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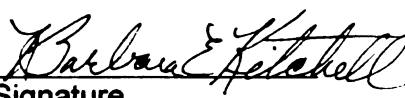
SURVEY TO ASSESS HEALTH-RELATED QUALITY OF
LIFE (HRQOL) IN SMALL ANIMAL CANCER PATIENTS
TREATED WITH CHEMOTHERAPY

presented by

Maria Andromachi Iliopoulou

has been accepted towards fulfillment
of the requirements for the

M.S. degree in Comparative Medicine and
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SMALL ANIMAL CANCER PATIENTS TREATED WITH CHEMOTHERAPY

By

Maria Andromachi Iliopoulou

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ABSTRACT

SURVEY TO ASSESS HEALTH-RELATED QUALITY OF LIFE (HRQOL) IN SMALL ANIMAL CANCER PATIENTS TREATED WITH CHEMOTHERAPY

By

Maria A. Iliopoulou

The medical treatment of dogs with cancer is largely palliative. Decisions made for the choice and duration of treatment often require that the clinician and the owner assess the quality of life (QOL) of the patient. Thus, it is important to have an efficient tool to assess QOL of the companion animal. We have utilized the extensive literature from pediatric and oncology proxy questionnaires, and the limited veterinary literature in order to develop a comprehensive but easy to use survey instrument focused on companion animals treated with chemotherapy for metastatic cancer. Their QOL was assessed before and during chemotherapy. This allowed a more objective assessment of QOL that will be of value to the animals, their owners and the veterinary professionals. Our results indicate that the dogs had decreased QOL due to their disease, but there was a significant QOL improvement during the first 6 weeks of their treatment. Statistically significant predictors of the owner-perceived QOL were the dog's level of illness, and their level of playfulness.

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INTRODUCTION

The practice of veterinary medicine has changed significantly over the past 20 years. A major determinant of success and professional satisfaction in veterinary medicine is considered to be the ability to address with empathy and compassion not only the small animal patients but also their owners.¹ Initially veterinary medicine largely focused on the economic value of farm animals. The altered perception of value has enabled veterinary medicine to proceed further with diagnostics and appropriate treatment particularly in companion animals. Today it is quite common for pet owners to spend thousands of dollars for cancer treatment.² As society has begun to consider animals as family members, the role of the veterinarian changes considerably as do the expectations of companion animal owners. The new model of treating animals has mostly shifted toward a pediatrician model, with the animal being treated as a direct object of moral and medical concern.² This evolution in thinking is not limited to the field of companion animal medicine, but also food animal medicine and laboratory animal welfare. Social concerns about animal well-being have brought attention and further research

toward what constitutes "Quality Of Life". In its simplest form, Quality of Life (QOL) is defined as having adequate food, water and shelter as well as being free from pain or distress.³

Quality of life in humans (QOL) is a growing field of research with established importance in human medicine. Treatment advances have led to increased survival rates for diseases previously believed to be incurable in human medicine. Thus, the need to realize the extent to which quality of life of the patient is compromised due to adverse treatment effects gave rise to the need to develop various QOL tools in order to quantitatively assess and evaluate QOL in humans. Different medical conditions require different treatments, with different complications and adverse effects requiring different disease-specific QOL tools.⁴ These instruments have been developed in order to precisely assess alterations in QOL. In human pediatric medicine however, it is considerably more difficult to assess QOL, especially in infants and very young children. This is true because QOL is multidimensional meaning that it includes, but is not limited to, the social, physical and emotional functioning of the infant and child, and his or her family. Quality of life assessment must also be

sensitive to the changes that occur throughout childhood development.⁵

Quality of life in social sciences is the study of standard of living for given populations. This is unique in that assessments focus on access to goods, income levels, and education and how these factors relate to opportunities. Other approaches evaluate endpoints such as freedom, happiness, creativity, environmental health, and innovation, which are harder to measure.⁶

By contrast, QOL in human medicine is the study of disease and treatment on an individual patient's social, physical and psychological well-being.^{4,7}

The terms "Quality of Life", "welfare", or "well-being" are interchangeably used in veterinary medicine. It is very challenging to define QOL for animals, as we can only infer psychological states in non-verbal species. Thus it is more difficult to assess the impact of health problems, environmental conditions, husbandry factors, nutritional adequacy and other changes in QOL. In a review article by McMillan in 2000⁸, 33 veterinary medicine reports were recovered from a Medline search in which the term QOL was used in the title. In no report was QOL quantified, but the term was nevertheless applied in the context of the

decision-making process of animal owners or clinicians. McMillan concluded that QOL in animals appears to be comprised of the balance between pleasant and unpleasant feeling states.⁸

In a more recent publication, Villalobos reported using a series of questions in order to provide a guideline to assess QOL for owners of a pet with cancer. Her questions specifically address issues of hurt, hunger, hydration, hygiene, happiness, mobility and "more good days than bad". She also mentions that owners expect the veterinarian to inform them of the appropriate time to euthanize a beloved pet. Villalobos also states that it is very important to be able to recognize and respect both the individual animal's and owner's needs in euthanasia counseling.⁹ The decision for humane euthanasia is difficult under the best of circumstances, and after the loss of a beloved pet, the owner experiences a very similar process as occurs after the death of human loved ones.¹⁰ It is therefore important to facilitate this grief process. Villalobos asserts that the use of a QOL scale alleviates the owner's feelings of guilt in electing to euthanize a pet.

One of the goals of the companion animal practitioner is to identify causes of discomfort and pain to the animal and to compensate for the problems that are identified. Medical or surgical treatments, and changes in the diet and exercise patterns might be effective to cure the disease or relieve associated clinical signs. Ultimately many disease processes encountered by geriatric patients, such as cancer, diabetes, arthritis and heart diseases remain incurable in pets. Therapies will eventually cease to be effective.¹¹

The process of assessing QOL in terminal cases is largely a question of determining when that point of debilitation, pain or distress has been reached that dictates alterations in treatment or supportive care, or even consideration of euthanasia.² Critically assessing QOL must be an ongoing process that helps both the owner and veterinarian to compare and identify the changes in the pet's QOL throughout the process of the disease.¹¹ Continued fluid QOL assessment may help animal owners understand the impact the specific disease process has the pet, to avoid either premature or excessively delayed euthanasia. Owners often carry the misapprehension of euthanasia as a stressful event for both the pet and for themselves, and

therefore many owners postpone the decision to euthanized in order to avoid the sadness they anticipate upon the pet's death.²

The Farm Animal Welfare Council is an independent advisory body established administratively by the government of the United Kingdom. Many European animal welfare laws are based on the principles of the "Five Freedoms" first defined in 1979 by the Farm Animal Welfare Council.¹² These 5 freedoms were originally developed for food animal welfare, and described the conditions required for any food animal to have a good QOL. These freedoms were originally enumerated as: 1) freedom from hunger and thirst; 2) physical and thermal discomfort; 3) pain and injury; 4) fear and distress and finally that animals have freedom to express normal behavior.³ Since the acceptance of these food animal QOL criteria, authors have extended the analogy to QOL studies of other animal species.

Researchers considering the welfare of animals have considered factors related to overarching domains of body, mind and nature,¹³ or subjective animal feelings in the presence or absence of pain.^{14,15} However, these factors

remain theoretical in the absence of validated QOL
assessment tools to provide objective data for comparison.

CHAPTER 1

LITERATURE REVIEW

Quality of Life (QOL) versus Health-Related Quality of Life in Humans

Quality of life is a broad concept that incorporates all aspects of an individual's existence,¹⁶ and has different meanings to different people. Quality of life may be defined as the degree of well-being felt by an individual or group of people, which is different than the term "standard of living", and QOL cannot be measured directly.¹⁷

Measurement of QOL typically consists of two components: 1) a physical aspect, which includes such factors as health, diet, and protection against pain or disease; and a psychological component that includes such factors as stress, worry, pleasure and other positive or negative emotional states. However, we can assume with some confidence that the higher the level of diet, shelter and safety, as well as the degree of freedoms and rights a

general population enjoys, the better the overall quality of life said population experiences.¹⁸

Understanding the concept of QOL is particularly important in health care today, where measurable monetary or material attributes do not readily counterbalance debilitating disease. Investigational therapeutics or new oncology treatments evaluated in the clinical trial setting are now evaluated not only on their outcomes in regard to medical endpoints such as survival and cure rates, but also with regard to QOL outcomes.¹⁹ According to the Centers for Disease Control (CDC), as concerns public health, the concept of health-related quality of life refers to a person or groups' perceived physical and mental health over time.²⁰

Physicians have often used health-related quality of life (HRQOL) to measure the effects of chronic illness on their patients, to better understand how an illness interferes with a person's day-to-day life. Similarly, public health professionals use HRQOL to measure the effects of numerous disorders, short- and long-term disabilities, and diseases in different populations. Tracking health-related quality of life in different populations can identify subgroups with poor physical or

mental health and can help guide policies or interventions to improve health in populations overall.²⁰

Clinicians and policymakers now acknowledge the major contribution of HRQOL assessment in patient management and policy decisions.⁴ Some researchers and clinicians support the concept that QOL is central to rationally contribute to all-important health care decisions. For other researchers, the medical concept of QOL is multidimensional and refers to all aspects of a person's life, beyond health care issues, and includes physical, psychological, social, and spiritual well-being.^{4 21}

There is significant variation in means of assessing QOL. Some researchers believe that QOL can be measured by objective parameters. Others view the objective parameters that are often associated with quality of life to be merely indicators, and that actual quality of life can only be measured by a subjective appraisal made by the individual living that life.²² Obtaining accurate subjective QOL data might be particularly challenging in people with intellectual disabilities. For these subjects, the use of proxies such as parents, guardians or caregivers might be the only alternative option. There is debate regarding the extent to which proxy assessments may converge with the

subjective assessment of the person with intellectual disability. Borthwick noted that, in such cases, concurrence "...was more likely to occur in objective measurement than in subjective measurement".^{22 23}

There are many logical reasons to employ QOL assessment. Quality of life assessments may serve as an endpoint in comparative evaluations of health care, as a monitoring measure in assessing the quality of care, or as a way of understanding the priorities of patients in decision-making. It has been estimated that more than one thousand new articles are published each year under the heading "quality of life". Despite the fact that QOL as a concept is not well defined, it is generally agreed that quality of life assessments should report the human patient's subjective viewpoint.²⁴ Interestingly, there has been more than a 180% increase in the number of MEDLINE citations between 1985 and 1993 referring to "quality of life" compared to only a 77% increase for all citations indexed by the term "health".^{25,26}

The assessment of a clinical intervention's effect on patients' overall life experience has engaged the interest of many researchers, clinicians and policy makers. Many survey instruments have been designed to record specific

activities and emotional responses that overall constitute a person's QOL. Assessments of QOL are increasingly being used to characterize treatment efficacy in clinical studies.⁴

There is a growing field of research concerned with developing, evaluating and applying QOL measures within health related research, as in randomized controlled trials, and especially in health services related research. Many of these studies focus on the measurement of HRQOL. These studies also focus on measuring HRQOL from the perspective of the patient and thus take the form of self-completed questionnaires. The International Society²⁷ for Quality Of Life Research was founded in 1994 to further this research. AS a consequence of the interest in QOL in human health care, many QOL instruments now available. In 2002, it was estimated that 3921 QOL questionnaires were under development or at some stage of evaluation.²⁷ The QOL questionnaires available today are generic, disease specific or a combination of both. These questionnaires can also be self-reports, proxy assessments or a combination of both methods. As previously mentioned, assessment of QOL involves a multidimensional approach that includes physical, functional, social, and emotional well-being.

The most comprehensive instruments measure at least three of these domains. There is also an increasing international collaboration in clinical trials, and thus there is a growing necessity for instruments that are valid across languages and cultures.^{28,29} The HARDIN library provides databases, print and web resources for the majority of currently available health assessment instruments and questionnaires for human patients.

Health Related Quality of Life in Human Cancer Patients

Quality of life has become of particular importance in the management of human cancer patients. Accurate assessment of QOL in this population can provide invaluable clinical information.²⁹ Changes in QOL are critical indicators of the impact of any new cytotoxic therapy. Alterations in QOL can affect a patient's willingness to continue treatment, while at the same time QOL changes may help in defining treatment responses. With QOL becoming an increasingly important aspect of cancer patient management, it is very important that the QOL instruments used are reliable, reproducible, and accurate.^{28,30}

As is the case for other disease processes, QOL assessment for the cancer patient includes measures of physical, functional, social, and emotional well-being. There are several instruments that are used in order to assess cancer patient QOL. Some instruments, such as the Nottingham Health Profile, are considered to be generic, while others are targeted toward specific neoplastic diseases (ie Functional Assessment of Cancer Therapy - Lung). Still other instruments combine survey questions related to QOL generically as well as QOL associated with

the underlying neoplastic process. Because there is also international collaboration in cancer clinical trials, it is essential that instruments be valid across many languages and cultures. QOL tools currently available to clinicians and researchers are reliable and valid, but are under continuous improvement.²⁸

Takeda³¹ argued that QOL in human medicine, and even more so in oncology practice, has a broad meaning and should be assessed based on a number of domains, encompassing subjective comfort and discomfort in terms of physical, psychological, social and spiritual well-being.³¹

In some of the past oncology literature, the issue of assessment of physical, psychological, and QOL problems of cancer patients has been surprising in that increased length of life was considered superior to improved QOL. Today, QOL issues are addressed as carrying equal weight in the health care system, especially as regards human oncology practice.³¹ According to Passik,³² QOL research has been very helpful because it provided an improved understanding of, and attention to, the human cancer patient's perspective and needs.³²

The field of cancer treatment has both been greatly influenced and benefited though major advances made at the

area of QOL research. Clinicians now take under consideration the advancements in this field, and use the QOL principles in order to select treatment modalities based on the anticipated treatment efficacy in combination with the cancer patient's wishes.³²

There are several effective instruments used to assess QOL of human cancer patients. These QOL surveys have been developed for easy, repeated patient self-administration, and usually involve a 20-50 item questionnaire that has been validated through use in large numbers of cancer patients.³¹ There are a large number of generic, or not disease-specific, questionnaires that are used in clinical trials and in practice. These include the Sickness Impact Profile, the Inventory of Current Concerns, the Symptom Distress Scale, the Ferrans and Powers Quality of Life Index, the Functional Living Index - Cancer (FLIC), the Acute Physiology and Chronic Health Evaluation Scale, and the Therapeutic Intervention Scoring System.³¹

Quality of life issues in human oncology have become increasingly important because of the increased number of newly diagnosed patients and continuously improving survival rates.³³ In 2002, Kaasa³⁴ et al. concluded that success in oncology had traditionally been measured in

terms of cure, survival time, and tumor response rates. However, health-related quality of life has recently emerged as an important outcome, particularly in the setting of palliative care.³⁴

Today many major endpoints in oncology include survival concomitant with improvement in quality of life parameters for patients.³⁵ However, it is clear that while QOL evaluation tools are generally helpful, such instruments need to be improved. Currently, the majority of tools only partially evaluate patient quality of life. These tools focus on the global impact of cancer and its treatment on patients' physical and psychological condition. However the impact on "sociability" or adaptability to cancer, its treatment and treatment related side-effects of individual patients is not commonly assessed.³⁵

