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Quality of Life Measurement in Prospective Studies of Cancer Treatments in Dogs and Cats

M.A. Giuffrida and S.M. Kerrigan

Background: Quality of life (QOL) is an important consideration in healthcare decision-making for pets with cancer. To determine the effect of disease and treatment on pet QOL, this important variable should be objectively measured as an outcome in veterinary cancer studies.

Objectives: To determine the prevalence and methodology of QOL measurement in a sample of recently published reports of prospective studies evaluating cancer treatments in client-owned dogs and cats; to characterize reporting of QOL outcomes and to identify article characteristics associated with QOL measurement.

Methods: English-language reports of prospective studies of cancer treatments in dogs and cats published from 2008 to 2013 were identified using medical research databases combined with a hand-searching strategy. Data pertaining to general article characteristics and QOL measurement were abstracted and summarized.

Results: Reports of 144 eligible studies were identified. QOL was measured in 16 (11.1%) studies, with 8 (5.6%) reporting the results. All studies that measured QOL reported using unvalidated instruments, or did not report how QOL was assessed. Only 1 study provided sufficient information for QOL measurements to be replicated. Recently published articles (2011–2013) were significantly more likely to report measuring QOL, compared with earlier articles.

Conclusions: Quality of life of pets undergoing cancer treatment is largely unreported and cannot be meaningfully compared across treatments or disease states using the existing literature. Reliable, validated instruments are needed to facilitate the measurement and comparison of pet QOL in veterinary cancer research. Consistent reporting practices could improve transparency and interpretation of QOL results.

Key words: Cat; Clinical trials; Dog; Evidence-based medicine; Oncology; Quality of life.

A fundamental goal of companion animal cancer care is to maintain each pet's quality of life (QOL) at an acceptable level, despite the effects of disease and veterinary intervention.¹ There is no universally accepted definition QOL, but it is generally considered a multidimensional concept that involves subjective evaluation of factors that contribute to overall well-being.^{2,3} QOL is an important factor in therapeutic decision-making for human patients and is commonly used as an endpoint in human clinical trials of cancer treatments.^{3,4} There is growing acceptance that a treatment can be valuable if it improves a patient's subjective well-being, even if it does not meaningfully impact other outcomes used to quantify success in cancer treatment, such as disease progression or survival.⁵

These principles also apply in veterinary oncology. Owners of pets with terminal illness tend to value QOL over longevity, and are willing to trade survival time to preserve QOL.^{6,7} In order for pet owners and veterinary care teams to choose treatments based on outcomes they value most, clinical oncology studies

Abbreviations:

CAB	Commonwealth Agricultural Bureaux
CONSORT	Consolidated Standards of Reporting Trials
KPS	Karnofsky performance status
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical Subject Headings
QOL	quality of life

should measure and report patient-centered outcomes such as QOL.

Measuring an individual's perspective is a challenge because it cannot be directly quantified, even in people. Scientific methodology used to construct and assess instruments intended to measure subjective states has been developed through the field of psychometrics. To be considered scientifically sound, an instrument should demonstrate the key psychometric properties of reliability, validity, and responsiveness in the clinical population of interest.⁸ Psychometric methods have been successfully applied to develop veterinary instruments that measure QOL among cats⁹ and dogs¹⁰ with diabetes mellitus, QOL among dogs with skin disease,^{11,12} musculoskeletal pain among cats with joint disease,¹³ and chronic pain^{14–17} and overall disability^{18,19} among dogs with orthopedic disease. Psychometrically sound instruments can facilitate comparisons both within individual studies and across different studies and populations. Conversely, ad hoc or unvalidated instruments are a major potential source of bias in clinical trials⁴ and are associated with inflated measures of treatment effect, compared with when validated instruments are used.²⁰ Regardless of what instrument is used, authors should clearly state

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how QOL measurements are made so that readers can assess the validity of measurements and compare results with those of similar studies.²¹

