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Universidade Estadual Paulista “Júlio de Mesquita Filho”
Faculdade de Medicina Veterinária e Zootecnia

RADIOGRAPHIC INDIRECT LYMPHOGRAPHY USING LIPOSOLUBLE CONTRAST FOR SENTINEL LYMPH NODE MAPPING OF DOGS WITH CUTANEOUS MAST CELL TUMOR

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Botucatu, SP
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Tese apresentada junto ao Programa de Pós-graduação em Biotecnologia Animal para obtenção do título de Doutor

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Orientadora: Profª. Dra. Juliany Gomes Quitzan

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“Passion is what gets you through the hardest times
that might otherwise make strong men weak, or
make you give up”
Neil deGrasse Tyson

RESUMO

ALBERNAZ, V.G.P. **Linfografia indireta utilizando contraste liposoluble para mapeamento de linfonodos sentinelas em cães com mastocitoma cutâneo** Botucatu – SP. 2022. 189p. Doutorado – Faculdade de Medicina Veterinária e Zootecnia, Campus Botucatu, Universidade Estadual Paulista.

O mastocitoma cutâneo (MCTc) é uma das neoplasias cutâneas mais comuns em cães. Metástase para o linfonodo (LN) drenante é a principal rota de disseminação sistêmica do MCTc. A detecção precoce de metástases em LNs é crucial no estadiamento e tratamento correto de cães com MCTc. O LN sentinela é amplamente variado entre indivíduos. O objetivo desta tese é realizar uma revisão descritiva do sistema linfático canino aplicado ao mapeamento de LNs sentinelas de cães com MCTc. Simultaneamente, foi conduzido um estudo clínico de cães com ocorrência natural de MCTc para avaliar se o papel da linfografia indireta (LI) com óleo iodado (OI) combinado com o método colorimétrico com azul patente (AP) na detecção do LN sentinela. A principal hipótese era que a LI ajudaria o cirurgião a detectar LNs intracavitários e mais LNs que a técnica do AP. Vinte e três cães fizeram parte do estudo prospectivo. LI OI detectou 29 LNs sentinelas em 19 cães, enquanto 4 não exibiram opacificação em LNs. O AP detectou 26 LNs em 19 cães, com 4 cães não demonstrando coloração azulada em LNs. Trinta e um LNs foram resseccionados, sendo que 10 estavam metastáticos. Laparotomia foi necessária para remover LNs ilíacos opacificados em 26% dos cães. A taxa de concordância entre a LI OI e LN regionais e AP e LNs regionais foi de 82,6%. A taxa foi de 78.2% quando comparando a LI com o AP. Somente um cão apresentou o LN sentinela drenante diferente do LN regional detectado pela LI. Em um contexto clínico, a LI com OI foi responsável por aumentar o número de LNs ressecionado em 41% (29% dos LNs removidos). Não houve diferença estatística quando comparando AP e a LI no cenário base do estudo ($p=0.01855$), contudo em um cenário clínico houve diferença significativa favorecendo a LI ($p=0.0081$). A opacificação desigual dos LNs sentinelas não teve associação significativa com a presença de metástase ($p=0.2264$). O mesmo ocorreu com a coloração azul clara do LN ($p=0.6673$). Contudo, o tamanho dos LNs metastáticos foi significativamente maior que os normais ($p=0.0456$). LNs aumentados de tamanho apresente 4.6 mais riscos de estarem metastáticos que os LNs não-palpáveis ou normais ($p=0.0374$). Locais de alto risco, limites de 3cm no tamanho, invasão profunda e sinal de Darier não estavam associados com metástase locorregional ($p>0.05$). Os resultados provenientes do mapeamento de LNs sentinelas foram responsáveis por 62,5% das indicações para quimioterapia adjuvante pós-operatória, mas somente um caso teve indicação alterada somente pela LI. Contudo, 60% dos cães com doença metastática apresentaram um LN sentinela metastático intracavitário que só pode ser detectado no pré-operatório pela LI. A LI com OI pré-operatória associada com o AP é um método eficiente de detectar LNs sentinelas em MCTc realizando cirurgia curativa. LI aumenta a taxa de detecção de LNs sentinelas em um contexto clínico. O padrão de opacificação do LN sentinela não deve ser utilizado para predizer metástases.