A major concern expressed by cancer patients with metastatic disease is the fear of experiencing constant pain. Management of chronic cancer pain has great influence on the patient's perceived QOL.^{36,37}

In addition to pain, fatigue is a major patient concern. Anemia is a typical cause of cancer related

fatigue.³⁸ Anemia occurs in 10-40% of cancer patients, with incidence dependent upon tumor type and the specific chemotherapy or radiation therapy used. Anemia occurs in nearly all patients diagnosed with leukemia and in 50% of patients with lymphoma after chemotherapeutic treatment. The consequences of anemia are fatigue and cardiovascular symptoms. These symptoms have a negative effect on the patients' QOL and also potentially on response to cancer treatment. Many clinical trials have included assessment of QOL to evaluate anemia treatment modalities, such as erythropoietin alpha therapy.³⁸ The majority of these studies suggest that erythropoietic agents have a positive impact upon cancer patients' QOL.³⁹ The Fatigue Symptom Inventory (FSI) was developed in order to assess the impact of fatigue, which is one of the most common and debilitating symptoms that cancer patients have to face.⁴⁰

Among the most feared and debilitating adverse effects associated with use of chemotherapy are intractable nausea and vomiting. The positive contribution of antiemetic therapy may be offset by adverse effects, including increased incidence of anxiety, fatigue, and restlessness, which are commonly reported by patients. The impact of these symptoms on the patient's QOL would be better

assessed with the use of an instrument that contains separate items for nausea and vomiting.¹²

Cytotoxic chemotherapy might be thought of as the "art of controlled poisoning", with the aim of treatment being destruction of tumor cells before the drugs kill the patient. Unfortunately, it is still distressingly easy to get the balance wrong, with potentially lethal toxicity consequences in patient overdose, or tumor recurrence and cancer-associated death in cases of chemotherapy underdose. Although some 40 different cytotoxic drugs are currently commercially available, all suffer from the same fundamental defect, in that cytotoxics are unable to distinguish between normal and malignant cells. Thus, all dividing cells within the body are at risk and some degree of toxicity is inevitable. Almost all these drugs cause some degree of bone marrow suppression and give rise to symptoms of anorexia, nausea and vomiting. In addition, individual agents have specific toxicities that may be debilitating and cause patient distress, such as alopecia (hair loss associated with doxorubicin, cyclophosphamide and other drugs), or painful peripheral neuropathy (associated with use of the vinca alkaloids or cis-platinum).⁴¹

Alopecia has few physically harmful effects, but the psychosocial consequences of anxiety and depression are prominent for human patients in specific cultural contexts. While chemotherapy can cause alopecia during therapy, hair growth generally recovers at conclusion of therapy, albeit sometimes with hair having an altered texture and appearance. Hair is essential to the identity of many women and men. Femininity, sexuality, attractiveness, and personality are symbolically linked to a woman's hair, more so than for a man. Hair loss can therefore seriously affect self-esteem and body image. In a study of cancer patients with and without alopecia, those with alopecia had a poorer body image. Furthermore, women's self-concept worsened after hair loss.³⁷

There are psychosocial effects associated with the administration of chemotherapy and with treatments such as mastectomy for breast cancer patients. The frequency and severity of physical adverse effects and psychosocial changes 1 year after the diagnosis of breast cancer in young women treated by adjuvant chemotherapy were studied by Hislop et al. (1991).⁴² The study questionnaire used in the study inquired as to the frequency, degree of distress induced, and duration of physical side effects. These

adverse effects included nausea, fatigue, diarrhea, dysuria, infection, hair loss, irregular menstruation, hot flushes, bone pain, and sexual difficulties. Psychological factors included anger, anxiety, depression, cognitive disturbance, and coping mechanisms. Physical side effects of adjuvant chemotherapy were common, but did not affect the QOL as much as the psychological side effects.⁴²

According to Fallowfield et al. monitoring quality of life in breast cancer should be a mandatory part of follow-up in clinical trials.⁴³

Psychological morbidity following mastectomy is high. Patients, who have undergone breast reconstruction, whether immediate or delayed, derived benefit from reduction of psychological side effects such as anxiety and depression. Women who elected to have reconstructive surgery done immediately had significantly improved body image, self-esteem and satisfaction when compared to women who elected to have the surgery later.⁴⁴

Factors such as the different phases of the patient's experiences might greatly influence QOL. These factors include time of diagnosis, type of primary treatment, genetic risk and its psychological management, special issues related to non-invasive breast cancer, tumor

recurrence, completing treatment and re-entry to normal living, survivorship issues and palliation for advanced or terminal cancer. Beyond chemotherapy and its side effects, the cancer patient can experience anger, grief, suffering, and pain, uncertainty about the outcome of disease treatment and cure rate.⁴⁴⁻⁴⁶

Cervical cancer (CCA) patients illustrate another example of the distressing psychosocial side effects.⁴⁷ According to research, the majority of African American and Caucasian CCA patients express feeling "damaged" and "worn out" after the diagnosis, with loss of libido mostly due to fear that sex would worsen their condition, and sexual avoidance for the women that still had sexual desires. Treatment-related side effects such as hair loss and the potential for passing CCA to their daughters were some of the most common concerns.⁴⁷

Prostate cancer is another example of a disease process wherein the sexual side effects of cancer and cancer treatment are of great concern. Diagnosis of prostate cancer in itself can cause sexual dysfunction. All forms of treatment for this cancer cause serious sexual problems for men.⁴⁸ Treatment for the erectile dysfunction that results from therapy has varying success rates.

Prostatectomy can cause erectile dysfunction in 30% to 98% of men, depending on whether both, one or neither nerve bundles are spared. Radiation therapy results in erectile dysfunction in more than 70% of those treated; brachytherapy using intratumoral radiotherapy implants produces the least amount of sexual deficit. Hormone ablation therapy has serious consequences, in that more than 80% of men report loss of erections at 1 year after therapy in addition to profound loss of libido.⁴⁸

Another important aspect of side effects of chemotherapy can be seen in survivors of childhood acute lymphoblastic leukemia (ALL).⁴⁹ Research suggests that despite the fact that response to therapy and prolongation of survival time is very favorable for childhood ALL patients, there is a risk of neuropsychological and psychosocial impairments in functioning. A subset of survivors of childhood ALL experience difficulties with mood, school or work adjustment, and cognitive functioning. Central nervous system treatment for ALL is believed to be one risk factor associated with the subset of survivors who are at risk for long-term adjustment difficulties. This potential negative consequence of high dose regimens in pediatric patients is very important and it is believed

that further research is needed in order to clarify this issue.⁴⁹ Thus, QOL instruments, must evaluate not only the impact of cancer and its treatment on a patient's QOL, but also the safety and contribution of new treatment modalities in the field of oncology.⁴⁹

In human oncology QOL assessment instruments are typically calibrated to the specific disease process or treatment modality under evaluation. Thus, a variety of disease-specific instruments have been developed in human oncology to assess QOL issues in different types of cancer.³²

The Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire was developed to address the needs of small-cell lung cancer patients. The data were highly prognostic of survival and also suggested the potential importance of this QOL survey in decision making.⁴⁵ Stalfelt et al. used three different instruments in order to assess the QOL of patients with acute myeloid leukaemia (AML) during a prospective study. He discovered that all three instruments were needed to adequately assess patient QOL as the instruments solicited complementary information.^{49,50} Kaasa et al. acknowledged the need to understand fatigue

and the impact it has on quality of life among Hodgkin's disease survivors.⁵⁰ For patients with adenocarcinoma of the pancreas, a simple and rapid assessment of QOL has been demonstrated to have utility in altering the course of critical care management. Alterations in treatment course may drastically improve pancreatic cancer patient QOL.⁵¹ Quality of Life assessment in brain tumor patients is crucial in order to understand the disease burden and the impact of the specific treatment.⁵¹

The EORTC QLQ-C30 is one among several cancer-specific QOL instruments that has been developed to contain disease and/or treatment specific assessment modules.⁵² The quality of life questionnaire (EORTC C30) and the head and neck specific module (H&N35) have been validated in many languages and cultural settings, and are found to be valid and informative tools in order to assess QOL of head and neck cancer patients.^{53,54} The EORTC QLQ-C30, the Functional Assessment of Cancer Therapy-General (FACT-G) and the MOS Short-Form Health Survey are some of the most widely used health related quality of life questionnaires.^{51,55} Other disease specific instruments include the lung cancer module (EORTC-QLQ-LC13), the Functional Assessment of Cancer

Therapy--Lung Cancer Quality of Life Instrument (FACT-L), and the Lung Cancer Symptom Scale (LCSS).⁵⁶ A brain tumor specific scale is the Brain Cancer Module and the Functional Assessment of Cancer Therapy - Brain (FACT-BR) modified, and a brain tumor Symptom Questionnaire which are used in combination with general questionnaires.⁵¹

Uni-and multi-dimensional QOL tools specific to cancer treatment modality have also been developed, including those created to address the issues of acute and chronic radiotherapy-related fatigue arising during the course of daily treatments.⁵⁷ The concept and assessment of QOL has been used in order to compare laparoscopic colon resection (LCR) with open resection (OCR) as treatment approaches for colon cancer.⁵⁴ The City of Hope Quality of Life (COH-QOL) questionnaire is a QOL instrument developed in order to assess the QOL of patients that were treated with colostomy.^{56,58} QOL instruments have also been used to assess the effects of different treatment modalities and voice and speech rehabilitation methods on the quality of life in patients with laryngeal cancer.^{56,59}

The efficacy of new treatment modalities are currently evaluated with inclusion of the effect these modalities

have on the patients' QOL during clinical trials. In fact, virtually all therapeutic trials conducted today include QOL parameters as part of their study endpoints. To give a single example, a three-year project evaluating the biopsychosocial effects of interleukin-2 (IL-2) therapy on the first 45 patients treated with the therapy revealed that compromise of the patient's QOL was a major issue.⁶⁰

A variety of methods for obtaining QOL data from patients has also been developed. Examples of innovation in data collection include a Talking Touchscreen (TT), developed for health related QOL assessment in low literacy populations.⁶¹ The Edmonton Symptom Assessment Scale (ESAS) employs a visual analogue scale developed in order to assess QOL of patients receiving palliative care.⁶² Attempts have been made to create instruments that cross language and cultural differences. A major priority of the internationalization of QOL research is to standardize the QOL measures.⁶³

Even though there are a variety of QOL instruments developed that aim to give information about the impact the cancer and/or the treatment had on the patients, there is no accepted gold standard QOL instrument available in human oncology. Therefore, it is preferable to use

multidimensional patient-rated measures with a standard format and scoring procedure.⁶⁴

There is accumulating evidence that cancer affects not only the cancer patient, but also his or her family and friends. There are studies focusing on the QOL of the family caregivers and the interventions needed in order to help them cope with the associated stresses.⁶⁵ There are now several QOL questionnaires developed for caregivers, including the Caregiver Quality of Life Index-Cancer Scale, the Caregiver Quality of Life Index, the Quality of Life Tool, and the Quality of Life Index-Cancer Version. According to Edwards et al. the development of reliable and valid caregiver QOL measures is an important factor in developing interventions to enhance quality of life for caregivers of patients with cancer.⁶⁶ A study was conducted to assess the ability of partners and clinicians in making proxy judgments on behalf of patients with prostate cancer.⁶⁷ Much more so than clinicians, partners of cancer patients were able to accurately assess the areas of life that were of greatest importance to the patient. This is consistent with the observation that conventional views held by most doctors are not always consistent with the priorities that patients set themselves when planning

treatment. This also highlights the need for enhanced communication between doctors and patients and how they arrive at treatment decisions.

Perhaps the most critical goal in all the QOL research, regardless of QOL instruments employed, is to answer one fundamental question: Are the risks of toxicity and/or the inconvenience of the proposed treatment justified by the expected therapeutic benefit? In some cases, the stress and debility of treatment may be more challenging than the effects of the disease. Under these circumstances, it is reasonable to entertain discontinuing the offending therapy.

Although all these QOL tools vary, each has the potential to be quite useful for patients, clinicians and researchers, because QOL assessment has been shown to contribute to a better and more individualized cancer patient care. According to Grumann et al. disappointment in the results gained by QOL assessment can be minimized by the choice of appropriate QOL instruments, with an emphasis on their goal-directed implementation, and commensurate expectations of the ability of the assessment to fulfill the anticipated aims. Competent utilization of QOL assessment contributes to an enhanced standard of patient-centered care in oncology.⁶⁸

The psychosocial distress engendered in cancer patients, regardless of tumor type, upon diagnosis and during treatment can be overwhelming and may in fact affect treatment outcome. Ancillary psychological treatments are believed to be necessary and very helpful for cancer patients in general. QOL assessment through validated instruments can help to identify and address the physical and psychological issues of these patients early in the treatment course. QOL assessments can be used in diagnosis, predicting prognosis, patient monitoring, clinical decision-making, communication, and treatment. Important factors in choosing which QOL assessment instrument to use include: the purpose of the assessment, the patient population targeted, and the timing and frequency of the administration of a given instrument. The assessment is recommended to start from the beginning of treatment in order to identify prospectively possible problems and to provide a reliable and valid patient-reported outcome.⁴⁶

Health Related Quality of Life in Pediatrics.

Considerable progress has been made during the past 2 decades in defining and measuring health-related quality of life (QOL), and there is a growing recognition that these measures provide important information about the impact of a chronic illness and its treatment on patients. Quality of life assessment is considered to be particularly important in pediatric practice.

According to Eiser et al.⁶⁹ in cases where cure is not possible, it is essential to be able to determine the effect of disease and treatment on the child's QOL. Accurate QOL assessment is very helpful when informed judgments can be made about whether or not a specific treatment is appropriate, and, where there is a choice, which treatment option might be the best for the child.