In searching the current literature, we found no validated instruments designed to measure QOL in pets with cancer. There are descriptions of ad hoc instruments intended to measure QOL in pets with cancer,^{22–24} and articles describing oncology-specific QOL questionnaires in early stages of scientific development.^{25–27} While there exist a number of published generic and disease-specific QOL questionnaires for use in pet animals, none have been designed for or validated in pets with cancer. A systematic review of QOL measurement in studies of cancer treatment or any other veterinary field has not been reported, so it is unknown if and how this critical parameter is being assessed. The primary objective of this study was to determine the prevalence and methodology of QOL measurement in a sample of published reports of prospective studies of cancer treatments in dogs and cats. Secondary objectives were to characterize reporting of QOL outcomes, and to evaluate whether QOL measurement was associated with basic article characteristics including year and journal of publication, geographic location where research was performed, species, study design, neoplastic condition, and treatment modality.

Materials and Methods

Reports were eligible for inclusion if they were published in a peer-reviewed English-language scientific journal from 2008 to 2013, studied the effect of an anticancer treatment in client-owned dogs or cats with naturally occurring malignant neoplasia, and utilized prospective subject recruitment and data collection. Studies that enrolled purpose-bred, random-source, institution- or shelter-owned animals were excluded, as were retrospective studies, systematic reviews, meta-analyses, single case reports, and case series consisting of fewer than 5 animals. Among studies that evaluated the effect of a treatment in animals with and without cancer (eg, a splenectomy technique in dogs with benign or neoplastic splenic masses), only studies where at least 50% of subjects received the treatment because of malignant cancer were eligible.

Potentially eligible reports were identified via OVID electronic multi-database search of MEDLINE and CAB Abstracts performed by the principal investigator (MAG) in January 2014 under the guidance of a research librarian. Search terms were created to identify studies published from 2008 to 2013 related to cancer treatment in either cats or dogs. The specific string of terms were: (exp Neoplasms/dh, dt, rt, su, tu, th) AND (dogs/ or cats/) AND [(clinical trial/ or comparative study/ or validation studies/) OR (prospective or random* or phase or trial)] NOT (“Mice”) NOT (“Cell Line, Tumor”) NOT (“Retrospective studies”) limit to yr=“2008-2013.” The resulting articles were screened for eligibility criteria by the principal investigator using information found in reports’ abstracts and full texts. For each eligible article identified via MEDLINE, both investigators performed a hand-search of its publishing journal to capture articles not identified in the database search. The hand-search strategy involved reading article titles, abstracts, and full texts to determine whether articles met study inclusion or exclusion criteria.

Each eligible report was read in its entirety by the principal investigator, and the following baseline data were extracted:

journal and year of publication, continent where research was performed, species (cat, dog, both), number of study subjects, study design (randomized or nonrandomized controlled trial, uncontrolled trial), neoplastic condition(s) being treated, and treatment(s) studied. Treatments were categorized as chemotherapy (cytotoxic antineoplastic drugs and small molecule inhibitors), radiationtherapy, surgery, other treatment (treatments that did not fit the aforementioned categories, such as gene treatment or immune modulation treatment), or multimodal treatment (protocols that include treatments from 2 or more of the aforementioned categories). Information about QOL assessment was also collected: whether there was any mention of measuring QOL, well-being, or performance status; whether a specific hypothesis was stated with respect to QOL outcome; what method or instrument was used to make the QOL measurement (s); and how the QOL results were reported. For studies that measured QOL, details of the measurement instrument were obtained from the manuscript text, published article supplements, and referenced publications when provided. Information about the instruments was collected: whether the instrument was devised for the study or previously published; whether there was any record of the instrument’s psychometric properties (reliability, validity, responsiveness) in any population of pets; whether sufficient published information was available to duplicate the QOL measurement; and what proxy (such as owner or veterinarian) made the QOL assessment(s). Quantifications of adverse events, clinical signs, or owner satisfaction were not considered QOL measurement.

