Abbreviations and Definitions
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Introduction

The purpose of this document is to define terms and abbreviations used in other guidelines. The definitions and abbreviations are organized by guidelines, browse and you will understand. Whenever a definition is repeated in multiple guideline sections, care has been taken to use the same wording to prevent confusion or contradiction Some information here goes beyond what is provided in guidelines. Each guideline has the options of co-listing and expanding those provided here therefore look in specific guidelines if the information you are seeking is not here. Definitions for CPATH are in the CPATH Guideline and only a few are provided here. If a colleague finds an omission or you want to add information, please contact one of the communication authors.

Websites to consult:
https://www.microscopyu.com/microscopy-basics/microscope-objective-specifications

https://www.translatorscafe.com/unit-converter/en-US/calculator/field-of-view/

https://www.microscopyu.com/microscopy-basics/microscope-objective-specifications

https://www.translatorscafe.com/unit-converter/en-US/calculator/field-of-view/

Mitotic Count and Mitotic Figure Morphology Guidelines:

AMF: Atypical mitotic figures

FN objective:

Field number in mm is engraved on some objectives; it indicates the maximum FOV diameter that can be achieved using this objective, however it is the ocular FN which limits the size of FOV in a standard light microscope, not the objective FN. All objectives have a FN but it may not be engraved on the objective. In configurations using objectives with no ocular (such as a scanning device or camera), the objective FN determines the FOV. Should an objective FN mm be smaller than the ocular FN mm, the margin of the field seen will be distorted. This happens when older objectives are used with newer oculars.

FN ocular:

Field number in mm engraved on side of eyepiece – that number is the maximum diameter (mm) that can be seen in the FOV with this eyepiece; the higher the number the larger the FOV diameter; FN ocular/objective magnification = diameter of FOV mm at specimen level; FN18mm 0.45 mm diameter FOV specimen level 40X objective, narrow FOV , present on older microscopes; FN 22mm common on modern microscopes for pathologists 0.55mm diameter FOV with 40 X objective, FN 26.5mm wide FOV 0.66 mm diameter with 40 X objective, modern microscopes. If a scope has 40X obj 10X ocular FN 22 and the diameter of FOV does not measure 0.55mm with a stage micrometer then check how the microscope is configured: e.g. tube lens, or get a higher quality stage micrometer and/or check with scope representative; the precision of

production of high end objectives and oculars is +99% (See Figure 9 in Guideline 2, Mitotic Count)

FOV Microscope:

Field of view – field visible through microscope, the diameter of one FOV can be calculated by dividing the ocular FN (mm) by objective magnification; or the diameter can be measured with a stage micrometer. Use the formula for area of a circle to determine the area of one FOV in a light microscopic field at a specified magnification= $\pi \times r^2 = mm^2$. Example: FN 22 mm and 40X objective = 22mm/40 = 0.55mm diameter/2= 0.277mm radius raised to the second power = $0.076mm^2 \times 3.14 = 0.237$ mm^2. When the radius doubles the area of the circle increases four-fold; therefore, incremental increases in FN mm result in large increases in area.

FOV WSI:

Field area displayed on monitor of scanned digital image, the actual area of which can be calculated through use of tools in the image management software. The FOV area in WSI varies between different monitors, viewing software, scanning methods etc. FOV and HPF are inaccurate definitions of tissue area. Ten HPF is not a specified area for a microscope or WSI. In digital images size of area should be given in mm^2.

HPF:

High power field, by convention is the area viewed through a 40X objective. However, the area seen varies with the specifications of the microscope ocular. Depending on the ocular specifications (FN mm), the field of view (FOV) with a 40X objective can vary by > 200%. HPF is not a valid unit of measure and should not be used to define area. Similarly, low power field should not be used to define an area.

MC: Mitotic count- the number of MF + AMF/unit area mm^2

MF: Mitotic figures

MI: Mitotic index- the number of MF + AMF/ number of tumor cells

MLF: Mitotic like figures

NA: Numerical aperture- number engraved on some objectives, NA is not used to calculate FOV area; it is critical for resolution and depth of field; resolution of an objective is its ability to distinguish closely spaced objects however, the final resolution of the image also depends on the NA of the substage condenser, the higher the NA of the entire system, the greater the resolution, “sharpness” of features; maximum NA with dry objectives is 0.95 and is approximately 1.0-1.5 with oil immersion objectives; objectives with higher NA can be configured with a focusing collar to adjust for thickness of coverslip; objectives may be engraved with a decimal number e.g. 0.17 that corresponds to the “expected” thickness of the coverslip on the glass slide, coverslip thickness for #1 is 0.13-0.16mm. Websites will provide what other information engraved on an objective means.

Objective:

Higher quality objectives are engraved with multiple initials and numbers, the definitions of a few are provided here: NA, FN, WD; websites will detail engraved information; objectives are the most important component of a light microscope, apochromatic objectives are the most highly corrected lenses, and the most expensive; objectives are the closest component to the object (specimen), hence their name.

WD:

Working distance, mm = engraved on side of some objectives; distance between the lens of the objective and the top of the cover glass when specimen is in focus. The higher the objective magnification the shorter the WD (ranges 0.13-10mm). High quality objectives will have focusing collars, cover glass adjustment gauge etc. Small cover glass plates are standardized to 0.17mm, variations in thickness can be compensated for by a focusing collar.

