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Mast cell tumour

Mast cell tumours are neoplastic proliferations of skin mast cells. They are the most common skin tumours in the dog (between 7 and 21% of all skin tumours and 27% of malignant skin tumours), occurring mostly in older dogs (average age of onset 8.5 years) although sometimes in dogs under 1 year old[1,2,3]. Mast cell tumours are clinically very pleomorphic and consequently form part of a vast differential diagnosis. Diagnosis is based on histopathological examination of skin biopsies and immunostaining which helps considerably in giving a prognosis. Therapeutic options include surgery, radiotherapy and chemotherapy, either alone or in combination.

Epidemiology

Although no sex predilection has been reported, the Boxer (at least 30% of cases), Boston terrier, English bulldog, mastiff, Labrador retriever, Golden retriever, Shar pei, Fox terrier, Dachshund, and Weimaraner are predisposed[4,5]. Mast cell tumours in Boxers are usually well-differentiated, less aggressive and, therefore, associated with a better prognosis. On the other hand, mast cell tumours in young Shar peis under 2 years old tend to be poorly-differentiated and associated with a poor prognosis.

Clinical signs

Distribution

The main areas affected are the trunk (50-60% of cases) and hind limbs (25-40% of cases). The head is much more rarely involved (10-15%)[3,5]. Distribution varies with breed. For example, mast cell tumours in the Boxer, English setter and Boston terrier are usually found on the hind legs whereas in the Boxer and Weimaraner the condition is often multicentric from the outset.

Clinical forms

Cutaneous mast cell tumours are much more common than oral, laryngeal, tracheal, mediastinal, intestinal, bony and bone marrow forms[6]. Cutaneous mast cell tumours are highly pleomorphic.

The most common presentation is a solitary, firm, dermal nodule measuring between a few millimetres and over 10 centimetres (under 3 cm in half of all cutaneous mast cell tumours) (Fig. 37:1). The overlying skin is alopecic, erythematous, eroded or ulcerated (Fig. 37:2), more rarely depigmented[1,2,5]. Ulceration occurs in 30% of cases, quite early on in high grade mast cell tumours. Palpating mast cell tumours without due care may trigger 'degranulation' of neoplastic cells causing severe erythema and dermal papules (Darier's sign).

A multicentric, cutaneous presentation is observed in 10-15% of dogs with mast cell tumours[5,7] (Fig. 37:3). Multiple, well-circumscribed, alopecic or non-alopecic, eroded or ulcerated nodules are found, usually over the whole body. They are sometimes very pruritic.

Other rarer presentations have been reported: oedematous thickening of the throat, perineum, sheath and scrotum (Fig. 37:6-7); atypical cutaneous or subcutaneous masses (large, soft masses resembling lipomas; pedunculated masses; solid, variably-ulcerated plaques resembling lava flow) and urticaria pigmentosa (Fig. 37:8-10).

Clinical signs associated with metastasis

Every mast cell tumour must be considered potentially malignant. About 20% of mast cell tumours actually become malignant (under 10% metastasis for grade 1 and over 90% for grade III). Metastasis occurs mainly via the lymphatics. The regional lymph node is the site of implantation in 75% of metastases and hypertrophy should always be checked for. Various clinical signs can follow metastasis, most commonly to the spleen and liver. The bone marrow (mast cell leukaemia), lungs (diffuse infiltration and pleural effusion), heart, diaphragm, brain, intestine, pancreas and prostate are less commonly affected.

Paraneoplastic syndromes

Paraneoplastic syndromes have regularly been reported. They are triggered by excessive release of various substances produced by neoplastic mast cells (eutopic paraneoplastic syndrome) rather than being linked directly to tumour growth or metastasis[7,8].

Vomiting and gastrointestinal haemorrhage (e.g. haematemesis, melaena) may cause anaemia. They occur because of gastric and duodenal ulceration, sometimes leading to intestinal perforation and even peritonitis9. Histamine released by neoplastic mast cells (which contain 50 times more histamine than non-neoplastic mast cells) preferentially stimulates gastric H2 receptors, leading to hydrochloric acid oversecretion and gastric hypermotility[8]. Histamine can also affect the vascular system, triggering thrombosis and ischaemic necrosis of the stomach mucosa and submucosa.