Statistical Analysis

Study characteristics were examined and summary statistics were calculated for all measured variables according to whether QOL measurement was reported. Continuous variables were not normally distributed and were expressed as medians and ranges; categorical variables were expressed as numbers and percentages. The nonparametric test for trend was used to test whether the number of eligible reports identified increased or decreased across the 6 publication years. Between-group comparisons were made using Fisher exact tests for categorical variables and Mann-Whitney *U*-tests for continuous variables. All tests were 2-sided and results were considered statistically significant if $P \leq .05$.

Results

A total of 144 eligible reports were identified: 100 (69.4%) via MEDLINE and 44 (30.6%) via hand-searching. Reports were published in 35 different scientific journals (Table 1). An approximately equal number of eligible reports was identified for each publication year, with no trend toward fewer or greater numbers of reports over the 6-year period ($P = .705$).

The study methodology of 16 (11.1%) reports indicated that QOL was measured as an outcome, but only 8 (6.3%) reported any QOL data in the study results. None of the 16 reports indicated a specific hypothesis relating to QOL outcome. General information about the sample of reports is presented in Table 2, according to whether QOL was measured.

No articles reported using a QOL measurement instrument that had undergone psychometric testing to determine validity, reliability, or responsiveness to

Table 1. Journal of publication for 144 reports of prospective studies of cancer treatments in dogs and cats.

	No Reports	% Cumulative
<i>Journal of Veterinary Internal Medicine</i>	47	32.6
<i>Veterinary and Comparative Oncology</i>	26	50.7
<i>Veterinary Radiology & Ultrasound</i>	9	56.9
<i>Journal of the American Veterinary Medical Association</i>	8	62.5
<i>Clinical Cancer Research</i>	7	67.4
<i>Veterinary Surgery</i>	6	71.5
<i>Journal of Small Animal Practice</i>	4	74.3
<i>Veterinary Journal</i>	4	77.1
<i>American Journal of Veterinary Research</i>	3	79.2
<i>Cancer Chemotherapy Pharmacology</i>	3	81.3
<i>Journal of the American Animal Hospital Association</i>	3	83.3
<i>PLoS One</i>	3	85.4
Other journals ^a	21	100.0
Totals	144	100.0

^aOne eligible report was identified in each of the following journals: *Anesthesiology*, *Applied Radiation and Isotopes*, *Canadian Journal of Veterinary Research*, *Canadian Veterinary Journal*, *Cancer Gene Therapy*, *Cancer Letters*, *Cancer Research*, *Clinical Orthopedics and Related Research*, *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, *Journal of Feline Medicine and Surgery*, *Journal of Gene Medicine*, *Journal of Immunotherapy*, *Journal of Urology*, *Molecular Therapy*, *Neuro-Oncology*, *Nutrition Research*, *Research in Veterinary Science*, *Translational Medicine*, *Veterinary Anaesthesia and Analgesia*, *Veterinary Pathology*, *Veterinary Record*.

relevant clinical change in any population of pets. Among trials that reported measuring QOL but did not report QOL results, 5 provided no information about how QOL was assessed, 1 used a previously published veterinarian-assessed Karnofsky performance status (KPS) method, 1 used a previously published owner-assessed cancer-specific QOL questionnaire, and 1 used an improvised owner-assessed questionnaire. Among trials that measured QOL and reported the results, 4 reported using previously published veterinarian-assessed KPS methods, 3 reported using improvised owner-reported questionnaires, and 1 reported using both a veterinarian-assessed KPS scale and an improvised owner-reported questionnaire. Among the 5 articles that used improvised questionnaires, only 1 provided the entire questionnaire; the others provided general information about the questionnaire items and scoring. Overall, only 1 article reported sufficient information for a reader to replicate the QOL measurements. For all other articles, sufficient details about QOL instrument, its scoring method, or the timing of administration were not reported.

Table 2. Characteristics of 144 reports of prospective studies of cancer treatment in client-owned dogs and cats published from 2008 to 2013, according to whether QOL was reportedly measured.