Many different approaches have been used to measure pediatric QOL.⁶⁹ Not surprisingly, most of the HRQOL measures currently used today in adult medicine have limitations in the pediatric setting. Therefore, efforts are ongoing to develop complete and multidimensional QOL instruments through pediatric psychosocial research. While maintaining a child's quality of life throughout the course

of treatment of chronic illness would intuitively seem to be of paramount importance, the aim of most clinical trials is to assess the impact of treatment on clinical outcomes. Unfortunately, QOL is often viewed to be at best of secondary importance.⁶⁹

With regard to pediatric medicine, Eiser et al.⁶⁹ concluded that QOL measures based on minimally accepted criteria should be brief, should allow for proxy- as well as self- reporting and should provide reliable and valid data with age appropriate survey instruments. In cases of younger children, proxy reports are necessary.⁷⁰ There are also limitations when considering the age at which a child can reliably report on his or her health status and QOL. It is estimated that self-reported QOL information can begin to be obtained from children between 4-6 years of age.^{71,72}

According to the numerous definitions of QOL for adults, the two commonly shared aspects cited are that QOL is subjective, and that QOL reflects an individual's perception of the impact of health status (disease and treatment) on physical, psychological and social function.^{70,73,74} Although these definitions also apply to children, there are some differences. It is well known that

children function within multiple social contexts and are shaped from these social interactions in a very different way than is the case for adults.⁷⁵ There are also limitations due to the level of language comprehension of each child that self-reports QOL.⁷⁶

Proxy assessment is critical in cases where children are not able to self-report due to very young age, disease symptoms, disability, or mental health issues. There are several studies that attempt to assess the level of agreement between the parent's observation and the child's self-report, and conclusions of these studies vary.^{77,78,79,80} The proxy method is inherently flawed because proxy evaluation cannot not reflect precisely the subjective view of the patient. It is unclear whether a parent or caregiver's perspective is appropriate, especially in longitudinal trials, as it is possible that the report will be biased by the degree to which the parent or caregiver is affected by the child's disease. It has also been shown that parents, as the most common proxy respondents, tend to give more accurate reports regarding their child's QOL status, than do physicians or nurses involved in the child's medical care.⁸¹

Parental perspective is considered to be very important due to the dependent nature of the relationship between parents and children. Parents are the ultimate arbitrators of changes in treatment modalities. Proxy ratings have been found to be more accurate or similar to patient ratings when the proxy lives in the same household, and the patient's symptoms are concrete and observable.^{82,83} When proxy assessment is the only one available in order to measure the child's QOL, doubts may arise about the validity of the proxy report.⁸⁴ In such cases, additional proxy reports may be provided by other caregivers, teachers, or clinicians. These additional sources for proxy evaluation are considered useful in order to obtain complementary information regarding the child's QOL.⁸⁴

An important aspect of proxy QOL assessment is considered to be the impact the child's disease has on parents and caretakers. The effect of the child's disease on the parent's life is referred to as the "caregiver's negative affect".⁸⁵ This may have a profound impact on the objectivity or on their judgment of the child's condition. Thus there is a potential bias in reporting.

Even though QOL evaluation has increased in popularity as an outcome measure in health research, the measurement

of QOL has been questioned on methodological grounds, particularly in the proxy setting.⁸⁶ Some feel that QOL measures show little association with objective measures of disease status. This is evident today with the development of pediatric intensive care. Even though the survival rate of critically ill children has improved, there are a number of physical and psychological sequelae that greatly affect the QOL of survivors and their parents.⁸⁶

In another example, Boruk et al.⁸⁷ studied the impact of otitis media on the child's family or caregivers. The authors described the degree to which the disease impact influenced the caregiver's perception of the patient's QOL. The Caregiver Impact Questionnaire (CIQ) is a 6-item survey that was developed to assess this effect. In this study, of 159 families and subjects, caregiver ratings of child QOL were largely influenced by caregiver's perceptions of their own personal situation.⁸⁷ In another study, Price et al. described the impact of caregivers negative affect in parental proxy reports of pediatric asthma QOL assessments.⁸⁸ Price concluded that caregiver negative affect influenced reporting of pediatric QOL and that it was therefore critical to understand the individual

characteristics of the respondent when using a QOL instrument as an outcome measure by proxy.⁸⁸

As is the case in adult QOL studies, pediatric QOL instruments are also either generalized or disease-specific.⁸⁹ One domain that is different from adult QOL instruments is an emphasis on family-related factors.⁹⁰ As with adults, pediatric QOL assessment instruments often include screening for psychological difficulties and pain, fatigue, cognitive deficits, sleep difficulties, or spiritual concerns.⁹¹ Some HRQOL measurements, such as the Multi-Attribute Health Status Classification (MAHSC)⁹², have been used for children treated in an intensive care unit. The MAHSC has domains that include changes in emotion, level of cognition, sensation and mobility, capacity for self-care and degree of pain.⁹²

Measures of QOL are frequently incorporated in evaluation of pediatric clinical trials in order to identify differences between interventions, treatment modalities, side effects, and improvement rates. Other approaches are to study the effect of the disease-related symptoms on the pediatric patients QOL compared with a

control group of healthy infants, young children, and adolescents of the same age.⁹³⁻⁹⁶

Ongoing research efforts in pediatric medicine employ QOL measures in children with central nervous system tumors, neural tube defects, extremely low birth weights, childhood and adolescent epilepsy, and adolescents with headaches. Grange et al. compared 17 generic proxy instruments and found that the Health Utilities Index was the most comprehensive in the setting of their study. These authors suggested that this instrument would be an appropriate tool to assess children under 5 years of age.⁹⁷

Due to an increased rate of long-term survivors in pediatric oncology, the study of QOL in pediatric survivors is considered of major importance in that field.⁹⁸ These longitudinal types of QOL surveys emphasize four major issues. First, assays seek to evaluate the QOL of the ill child compared to that of a healthy child of the same age. A longitudinal study determines the extent to which the level of parental anxiety influences the current status of the child. This is considered to be a factor that may contribute to the child's QOL and is therefore appropriate for evaluation. Impact of disclosure or withholding of the medical diagnosis on the child's QOL is also assessed.

These issues are addressed to be answered by the proxy-parents.⁹⁸

The Scottish Intercollegiate Guidelines Network (SIGN) and the Children's Oncology Group (COG)⁹⁹ developed clinical practice guidelines and provided long-term childhood cancer survivors and healthcare providers with accurate information in order to guide screening and risk-reducing interventions. According to previous studies, childhood cancer survivors had important deficits and misinterpretations about their diagnosis, treatment and associated risks.⁹⁹ Additionally Sherman et al.⁹¹ discussed the need to provide QOL screening in centers performing pediatric stem cell transplantation, because stem cell transplantation has been associated with elevated risks for QOL deficits in adult recipients.⁹¹

The value of treatment with recombinant human granulocyte colony-stimulating factor (rhG-CSF) in children with congenital agranulocytosis was the subject of a clinical trial to assess the impact of this treatment on the child's QOL.¹⁰⁰ A questionnaire was developed and administered to the parents of study patients prior to the initiation of treatment, and then monthly thereafter for

six months. The instrument focused on the following aspects of QOL: functional status, general health perceptions, activity limitation, disease symptoms, and discomfort associated with therapy. One of the most critical conclusion of this study was the recognition of the primary importance of the sequence and frequency of serial surveys for accurate comparison and assessment of changes in the patient's QOL.¹⁰⁰

Unfortunately QOL assessment in pediatric oncology has not been studied extensively to date. This is due to the additional level of methodological complexity that pediatric evaluations require in order to be considered accurate and valid.¹⁰¹ Pediatric survey instruments must be carefully designed to be easy and accessible for pediatric patients, and proxy informants, pediatric oncologists, and other caregivers involved in childhood cancer care.^{102,103}

Disease-specific QOL measures, similar to those developed for children with asthma, have been used as examples to guide the development of other disease-specific QOL surveys, such as the Cystic Fibrosis Questionnaire (CF).¹⁰⁴ Disease-specific QOL instruments have been used in clinical trials for diseases ranging from less life-threatening conditions such as rhinitis, otitis media,

dermatitis, eczema, amblyopia, and idiopathic short stature, to more severe clinical entities such as diabetes mellitus, obesity associated with brain tumor therapy, and congenital agranulocytosis.¹⁰⁵ Some commonly used generic instruments are the Infant and Toddler Quality of Life Questionnaire (ITQOL), Health Status Classification System Preschool Version (HSCS-PS), and Child Behavior Checklist/1.5-5 (CBCL).¹⁰⁶

There are no specific boundaries between disease specific and generic instruments, and of course these surveys can be used in combination. The TNO-AZL Preschool Quality of Life Questionnaire (TAPQOL) is a generic instrument developed in order to assess health-related quality of life in preschool children.¹⁰³ It can be also used as a disease specific test in the area of otolaryngology.¹⁰⁷ The TAPQOL survey has also been translated in order to be used in other countries.¹⁰⁸

In the field of pediatrics, QOL assessment is now acknowledged to be of great importance to continue to advance our understanding of the impact of different diseases and medical treatments on pediatric patient's QOL. The ultimate goal of improved understanding of pediatric QOL is to provide better and individualized patient care.

Quality of Life and Health Related Quality of Life in Animals.

Animal welfare, animal well-being and quality of life in animals are terms that are used interchangeably and confusion arises when authors attempt to make a distinction between them. Animal welfare is stated to be the protection of the health and well-being of animals, or the viewpoint that animals, especially those under the care of humans, should not suffer.

Fraser ¹⁰⁹ provides dictionary definitions of "welfare" and "well-being" of animals as incorporating phrases such as "the state of being or doing well" and "a good or satisfactory condition of existence". ¹⁰⁵ These phrases tell us that the "welfare" or "well-being" of animals has to do with their quality of life. To be more precise about the meaning of welfare and well-being requires that we address the degree to which value judgment issues color what we consider important for animals to have a good quality of life (*Encyclopedia of Animal Rights and Animal Welfare*, Westport, Connecticut: Greenwood Press, 1998). ¹⁰⁹

McMillan ⁸ defines QOL in animals as the balance between pleasant experiences such as joy, play, social

companionship, mental stimulation, physical contact, gustatory sensation, nurturing young, sexual activity. McMillan goes on to enumerate the negative impacts on animal QOL that are introduced by unpleasant experiences including fear, anxiety, boredom, loneliness, separation anxiety, grief, depression, frustration, anger, hypoxia, pain, thirst, hunger, cough, dizziness, full bladder, constipation, nausea and pruritus.⁸ McMillan adds that the balance between the pleasant and unpleasant aspects describe above determine the QOL of the animal.⁸

The Dictionary of Farm Animal Behavior defines QOL as the result of many factors that can range from positive to negative extremes.¹¹⁰ Fraser states that welfare is a multidimensional construct that incorporates the 3 categories of body, mind and nature.¹³ Fraser¹³ also claims that well-being consists of a physical and a mental component, even in non-human animal species. Physical well-being is mainly clinical health, while psychological well-being in animals is interpreted through animal behavior.¹¹¹

Finally, we have "The Five Freedoms"¹¹² that are considered essential guidelines to define a good quality of life for animals. These freedoms are defined as: freedom

from hunger and thirst; freedom from physical and thermal discomfort; freedom from pain, and injury; freedom from fear and distress; freedom to express normal behavior.¹¹²

The terms of animal well-being and QOL are closely related. When there is a need for distinction, the public seems to perceive QOL as being more aligned to well-being than to the animal's health.¹¹³ One commonly used prerequisite for determining QOL is thought to be freedom from chronic pain. In the case of severe debilitating illness, as is the case when an animal is unable to eat and walk, most observers would judge QOL of life to be poor. In animals, the pros and cons of whether it is appropriate to continue treatment, or whether it is more humane to euthanize the animal suffering chronic debility, must be weighed.¹¹³ As a routine consideration, the availability of humane euthanasia for animals provides a clear distinction for use of QOL assessment in veterinary as compared to human medicine.

The term "animal welfare" itself does not express a scientific concept, but is rather a theoretical construct.¹¹⁴ Because scientific methods are used to identify, interpret, and implement societal concerns about animal welfare issues, the study of animal welfare has evolved to

become a scientific field. Despite the fact that it is impossible to give a precise scientific definition of animal welfare, a broad description of welfare is suggested and includes complete mental and physical health, and adaptability without suffering in artificial environments made by humans. Investigators and animal advocates posit that animal feelings should be taken into account when assessing animal welfare. Since asking the animal directly is impossible, the science of animal behavior (applied ethology) provides more reliable criteria to assess welfare and QOL in animals and more precisely in companion animals.¹¹⁴

According to Hewson,¹¹⁵ animal welfare, well-being and QOL issues concern physical health, the state of an animal's mind and also focus on the extent to which species-specific needs are satisfied. Disease severity and animal welfare exist along a continuum and are amenable to qualitative assessment. As disease and associated clinical signs range from nonexistent to extreme, similarly QOL ranges from optimal (body, mind are in optimal state and nature is satisfied) to minimal (all three aspects are severely compromised). When assessing health and disease severity, there are some specific and well-established normal measures, but QOL assessment is based on a wide

range of measures of which health assessment in part pertains to the animal's body. Most QOL measures are complex and normal ranges are very difficult to establish and interpret in animal species.¹¹⁵

Hewson^{116,117} argues that animals, even members of the same species, have different individual behaviors that might be "normal" for one animal but not for another. Breed, temperament, environment, and the husbandry practices under which the animal was raised, and whether animals were kept as groups or individuals, are only a few of the factors that can influence an animal's behavior. Understanding of normal behavior for the individual is a necessary prerequisite to understand the animal's optimal QOL level. Especially for species kept as individuals, it is very difficult to generate a valid method for weighting all factors appropriately for each individual animal. For example, playing with a ball might be one dog's favorite activity, but for another dog it might be a terrifying, and even traumatic, experience. Hewson^{116,117} mentions that it is very important for veterinarians to be aware of the developments in animal welfare science and to ensure that physical and non-physical aspects of animal welfare are included when making an assessment.^{116,117}

Dawkins also emphasizes the health status of the animal and whether the animal has the necessary prerequisites to maintain health and contentment, taking into consideration the practicalities of what is physically feasible.^{118,119}

The concerns for food animal well-being and QOL are serious issues facing intensive animal agriculture.¹²⁰ The humane treatment of farm animals is an issue that greatly concerns society, and in this context, satisfaction of farm animal needs is very important.¹²⁰ When focusing on the actual well-being of the animal, most issues are centered on how the animal "feels" while managed within a specific level of confinement, and associated with certain agricultural practices.¹²¹ In order to solve problems concerning animal well-being in intensive production systems, there are three main proposed domains of concern. These domains pertain to environmental, genetic, and therapeutic factors.¹²⁰ Animal welfare science has already contributed a number of significant improvements in the welfare of farm animals. However, an evaluation of broader QOL questions and their applications to improve farm animal welfare is an ongoing need.¹²¹

The Cruelty to Animals Act of 1876 prohibited painful scientific experiments that included dissection of living, conscious animals, and required anyone wishing to experiment with animals to obtain a license from the Secretary of State.¹²² Even today, conditions for issue of these licenses remain strict. According to the Act, animal experimentation is allowed under controlled conditions and experiments must have the clear objective of improving the welfare of man and/or animals. Benefits from experiments carried out under the Act have been enormous, covering every aspect of diagnosis, treatment, and prophylaxis in human and veterinary medicine. As a consequence, the welfare of laboratory animals has also been greatly improved.¹²² Societal concerns regarding use of animals as experimental subjects have emphasized the need to look constantly at animal welfare to ensure humane treatment. Scientists, as well as the general public, are concerned about the moral and ethical responsibility for the humane treatment of experimental animals.¹¹⁹ Appropriate use of animals in experimentation must consider reducing the numbers of animals used for experimentation, avoiding unnecessary duplication of experiments, and minimizing pain and distress of the animals used.¹¹⁹

The implementation of what has been referred to as the "three R's principle" (Replacement, Reduction, and Refinement), has become a very important objective of European and US research communities.¹²³ Animal Care and Use Committees promote animal welfare and ethical scientific use of animals.¹²³ Research data from a variety of fields, such as animal biology and behavior, the biology of stress, and psychoneuroimmunology, increasingly support a holistic view of well-being.¹²⁴ Existing data suggest an interactive system linking internal psychological, neurologic, physiologic, immunologic, endocrine, and biochemical events with the external psychosocial and physical environment.¹²⁴

Because of the well identified societal concerns regarding use of animals in research, laboratory animal welfare was one of the first fields to attempt to define and assess animal QOL.¹²⁴ Many methods and publications have been produced to date in this growing research field.

