

## **Cutaneous mast cell tumours in canines – part two: treatment**

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**Categories :** [Vets](#)

**Date :** November 3, 2014

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in the second of a two-part article, discuss treatment options for mastocytomas in dogs

**IN part one of their article the authors looked at mast cell tumours (MCT), reportedly the most common cutaneous tumour in dogs, and covered the diagnosis and staging of the condition (VT44.38). This final part continues with options for treatment.**

### **Surgery**

Surgery is generally considered to be the treatment of choice for MCTs that are localised and non-metastatic<sup>10</sup>. The authors prefer to administer antihistamines at the time of anaesthetic induction to reduce any local and systemic effects of degranulation and use 0.4mg/kg of chlorphenamine intramuscularly, which is off-licence. Administration of alternative H1 or H2-blockers would also be appropriate<sup>10</sup>.

Several studies have investigated excisional margins and found margins of 2cm laterally and one fascial plane deep is sufficient for intermediate and low-grade tumours that are less than 4cm in

diameter<sup>29, 30</sup>.

A single study also looking at intermediate and low-grade MCTs found no recurrence was documented where tumours were excised with 1cm lateral margin and 4mm deep margin<sup>31</sup>, but despite this, the authors believe further studies are required before excisional margins less than 1cm can be recommended and would always include fascia or a superficial layer of musculature deeply, rather than relying solely on a numerical margin<sup>29, 30</sup>. High-grade MCTs should be excised with a lateral margin of at least 3cm and one deep fascial plane<sup>10</sup>. Where the margins of the tumour are unclear, advanced imaging (for example, MRI) may be useful to determine tumour extent, particularly the deep margins, but it is important to appreciate that in high-grade MCTs, the risk of local recurrence and metastasis is high, so multimodal therapy should be pursued<sup>10</sup>. Where dogs have multiple MCTs, all tumours should be excised with appropriate margins and the prognosis for multiple MCTs is not worse compared with solitary masses<sup>32, 33</sup>.

Potential complications seen intraoperatively may include degranulation of the MCT and release of histamine (resulting in potentially life-threatening hypotension) or heparin (resulting in prolonged coagulation in up to a third of dogs<sup>1, 34</sup>). In the authors' experience, local coagulopathies appear to be more commonly seen in higher grade incompletely resected mast cell tumours and haemorrhage may continue for several days.

The surgeon should be aware that following surgical excision of the MCT, samples may decrease in length and width by up to 32 per cent and increase in thickness by 75.8 per cent when placed in formalin and, therefore, histopathological measurements of free margin diameters may not match those achieved surgically<sup>35</sup>. Pinning out the mass following excision may help to reduce this shrinkage.

Where surgery is not possible initially, reduction in tumour maximal diameter of up to 45.2 per cent and volume of up to 80.6 per cent can be achieved with neoadjuvant prednisolone (usually given for seven to 10 days at 1mg/ kg to 2mg/kg). This occurs because of a reduction in inflammation and the resultant decreased production of stem cell factor by fibroblasts and epithelial cells<sup>36</sup> and may be sufficient to allow surgery to be performed on a hitherto unresectable mass.

In one study, surgical planning for MCT resection after prednisolone was based on post-treatment mass size and 3cm lateral margins and one fascial plane deep reliably yielded tumour free margins; however, long-term follow-up demonstrated an overall local recurrence rate of 23.8 per cent, with the local recurrence rate for dogs with apparently completely resected MCTs being 17.6 per cent<sup>36</sup>. Interestingly, there is no evidence for the benefit of long-term adjuvant prednisolone<sup>1</sup>.

Histopathological margins are defined as completely resected (no tumour cells within 1mm of the excisional margin), complete but close (mast cells within 1mm of the surgical margin), or incomplete (mast cells at the surgical margin<sup>10</sup>).

Where low or intermediate-grade MCTs are completely resected with wide margins and no evidence of metastasis is found, further treatment is generally not indicated<sup>11</sup>, although monitoring is required. Adjunctive therapy may be appropriate if metastatic disease has been demonstrated and owners should be warned that even after apparent complete surgical excision, local recurrence may occur in up to 23 per cent of intermediate-grade MCTs<sup>10</sup>.

Where incomplete margins have been demonstrated following excision of low or intermediate-grade MCTs, local recurrence is not guaranteed: only 26 per cent of incompletely resected intermediate-grade MCTs recur<sup>37</sup>, suggesting some of the observed mast cells on the periphery are physiological (attracted by chemotaxis) and not neoplastic.

Decision making in such a situation is not straight-forward and current recommendations for such cases include monitoring of the site, follow-up radiation, or en-bloc excision of the scar with appropriate gross margins (2cm laterally and one fascial plane deep; [Figure 110](#), depending on owner and clinician preference. If macroscopic residual disease or recurrence is identified, radiation or surgery should definitely be pursued.