	No QOL (n = 128)	QOL (n = 16)	P-Value
Species			
Dog	107 (83.6)	14 (87.5)	.308
Cat	19 (14.8)	1 (6.3)	
Both	2 (1.6)	1 (6.3)	
Continent			
North America	86 (67.2)	9 (56.3)	.231
Europe	31 (24.2)	4 (25.0)	
Other	10 (7.8)	2 (12.5)	
Multiple	1 (0.8)	1 (6.3)	
Sample size	24 (4–202)	30 (6–408)	.321
Publication year			
2008–2010	72 (56.2)	3 (18.8)	.007
2011–2013	56 (43.8)	13 (81.2)	
Study design			
Randomized controlled	16 (12.5)	4 (25.0)	.181
Nonrandomized controlled	10 (7.8)	2 (12.5)	
Uncontrolled	102 (79.7)	10 (62.5)	
Cancer type			
Multiple tumors	34 (26.6)	7 (43.7)	.572
Lymphoma	27 (21.1)	2 (12.5)	
Carcinoma	24 (18.8)	2 (12.5)	
Sarcoma	21 (16.4)	1 (6.3)	
Mast cell tumor	15 (11.7)	3 (18.7)	
Other	7 (5.5)	1 (6.3)	
Treatment evaluated			
Chemotherapy	67 (52.3)	12 (75.0)	.369
Radiationtherapy	8 (6.3)	0 (0.0)	
Surgery	11 (8.6)	0 (0.0)	
Multimodal treatment	28 (21.9)	4 (25.0)	
Other	14 (10.9)	0 (0.0)	

Discussion

Quality of life was rarely reported as an outcome in this sample of prospective studies of cancer treatments in dogs and cats. When QOL was measured, unvalidated instruments were used, specific hypotheses were not tested, and the results of measurement were often not even reported. Despite the supposedly critical role of expected QOL in pet healthcare decision-making, we found no valid published data to aid veterinarians and pet owners attempting to compare oncologic options on the basis of QOL outcomes.

There is no generally accepted theory of what QOL means in pet animals, or how the concept can or should be applied to veterinary clinical practice or research.^{28–30} Quantitative QOL measurements are rarely mentioned in the veterinary literature; QOL scales are instead suggested as means to facilitate discussions about euthanasia and palliative treatment goals.^{1,28,30,31} Unvalidated instruments could be adequate in these circumstances because the goal is not truly to measure or compare QOL among pets or time points. Conversely, the purpose of QOL measurement in oncology trials is not to spark discus-

sion, but to quantify subjective experiences that affect the overall clinical benefit or harm associated with a given treatment.³ Given that maintaining normal QOL for as long as possible is usually the goal of treatment among pets with cancer,³² it seems unlikely that QOL outcomes are omitted from investigations because they are considered unimportant. Rather, we believe that pet QOL is often viewed as an abstraction that cannot be scientifically measured. The lack of psychometrically sound QOL instruments for pets with cancer could be both a cause and effect of this view.

A test is considered reliable if it measures something in a reproducible manner, valid if it measures the attribute it was intended to measure, and responsive if it measures clinically relevant changes in the attribute it was intended to measure. Because each property is multifactorial, evaluating the psychometrics of a health measurement instrument requires stepwise testing in multiple or large studies; even then an instrument is only considered sound when applied to the population or clinical setting in which it was tested.⁸ At some point, idealistic scientific rigor must make concessions to reality; no instrument can be tested for every possible facet of psychometry in every possible clinical scenario, and it would be wrong to dismiss an instrument unless it meets such a high burden of proof. On the other hand, it is fair to expect veterinary instruments to conform to some minimum standard of validity and reliability beyond investigator judgment or prior use. The use of instruments whose psychometric properties are entirely unknown can result in biased data and unsubstantiated conclusions that can impede clinical progress.

