Outcome Assessments
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Introduction

It is essential to have standardized methods for pathological evaluation of tumors and for assessment of patient outcomes to compare studies and to evaluate prognostic utility of pathological parameters. These two components of oncology must be linked as the goal of prognostic studies is to identify markers predictive of disease outcome. Outcome assessment results ultimately determine the utility of tumor classification and grading systems. Studies seeking to provide clinical validation of proposed prognostic or predictive markers must adhere to the highest standards and be reproducible, to convince their readership that the new methodology is clinically relevant and therefore worth investing time and effort to adopt. Recommended guidelines for the conduct and evaluation of prognostic studies in veterinary oncology were published in 2011 with the goal to-*increase the quality and standardization of veterinary prognostic studies to facilitate independent evaluation, validation, comparison, and implementation of study results. These guidelines should be considered a recommendation based on the current state of knowledge in the field, and they will need to be continually reevaluated and revised as veterinary oncology continues to progress.*[1] This reference is an excellent resource and Figure 1 summarizes the key elements required of a prognostic study.[11] In addition to this, the Veterinary Cooperative Oncology Group created a consensus document to establish a framework for standardization of procedures for response assessment in canine solid tumors.[2] Much of the information in this guideline is derived from these two publications.

A difficulty in organizing this guideline is that there are generic parameters of outcome assessment that can be broadly applied but there are also unique features that must be assessed which are tumor specific. For example, mast cell tumor (MCT) and lymphoma rarely to never metastasize to lungs, mast cells in lymph nodes can be present for non-neoplastic reasons and there is no marker to distinguish neoplastic vs

non-neoplastic mast cells. Some tumors have a predilection to metastasize to bone (prostate) and some spread to unusual locations such as the digits of cats with primary pulmonary carcinomas. Recurrence may be more important for certain tumors and for some tumors it is difficult or impossible to determine if it is multicentric vs metastatic (hemangiosarcoma, disseminated histiocytic sarcoma). This guideline is designed as a general guideline and unique features which are specific for a tumor type are not listed individually. A common feature for all tumors is that outcome assessment determines which histologic or gross parameters are clinically important.

With the aim of minimizing redundancy, the discussion will quote extant publications to emphasize major points whenever possible. Development of new potential standards or techniques will be cited separately and presented in relation to the original recommendations. An emphasis of histopathology, or cytology at a minimum, is emphasized as the gold-standard for confirming local recurrence and metastatic lesions, and this should be retained. Sentinel lymph node (SLN) mapping is mentioned, and since this publication, has undergone notable advances with multiple publications on several methods of SLN identification from a wide range of institutions.[3-11] In the absence of SLN mapping, locoregional lymph node drainage patterns have been published and can be used to guide presumptive SLN testing.[12] Although limited to canine mast cell tumors (MCT) at this point, a clinically-prognostic lymph node metastasis grading scheme has been published, suggesting an analogous scheme for solid tumor lymph node metastasis may be worth investigating.[13] Similarly, a recent publication in canine MCT demonstrated that approximately 50% of non-palpable/normal-sized regional lymph nodes harbored metastatic cells (HN2 or HN3), a finding that warrants investigation in other canine solid tumors as it may impact study design, patient staging, and outcome measurements.[14] Long term follow up is essential on these studies as presence of possible tumor cells in lymph nodes may not be as negatively prognostic as once thought. Originally, survival times of approximately 8 months were reported in dogs with cytologically confirmed lymph node metastasis of

MCT as compared to 6 years for dogs with normal or reactive lymph nodes.[15,1] However, this can be a self-fulfilling prophecy. Once owners are informed of the situation and the published survival statistics, this information can influence decisions to treat which in turn affects survival data. Other studies have reported prolonged survival times in dogs with Stage 2 MCT, however, the sample size in each study is low and treatments varied, both of which are common problems in veterinary publications.

The following elements are key features of study design discussed in these manuscripts.

