Treating mast cell tumours in first opinion practice: is it time to put down the knife?

Georgie Hollis, Vet Wound Library, discusses some of the challenges faced following surgical resection of mast cell tumours and explores the potential benefits and risks associated with a non-surgical approach using intratumoural injection of tigilanol tiglate.

https://doi.org/10.12968/coan.2022.0041

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Key words: mast cell tumour | proportional margins | intratumoural injection | tigilanol tiglate | wound dehiscence | wound healing

Mast cell tumours account for up to 21% of all canine tumours presenting to veterinary practice (Shoop et al, 2015). The diverse range of inflammatory and angiogenic properties made possible through degranulation means that not only do symptoms range widely but so does the level of risk and aggression.

Grading of mast cell tumours allows for planning for surgery to clear a lateral and fascial margin relative to the potential for the tumour to spread and metastasise.

Resolution is recommended through full resection, using proportional margins and appropriate anti-inflammatories and chemo-therapeutics to reduce tumour size, as well as the risks associated with degranulation of tumour cells.

Management of mast cell tumours aims for complete resolution while preserving enough viable tissue to close the deficit according to Halsted's principles of surgical technique (Hunt, 2012) (*Table 1*) and in keeping with the aims of wound healing in *Table 2*.

Surgical approach to mast cell tumours

The standard surgical approach to treating mast cell tumours has been to excise wide 2–3 cm margins to the depth of one fascial plane (Blackwood et al, 2012; Selmic and Ruple, 2020; Saunders et al, 2021). More recently, a proportionate approach of 1 cm of grade I and 2 cm for grade II tumours has reduced the amount of lateral tissue lost to surgery while maintaining a high rate of tumour resolution.

Diagnosis and grading of mast cell tumours will guide the extent of surgery required. A fine needle aspirate at presentation allows diagnosis but does not indicate the grade and propensity for metastasis. Histology using the Patnaik grading system is the standard for grading tumour type for animals with haired skin, from grade I for the least aggressive to grade III being the most aggressive. The Kuipel system may be used alongside this to indicate if the tumour is low to highly metastatic. The combined results give a good prognostic assessment for decision making (de Nardi et al, 2022).

Location, location, location

The aims of wound management (*Table 2*) are relevant to excision of mast cell tumours but may not always be fully considered until the time of surgery. Planning for tissue deficit, tension at the

Table 1. Halsted's principles of surgical technique

Gentle tissue handling
Control of haemorrhage
Preservation of blood supply
Strict asepsis
Minimise tissue tension
Accurate tissue apposition
Elimination of dead space
Importance of rest
From Hunt (2012)

Table 2. The aims of wound management

To achieve functional and reasonably cosmetic repair
To minimise pain and distress
To achieve a rapid return to normal use
At a reasonable cost

wound site and potential complications that may lead to breakdown is essential to establish if the site is operable or not (*Table 1*).

Around 50% of mast cell tumours are located in the thorax, abdomen, perineum or inguino-genital regions, and most are at a cutaneous level. Surgical excision of mast cell tumours in these areas should be fairly straightforward. The fascia should be clearly defined and direct closure may be achievable if the margins are limited, dead space is managed and the wound is not in an area of high motion. High grade mast cell tumours in these areas require bigger margins, and thus may require more advanced methods of closure to avoid tension and close off the dead space.

Around 40% of mast cell tumours are on the limbs which offers distinct challenges for surgical excision. The fascial plane may be thin, complicated or absent. Wound complications are more likely in these areas because of the movement of tissue over joints (*Figure 1*) as well as tension at areas on the limb where the wound deficit is more than one-third of the circumference of the limb (*Figures 2* and *3*).

