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Response evaluation criteria for peripheral nodal lymphoma in dogs (v1.0) – a veterinary cooperative oncology group (VCOG) consensus document

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Abstract

Standardized assessment of response to therapy for lymphoma in dogs is lacking, making critical comparisons of treatment protocols difficult. This Veterinary Cooperative Oncology Group (VCOG) consensus document, based on the recommendations of a subcommittee of ACVIM board-certified veterinary oncologists, was unanimously adopted at the 29th Annual Conference of the Veterinary Cancer Society (VCS) by the VCOG membership. It has integrated guidance from the response assessment criteria established for lymphoma in human patients using standards available in routine veterinary oncology practices that are simple, repeatable and consistently applicable. These guidelines are intended only for use in dogs, where peripheral lymphadenopathy represents the principal component of their disease and as such do not critically assess extranodal disease (e.g., primary cutaneous, central nervous system, gastrointestinal). It is hoped these guidelines will be widely adopted and serve to facilitate the comparison of current and future treatment protocols used in the therapy of dogs.

Keywords
comparative oncology, dog, hematology, lymphoma, oncology

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Background

Within the practice of human oncology, standardized response criteria for malignant lymphoma have existed for decades and are periodically reviewed and updated, allowing for more consistent and meaningful comparisons of treatment protocols and outcomes.[1,2] In veterinary medicine, standardized assessment of response to therapy for malignant lymphoma is lacking, making these critical assessments of current and future treatment protocols difficult at best. While the production of standardized assessment criteria is a laudable goal, there exist some obstacles that are unique to the practice of veterinary oncology when compared with physician-based practice. First and foremost, advanced diagnostic technologies that are currently the norm for standardized assessment of disease stage and treatment response for lymphoma in people,[1] namely whole body CT and PET/CT imaging, flow-cytometric, cytogenetic and molecular

studies are not uniformly applied either because of a lack of availability or cost. More importantly, while these techniques have been standardized in human medicine, none have been standardized adequately for any veterinary species, diminishing their value as modalities for the reliable assessment of disease response regardless of the level of clinical trial funding. For the most part, a clinical standard for response assessment in lymphoma includes clinical examination and caliper measurement of enlarged lymph nodes. These clinical assessments of lymph node size are further complicated within veterinary oncology by the wide variation in body size seen in distinct breeds of dogs. This variation complicates the definition of a 'normal' sized lymph node. These limitations are addressed in the current document.

The standards presented in the following VCOG consensus document are an attempt to outline realistic and reproducible measures of clinical response that can exist within the constraints of current veterinary oncologic practice. The consensus draws heavily on published human guidelines essentially creating a hybrid document incorporating portions of standardized lymphoma assessments and Response Evaluation Criteria for Solid Tumours (RECIST).[1–3] While this document does not necessarily include the 'best' available components of response assessment, it strives to embrace the most 'applicable' methods that are currently widely available within the realities of veterinary medical practice. As with guidelines produced for human oncology prior to routine availability of PET/CT,[2] the VCOG guidelines do not critically assess extranodal disease (e.g., primary cutaneous, central nervous system, gastrointestinal, hepato-splenic) and are only intended for use in dogs, where **peripheral** lymphadenopathy represents the principal component of their disease presentation. No system is perfect for standardization and, indeed, the current document has sacrificed perfection for uniformed applicability and reproducibility. Additionally, this document (v1.0) is not intended to be permanent, rather the first working version of a system that should evolve over time as the practice of veterinary oncology evolves. It is hoped that where clinical assessment of peripheral lymph node (PLN) size is used in dogs with peripheral nodal lymphoma, that the suggested standards, presented herein, will be used. It is reasonable that for studies where additional assessment tools (e.g., PET/CT) are required to answer study-specific end points, they may supplement these guidelines, however, care must be taken to apply these evenly across study-specific groups for comparison.