Delayed healing can also be associated with production of antifibroblastic factors such as proteases, vasoactive amines and possibly fibroblastic suppressor factor released by macrophages (following stimulation of macrophage H1 and H2 receptors)[10].

Clotting problems (usually local haemorrhage), associated with heparin from neoplastic mast cells, can develop 5 to 20 hours after mast cell tumour excision. Antihistamine treatment is usually effective.

Other paraneoplastic syndromes are more rarely reported, for example, immune-mediated disorders (e.g. thrombocytopenia and glomerulonephritis) and severe anaphylactic shock caused by massive release of histamine and other vasoactive substances.

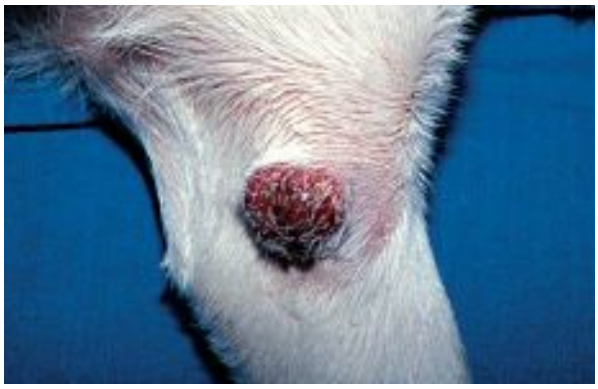
Diagnosis

The diagnosis is based on clinical appearance of lesions, systemic signs associated with metastasis and/or paraneoplastic syndromes, cytology, lesional biopsies and any additional tests appropriate for investigating the possibility of metastasis and/or paraneoplastic syndromes.

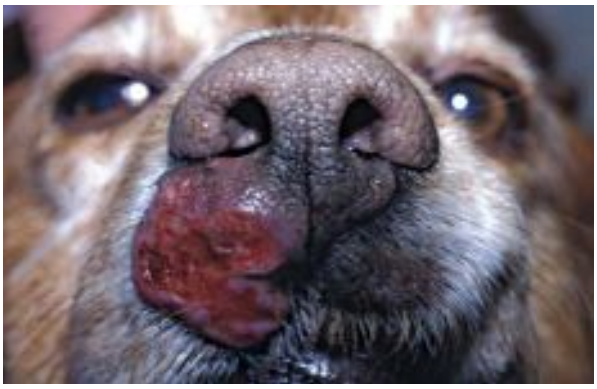
The differential diagnosis is vast. It includes mainly granulomas, Langerhans' cell tumour (chapter 36), nodular epitheliotropic mucocutaneous T cell lymphoma (chapter 38) and lipoma.

Fine-needle aspirate cytology can be used to make a diagnosis in over 90% of cases of mast cell tumour. Mast cells (round cells containing basophilic cytoplasmic granules which can mask the central nucleus (Fig. 37:11)) and eosinophils (attracted by a chemotactic factor secreted by mast cells) may be seen. In poorly-differentiated mast cell tumours, mast cell granules are rare and it is the presence of eosinophils that reinforces diagnostic suspicions. Diagnosis is often hard in such cases[7]. Cytology can lead to early, effective surgery but cannot provide a grading for the tumour or a prognosis.