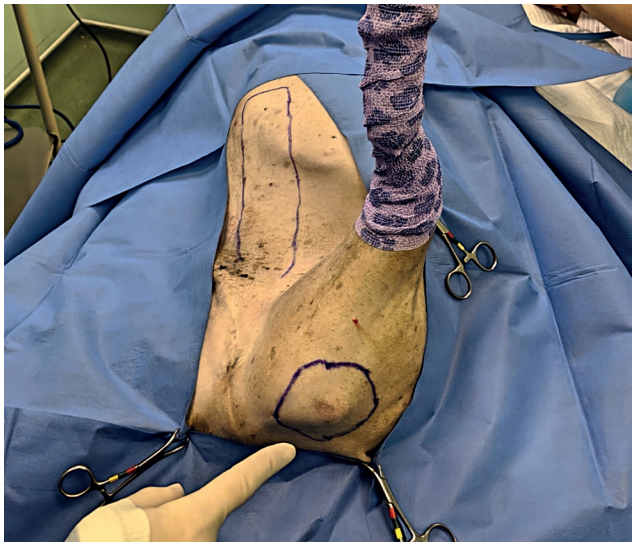

Figure 1. Mast cell tumour location relative to caudal superficial epigastric flap to be used for subsequent reconstruction.

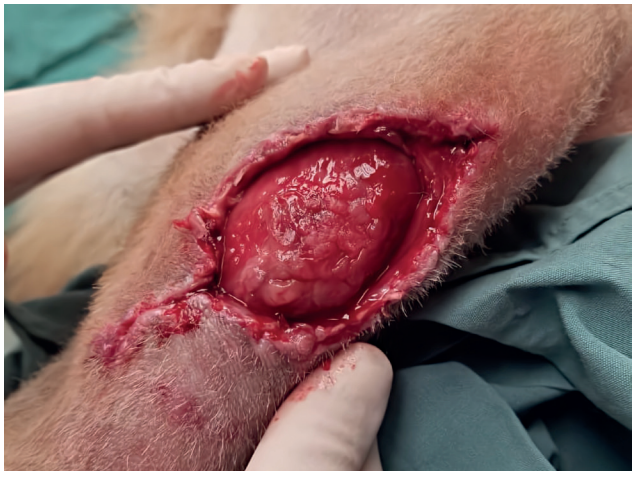

Figure 2. The wound location (over the stifle) contributed to dehiscence of the wound following en-bloc excision of a mast cell tumour. The case was managed by second intention healing over 2 months following surgery.

The other 10% of mast cell tumours arise on the head and neck. Localised mast cell tumours on the neck may be more amenable to surgical closure, either through direct apposition, advancement or local axial pattern flap. Mast cell tumours to the muzzle and periorbital regions are less common but appear to be more likely to be aggressive (Elliott et al, 2013; Garrett, 2014), and the complexity of structures in this area will make clean excision of affected tissue near impossible. A conclusion of inoperability may lead to consideration of intratumoural management with tigilanol tiglate (*Figure 4*).

Complications arising from a surgical approach

While surgery is the first line approach, subsequent wound management may be an unanticipated challenge. Advanced reconstruction may be required to close what may appear to be moderately sized wounds if the location is vulnerable once the patient is out of lateral recumbency.

Data from cases submitted for advice to the Vet Wound Library showed that 15% of 732 wound cases over a 5-year period (2017–22) were presented with postoperative wound management complications or challenges faced post tumour excision. The majority of these involved mast cell tumours, reflecting their relatively high incidence.

Associated complications included, but were not limited to, wound dehiscence post reconstruction, bandaging complications and wound chronicity where wounds became static and were non-healing at more than 6 weeks after initial surgery (*Figure 5*).