Two of the most popular current methods of assessing research animal welfare, pain, distress and suffering are clinical observation sheets and score sheets.¹²⁵ The ability to recognize a "normal" animal is considered a fundamental skill in order to define what constitutes an "abnormal"

animal with behavioral and physiological changes due to pain and discomfort. The ability to observe changes for each individual animal is also critical. Some laboratory technicians state that it is very helpful to have the animal initially assessed before the experiment, so that deviations from the animal's initial state of being can be easily detected.¹²⁵ The Laboratory Animal Care Facility of Boston University and Boston Medical Center provides a list of signs of pain regardless of species. Signs of acute and chronic pain are summarized in Table 1.

The thorough and complete examination of an animal's appearance is essential for both health and welfare assessment. The laboratory animal technician organization called Assessing the Health and Welfare of Laboratory Animals (AHWLA.org) maintains a website that provides a tutorial with pictorial illustrations of the definitions of the various criteria of assessment. This pictorial information makes the website particularly helpful. While there is overlap of common points with the approach provided by the Laboratory Animal Care Facility of Boston University and Boston Medical Center criteria, the AHWLA tutorial provides a more detailed approach.^a

^a <http://www.ahwla.org.uk/>

The International Association for the Study of Pain has defined pain in human beings as "an unpleasant sensory and emotional experience associated with potential or actual tissue damage, or described in such terms". It is believed that animals and humans experience pain in similar ways. The Interagency Research Animal Committee (IRAC) in 1985 advised that investigators should be aware of this fact because it is important to recognize and alleviate pain in research animals to minimize suffering. Distress is also difficult to define. Carstens and Moberg in "Recognizing Pain and Distress in Laboratory Animals" (ILAR 2000) defined stress as "...the biological responses an animal exhibits in an attempt to cope with a threat to its homeostasis." When stressors have a prolonged duration and are of acute nature, stress becomes distress. Distress arises from stress when the stress causes such a disruption of biological functions that compromise an animal's well-being and pathology might occur.

According to Clark,¹²⁶ an animal's QOL is an individual's internal somatic and mental state that is affected by what the animal knows or how it perceives certain situations and changes in its environment.¹²⁶ An owner or caregiver might know that an event or situation is no threat, but the animal may be incapable of such

understanding. Animals obviously do not function with the same information base as do humans. It is important, therefore, to understand how an animal perceives a specific situation in order to minimize stress and distress.¹²⁶ Obviously, the recognition and quantification of stress in animals is very difficult task to achieve, because animals cannot express their feelings verbally.¹²⁷

In domestic animals, well-being is defined as absence of stress and it is critical to appreciate the fact that stressful situations are potentially more important factors in determining the well-being of research animals than is actual pain.¹²⁸ Therefore, observation and recognition of stress is critical in domestic animals is critical. Recognition of stress may be easier for companion animals, when compared to research subjects, because observations of companion animals may be more comprehensive due to proximity and continued contact with owners, as compared to the potentially less frequent observations of laboratory animal species.¹²⁸

According to Breazile,¹²⁹ there are three behavioral categories of stress: eustress (good stress associated with survival); neutral stress (neither harmful not hurtful on the long term); and distress (which can elicit responses

that interfere with the animal's well-being, comfort, and reproduction and can be present as pain.) Mating and feeding are two behaviors associated with a level of stress. Acute stress induces polyphagia, while chronic stress induces decreased feeding and anorexia. The reproductive effects of stress levels are usually detected earlier in research animals than in pet animals. Even though anxiety-related disorders are among the most common class of disorders in both humans and animals, their presence in companion animals can remain unrecognized longer. This is because of the general assumption that if our pets are not in pain they have a "good" QOL. This suggests a need for change in the way we in which we view QOL, well-being and discomfort in animals. Many of these factors are intangible and therefore difficult or impossible to quantify.¹²⁹

According to Overall,¹³⁰ fear is a feeling of apprehension associated with the presence or proximity of an object, individual or social situation. Fear is usually indicated by fight and flight responses (in an attempt to escape), facial and body signals (lowering and tacking of the tail, piloerection, flattening of the ears), and physiological responses of increased heart and respiratory

rate, muscle tremors, urination, defecation, and anal sac expression. When fear progresses to anxiety, the animal might exhibit panting, pupillar dilatation, pacing, drooling, hiding, shaking, whining or destruction of objects in the environment.¹³⁰

Both pain and fear can induce aggressive behavior in animals, especially when manipulated or are undergoing painful medical treatment. Obviously an animal is not aware of the beneficial aspect of the treatment and it perceives this interaction as a threat. Behavioral responses must be interpreted within each situational context, and include individual breed traits or differences of which the animal's owner may be aware.¹³⁰

Another important situation that acts as both a stressor and is also associated with an animal's hospitalization is the reintroduction of an animal to its housemates. Though dogs have fewer problems in this social setting than do cats, reintroduction to housemates can be challenging; if the animal harbors uncharacteristic smells, carries peculiar apparatuses, such as catheters, and exhibits abnormal postsurgical behaviors or postures or when animals are chronically ill. Negative interactions

between formerly compatible animals may become a stressful situation for the owner.¹³⁰

As Loeffler et al¹³¹ stated, it is very important to be able to recognize the symptoms and behaviors that accompany pain.¹³¹ Pain is a function that is essential for survival, since it makes the animal pay attention to any injuries and abnormalities of the body. When pain is persistent though, it can result in anxiety, depression and a diminished QOL.¹³² Lee argued that pain has been historically undertreated, not only in animals, but also in human pediatric patients. A typical reason is the difficulty in assessing pain. Infants and young children are not able to verbalize their pain and they depend upon their parents and caregivers to recognize, assess and manage their pain.¹³³ It was common among health care providers to have a lack of awareness of pain perception, assessment and management in human neonates.¹³³ This is also true for animals.

Anand and Graig¹³⁴ have suggested a broader definition of pain that includes those who are not able to self-report. The use of behavioral alterations and physiologic changes should be considered as an indirect manner of self-reporting QOL. Thus, this also becomes a point of

similarity between veterinary patients and human pediatric patients regarding pain assessment.¹³⁴

Cancer therapies have increased patient survival rates in both human and veterinary medicine. With increased survival rates come new challenges resulting from severe, chronic tumor-induced pain.¹³⁵ Unrelieved pain significantly decreases the quality of life of patients. Animal models have been developed to study cancer pain. These models can be divided into five categories: bone cancer, non-bone cancer, cancer invasion, cancer chemotherapeutic-induced peripheral neuropathies, and spontaneous occurring cancer pain. Each model is important for enhancing our knowledge about how and why cancer pain is generated. Hopefully, these models will aid in developing novel therapeutic approaches for cancer pain in domestic animals as well as in humans.¹³⁵

Veterinary ethology is a science that can enhance our knowledge regarding pain-associated behaviors.¹³⁶ The ethological perspective in assessing animal well-being and QOL is very important, because it helps us to avoid either a mechanistic or an emotional evaluation of the QOL of an animal.¹³⁶

Veterinary ethology is also very important because it is a scientific area that focuses on teaching responsible animal ownership.¹³⁶ Appreciating normal species behavior, whether stressed or happy is a matter of owner education. The key to a better understanding of pets is the knowledge of the ecological environment of these species and species-specific behavior.¹³⁷ As animals that are treated with chemotherapy might experience pain, fear, and distress, and they might be treated at the hospital and at home between visits, it is crucial for the owners to be aware of the anticipated normal species behavior, possible changes in this behavior, and how to interpret behavior change with an eye to addressing potential problems as they arise.

The mission of medicine is maintenance of health, elimination of suffering and prolongation of life.^{138,139} Companion animal medicine has emerged as the dominant social function of veterinary medicine, and pets are currently considered more and more as family members and their value is not primarily economic. As a consequence, the goals of small animal veterinary medicine have approximately the same mission as pediatric medicine. A major difference is that veterinarians always have to work through a financially responsible third party that is able

to make fiscal and medical decisions for the animal. This situation is quite similar to the human pediatrics, gerontology and psychiatry. An important difference is that the animal's owner has the option to elect humane euthanasia of the animal. This is a critical issue since, even though both the assigned veterinarian and the owner share responsibilities in decision making, the ultimate decision remains the owner's.^{138,139}

Veterinarians advise the owners about humane euthanasia when there is clear evidence of suffering and further prolongation of life is not meaningful for the animal.¹⁴⁰ Veterinarians who adhere closely to the pediatrician model are not willing to perform convenience euthanasia. For these individuals, any euthanasia is a stressful part of their professional life. On the other hand, the animal perceives the world through subjective states and any further painful treatment that the animal cannot conceptually understand and weigh as regards future benefits should be reconsidered and discussed by the owner and the veterinarian.¹⁴⁰

Having an animal with a life-threatening illness might cause the owner to consider a transient suffering induced by a therapeutic modality to be a small price for a

potential increased survival probability. The most important factor in selecting a treatment is the QOL of the animal during the treatment period. This is complicated if the owner excessively anthropomorphizes or denies anthropomorphic considerations when making decisions about therapy.

Having an animal with a life-threatening illness might cause the owner to consider a transient suffering induced by a therapeutic modality to be a small price for a potential increased survival probability. The most important factor in selecting a treatment is the QOL of the animal during the treatment period. This is complicated if the owner excessively anthropomorphizes or denies anthropomorphic considerations when making decisions about therapy. Some owners might elect to prolong their pet's life at any QOL cost. The role of the morally responsible veterinarian is to assume the role of animal advocate and explain what may be important to the animal. It is also crucial that the veterinarian establish a type of relationship with the owner that allows agreement on QOL goals.¹⁴⁰ Some owners might elect to prolong their pet's life at any QOL cost. The role of the morally responsible veterinarian is to assume the role of animal advocate and explain what may be important to the animal. It is also

crucial that the veterinarian establish a type of relationship with the owner that allows agreement on QOL goals.¹⁴⁰

Humane euthanasia is considered to be the rapid and painless introduction of death.¹⁴¹ Villalobos¹⁰ has developed a life scale in order to help owners to make this difficult decision for their animals. She asserts to this scale that helps owners maintain a rewarding relationship with their pets that nurtures the human-animal bond. At the same time, this scale provides a guideline that alleviates the owner's feeling of guilt and "engenders the support of the veterinary team to actively help in care and decision making for end-of-life patients".¹⁰

Several questionnaires have been developed in order to evaluate QOL in companion animals treated for different diseases. Tzannes et al.¹⁴² developed a questionnaire regarding the perceptions of owners of cats diagnosed with Lymphoma (LSA) and receiving chemotherapy and its impact on QOL. There were 31 cat owners participating in the study. All the cats were treated with the same chemotherapeutic protocol (Cyclophosphamide, Vincristine, and Prednisone). The owners were surveyed with a postal questionnaire once after the cat had completed three treatments. The owners

were asked to evaluate the cat's QOL retrospectively regarding the cat's QOL before initiation and after their cat received the last chemotherapeutic treatment. The questions were also pertaining to gather information about the perception of owners regarding chemotherapy in pets, if the owners had previous personal experience of receiving chemotherapeutic drugs and why they elected to proceed with such treatment for their cats. A major finding was that QOL scores prior to the onset of cancer had been significantly higher than the QOL scores after the onset of cancer but before initiation of chemotherapy. Quality of Life scores during chemotherapeutic treatment were also significantly lower than prior to the onset of cancer, but significantly higher during treatment than prior to starting treatment. The study revealed that 87% of the cats had adverse drug effects during chemotherapy. Overall, 83% of the owners were pleased they had pursued chemotherapeutic treatment for their cat and 87% of them stated that they would treat another cat with the same chemotherapy protocol.^{142,143}

Brown et al.^{144,145} attempted to validate the Canine Brief Pain Inventory (CBPI), which is based on the human Brief Pain Inventory (BPI), in a canine model of spontaneous bone cancer. One hundred owners of dogs with

bone cancer self administered and completed the CBPI three different times (at baseline, upon bone cancer diagnosis, 1 week after diagnosis and analgesic treatment, and 3 weeks later after diagnosis and analgesic treatment) in order to test reliability, validity and responsiveness of the tool. Internal consistency was high (Cronbach's alpha, 0.95 and 0.93), as was test-retest reliability (kappa, 0.73 and 0.65). Convergent validity was demonstrated with respect to quality of life ($r = 0.49$ and 0.63). The CBPI reliably measures the same pain constructs in dogs with spontaneous bone cancer, as a similar inventory tool (CBPI) does in people. If it could be applied to a readily available animal model of spontaneous disease, this innovative approach to preclinical outcomes development, could transform the predictive ability of preclinical pain studies.^{144,145}

Another study aimed to evaluate the changes in QOL of dogs with spinal cord injury, as perceived by the owner.¹⁴⁶ In this study, 100 owners of dogs with spinal cord injuries participated in this cohort study design. Duration of dysfunction, modified Frankel neurologic injury score, and etiology were recorded. Dogs were evaluated initially and after 4-6 weeks of injury. The results indicated that

owner-assigned, weighted QOL scores for dogs with spinal cord injuries did not vary significantly based on underlying etiology or duration of injury but were higher for ambulatory than for non-ambulatory dogs.

Another questionnaire evaluated the owner's assessment of QOL of dogs with spinal cord injuries.¹⁴⁷ In this work, 100 dogs with spinal cord injuries and 48 healthy control dogs participated. This questionnaire was also adapted from a human oriented QOL tool. Five broader domains were evaluated including mobility, play, mental stimulation, health, and companionship. The scores values were assigned from 0-100%. Dogs with spinal cord injuries had significantly lower scores than do control dogs. The results suggested that this tool could be used to obtain proxy (owner) QOL assessments for dogs with spinal cord injuries. This QOL assessment tool could be very useful in order to help veterinarians address QOL issues in paraplegic dogs.¹⁴⁷

Mullan and Main¹⁴³ developed a repeatable, feasible tool with good internal consistency and validity, making it suitable for use in veterinary practice to assess welfare of pet dogs. Twenty-seven owners of healthy dogs completed the questionnaire once. They were asked to provide

biographical information about their dog such as comfort, exercise, diet, mental stimulation and companionship.¹⁴³

Wiseman et al.¹⁴⁸ developed a questionnaire in order to assess the effects of chronic pain on QOL in dogs. Owners of 17 dogs with degenerative joint disease participated. The questionnaire had 109 terms associated with good health and chronic pain, and there were 7 choices for each question. The use of simple, familiar terms to describe subtle aspects of behavior that reflect subjective experiences facilitated the proxy rating of QOL of these dogs. This questionnaire represents a novel approach that might be helpful for the accurate proxy assessment in a range of animals and nonverbal humans.¹⁴⁸

Wojciechowska et al.¹⁴⁹ developed a QOL questionnaire in order to evaluate the ability of this QOL instrument to differentiate sick and healthy dogs based on nonphysical aspects of QOL. Scores were similar for both sick and healthy dogs. Thus there was no evidence that this questionnaire could differentiate these two categories of dogs.¹⁴⁹

Yazbek and Fantoni¹⁵⁰ developed and validated a QOL scale for dogs with signs of pain secondary to cancer. The

3 groups consisted of 40 healthy dogs and 20 dogs with dermatologic disease and 20 dogs with cancer. The questionnaire was composed of 12 questions that had 4 possible responses for each question. The QOL score ranged from 0 (lowest possible score) to 36 (highest possible score). This was an-easy-to complete questionnaire according to the participating owners. The results suggested that this questionnaire was able to differentiate changes in QOL due to cancer pain, since dogs with cancer had much lower scores than healthy dogs and dogs with dermatologic disease.¹⁵⁰

McMillan¹⁵¹ developed a six-item questionnaire in order to assess QOL of dogs. This QOL instrument is appropriate for both healthy and sick dogs. The proxy owners were asked to rate their dog's positive and negative experiences. This tool included 6 major contributing factors to QOL. These included social relationships, mental stimulation, health, food consumption, stress and sense of control over one's life.¹⁵¹

Hjelm-Bjorkman et al.¹⁵² evaluated methods for assessment of pain associated with chronic osteoarthritis in dogs. In this study, owners of 41 dogs with hip dysplasia (CHD) and owners of 24 healthy dogs participated.