WSI:

Whole slide image – an entire histopathological glass slide is digitized at a specified scanning magnification and resolution. Software permits viewing of the image like a light

microscope. Resolution and different magnifications are limited by scanning technology. See CPATH

Evaluation of Margins Guideline

Compartment:

An anatomic space containing a particular tissue type (e.g. fat, muscle, bone, etc) that is believed to inhibit tumor extension due to natural barriers separating adjoining tissue types.[5] Tumors can grow within, or infiltrate into, tissue compartments. The barriers formed by compartments are believed to be variable in effectiveness for reducing tumor spread.[10] For example, adipose tissue, loose connective tissue, and muscles in the skin and subcutis are considered to be less effective, if at all, compared to dense mesenchymal tissue or cortical bone. Compartments to consider include the connective tissue sheath present around most skeletal muscles (commonly referred to as “fascia”), bone (which may include periosteum and/or cortical bone), skeletal muscle (epimysium), joints (joint capsule), CNS (dura mater) and peripheral nerves (perineurium). Pathologists should describe the histologic relationship of the tumor to the compartmental boundaries. The HTFD (histologic tumor-free distance, see below) may not need to be as large with a more effective barrier as opposed to an ineffective barrier.

Curative-intent therapy/treatment:

Treatment that is intending to eliminate the tumor (and any associated metastatic lesions) from the patient such that recurrence or metastasis does not occur within their lifetime. This is balanced against the overarching goal of preserving quality of life, and hence a true “cure” is rarely reached for more aggressive tumor types. Quantity of life is often extended longer than with palliative treatment (but not always) while attempting to preserve quality of life through minimizing risk for adverse events.

Cytoreductive surgery:

A non-specific term indicating surgical reduction of tumor cell numbers. Roughly synonymous to debulking. These terms are often used when complete removal (eradication of all tumor) is not the goal of surgery and rather palliative surgery is performed, leaving gross disease in the patient; expect tumor to be at margin. However, a curative-intent surgery that entirely removes the tumor (with no tumor at the surgical margin) has also technically cytoreduced/debulked the tumor and therefore these words can be confusing and should ideally be avoided in favor of more specific terminology (see below).

Fascia:

An anatomic structure that has layers: superficial, deep, visceral, and parietal. Fascia have been defined as sheets, sheaths or other dissectible connective tissue that attaches, encloses, or separates muscles.[1,6,16] Thickness and tensile strength of fascia is markedly variable in different anatomical locations. Some are thin, barely discernible, torn easily (subcutaneous superficial fascia) while others are thicker, visible grossly and histologically (deep fascia on muscles). Recent publications detail fascia for the dog and horse.[2,16] Masson's trichrome may help visualize collagen in fascia.

Fascial Plane:

The term "fascial plane" is used as a concept and is not a specific anatomical structure. A recent publication describes fascia and surgically identifiable fascial planes for the dog.[16] Fascial planes are described in the surgical literature and can be used to dissect along to isolate and excise tumors from the skin, subcutis, and musculoskeletal system, more so than when removing tumors from internal organs. It is recommended that excision of potentially aggressive tumors from the subcutaneous tissue include at least one uninvolved fascial plane, deep to the tumor.[3,7,14] The intact fascial plane below the tumor provides a physical barrier of normal tissues such as collagen, muscle and other tissues that may help prevent extension of the tumor. Pathologists rely on the morphological features of anatomical structures to identify fascia and boundaries of the fascial plane indicated by the surgeon. Information provided by the surgeon on the pathology requisition form is critical and can clarify what tissues they envision are in the

specimen, what margin they want evaluated and if fascia is to be searched for. The terms “fascial plane” or “tissue barrier” are routinely used by surgical oncologists and are suggested to provide a natural anatomic barrier to tumor growth and invasion.[5,10] Both terms need to be clearly defined with gross, histological and functional criteria such that surgeons and pathologists know what each is, especially for vaguely defined compartments such as the subcutaneous tissue. Fascial plane is not synonymous with “fascia”. See Tissue barrier.

HTFD:

Histologic tumor free distance is a microscopic measurement, performed by a pathologist, of the shortest distance from the neoplasm to the surgical (e.g. inked) margin; measure lateral (peripheral; circumferential) and deep margin for skin subcutaneous tumors. Measurement should be in whole numbers (i.e. millimeters). Ink should be applied by the surgeon – clinician to the gross specimen. Any HTFD reported if the gross margin was not inked by the clinician is of questionable value.

HTFM:

Histologic tumor free margin – synonym of HTFD; see HTFD

HSM:

Histologic safety margin- the minimum microscopic distance that purportedly will prevent local recurrence of a specific tumor type; defined for some human tumors but remains largely undefined in veterinary species. The singular example in veterinary oncology is canine MCT in which a HSM was not found for high grade MCT and for low grade MCT the HSM was “inconsequential” since they did not recur even with tumor cells at the margin.[4]

Incisional biopsy:

See Intralesional Excision.

