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Prognostic factors and complications attributed to surgical resection of cutaneous mast cell tumors in 62 dogs attended in UNESP-Jaboticabal veterinary hospital from 2013 to 2019

Fatores prognósticos e complicações atribuídas à ressecção cirúrgica de mastocitoma cutâneo em 62 cães atendidos no hospital veterinário da UNESP-Jaboticabal de 2013 a 2019

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ABSTRACT: Mast cell tumors, which are neoplasms with variable behavior, from less aggressive to highly metastatic tumors, account for 16%–21% of cutaneous neoplasms in dogs. The diagnosis and grading of mast cell tumors are based on cytological analysis and histological evaluation, which facilitate appropriate planning for surgical and chemotherapeutic treatment. Surgical resection with safety margins of 2–3 cm is considered the best therapeutic option; however, postoperative complications, such as delayed healing, necrosis, suture dehiscence, and occurrence of seroma, are reported. It is essential to understand the biology of mast cell tumors because prognostic factors directly influence the efficacy of the treatment and the quality of life of the patient. Here, we conducted a retrospective study of dogs submitted to surgical resection of cutaneous mast cell tumors, and analyzed the prognostic factors and occurrence of postoperative complications. The results showed that low grade mast cell tumors were associated with a lower occurrence of ulceration, metastasis, recurrence, lack of need for adjuvant therapy, and occurrence of paraneoplastic syndrome compared to those of a higher grade. We also compared the association between demanding or compromised margins with the presence of postoperative complications. The results showed that high grade mast cell tumors have a greater metastatic potential and that the presence of neoplastic cells in the adjacent tissues leads to a greater malignancy and postoperative complications.

KEYWORDS: Mast cell; neoplasm; oncology.

RESUMO: Mastocitomas representam de 16 a 21% das neoplasias cutâneas em cães. São neoplasmas com comportamentos variáveis, de tumores pouco agressivos até altamente metastáticos. Seu diagnóstico é baseado na análise citológica e avaliação histológica para determinação da graduação, sendo possível realizar o adequado planejamento do tratamento cirúrgico e quimioterápico. A ressecção cirúrgica com margens de segurança de 2 a 3 cm é considerada a melhor opção terapêutica, entretanto, são relatadas complicações no pós-operatório como retardado na cicatrização, necrose, deiscência de sutura e ocorrência de seroma. É indispensável o entendimento da biologia do tumor, pois fatores prognósticos implicam diretamente na eficácia do tratamento e na qualidade de vida do paciente. O presente trabalho objetivou a realização de estudo retrospectivo de cães submetidos à ressecção cirúrgica de mastocitoma cutâneo, com análise dos fatores prognósticos e da ocorrência de complicações pós-operatórias. Foi possível observar que os mastocitomas de baixo grau apresentam menor ocorrência de ulceração, metástase, recidiva, ausência de necessidade de terapia adjuvante e ocorrência síndrome paraneoplásica comparativamente aos de maior grau. Foi possível ainda, a comparação da associação entre margens exíguas ou comprometidas com a presença de complicações pós-operatórias. Os resultados demonstraram que mastocitomas de alto grau tem maior potencial metastático e a presença de células neoplásicas nos tecidos adjacentes acarretam em comportamento de maior malignidade e complicações pós-operatórias.

PALAVRAS-CHAVE: Mastócitos; neoplasia; oncologia.

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INTRODUCTION

Mast cell tumors are formed by neoplastic proliferation of mast cells that undergo differentiation in the cutaneous, subcutaneous, and mucous tissues. These tumors represent 16%–21% of cutaneous neoplasms in dogs, and have variable behavior, from slightly aggressive to highly metastatic tumors (PAZZINI et al., 2016; SABATTINI; BETTINI, 2019).

The grading system for canine cutaneous mast cell tumors was determined by Patnaik; Ehler; Macewen (1984), and later by Kiupel et al. (2011). According to the histological classification based on Patnaik; Ehler; Macewen (1984), mast cell tumors can be classified into three grades: Grade I or well-differentiated, which presents cells with a well-defined cytoplasm, spherical or ovoid nucleus, rare or absent mitosis figures, cytoplasm with granules, and well-demarcated cell staining; Grade II or intermediate, characterized by moderately pleomorphic cells, rounded or pleomorphic nuclei, with intracytoplasmic granulations of varying sizes and the presence of up to two mitotic figures; and Grade III or undifferentiated, characterized by high cellularity, marked pleomorphism, prominent nucleoli, three to six mitotic figures per field, vesicular, rounded, and pleomorphic nuclei, and areas of hemorrhage, necrosis, edema, and collagen hyalinization.