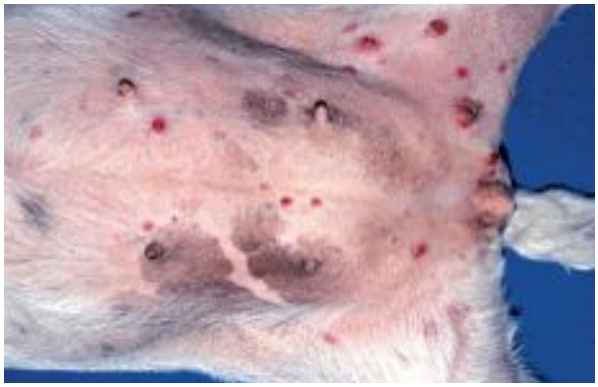
Histopathological examination of biopsies from well-differentiated mast cell tumours reveals mast cells with basophilic cytoplasmic granules, and eosinophils. In poorly-differentiated mast cell tumours, cytoplasmic granules (metachromasia) (stained with Toluidine blue) are rare and eosinophils and collagen fibre degeneration should always be looked for[4,11,12]. Histopathology can be used for grading (Patnaik grading) and to provide a prognosis (Table 37.1)[13,14] (Fig. 37:12-14). Grade 1 mast cell tumours are benign, grade III mast cell tumours malignant. Grade II cases are intermediate with about half being benign and half malignant[13,14,15].



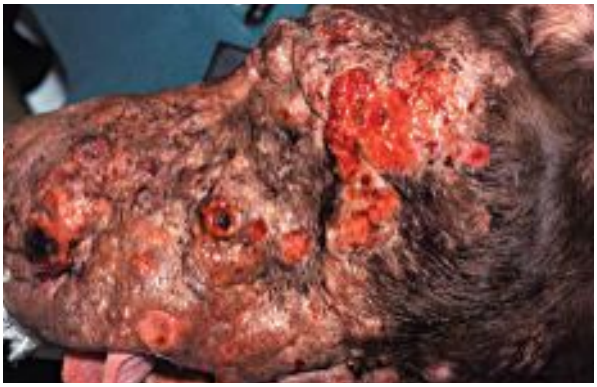
37.1: *Mast cell tumour in a Labrador retriever: firm, alopecic, eroded, solitary, dermal nodule on the medial limb.*



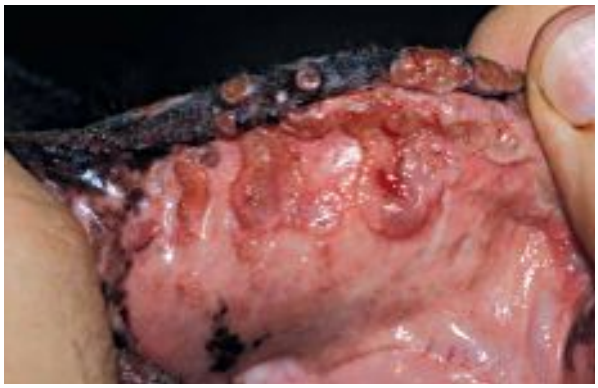
37.2: *Mast cell tumour in a Brittany spaniel: solid, eroded plaque on the nose and lip.*



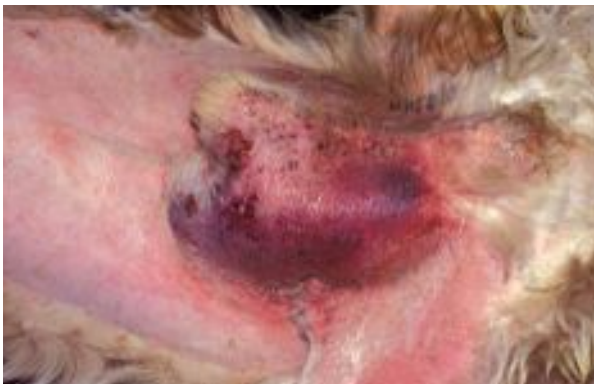
37.3: *Multicentric mast cell tumour: multiple, erythematous, alopecic, reddish papules and nodules of various sizes.*



37.4: *Multicentric mast cell tumour in a Great Dane: multiple, alopecic, eroded, facial nodules and plaques.*