Lymph node size evaluation

The size of a 'normal' lymph node has undergone considerable debate and refinement in the human literature and owing to the wide variation in companion animal breed size, the assessment of norms in veterinary practice becomes even more subjective. Currently, no guidelines or basis exists for the standardized assessment of normal lymph node size in veterinary medicine. Some authors have used human lymphoma guidelines,[1,2] others use WHO criteria, old and new RECIST criteria for solid tumours,[3] and others have created hybrids. The setting of minimum measurable size guidelines that supersede breed size variation is necessary to ensure reproducibility and accuracy. This is critically important as even small variations in measurement assessment can have profound effects on response rates and, in particular, assessment of progressive disease (PD). In both RECIST and human lymphoma guidelines, 10 mm represents the minimum size for consistent measurable nodes/lesions (even with the use of CT imaging).[1–3] This becomes even more critical when assessing recurrence (see later section) where a minimum of a 5-mm increase in lesion size for any single LN is used as part of the definition of PD. For this reason, we have chosen to set 10 mm as the minimum measurable node/lesion for dogs with lymphoma. Additionally, we have concluded, for the purposes of assessing response, at least one target lesion (see definitions below) must measure $\geq$20 mm at pretreatment baseline for reliable assessment of response and progression. It is recognized that some dogs with lymphoma have involved lymph nodes that are all smaller than 20 mm at presentation; however, an assessment of a contemporary case-series of 100 dogs with lymphoma at two institutions (UW-Madison, Madison, WI; The Oncology Service, LLC at

Friendship Animal Hospital, Washington, DC) with body sizes ranging from 4.2 to 61 kg body weight, only two dogs did not meet the criteria of having at least one involved node ≥20 mm at presentation (data not shown). It is concluded, therefore, that the exclusion criteria of 20 mm are reasonable to provide for accurate and repeatable lesion and response assessments. Based on consensus, we recommend the use of the longest diameter (LD) in millimetres as the measure of single lymph nodes, as well as the sum of the LD as the measure of target lesion (defined below) lymph node burden in a dog. Alternatives, such as the sum of the products or volumetric measures are more complicated and have not provided more informative assessments of response in lymphoma and other disease states.

Definitions:

At baseline, pathologic PLNs should be categorized as measurable or non-measurable as follows:

- **Measurable disease**: The presence of at least one measurable lesion ≥10 mm. At baseline, tumour lesions must be accurately measured in at least one dimension (LD) with a minimum size of 10 mm caliper measurement (measured to the closest whole mm) by clinical examination.
- **Measurable lesions**: Lesions that can be accurately measured in at least one dimension using calipers.
- **Non-measurable lesions**: All other lesions, including small (<10 mm) lesions, ascites, pleural effusion, lesions visible on thoracic radiographs, bone marrow lesions, lymphoma-related clinical pathology abnormalities (e.g., hypercalcemia).
- **Methods of measurement**: For PLNs, lesions should be measured by physical examination using calipers.

Tumours followed only by physical examination require assessment by two evaluators that may include veterinarians or qualified, experienced veterinary technicians. This duplication helps to confirm the measurement and substantiate any conclusions drawn for the purposes of a study. Remeasurement is required if the two evaluator measurements diverge by greater than 20%; if remeasurement is made, the mean of the resulting measurements should then be used.

Target lesions

All target lesions should be measurable involved PLNs with an LD ≥20 mm at baseline measurement. A minimum of one and a maximum of five involved PLNs should be identified as target lesions, and measured and recorded at pretreatment baseline and at stipulated intervals during treatment and follow-up. Target lesions should be selected on the basis of their size (PLNs with the LDs) and their suitability for accurate repetitive measurements (i.e., clinically, without imaging techniques). All remaining measurable and non-measurable lesions should be categorized as non-target lesions.

The LD should be recorded for each target lesion. The sum of the LD for all target lesions should be calculated and recorded as the baseline sum LD. Two evaluators should measure LDs; hence, the mean of the two sum LDs should be calculated (referred to as mean sum LD) and used as the reference to characterize the objective tumour response of the measurable dimension of the disease during treatment.

Special notes on the assessment of target lesions

- RECIST considers any lesion LD <10 mm by caliper measurement by clinical examination to be non-measurable;[3] however, these guidelines require measurements for target lesions to be recorded, even if they measured <10 mm. All target lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when they are very small (e.g., 5 mm). However, sometimes target lesions become so small when they return to normal LN size that the evaluator may not feel comfortable assigning an exact measure, and have historically reported them as 'too small to measure' or 'not palpable' (e.g., axillary LN). When this occurs, and if it is the opinion of the evaluator that the PLN is not palpable because it has returned to normal size,

a default value of 5 mm should be assigned. The measurement of these PLNs is potentially non-reproducible; therefore, providing this default value will aid in preventing false responses or progressions based upon measurement error. However, if the evaluator is able to provide an actual measure, that should be recorded even if it is below 5 mm.
- The term *nadir* is defined as the smallest mean sum LD at any time following initiation of treatment.