Study Objective

_____ Clearly defined, testable hypothesis

Study Population See Note D E

_____ Tumor type (histological classification, location, other criteria)

_____ Define treatment groups

_____ Uniform therapeutic treatment

_____ Signalment

_____ Inclusion criteria

Reference Population See Note D E

_____ Case definition similar to study population but differing in prognostic factor

Sample Size

_____ Justify sample size (adequate to avoid type II errors)

_____ Number of prognostic factors monitored

_____ Number of events to be monitored

Assessment of tumor burden at baseline

_____ Clinical examination

_____ Imaging

_____ Radiographs

_____ CT

Outcome

_____ Event definition (criteria must be defined)

_____ Confirmation by imaging (indicate method)

_____ Confirmation by cytology

_____ Confirmation by histology

_____ Confirmation by autopsy (Note B)

_____ Define frequency of monitoring

_____ Determine 1,2 and 5 year survival probabilities, ideally with hazard ratios reported between groups[1]

Recurrence: See Notes B,C

_____ Local (presence of the same tumor within the region of the previous surgical site)

_____ Confirmed

_____ Histology

_____ Cytology

_____ Imaging (indicate method; (radiographs, ultrasound CT, MRI)

_____ Other (specify)

Palpation

_____Measurement (mm, cm)

_____Location

_____ Suspected

Follow Up

_____ Establish follow up interval times (prospective study) and include minimum length of follow up

_____ Determine 1, 2 and 5 year outcomes

_____Progression Free Survival (PFS)

_____Overall Survival Time (ST)

_____Disease Free Interval (DFI)

Establish RECIST Parameters for Documenting Response to Treatment
(see Note F)

_____Complete Response (CR)

_____Progressive Disease (PD)

_____Stable Disease (SD)

_____Partial Response (PR)

_____Not Evaluable (NE)

_____ Include animals with no treatment

_____ Complete physical examination

_____ palpation of treated site

_____ examination of locoregional lymph nodes

_____ thoracic cavity imaging

_____ 3 view radiographs

_____ CT

_____ Autopsy (Note B)

Data Censoring
see Appendix 1 Definitions Supplemental file 12

_____ Right (point) censoring[11]

_____ No relevant event by end of study *(remains alive, no recurrence, no metastasis, lost to follow up)*

Metastasis

See Note A. *Metastasis should be classified as "regional" (defined as locoregional lymph node involvement) or "distant." As with local recurrences, metastatic lesions should be stratified as either "confirmed" (i.e. histologically or cytologically confirmed, with histology preferred), or "suspected" (Note A). Refer to lymph node guideline 8.0 in development*

_____Diagnostic modality

_____histopathology

_____ cytology

_____imaging

_____radiographs

_____CT scan

_____MRI

_____Other

_____ Regional lymph nodes

tumor metastasis present

_____ How determined?

_____ How many lymph nodes evaluated

_____histologically ____cytologically

_____ No evidence of tumor metastasis

_____ How determined?

_____ How many lymph nodes evaluated

_____histologically ____cytologically

_____ Distant metastasis

_____ Present

_____ Absent

_____Location

_____How determined?

Euthanasia:

_____Euthanasia caused by tumor

How determined?

_____Euthanasia not caused by tumor

How determined?

Notes

A. Metastasis should be classified as “regional” (defined as locoregional lymph node involvement) or “distant.” As with local recurrences, metastatic lesions should be stratified as either “confirmed” (i.e. histologically or cytologically confirmed, with histology preferred), or “suspected.” Suspected metastatic lesions should be further described by clearly stating which diagnostic modalities were used in the study: fine needle aspirate cytology, imaging (e.g. radiology, ultrasound, contrast-enhanced computed tomography, etc.) or palpation alone. When using radiography to evaluate for pulmonary metastasis, a minimum of 3 views (right lateral, left lateral, and ventro-dorsal or dorso-ventral) should be used. Computed tomography provides superior spatial resolution to radiography and therefore studies should clearly state which imaging methods were used for which body regions. Confirmation of suspected metastatic disease is accomplished by histopathology, which is the gold standard. If the metastatic lesion cannot be safely sampled, it should be categorized as “suspected.” Reporting locoregional and pulmonary metastasis (or other organ metastasis) distinct from one another is important to facilitate identification of tumor biologic behavior patterns. Journals need to require the same terminology and definitions.

A future study should compare accuracy between physical examination characteristics, cytology, imaging, autopsy (gross appearance), histopathology, and molecular biology to confirm recurrence/metastasis, which likely may vary by tumor type.