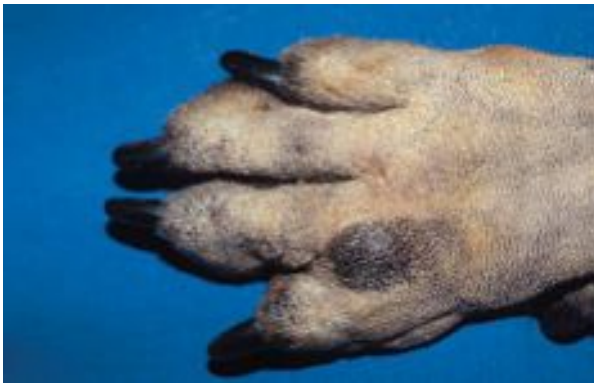


37.5: *Multicentric mast cell tumour in a Shar pei: multiple nodules and papules on the lip and labial mucosa.*



37.6: *Mast cell tumour in a Golden retriever: oedematous thickening and haemorrhage of the sheath.*

37.7: *Mast cell tumour in a Beauceron sheepdog: oedematous thickening of the throat.*



37.8: *Mast cell tumour in a Boxer: small, soft, interdigital swelling.*

Table 37.I: Grading of canine cutaneous mast cell tumours (Patnaik).

Grade	I	II	III
Incidence	35 %	45 %	20 %
Invasiveness	Dermis	Dermis and subcutaneous tissue	Dermis, subcutaneous and deeper tissue
Cellularity and cellular morphology	Paucicellular Round, monomorphic and well-differentiated cells Cells in clusters Well-defined cytoplasm Lots of average-sized granules	Increased number of cells Round or oval cells (moderate pleomorphism) Cells in groups Well-defined cytoplasm Variably-sized granules (small to very large)	Cellularité importante Highly pleomorphic Numerous giant cells Poorly-defined cytoplasm Small granules, few in number
Mitoses	None	Rare (1-2 per high power field)	Common (3-6 per field)
Stromal reaction	Low (no oedema or necrosis)	Fibrous stroma Diffuse regions of oedema and necrosis	Fibrous stroma Many regions of oedema, haemorrhage and necrosis.
Metastasis	< 10 %	30-40 %	55-95 %
1-year survival	95 %	60 %	10 %
4-year survival	93 %	44 %	6 %

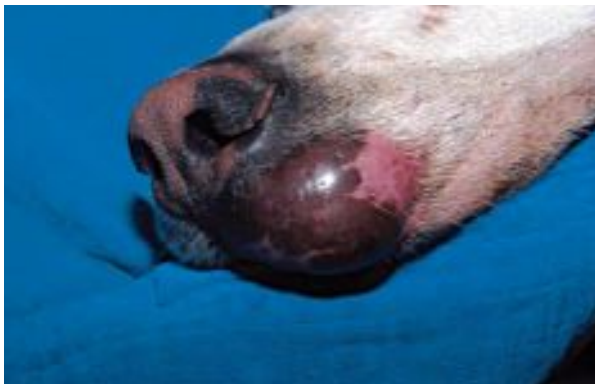
The Ki-67 proliferation index is extremely useful for differentiating the two types of Grade II mast cell tumour (Table 37.II, Fig. 37:15-16). Eighty eight per cent of grade II cases with a Ki-67 under 10% survive 2 years (benign, grade 1-II). Only 34% of cases with a Ki-67 over 10% survive 2 years (malignant, grade II-III)15.

Unlike the protein p53 marker, which has no prognostic value in mast cell tumours, the proto-oncogene c-kit markers appear from initial studies to be useful. Intense staining in membrane and juxtamembrane regions occurs in grades I and II. C-kit staining in grade III cases is less pronounced and more cytoplasmic (M.C. Cadiergues, personal observations).

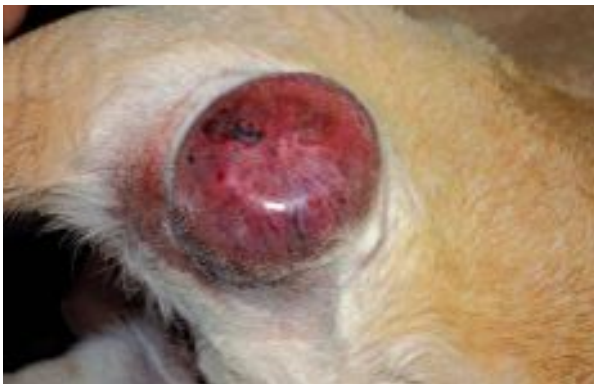
Table 37.II: prognostic value of Ki-67 proliferation index (Labadie et al).