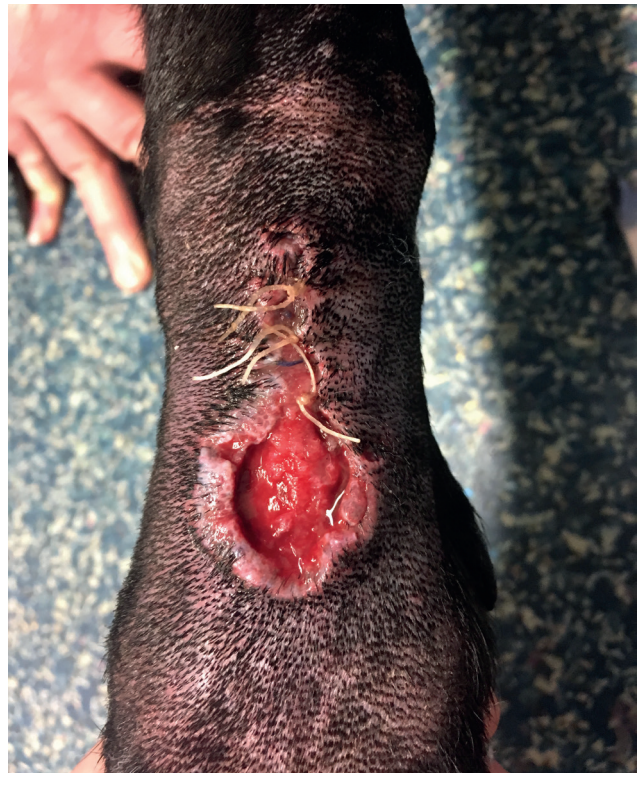

Figure 3. Distal limb wound closed post tumour excision. Sutures were removed to reduce the tourniquet effect caused by limited tissue availability.

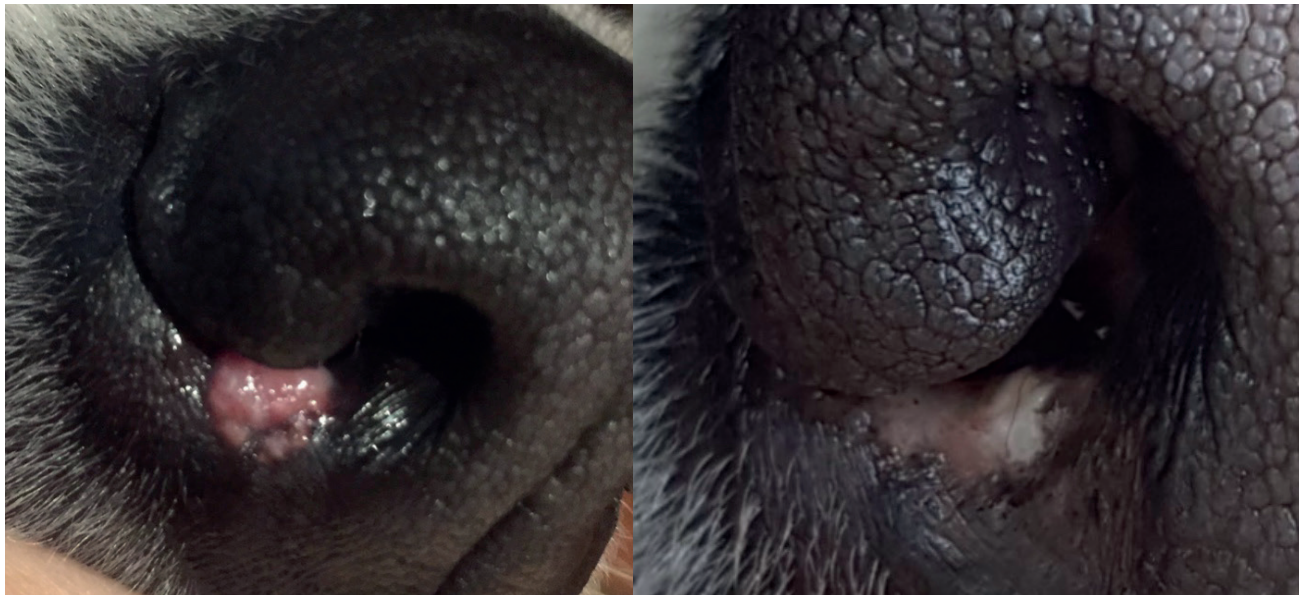

Figure 4. a. A positive diagnosis of mast cell tumour of the nares with inoperable margins resolved with one application of tigilanol tiglate. b. Complete remission was seen after 18 months.