None of the studies in this review reported measuring QOL with an instrument known to be valid or reliable on the basis of psychometric testing. Among studies that referenced or provided a complete QOL instrument, a modified Karnofsky performance status (KPS) scale was most commonly used (Supporting Information). The human KPS scale is an indicator of patient functional impairment as assessed by the clinician,³³ and is an acceptably reliable and valid method to measure functional status, but not QOL itself.³⁴ Functional status is only one aspect of human QOL, and loss of function does not have a linear relationship with QOL.³³ The domains of dog or cat QOL are not well established, but functional status could reasonably be more fundamental to pet QOL than it is among people. A modified veterinary KPS scale is recommended to measure pet QOL,³⁵ but the scale has not been psychometrically evaluated and its ability to measure functional status or QOL is unknown. If a veterinary KPS scale were shown to be reliable and valid, it could be a valuable method to measure function and possibly QOL in pets. Until such properties are demonstrated, the meaning of data obtained via veterinary KPS scales is uncertain.

There were many inconsistencies in how QOL was measured and reported in this sample of veterinary oncology trials, a problem also recognized in reports

of human trials. In a recent systematic review of QOL outcomes in human randomized trials,³⁶ most published reports cited evidence of the QOL instrument's psychometric properties and quantitatively described QOL measurement results. However, other important information was often missing and only half of the articles provided a discussion of the QOL results. In response to these findings, a guidance document for the reporting of patient-reported outcomes such as QOL in randomized trials was developed as an extension to the CONSORT (Consolidated Standards of Reporting Trials) Statement.²¹ The extension recommends that when QOL is measured, it should be identified as a primary or secondary outcome, a hypothesis should be described, and evidence of the instrument's reliability and validity should be cited. Although these guidelines were designed specifically for patient-reported outcomes, they can also be applied to proxy-reported outcomes such as those measured in companion animals.²¹ We propose that the clinical applicability and interpretation of veterinary QOL outcomes could be improved if investigators consult the CONSORT statement and its relevant extensions when planning and reporting prospective veterinary trials.

We found that the rate and method of QOL measurement did not vary significantly among studies of different species, numbers of subjects, types of cancer, treatment modalities, geographic locations, or journals of publication. Although most studies reported using an uncontrolled design, studies that utilized a control group, random allocation to treatment groups, or both were not more likely to measure QOL. One encouraging finding was that recently published studies were significantly more likely to report measuring QOL, when compared with earlier studies. This could indicate that clinical investigators increasingly recognize the value of QOL measurement as a research outcome. We are hopeful that this finding manifests as more widespread inclusion of QOL outcomes in future veterinary oncology trials. A cost-effective, easy-to-use, and psychometrically sound QOL instrument for pets with cancer could have a major role in increasing the frequency and quality of QOL measurement in companion animal clinical research.

Our literature search strategy was designed to be sensitive, but reasonably specific, to complete data collection within the available time and budget. This proved to be a difficult task because studies of cancer in dogs and cats were frequently not indexed under logical MeSH headings. Hand-searching was used to identify articles indexed in the database but missed in the bibliographic search because of indexing inconsistencies. A systematic review attempting to identify all prospective studies of cancer therapies in dogs and cats would require the use of very broad search terms, resulting in extremely low search specificity and investigator review of an unrealistic number of largely ineligible articles. Such an approach, if feasible, would minimize selection bias that could have been introduced through our approach. Relevant articles were

necessarily missed by our approach because of language ineligibility, database limitations, or investigator oversight. Any of these omissions could have introduced selection bias if excluded or unidentified articles were different in some important way from those included in this study. Systematic misclassification of article characteristics could have occurred because a single investigator assessed each article; consensus from a team of assessors blinded to the study objectives could have further reduced the potential for information bias.

There is wide agreement on the importance of QOL in clinical decision-making for pet dogs and cats with cancer. Nevertheless, QOL of pets undergoing cancer treatment is largely unreported and cannot be meaningfully compared across treatments or disease states using the existing literature. QOL should be measured and reported with methodologic rigor, just like any other important trial outcome. Reliable, validated instruments are needed to facilitate the measurement and comparison of pet QOL in veterinary cancer research. Even when psychometrically sound measurement tools are not used, adherence to consistent reporting practices could improve transparency and clinical applicability of QOL outcome results.

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Conflict of Interest Declaration: The authors disclose no conflict of interest.

Off-label Antimicrobial Declaration: The authors declare no off-label use of antimicrobials.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Modified Karnofsky performance status scales reported for use in pet cats and dogs.