Intralesional excision:

Synonymous with incisional biopsy. Macroscopic or microscopic tumor is left at the margins of the incision, typically performed in order to obtain a diagnosis, but may also be used as part of a multi-modal palliative treatment strategy.[5]

Marginal excision:

Synonymous with excisional biopsy. Surgery in which the neoplasm is excised with no margin of grossly normal tissue (the plane of dissection is through the pseudocapsule or reactive tissue adjacent to the neoplasm). Marginal excisions are usually performed in areas in which critical anatomic structures makes wide excision difficult (e.g. excessive patient morbidity is expected with surgical manipulation of neighboring anatomic structures, such as nerves or arteries), or marginal excision is used in combination with adjunctive chemotherapy or radiotherapy to provide more durable tumor control (may be considered curative-intent, depending on the tumor type). Neoplastic cells are expected at the surgical margin and the clinical significance of this finding will depend on the tumor type (e.g. marginal excision of a benign or low-grade neoplasm may not result in tumor regrowth vs. marginal excision of a malignant tumor will frequently lead to tumor recurrence).[5]

Panniculus carnosus:

The band of skeletal muscle within the subcutaneous tissues (deep to the panniculus adiposus), associated with a band of connective tissue that may act as a thin tissue barrier, and may or may not be adequate to prevent tumor invasion depending on the biological behavior of the neoplasm. Synonymous with cutaneous trunci or subcutaneous striated muscle.

Palliative-intent therapy/treatment:

Treatment of a neoplasm with the intent to improve patient quality of life (e.g. palliate a particular clinical sign or constellation of clinical signs associated with the tumor's presence) without necessarily extending quantity of life, although the latter often occurs due to owners electing not to pursue euthanasia if their pet's quality of life is improved.

Notably, this requires the patient to be experiencing some degree of morbidity from the tumor (e.g. bone pain from an osteosarcoma) that the planned treatment will alleviate (e.g. radiation or amputation). In some scenarios, this may slow the progression of neoplastic disease by removing tumor cells (either via surgery, radiation, chemotherapy, or combinations thereof), but generally does not achieve long-term complete remission.

Radical excision:

Excision that includes removal of the tumor, capsule, reactive zone, and entire muscle or bone involved (eg amputation). The planes of dissection are outside the involved tissue compartment. Does not necessarily imply a greater margin distance than a wide margin, depending on tumor location relative to the excision site.[5]

Surgical dose:

A phrase meant to encapsulate how large or aggressive of a surgery was performed and most typically uses widely-accepted Enneking categorization of surgical margins (i.e. Intralesional, Marginal, Wide, or Radical).[5] More recent surgical dosing strategies include consideration of quality of the surgical margin (e.g. tissue compartments with fascial planes) and biological behavior of the specific tumor being removed (e.g. evidence of growth within a tissue compartment vs. invasion through a compartment's natural barrier).

SSM:

Surgical safety margin (synonym: safe surgical margin) is the length of the grossly-normal surgical margin (measured by the surgeon prior to skin incision, typically intra-operatively) associated with a high probability of achieving adequate local control (i.e. high probability of no tumor regrowth at the surgical site). This may include lateral (peripheral; circumferential) and/or deep margin sizes (e.g. two cm wide and one fascial plane deep). Such recommendations need clinical validation in veterinary medicine via prospective longitudinal clinical studies and are expected to vary by tumor type, grade, location, and other relevant variables associated with biological behavior of the tumor.

Tissue barrier:

Tissues within anatomic compartments and fascial planes may provide natural barriers to tumor extension.[5] If tissues are functional barriers to tumors the mechanisms by which this is accomplished needs to be defined. Are they physical barriers that depend on the quantity or quality of the tissue (fascia, muscle, bone) and or are there inhibitors present that limit tumor growth? Experimental data to support these theories and studies which define the mechanisms in which tumor spread is limited are needed. The peritoneal serosa is a reported barrier to tumor cell migration invitro.[8] The type of tumor, grade of tumor, whether it expands circumferentially, infiltrates, or skips (discontinuous growth pattern) influences how effectively a potential tissue barrier may function.

Wide excision:

Excision in which the pseudocapsule or adjacent reactive tissue are removed *en bloc* with the neoplasm. The plane of dissection is through grossly normal tissue but may remain within the involved compartment. Depending upon the type of tumor, the definition will vary but the concept is: 2-5 cm and 1-2 fascial planes; no tumor at surgical margin is goal. Studies will need validation for clinicians and pathologists to be confident that HTFD margins as close as 1mm, or “no tumor touching ink” are actually sufficient for sarcomas and other aggressive tumors. Readers should consult references for additional definitions and use of the residual tumor system.[5,11,20]

References for Margins and Outcomes are at end of Outcome Assessments:

Lymphovascular Invasion Guideline

LVI:

Lymphovascular invasion – neoplastic cells gaining access to lymphatic or blood vascular channels, is recognized as a criterion of malignancy; invasion of tumor cells into blood and or lymphatic vessel.

IMD:

Intratumoral microvascular density, quantitation of blood vessels as a measure of angiogenesis.

LVD:

Lymphatic vessel density - enumeration of lymphatics in a defined area of the tumor or peritumoral tissue is used as an indicator of lymphangiogenesis.

Outcome Assessments Guideline
(See references for details and complete definitions)

Comment:

A partial list of the commonly used terms and lexicon used in reporting outcomes are summarized here. They are primarily for easy reference and for pathologists who may not be as familiar with these definitions as clinicians and radiologists. The assessment of outcomes, and the modalities used to assess them, is a topic in oncology 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 that were measured, the modalities used and the statistical methods applied, such that others can replicate the study. Complete definitions are found in widely adopted references[12,19] (and readers are encouraged to consult these or other publications for details). Some definitions below simply reference those resources.