Common factors that inhibited or led to complicated and extended healing included movement, tension at the wound site, and accumulation or lack of management of dead space, with some presenting as non-healing wounds as a result of tumour proliferation.

Commonly cited issues that may have led to complications included:

- Limited funds – client declines cytology on grounds of cost, client declines referral
- Incorrect interpretation of an advanced surgical technique of which the surgeon did not have much experience
- Lack of experience to perform more advanced surgery
- Lack of facilities or resources to perform optimal technique
- Non-compliance (contributing to excessive movement and/or bandaging complications)
- Lack of remaining funds available through insurance for specialist referral.

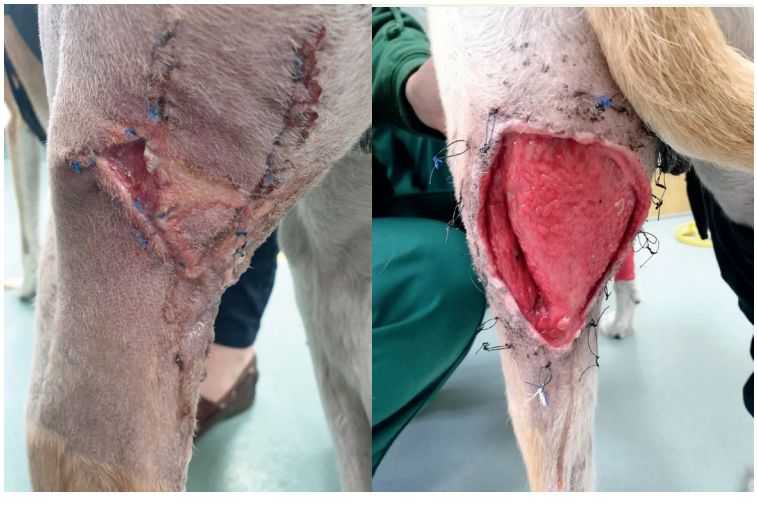

Figure 5. a. Wound breakdown post surgical closure using an advancement flap. b. The same wound managed through secondary intention before a second surgery and successful closure using a caudal superficial epigastric flap.

The most common cases presented were lower limb wounds with 3–5 cm deficits, and breakdown of surgically closed wounds in mobile areas over the stifle, elbows and hip (*Figure 6*). The mean time to resolution of healing in these cases was 60 days, with an average healing time of 59 days. The cases that took the longest to heal by secondary intention (between 100 and 170 days) involved the lower limb, elbow or stifle.

Only three clinicians sought advice from the Vet Wound Library team before surgery to assist with planning for high grade mast cell tumour removal and reconstruction. All cases were successful using advanced reconstruction techniques.

This suggests that clinicians face challenges in terms of choice of surgical technique to resolve the tissue deficit associated with mast cell tumour excision. While most surgeons are well informed about the approach to mast cell tumours, the reconstruction required may be more advanced than anticipated.

Intramural injection of tigilanolol tiglate for inoperable tumours

Tigilanol tiglate (Stelfonta, Virbac) gives clinicians an option for non-surgical management for mast cell tumours (De Ridder et al, 2021a,b). Tigilanol tiglate is a novel molecule derived from the Australian blushwood tree (*Fontainea picrosperma*). While the licence for tigilanol tiglate is for inoperable cases of mast cell tumour, the interpretation of what is operable depends upon the expertise and resources available to the operating clinician, as well as patient and owner considerations.

Clinical trials of tigilanol tiglate in humans are underway, potentially creating a pipeline of minimally invasive approaches that appears to have both local and systemic effects on tumour tissue. Effects on biofilm reduction and improved wound healing are being explored (https://qbiotics.com/product-pipeline/oncology/human).

As licensing for animal use is a shorter process than for human use, dogs are likely to be the first to benefit from this next generation of oncology treatments.