Non-target lesions

All other lesions should be identified as non-target lesions and their existence should be recorded at baseline. Each evaluator should describe and record the location, type, number and size (as appropriate to accurately identify the lesion).

- Measurements may be used to assist in tracking non-target lesions but are not required.
- Radiographic measurement of LN(s) (e.g., sublumbar LN, cranial mediastinal LN) may be used to assist in tracking non-target lesions but are not required; in this case, a single examiner is permitted and the measurement derived from this examination may be the only measurement made.
- Ultrasound measurements are not required and should be assessed with caution. In human oncology, ultrasound is not useful in assessing lesion size because of the dependence on operator, technique, lack of reproducibility and limited opportunity for validation.[3]
- Spleen and liver assessment are equally difficult as size may reflect variations in breed, anatomy, blood volume, treatment effects and cause other than lymphoma.[1,2,4] For the purposes of response guidelines presented below, if spleen/liver were considered 'enlarged' or abnormal at baseline, they should be considered normal by the same diagnostic modality(ies) used to assess them at baseline when evaluated on subsequent evaluations (physical examination, radiography).

Non-target lesions should not be used in calculations of changes in LD. Note that any LN [peripheral or other lymph node (e.g., cranial mediastinal LN, sublumbar LN)] spleen, liver, bone marrow or abdominal/thoracic effusions can qualify as a non-target lesion.

Special notes on assessment of progression of non-target lesions

- *When the patient also has measurable disease*. To achieve unequivocal progression on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR/CR in target disease, the overall tumour burden has increased sufficiently to require a change in therapy. A modest 'increase' in the size of one or more non-target lesions, in the absence of progression in target lesions, is not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease is expected to be rare.
- *When the patient has only non-measurable disease*. This circumstance may arise when a patient has a CR such that all non-target lesions return to normal size (e.g., PLNs) and do not meet criteria for 'measurable' disease (e.g., LD <10 mm). Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider whether the increase in overall disease burden, based on the change in non-measurable disease, is considered by the investigator to be sufficient to require a change in therapy. If 'unequivocal progression' is seen, the patient will be considered to have overall PD at that point.

New lesions

The appearance of new malignant lesion during the study should be classified as PD and the location,

type, number and size (as appropriate to accurately identify the lesion) of the new lesion should be recorded. A new lesion is one that was not previously a target or non-target lesion. A new lesion that is a PLN must be >15 mm in its LD to be considered a new lesion.[1]

If a new lesion identified by clinical examination is equivocal, (i.e. <15 mm) and could represent a previously overlooked lesion, continued therapy and/or follow-up evaluation will clarify if the new lesion truly represents PD. If repeat examination at the next scheduled evaluation period (See section on Follow-up Evaluations) confirms progression of the new lesion, the date of PD will be defined as the date of initial new lesion detection; however, if the new lesion has not progressed (i.e. still <15 mm and equivocal) at the next evaluation period, then the date of PD is deferred until unequivocal PD is documented.

There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to a difference in imaging technique, change in imaging modality or findings thought to represent something other than tumour. This is particularly important when the patient's target lesions show partial or complete response.

A lesion identified on a follow-up study in an anatomical location that was not imaged at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who develops a neurological sign during follow-up that was not present at baseline, necessitating further evaluation (e.g., brain CT) that reveals disease involvement. The brain involvement should be considered to be evidence of PD, even though there was no brain imaging at baseline.

If a new lesion identified by imaging is equivocal, for example because of it small size, continued therapy and/or follow-up evaluation should clarify if it truly represents new disease. If repeat imaging confirms that there is definitely a new lesion, the progression should be declared using the date of the initial imaging.

