2 - 8 years had an incidence of 3,33% and out of 225 intact male dogs, 8 were diagnosed with mast cell tumors, which are 3,56%.

In case of female Golden Retrievers, the differences between spayed and intact dogs reached significance in certain groups. While 0% of intact female dogs were diagnosed with mast cell tumors, the group for females spayed under 6 months of age reached significance with an incidence of 2,94%. Females that were spayed between 6 - 11 months had an incidence of mast cell tumors of 1,23%, and this did not reach significance. For the remaining two groups the difference reached significance with 3,13% for females spayed at 1 year of age and 5,68% for females spayed between 2 - 8 years of age.

In comparison, Labrador Retrievers of neither sex had a significant increase in the occurrence of mast cell tumors. This includes that none of the age groups stood out in that respect [25].

White et al. conducted research on cutaneous mast cell tumors and their connection with neuter status, breed, and body size, and other factors. In terms of the neuter status, they investigated multiple breeds including mixed breed dogs rather than focusing on a single one.

For this purpose, they categorized dogs based on their sex and their neuter status. The results of the comparison between spayed and intact females were highly significant, indicating that spayed females were 4.11 times more likely to be diagnosed with mast cell tumors than intact females. In male dogs, the significance was not as pronounced, with a p-value of 0.14,

compared to the p-value of  $<0.001$  in female dogs. The results showed that neutered male dogs were 1.37 times more likely to develop mast cell tumors than intact males.

Comparing intact dogs by gender revealed that females were less likely to develop mast cell tumors. However, the comparison between castrated dogs of the two genders revealed that females were 1.48 times more likely to be diagnosed with mast cell tumors [8].

Zink et al. researched the risk of development of various cancer types in Magyar Vizslas. Among others, they examined mast cell tumors, lymphosarcoma and hemangiosarcoma. As discussed in the review of the other publications they also categorized dogs by their age at castration. Beginning with dogs that were sterilized at under 6 months, followed by the 7 - 12 months category and the dogs that were castrated at the age of over 12 months. However, for the examination of mast cell tumors, they did not distinguish male and female dogs in those categories.

Nevertheless, they differentiated by gender, when not accounting for the different age categories, but did not find any significant difference between male and female Magyar Vizslas.

Looking at the results for the distinct age groups, it can be observed that all of them had a significantly higher risk of developing mast cell tumor than intact Magyar Vizslas.

Dogs neutered under the age of 6 months were 2.8 times more likely, those castrated between 7 - 12 months were 2 times more likely, and those sterilized over 12 months of age were 2.5 times more likely to be diagnosed with mast cell tumors. All of these results reached significance with p-values ranging from  $<0.001$  ( $<6$  months and  $>12$  months) to 0.03 (7 - 12 months) [3].

A study conducted by Shoop et al. aimed to assess the prevalence of mast cell tumors of the English dog population in order to gain more knowledge about local circumstances regarding this disease. Their results were contradictory to other reviewed publications and studies. While they also found an association between mast cell tumors and dog sterilization, they discovered that sterilized individuals were less likely to develop those types of tumors compared to intact dogs. This result was highly significant, with an odds ratio (OR) of 0.1 for neutered dogs compared to intact ones and a p-value of  $<0.001$ .

Their statistics revealed that 71% of the dogs with mast cell tumors, that were included in this study were neutered. However, they noted that the number for entire dogs might have been underestimated. The discrepancy was due to the system from which they obtained their data, which updated promptly without notification when the neuter status of a dog was changed within it.

Hoffman et al. examined reproductive capability in association with life span and cause of death in dogs. While they researched many different factors, they also found mast cell tumors to be more common in sterilized than intact dogs [23].

In summary, it is noteworthy that the majority of studies indicated an association between sterilization and the development of mast cell tumors, to varying degrees.

## **6.2 Other cancer types**

As mentioned earlier, some of the previously discussed studies also explored various cancer types in addition to mast cell tumors. A selection of their statistically significant findings shall be presented in this paragraph to provide an overview of the relationship between dog sterilization and the development of other types of cancer.

The study conducted by de la Riva et al. examined Golden Retrievers also regarding the development of hemangiosarcoma and lymphosarcoma. In case of hemangiosarcoma they found a significant difference between the incidence of late-neutered females compared to early-neutered or intact female dogs. With an incidence of 7.35% in late-neutered, 1.76% in early-neutered and 1.62% in intact Golden Retrievers, the increase in frequency was over fourfold.

In case of lymphosarcoma the results were significant only in male dogs. Intact dogs showed an incidence of 3.47%, late-neutered dogs had a 0% incidence and early-neutered dogs were significantly more affected with an incidence of 9.66% [2].

Both cancer types were also analyzed in the research of Hart et al., who compared Golden Retrievers and Labrador Retrievers. Similar as in mast cell tumors, only Golden Retrievers showed statistically significant findings, but exclusively for lymphosarcoma and not for hemangiosarcoma. The incidences were increased in the group of male dogs, which were castrated between 6 - 11 months of age (11.48%) and in female dogs of the same age group (10.98%) [25].