Censoring:

There are various types of censoring and as with all statistical analyses, the reader is encouraged to consult with a biostatistician familiar with clinical research to ensure appropriate use of statistical methodology. Censoring is necessary if an animal has not experienced the relevant event (such as death or relapse) by the end of the study period, is lost to follow-up, or has experienced a different event that makes further follow-up impossible, such as death from an unrelated illness. Animals experiencing these situations are censored (some use the term right censored) and must be accounted for by using survival analysis methods. Other terms in the literature are left censored data and interval censoring.[19]

Confirmed metastasis:

Microscopic confirmation, performed by a pathologist, that the same tumor type has metastasized. See suspected metastasis. Histopathology is preferred but feasibility will depend on tumor type and suspected metastatic lesion location.

CR:

Complete response (cRECIST v 1.0)[12]: Disappearance of detectable neoplastic (target and non-target) lesions following treatment. Complete remission, synonym, response preferred. See PR.

Curative-intent therapy/treatment:

Treatment that is intending to eliminate the tumor (and any associated metastatic lesions) from the patient such that recurrence or metastasis does not occur within their lifetime. This is balanced against the overarching goal of preserving quality of life, and hence a true “cure” is rarely reached for more aggressive tumor types. Quantity of life is often extended longer than with palliative treatment (but not always) while attempting to preserve quality of life through minimizing risk for adverse events.

DFI/DFS:

Disease-Free Interval/Survival: The length of time between complete response and disease recurrence, metastasis, death due to disease, or acute toxicity of treatment. Although disease-free “interval” and “survival” are often used interchangeably in the literature, DFI should be reserved for individual patients while DFS should be used when calculating a value for a population (e.g. using a Kaplan-Meier survival curve where the event is defined as disease progression). For this reason, in contrast to DFS, DFI is not censored, and it is used for patient classification and not for outcome analysis. A problem with DFI/DFS is that patients are difficult to confidently classify as completely disease-free unless they are *cured* which can depend on how extensively the tumor is searched for and with which modalities, therefore it is considered highly subjective. Example: in appendicular osteosarcoma the dog is “disease free” at the time of amputation but micrometastasis is expected within the lungs and chemotherapy

treatment may go over many weeks and they can develop metastasis while on chemotherapy. For this reason, the alternate and preferred outcome measure is PFI – progression free interval (see below). Terms and definitions must be clearly stated in materials and methods section of publications so others can understand the methods and statistics.

Grade of Cancer:

Histologic or cytologic system (scheme) used to estimate the aggressiveness of a neoplasm. One or more parameters (MC, differentiation, necrosis, pleomorphism, multinucleation, LVI) assessed by a pathologist that are used individually or in combinations to assign a score which helps clinician predict prognosis and or decide on treatments. Grading systems are specific for tumor type and species. Grades are usually assigned by a pathologist and stage is determined by a clinician.

Imaging:

Modalities used to assess tumor size, invasion, recurrence or metastasis of neoplastic diseases. Imaging can be used to facilitate obtaining specimens for microscopic analysis, including fine needle aspiration for cytology or true cut biopsies. Commonly used modalities include radiography, ultrasonography, CT, MRI and PET/CT.

Immune related response criteria:

Distinct criteria for therapeutic response in human patients undergoing immunologic tumor therapy has prompted development of distinct response criteria for evaluation of therapeutic response. Favorable survival times can be associated with slower initial response times relative to other forms of therapy and reduction in tumor burden may follow initially increased tumor burden or tumor pseudo-progression. Veterinary-specific immune related response criteria have not been developed but oncologists should be cognizant of the distinctions in tumor response to immunologic therapy.[9,18] Also see iRECIST (below).

Multivariate:

Refers to statistical analysis with multiple outcomes.[15]

Multivariable:

Preferred usage for oncologic studies. A statistical tool used for determining relative contributions of different causes to a single event or outcome. With multivariable analysis, there are many explanatory variables" (e.g. multiple predictive factors such as histologic parameters). This type of analysis allows simultaneous assessment of the independent contribution of each risk factor to the development of the outcome.[15] The most common types of multivariable analysis include linear regression, logistic regression and proportional hazard regression (Cox).[15]

MRI:

Magnetic Resonance Imaging.

NE:

Not evaluable: The point at which a patient cannot be evaluated for recurrence or progression of neoplastic disease, due to the inability to obtain measurements at this time point.

Overall Survival (OS):

The length of time between initiation of treatment and death of any cause. Overall survival data can be misleading, due to the availability of euthanasia in veterinary patients, the multiple reasons for euthanasia, and the owners' choice to pursue treatment. See survival time (ST).

Overall Survival Rate:

The proportion of animals that are alive for a certain period of time after initiation of treatment (e.g., 6 months, 12 months).

Palliative-intent therapy/treatment:

Treatment of a neoplasm with the intent to improve patient quality of life (e.g. palliate a particular clinical sign or constellation of clinical signs associated with the tumor's presence) without necessarily extending quantity of life, although the latter often occurs due to owners electing not to pursue euthanasia if their pet's quality of life is improved. Notably, this requires the patient to be experiencing some degree of morbidity from the tumor (e.g. bone pain from an osteosarcoma) that the planned treatment will alleviate (e.g. radiation or amputation). In some scenarios, this may slow the progression of neoplastic disease by removing tumor cells (either via surgery, radiation, chemotherapy, or combinations thereof), but generally does not achieve long-term complete remission.

PD (cRECIST v 1.0)[12]:

Progressive Disease: Either the appearance of one or more new lesions or at least a 20% increase in the sum of the diameters of the target lesions, taking as reference the smallest sum on study. The sum must show an absolute increase of 5mm.

PET/CT:

Positron Emission Tomography/Computed Tomography: A scan that can be used to confirm the presence of regression of lesions but cannot be used to measure lesions. PET/CT uses radioactive tracers for visualization of neoplastic cells.