	Ki-67 < 10%	Ki-67 >10%
2-year survival for all grades of mast cell tumour	92 %	24 %
2-year survival for grade II mast cell tumour	88 %	34 %

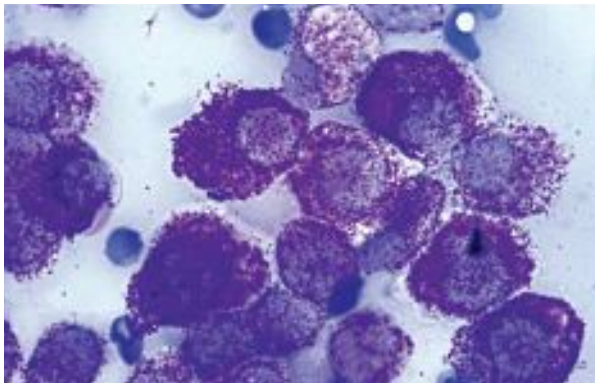
Additional tests including fine-needle aspirate of satellite lymph nodes, haematology, bone marrow aspirate, pulmonary radiography, and liver and spleen ultrasound (+/- aspirates) must be performed.



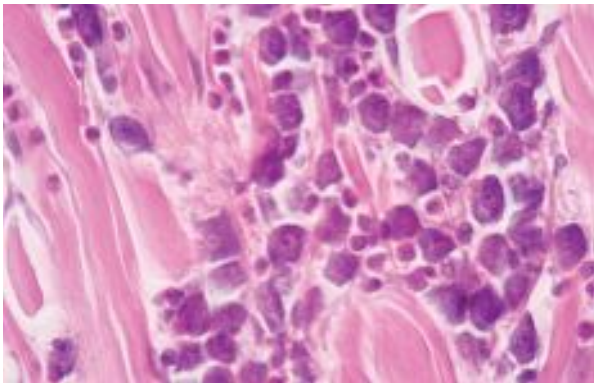
37.9: *Mast cell tumour in a Brittany spaniel: soft, alopecic swelling on the upper lip.*



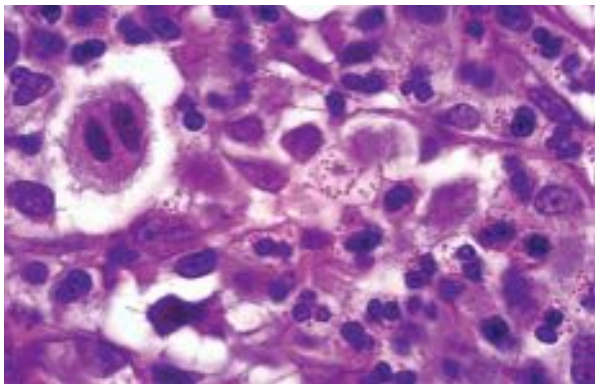
37.10: *Mast cell tumour in a Labrador retriever: soft, well-circumscribed, alopecic swelling on the lateral thigh.*



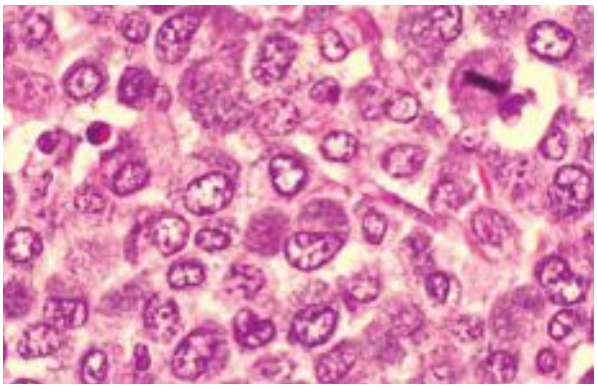
37.11: *Nodule cytology (fine-needle aspirate): well-differentiated mast cells (GGM stain) (courtesy of L. Ferrer).*