Bone marrow assessment

The assessment of bone marrow is not required under these VCOG guidelines. For lymphoma where peripheral lymphadenopathy represents the principal component of the disease, major treatment decisions are rarely made based on bone marrow involvement in dogs and its benefit to the patient, and the care-givers decision-making process is questionable based on limited association with prognosis (unless heavy involvement resulting in peripheral cytopenia is present) and a lack of protocol-altering decision value.[5] Quantification of bone marrow involvement is inherently difficult in both veterinary and physician-based oncology because of the lack of universally accepted standards/techniques and an inability to accurately quantify involvement.[1,2,6] In current human oncology guidelines, bone marrow aspirate/biopsy should only be performed to confirm CR if there was initially unequivocal positive bone marrow assessment at baseline, or if it becomes clinically indicated by a new abnormality in the peripheral blood count/smear at follow-up. As bone marrow assessment is not required at baseline in the VCOG guidelines, it is recommended that bone marrow aspirate/biopsy should only be performed to confirm CR if it becomes clinically indicated by a new abnormality in the peripheral blood count/smear at follow-up. A yes/no assessment of bone marrow would only alter the designation of response from a CR to a PR in these guidelines and would not affect the preferred outcome standard, progression-free survival (PFS) (see response end point discussion that follows) further diminishing its diagnostic value. These guidelines do not speak to the values of clinician's preference for baseline assessment of bone marrow.

Definition of response

The response definitions for target and non-target lesions are provided in Table 1. The Overall Response (PR, CR, SD, PD) is a function of the behaviour of target, non-target and new lesions; Table 2 provides the criteria for defining Overall Response (OR). All assessments of therapeutic efficacy should be based on the 'Overall Response'. Note that minimum size caveats are placed on

Table 1. General disease response definitions

Lesion response	Definition
Complete response (CR)	Target lesions: Disappearance of all evidence of disease. All lymph nodes must be non-pathologic in size in the judgment of the evaluator(s). Non-target lesions: Any pathologic lymph nodes must be considered to have returned to normal size in the judgment of the evaluator(s), and no new sites of disease should be observed. Spleen and liver should be considered within normal limits by the evaluator(s).
Partial response (PR)	Target lesions: At least a 30% decrease in the Mean Sum LD of target lesions taking as reference the baseline mean sum LD. Non-target lesions: Not applicable.[a]
Progressive disease (PD)	Target lesions: At least a 20% increase in the Mean Sum LD taking as reference the *smallest* mean sum LD at baseline or during follow-up (this includes the baseline mean sum LD if that is the smallest on study). The LD of at least one of the target lesions must demonstrate an absolute increase of at least 5 mm compared with its nadir for PD to be defined. For target lesions $<$10 mm at nadir, an increase in LD of any single previously identified target lesion to $\geq$15 mm. Non-target lesions: *unequivocal progression* of existing non-target lesions, in the judgment of the evaluator. (Note: the appearance of one or more new lesions is also considered progression).
Stable disease (SD)	Target lesions: Neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD. Non-target lesions: Not applicable.[a]

[a]Non-target lesions will be assessed as 'CR', 'PD', 'non-CR/non-PD' or, if there are no non-target lesions, 'None'.

the definition of PD in Table 1; that is, at least one target lesion must have an absolute increase of at least 5 mm compared with nadir, and if all target lesions at nadir are $<$10 mm, an increase to $\geq$15 mm is required for at least one target lesion to ensure minimum size for consistent measurable nodes are met (as discussed under 'Lymph Node Size Evaluation' section). Additionally, no temporal limit has been applied to the stable disease (SD) category; this is based both on the human convention for lymphoma[1,2] (unlike RECIST solid tumour assessment) and the similar clinical course in dogs where the majority of canine lymphoma represents a rapidly changing, initially highly responsive (so called 'liquid) tumour where durability and relevancy of the SD category are low. The timing of OR assessment should follow that outlined in the subsequent 'Follow-Up Evaluation' section; while OR is an important comparative efficacy criteria, the clinical relevancy of response should be best determined by temporal measures of efficacy defined below.

The Mean Sum LD for target lesions at re-evaluation should be compared with the Baseline Mean Sum LD for calculation of percent reduction or to the smallest Mean Sum LD (nadir) for percent increase. Although the assessment of target and new lesions will be a quantitative measurement, non-target lesions will be subjective. The evaluation of non-target lesions should be based upon whether lesions completely disappear or return to within normal limits in the judgment of the evaluator(s) (CR), were stable (non-CR/non-PD), or were progressively worse (PD) in the judgment of the evaluator(s) (see above definition of unequivocal progression of non-target lesions). In Table 2, the term 'non-CR/non-PD' refers to the persistence of one or more non-target lesions. Progressive disease of the non-target lesions is defined as 'unequivocal progression' based on the judgment of the investigator. If CR, PR or PD did not apply, a response of SD should be assigned. Unless there is unequivocal clinical progression, investigators should refrain from recording measurements at visits outside the standard assessment periods (see below) as more frequent repeated measures increase the likelihood of spurious errors.