In case of sterilized female Magyar Vizslas the risk of development of hemangiosarcoma was increased by 9 times, which was a significant difference compared to intact females. Male Magyar Vizslas on the other hand merely reached a significant difference in dogs castrated at over 12 months of age. They were 5.3 times more likely to develop hemangiosarcoma compared to intact males.

This breed also had a significant increase in risk of development of lymphoma in sterilized dogs compared to intact dogs. All age groups combined were 4.3 times more likely to develop this cancer type [3].

In case of prostate and urinary tract cancer the results were similar in the reviewed publications.

Bryan et al. discovered statistically significant increase for the risk of development of urinary bladder transitional cell carcinoma, prostate transitional cell carcinoma, prostate adenocarcinoma, and prostate carcinoma in neutered male dogs compared to intact dogs [21].

During their research on the immunohistochemical characterization of prostatic carcinoma, Sorenmo et al. observed a significantly increased risk of neutered male dogs compared to intact male dogs. The risk was 3.9 times higher for neutered dogs [32].

Overall, it is evident that the development of cancer types other than mast cell tumors is also linked to the neuter status of dogs. Undoubtedly, further research is required to establish whether this connection is merely correlational or causal.

## **7. Discussion**

The knowledge regarding the presence or absence of differences in the occurrence of mast cell tumors in sterilized and intact dogs is valuable in various different aspects.

It not only forms the basis for further research aimed at potentially preventing mast cell tumor development to some extent but also serves as a potential starting point for understanding the etiology of these tumors.

Moreover, this knowledge can lead to the development of new treatment approaches.

In this context, it is crucial to emphasize the previously discussed hypothesis put forth by Kutzler et al. They discovered that in sterilized dogs, mast cell tumors express significantly higher amounts of luteinizing hormone receptors. This mechanism could serve as a foundation for the treatment approach involving gonadotropin-releasing hormone agonists, as GnRH stimulates the release of luteinizing hormone [20, 24, 33]. However, further research on this topic is needed to consolidate this hypothesis.

Additionally, existing studies can inform and enhance the design of future research, enabling more precise and significant results.

In the context of mast cell tumors and other cancer types examined for variations in risk between sterilized and intact dogs, future studies should consider the limitations encountered in previous research.

As mentioned earlier, the frequently utilized databases from university hospitals may not provide a comprehensive representation of the entire dog population. This is because these databases primarily include data from pet owners who seek secondary or tertiary care for their animals. It is also conceivable that pet owners with limited financial possibilities, who cannot afford the cost of pet sterilization, may face challenges in providing specialized care for their pets in the event of serious health issues, like mast cell tumors.

Another limitation researchers have to face in veterinary medicine is that there is only limited data on the surrounding factors, that have influence on disease development. Data on factors such as genetics, diet, environmental risks, and the administration of pharmacological agents are frequently omitted in veterinary studies, unlike in research conducted in human medicine. Additionally, research in veterinary medicine does not have access to population studies, like those in human medicine, that are important to determine a baseline incidence. Moreover, a distinctive aspect in veterinary medicine that researchers must consider is the option of euthanasia in pet animals. This implies that some animals may be euthanized without a definitive diagnosis, which should have been taken into account in the incidence of a disease. This also applies to animals that are treated without a definitive diagnosis, possibly because complete diagnostic methods were omitted due to financial restrictions or other reasons. It also pertains to study designs that include data from necropsy reports, as not all owners are willing or able to opt for pathological examination.

Cases where the method of diagnosis is not known should also be handled with caution when incorporating the data into the study, as it is not completely assured that the diagnosis is definitive.

As mentioned earlier, breed specific studies hold some limitations as well, as their results may not be extrapolated to the general dog population. Those studies are often conducted with the help of kennel clubs. As members of these breeding clubs constitute a distinct population, the findings may not be applicable to the broader population, much like the results derived from extensive databases maintained by university hospitals.

It is essential to take into account all existing limitations and potential unforeseen constraints when reviewing existing literature as well as designing new studies.

Additionally, factors like age at sterilization, time interval between castration and diagnosis, gender, and administration of hormone derivatives should be considered, when conducting a



study. To gain insight into the difference in the risk of developing mast cell tumors in the broader dog population, it is necessary to conduct studies that include various breeds.

Nonetheless, the current body of knowledge is advantageous for veterinarians and dog owners to take into account when making decisions regarding the timing and necessity of neutering their pets. Advantages and disadvantages of all realms should be considered carefully, including the risk of development of neoplasias.

In this scenario, the breed-specific studies also prove to be advantageous when dealing with a dog of that breed.

To conclude the findings in the reviewed literature, it is to say that there is an association between the risk of development of mast cell tumors and sterilization, at least to some extent. Results indicate that female dogs seem to be more affected by the hormonal changes that come with sterilization than male dogs.

The findings from various studies underscore the significance of the timing of sterilization, particularly when distinguishing between pre- and post-pubertal gonadectomy. This highlights the influence of the duration for which the dog has been exposed to sexual hormones.