PFI/PFS:

Progression-Free Interval/Survival: The length of time between initiation of treatment and worsening of clinical disease (i.e. experiencing progressive disease). Although progression-free "interval" and "survival" are often used interchangeably in the literature, PFI should be reserved for individual patients while PFS should be used when calculating a value for a population (e.g. using a Kaplan-Meier survival curve where the event is defined as disease progression). For this reason, in contrast to PFS, PFI is not censored, and it is used for patient classification and not for outcome analysis. Progression-free survival is generally considered a preferred outcome measure due to the inherent limitations of definitively diagnosing disease-free status and/or recurrence.

This end point is accessible sooner than overall survival and is preferred over overall survival (OS) since overall survival is influenced by factors not necessarily related to the neoplastic disease itself, for example the choice of an owner to continue treatment after relapse vs. electing palliative care or euthanasia. Reporting of PFI/PFS allows for presence of neoplastic disease, but it is not progressing/growing/metastasizing (is stable disease; SD) for a specified period of time and does not meet the criteria for progressive disease (PD). Terms and definitions must be clearly stated in materials and methods section of publications so others can understand the methods and statistics.

PFS rate:

Progression-free survival rate: The proportion of animals that are alive and progression-free at a defined time point (e.g., 6 months, 12 months).

PR:

Partial response (cRECIST v 1.0)[12]: At least 30% reduction in the sum of diameters of the target neoplastic lesions, taking as reference the baseline sum, and a reduction or stable persistence of non-target lesions. Also referred to as partial remission – preferred term is response; see CR.

Prognosis:

Prognosis is the prediction of probable clinical outcome or course of the disease made from the patient data (e.g., clinical signs, underlying diseases) and disease characteristics (e.g., grade, molecular markers, other parameters) and the administered treatment(s). It is assigned by the attending clinician. The pathologist provides results of specific parameters which in turn are used by the clinician to aid in providing a prognosis.

Because so many variables impact prognosis, oncology studies must control for as many as possible by standardizing inclusion and exclusion criteria and defining and strictly adhering to uniform treatment protocols for enrolled patients. Studies need to be validated before oncologists and owners rely on the results. Our present system of adopting new methods of tumor assessment from published studies lacking appropriate

numbers of cases with insufficiently detailed methods needs to be changed. Initial studies need to evaluate multiple parameters and apply rigorous statistical evaluation before they are trimmed to the core, essential criteria that are prognostic. When these core parameters are identified, they need to be tested in an independent population to confirm their broad applicability and prognostic significance. Once validated, these core criteria can then be added to the workflow of diagnostic pathologists and oncologists. Investigations that are validated with other patients, pathologists and clinicians add credibility and will ultimately improve patient care. Oncology studies provide statistical probabilities of an outcome for a population of pets with like tumors but cannot predict the outcome for a specific patient. However, larger studies that include diverse representation of the patient population, while controlling for inclusion and exclusion criteria, will increase the likelihood that the results of a study will be clinically applicable to a given patient.

Prognostic markers are characteristics of a patient or its tumor, used to estimate the chance of disease recovery, or the chance of the disease recurring / metastasizing. These markers are associated with a relative risk of disease progression and are used by clinicians to help assign a prognosis. Prognostic markers are often generated from ancillary labs: -histologic parameters, cytologic parameters, molecular profiles, and immunohistochemical results. Prognostic markers may be also patient characteristics (breed, age, geographical location of the patient). Common histologic parameters reported by pathologists are: MC, margins, LVI, differentiation, and necrosis. For oncology, these parameters are *measured* or correlated to an outcome: recurrence rate, disease-free interval, time to tumor progression, and or one of the survival metrics. Parameters may be used individually or combined to form a score; “prognostic scoring” as used in canine STT/STS. Prognostic scoring is used in human oncology for numerous tumor types: breast, prostate, lung cancer, non-Hodgkin lymphoma. No single parameter should be relied on too heavily. Combining parameters and weighing them differently may provide more reliable prognostic and or predictive data.

Predictive markers are patient or tumor characteristics used to help select and predict whether a patient’s cancer will respond to a specific treatment. Predictive markers may

also describe an attribute that increases a patient's risk of developing a specific condition or disease. Predictive markers are relevant in cancer therapy as they attempt to identify patients who will benefit by a targeted therapy. One of the best examples of predictive markers in human cancer is the use of hormone receptor or HER2 expression in breast cancer patients to determine the optimal treatment options. Predictive markers are focused on treatment response and prognostic markers are focused on the overall tumor biology or course of disease. In human oncology, predictive markers can now be determined for how an individual (specific patient, theranostics) will likely respond as opposed to how a population of individuals might respond.

For prognostic markers to be useful they should target these goals:

- Have strong associations with outcomes. Weak or statistically marginal associations will not hold up in larger populations and do not incentivize their utilization.

- Markers should be feasible, something that every diagnostician can do already, or can be accomplished by providing the tools needed. However, as pathologists we should learn from our microbiology/ virology colleagues that technical molecular tests can be used routinely in diagnostic cases. If a test is overly complex, cumbersome, requires large expertise, infrastructure or is too costly it will fall out of use.

- Results must be reproducible between labs and have high interpathologist reproducibility. Multi-institutional studies, and the proposed biobank can help accomplish this.

- Prognostic ability of new tests or modified methods should be compared to existing tests so others can decide if they will adopt the test (method).