If the MCT is high-grade and completely excised, chemotherapy should be pursued; if excision is incomplete, chemotherapy with revision surgery or radiation therapy is the gold standard<sup>11</sup>.

## Radiotherapy

Radiation therapy is the primary choice for residual postsurgical microscopic disease if revision surgery is not an option, or where local/regional nodal metastasis is present<sup>38</sup>.

Radiation has also been used as a palliative modality and results in an improved quality of life, but is unlikely to improve survival time significantly and some authors report associated clinical signs such as hypotension and gastrointestinal ulceration secondary to mast cell degranulation<sup>1</sup>. A prospective

study of 17 dogs with measurable disease showed toxicity from radiation therapy was minimal, with the most common (n=8) acute effects being dry desquamation and alopecia and the most common (n=10) late radiation effects being alopecia and leukotrichia. No severe adverse events were observed<sup>42</sup>.

In some cases, surgery might be planned to achieve microscopic disease prior to radiation, where complete excision is not surgically possible. This may be the case in distal limbs, for example, where achieving clean deep margins are not possible because the MCT is wrapping around tendons. In such a case, there is little to gain in attempting to achieve clean lateral margins and the surgeon should aim for the removal of all gross disease and the imperative achievement of a simple primary closure.

The surgeon should collaborate closely with the radiotherapist and take numerous pre, intra, and postoperative photographs to ensure there is not a geographical miss when radiation therapy is performed.

The authors regularly place vascular clips at the lateral and deep surgical margins (particularly on the abdominal or thoracic wall, or proximal limbs), which can be visualised radiographically to aid radiation treatment planning and delivery. The authors avoid the use of any flaps or grafts that can inadvertently increase the radiation field, and strive to achieve primary closure as a straight scar to keep the radiation field to a minimum. This is particularly important in the distal limbs, where scars must be straight and longitudinal because a strip of skin must be excluded from the radiation field to prevent damage to the lymphatic system and lymphoedema<sup>10</sup>.

Finally, the provision of prednisolone and H1 or H2 blockers may help to minimise the effects of mast cell degranulation during radiation treatments<sup>10</sup>.

Radiation offers a three-year control rate of more than 90 per cent after incomplete excision of low and intermediate-grade MCTs<sup>39, 40</sup>. Disease-free intervals of greater than 40 months can be expected in dogs with low or intermediate-grade MCTs with regional lymph node metastases treated with surgery and radiation<sup>20</sup>.

## Chemotherapy

Chemotherapy is useful in several situations for the management of MCTs:

- neo-adjuvantly to reduce tumour burden prior to complete surgical excision or radiation (such as prednisolone);
- where systemic therapy is required, such as in high-grade tumours, or where metastasis has been documented or is likely, such as high proliferation marker values; or
- where microscopic disease is present and further surgery or radiation is not possible<sup>10</sup>.

First line chemotherapeutic protocols may comprise vinblastine and prednisolone, with second line therapies involving lomustine, but variations are common<sup>10</sup>. A variety of protocols have been reported and some are listed in [Table 1](#).

In one study, 61 dogs with intermediate or high-grade MCTs underwent surgical excision of the primary tumour, with or without radiation therapy. Prednisolone and vinblastine were provided and all patients were alive three years later, which is a significant improvement compared with dogs undergoing only surgical resection of high-grade MCTs and of whom only six per cent to 27 per cent were alive after one year<sup>10, 15, 41</sup>.

The advice of a veterinary oncologist should be sought before proceeding with the chemotherapeutic protocol and the clinician in charge should be familiar with the potential toxic effects of the drugs administered and the intensive protocols and patient monitoring required.

For example, vinblastine is severely irritant when injected perivascularly, and can also cause myelosuppression and gastrointestinal toxicity. Lomustine can cause severe myelosuppression and hepatic toxicity, so haematology and biochemistry should be assessed regularly. The clinician must consider the health and safety of those working in the practice and in the patient's family when formulating a chemotherapeutic protocol.

## Tyrosine kinase inhibitors

One of the most recent significant developments in the treatment of canine MCTs is the use of KIT receptor tyrosine kinase inhibitors.

Such molecules competitively block extracellular domains of receptor tyrosine kinases, which then prevents the activation and phosphorylation of the intracellular domains responsible for cell proliferation, differentiation and survival, and angiogenesis and metastasis<sup>10</sup>. Toceranib is licensed for use in recurrent, non-resectable intermediate or high-grade MCTs and masitinib is licensed for use in non-resectable intermediate or high-grade MCTs with demonstrable c-KIT mutations.

