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REVIEW

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Histologic margins and the residual tumour classification scheme: Is it time to use a validated scheme in human oncology to standardise margin assessment in veterinary oncology?

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Abstract

There is no consensus on the definition of a complete histologic excision in veterinary oncology; many definitions have been used in various studies, but these have been arbitrarily selected with no apparent justification. The residual tumour classification scheme, where a complete histologic excision is defined as a histologic tumour-free margin >0 mm, has been used for >40 years in human oncology by all of the major clinical staging organizations and is considered highly prognostic for the vast majority of malignant tumours in people. Because of the widespread use of the residual tumour classification scheme both clinically and in research studies, this standardized approach permits better communication between clinicians, an evidence-based decision-making process for adjuvant treatment options following surgical resection, minimizes exposing patients to unnecessary adjuvant treatments and a better ability to compare local tumour control for specific tumours between different studies. The adoption of the residual tumour classification scheme in veterinary oncology would likely achieve similar outcomes and minimize the prevalent confusion within the veterinary community, amongst both general practitioners and specialists, regarding the definition of what constitutes a complete histologic excision.

KEYWORDS

surgical margins, histologic tumour-free margins, local tumour recurrence, residual tumour classification scheme

1 | INTRODUCTION

The terminology used for describing margins in veterinary oncology can be confusing. This includes the definitions used for surgical resection margins, which will not be discussed in this review, and histologic margins. There is no consensus on what constitutes a complete histologic excision in veterinary oncology with a wide range of histologic tumour-free margin (HTFM) widths being used, invariably arbitrarily with no supporting evidence for the use of these definitions. This is further confused with the use of an intermediary margin definition, close or narrow margins, again arbitrarily with no supporting evidence for the use of these terms. The evaluation of histologic margins is also impacted by surgical margin inking practices, specimen shrinkage and specimen trimming techniques; however, the significance of these factors on margin evaluation requires further elucidation. This confusion is then compounded when clinicians use these arbitrarily selected definitions for decision making on the need for further local adjuvant therapy, especially as further therapy is both costly and

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associated with a higher risk of morbidity, possibly for no benefit in local tumour control or survival.

2 | HISTOLOGIC MARGINS: COMPLETE, INCOMPLETE AND CLOSE

Histologic margins are commonly described as being incomplete or complete, with incomplete histologic margins being defined as neoplastic cells extending to the edge of the surgical resection margins or 'tumour on ink'.[1-6] However, in some studies, an incomplete histologic excision has been arbitrarily defined as a HTFM ≤1 mm,[7-22] ≤2 mm[23] or ≤5 mm.[24] The assessment of histologic margins is further complicated by the common use of 'close' or 'narrow' histologic margins in veterinary oncology.[25] This term is rarely used in human oncology and the use of this term is not recommended according to a consensus paper by the American College of Veterinary Pathologists Oncology Committee on the evaluation and reporting of histologic margins in veterinary oncology.[26] Furthermore, there is no consensus on what constitutes a close margin and this has not been clinically validated; 1 mm,[13,15] 2 mm,[20,22,27-29] 3 mm,[12,14,30-34] 5 mm[7,10,12,23,35-37] and 10 mm[16] have been variably used in published veterinary studies, and 4 mm was preferred according to an online poll of veterinary pathologists.[38] In some studies, close histologic excisions have been combined with incomplete histologic excisions,[7,32,34,35] but there is no supporting literature to consider these two groups as equivalent because their outcomes have not been assessed separately.[39] Lastly, there is minimal evidence that close HTFMs result in a clinically relevant increased risk of local tumour recurrence in comparison to tumours excised with wider HTFMs.[14,33,35]

To date, there has only been one study published in the veterinary literature which found close histologic margins have an impact on local tumour control.[27] This study included malignant tumours from 40 dogs and 20 cats and these were grouped into soft tissue sarcomas (STSs), mast cell tumours (MCTs) and carcinomas; however, these groups were highly heterogenous with a wide range of tumour types and histologic grades, and included tumours with a low risk (eg, hemangiopericytoma) to a high risk of local recurrence (eg, vaccine-associated sarcoma (VAS)). Histologic margins were defined as complete (HTFM >2 mm), close (HTFM 0-2 mm) and incomplete. Overall, surgical resections were complete, close and incomplete in 48%, 18% and 34% of animals, respectively. The overall local recurrence rate was 45%, including 80% of dogs with incomplete histologic margins and 73% of dogs with close histologic margins.[27] These local recurrence rates are disproportionately higher than reported in the vast majority of other veterinary studies. The clinical applicability of these results is questionable because of low sample size, heterogeneity within the groups, disproportionately high local recurrence rates and the lack of other supporting published studies.