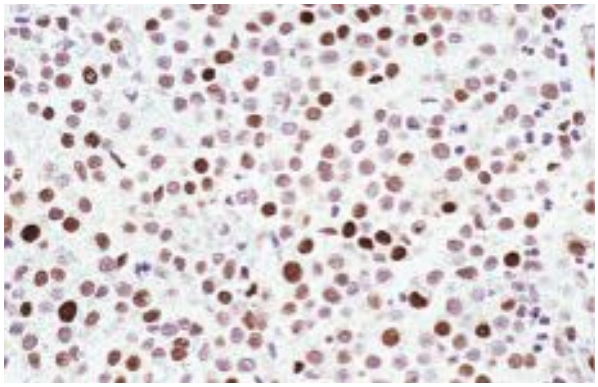
37.12: *Nodule histopathology: grade I mast cell tumour (H&E stain).*



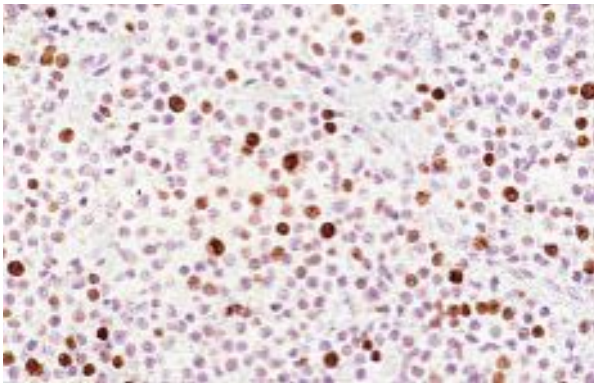
37.13: *Nodule histopathology: grade II mast cell tumour (H&E stain).*



37.14: *Nodule histopathology: grade III mast cell tumour (H&E stain).*



37.15: *Immunohistochemistry: proliferation index Ki-67 >10% (courtesy of M. Delverdier).*



37.16: *Immunohistochemistry: proliferation index Ki-67 <10% (courtesy of M. Delverdier).*

Prognosis

In addition to histopathological grade and Ki-67 value, other factors need to be considered when giving a prognosis. These include breed (mast cell tumours in Boxers are usually less aggressive, unlike those in Shar peis which, as a rule, are very aggressive), distribution (mast cell tumours in mucocutaneous regions – oral, perineal, perigenital and ungual – carry a guarded prognosis), speed of growth (mast cell tumours which have been present for several months or years are usually benign), signs associated with metastases and/or paraneoplastic syndromes, and local recurrence (recurring tumours are usually less well-differentiated and, hence, more aggressive).

Treatment

Clinical examination and diagnostic procedures can be used to determine the clinical stage of the tumour and hence, the most suitable treatment (Table 37.III). Mast cell tumours must be considered potentially malignant (20-30% metastasis and 50% post-surgical recurrence)[3,5]. Hence, the need for aggressive treatment. By separating tumour types into differently-behaving sub-groups, the Ki-67 index can now be used to determine more precisely the most appropriate treatment for grade II mast cell tumours[15,17].

Surgery

Radical excision is the treatment of choice for individual mast cell tumours. It is curative for grade I cases. A 3 cm margin of excision (all around the tumour) is required. If histopathology reveals inadequate margins of excision, further, more radical surgery must rapidly be performed.

Radiotherapy

Radiotherapy is indicated if there is infiltration of surgical margins, if repeat surgery would be too difficult, or for pre-surgical cytoreduction. Radiotherapy can even be used alone in cases where surgery is not feasible. The typical regime involves 9-12 sessions over 3-5 weeks with a total dose of 40 Gray. It is a very useful adjunctive treatment, especially for limiting local recurrence of grade III mast cell tumours[18].