In one study assessing masitinib in non-metastatic recurrent or non-resectable intermediate or high-grade MCT, masitinib increased the overall time to progression from 75 days (placebo) to 118 to 253 days, with minimal side effects<sup>42</sup>.

In a subsequent study by the same group using a similar population, masitinib increased median survival from 322 days (placebo) to 617 days<sup>43</sup>.

Similarly, promising results have also been reported with toceranib<sup>44</sup>, which yielded a significantly longer time to disease progression in dogs with non-metastatic intermediate-grade MCTs compared with placebos. A response rate of 42.8 per cent was achieved with toceranib, which is significantly higher than the 7.9 per cent seen in placebo-treated dogs<sup>44</sup>.

A handful of studies have also looked at the use of receptor tyrosine kinase inhibitors combined with chemotherapy and radiation therapy, but further work is required and the European consensus group recommends receptor tyrosine kinase inhibitors should not be considered as first line therapy against MCTs, instead recommending they are reserved for masses where clean surgical excision is not possible, or where surgical excision to microscopic disease followed by radiation is also not possible<sup>10</sup>. This evidence-based algorithm may change as further research is completed.

## Prognosis

Generally, poorer prognosis associated with cutaneous MCTs has been reported with:

- increased histological grade<sup>50</sup>, increased mitotic index<sup>51</sup> and increased intratumoural microvessel density<sup>52</sup>;
- metastatic disease in the lymph node (although this is not the case where locoregional control is obtained, either via removal of the lymph node and provision of chemotherapy, or irradiation of the lymph node<sup>20, 53</sup>);
- tumour ulceration, erythema or pruritus<sup>32</sup>;
- incomplete excision, local recurrence, size greater than 3cm, or use of adjuvant treatment<sup>32</sup>;
- recent, rapid growth<sup>41, 50</sup>, and
- poor response to therapy<sup>50</sup>.

Proliferation markers, especially Ki-67 (a nuclear protein proliferation marker), AgNOR (argyrophilic staining of nucleolar organiser regions) and MCM7 (minichromosome maintenance protein seven), can aid in prediction of biological behaviour prognostication, which is particularly useful in Patnaik intermediate-grade MCTs because they exhibit the largest variation in biological behaviour<sup>22</sup>. Increased proliferation markers results in reduced survival and increased MCT grade<sup>54</sup>. Expression of mutations of the proto-oncogene c-KIT is also strongly correlated with recurrence of disease and shortened survival<sup>55</sup>.

Mutations in the tyrosine kinase receptor, KIT, may be seen in around 26 per cent of canine MCTs<sup>56</sup> and is associated with a higher grade of tumour<sup>57</sup>, decreased disease-free interval and decreased overall survival<sup>58</sup>.

## Summary of canine mast cell tumours

- MCTs are the most common canine cutaneous skin tumour.
- They may be associated with gastrointestinal signs, delayed wound healing or local coagulopathies.
- Multiple MCTs on the same dog may be multiple primary masses, rather than metastasis.
- Metastasis increases as MCT grade increases, with high-grade tumours metastasising in up to 96 per cent of postmortem cases.
- Diagnosis of MCT can be readily achieved with FNA cytology.

- MCTs respond readily

to treatment with surgery, chemotherapy and/ or radiation therapy.

- Receptor tyrosine kinase inhibitors also show promise as a treatment option for MCTs.