B. Study participants with suspected metastatic and/or locally recurrent lesions may in fact have lesions unrelated to the primary tumor. Dogs with cancer have been documented to develop more than one tumor. Therefore, results from studies with large proportions of suspected lesions should be interpreted with caution. It should be noted that increasing the post-mortem examination rate in studies is crucial to generating valid results by maximizing the number of dogs that are histologically evaluated for metastasis and/or local recurrence. In particular, high autopsy rates (e.g. goal of at least 20% of patients) in future studies is essential to definitively resolve the variation seen in metastatic and local recurrence rates reported in the current literature, many of which lack histologic lesion confirmation and/or autopsy data. To assist in ensuring post-mortem exams and histologic confirmation of metastasis and or local recurrence, it should be included as a component of study design and its utility and significance described on the patient consent form as well as conveyed directly to owners choosing to enroll in the study.

C. Local recurrence is defined as the presence of the same tumor within the region of the previous surgical site confirmed via histopathology or cytology. Histopathology is preferred, however, tumor type influences which technique is used and more importantly, what is deemed best care for the patient. There are multiple reasons that histopathology is preferred to confirm recurrence. Histology is required to exclude benign causes of a mass in the region of the surgical scar (e.g. reactive fibroplasia, gossypiboma) or unrelated de novo tumors (e.g. mast cell tumor). Additionally, cytologic evaluation of fine needle aspirates cannot distinguish granulation tissue from neoplastic spindle cells or identify the type of

STT. All recurrent masses should be measured by the clinician, surgeon, histotechnologist handling/trimming the gross specimen and pathologist. Local recurrence data should be stratified as either “confirmed” (e.g. histologically confirmed STT/STS) or “suspected.” Suspected local recurrences should be further described by clearly stating which diagnostic modalities were used in the study: fine needle aspirate cytology, imaging (e.g. ultrasound, contrast-enhanced computed tomography, etc.) or palpation alone. Standard RECIST VCOG v1.0 criteria should be used in reporting recurrences. A local recurrence should be counted as a single event regardless of the number of tumor nodules that may have appeared at the original surgical site. If a STT/STS arises at a different soft tissue site it should be categorized as a “de novo STT/STS at a different site” and not a metastasis.

D. Treatment Groups

Studies should clearly define the treatment groups evaluated in the study. Differences between treatment groups should be minimized such that any observed outcome differences can be attributed to the treatments evaluated. Study design, with specific attention to number of groups and sample size, should be carefully considered to avoid type II statistical errors. Manuscripts must provide detailed descriptions of the treatments used. Furthermore, patient tumor descriptions should be adequately detailed with appropriate staging information provided. In addition to complete staging information (standardized RECIST VCOG v1.0 measurements, locoregional lymph node status, and presence of metastasis), tumor location should be included as distally located STT/STS may display a unique biologic behavior pattern.

The start time (T=0) of survival studies needs to be clearly and consistently defined in the materials and methods section of manuscripts.[2] There are a variety of potential events to establish start time: the day of first treatment is

recommended (surgery, chemo, RT) but options include the date of clinical diagnosis, the date of surgical tumor removal and the date of histopathological tumor diagnosis.[2] This is an example of why the materials and methods section of manuscripts need detailed descriptions of methods, so others can understand what was done and perhaps replicate the study design for validation.

E. Clinical data must be collected with the same rigor applied to pathological data and standardization is requisite. Studies should document standard clinical parameters such as the presence, absence, and/or development of regional and distant metastasis as well as local recurrence in a standardized manner and at fixed time intervals. Information on all treatments the patient received should also be documented, although the development of the grading scheme ideally should be restricted to patients treated with surgery only. Therefore, the inclusion of additional endpoints such as time to first event and disease-free interval must be reported, as these may represent more objective measures of treatment effects. If survival times are reported, then the manuscript's methods section needs to clearly define if the patient was euthanized and how it was determined that the tumor contributed to the cause of death (e.g. owner could no longer administer nursing care, dog developed a new tumor, etc.). This information should be published in a table as supplementary data.

F. Definitions and terminology used for clinical outcome measures should be consistent across studies to facilitate comparisons in the literature. Appendix 1 Supplemental file 12 summarizes some of the most important terminology for readers, especially pathologists who may be less familiar with these clinical definitions, for ease of reference while using the online resource. However, complete definitions are found in widely adopted references[2,1] and readers are encouraged to consult these publications for details.