Chemotherapy

Chemotherapy is indicated for mast cell tumours other than grade I and grade I-II, stage I cases (Table 37.III). Polychemotherapy is more effective than monochemotherapy (prednisolone per os, 0.5-1 mg/kg/d, or triamcinolone by intratumour injection, 1 mg/cm of tumour diameter)[5]. The most effective polychemotherapy regimes are: prednisolone/cyclophosphamide/vinblastine (78% partial or complete response), prednisolone/cyclophosphamide/vincristine/hydroxyurea (59%), prednisolone/vinblastine (47%, 20% for prednisolone alone)[17,19,20], prednisolone/lomustine (no studies published, 42% for lomustine alone)[17,21]. The authors recommend the last two regimes which combine efficacy, ease of use and moderate cost. L-asparaginase (IM injection) can be added at induction (Tables 36.IV and 36.V).

Side-effects, especially haematological, are not inconsiderable. Neutropenia is seen with vincristine (haematology profiles are necessary before each injection, especially in induction phase); acute or chronic neutropenia and cumulative hepatotoxicity with lomustine (haematology profiles to be measured before each chemotherapy session and 7 days after; transaminase and alkaline phosphatase enzymes every 2-3 months)[17,19,22].

Other treatments

The use of hyperthermia (420C to 460C, locally, for 30-60 minutes, 4 times at 7-day intervals) and local injections of distilled water (3 injections at 10-21 day intervals) appear to be effective to some degree, but further studies are needed to assess their efficacy in high grade mast cell tumours[23-26].

Table 37.III: Treatment according to clinical stage and histological grade[1,4,6,14,18,23]

Clinical stage	Definition	Primary treatment	Additional treatment
Stage I	Solitary tumour confined	Surgical excision	If margins infiltrated (all grades): repeat surgery and/or radiotherapy Grades I-II: glucocorticoids Grades II-III and III: polychemotherapy
Stage II	Solitary tumour confined to the dermis and evidence of systemic signs OR several tumours confined to the dermis, able to be removed surgically	Surgical excision (tumour +/- LN) and/or radiotherapy	If margins infiltrated (all grades): repeat surgery and/or radiotherapy If lymph node infiltrated, excision of whole lymphatic tract Grades I-II: glucocorticoids Grades II-III and III: polychemotherapy
Stage III	Multicentric skin involvement, very infiltrating tumour, liable to recur	Radical surgery or cytoreduction (tumour +/- LN) and/or radiotherapy	Grades I and I-II: glucocorticoids Grades II-III and III: polychemotherapy
Stage IV	Skin tumour with distant metastasis (e.g. spleen, liver and bone marrow)	Cytoreductive surgery and/or radiotherapy	All grades: polychemotherapy

Each clinical stage is divided into 2 sub-groups: a) systemic signs absent b) systemic signs present

Table 37.IV: Vinblastine polychemotherapy regime for treatment of canine cutaneous mast cell tumour (Lanore and Thamm)[17,19].

Week	L-asparaginase (400 IU/kg IM)	Vinblastine (2 mg/m2 IV)	Prednisolone (1 mg/kg/d) PO
1	●		Every day
2		●	Every day
3		●	Every day
4		●	Every day
5		●	Every other day
7		●	Every other day
Every 2 weeks (until week 13)		●	Every other day

Table 37.V: Lomustine polychemotherapy regime for treatment of canine cutaneous mast cell tumour[17,21].

Week	L-asparaginase (400 IU/kg IM)	Lomustine (60 mg/m2 PO)	Prednisolone (1 mg/kg/d) PO
1	●		Every day
2		●	Every day
5		●	Every day
8		●	Every day
11		●	Every other day
Every 4-6 weeks		●	Every other day

Paraneoplastic syndrome treatment

When present, paraneoplastic syndromes should always be taken into account when devising treatment regimes. Gastro-duodenal ulcers can be treated with cimetidine (4 mg/kg TID), omeprazole (1 mg/kg/d in one dose) and sucralphate (0.5 –1 g/dog TID).

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