Furthermore, carrying results among different breeds may suggest a genetic factor at play.

In summary, there is a need for additional research on the topic that takes into account the aforementioned limitations when planning new studies and incorporates data that is representative of the broader dog population, whenever feasible.

## **8. Summary**

The majority of the results indicated a significant increase in the risk of mast cell tumor development in sterilized dogs, establishing an association between the two. This relationship was notably influenced by the breed, gender and age at which sterilization occurred, with a greater impact on female dogs.

Some of the examined breeds were affected more strongly by the increase in risk, while others appeared to be less affected. Labrador Retrievers and German Shepherds, for instance, displayed minimal variations between intact and sterilized dogs, whereas the findings for Golden Retrievers and Magyar Vizslas were statistically significant.

One of the studies reported contradictory results, with sterilized dogs being less likely to develop mast cell tumors compared to intact dogs.

In summary, most studies suggest an association between sterilization and mast cell tumor development, with varying degrees of significance.

Understanding the differences in mast cell tumor occurrence in sterilized and intact dogs is valuable for research and treatment. However, the limitations that were faced in the reviewed literature should be considered in future research. They included incomplete data on factors like genetics and environmental risks, as well as financial constraints affecting pet care. Furthermore, while breed-specific studies may not have universal applicability, they do yield valuable insights into the unique characteristics of each breed. Veterinarians and breeders can use this information to make informed decisions when selecting breeding pairs and educating potential dog owners about a particular breed.

Nonetheless, the obtained knowledge from the reviewed literature is valuable for veterinarians and dog owners, who are in the process of making a decision regarding the timing and necessity to sterilize their dog.

In conclusion, there is evidence of a correlation between sterilization and the development of mast cell tumors. Future research can build upon this foundation to delve deeper into the connection between the two.

## **8.1 Összefoglaló**

A kutatások túlnyomó többsége a hízósejtes daganatok kockázatának szignifikáns növekedését találta az ivartalanított kutyákban, összefüggést ismertek fel a kettő között. Ezt a kapcsolatot jelentősen befolyásolta a fajta, a nem és az életkor amikor az ivartalanítás megtörtént, mely nagyobb hatással bírt szuka kutyák esetében.

A vizsgált fajták egy részét fokozottabban érintette a kockázat növekedése, míg másokat kevésbé érintett; így a labrador retrieverek és a német juhászkutyák esetében például minimális eltérést figyeltek meg az intakt és az ivartalanított kutyák között, míg ugyanez a golden retrieverek és a magyar vizslák esetében viszont statisztikailag szignifikánsnak bizonyult.

Az egyik tanulmány viszont ellentmondó eredményekről számolt be, az ivartalanított kutyáknál kisebb valószínűséggel alakult ki hízósejtes daganat, mint az intakt kutyáknál.

Összefoglalva, a legtöbb tanulmány, bár eltérő mértékben, összefüggést sugallt az ivartalanítás és a hízósejtes daganat kialakulása között.

Az ivartalanítás és a hízósejtes daganatok előfordulása közötti összefüggés vizsgálata kutatási és kezelési szempontból is jelentős. Azonban figyelembe kell vennünk az eddigi kutatások során felismert problémákat, korlátozó tényezőket a későbbi kutatások tervezése során. A korábbi felmérések sokszor hiányos adatokat tartalmaztak olyan tényezőkkel kapcsolatban, mint a genetika és a környezeti adottságok, valamint a kisállatok gondozását és gyógyítását érintő pénzügyi korlátok. Továbbá, bár a fajtaspecifikus vizsgálatok nem biztos, hogy univerzálisan alkalmazhatók, értékes betekintést nyújtanak az egyes fajták egyedi jellemzőibe. Az állatorvosok és tenyésztők ezeket az információkat felhasználhatják olyan döntések meghozatalára, mint a tenyész párok kiválasztása, illetve a potenciális kutyatulajdonosok oktatása során bizonyos fajtákkal kapcsolatban.

Mindazonáltal az áttekintett irodalomból megszerzett ismeretek értékesek mind az állatorvosok, mind a kutyatartók számára, akiknek együttes döntést kell hozniuk kutyájuk ivartalanításának legkedvezőbb időpontjáról és szükségességéről.

Összefoglalva, az irodalmi adatok alapján, hogy korreláció van az ivartalanítás és a hízósejtes daganatok kialakulása között. A jövőbeli kutatások feladata a kettő közötti kapcsolat, és az ok-okozati viszonyok megismerése és megértése.

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I hereby confirm that I am familiar with the content of the thesis  
entitled

Occurrence of mast cell tumors in intact and neutered dogs - Literature Review  
.....

..... written by Katrin Wansing.....

(student name) which I deem suitable for submission and defence.

Date: Budapest, 16 day 11 month 2023 year

  
.....  
DR SILVIA FARKAS  
..... Supervisor name and signature

Obstetrics and Food Animal Medicine Clinic  
.....

..... Department