Follow-up evaluations

Standardization of follow-up is equally important for comparability of varied treatment protocols in veterinary oncology. In the human literature, the frequency of follow-up schedules varies based on whether the disease is intermediate or high grade versus follicular or low-grade; for diffuse large B-cell lymphoma (also the most common histology in the dog), the human recommendation being assessments every 3 months for 2 years, and

Table 2. Overall response definitions

Target lesions	Non-target lesions[a]	New lesions	Overall response[b]
Complete response	Complete response or none	No	Complete response
Complete response	Non-CR/Non-PD	No	Partial response
Partial response	Non-PD	No	
Stable disease	Non-PD	No	Stable disease
Progressive disease	CR, PD, Non-CR/Non-PD, None	Yes or No	Progressive disease
CR, PR, SD, PD	Progressive Disease	Yes or No	
CR, PR, SD, PD	CR, PD, Non-CR/Non-PD, None	Yes	

[a]Non-target lesions may be assessed as 'CR', 'PD', 'non-CR/non-PD', or, if there are no non-target lesions, 'None'.
[b]Overall Response is a function of target, non-target and new lesions.

then every 6 months for 3 years.[7,8] For the VCOG guidelines reported here, it is recommended to standardize clinical re-evaluation to every month for 1.5 years, then every 2 months thereafter. This is based on the fact that in veterinary medicine, we are dealing primarily with intermediate and high-grade disease, the disease typically recurs more quickly than in humans and the median response intervals reported are generally less than 10 months. This re-evaluation schedule should allow for group comparisons over time that are meaningful within the context of the liquidity of canine lymphoma in general. Veterinary treatment protocols for lymphoma vary in dosing frequency and overall length, therefore the timing of the initial follow-up evaluation has been standardized at 6 weeks (42 days) after initiation of treatment. This will best coincide with treatment visits for both q3week treatment protocols and more intense weekly protocols, ensure sufficient time for inclusion of all agents represented in a multi-drug protocol, allow comparisons of protocols with varying lengths and limit the contribution of short-lived, clinically irrelevant responses in the assessment of response rate and duration.

The method of re-evaluation at scheduled time points is equally important to ensure valid comparisons. In human oncology, 'good clinical judgment and a careful history and physical examination are the most important components of monitoring patients after treatment'.[1] Importantly, the patient or physician identifies relapse more than 80% of the time without supporting evidence from imaging studies.[9–12] Based on the human experience, therefore, and the collective experience of the authors, the VCOG recommendations are for each evaluation to include a complete history, physical examination (including abdominal and rectal palpation) and measurement of peripherally measurable target lesions and assessment of non-target lesions. A complete blood count should be performed at every other re-evaluation period (i.e. every 2 months) following completion of therapy. Further imaging and/or advanced diagnostics should be reserved for those cases where PD from nadir is suspected based on routine assessment but requires advanced diagnostics to confirm, or a new clinical indication arises (e.g., new or recurrent clinical sign, peripheral blood cytopenia) which warrants further assessment.

Response duration end points

Beyond the assessment of objective responses by the criteria outlined above and in Table 1 and 2, the temporal nature of response requires standardization. Indeed, as is recognized in human oncology, the objective response rate does not necessarily address the clinical benefit or outcome of patients under our care.[13] VCOG consensus definitions for temporal measures of response are outlined in Table 3. In human lymphoma response guidelines, PFS is the preferred temporal assessment, in particular for generally incurable histologies.[1,2] As cure rates for canine peripheral node lymphoma generally meet the definition of incurable (< 10%) regardless of histology, this preference should hold true in veterinary medicine and is the current VCOG recommendation. The date of progression is defined as the first date that criteria for progressive disease are met (Table 1), or the date of death from any cause. In cases where data