Numerous studies have shown that close histologic excisions have no prognostic significance for local tumour control in dogs with subcutaneous and cutaneous MCTs. In one study of 340 dogs with cutaneous MCTs, the local recurrence rates were 3.3%, 4.9% and 16.9% for dogs with complete (HTFM >5 mm), narrow (HTFM 0-5 mm) and incomplete histologic excision.[35] There was no significant difference in local recurrences rate between dogs with complete and close histologic excisions. In another study of 73 dogs with complete histologic excision of 90 low-grade MCTs, the local tumour recurrence rates were 4% and 0% for dogs with complete (HTFM >3 mm) and narrow (HTFM 0-3 mm), respectively; local tumour recurrence was reported in two dogs, one with a HTFM of 4 mm and the other with a HTFM of 20 mm.[33] In a study of 28 dogs with 30 incompletely excised MCTs,[18] the local recurrence rates were 23% and 27% when incomplete excision was defined as HTFM ≤1 and 0 mm, respectively; none of the dogs with an incompletely excised MCT which subsequently developed local recurrence had tumour cells within 1 mm of the surgical resection margin. Similarly, there was no significant difference in local recurrence rates for dogs with oral squamous cell carcinoma resected with narrow (HTFM ≤2 mm) and complete (HTFM >2 mm) histologic margins.[28] In one study of 263 dogs with oral acanthomatous ameloblastomas,[10] no dog developed local tumour recurrence despite incomplete (HTFM <1 mm) and close (HTFM 1-5 mm) histologic excisions in 22% and 44% of dogs, respectively.

Despite this evidence, there is an unfounded dogma in veterinary surgical oncology that close histologic excision is equivalent to incomplete histologic excision, and that treatment recommendation for cats and dogs with close histologic excisions should be the same as an incomplete histologic excision (eg, re-excision or radiation therapy). This approach has even been advocated in the published literature.[32,35]

In one study of 64 dogs with 70 incompletely or closely (HTFMs ≤3 mm) MCTs, the effect of re-excision or radiation therapy as further local treatment on survival was investigated.[32] The reason for combining incompletely and closely excised MCTs was not reported. While further local treatment significantly improved survival time in these dogs, this effect was lost when dogs with close histologic excisions were excluded from analysis.[32] In another study of 115 dogs with incompletely (78%) or closely (defined as HTFM <5 mm, 22%) excised cutaneous MCTs,[37] 23 dogs were not treated and 92 dogs received further local treatment. No statistically significant differences were found in local recurrence rates, disease-free intervals, metastatic rates, survival times and 1- and 2-year survival rates between treated dogs and non-treated dogs, or between dogs treated with different modalities.[37] Treatment complications associated with further local treatment were reported in 22% of dogs treated with re-excision and 90% of dogs treated with radiation therapy.[32] In another study of 27 dogs with incompletely or closely excised MCTs, where incomplete excision was defined as <2 mm and close excision was defined as 2 to 5 mm, treated with vinblastine and prednisone for local tumour control,[23] 13% of doses were associated with adverse effects and one dog died as a result of treatment. The exposure of dogs with close histologic excisions of their MCTs to further treatment, especially when the additional costs and morbidity of this treatment are considered, seems unnecessary when there is no evidence of an increased risk of local tumour recurrence in these dogs.

A similar situation has been reported with invasive breast cancer in women. The completeness of histologic excision had been

arbitrarily divided into incomplete, close (≤2 mm) and complete (>2 mm). Women with close histologic excisions were often treated with further local therapy despite the majority of meta-analyses, cooperative group trials and single institution studies showing no significant differences in local recurrence rates between close and complete histologic margins following appropriate adjuvant therapy.[40-43] In one meta-analysis, there were no significant differences in local recurrence rates with HTFMs of 1, 2 and 5 mm following resection of multidisciplinary breast conserving therapy for invasive breast cancers.[44] This is further supported by a study of 577 women treated with either skin-sparing mastectomy or simple mastectomy where 8-year local recurrence rates were significantly higher for incompletely excised tumours than completely excised tumours (HTFM >0 mm).[45] As a result of this study, the Society of Surgical Oncology and American Society of Radiation Oncology jointly published consensus guidelines on histologic margins for breast conserving therapy with no ink on the margin (ie, HTFM >0 mm) being defined as an adequate surgical margin.[46,47] Despite these recommendation, re-excision rates of up to 70% have been reported following close HTFMs of invasive breast cancer.[48] Re-excision in patients with close HTFMs, when close HTFMs have no prognostic significance on outcome, results in increased costs, poorer cosmetic results, emotional distress, increased risk of postoperative complications and a delay in starting adjuvant therapy.[40] In a cost-analysis study investigating the costs associated with re-excision of invasive breast cancers, if all invasive breast cancers with close HTFMs were re-excised, then this would represent an $18.8 million increased annual cost of surgical treatment per annum in the United States, 9% greater than if re-excision were not included in the recommended multimodality treatment plan. These costs did not include hospital costs or the costs of managing complications following re-excision.[40]

