CANINE CUTANEOUS MAST CELL TUMOR

The importance of prognostic factors in the determination of surgical margins

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INTRODUCTION

The mast cell tumor (MCT) is the most common cutaneous neoplasia in dogs and presents a widely variable biological behavior. Historically 3 cm surgical margins have been recommended to achieve a correct excision, although the original source of the recommendation is unknown. The problem appears when the tumor is located in difficult areas where no large margins can be performed without aggressive surgery.

OBJECTIVES

The main objective of this research is to analyze the actual method used to determinate and evaluate the surgical margins and do a bibliographical research of other tools, as clinical or histological prognostic factors, that can help in the determination of surgical margins.

KEY DATA

INCIDENCE AND RISK FACTORS

Incidence: 7-21% to 16-21% of cutaneous tumors.
Age: 8-9 years old.
Gender: no predilection.
Breed: bulldog's descendants, labrador and golden retriever, cocker spaniels, schnauzers and shar-peis.

ETIOLOGY

Unknown. C-kit mutation allows the activation of the KIT receptor without SFC (*Stem Cell Factor*) inducing cell proliferation.

DIAGNOSTIC APPROACH

CLINICAL PRESENTATION

Solitary tumor but 10-15% of dogs present multiple nodules.
Localization: 50% trunk and perineal zone, 40% limbs and 10% head or neck.
Darier's sign: changes in size in short periods **+** development of erythema and papules.
Paraneoplasic signs: gastrointestinal ulcers or even an anaphylactic shock.

DIAGNOSTIC TOOLS

Cytology: FNA (*Fine needle aspirate*) is diagnostic for 92-96% of MCTs.
Incisional biopsy: tru-cut or punch is preferred to a large incisional biopsy.

Figure 1: MCT with erythematous surface.
Source: Courtesy of Dr. Félix García, HCV-UAB.

Figure 2: MCT on the upper lip.
Source: Courtesy of Dr. Félix García, HCV-UAB.

ACTUAL DETERMINATION OF SURGICAL MARGINS

Determination based on histological grade

The histological grade is considered to be the **best prognostic factor**, but it doesn't predict every tumor's behavior and requires a biopsy. There are two main histological grading systems (see Table 1).

TABLE 1 *COMPARISON BETWEEN THE MAIN HISTOLOGICAL GRADING SYSTEMS*

System	Grades	Selection criteria	AH	UM
Patnaik	I, II and II	From **well** to **poorly** differentiated : Extension of the affected tissue, cellularity, cellular morphology, mitotic index and stromal reaction	64% (I/II) & 75% (II)	I (5.8%) , II (16.5%)
Kiupel	LG and HG	**HG:** ≥7 mitosis; ≥3 aberrant nucleus; ≥ 3 multinucleate cells or cariomegaly presence in 10 hpf	96%	LG (14.9%)

***AH**: Agreement between histopathologists; **UM:** Unexpected metastasis; **LG**: Low grade; **HG**: High Grade; **hpf**: high power field*

Several studies have been analyzed in order to evaluate the efficiency of the histological grade to determine the margins (see Table 2). Although the results are disparate, it has been accepted that lateral margins of **1 cm for grade I and 2 cm for grade II** would be sufficient, while for **grade III >3 cm** margins are still the recommended due to the lack of a general agreement.

Determination based on tumor size

Surgical lateral margins equivalent to the **maximum diameter** of the tumor have been proved to achieve clean margins in **85%** of cases and this option allows avoiding the pre-surgical biopsy.

Histological evaluation of surgical margins

- The **efficiency** is around **76%** due to the difficulty of differentiating neoplastic mast cells from inflammatory ones.
- There is no established **histological safety margin (HSM)** since it was not possible to find a relation between the histological margins and the recurrence.
- The **recurrence ratio** depends more on the **histological grade** than on the state of the margins.