The histological classification of cutaneous mast cell tumors based on Kiupel et al. (2011) is divided into two histological grades, namely high and low grade. The system is based on counting the morphological alterations in the sample, such that tumors with ≥ 3 nucleated cells, ≥ 3 bizarre nuclei in 10 higher-magnification fields, and cells with karyomegaly are classified as high grade mast cell tumors; otherwise, they are classified as low grade mast cell tumors (KIUPEL et al., 2011).

The diagnosis is based on cytological analysis and/or histopathological examination (SCARPA; SABATTINI; BETTINI, 2014; DE NARDI et al., 2018). The treatment of choice is surgical removal with delimitation of the lateral margins of 2–3 cm (including a deep margin) (GARRETT, 2014; KIUPEL, 2016). In extensive neoplasms, the use of reconstructive techniques is possible; however, these may be associated with complications such as suture dehiscence, seroma, and tissue necrosis (FIELD et al., 2015; HUPPES et al., 2016). Furthermore, cellular degranulation of tumor mast cells interferes with wound healing, aggravating the risk of post-surgical complications (ROGERS, 1996).

The behavior and progression of mast cell tumors are variable; however, the determination of the histopathological grade is crucial for an accurate prognosis. Most grade I mast cell tumors are benign, persisting for years without increasing in size or with slow growth, with the occurrence of metastasis being less than 10%. Grade II tumors have variable prognoses, with tumor metastases occurring in 5%–22% of cases and may cause death in 17%–57% of cases due to treatment failure or metastatic disease. Grade III tumors show aggressive growth and have a high potential for recurrence after surgical excision; these tumors are found in more than 80% of cases with metastasis and often lead to death (PATNAIK; EHLER; MACEWEN, 1984; BLACKWOOD et al., 2012).

Considering factors such as histopathological grade, postoperative complications, location, and tumor size, we conducted a retrospective evaluation of dogs submitted to surgical resection of cutaneous mast cell tumors, with the aim to analyze the prognostic factors and occurrence of postoperative complications.

MATERIAL AND METHODS

The medical records of canine patients treated at the Oncology Service at the Veterinary Hospital Governador Laudo Natel of UNESP Jaboticabal, from 2013 to 2019, were analyzed at the time of surgical intervention according to clinical staging. Patients diagnosed with neoplasms of lesser malignancy were followed-up for at least 360 postoperative days.

Data on age, sex, breed, and information related to the mast cell tumors, such as location, volume, and histopathological grade, were collected according to Patnaik; Ehler; Macewen (1984) and Kiupel et al. (2011), as well as associated adjuvant therapies, metastasis, reconstructive surgical technique employed, ulceration, paraneoplastic syndrome, postoperative complications and margins obtained with surgical removal. Sequentially, sample analysis was conducted using the Excel program to perform descriptive statistics.

RESULTS AND DISCUSSIONS

The histopathological grade, location, recurrence, presence of metastasis, paraneoplastic syndrome, age, breed, sex, and tumor size were considered as prognostic factors for cutaneous mast cell tumors in dogs (LONDON; THAMM, 2013). A total of 312 files were analyzed, and considering the inclusion criteria, 62 animals were selected, including 25 males (40.3%) and 37 females (59.7%). Previous literature has shown no significant difference in tumor prevalence in relation to sex (BLACKWOOD, 2012; MILLER et al., 2016; PAZZINI et al., 2016; SOUZA et al., 2018).

The mean age of the patients was 8 years, which is similar to those described by London and Thamm (2013), Pazzini et al. (2016), and De Nardi et al. (2018); however, these studies also described the incidence of cutaneous mast cell tumors in young animals, less than 1 year old.

Mast cell tumors were observed in mongrel dogs (SRD) (35.5%), American Pitt bulls (12.9%), boxers (12.9%), and labradors (11.3%) (Table 1), in line with the results of London and Thamm (2013) and De Nardi et al. (2018).