Clinicians assign a prognosis and develop treatment plans. Pathologists report gross and histologic parameters which clinicians use to formulate a prognosis and consider treatment options. Comments by the pathologist about predicted behavior of the tumor from study populations are not needed by oncologists. Primary care veterinarians may want and expect these comments. They may like some guidance on how the tumor might behave and this information may help owners decide if they should be referred to an oncology center. However, predicting how a tumor will behave and affect a specific patient is unknown, which of course is what the owner wants to know. The best that can be provided is a relative risk of recurrence, metastasis and a survival metric based on statistical analyses of a population of other pets. How well this translates to an individual patient or even a larger population is dependent on how well the original study represents the larger population, and how well the study was conducted overall. Until study methods are replicated and the results validated, which happens rarely in veterinary oncology, the results should be used cautiously before applied to clinical patients. Therefore, comments about relative risks should be worded carefully to primary care veterinarians and cite the literature they were extracted from. A comment could state the risk of disease progression is based on published studies (cite primary literature) followed by a statement that this should be considered in the context of the entire clinical picture.

RECIST:

Response Evaluation Criteria in Solid Tumors: A human based system adapted for use in veterinary oncology patients. A consensus framework for standardizing procedures in reporting assessments of solid tumors, treatments and outcomes aimed to facilitate comparisons of treatment protocols for neoplastic diseases of animals. cRECIST v 1.0[12] is the canine version and needs validation.

iRECIST:

A modification of RECIST is being developed and validated for monitoring human cancer patients undergoing immunotherapy. Although many elements of RECIST are the same, the determination of tumor progression can differ and it is critical to determine

the thresholds which accurately reflect tumor response to avoid the risk and expense of unnecessary therapy. Comparable guidelines have not been developed for use in veterinary oncology.[17]

SD (cRECIST v 1.0)[12]:

Stable Disease: Neither sufficient to qualify for PR or PD. Therefore, a less than 30% reduction (PR) or less than 20% increase (PD) in the sum of the diameters of the target lesions, taking as reference the smallest sum of diameters while on study.

Standard of care:

By design, standards of care will vary and evolve over time according to circumstances and due to medical progress but can be considered to represent a benchmark that a veterinary medical community has generally accepted to be appropriate for diagnosis and treatment of a disease or condition based upon scientific evidence. Such standards can be formal or informal and may be developed by a professional society (often of specialists) devoted to a disease process, which then may be promulgated as a clinical practice guideline intended for a doctor to consider appropriate when confronted with a certain disease (tumor). In some instances, medical evidence may be insufficient for a well-formed and generally accepted standard of care to exist. There can also be legal definitions of standard of care that may be distinct. Therefore, there may be standard of care recommendations, but they are not the "only" level of standard of care. State practice boards may be arbiters of standards of care and should consider community practices as well as available guidelines. Clients may elect to accept other than a standard of care, at their discretion, with suitable informed consent. Importantly, oncology publications should define any standard of care for the particular study design and consider/discuss if or how this may have influenced survival metrics e.g. patients with high grade malignancies may have received palliative treatments only, or were euthanized early in study (censored or not), thereby biasing outcomes such that high grade tumors had poor prognoses.

ST:

Survival Time (synonym: overall survival, OS): The time from treatment of a neoplastic process (chemotherapy, radiation therapy, surgical removal) to the date of death (from the neoplastic process or other causes). Cause of death should be characterized as accurately as possible. Survival data in veterinary oncology can be misleading, due to the availability of euthanasia in veterinary patients and the reasons for euthanasia. There are multiple terms and means to define survival in oncology studies, therefore the term and definition must be detailed in M&M e.g. Disease Free Survival; Overall Survival; Survival Rate; Survival Probabilities etc see ref 2. Note: A survival rate (see also definition of overall survival rate) can be obtained if the status (recurrence/no recurrence, metastasis/no metastasis, alive/dead) is known for all patients at a defined time point (e.g., 6 months, 1 year etc. post first treatment). However, usually the survival probabilities in the survival time are calculated using Kaplan-Meier statistics and as such, represent survival probabilities rather than rates.

Staging:

The process of determining how much cancer is in the body and where it is located. Staging is performed in order to define the size and location of the primary neoplastic process as well as the extent of spread within tissues surrounding the primary process and throughout the body. Staging is performed by the clinician (not pathologist). Note: As more sensitive staging methods are evolving (e.g., advanced diagnostic imaging, molecular methods) and will be performed, patients will likely be reclassified at a higher disease stage (stage migration). This will affect comparison of patients across studies using different staging methods and ideally, methods for staging should be standardized to determine the clinical stage.

Suspected metastasis:

Metastases as determined by a means other than microscopic examination (e.g. imaging such as radiographs, CT scan etc.) These modalities cannot confirm the lesion(s) seen is in fact the same tumor type or even that the lesion is neoplastic. See confirmed metastasis.

Synoptic Reporting:

A method for reporting specific pieces of data in a discrete format in pathology reports (data elements and responses).

Target Lesions:

Lesions that are measured and followed for assessment of tumor response to therapy. Target lesions are those with the longest diameter, should be representative of organs involved and lend themselves to multiple measurements. A maximum of five target lesions total should be chosen. The baseline sum should be calculated and subsequent measurements are referenced against this sum. Non-target lesions are tumor lesions that are documented (but not measured) and reported as 'present' or 'absent' at follow-up time points.

T=0 Start time:

(T=0) of survival studies needs to be clearly and consistently defined in the materials and methods section of manuscripts. 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, or the date of histopathological tumor diagnosis.