Palavras-chave: Linfático; Metástases; Mastocitoma; Óleo Iodado, Radiografia;

ABSTRACT

ALBERNAZ, V.G.P. **Indirect lymphography using lipossoluble contrast for sentinel lymph node mapping in dogs with cutaneous mast cell tumor**. Botucatu – SP. 2022. 189p. Doctorate Degree– Faculdade de Medicina Veterinária e Zootecnia, Campus Botucatu, Universidade Estadual Paulista.

Cutaneous mast cell tumor (cMCT) is one of the most common skin cancers in dogs. Metastasis to draining lymph nodes is the main route to systemic dissemination of cMCT. Early detection of lymph node metastasis is crucial to correctly stage and treat dogs with cMCT. The sentinel lymph node (SLN) is widely variable among individuals. The objective of this thesis was to make a descriptive review of the canine lymphatic system applied to SLN mapping of dogs bearing cMCT. Simultaneously a clinical study of dogs with naturally occurring cMCT was conducted to evaluate the role of iodized oil (IO) indirect lymphography (IL) combined with patent blue colorimetric method in detecting SLN. The main hypothesis was that IL would aid the surgeon to detect intracavitary or more lymph nodes than the patent blue technique. Twenty-three dogs were enrolled in the prospective study. IO IL detected 29 contrasted SLN in 19 dogs, while 4 dogs did not exhibit lymph node opacification. Patent blue detected 26 SLN in 19 dogs and 4 dogs did not have blue-colored nodes. Thirty-one lymph nodes were resected, of which 10 were metastatic. Laparotomy was necessary to remove opacified iliac lymph nodes in 26% of the dogs. The rate of agreement between IO IL and patent blue with regional lymph nodes was 82.6%. The rate was 78.2% when comparing IL and patent blue. Only one dog had a draining SLN different from the regional lymph node as detected by IL. In a clinical setting, IO IL was responsible to increase the number of resected lymph nodes by 41% (29% of the resected SLN). There was no difference in detected SLN by PB and IO IL in the base scenario (p=0.1855), however, in a clinical scenario, there was a significant difference favoring IL (p=0.0081). Unequally opacified SLN could not be significatively associated with metastasis (p=.2264). The same occurred with light-blue color SLN (p=.6673). However, tumor size was significatively higher in dogs with lymph node metastasis (p=.0456). Enlarged lymph nodes had 4.6-fold more risk of being metastatic than non-palpable/normal-sized nodes (p=.0374). High-risk sites, 3cm size cut-off, deep invasion, and Darier's sign could not be associated with locoregional metastasis (p>.05). The SLN mapping was responsible for 62.5% of the postoperative indications of adjuvant chemotherapy, however, only one case was indicated solely by the IL. However, 60% of dogs with metastatic disease had an intracavitary metastatic SLN that could only be detected preoperatively by IL. Preoperative IO IL associated with patent blue is an efficient method to detect SLN in cMCT undergoing curative surgery. IL increases the rate of SLN detected in a clinical setting. The pattern of SLN opacification should not be used to predict metastasis.