Surgical treatment of the neoplasm resulted in the removal of 78 nodules, with 48 animals (77.4%) having a single nodule and 14 animals (22.6%) having more than one nodule. Patients with more than one nodule had tumors with a higher histological grade. Scarpa; Sabattini; Bettini (2014) and Pazzini et al. (2016) reported that cutaneous mast cell

tumors can present in multiple nodules, although with a lower incidence.

Following the methodology of Souza et al. (2018) and De Nardi et al. (2018), grouping tumor sizes into < 3 cm and > 3 cm, 31 (40%) nodules were < 3 cm and 47 (60%) were > 3 cm. According to Welle et al. (2008), most tumors of lesser malignancy are 1 to 4 cm in size, while Souza et al. (2018) observed that tumors > 3 cm had fast growth and worse prognosis. In the present study, histological analysis was conducted in 74 nodules, among which, for nodules M 3 cm, 17 (23%) were of low grade and 14 (19%) of high grade, whereas for nodules > 3 cm, 22 (30%) were low grade and 21 (28%) were high grade (Table 2).

According to De Nardi et al. (2018), approximately 50% of mast cell tumors are reported in the trunk, perineal, genital, and inguinal regions, 40% in the limbs, and 10% in the head; this is consistent with the analyzed medical records, where a higher incidence of tumors was observed in the limb region (45%), followed by the chest region (24%), head (18%), and inguinal region (13%) (Table 2). Similar results were reported by Souza et al. (2018), who determined that the pelvic limbs (16.7%) were the most affected body regions, followed by the thoracic limbs (10.42%), head, and neck (9.46%).

Some authors report that mast cell tumors that develop in the mucocutaneous junctions and inguinal region are more malignant, regardless of their histological grade. Additionally, locations such as the oral cavity, head and neck, inguinal, preputial, and perineal regions are considered more predisposed to recurrence or metastasis when compared to other locations, while the worst prognosis is related to difficulties in performing surgical procedures with adequate safety margins in these locations (BLACKWOOD et al., 2012; DE NARDI et al., 2018).

Regarding surgical margins, 20 nodules (32.2%) had free margins, 8 nodules had narrow margins (12.9%), and 41 nodules had compromised margins (66.1%). De Nardi et al. (2018) mentioned that the occurrence of compromised surgical margins is associated with the presence of recurrence. Moreover, Michels et al. (2002) demonstrated that mast cell tumors that underwent surgical excision and presented compromised margins recurred approximately 12–24 months after surgery. In this sense, the work by Prado et al. (2012) shows that it is necessary to perform surgical intervention as soon as possible in cases where margins are compromised by neoplastic cells. However, the first surgical intervention offers the greatest chance of cure, as the facial planes are interrupted and there is no scar tissue to impair visualization of the margins (BLACKWOOD et al., 2012).

Exiguous or compromised margins were more frequent in higher grades of cutaneous mast cell tumors (high grade/grade II or high grade/grade III), representing 43% of all nodules (Table 2). Scarpa; Sabattini; Bettini (2014) reported that low grade/grade I mast cell tumors, excised with free margins, were not associated with local recurrences of the neoplasm. In the present study, the recurrence rate was 22.5%,

Table 1. Incidence of cutaneous mast cell tumors, according to breed, in canine patients who attended at the Oncology Service at the Veterinary Hospital Governador Laudo Natel of UNESP Jaboticabal, from 2013 to 2019.

Breed	No.	%
American Pit Bull	8	12.9
Boxer	8	12.9
Bulldog	1	1.6
American Cocker Spaniel	2	3.2
England Cocker Spaniel	1	1.6
Dachshund	4	6.4
Golden Retriever	3	4.8
Labrador Retriever	7	11.3
Pinscher	2	3.2
Poodle	1	1.6
Schnauzer	1	1.6
Shar Pei	1	1.6
Shih Tzu	1	1.6
Mixed-Breed	22	35.5
Total	62	100.0

Table 2. Association between the histopathological report and the location, surgical margins, and tumor size considering the total number of nodules investigated in canine patients that attended at the Hospital Governador Laudo Natel on the Veterinary Oncology Service at the Faculdade de Ciências Agrárias e Veterinárias, UNESP Jaboticabal between the years 2013 to 2019.