The assessment of outcomes, and the modalities used to assess them, is a topic in oncology studies that will change as technology and derived clinical methodologies evolve. The materials and methods section of manuscripts must contain complete and clear definitions of the outcomes measured and the modalities used, such that others can replicate the study. Recurrence or metastasis are straightforward to a pathologist, for both of which histopathology remains the gold-standard test. However, histopathology is not always feasible due to concerns for patient morbidity and therefore other metrics are frequently employed (e.g. survival times or intervals; cytology). However, survival can be defined in multiple ways; for example, “overall survival” or "disease-specific survival." Overall survival time (and relatedly, all-cause mortality rate) is a metric that frequently is confounded due to the availability of euthanasia in veterinary patients. Use of a generic term such as “survival time” is vague and does not differentiate if death was from any cause, death from the cancer being studied, or due to euthanasia motivated by any number of factors (e.g. perceived quality of life, financial considerations, limitations in providing requisite nursing care, etc).

Reporting “progression-free survival” (PFS) is considered a more accurate measure of treatment effect since it quantifies the duration of time until the disease is observed to progress. This metric captures both patients that have all detectable disease removed (e.g. post-operative patients in which no gross disease remains), as well as those with some amount of residual disease (i.e. either post-operatively or tumors treated with radiation and/or chemotherapy) that will be undergo active surveillance (details of which must be provided in the study's methodology) until the tumor increases in size or metastasizes. The phrase "disease-free survival" (also termed "disease-free interval") is a subset of PFS which is predicated on the patient experiencing a complete response and being disease-free; however, thorough documentation of a truly disease-free state is considered controversial due to limitations in diagnostic techniques and

hence PFS is the preferred clinical outcome metric as it more accurately represents the unknowns related to occult disease (e.g. microscopic) within the patient. Determining survival probabilities at defined time points (1, 2, 5 years) is critical to compare different prognostic studies; moreover, reporting *hazard ratios* between groups is considered the best indicator of the prognostic significance for a given parameter (e.g. mitotic count) or treatment effect. Clinicians are positioned to determine outcomes, through careful use of correct terminology and diagnostic methodology, and report the findings with appropriate statistical methods. They also are the individuals that must balance patient care and individual owner scenarios while striving for accurate outcome data, which is a difficult task, emphasizing the need for transparency and consistency in outcome reporting.

RECIST

Canine response evaluation criteria for solid tumors in dogs (cRECIST v1.0) provides the framework for the measurement of tumor burden before, during and after therapy.[2] The following are a summary of key points from that publication related to clinical outcome measures. This includes establishing baseline measurements of the primary tumor as well as metastatic lesions (lymph nodes and/or distant metastasis). Thorough definitions of complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD) are provided and many can also be found in Appendix 1; Supplemental file 12. Frequency of re-evaluation is generally recommended every 6-8 weeks with shorter or longer intervals justified depending on the tumor type, nature of therapy, etc. Cytology and histology are recommended to confirm response to treatment. When not possible, presumptive assessment via imaging is acceptable and guidelines on specific imaging modalities are provided (e.g. CT preferred over ultrasound due to inter-operator error and over radiographs due to increased sensitivity for size and presence of lesions; CT 5mm maximum slice thickness; PET/CT cannot be used for measurements due to poor spatial resolution). Reporting of progression-free survival (PFS; which allows for presence of neoplastic

disease, but it is not progressing/growing/metastasizing for a period of time), in contrast to overall survival time (due to potential confounding due to varied reasons for euthanasia in veterinary medicine), is emphasized.

A forthcoming consensus statement on grading of canine soft tissue sarcomas from the Veterinary Cancer Society-American College of Veterinary Pathologists Oncology Pathology Working Group contains a relevant guideline on measurement and reporting of clinical data, including outcomes.* The following italicized text is quoted from this document (references removed from quoted text below but available in original document), emphasizes similar points as the above publications, *"… with further explanation as applicable to canine STS … to encourage uniform use of terminology, transparency in data reporting, and comparisons among future studies*."

* = Guideline 2 "Clinical Data" from VCS ACVP OPWG Soft Tissue Sarcoma Subgroup Consensus on Grading Canine Soft Tissue Sarcomas; to be published

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