Two veterinarians evaluated each dog's locomotion and signs of pain. The dog owners completed QOL questionnaire asking information about their dog's QOL, locomotion and pain. Plasma concentration of stress hormones and radiographic orthopedic changes were also evaluated. The study results suggested that chronic pain and QOL in dogs with CHD can be accessed through completion of this QOL instrument by the animal's owner or caretaker that is familiar with the dog.¹⁵²

Oyama et al.¹⁵³ developed a questionnaire in order to ascertain the relative importance of quality versus quantity of life among owners of dogs with heart disease. In that prospective study, 201 owners of dogs with cardiovascular disease participated. There was one questionnaire administered to the owners in person after their dog was diagnosed (only inclusion criterion). The questions of the instrument were pertaining to gather information regarding the animal's QOL and important parameters in decision-making. Results underscored the importance of QOL issues to owners of dogs with heart disease. Owner's age and pet's clinical condition were critical parameters in decision-making. The efficiency of clinician-client communication was considered to be highly

important in order to optimize treatment success as perceived by the individual owner.¹⁵³

Canine lymphoma (LSA) is one of the most common canine neoplasms.¹⁵⁴ The classification of cancer based on anatomic location is helpful because these forms each have common histories and clinical signs. Anatomic forms include multicentric, alimentary, mediastinal, and cutaneous forms. Due to the systemic nature of the disease, chemotherapy is the treatment of choice. The success of this modality is based on the fact that lymphoma cells are sensitive to chemotherapy, and thus there is a high percentage of complete remission rates for patients treated with chemotherapy. It is important to mention that dogs undergoing chemotherapy for LSA maintain a good quality of life, and treatment can provide resolution of many presenting signs and abnormalities. The goal of Chemotherapy is to induce a durable remission and to re-induce a remission after one or more relapses. Adjunctive surgery and radiation therapy are also appropriate depending on the cases.¹⁵⁴

One of the first reports in veterinary medicine to include an objective assessment of QOL for canine patients treated with chemotherapy, was performed by Mellanby, et

al.¹⁵⁵ These investigators followed 25 dogs with lymphoma retrospectively. The owners of dogs that were treated with chemotherapy for a time period of 7 years were contacted by telephone and were interviewed. The owners were asked 5 questions regarding the dog's QOL during chemotherapy, if treatment improved the patient's QOL, if there were any adverse effects, if the owner regretted treating the dog and if he or she would elect for chemotherapy again in the future. An interesting result of this study was that while dogs developed side effects during chemotherapy, the owners had an impression that the dog's QOL was good and had no regrets about treating their pets with chemotherapy. However, the authors stated that it would be helpful if future studies focusing on QOL of tumor bearing dogs, could include a more objective (data based) assessment of the chemotherapy effects on QOL. Such studies might include survival time and haematological abnormalities that arose from chemotherapy treatment.^{155,156}

CHAPTER 2

QUALITY OF LIFE SURVEY INSTRUMENT DEVELOPMENT

The medical treatment of dogs with cancer is largely palliative. Decisions made for the choice and duration of treatment often require that the clinician and the owner assess the quality of life (QOL) of the patient. This is usually done in an impressionistic manner, which may or may not be a true reflection of the patient's status. Thus, it is important to have an efficient tool to assess QOL of the companion animal. Assessing QOL of human neonates, infants, and mentally disabled adults shares similar difficulties and challenges as assessing QOL in companion animals.

Literature from pediatric and oncology proxy questionnaires, as well as the limited veterinary literature was studied in order to develop a comprehensive and easy-to-use survey instrument for canine cancer patients. The prototype survey created to accomplish the research goals of this project included: 1) Owner reported QOL when the animal was considered to be healthy and free of disease; 2) Changes in QOL since the manifestation of disease; 3) Changes in QOL with regard to response to treatment; 4) Owner priorities in the process of decision

making through the different stages of disease and treatment; 5) Clinician impressions of the owner's QOL and priorities in decision-making; 6) Clinician impressions about the patient's QOL. The survey was to be administered to owners of canine patients admitted to the MSU Animal Cancer Care Clinic for evaluation and treatment of metastatic neoplasia. The goal of this research project was to assess canine cancer patient QOL, using the above-described 6 points of assessment, before and during chemotherapy treatment.

The purpose of this study was to develop an instrument that would identify the QOL changes of the canine cancer patient, as perceived by the owner, in a longitudinal evaluative process. Assessments were designed to occur at baseline, defined as six months prior to cancer diagnosis, at the time of cancer diagnosis but immediately preceding the first chemotherapeutic treatment, at the time of the second chemotherapeutic treatment, or 3 weeks after initiation of therapy, and time of the third chemotherapeutic treatment, or 6 weeks after initiation of therapy. A similar questionnaire was used to longitudinally assess changes in QOL within dogs as perceived by the same evaluators, defined as the primary animal caregiver and the primary attending veterinary clinician. At the first visit,

the questionnaire had 5 parts pertaining to pet ownership history for the animal, QOL before cancer diagnosis, QOL at the current point in time, owners QOL, and information relevant to taking the survey itself. At all subsequent visits, the questionnaire had only 4 parts, omitting QOL before cancer diagnosis.

The development of a prospective proxy survey instrument for veterinary cancer patients was complicated. The first and most important step was to determine appropriate survey question content. Input was obtained from literature regarding previous research on the subject of QOL tools in veterinary medicine. Also evaluated was literature regarding QOL assessment in laboratory animal welfare, veterinary medicine and proxy questionnaires used in human pediatrics medicine and oncology. Additionally, research on adverse effects and complications resulting from chemotherapeutic treatment in veterinary patients was examined.¹⁵⁷ Survey items were then generated using additional input obtained through focus groups of veterinary oncologists, clinicians, epidemiologists, and researchers.

The second step was to identify pertinent information that would be retrievable from the owner and information that would be retrievable from the medical record data.

Information from the medical record would be correlated with QOL changes as identified by the owner in order to determine statistically significant predictors of QOL. The medical record data that was obtained is provided in Table 2.

Owners were assumed to be less knowledgeable than attending clinicians regarding their dog's physical health. However, some clinical signs associated with cancer or adverse effects of chemotherapy would be recognized by the canine cancer patient owner. Among these signs were changes in appetite, physical activity, sleep-wake patterns and signs of fatigue, discomfort, pain or altered behavior toward the owner. Therefore, the survey included these factors as possibly affecting QOL in the canine cancer patient. These factors are provided in Table 3.

Most QOL questionnaires include 3 broad domains of physical, psychological and social functioning. Physical functions assess symptoms associated with disease, treatment and ability to perform daily activities. Psychological functions assess distress and /or a positive sense of well-being. Social functions assess aspects of social relationships and interactions.¹⁵⁰ In this study, specific questions associated with these 3 domains were represented in two major ways in the proxy survey

instrument: at the current visit and through comparisons to the previous visit (table W: 3 broad domains and cancer specific clinical signs identifiable by owner).

McMillan¹⁵⁸ reported on the importance of identifying favorite activities as one measure of an individual animal's QOL, and changes in these favored activities as significant indicators of an improved or compromised QOL.¹⁵⁸ Thus, changes in favorite activities of the canine cancer patients' participant in this study were included in the questionnaire. Likewise, recognition of changes in patient comfort and discomfort were assessed through several questions at each visit. Together, questions about favorite activities and level of comfort or discomfort for the canine cancer patient totaled more than 50% in our questionnaire, as this 2-domain model is critical in assessing QOL.

In the United Kingdom, technical training tutorials have been developed to improve the technicians' ability to assess physical conditions and states of normal mentation versus depression in research animals.^b Specific questions pertaining to a perceived state of happiness were included from this UK tutorial (Table 3, canine "happiness"

^b AHWLA.org

questions: SV1Q2Q9, SV1P3Q12, SV2P2Q12, SV3P2Q12). During the recruitment to the study, and also during the phase of responding to the questionnaires, owners of canine cancer patients were referred to the website for additional information and clarification of any questions that arose as to the appropriate answers the questionnaire.

Most research directed toward the topic of animal welfare tends to focus on negative experiences. Boissy et al.¹⁵⁹ examined the importance of positive experiences and concluded that play behaviors, even in laboratory and farm animals, can be easily identified as factors consistent with improved QOL.¹⁵⁹ Two questions in the current survey specifically targeted the level of playfulness and changes associated with this factor over time (Table 3).

Another key factor associated with QOL in cancer patients is pain due to the disease process itself, and pain associated with adverse effects of chemotherapy. Wiseman-Orr et al.¹⁴⁸ studied chronic pain in a population of 17 dogs with chronic degenerative joint disease and 165 dogs with no specific health problems. The critical indicators of improved or compromised QOL were found to be appetite, activity, aggression, anxiety, agitation and posture.¹⁴⁸

The survey included 7 questions pertaining to factors associated with pain or discomfort (summarized in Table 3).

Separate from the issue of pain, behaviors associated with stress and social functioning must be considered in patients presented to a veterinary hospital for treatment. In a recent study of more than 1000 dogs presented for routine veterinary care, Hsu and Serpell¹⁶⁰ developed and validated a questionnaire to measure changes in specific behaviors related to stress, excitability, fear and anxiety, aggression, separation, attention-seeking, and attachment.¹⁶⁰ Four questions associated with stress and social function behaviors were included in the proxy survey instrument used to conduct the present study.

In the HAEMO-QoL instrument^c used in human pediatric hematology practice, a proxy questionnaire addressed to the parents of the child with hemophilia asked directly: "How much is your child bothered by his hemophilia?" We considered it important to ask a similar question to the owners of the canine cancer patient regarding the impact of the neoplastic disease. Thus we added the question: "How much is your dog bothered by cancer?" (Table 3: cancer impact questions).

^c <http://www.haemoqol.de/quests.htm>

Marinelli et al.¹⁶¹ observed owner factors such as length of time of ownership, conditions under which the animal was adopted, use of the animal in the household, and dog breed characteristics had an effect on owner perceived QOL of pet dogs.¹⁶¹ More specifically, factors such as length of time and ownership and adoption as a puppy versus adoption as an adult were found to impact the strength of the human-animal bond. Questions pertaining to these factors were included in the current questionnaire (Appendix A questionnaire of 1st visit, section 1, questions 1 and 2).

The next step was to identify controls for the canine cancer patients' QOL throughout the disease and treatment process. McMillan mentioned the importance of individualizing QOL assessments since "...all factors eliciting the feelings contributing to QOL matter to different degrees for individual animals". He also pointed out the importance of serially assessing QOL during the course of illness. Using his quick QOL assessment tool, McMillan induced the owners to compare the current and past pleasures of the animal observed at a time when the animal was feeling his best. However the same comparison was not reinforced at his QOL questionnaire (Quick assessment QOL

questionnaire) regarding clinical signs or other parameters such as appetite, sleeping, presence or absence of disease and pain or distress.¹⁵⁸ The importance of serially assessing QOL in animals is also mentioned in laboratory animal literature. The ability to recognize the "normal" for each individual animal is a fundamental skill in order to define and recognize what is the "abnormal" state for this animal when it presents behavioral and physiological changes due to pain and discomfort. Thus, it is very common for laboratory technicians to assess the animal before an experiment so changes from that "normal" initial state can be easily detected.¹²⁵ Accordingly we decided to longitudinally assess the QOL of the canine cancer patients and use as control the same animal itself while considered healthy and free of neoplastic disease. This aspect of survey development was considered critical to identify potential changes from that "normal-baseline" state upon cancer diagnosis and throughout the first 6 weeks of chemotherapeutic treatment.

Since there was no other study identifying the appropriate time interval important to identify QOL of the dog while healthy compared to QOL at time of the first referral visit in a veterinary oncology setting, we

considered that a time interval of 6 months before referral would be adequate. This was based on the recommendations of the senior care guidelines task force which states that in senior pets, routine health visits are required every 6 months in order to establish baseline values.¹⁶² Thus, our questions pertaining to the QOL of the canine cancer patient contained a critical internal control element for each individual dog that reported behaviors while the dog was considered healthy and free of neoplastic disease at 6 months before cancer diagnosis. Duplicate questions with the same wording were repeated during all three visits in order to facilitate accurate reporting by the owner and for precision in data analysis to identify any changes. Repeating questions also helped the owner think clearly about all the parameters of the animal's QOL during treatment and to recognize any changes based on comparisons with the baseline (6 months before) as well as with the most proximate prior report.

The 4th section of the first visit questionnaire, as well as the 3rd section of the second and third visit surveys provided information regarding the affect that the dog's condition had on the owner's QOL. The human pediatric literature was very helpful in guiding the development of this part of the questionnaire. Proxy

assessments are available in cases where children are not able to self-report due to disability, very young age, disease symptoms or mental health issues.⁷⁷ One major issue affecting pediatric proxy assessment is that it is possible that the report will be biased by the impact of the child's disease on the parent's life.¹⁶³ Price, et al concluded that caregiver negative affect indeed influences the report of pediatric QOL and that is critical to understand the individual characteristics of the respondent when using a QOL instrument as an outcome measure by proxy.⁸⁸ It is not known whether or not such a caregiver negative affect influences reporting in animal QOL assessment. In order to better evaluate this potential for owner bias in reporting, we adapted questions from the human pediatric hematology literature relative to immune thrombocytopenic purpura (ITP) in childhood. The ITP-Parental Burden Quality-of-Life Questionnaire included the following domains: concerns related to diagnosis/investigation, treatment/disease monitoring, monitoring of child's activities, interference with daily life, disease outcome, and emotional impacts.⁹⁰ We followed this model in our questionnaire and evaluated the following domains with regard to their impact on the canine cancer patient's owner: treatment/disease

monitoring, interference with daily life, disease outcome, and emotional impacts. These domains and questions are provided in Table 4.