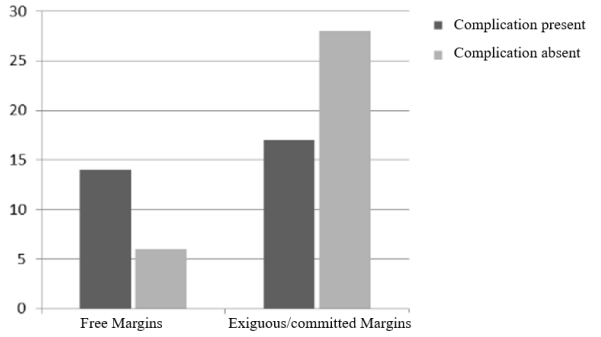
Variable	Low Grade, Grade I Low Grade, Grade II	High Grade, Grade II High Grade, Grade III
Local		
Head	9	5
Stem	8	11
Inguinal	7	3
Member	16	19
Total	40	38
Margins		
Free	16	4
Exiguous/committed	19	30
Total	35	34
Size		
≤ 3 cm	17	14
> 3 cm	22	21
Total	39	35

representing a total of 14 animals. Of these patients, 8 with high grade/grade III, 5 with low grade/grade II, and only 1 with low grade/grade I histological grading had tumor recurrence; however, the surgical margins were compromised. Blackwood et al. (2012) reported that cases with compromised margins are significantly more common compared to those with clean resections.

In the present study, the occurrence of narrow/compromised margins in the postoperative period was associated with the presence of postoperative complications, the most common of which were suture dehiscence, seroma, edema, hematoma, necrosis, slow healing and presence of pus in the wound (Figure 1). These data highlight the need to obtain wide margins in the surgical bed, as indicated in the literature (LONDON; THAM, 2013; PAZZINI et al., 2016; DE NARDI et al., 2018).

The collected data demonstrated that three animals had a delay in the wound healing process concomitant with compromised surgical margins; this may be explained by the fact that neoplastic mast cells, present in the compromised surgical margins, delay the healing process (ROGGERS, 1996; PAZZINI et al., 2016). Moreover, all patients who had suture dehiscence (n = 9) had nodules > 3 cm. According to the results found by Killick et al. (2011), larger tumors are associated with dehiscence and delayed healing.

Analyzing the total number of animals studied, lower-grade cutaneous mast cell tumors were associated with a lower occurrence of ulceration and paraneoplastic syndromes compared to higher grade tumors (Table 3), which is in agreement with Blackwood et al. (2012), London and Tham (2013), Scarpa; Sabattini; Bettini (2014), and Pazzini et al. (2016), all of whom mention that lower-grade tumors do not tend to present ulceration. According to De Nardi et al. (2018), high grade mast cell tumors have a greater metastatic potential and their neoplastic cells extend to deeper tissue, which leads to increased malignant behavior when compared to lower-grade tumors.



Source: Author's collection.

Figure 1. Relationship between the presence of free and narrow/compromised margins with the absence or presence of complications in canine patients treated at the Oncology Service at the Veterinary Hospital Governador Laudo Natel of UNESP Jaboticabal, from 2013 to 2019.

CONCLUSIONS

In this study, we establish a relationship between the prognostic factors associated with canine cutaneous mast cell tumors, and conclude that the occurrence of compromised margins and postoperative complications is more frequent in tumors with a high histopathological grade.

Table 3. Association between the variables of interest of canine patients treated at the Hospital Governador Laudo Natel on the Veterinary Oncology Service at the Faculdade de Ciências Agrárias e Veterinárias, UNESP Jaboticabal between the years 2013 to 2019 .

Variable	Low Grade, Grade I / Low Grade, Grade II	High Grade, Grade II / High Grade, Grade III
Sex		
Male	11	14
Female	23	14
Total	34	28
Age (years)		
≤ 3	2	2
4 to 7	10	7
≥ 8	22	19
Total	34	28
Ulceration		
Absent	27	13
Gift	7	15
Total	34	28
Complication		
Absent	18	11
Gift	16	13
Total	34	24
Metastasis		
Absent	32	12
Gift	2	13
Total	34	25
Relapse		
Absent	23	13
Gift	5	11
Total	28	24
Adjuvant therapy		
Absent	20	3
Gift	12	24
Total	32	27
Paraneoplastic syndrome		
Absent	24	12
Gift	8	16
Total	32	28

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