TABLE 2 *RESULTS OF THE PRINCIPALS STUDIES ABOUT CUTANEOUS MCT IN DOGS*

Study	Method	MCT	CHM Criteria	Surgical margins	Histological margins		Recurrence
Séguin *et al.* 2001	Patnaik system	60 II	>1 mm	2-3 cm	**Clean**	90%	2%
					Close	5%	33%
					Incomplete	2%	0%
					N/A	3%	50%
Michels *et al.* 2002	Patnaik system	31	---	3 cm	**Clean**	65%	5%
					Incomplete	35%	18%
Simpson *et al.* 2004	Patnaik system	3 I 20 II	>1 mm	1 cm	**Clean**	100% I 75% II	0%
				2 cm	**Clean**	100% I/II	
				3 cm	**Clean**	100% I/II	
Murphy *et al.* 2004	Patnaik system	87 I 199 II 54 III	>5 mm	3 cm	**Clean**	42%	3%
					Close	19%	5%
					Incomplete	39%	17%
					N/A	37%	N/A
							I: 1% II: 6% III:19%
Fulcher *et al.* 2006	Patnaik system	4 I 19 II	>1 mm	1 cm	**Clean**	100 % I 68% I	0%
				2 cm	**Clean**	90% II	
					Incomplete	10% II	
Schultheiss *et al.* 2011	Patnaik system	25 I 85 II 5 III	>10 mm	≤2 cm	**Clean**	96% T	0%
					Close	3% II 20% II	
Pratschke *et al.* 2013	Tumor diameter	21 I 18 II 2 III	37 LG 4 HG	> 1mm	Maximum diameter	**Clean**	85%
						Incomplete	15%
Donnelly *et al.* 2015	Histological grade	55 II 35 III	51 LG 39 HG	> 3mm	2-3 cm	**Clean**	70% LG
						Incomplete	30% LG

***CHM:** Clean histological margins; **N/A:** Unknown; **T**: total; **LG:** Low grade; **HG:** High Grade.*

USE OF OTHER PROGNOSTIC FACTORS IN THE DETERMINATION OF SURGICAL MARGINS

TABLE 3 *USEFUL PROGNOSTIC FACTORS*

Factor	Comentary
Localization, appearance, size and growth	Oral cavity, muzzle, nail bed, and preputial or inguinal zones are correlated with an aggressive behavior. **LG:** hairless solitary lesions growing slowly for months; **HG:** rapidly growing, ulcerated and pruritic lesions sometimes with small "satellite lesions". **Size** may be associated with a poorer surgical prognosis.
Breed, age and sex	Boxers and pugs tend to have well differentiated MCT unlike shar-peis and labradors. Old age and male sex correlate with ineffectiveness in radiotherapy and chemotherapy respectively.
Citological grade	The cytological grade can reach a concordance of up to 94% with the histological grade.
Clinical stage	The presence of regional lymph node or visceral metastasis is usually indicative of high grade MCT.
Proliferation markers	A mitotic index >5 with a Ki-67 x AgNORs score> 54 is predictive of MCT with aggressive behavior.
C-kit and KIT mutation	It appears to be present in 25-30% of high grade MCTs.

***AH**: Agreement between histopathologists; **LG**: Low grade; **HG**: High Grade; **AgNORs:** Argyophilic Nucleolar Organizer Regions.*

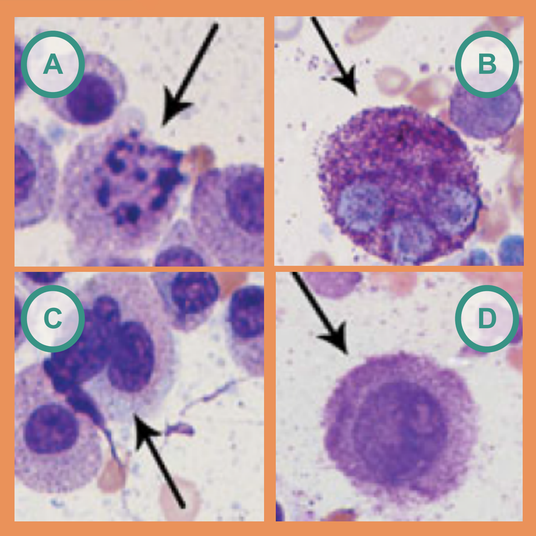

Figure 3. Cytological grade criteria : Arrows indicate mitoses (A), trinucleated cell (B), bizarre nucleus (C) and karyomegaly (D).
Source: *Scarpa F, Sabattini S, Bettini G. 2014. Cytological grading of canine cutaneous mast cell tumours. Vet. Comp. Oncol. 14(3):245–251.*

CONCLUSIONS

1. **The Patnaik system is not enough to fully predict the biological behavior, neither the probability of complete excision nor the risk of *recurrence* and involves a pre-surgical biopsy, with the implied risk, so many surgeons choose to perform 3 cm margins regardless the tumor's grade.**
2. **The determination based on tumor size supposes a risk for high grade but small dimension MCTs. However, the use of other independent histopathology factors, especially the cytologic grade, could be an alternative to the pre-surgical biopsy.**
3. **The Kiupel system together with proliferation markers would allow the detection of those histologically benign MCTs that act aggressively or help in the decision to perform a second surgery on low grade MCTs with incomplete histological margins.**