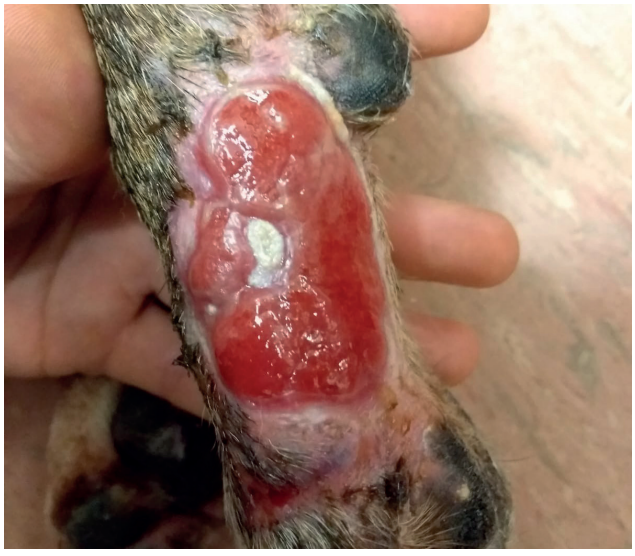

Figure 6. Static distal limb wound following wide margin surgical excision. Healing by secondary intention can be slow and frustrating.

What to expect

Injection into mast cell tumour tissue results in a powerful localised inflammation, vascular disruption and tumour oncolysis associated with stimulation of protein kinase C (Cullen et al, 2021).

Tigilanol tiglate is injected directly into the tumour at 0.5 mg/cm^3 of tumour volume. A maximum dose per patient of 0.15 mg/kg is advised with a maximum tumour size of 8 cm^3.

A randomised, blinded, controlled field clinical study explored the efficacy and tolerability of intratumoural administration of tigilanol tiglate (De Ridder et al, 2021a,b). This demonstrated complete resolution of the mast cell tumour within 28 days of a single dose in 75% of cases (Wiest et al, 2019). When those treated with a second dose were included, this increased to 87% complete resolution, as defined by the RECIST criteria (Eisenhauer et al, 2009). *Figure 7* illustrates a typical response and resolution within this timeframe.

The product summary (Virbac, 2020) emphasises the importance of avoiding any local and systemic adverse events related to mast cell degranulation and histamine release. All treated dogs must be given concomitant supportive therapies (corticosteroids and H1 and H2 receptor blockers) before and after treatment.

Within a few hours of injection of tigilanol tiglate the area will become swollen, reddened and visually bruised as the agent selectively degrades the vascular structure supporting the tumour (*Figure 8, Table 3*).

Application can be performed within a routine clinical appointment. Localised inflammation occurs rapidly and extends to all the areas affected by the tumour, which means that the area of sloughing may be more extensive than anticipated (*Figure 9*).

Pain relief to cover immediate inflammation, sloughing and demarcation is essential. The client and the team should be informed of the process of tumour degradation and briefed on what to expect at daily intervals. The client should be advised that the wound may begin to exude and slough at around day 3–4 and the area will look worse before it improves (*Figure 9a*).

From day 7 onwards the wound should begin to granulate underneath and the redness around the wound will subside. Pain will have reduced markedly but exuberant exercise should still be avoided from days 10–14 to allow the wound to heal and contract.

The eschar that forms as slough dehydrates will create a natural seal over the wound and will be shed once the wound begins to granulate. Once a full bed of granulation tissue is seen and sloughing (*Figure 9b*) is complete the wound can be managed with minimal intervention and allowed to heal by second intention.