3 | RESIDUAL (R) TUMOUR CLASSIFICATION SCHEME

Based on the high variability in the arbitrary assignment of what is considered a complete histologic excision and the lack of evidence to validate the use of close histologic excisions, the use of a simple scheme to standardize the definition of histologic margins seems warranted in veterinary oncology. The R tumour classification scheme is widely used in human oncology for this purpose.

The R tumour classification scheme was recommended by the American Joint Committee on Cancer (AJCC) in 1977[49] and has been used by the AJCC[50] and World Health Organization (WHO), and modified by the Union for International Cancer Control (UICC)[51] for over 40 years because of its 'outstanding prognostic importance'.[52] One of the original advantages of this classification scheme was its simplicity; the three classifications were R0 (complete histologic excision with HTFM >0 mm), R1 (incomplete histologic excision) and R2 (intralesional resection with residual gross disease), and this classification scheme was only used for definitive surgical resections at the primary tumour site, not lymph nodes or distant metastatic sites.[49]

TABLE 1 Expanded residual tumour classification scheme[50,51]

RX	Residual tumour presence could not be assessed
R0	No residual tumour
	Complete histologic excision (HTFM >0 mm)
R1	Microscopic residual tumour
	Incomplete histologic excision Satellite tumour cell populations distant to the tumour Lymphatic, venous or perineural invasion Lymph node or microscopic distant metastasis
R2	Macroscopic residual tumour
	Gross residual disease Macroscopic distant metastasis

However, the UICC expanded the scope of the R tumour classification scheme in 1987 to include locoregional and distant residual tumour burdens, and this was soon adopted by the AJCC and WHO (Table 1).[50,51]

The expanded R tumour classification scheme describes the tumour status following treatment and denotes the absence or presence of residual tumour after treatment. Whereas the initial R tumour classification scheme was primarily a histopathologic assessment, the expanded scheme is based on a combination of clinical and histopathologic findings. This scheme has been further expanded to include R0 ≤ 1 mm, R0 > 1 mm, R0(un), R1(is) and R2a, R2b and R2c classifications; where R0 is sub-classified according to HTFMs, R0(un) refers to a complete histologic excision but with incomplete clinical staging,[53] R1(is) is the presence of carcinoma in situ at the surgical margin, and R2a, R2b and R2c signify gross residual local disease, gross residual metastatic disease and gross residual disease at both sites, respectively.[54] The reliability and reproducibility of this expanded scheme relies on using standardised clinical staging methods, tailored to each tumour type, and a standardised, thorough histologic examination of surgical margins.[55,56]

After surgical treatment, assessment for the R tumour classification requires close cooperation between the surgeon and pathologist in a two-step process.[52] The pathologist should report on the absence (R0) or presence (R1/R2) of tumour at the surgical resection margins, using a standardized method to prepare specimens and examine histologic margins.[52,55,56] However, when using the expanded R tumour classification scheme, the R0 status also depends on clinical staging results and is not solely dependent on a pathologic assessment of margins. For this reason, the assignment of an R classification should be performed by a designated individual who has access to the complete medical record of the patient.[52] The reliability and reproducibility of this expanded R tumour classification scheme relies on using standardized methods of clinical staging and preparation and assessment of histologic margins. In a survey of experts in certified lung cancer centres in the United States,[57] there was high heterogeneity in the application and interpretation of the R tumour classification scheme. These discrepancies included the methods of routine margin assessment, interpretation of the criteria for R0, R1 and R2 classifications, and whether

R status was being determined locally or regionally and distantly.[57] As a result of these difficulties, many pathologists have advocated a further refinement to the R tumour classification scheme where the pathologist uses the original definition described in 1977 (pR or pTNM classification) and clinicians can then modify this based on the results of clinical staging (cR or cTNM classification).[58]