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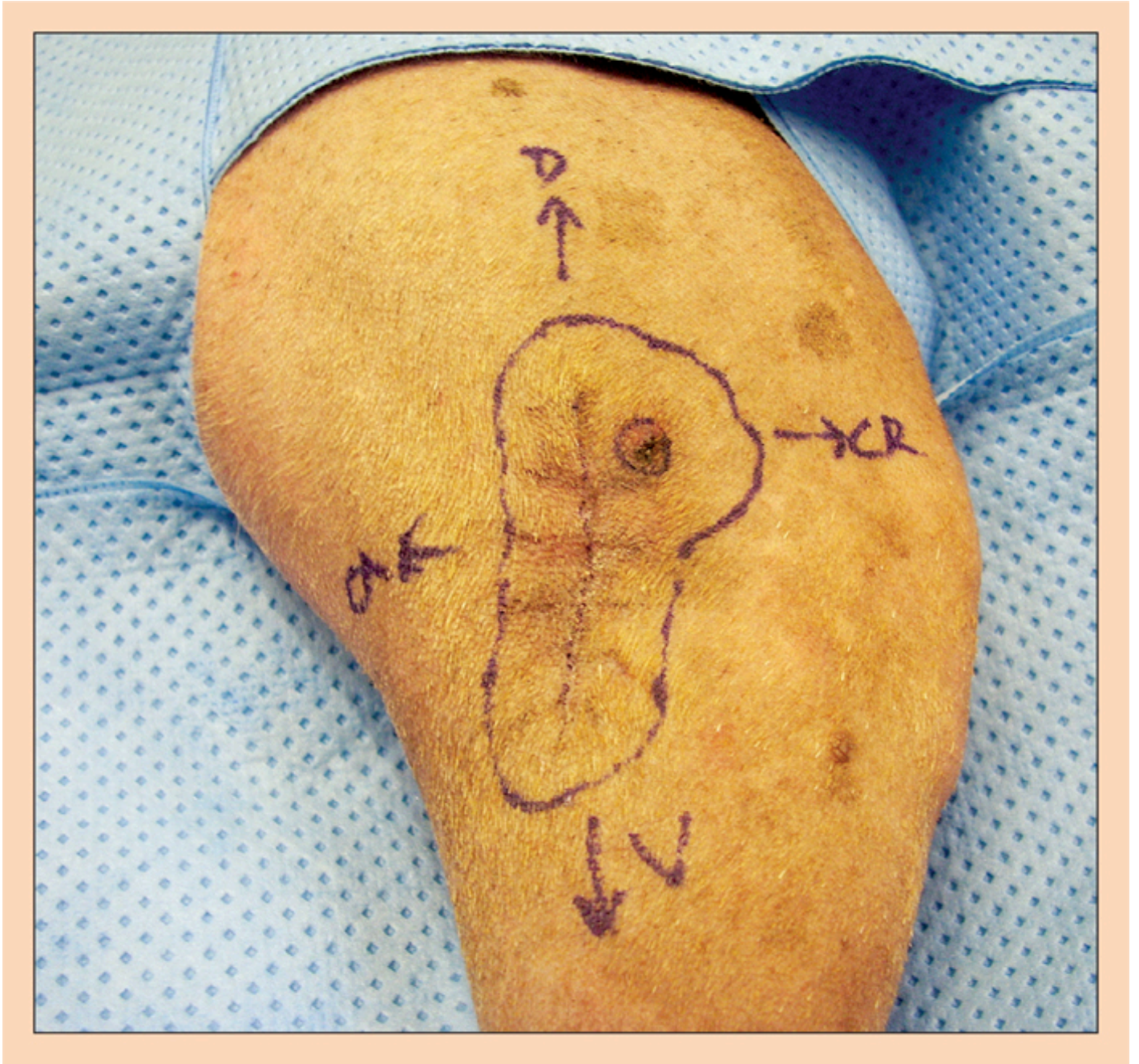
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**Figure 1.** Preoperative planning for a resection of a thin, well-healed scar from a previous mast cell

tumour (intermediate-grade) on the right stifle region of a five-year old golden retriever. There is a small circular mass cranial to the scar, cytology of which is consistent with mast cell tumour. Resection of the scar and the gross tumour is performed with 2cm lateral margins and one fascial plane deep, and yielded clean histopathological margins. The labelling on the limb (D, dorsal, Cr, cranial, Ca, caudal, V, ventral) is to aid photography in preparation for any potential postoperative radiation therapy (which was ultimately not required). To minimise contamination, the resection and (after changing gloves and kit) suturing will be performed from the site most likely to be “clean” (in this case the ventral aspect, with no gross disease) to the site most likely to be “dirty” (in this case the dorsal aspect). A new suture packet will be used for each layer, to avoid dragging potentially contaminated suture material from the dorsal to ventral sites.

Protocols	Response rate	Median survival time	Median disease free interval or time to disease progression (days)	Complications necessitating changes to treatment plan
Prednisolone/vinblastine (Thamm D H et al, 2006): microscopic disease		Not reached (65% alive at three years)	1,305	6.5% severe neutropaenia
Prednisolone/vinblastine (Thamm D H et al, 1999): microscopic and gross disease	65%	Not reached (100% alive at 573 days)	154	5% severe neutropaenia
Vinblastine, cyclophosphamide, prednisolone (Camps-Palai, 2007): microscopic disease		>2,092	865	2.8% gastrointestinal toxicity, 2.8% moderate neutropaenia, 2.8% peripheral neuropathy
Vinblastine, cyclophosphamide, prednisolone (Camps-Palai, 2007): gross disease	7/11	145	74	
Lomustine (Rassnick et al, 1999): gross disease	42%		85.5	41% grade 3 and 4 neutropaenia, 18% gastrointestinal toxicity

*\*Grade 3/moderate and 4/severe neutropaenia is defined as a neutrophil count of 500/L to 999/L and less than 500/L respectively.*

**Table 1. Some examples of chemotherapeutic protocols (including outcomes and complications) described in the literature to date\***