Univariate:

Statistical analysis that involve a single outcome.[13]

Univariable:

Statistical analysis used for determining the contribution of a single factor to an event or outcome.[15] See multivariable.

Validation (method or grading system):

Studies performed to ensure reproducibility of a method or tumor grading scheme which involve use of published methods and materials to assess tumors in separate

population of patients. The method or grading scheme is validated if investigators at different institutions can replicate the results of the published study.

VCOG:

Veterinary Cooperative Oncology Group, a section of the Veterinary Cancer society.

References: Margins and Outcome Assessments:

1. Adstrum S, Hedley G, Schleip R, Stecco C, Yucesoy CA. Defining the fascial system. *Journal of bodywork and movement therapies*. 2017;21**:** 173-177.
2. Ahmed W, Kulikowska M, Ahlmann T, Berg LC, Harrison AP, Elbrond VS. A comparative multi-site and whole-body assessment of fascia in the horse and dog: a detailed histological investigation. *J Anat*. 2019;235**:** 1065-1077.
3. Dernell WS, Withrow SJ, Kuntz CA, Powers BE. Principles of treatment for soft tissue sarcoma. *Clinical techniques in small animal practice*. 1998;13**:** 59-64.
4. Donnelly L, Mullin C, Balko J, et al. Evaluation of histological grade and histologically tumour-free margins as predictors of local recurrence in completely excised canine mast cell tumours. *Vet Comp Oncol*. 2015;13**:** 70-76.
5. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. *Clinical Orthopaedics and Related Research®*. 1980;153**:** 106-120.
6. Fasel JH, Dembé J-C, Majno PE. Fascia: a pragmatic overview for surgeons. *The American Surgeon*. 2007;73**:** 451-453.
7. Fulcher RP, Ludwig LL, Bergman PJ, Newman SJ, Simpson AM, Patnaik AK. Evaluation of a two-centimeter lateral surgical margin for excision of grade I and grade II cutaneous mast cell tumors in dogs. *Journal of the American Veterinary Medical Association*. 2006;228**:** 210-215.
8. Gao Z, Ye Y, Zhang W, et al. An anatomical, histopathological, and molecular biological function study of the fascias posterior to the interperitoneal colon and its associated mesocolon: their relevance to colonic surgery. *Journal of anatomy*. 2013;223**:** 123-132.
9. Hoos A, Parmiani G, Hege K, et al. A clinical development paradigm for cancer vaccines and related biologics. *Journal of immunotherapy*. 2007;30**:** 1-15.
10. Kawaguchi N, Matumoto S, Manabe J. New method of evaluating the surgical margin and safety margin for musculoskeletal sarcoma, analysed on the basis of 457 surgical cases. *Journal of cancer research and clinical oncology*. 1995;121**:** 555-563.
11. Liptak JM. 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? *Veterinary and Comparative Oncology*. 2020;18**:** 25-35.
12. Nguyen SM, Thamm DH, Vail DM, London CA. Response evaluation criteria for solid tumours in dogs (v1.0): a Veterinary Cooperative Oncology Group (VCOG) consensus document. *Vet Comp Oncol*. 2015;13**:** 176-183.
13. Peters TJ. Multifarious terminology: multivariable or multivariate? univariable or univariate? *Paediatric and Perinatal Epidemiology*. 2008;22**:** 506-506.

14. Prpich CY, Santamaria AC, Simcock JO, Wong HK, Nimmo JS, Kuntz CA. Second intention healing after wide local excision of soft tissue sarcomas in the distal aspects of the limbs in dogs: 31 cases (2005–2012). *Journal of the American Veterinary Medical Association*. 2014;244**:** 187-194.
15. Reboldi G, Angeli F, Verdecchia P. Multivariable Analysis in Cerebrovascular Research: Practical Notes for the Clinician. *Cerebrovascular Diseases*. 2013;35**:** 187-193.
16. Schroeder MM, Skinner OT. Fascial plane mapping for superficial tumor resection in dogs. Part I: Neck and trunk. *Veterinary Surgery*. 2021.
17. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *The Lancet Oncology*. 2017;18**:** e143-e152.
18. Somarouthu B, Lee SI, Urban T, Sadow CA, Harris GJ, Kambadakone A. Immune-related tumour response assessment criteria: a comprehensive review. *The British journal of radiology*. 2018;91**:** 20170457.
19. Webster J, Dennis MM, Dervisis N, et al. Recommended guidelines for the conduct and evaluation of prognostic studies in veterinary oncology. *Veterinary pathology*. 2011;48**:** 7-18.
20. Wittekind C, Compton C, Quirke P, et al. A uniform residual tumor (R) classification: integration of the R classification and the circumferential margin status. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 2009;115**:** 3483-3488.

Synoptic Reporting Guideline

Synoptic reporting is a method for reporting specific pieces of data in a discrete format in pathology reports (data elements and responses).

CAP: College American Pathologists

ICCR: International Collaboration on Cancer Reporting

grep: a program to find matching patterns of text from a specified text source.

CPATH Guideline

Terms, initials and a complete list of definitions for CPATH are included in the CPATH Guideline.

AI:

Artificial intelligence: AI is a branch in computer science commonly used for computerized gathering of information from raw data, such as histological images, by

simulating intelligent behavior in computers (as opposed to natural intelligence displayed by humans and animals). Machine learning is a subset of artificial intelligence.