The R tumour classification has been shown to be a strong independent prognostic factor for virtually all malignant tumours in people.[52,55,56] For the vast majority of malignancies, prognosis differs significantly according to the R classification and hence this scheme merits inclusion in any prognostic system investigation.[52,55,56] In human oncologic studies, prognostic factors are recommended to be analysed separately for each of the R0, R1 and R2 classifications; furthermore, for multivariate analyses of prognostic factors, sub-stratification of tumours within the same stage grouping by the R classification is also recommended.[52]

3.1 | Proposed residual tumour classification scheme in veterinary oncology

While the expanded R classification scheme is not as simple as first proposed, the original R classification scheme has merit in veterinary oncology because it relies solely on a standardized definition of complete histologic excision (ie, HTFM >0 mm). The use of this scheme is attractive because of its simplicity and reproducibility. In the absence of evidence to support definitions of incomplete histologic excision other than 'ink on margin' and the high prognostic value of using a HTFM >0 mm for the vast majority of malignant tumours in people, the use of this latter definition would be appropriate in veterinary oncology. The use of this proposed R tumour classification scheme has been used in a recently published meta-analysis of canine STSs and was found to be prognostic,[4] further supporting the implementation of this scheme in veterinary oncology.

From a procedural perspective, it is imperative that the importance of inking lateral and deep surgical margins be mentioned. The application of ink to the surgical resection margins is recommended to orientate the pathologist and provide accurate histologic identification of the true surgical margins.[26] Purple or red coloured inks are not recommended because the surgical ink is difficult to differentiate from the colours of haematoxylin and eosin stains.[59,60] In one study in which a consistent ink application method was used, the ink dissected along fascial planes in 28.1% of samples and inadvertently adhered to surfaces other than the surgical margin in 68.1% of samples.[4] While inking has the potential to confound the interpretation of histologic margins, the application of ink to the lateral and deep surgical margins is essential for margin assessment and should be performed routinely using a technique which minimises these potentially confusing artefacts.

The use of a HTFM >0 mm to define a complete histologic excision also minimises the effects of specimen shrinkage on the assessment of histologic margins. Shrinkage of the tumour specimens can result in tumour cells being closer to the surgical resection margins than in vivo. The majority of this specimen shrinkage occurs immediately after surgical resection because of the effects of myofibril contractility and tissue elasticity following release from adjacent tissues.[61-64] In one study of 216 canine tumour specimens, the total overall shrinkage was 15.6% with 13.7% shrinkage occurring immediately after surgical resection and only 1.7% after formalin fixation.[61] Similarly, in cats with VASs,[65] the overall HTFM width was decreased by 33% between surgical resection and histologic examination of the specimen, with 29% of this shrinkage occurring immediately after surgical resection. Furthermore, the majority of this post-resection shrinkage occurs in the grossly normal skin surrounding the tumour. In one study of 19 resected canine cutaneous MCTs, the overall specimen shrinkage was 17.7% with 24.4% shrinkage in the grossly normal adjacent skin and only 4.5% shrinkage in the tumour.[63] Other studies have also found a significant effect of both histologic processing and biologic factors, such as tumour infiltration into the grossly normal surgical margin, on shrinkage of specimens.[64] Regardless, specimen shrinkage will result in HTFMs being less than the true tumour-free margins obtained during surgery. In one study of 51 cutaneous and subcutaneous MCTs resected with curative-intent from 46 dogs,[38] the mean histologic margins were 58% to 65% smaller than the surgical resection margins, representing a 35% to 42% decrease in margin width. Despite these significant reductions in margin width, this is unlikely to convert a complete histologic excision to an incomplete histologic excision if complete histologic excision is defined as >0 mm HTFMs; however, if excision is considered incomplete with HTFMs of ≤1 mm or greater, then the effect of specimen shrinkage needs to be both considered and quantified.[63]

Equations have been developed to account for specimen shrinkage following surgical resection of cutaneous melanomas in people; these equations have an accuracy rate of approximately 85% for determining the pre-excision histologic margin within ±3.5 mm.[66,67] A similar equation was used to account for specimen shrinkage following surgical resection of canine cutaneous MCTs, but the accuracy of this equation was only 18%.[63] The inaccuracy of these equations is because of the assumption that the entire specimen shrinks in a uniform matter; however, numerous studies have demonstrated that healthy adjacent tissue shrinks to a greater extent than the tumour itself.[63,68,69] As a result, the HTFM will be less than the true tumour-free margin obtained during surgery. This has the potential to impact the evaluation of the completeness of excision for any other definition of complete histologic excision than a HTFM >0 mm.