Keywords: Lymphatic; Metastasis; Mastocytoma; Iodized Oil, Radiographic

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LIST OF ABBREVIATIONS

PB: Patent Blue

IO: Iodized Oil

IL: Indirect Lymphography

cMCT: Cutaneous Mast Cell Tumor

MCT: Mast Cell Tumor

CT: Computer Tomography

SLN: Sentinel Lymph Node

RLN: Regional Lymph Node

LN: Lymph Node

SUMÁRIO

CHAPTER 1

1. INTRODUCTION

The lymphatic draining system is the main pathway for metastasis of canine cutaneous mast cell tumor (cMCT), which makes the histological evaluation of the lymph nodes (LN) one of the central aspects of MCT staging as a predictive of distant metastatic potential (Warland et al., 2014; Lejeune et al., 2015). The LN evaluation is a prognosis factor for survival time and can also be a determinant to decide whether to pursue adjuvant chemotherapy after surgical resection of the primary cMCT (Worley et al., 2014; Lejeune et al., 2015).

Metastatic disease of the LNs is often suspected on clinical examination and confirmed on fine needle aspirate biopsy (FNA) or histology after LN sampling or resection (Lejeune et al., 2013). However, both palpation and FNA have low sensitivity and specificity for MCT metastasis (Lejeune et al., 2015; Grimes et al., 2017; Fournier et al., 2018), and histology remains the gold-standard method for diagnosis of nodal metastasis (Liptak et al., 2019). Furthermore, detection of which LN must be sampled or removed, especially when these are normal-sized or could not be palpated, can be challenging as the anatomical location does not precisely reflect the LN that drains the tumor site (Mayer et al., 2013; Worley et al., 2014).

The non-selective dissection of LNs of women with breast cancer was associated with increased postoperative morbidity and complication without a real benefit on survival time (Ball et al., 2010; Abass et al., 2018). In these human patients, a sentinel lymph node (SLN) mapping approach is preferred as it allows the detection of the most probable LN to bear a metastasis while sparing the remaining nodes (Ball et al., 2010; Beek et al., 2015; Abass et al., 2018). Although extensive lymphatic dissection in dogs and cats may result in a lower complication rate compared to humans, there is a potential risk of not removing an affected LN thus missing a metastatic focus (Qiu et al., 2018; Liptak et al., 2019). In this context, techniques to detect SLNs have been considered an alternative to the non-selective dissection of LNs in both humans and animals (Liptak et al., 2019).

The SLN is the first draining LN of a lymphatic chain to drain the tumor site, and, therefore, is a representative sample of the remaining lymphatic chain.

The challenge for SLN detection is that lymphatic draining is anatomically unpredictable and variable, especially when a neoplasm is present, whose process of tumoral lymphangiogenesis can open inactivated lymphatic vessels, altering the normal lymphatic pattern (Werner 1995; Pereira et al., 2003; Liptak et al., 2019).

Among the techniques for the detection of SLN, the intraoperative peritumoral injection of methylene blue or patent blue is the most straightforward. However, the techniques depend on the active search of the LNs by the surgeon as there is no prior information on which LN is the sentinel and must be removed. Furthermore, deep LNs located inside the abdominal cavity cannot be accessed during superficial skin surgery, even when colored, requiring a laparotomy for visual confirmation. To overcome this limitation, other techniques were developed, such as contrast-enhanced ultrasound, lymphoscintigraphy, computed tomography lymphangiography, and indirect lymphography with hydrosoluble or liposoluble contrast (Masannat et al., 2006; Somasundaran et al., 2007; Giuliano et al., 2010; Gelb et al., 2010; Layfield et al., 2011; Morton, 2012; Zengel et al., 2013; Lyman et al., 2017; Van der Noordaa et al., 2017; Qiu et al., 2018). The techniques of indirect lymphography acts in complement to the intraoperative mapping as contrasted LNs retain their normal appearance which is often hard to locate when dissecting the subcutaneous fat (Liptak et al., 2019; Brissot et al., 2016).

This thesis aims to provide a throughout review of the current literature about mast cell tumor focusing on the lymphatic metastatic process and the sentinel lymph node mapping techniques. Finally, a scientific manuscript evaluating the indirect lymphography with liposoluble contrast for radiographic sentinel lymph node mapping of dogs bearing cutaneous mast cell tumor is presented.

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CHAPTER 2