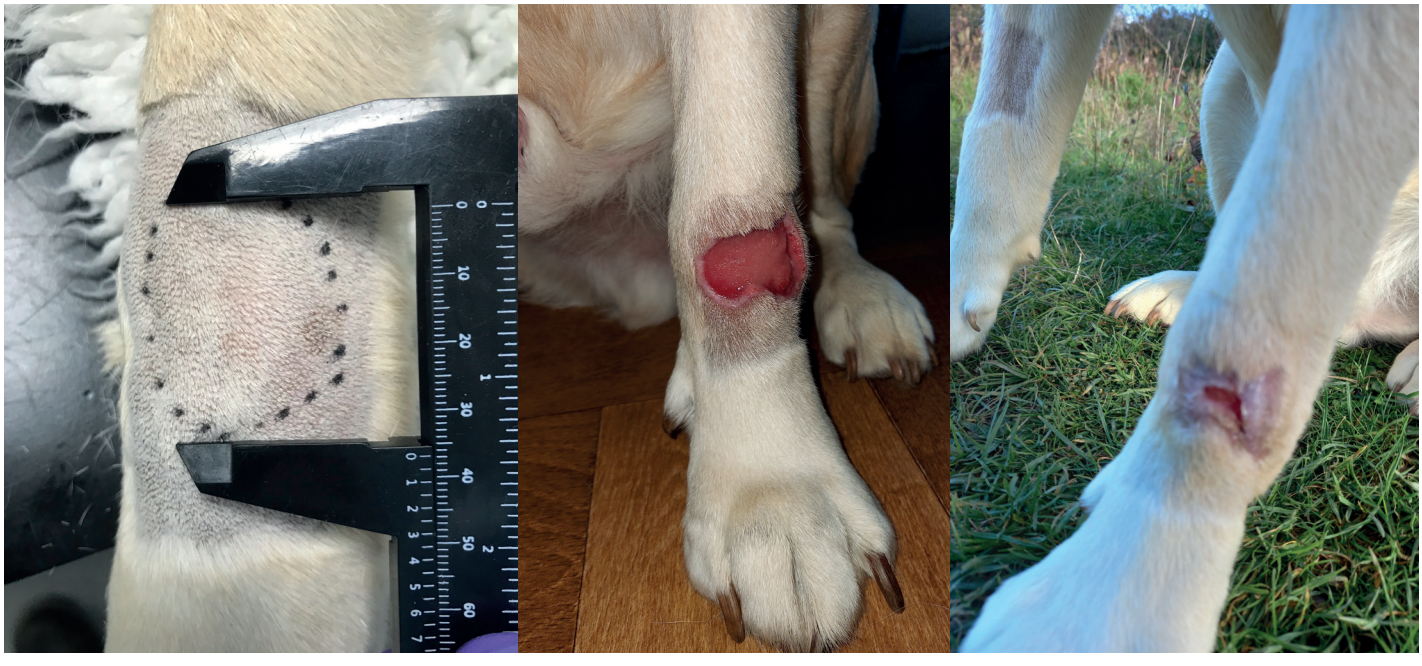

Figure 7. a. Measurement of area to be treated before use of tigilanol tiglate. b. Appearance of site post sloughing at 10 days post tigilanol tiglate. c. Appearance 1 month post intratumoural injection of tigilanol tiglate.