The use of this proposed R classification scheme, unencumbered by arbitrary definitions of complete histologic excision more prone to the effects of specimen shrinkage, provides standardised criteria for future studies of local tumour control in dogs and cats. These studies should investigate the association of histologic margins on local tumour control (ie, disease-free interval and 1- and 2-year local recurrence rates), and not solely on survival outcomes, to provide information on the prognostic importance of the R classification scheme for local tumour control of specific tumour types in dogs and cats.

4 | CLINICAL RELEVANCE OF HISTOLOGIC MARGINS: ASSESSING THE RISK OF LOCAL TUMOUR RECURRENCE

The completeness of histologic excision is used to determine the risk of local tumour recurrence and the requirement for further local treatment, such as re-excision or radiation therapy. However, incomplete histologic excision does not necessarily result in local tumour recurrence (see below for specific examples), and other factors can have an impact on local tumour recurrence, such as tumour size,[8,12,70] tumour type, tumour subtype,[31,70,71] mitotic rate,[17] histologic grade,[1,13,70,72,73] degree of invasiveness,[8,12,17] proliferation markers[18,24,72,74] and molecular factors (eg, mutations in KIT exon 11 in canine cutaneous MCTs).[33,75]

The reasons for why incompletely excised tumours do not uniformly recur have not been elucidated. Some proposed theories are related to the post-surgical healing environment and tumour cell heterogeneity, and some are tumour-specific, such as for MCTs. Inflammatory cells recruited to the surgical site, in conjunction with release of cytokines or disturbance of local vasculature, may play a role in phagocytising residual neoplastic cells.[18,76-78] Neoplastic cells from the periphery of the tumour may represent a more committed cell type than those located centrally, and these peripheral cells may not be able to survive because of a lack of key growths factor may inhibit growth.[18,77-79] Anti-invasion factors have been isolated from connective tissues and these may have an inhibitory effect on residual tumour cells.[77] The relatively low recurrence rate of incompletely excised canine cutaneous MCTs has been associated with low proliferation indices, such as Ki67, PCNA and AgNORs.[18,24] Mast cells observed at the periphery of histologic sections of resected MCTs may be associated with a local inflammatory reaction, which highlights the difficulty in differentiating between normal and neoplastic mast cells.[15,78] Logistically, local tumour recurrence may be missed because follow-up times may be inadequate in some studies. This has been recognized as a design flaw with one recent meta-analysis of margins and STSs in dogs only including studies with a minimum of 2 years follow-up.[80]

While complete histologic excision is the goal of oncologic surgery, complete histologic excision does not preclude the possibility of local tumour recurrence. Local recurrence rates of 3% to 22% have been reported following complete histologic excision of cutaneous and subcutaneous STSs,[2,3,14,36,71,81,82] 2% of dogs with subcutaneous MCTs,[17] and 2% to 11% of dogs with low-grade cutaneous MCTs,[11,15,24,33,35,78,83] and 36% of high-grade cutaneous MCTs.[33] In one meta-analysis of cutaneous and subcutaneous STSs in dogs, the overall local recurrence rate was 9.8% following complete histologic excision, defined as a HTFM >0 mm, in the 10 included studies.[80] However, as discussed previously, the histologic assessment of the completeness of excision in all planes can be highly flawed.[26,39,84]

The majority of commercial veterinary laboratories use a radial sectioning technique to evaluate surgical margins. This involves bisecting the tumour through its shortest axis and then each half is bisected along its longest axis, resulting in four quarters. This results in five margins (cranial, caudal, ventral, dorsal and deep) for assessment; however, it has been estimated that approximately 4000 sections would be required to assess the entirety of a 1 cm tumour resected with 2 cm margins.[85] These limitations can result in false negative histologic margin assessments.[26,85] Tangential sections are considered the gold standard for evaluating the surface area of the surgical margin.[26] Multiple 2 to 3 mm sections are shaved off the edge of the sample and laid into cassettes with the cut surface down. This technique allows for a more thorough evaluation of the completeness of histologic excision.[26] In one study, incomplete histologic excision was diagnosed in 49% of samples sectioned using a tangential technique, but only 15% of samples sectioned using a radial technique following breast conserving surgery for breast cancer.[86] In a study of low grade and subcutaneous canine MCTs,[84] incomplete histologic margins were detected in a significantly higher proportion of samples sectioned using a tangential technique compared with a radial technique; 23.1% of margins classified as complete (HTFM >0 mm) on radial sections were reclassified as incomplete on tangential sections. While tangential sectioning provides superior assessment of the completeness of histologic excision to other sectioning techniques, which are described in detail elsewhere,[4,26] the entire surface area of the tumour is not examined (32.6% in one study following breast conserving surgery for breast cancer[87]) and the width of the HTFMs cannot be assessed.[4,26] The latter may be an important consideration if the width of the HTFM has prognostic significance for the risk of local tumour recurrence, but not if a binary assessment of complete vs incomplete histologic excision is the only requirement to determine this risk, as defined in the R tumour classification scheme.