Another goal of our study was to determine the feasibility of conducting such QOL survey based research in veterinary medicine. Thus, we added questions relevant to the ease with which the owners and clinicians were able to complete the surveys. To further evaluate this aspect of the instrument we created for this research, we examined the criteria of acceptability and practicality as mentioned by previous authors.¹⁵⁰ Thus, the last part of our survey included questions pertaining to practicality of the questionnaire. Only two questions were added to evaluate this factor. Specifically, owners were asked: How easy was the questionnaire to complete? To determine the client's perception of acceptability of the questionnaire, a second question was added: Did you like the opportunity to evaluate the dog's QOL with the survey? Finally, we included an open-ended question soliciting comments about how the survey could be improved.

At the first part of the questionnaire we requested that "only one owner, the person with whom the animal relates most, should answer the questions and they should do so on their own". We adopted this requirement for

single and closest interacting owner reporting from the pediatric hemophilia questionnaire HAEMO-QoL (parent's long version).^d We considered it very important to have only one person, the person closest to the dog, serially evaluate the dog on a longitudinal basis. We reasoned that the closest single monitor of the dog would provide the most accurate understanding of normal behavior for the individual, and therefore would be best able to detect changes over time deviating from this state of normalcy.¹¹⁶ Furthermore, Gosling and Kwan¹⁶⁴ conducted a research study to examine whether differences in personality traits exist and can be measured in animals. The method that was found to be the best suited for evaluating personality traits in dogs included judgments made by owners who were best acquainted with the target individual.¹⁶⁴

As stated previously, an important consideration when evaluating proxy QOL assessment is considered to be the impact the negative caregivers affect might have on the owner's critical judgments. In human pediatrics proxy assessment is often the only one available to measure the child's QOL, but doubt as to the validity of the proxy report may arise. Additional proxy reports provided from

^d <http://www.haemoqol.de/>

caregivers, teachers, or clinicians are considered useful in order to obtain complementary information on the child's QOL.⁸⁴ The second proxy assessment may provide corroborative or contradictory information. Thus, in our case we considered it important to have an additional proxy QOL assessment for the canine cancer patient provided by the assigned clinician.

This questionnaire was shorter due to practicality issues. Clinicians are likely to be less able to invest 20 minutes to complete QOL questionnaires for each patient. Thus the clinician's questionnaire consisted of 4 questions for the first visit and 6 questions for the second and third visits. In the absence of published research on validity of the QOL construct or on factors that should be evaluated by proxy assigned veterinarians, questions were derived by applying the author's best judgment of the domains of interest. The following components related to second proxy assessment were included: 1) The clinician's assessment of the canine cancer patient's QOL in comparison to the previous visit's assessment; 2) The clinician's assessment of the owner's QOL in comparison to the previous visit's assessment; 3) The clinician's opinion of the most important factor for the owner in the process of decision making in comparisons to the previous visit's assessment;

4) The clinician's perception of the bond between the owner and the canine cancer patient. For the clinician's questionnaires completed during the second and third visit, we added two additional questions. These addressed the clinician's assessment of changes in the dog's QOL as compared to the most proximate visit, and also the clinician's opinion regarding changes in the owner's QOL compared to observations of the most proximate visit (Appendix A: clinicians questionnaires for 1st, 2nd, 3rd visits).

Our prototype questionnaire was reviewed for content, structure, readability, and ambiguity by 5 individuals involved in veterinary oncology practice. Additionally, veterinary technicians in the Veterinary Teaching Hospital were given the survey to complete as a trial of feasibility as well as to solicit additional opinions as to the survey content as described above. All of these individuals suggested modifications and refinements that were adopted before the survey instrument was implemented for the study. Thus, the survey was distributed to the animal cancer owners after suggested modifications and refinements were complete.

Our survey was administered either in the paper format, in person during the animal's visits, or

electronically through Survey Monkey.^e We considered these immediate solicitations of response to be superior for accruing data than mailed or telephone-based surveys. Because the canine cancer patient owner's often had available time while awaiting completion of their pet's care during each visit, it was highly feasible to distribute surveys and solicit responses during the time of the animal's visit to the clinic. We felt that this would be the best method of survey administration to facilitate optimum access to our target group, as well as compliance with survey completion.

The length of any survey is known to influence survey response rates, in that the longer the survey, the more likely it is that the response rate will be lower. As a general rule, it is recommended that as few questions as possible to reach the survey's objectives be included. Investigators consider the optimal survey format to have 25-35 straightforward questions that can be answered in 15-20 minutes. Shorter questionnaires generally have better response rates.¹⁶⁵ Thus, in our questionnaires we had 36 questions addressed to the owner for the first visit, 20 questions addressed to the owner for the second and third

^e <http://www.surveymonkey.com/>

visit. Only 4 questions were addressed to the clinician for the questionnaire of the first visit and 6 questions were addressed to the clinician for the second and third visits. The objective of the clinician's version of canine cancer patient QOL questionnaire was to develop a valid and reliable, but brief, QOL instrument for use in routine veterinary visits, with specific actionable items to improve provider-owner communication and treatment compliance.

Although there are a number of different scaling techniques available, Likert-type scales are the most frequently used in survey questionnaire research. They also are most suitable for use in factor analysis.¹⁶⁶ Although researchers have used 7-point and 9-point scales, Likert developed scales to be composed of five equal appearing intervals with a neutral midpoint, such as strongly disagree, disagree, neither agree nor disagree, agree, strongly agree. Coefficient alpha reliability with Likert scales has been shown to increase up to the use of five points, after which reliability levels off. Thus it was recommended that our survey items be scaled using 5-point Likert-type scales. In our study, we used a 1-5 Likert scale with 1 being the best measure, 3 being a neutral measure and 5 being the worst measure of outcome.

For conduct of this study, we developed 4 surveys: a 36-item survey (1st visit) and a 20-item survey (2nd and 3rd visit) for the canine cancer patient owner, with a 4-item survey (1st visit) and a 6-item survey (2nd and 3rd visit) for the assigned clinician. The survey questions were written at the 5th-6th-grade level of comprehension. Our questions were screened for readability, absence of ambiguity and use of jargon. We avoided any "double barreled" questions that had 2 questions in one, to avoid respondent confusion.

All survey instruments are provided in Appendix A.

CHAPTER 3

METHODOLOGY

Literature from pediatric and oncology proxy questionnaires, as well as literature detailing veterinary studies on animal QOL, were reviewed to develop a survey instrument that featured six components:

- Canine cancer patient QOL at a point in time when the animal was healthy, and free of disease. Each subject serves as its own control before and after diagnosis of cancer, and during initial phase of chemotherapy.
- Canine cancer patient QOL since the manifestation of disease.
- Canine cancer patient QOL with regard to response to treatment.
- Canine owner QOL (and priorities on decision-making at time of diagnosis and during initial phase of chemotherapy.
- Attending clinician impressions of the owner's (proxy) QOL and ability to prioritize decisions for patient/pet.

- Attending clinician impressions about canine cancer patient QOL.

The project was initially reviewed and approved by the Michigan State University Institutional Review Board (IRB) human research protection program in order to assure compliance with applicable federal regulations and University policies. Accordingly, study objectives and methods were presented (written and verbally) to owners and clinicians at the initial visit and all study participants signed a consent form (Appendix B: consent forms.)

Subjects recruited to the study were canine patients referred to the Animal Cancer Care Clinic of the College of Veterinary Medicine of Michigan State University. Between March-August 2008, dogs were recruited using the following inclusion criteria: disseminated metastatic cancer requiring chemotherapy (i.e. lymphoma, metastatic carcinoma, and metastatic sarcoma). Dogs and their owners were included in the study at their initial referral visit. Excluded were canine patients diagnosed with acute leukemia or with non-neoplastic life-limiting diseases. Dogs having prior chemotherapy for any reason were excluded.

This study was designed as a longitudinal evaluation of QOL in a small animal oncology setting. Patients were evaluated both by owners and an attending clinician at the

time of their first visit to the clinic, and then at 3 and 6 weeks after the initiation of chemotherapy.

Relevant clinical data regarding the patient's physical and laboratory findings, along with responses to treatment and potential adverse effects of the treatment, were obtained from each patient's medical record at each visit. This data was subsequently correlated with the results of the QOL survey in order to identify any statistically significant predictors of the dog's QOL.

Initial evaluation (time 0):

The study objectives and methods were presented to the clients. A brief verbal and written description of the research and an oral review of the informed consent form were provided and then an informed consent form was reviewed and signed. Two different survey forms were used. One survey form was to be completed by the owner of the cancer-bearing dog, and the other to be completed by the attending veterinary clinician. Thus, at the initial visit, an initial survey form was presented to the owner and attending clinician. The patient's relevant medical record information was retrieved.

Second evaluation (3 weeks):

During the 3rd week chemotherapy visit, another survey form using a very similar format to that used for the initial survey was distributed in order to assess changes that had occurred during the intervening 3 weeks. Surveys were distributed again to both the owner and the attending clinician and the patient's medical record information was updated.

Third evaluation (6 weeks):

Six weeks after the initial visit, the animal was reevaluated by an attending clinician to determine response to therapy. Based on this reevaluation, changes in treatment plan were implemented. An identical survey form as that used during the second evaluation was redistributed to both the owner and an attending clinician to assess changes in the interval between the 3rd and 6th week evaluations. The patient's medical record information was again updated.

The medical record information for each patient was included and interpreted based on literature regarding chemotherapy adverse effects and on the Veterinary Cooperative Oncology Group's criteria as presented in the document entitled VCOG-Common Terminology Criteria for

Adverse Events Following Chemotherapy or Biological Antineoplastic Therapy in Dogs and Cats.¹⁵⁷ A 5-point Likert-type scale was used to grade chemotherapy-associated side effects.

Statistical analysis

To evaluate correlation between the perceived QOL of the dogs, as assessed by the dog owners and the clinicians who treated the animal, the data were ranked, and calculations were based on the ranks of corresponding values. The Spearman's rho correlation coefficient and the corresponding p-value were calculated. For comparisons of QOL parameters between the sequential visits of the dogs to our clinic, the Wilcoxon test for paired samples was used.

All reported *P* values are 2-sided. Values of $P < 0.05$ were considered significant. Statistical analyses were performed with standard software.^f

The study participants had the opportunity to participate electronically through Survey Monkey (SurveyMonkey.com) or in a written paper format for all three visits. In order to facilitate electronic online participation through Survey Monkey, the College of

^f MedCalc for Windows, version 10.2.0.0 (MedCalc Software, Mariakerke, Belgium)

Veterinary Medicine of Michigan State University ITC service established a computer in the receiving area of the Animal Cancer Care Clinic. Participants could also participate by filling out paper surveys by hand, and thus printed copies of the online version of the survey instruments were also provided.

CHAPTER 4

RESULTS

Surveys were distributed to 81 dog owners visiting the Michigan State University Center for Comparative Oncology Animal Cancer Care Clinic between March 2008 and August 2008.

A total of 81 client questionnaires were collected during the 1st visit. During the 2nd visit 36 client questionnaires were collected. Between the 1st and the 2nd visit, some patients were lost to follow up (n = 29), some clients declined chemotherapy (n = 8), and in some cases chemotherapy was not recommended as a treatment option (n = 4), or patients were euthanized (n = 3), or no cancer was diagnosed (n = 1). During the 3rd visit, 31 client questionnaires were collected. Between the 2nd and 3rd visits, some clients did not complete the questionnaire in a timely manner (n = 2), some clients moved out of state (n = 1), some patients were euthanized (n = 1), or owners did not submit the questionnaire (n = 1). Finally, 2 medical records could not be located until 6 months after the end of the study, and the questionnaires corresponding to these patients were excluded from the statistical analysis,

resulting in a total of 29 cases ultimately being evaluable in our study.

In our study we had 21 completed questionnaires from the assigned clinicians at the time of treatment initiation, 19 completed questionnaires from the assigned clinicians at the time of 3rd week of chemotherapy and 16 completed questionnaires from the assigned clinicians at the time of 6th week of chemotherapy.

A total of 29 dogs were included in the study. There were 15 females and 14 males. The median age was 8.3 years (range 3-15 years).

Of the 29 dogs that participated in our study, 7 dogs were treated in the setting of adjuvant therapy and 22 dogs were evaluable for response to chemotherapeutic treatment. Of the 22 dogs that were evaluated for response, 6 dogs had progressive disease (no response), 12 dogs were in complete remission (complete response), and 4 dogs were in partial remission (partial response). Thus overall 2/3 of the dogs responded to treatment and 1/3 of the dogs did not respond.

The following breeds were represented in our study: Mixed breed (n = 7), Golden retriever (n = 6), Boxer (n = 3), American Pit-bull terrier (n = 3), German shepherd (n = 2), Labrador retriever (n = 1), Flat coated retriever (n = 1), German short haired pointer (n = 1), Basset hound (n =

1), Bernese mountain dog (n = 1), Brittany spaniel (n = 1), Schnauzer (n = 1), and Yorkshire terrier (n = 1)

The dogs that participated in our study were diagnosed with the following neoplastic diseases: lymphoma (n = 17), osteosarcoma (n = 5), hemangiosarcoma (n = 2), mast cell tumor (n = 1), thymoma (n = 1), mammary carcinoma (n = 1), pancreatic carcinoma (n = 1), and histiocytic sarcoma (n = 1). Upon initial diagnosis and throughout the first six weeks of treatment, six of these dogs had intrathoracic metastases, twelve of the dogs had intrabdominal metastases, two of the dogs had lymph node metastases, one dog had skin metastases and another had bone metastases. Two dogs diagnosed with lymphoma also had comorbid conditions undergoing treatment concurrent with chemotherapy administration. One Golden retriever was diagnosed with diabetes mellitus and one American Pit bull terrier had a lifelong history of seizures.

Since the dogs that participated in our study were diagnosed with various neoplastic diseases, protocols used for treatment were not consistent across the patient population. The chemotherapeutic drugs used included carboplatin, doxorubicin, vincristine, cyclophosphamide, L-asparaginase, chlorambucil, mustargen, pamidronate, lomustine and gemcitabine. Of the dogs that were treated

with chemotherapy, six had surgery before initiating chemotherapy and two of the dogs were concurrently treated with radiation therapy while also receiving chemotherapeutic treatment. One Golden retriever received palliative radiation therapy for osteosarcoma and the Yorkshire terrier in our series received palliative radiation therapy for spinal lymphoma in conjunction with systemic lymphoma therapy.

According to the owners, 82% of the dogs were adopted as puppies. The main role of the dog in the household was either that of "family member" according to 93% of the owners, or was as a companion according to 58% of the owners. Owners were allowed to respond in multiple categories when describing the role of the animal in the family. Thirteen percent of dogs were reported as being guard dogs, while thirteen percent were also classified as hunting dogs. Three percent of dogs were show dogs and there was no dog participating in our study that was reported as a working dog.