Automated image analysis (AIA)/digital image analysis (DIA):

AIA is the process of extracting information from a digital image (typically whole slide image, WSI) by computerized methods. Some algorithms for automated image analysis are based on AI (including traditional machine learning and deep learning), others on simple image processing steps (including thresholding-based approaches).

Artificial Neuronal Networks:

ANNs are machine learning models that are inspired by natural neuronal systems of humans and animals. Artificial neurons are organized in layers (input, hidden, output layer) that are connected to each other and can receive (with a specific weight), process and transmit signals. By modifying/adjusting the weights of neurons and their connections during training, a network is trained to predict a certain task. A highly relevant type of an ANN for deep learning is a convolutional neural network (CNN).

Black box algorithm:

A black box (opposed to glass box) algorithm is characterized by the lack of an understandable relationship of input data and algorithmic output, i.e. the used decision criteria are too complex to understand. Deep learning-based algorithms, which extract relevant features of the pattern of interest by themselves, are often considered to be a ‘black box’. Display of intermediate results (e.g., object detections as an overlay in the digital images) can increase comprehensibility of these algorithms.

Black box vs glass box:

The artificial neural networks in machine learning generate decisions on data/images but decision criteria used by these systems are not clear. Methods to understand how input parameters go to output data result in a glass box.

CPATH:

Computational pathology: A branch in pathology using computerized methods to gather relevant information on a disease in a patient from one or multiple sources of raw data such as histology images, macroscopic images and gene sequences. In Guideline 11 (CPATH), CPATH especially refers to the field in pathology using automated image analysis (AIA) methods for digitized microscopic tumor sections (WSI). Methods commonly used for AIA come from the field of artificial intelligence (AI), more specifically deep learning. A broader definition of CPATH is the extraction of relevant information from any source of raw data including clinical electronic medical records, laboratory data, diagnostic imaging, genomics and others. CPATH uses computerized methods (AI and others for histological images) analogous to molecular pathology using molecular methods (PCR and others for detection of mutations).

Digital pathology:

An umbrella term for digitized pathology including wide variety of “tools and methods”: WSI, scanners, monitors, servers, storage, analysis, computational processing, and additional infrastructure.

Gold standard:

The gold standard is the practical method that is well-established and most suitable for development of the ground truth labels. For histological and immunohistochemical specimens, trained pathologists are most commonly used as gold standard, regardless of their visual and cognitive limitations leading to some degree of inter- and intra-observer variability. As automated image analysis is designed to overcome human limitations, this approach seems to be somewhat paradoxical. However, a true gold standard is often lacking for most morphological patterns, whereas global features may have a more objective gold standard, such as presence/absence of genetic mutation.

Ground truth:

Ground truth is the information of the ‘true’ label class derived by the defined gold-standard method. These ground truth labels are critical as they represent the reference during model training. They are also the reference for testing the algorithmic model’s

performance (see Table S7). As manual assessment by human experts (pathologists) with well-known inter- and intra-rater variability are the gold standard for most histological patterns of interest, the ground truth can be subject to various biases and can include annotation errors. It is the aim of a highly diligent dataset creation to limit these errors.

Machine Learning (ML):

ML is a subset of artificial intelligence in which an algorithm learns from representative data in order to create a model that can make decisions on new data without human interaction. ML can be categorized into “traditional” ML and deep learning (DL) methods. While the relevant features of the patterns of interest are given to the model with traditional ML (also called "hand-crafted"), DL networks are capable of extracting these features by themselves. Compared to traditional ML, DL systems are generally more powerful but often require more data (‘big data’) for training.

Supervised Learning (SL):

Supervised learning is a specific form of machine learning (as opposed to unsupervised learning) that results in algorithmic predictions based on both input and output data. Labelled data (output data) assigned the training image patches (input data) is required for training the artificial networks. It is the most commonly used form of artificial learning for CPATH in tumor histology. Pattern recognition tasks of supervised learning can be image classification, object detection, segmentation or regression.

WSI:

Whole slide image – an entire histopathological glass slide is digitized at a specified scanning magnification and resolution. Software permits viewing of the image like a light microscope. Resolution and different magnifications are limited by scanning technology.

PATHOLOGY TERMS

Autopsy:

Derived from Greek *autopsia* to see for one self; *autos*, "oneself" and *opsis*, "sight, view". Synonym: post-mortem examination. Terms for human or animal dissection post-mortem, usually to establish the cause of death or diseases present. Autopsy often reserved for human post-mortem examination. The derivation of the word *autopsia*, has been misinterpreted to mean dissection of self (human), however, it means to see for oneself and can be used for post-mortem examination of non-humans.

Cachexia:

Derived from Greek *kakos*, "bad", and *hexis*, "condition". Underlying illness often end stage cancer, that causes severe muscle wasting, typically with adipose being preserved. Multifactorial pathogenesis; multiple disease pathways involving inflammatory cytokines such as TNF (tumor necrosis factor or 'cachexin' or 'cachectin'), interferon gamma and interleukin 6.

Confirmed metastasis:

Microscopic confirmation, performed by a pathologist, to substantiate that the same tumor type has metastasized. See suspected metastasis. Histopathology is preferred to cytology but feasibility will depend on tumor type and suspected metastatic lesion location.

Suspected metastasis:

Metastases as determined by a means other than microscopic examination (e.g. imaging such as radiographs, CT scan etc.) These modalities cannot confirm the lesion(s) seen is in fact the same tumor type or even that the lesion is neoplastic. See confirmed metastasis.