4.1 | Sarcomas

For dogs with subcutaneous or cutaneous STSs, local recurrence rates of 17%,[14] 19%[13] and 28%[3] have been reported following incomplete histologic excision. In a systematic review and meta-analysis of the impact of the completeness of histologic excision on local tumour recurrence in dogs with subcutaneous or cutaneous STSs,[80] complete histologic excision was defined as a HTFM >0 mm and studies which included close histologic margin terminology were considered completely excised. Ten studies were included in this meta-analysis with a total of 278 STS surgical resections with a minimum follow-up time of 2 years; the local recurrence rates for completely and incompletely excised STSs were 9.8% and 33.3%, respectively.[80] In one study of 236 marginally excised subcutaneous STSs,[13] the local recurrence rate was 0% following complete histologic excision and dependent on histologic grade if incompletely excised with local recurrence rates of 7%, 34% and 75% in dogs with incompletely excised grade I, II and III STSs, respectively; however, the minimum follow-up time in this study was only 12 months. Local recurrence is 10.5 times more likely after incomplete excision,[3] and the relative risk for local tumour recurrence was 0.396 for completely excised vs incompletely excised STSs in a recent meta-analysis.[80] Incomplete histologic excision has been inconsistently associated with local recurrence of canine STSs

with some studies finding a significant association[3,13,14,82,88,89] and others finding no association with local recurrence.[1,12,30,71]

Feline VAS is a locally aggressive disease with local tumour recurrence rates of 35% to 59% following surgery[90-92] and 26% to 52% following surgery combined with adjuvant therapies, such as radiation therapy.[91-100] In earlier studies where wide surgical resection was defined as 2 to 3 cm lateral margins and one uninvolved fascial plane for deep margins, only 46% to 80% of cats had complete histologic excision[90-94,97]; however, 97% of 91 cats had complete histologic excision following resection of the VASs with 5 cm lateral margins and two uninvolved fascial layers for deep margins.[101] In two studies, cats with incomplete histologic excision had significantly higher local recurrence rates (58% to 69%) than cats with complete histologic excision (19% to 22%).[90,98] Furthermore, complete histologic excision is associated with a significantly longer time to first recurrence[102] and tumour-free interval than incomplete histologic excision of feline VASs.[93] Local tumour recurrence significantly decreases survival times,[101] emphasizing that complete histologic excision with aggressive, wide surgical resection is the primary goal for cats with VASs.

4.2 | Mast cell tumours

For dogs with cutaneous MCTs, overall local recurrence rates of 17%,[35] 18%,[78] 27%[18] and 30%[77] have been following incomplete histologic excision. Similar to canine STSs, local recurrence rates are also dependent on histologic grade with local recurrence reported in 0% to 1%,[9,11,35] 0% to 33%[9,11,15,19,35,77,78] and 19%[35] of incompletely excised grade I, II and III MCTs, respectively. In the vast majority of published studies, there is no statistically significant association between incomplete histologic excision and local tumour recurrence,[15,24,78,103] with only one study reporting an association with local recurrence and decreased disease-free interval.[73] Histologic grade and proliferation indices are more important predictors of local tumour recurrence than incomplete histologic excision. In one study of 90 dogs with completely excised cutaneous MCTs, the local recurrence rates for dogs with low- and high-grade MCTs were 4% and 36%; high-grade tumours were significantly more likely to recur locally with an odds ratio of 13.7.[33] Proliferation indices, such as Ki67, PCNA, Ki67 combined with PCNA, and AgNOR, are predictive of local tumour recurrence following incomplete excision of low grade and grade II MCTs.[18,24]