Owners described the dog's favorite activities as being playing (86%), human/animal interaction (86%), eating (82.8%), walking (79%), exercise (75.9%), car ride (65%) and staying at home (62%). Fifty-five percent of dogs were reported as enjoying all of the above-mentioned categories,

and twenty seven percent were also enjoying other activities that were not mentioned. For this question owners were allowed to respond in multiple categories.

Our results indicated that 69% of owners were extremely worried about the cancer diagnosis for their dog on initial presentation. Owners reported a significantly decreased level of worry during the 6th week ($p < 0.0001$). The owners responded that their worry arose from the incurable nature of the neoplastic diseases (72%), decrease in the dog's QOL (65.5%) and concern for the chemotherapeutic treatment and side effects (40%).

The owners evaluated our QOL questionnaire as being extremely easy (54.3%) and very easy (42.9%) to complete. Also the owners overall enjoyed the opportunity to evaluate their dog's QOL. Of the 29 owners completing the questionnaire, 60% enjoyed this opportunity very much, 20% enjoyed this opportunity quite a bit, 16.7% enjoyed this opportunity moderately and 3.3% enjoyed this opportunity somewhat. These results were representative for the questionnaires obtained during all three consecutive visits.

The study participants had the opportunity to either participate electronically (through Survey Monkey) or on paper for all three visits. There was only one owner that

participated to the study electronically for all three visits.

Comparisons between before versus upon the cancer diagnosis

According to the owners, dogs had higher QOL 6 months prior to cancer diagnosis than at the time of presentation and enrollment to the study ($p = 0.0078$). Dogs were reported to be more active ($p = 0.0002$), had a better appetite ($p < 0.0001$), appeared happier ($p = 0.001$), did not appear bothered by their disease ($p < 0.0001$), and exhibited fewer signs of anxiety ($p = 0.002$). The dogs had better mobility level ($p < 0.0001$), had less pain ($p < 0.0001$), more playful ($p < 0.0001$), exhibited fewer clinical signs associated with illness ($p = 0.0001$), and had a better QOL ($p = 0.0001$) according to their owners.

Comparisons between before versus the third chemotherapy treatment

When comparing behaviors at 6 months prior to a cancer diagnosis and 6 weeks after initiation of chemotherapy, owners reported that, before cancer diagnosis, dogs exhibited fewer signs of anxiety ($p < 0.0001$), had a better

appetite ($p = 0.0001$), appeared happier ($p = 0.0078$), did not appear bothered by cancer ($p = 0.0078$), were not exhibiting clinical signs of illnesses ($p = 0.0156$), had better mobility ($p < 0.0001$), were more playful ($p < 0.0001$) and had a better QOL ($p < 0.0001$).

Comparisons between the time of cancer diagnosis versus the second chemotherapy treatment

The owners worried less about their dog's health ($p < 0.0001$) and found completing the questionnaire easier ($p = 0.0039$) during the 2nd visit compared to the 1st visit that took place at presentation and enrollment into the study. There were several improvements in the following areas during the second visit: activity level ($p = 0.0156$), clinical signs ($p = 0.0078$), mobility level ($p = 0.001$), less pain ($p = 0.0002$), play activity ($p = 0.0156$), and appetite ($p = 0.002$). Owners also reported that their dog appeared less bothered by the neoplastic disease ($p = 0.0039$). The only declining result was a limitation of the owner's activities, which were reported to be greater at the first visit compared to the second ($p = 0.001$).

Comparisons between the time of cancer diagnosis versus the third chemotherapy treatment

When comparing QOL parameters at the third chemotherapeutic treatment to the time of presentation and enrollment in the study, improvements were noted in the following areas: activity level ($p = 0.0137$), motility ($p = 0.0312$), play activity ($p = 0.0137$), appetite ($p = 0.0171$), perceived enjoyment of favorite activity ($p = 0.002$), and perceived pain level ($p < 0.0001$). The dogs were reported to be less bothered, by the clinical signs associated with cancer ($p = 0.0002$), and they exhibited decreased clinical signs of illness ($p = 0.0039$). The owners reported that the questionnaire was easier to complete during the 3rd visit ($p = 0.0005$), and they worried less about their dog's health issues during the 3rd visit ($p < 0.0001$). The only declining result was regarding vocalization of the dog ($p = 0.0312$).

Multiple regression analysis for the 1st visit of the dogs' QOL as perceived their owners indicated statistically significant predictors to be: the illness of the dog (coefficient 0.41, $p = 0.0001$) and playfulness (coefficient 0.46, $p < 0.0001$). The regression model was statistically

significant ($p < 0.001$) with the significant predictors explaining 85.21% of the variability in the dog's QOL. Multiple regression analysis of the dogs' QOL as perceived their owners for the 2nd visit indicated as statistically significant predictors: the happiness of the dog (coefficient 0.39, $p = 0.0169$) and the playfulness (coefficient 0.61, $p < 0.0001$). The regression model was statistically significant ($p < 0.001$) with the significant predictors explaining 82.56% of the variability in the dog's QOL at the second visit time point.

Multiple regression analysis of the dogs' QOL as perceived their owners for the 3rd visit indicated as statistically significant predictors to be: the illness of the dog (coefficient 0.33, $p = 0.0145$) and the playfulness (coefficient 0.44, $p < 0.0058$). The regression model was statistically significant ($p < 0.001$) with the significant predictors explaining the 55.53% of the variability in the dog's QOL.

According to our study results, responses of the 29 owners agreed with those of the attending veterinary clinician when both were asked about the QOL of the dog. Correlation was found to be statistically significant for all 3 visits. The greatest agreement was noticed during the 3rd visit ($\rho=0.8133$, $p = 0.0001$ and the 1st visit

(rho=0.807, $p = 0.0003$) while during the 2nd visit it was noticed that there was still statistically significant agreement, but the percentage of agreement was 56% (rho=0.562 and the $p = 0.0172$).

CHAPTER 5

DISCUSSION

In the questionnaire developed for the purpose of this study we included 3 main domains. These are the main domains that are included in most QOL questionnaires currently available and include physical, psychological and social functioning. Physical functioning assesses symptoms associated with disease, treatment and ability to function in daily activities. Psychological functioning assesses psychological distress and positive sense of well-being. Social functioning assesses aspects of social relationships and interactions.¹⁵⁰

Thus in the QOL instrument created for this study we included questions assessing changes in QOL due to chemotherapy, as animals that are treated with chemotherapy might experience pain, fear, and distress. The next series of questions assessed changes attributable to pain secondary to cancer. Finally, questions are included to evaluate the animal's level of distress, because distress obviously interferes with the animal's well-being and comfort. Quality of life parameters and changes associated

with physical functioning are more intuitively more objective to assess. Quality of life parameters and changes associated with psychological functioning are more challenging in domestic animals and survey questions relative to this domain must be carefully crafted. Finally, QOL parameters and changes associated with social functioning are also quantifiable with careful observation. The questions used in this study's QOL instrument that addressed such parameters are summarized in Table 3.

Questions that assess overlapping factors, these questions may pertain to more than one domain (physical, psychological and social) simultaneously. However, this does not detract from their usefulness as indicators of QOL. For example, anorexia is a potential adverse effect from chemotherapy, but the animal can also be anorexic due to chronic stress, pain or another disease processes. Also depression might be due to the neoplastic disease, the chemotherapeutic treatment, stress, pain, or another disease processes. Regardless of the etiology inducing a clinical sign or manifestation, the importance is that anorexia and depression are factors that may significantly compromise the animal's QOL. This questionnaire was created to identify many potential behavioral alterations and

physiologic changes that pertain to many domains and may be recognized in dogs experiencing compromised QOL.

Comparing the animal's baseline QOL, as assessed by the owner at 6 months before cancer diagnosis, with the QOL of the animal at the time of cancer diagnosis and throughout treatment, as assessed by the same owner, would be might ultimately help identify potential treatment modifications that could result in canine cancer patient benefit. This supposition posits that an animal that was previously described as being healthy, but upon cancer diagnosis and during chemotherapy has a compromised QOL, has QOL changes induced by the cancer disease process and the chemotherapeutic treatment rather than extraneous causes. Accordingly, any states of improved QOL attained throughout the treatment course may be attributable to the positive impact of the therapeutic interventions.¹²⁵

Furthermore it is of major importance when assessing QOL in ill pets to identify underlying causes of discomfort and pain to the animal and to try to intervene and alleviate compensate for the problems we identify. Evaluation of QOL must be an ongoing process that helps both the owner and veterinarian to compare and identify the changes in the pet's QOL throughout the process of the

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disease.¹¹ Accordingly, our longitudinal research design attempted to reinforce the ongoing nature of appropriate serial QOL assessment of the canine patients for both the owners and the attending veterinarians. Thus both the clinician and the owner evaluated the animals at the time of their initial visit to the clinic, and then at 3 and 6 weeks after the initiation of chemotherapy.

A critical aspect of this QOL instrument was the use of each animal as its own internal control. By querying the owner regarding the animal's health and behavior 6 months prior to cancer diagnosis, we attempted to establish a baseline of normal behaviors for every dog that participated in our study. These baseline behaviors were used in order to assess changes as perceived by the owner during the first (first visit, upon cancer diagnosis), second (three weeks after initiation of chemotherapy) and third visits (six weeks after initiation of chemotherapy) at VTH. To our knowledge, this QOL instrument is the first in canine cancer medicine to utilize the approach of the animal's pre-diagnosis status as an internal control.

An ideal QOL survey would provide a quantitative score to characterize the dog's QOL as an absolute value. Most QOL surveys that employ such scoring weight each survey question with a specific factor, and then add all the

products to conclude the final QOL score. While this approach is theoretically possible, in our study we did not attempt to use this quantitative methodology for a number of reasons, including lack of a "gold standard" upon which to base the weights for each survey question, the unknown interactions between the different survey questions, the inherent difficulty to accurately describe clinical signs in animals, and the small sample size of our pilot study.

The lack of a "gold standard" it makes practically impossible to calculate a total score in veterinary oncology that would be accurately representative of the dog's overall QOL. To date, no cancer-specific surveys have been developed and validated in a large veterinary population. This essential lack of preliminary data in the veterinary literature forced us to develop a survey instrument to establish basic relationships between clinical, demographic, and QOL characteristics as perceived by pet owners and their veterinarians.

The interactions between different questions on the same survey are largely unknown. Not enough data exist in the current literature to measure the effect of a clinical sign, such as pain, to the dog's everyday activity or appetite. Thus, in not being able to quantify such interactions, it would be extremely difficult to weight the

relative score of each survey question against another asked on the same visit.

The inherent difficulty of owners and clinicians ability to grade or even recognize mild clinical signs in dogs further complicates the effort of accurately scoring each survey question. Even if some interactions can be estimated, the presence of vague symptomatology, which is a common occurrence in small animal oncology practice, increases the difficulty of accurate scoring by the dog's owners.

Finally, in addition to the difficulties and limitations described heretofore, our study was essentially a small pilot. We attempted to establish basic relationships between the dogs' owners and clinicians' assessments. We used a multiple regression model to examine relationships between the dog's QOL as perceived by their owner, and the individual survey questions, along with clinical and demographic information. The results of these analyses could be used in a prospective manner in a future study as a guideline to assign weight for each survey question contributing to the total QOL score.

For example, the global summary question regarding the dog's QOL asked after the owner had answered all the detailed individual questions regarding the dog's QOL would

have a higher weight, as this question would be asked after the owner had time to reflect and focus through the process of answering detailed individual questions. Thus, in our data analysis this question would not be scored as having the same weight as those that preceded it.

One option for improved survey construction would be to limit the number of questions to the 4 that were most statistically significant predictors as determined by the present survey.

Since one goal is to reinforce the owners' and clinicians' thinking process with regard to the dog's QOL, asking additional questions may facilitate not just data gathering per se but also contribute to owner satisfaction with the service provided as well as improved clinician-client interactions. In comments provided by owners who completed the survey, a positive overall feeling was generated by participation in the survey. Several owners commented that they appreciated the opportunity to reflect more deeply about the QOL of their pet and themselves through the process of cancer treatment. The fact that such a survey was offered indicated to many participating clients that the service provided by the Animal Cancer Care Clinic extended beyond the realm of the purely medical into a true support service for the owners as they experienced

considerable stress during their pet's cancer treatment. The survey was in fact reported by many clients to have added value to their experience at Michigan State University College of Veterinary Medicine.

McMillan mentioned the importance of individualized QOL assessment and the importance of serially assessing QOL during the course of illness. In his 5-item QOL instrument, he induced the small animal owner to compare the animal's current and past pleasures. However, he did not reinforce that comparison for specific clinical signs and specific disease entities such as cancer or in canine patients undergoing chemotherapy.¹⁵⁸ Our study differs from McMillan's published work in that it singles out disease-specific factors for evaluation with comparison to past baseline behaviors. Our study also queries many additional factors than those assessed by McMillan. In addition to assessing the degree of participation in the animal's previous favored activities during the course of therapy, our study also uses the animals past behaviors and state of health as a baseline comparator.

Other researchers including Budke¹⁴⁷ used another population of healthy dogs as controls in order to evaluate the owner's assessment of QOL of dogs with spinal cord

injuries.¹⁴⁷ Wojciechowska et al.¹⁴⁹ used another population of healthy dogs as controls in order to assess the ability of a tool to differentiate sick and healthy dogs based on nonphysical aspects of QOL.¹⁴⁹ Yazbek and Fantoni¹⁵⁰ used healthy dogs and dogs with dermatologic disease as controls in order to develop and validate a QOL scale for dogs with signs secondary to cancer.¹⁵⁰ Hielm-Bjorkman et al, used healthy dogs as controls in order to evaluate methods for assessment of pain associated with chronic osteoarthritis in dogs.¹⁵² Our current work differs from these examples in the veterinary literature by the fact that we utilized the individual animal as its own internal control rather than using another population of healthy dogs and we used the owners and the veterinarians as comparators.

Hewson¹¹⁶ mentioned that breed, temperament, environment, and the husbandry practices under which the animal was raised and whether animals were kept as groups or individuals are only few of the factors that can influence an animal's behavior.¹¹⁶ Since the dogs that were assessed in our study were raised individually in various environments and had different environmental stimuli, we considered it necessary to assess each animal individually.

Thus we had the same animal while healthy act as control of itself to address the individual animal's normal behavior pattern. Understanding of normal behavior for the individual and weighting all factors appropriately is an important factor and a necessary prerequisite to understand the animal's optimal QOL level.¹²⁹

Overall mentions that fear is a critical aspect that needs to be evaluated especially for animals that are being treated for neoplasias, because fear can compromise an animal's QOL.¹³⁰ Since animals cannot perceive the beneficial aspect of treatment, it is possible that they feel threatened especially when they are under painful medical treatment. Our survey instrument included domains addressing fear and pain issues in the animal subjects. Though our survey addressed these questions, pain and fear were not identified as statistically significant predictors of the animal's QOL. Signs of illness might include pain and fear, but overlap in these categories may have obscured their relevance to the animal's QOL in our results. This aspect of QOL research may become more important over time, however, as advanced cancer therapies and the associated increased survival rates in veterinary medicine may

increase the challenges resulting from chronic tumor-induced pain.¹³⁵

Breazile mentioned the three categories of stress: eustress which is associated with survival; neutral stress which is neither harmful nor hurtful; and distress that might interfere with the animal's well-being, comfort, and reproduction. Anxiety-related disorders are among the most common class of disorders in both humans and animals. However, their presence in companion animals can remain unrecognized longer because of the general assumption that in the absence of pain an animal has a good QOL.¹²⁹ Thus specific questions intended to identify indicators or behaviors consistent with stress (questions z at table x) were included in our survey. However, we were again surprised to find a lack of statistical correlation between the animal's perceived level of stress and its overall QOL.