Table 3. Response duration end point definitions

End point	Patients	Definition	Measured from
Progression-free survival (PFS)[a]	All	Disease progression or death from any cause	Initiation of treatment
Progression-free survival rate	All	The proportion of dogs that are alive and progression-free at a defined time point (e.g., 6 months, 12 months)	Initiation of treatment
Overall survival	All	Death as a result of any cause	Initiation of treatment
Event-free survival	All	Failure of treatment or death from any cause	Initiation of treatment
Time to progression	All	Time to progression or death from lymphoma	Initiation of treatment
Disease-free survival	In CR	Time to relapse or death from lymphoma or acute toxicity of treatment	Documentation of response
Response duration	In CR or PR	Time to relapse or progression	Documentation of response
Lymphoma-specific survival	All	Time to death from lymphoma	Initiation of treatment
Time to next treatment	All	Time to new treatment	End of primary treatment

Modified with permission from ref. 2.
[a]Preferred temporal assessment.

is incomplete with respect to PFS, the data should be censored at the last date at which progression status was adequately assessed or the first date of unscheduled new antilymphoma treatment. Other temporal measures outlined in Table 3 may also be reported and compared in addition to PFS. Note that progression-free survival rate (PFSR) is also included in Table 3. These can be calculated at predetermined time points such as 6-month and 12-month PFR and may be useful secondary end points.

Advanced diagnostics and imaging: the concept of complete response-advanced (CR_A)

This document is not intended to diminish or suppress the application of more advanced diagnostic or staging technologies when they are available. In fact, we implore those that have access to more advanced technologies to collect this information such that analysis could support their inclusion in future versions of VCOG response criteria when availability widens. Advanced assessments include but are not limited to whole body CT and PET/CT imaging, flow-cytometric, cytogenetic and molecular studies. Currently, a subset of veterinary and translational-based clinical trials involving pet dogs with lymphoma have applied such technologies,[5,14–25] however, they are not uniformly applied or standardized in veterinary practice either because of a lack of physical/technological availability or, when available, are outside the financial capabilities of most veterinary care-givers.

A distinction should be made between well-funded 'clinical trials' and 'routine practice'. In some well-funded veterinary clinical trials, a specific scientific question may require veterinary lymphoma patients be subject to more sophisticated or precise response assessments (e.g., PET/CT, bone marrow). Intuitively, such response assessments would not be comparable to those outlined in this document. When this occurs, it is recommended that the designation of CR_A be reported and more specifically, that a detailed description of the assessment methods and schedule be included in the materials and methods section of the published protocol. It is extremely important that the same criteria for determining CR_A needs to be applied across all treatment groups within such a study. Similarly, caution (and indeed avoidance) should be exercised when comparing these trials with others that use the more clinically simplistic assessments outlined in this VCOG document.

Support in the veterinary literature for the 'minimalist' diagnostic approach taken in this document is provided to a degree by the work of Flory *et al*.[5] who analysed a group of similarly treated dogs with lymphoma who were divided into WHO disease stages I–V[26] using five different diagnostic staging methods, each method represented by more advanced diagnostic analysis. Importantly, while they found that stage migration occurred with each ever-increasing diagnostic analysis grouping, there was no statistical difference in remission rate, duration or survival between the staging methods used.

Summary

This document is not intended to set mandatory guidelines for clinical trials, where response end points may be tailored to the treatment and study questions being investigated. Rather, the intent is to provide minimum guidelines for the description and comparison of treatment outcomes in routine clinical practice that are simple, repeatable and consistently applicable under the limitations (availability, cost) that currently exist in veterinary oncology. In some instances, accuracy has been compromised in favour of reproducibility. It is very likely that the current VCOG guidelines presented here will tend to overstate CR rates and understate PR rates. We must recognize and accept the fact that distinction between CR and PR rates will be subject to variation, however, the relative categorization into one or the other of these two groups ultimately will not affect the more important and preferred temporal end point of PFS. This is particularly germane in light of the fact that the current success of lymphoma therapy in veterinary oncology rarely results in cure and progression is inevitable, making a repeatable and widely applicable measure of progression, the most important component of any response guideline.

As is the case with guidelines established for human RECIST documents, we have created a web site (http://www.vetcancersociety.org/vcog-response-criteria.html) linked to the Veterinary Cancer Society (VCS) web site that presents clinical examples and answers to frequently asked questions (FAQs) regarding the application of these v1.0 guidelines. This should help to ensure a more uniform application of the guidelines.

As the availability and technical validity of more advanced methods of disease burden and response assessment progress in veterinary oncology, the easily adaptable guidelines presented in the current document should be periodically revised and submitted for consensus within the veterinary community.

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