In one study of 306 dogs with subcutaneous MCTs, 56% of tumours were incompletely excised (HTFM ≤1 mm).[17] The local recurrence rates were 8% overall, 12% in dogs with incompletely excised subcutaneous MCTs, and 2% in dogs with completely excised subcutaneous MCTs.[17] Incomplete histologic excision, a mitotic rate >0 per 10 hpfs, and tumours with an infiltrative histologic pattern were independent prognostic factors for local tumour recurrence. The importance of contributing factors to local tumour recurrence was highlighted in this study with the risk of local tumour recurrence being 130 times in dogs with a mitotic rate >4/10 hpfs (compared with a mitotic rate of 0/10 hpfs) and five times in dogs with infiltrative subcutaneous MCTs (compared with circumscribed subcutaneous MCTs).[17] These factors also had an impact on the median time to local recurrence with predictions of 70, 365 and 1000 days for incompletely excised subcutaneous MCTs with an infiltrative histologic pattern, incompletely excised subcutaneous MCTs with a circumscribed histologic pattern, and completely excised subcutaneous MCTs with an infiltrative histologic pattern, respectively.[17] Similar to cutaneous MCTs, Ki67 (>21.8, odds ratio 9.0), AgNOR (>2.7, odds ratio 9.0), the combination of Ki67 and AgNOR (>55.0, odds ratio 11.1), and cytoplasmic KIT localization pattern (diffuse vs focal or stippled, odds ratio 19.8) were significantly associated with local recurrence on univariable exact logistic regression analysis in dogs with subcutaneous MCTs.[74]

In cats with MCTs, the completeness of histologic excision is not associated with local tumour recurrence.[104-107] Tumour recurrence has been reported in up to one-third of cats with cutaneous MCTs, regardless of the completeness of surgical excision.[104,106] The reported recurrence rate for periocular MCT is lower (<5%), but also shows no correlation with completeness of surgical excision.[105,107]

4.3 | Head and neck cancers

In the majority of studies published on head and neck cancers in dogs, the completeness of histologic excision is not reported,[108] included as descriptive statistics only and not analysed,[109,110] or analysed for survival outcomes but not local tumour control.[20,22,34,111-113]

In a study of 21 dogs with surgically treated oral squamous cell carcinoma,[28] histologic margins were defined as incomplete, close (HTFMs ≤2 mm), and complete (HTFMs >2 mm). Histologic margins were incomplete in two dogs, narrow in four dogs and complete in 15 dogs; local recurrence was reported in one dog with incomplete histologic excision and no dogs with either narrow or complete histologic excisions. Histologic margins were not associated with local tumour recurrence, but the power to detect an association was likely inadequate with such low case numbers and only one dog diagnosed with a local recurrence.[28]

In one retrospective study of 29 dogs with oral fibrosarcoma,[114] complete and incomplete margins were not defined, but 15 dogs had complete histologic excision and 11 dogs had incomplete histologic excision. Seven dogs were diagnosed with local tumour recurrence, and five of these dogs had incomplete histologic excision of their oral fibrosarcomas. Dogs with incomplete histologic excision were significantly more likely to develop local tumour recurrence.[114]

In a study of 183 dogs with mandibular, maxillary or calvarial osteosarcoma,[115] histologic margins were defined as complete (HTFM >0 mm) or incomplete. The overall local recurrence rate was 30% in surgically treated dogs, with local recurrence or disease progression reported in 24% of dogs with calvarial osteosarcoma, 16% with mandibular osteosarcoma, and 40% of dogs with maxillary osteosarcoma. In a multivariate analysis, complete histologic excision was an independent predictor of local tumour control (hazard ratio 0.4); calvarial osteosarcomas had a significantly higher risk of local tumour recurrence (hazard ratio 2.1).[115]

5 | FUTURE CONSIDERATIONS FOR THE PROPOSED RESIDUAL TUMOUR CLASSIFICATION SCHEME IN VETERINARY ONCOLOGY

While the initial goals of the proposed R classification scheme are to standardise the definition of complete histologic excision in veterinary oncology and provide a standardised framework to investigate the prognostic significance of this scheme for local tumour control, the R classification scheme has the potential to be modified, both overall and for specific tumour types, based on the findings of rigourously performed research studies involving large case numbers with long follow-up times. For instance, HTFMs could be studied as a continuous variable to determine if there are appropriate histologic safety margins for specific tumour types. As described above, the completeness of histologic excision is not the only determinant of the risk of local tumour recurrence. Other histologic criteria could be investigated to determine their effect on local tumour control, such as lymphatic invasion,[116,117] vascular invasion,[118,119] perineural invasion,[28] tissue invasion,[8,12,17] histologic grade,[1,13,70,72,73] proliferation indices[18,24,72,74] and molecular markers.[33,75] Based on the findings of these studies, the R classification scheme could be modified to develop a more refined treatment algorithm for specific tumour types.