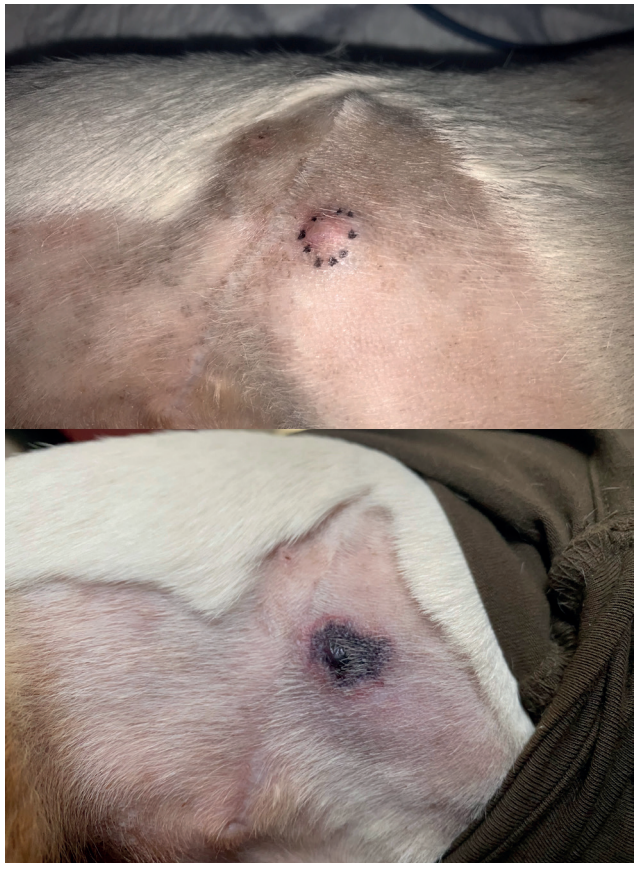

Figure 8. a. The process of tumour necrosis is rapid with the initial inflammatory response and intended tissue degradation resulting in demarcation and sloughing of affected tissue. b. Appearance 48 hours post tigilanol tiglate injection.

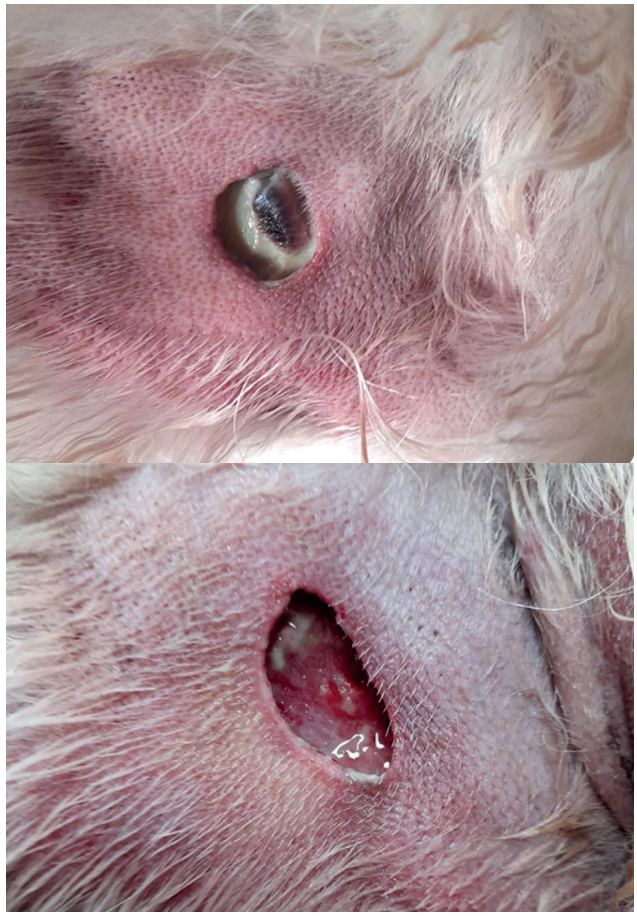

Figure 9. a. Appearance of sloughing tissue. b. Sloughed tissue reveals a pocket of healthy granulating tissue.

Owners should be advised to check for signs of potential mast cell degranulation reactions. These include vomiting, anorexia, severe pain, lethargy, inappetence or extensive swelling. If signs of degranulation are seen, the treating veterinarian should be contacted straight away, so that appropriate treatment can be started immediately.

Is the mast cell tumour inoperable and a candidate for tigilanol tiglate or should surgical excision be attempted?

There are a number of different factors that should be considered when judging whether a mast cell tumour is operable or not.