5.1 | Histologic safety margin

Histologic safety margin is the minimal HTFM required to significantly decrease the risk of local tumour recurrence.[120] The histologic safety margin has been defined for basal cell carcinoma in people,[121,122] but not for other tumour types in human oncology and not at all in veterinary oncology. One veterinary study attempted to define histologic safety margins in 90 dogs with completely excised cutaneous MCTs[33]; however, a histologic safety margin was not identified for either low- or high-grade MCTs. In some studies, conflicting results have been found and hence it is difficult to convincingly determine the histologic safety margin. For extremity and truncal STSs in people, some studies have found no difference in local tumour recurrence rates between HTFMs ≤1 and >1 mm,[123-125] or HTFMs <1, 1 to 4, 5 to 9, 10 to 19 and ≥20 mm[126]; however, HTFMs ≥10 mm were an independent predictor of local recurrence-free interval compared with 0 and 1 to 9 mm in one study,[123] and increasing HTFM width resulted in significantly better local tumour control rates (with 0 mm being worst and >4 cm being best), distant metastasis-free intervals and overall survival times in another study.[127] Based on these studies, a histologic safety margin for extremity and truncal STSs in people is commonly considered as 'no ink on tumour' (ie, HTFM >0 mm). Similarly, R0 resections with HTFMs >0 mm are sufficient for local tumour control following limb-sparing surgery for patients with osteosarcoma.[128,129] Histologic safety margins for soft tissue tumours are also subjected to the variances of specimen shrinkage, as described above.

5.2 | Treatment algorithms

While the R classification scheme may be overly simplistic in its original definition, it is a starting point for veterinary oncologists because the status of the histologic margins is an important determinant of whether further local treatment should be recommended. This scheme is admittedly simplistic as incomplete histologic excision does not inevitably result in local tumour recurrence and there are other factors that have a contributory role, such as mitotic rate, histologic grade, degree of invasiveness and molecular factors. Some of these factors are more universal and others are more specific to certain tumour types. As a result, future endeavours should be directed at developing treatment algorithms for specific tumour types which incorporate the completeness of histologic excision with some or all of these possible contributory factors to decide on the preferred treatment options. Some effort has been made in developing treatment algorithms for cutaneous and subcutaneous STSs in dogs[39] and cutaneous MCTs in dogs[130]; while these are encouraging, some of these recommendations are based on either poorly designed studies or arbitrarily decided cutoffs. For instance, in one study, local tumour recurrence was not reported following resection of canine cutaneous MCTs with HTFMs ≥10 mm laterally and ≥4 mm deeply.[131] The authors of this article and a subsequent review paper[130] stated that the goal of surgical resection of canine cutaneous MCTs <4 cm should be 'at least 1 cm lateral margins and a deep margin of at least 4 mm'. This recommendation is clinically inappropriate because it makes the assumption that surgical resection margins and histologic margins are equivalent, which is an incorrect assumption because of specimen shrinkage between resection and histologic assessment and tumour infiltration into grossly normal margins. Future treatment algorithms should be based on the results of rigorously performed studies specifically investigating the effects of certain histologic criteria on local tumour control.

6 | CONCLUSIONS

The R classification scheme, in both its original and expanded versions, is a simple and highly prognostic scheme used for over 40 years in human oncology. The use of a standardised definition for complete histologic excision (HTFM >0 mm), especially a definition that is less prone to the effects of specimen shrinkage and other variables, simplifies the decision-making process for recommending adjuvant local therapy and provides a standardised benchmark to perform clinical research studies to determine the true effect of the completeness of excision on local tumour control. Similar to human oncology, the R classification scheme has the potential to be modified with the addition of contributory factors for local tumour control, such as histologic grade or tumour invasiveness, if validated through rigourously performed, highly powered studies. The adoption of the R classification scheme in veterinary oncology would minimise the existing confusion regarding the adequacy of surgical resection and minimise the number of patients treated unnecessarily with further local therapy.

CONFLICT OF INTEREST

The author has no potential sources of conflict of interest related to this work to declare.

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