Table 3. Tissue response and management following intratumoural injection using tigilanol tiglate

		Client advice
Day 0	Intratumoural injection	Patient can return home. Cover area to avoid interference and direct contact for 24 hours. Swelling and pain is normal, but monitor for signs of degranulation or anaphylaxis
Day 0–2	Strong inflammatory reaction indicated by redness, swelling and pain	Limb sites may be accompanied by lower limb oedema. Contact vet if concerned. Analgesia may be required in most cases
Day 2–4	Inflammatory margins visible and tumour area begins to become ischaemic	Leave the wound to slough
Day 4–7	Demarcation and sloughing begins	Gently wash the wound with warm saline to remove exudate and loose slough
Day 7–14	Granulation tissue apparent. Eschar may have become fully detached. Wound contraction may begin at day 10–14	Once the eschar is detached granulation tissue can be left to heal without further intervention
Day 14 onwards	Wound contraction and epithelialisation	The wound will shrink in size depending on the location on the body. Lower limb wounds less so that wounds to the upper body. Epithelial (scar tissue) will being to migrate across the wound bed to complete healing. Healing may take from 30 to 90 days depending on the extent of tissue affected and the location of the wound

Tumour factors

The type, location and size of tumour will influence the approach to resolution. Lower grade tumours being more forgiving, but higher or unknown grades may require more extensive surgery. Consider if removal can be achieved without functional or cosmetic compromise and will primary surgical closure be possible?

Note that up to 40% of mast cell tumours are on the limb, where surgical removal can be challenging. Anatomical research and illustrations by Latifi et al (2022) and Schroeder and Skinner (2022) defined the deltoid, elbows, carpus and manus as areas with thin or absent fascia. There is also the added difficulty of achieving full clearance around tendons and muscle groups that pass through these regions.

Patient factors

Is the patient a suitable candidate for general anaesthesia? Older dogs, those with coexisting disease and brachycephalics may be best managed without repeated surgery. Fractious patients may also be considered challenging to approach surgically because the aftercare needs may not be tolerated.

Owner factors

A surgical approach may be daunting to some owners who do not wish to be parted from their pet or for those cases where postoperative care may be challenging. If the client is not wholly committed to longer term adjuvant therapy alongside surgical excision, the risk of recurrence (33%) may be higher than that of an injectable approach.

Vet factors

Does the clinician have the surgical time, availability and skill for more advanced reconstruction? The surgical skills required will vary from basic to advanced based on the location of the tumour. Movement, tension at the wound site and tissue deficit will all contribute to the clinical challenge and potential for wound breakdown post surgery.

Conclusions

Noble attempts at reconstruction post-surgical excision of mast cell tumours can become a frustrating wound management challenge. Complications arising from unanticipated tension, movement and tissue deficit are the most common reasons for failure.

Tigilanol tiglate is a novel method of tumour resolution that does not require any surgical intervention – wounds are left to heal by second intention without reconstruction. The demarcation and sloughing process can be dramatic but it facilitates a version of selective tissue removal through what is a normal (albeit induced) inflammatory, sloughing action that has a predictable trajectory towards healing.

Tigilanol tiglate should be used under licence for non-resectable, non-metastatic mast cell tumours, although the definition of non-resectable is in the hands of the clinician, based upon the resources and skill available. If the patient is not suitable for surgery, if tissue loss will be too extensive to allow for timely, functional wound closure, or it is not possible to navigate to a clear depth of fascia without compromising vital structures, then it could be reasonable to try using tigilanol tiglate. CA

KEY POINTS

- Surgical excision of mast cell tumours remains the first-line approach to management where complete removal is possible.
- Wound management and reconstruction should be planned before surgical excision to ensure healing is optimal.
- Mast cell tumours may be considered non-resectable if the clinician feels unable to achieve adequate margins without significant risk to the functionality and welfare of the patient.
- Post-surgical complications are most commonly attributed to tension at wound margins, movement and tissue deficit on lower limbs.
- Tigilanol tiglate offers a non-surgical, anaesthesia-free approach to management of mast cell tumours that does not require dressings or bandaging. Excellent wound healing rates have been observed.

Acknowledgements

Figures 4 and 8 are reproduced courtesy of Gerry Polton, North Downs Specialist Referrals.

Conflicts of interest: The author declares that there are no conflicts of interest.

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