There are many similarities between the proxy assessment of pediatric patients that are unable to self-report and those appropriate to QOL assessment of small animal-patients. Our survey instrument was constructed to provide for proxy assessment by the most prominent caregiver serially throughout the duration of the study. This proxy survey instrument is the first to assess the

potential issue of caregiver's negative effect. According to Knoester QOL might be greatly affected by the physical and psychological sequelae both cancer survivors and their parents are going through.¹⁶⁷ According to Price et al.

"caregiver affect indeed influences the report of pediatric QOL". Caring for a family dog with neoplastic or terminal disease can be highly distressing and heart breaking for their owners/guardians.

We attempted to assess caregiver negative affect, as is observed in pediatric practice, by inclusion of specific owner QOL questions. We wanted to determine the extent to which the owner's report had been biased due to the impact the dog's disease the owner's lifestyle and QOL.

Specifically, the owner was asked how much worry or anxiety he/she was experiencing due to different variables such as chemotherapy and side effects, the dog's QOL, the incurable nature of the disease, financial issues, perception of others, time and scheduling concerns. Also, the owner was asked about the negative lifestyle impact that the animal's condition was inducing to his/her QOL. These identical questions were asked during the 1st, 2nd and 3rd survey (visit) in order to identify potential serial changes.

This potential for negative caregiver affect was further validated by soliciting observations from the

attending veterinary oncologist. We created questions to specifically solicit information about the impact of the pet's health status on the owner's QOL from the perspective of the veterinarian in charge of the patient's care. To our knowledge, this is the first survey in veterinary medicine to address the aspect of negative caregiver affect directly and indirectly through veterinary secondary proxy assessment.

Importantly, we did not identify a correlation between owner's stress or affect on perceived canine patient QOL. This is interesting because the dependent nature of the relationship between pets and owners is a very close parallel to the relationship dynamics encountered between parents and children. We speculate that the owners of companion animals may be less intensely emotionally involved with the pet's illness as compared to the level of involvement of a parent with their offspring. Alternately, pet owners may be intensely involved in the disease process encountered in their pet, but less reporting bias is engendered in the companion animal/owner relationship. This may be because of an inherent interspecies difference in the way the owner perceives the pet, or may be related to the level of guilt engendered when an animal is ill as opposed to the level of guilt engendered by illness in a

child. Animals with cancer are frequently geriatric, and thus the emotional impact of illness may be less than when a cancer diagnosis is given to a young child.

In the case of proxy decision-making for ill children and for pets, parents as well as owners are the ultimate arbitrators of changes in treatment modalities. However, a relatively smaller contingent of therapeutic approaches is offered to the companion animal owner due to practical limitations in the level of cancer care available for treatment of companion animals. For example, potentially curative therapy such as stem cell transplantation may be offered to the pediatric cancer patient, and the parent must weigh the risk of treatment failure, complication, decrement in the child's short and long term quality of life, and potentially even the child's death due to transplant complications, against the potential for life-saving curative therapy. Curative therapy for most animal cancer patients that require chemotherapy treatment is virtually non-existent, so the level of owner stress in decision-making may not approach the level of stress engendered in the parent of a critically ill child. It would be helpful in future studies to have representatives from the field of human psychology to assist in clarifying such issues as negative caregiver affect.

Another difference between human and companion animal medicine is the potential therapeutic decision of active euthanasia for a pet, which adds considerable stress to the companion animal owner that is not present for the parent of a cancer-stricken child. Given both the similarities and differences between companion animal and pediatric oncology concerns, it is of interest that negative caregiver bias was not identified as a significant factor in QOL assessment for companion animals in our study.

Veterinarians always have to work through a financially responsible third party that is able to make fiscal and medical decisions for the animal. This situation again is quite similar to the areas of pediatrics, gerontology and psychiatry in human medicine. Owners must weigh cost of therapy against potential benefit and risk to their companion animal, while in human medicine in the United States availability of third party payment renders cost of therapy a minor concern for parents in the vast majority of cases.

In the field of human pediatrics when proxy assessment is the only one available in order to measure the child's QOL, but there is doubt about the validity of the proxy report, additional proxy reports provided from caregivers, teachers, or clinicians, are considered useful in order to

obtain complementary information on the child's QOL. To our knowledge, this is the first study that assessed the QOL of canine cancer patients by combining information coming from two proxy respondents: the owner and the clinician.

According to our study results, observations of the owners of dogs that were diagnosed with neoplastic disease and underwent chemotherapeutic treatment agreed with the assigned clinician when both were asked specific questions regarding the dog's QOL for all 3 visits.

This finding suggests that both owners and clinicians when reinforced to make QOL assessments were able to objectively evaluate the QOL of the animal and proceed with the appropriate decisions regarding the individual animal's case management. There is always the possibility that we have a subjective component, a placebo effect or even influences of anthropomorphism in the assessments done by both the clinicians and the owners while inferring the emotional and psychological state of a non-verbal individual of another species. If that were the case in our study, we would expect to have a disagreement between the owner and the clinician, as we would not expect both individuals (owner and clinician) to make identical observations. Also, clinicians are individuals trained to make objective assessments. If veterinarians were affected

by excessive anthropomorphism or subjective projection of feeling states in the assessments done for their patients, they would not be able to make correct clinical decisions nor to proceed with the appropriate treatment plan for their patients.

General considerations for errors in owner reporting in our study include the fact that, while painful and debilitating conditions such as neoplastic diseases could affect the behavior of dogs, owners could interpret such behavior changes in overly optimistic or pessimistic ways. Some owners might react under stress and misinterpret their animal's behavior after cancer diagnosis as indicating excessive animal suffering. Other owners might deny negative aspects of the animal's behavior, and be inappropriately optimistic due to the fact that the animal is under treatment in the absence of appreciable tumor response (placebo effect).

Continued fluid QOL proxy assessment of the canine cancer patient was considered to be very important also because such ongoing assessment would help the owners understand the impact the specific disease process was having on their pet's QOL. When the owners are aware of these changes, we considered it is less likely that they would euthanize prematurely because of the

misinterpretation of a stressful event, or that they would inappropriately postpone the decision for active euthanasia in order to avoid the sadness they anticipate upon the pet's death. This is a very critical issue, since as both the assigned veterinarian and the owner share responsibilities in decision-making, but the ultimate decision remains the owner's. Valid and accurate QOL assessment may be invaluable in clarifying the owner's mind around necessary animal care decisions. Further, longitudinal QOL assessment may help not only to facilitate decision-making for treatment changes and appropriate end-of-life decisions, but may also support owners during the difficult grief period.

The survey QOL tool created for this endeavor successfully identified that canine cancer patients treated with cytotoxic chemotherapy had a better QOL while healthy and free of neoplasia compared to an initial visit or at the time of the 2nd and 3rd hospital visits. Subjects had a better QOL at 3 and 6 weeks after initiation of chemotherapy treatment compared to the time of cancer diagnosis (1st visit). Treatment appeared to improve QOL, but did not restore the original QOL level that the dog enjoyed 6 months prior to the diagnosis of cancer.

The decreased QOL observed during treatment as compared to the time of the dog's baseline state of health might be attributable to the relatively brief duration of observation after initiation of treatment. Longer duration of follow up might be required in order to identify a complete restoration of the animal's QOL level. Alternately, it is possible that treatment with chemotherapy was responsible for the decrement in quality of life from baseline, and evaluation after conclusion of chemotherapy might be better able to assess a return to normal baseline QOL. Another study with a more protracted evaluation period would help answer this question.

Another possible reason for decreased quality of life while the dog was undergoing chemotherapy treatment might be that the animal's QOL improved due to the treatment, but since the animal was not expected to be completely cured from the neoplastic disease, it might be perceived to have lower QOL than while healthy. A possible explanation would be that the cancer impact was not completely controlled by the treatment modalities employed, resulting in improved but not optimal QOL. The animal might have improved QOL because the treatment proved effective, but the animal might still experience a degree of compromised QOL due to the chemotherapy's adverse effects. Also, owner may

subconsciously react to the lack of curative therapy for their pet, and thus may interpret behaviors and physical signs in a more negative way than if the diagnosis was of a curable disease rather than cancer.

As suggested by Mellanby et al.¹⁵⁵ our study included relevant medical record information for the 1st, 2nd and 3rd visits. Clinical data regarding the patient's physical and laboratory findings, along with responses to treatment and potential adverse effects due to chemotherapy were obtained from each patient's medical record and correlated with the results of the QOL survey. Medical record information did not reveal any statistically significant predictors of QOL for any of the 3 visits.¹⁵⁵

Multiple regression analysis for the 1st, 2nd and 3rd visits indicated statistically significant predictors of QOL of the canine cancer patient to be play behaviors, signs of illness, and canine happiness as perceived by the owner. These three domains might have been more distinct and easier to identify and quantify for the owners than other parameters on the questionnaire. Since the owners were specifically asked to recall "normal" or usual behaviors of their dog as recollected from 6 months before

the cancer diagnosis, they were better able to compare usual with "abnormal" behaviors during the study.

Owners were able to identify that the dog exhibited signs of illness, but were uncertain of the impact these clinical signs had on the dog's QOL. We assume this to be the case because the question "How much is your dog bothered by the disease process?" was not found to be a statistically significant predictor of QOL. This might mean that the dog exhibited clinical signs of illness but was not bothered by the disease from the owner's perspective, or that the owners were not able to accurately evaluate their dog's discomfort in an objective rather than subjective frame of reference.

Another question that was revealed to be a statistically significant predictor of the dog's QOL is the question regarding the dog's playfulness and activity level. This is another easily identifiable change, in that a dog that feels physically well is more likely to be playful and to behave as it did at baseline before the cancer diagnosis. Most owners and clinicians would assume that the dog that experiences pain and depression would be unlikely to be highly active or to participate in play behaviors. Play behavior and activity level are observable and quantifiable, making them more reliable indicators of

the animal's QOL. The statistical association of play behaviors with QOL reinforces the notion that QOL questions should aim to address changes that the proxy can identify, compare and quantify. The findings of the current study seem to agree with Boissy et al,¹⁵⁹ who argued that play behaviors appear to be one of the "most promising and convenient indicators" of good QOL in laboratory and farm animals. Our study supports the view that play behavior is a good QOL indicator for canine cancer patients as well.¹⁵⁹

The 3rd statistically significant predictor of the dog's QOL detected in our study was the dog's happiness as perceived by the owner. The owner might have answered this question from the perspective of self-projection, because she or he was satisfied by the fact that the dog's health was objectively improving. Owner assumed guilt associated with the dog's cancer diagnosis might be alleviated by the owner's commitment to pursue chemotherapy for the pet, resulting in transference of the owner's subjective feeling state to the dog. Owners may interpret positive changes even if they are not present because of a placebo effect engendered by commitment to cancer therapy.

On the other hand, in laboratory animal literature and more specifically in the tutorials provided by AHWLA, happiness was assessed by facial expressions of the animal

as interpreted by a trained laboratory animal technician.

McMillan¹⁶⁸ argued, "...animals form life-as-a-whole evaluations". Even though these evaluations are not as complex as those of human beings, they collectively support the notion that happiness exists in animals and bears strong resemblances to human happiness. There are enormous individual differences in humans as to what contributes to happiness and the same must be assumed to be true for animals.¹⁶⁸ McMillan also argued that even though happiness is difficult to describe for humans or animals, it is something that we all intuitively understand. Thus, another explanation for our finding might be that the animal is indeed "happy" according to the owner because the animal feels better and behaves more normally. Thus, a playful dog, or a dog that does not exhibit clinical signs of depression or physical signs of illness may be perceived to be a happy dog. In our study we sought to interpret canine happiness from the perspective of comparisons of behavior over time, ranging from the time of normalcy to the time of disease diagnosis, to the time of therapeutic intervention.

The three questions identified as statistically significant QOL predictors will be helpful in defining future studies in QOL of canine cancer patients as

perceived by the owners. The level of importance each factor contributes to the overall animal QOL score should be further evaluated. McMillan argued that not all items included in a questionnaire carry the same level of importance for QOL. Most currently available QOL instruments that assign equal numerical scores to all factors evaluated may not reflect the true state of the animal's QOL.

One question in our study regarding barking and vocalization behaviors was found to be confusing to owners. Owners appeared uncertain as to how to correlate the level of vocalization and barking with the animal's quality of life. Barking as an expression of excitement and happiness might reflect normal behavior for the dog, while other dogs might bark or vocalize as a sign of distress. In future efforts, the owner's perceived reason for vocalization should be factored into any question that attempts to solicit information about this aspect of canine behavior.

Despite the fact that the clinician's questionnaire was very brief, we did not have 100% participation in the study, but we had 72% participation rate for the survey of the first visit, 65% participation rate for the survey of the 2nd visit and 55% participation rate for the survey of the 3rd visit. This occurred despite the fact that all

clinicians signed consent forms and agreed to participate in the study from the outset. Compliance in participation in any survey-based study is always challenging, and 100% participation is never expected, 25% to 72% return rate is considered to be the norm in most survey-based studies.^{169,170} However, a robust reminder system and making the survey easy to complete would be expected to improve clinician compliance. Clinicians are busy people, and other priorities relative to patient care make survey completion a low priority for them. However, thorough explanation of the importance of achieving the study goals might help to improve clinician "buy in" and hence improve compliance with questionnaire completion.

In contrast, animal owners, who participated in this study expressed that they enjoyed the opportunity to participate and appreciated the opportunity to evaluate their dog's QOL. They reported that completing the questionnaire was easy. In our study, 65.5% of responding owners were extremely concerned about their dog's QOL while pursuing chemotherapeutic treatment. Allowing them an opportunity to complete a QOL study might have been perceived as the clinic's being supportive of those concerns. Judging from the high owner participation rate, we assume survey completion was a positive experience for

the owners, and that in some cases at least survey participation may have enhanced the perceived value of the cancer care services provided.

Furthermore, owners completed the survey sections detailing their evaluation of the study. In fact, owners wished to communicate any changes regarding their dog's QOL to the study data collectors, even when the individual animal's participation in the study was not to be continued, as in the case of therapy discontinuation or patient euthanasia. This finding is consistent with similar study effect observed in human medicine, where the inclusion of QOL assessments are perceived by patients with chronic illnesses to contribute to the concept of patient centered care.¹⁷¹

We argue that focus on patient centered care in veterinary medicine may also improve the interaction between the owner and clinician by focusing on shared decision making, reinforcing fluent QOL assessment and addressing issues regarding the canine cancer patient's QOL and case management when they arise during the course of therapy.

It is of great interest that even though only 2/3 of dogs participating in this study ultimately responded to their treatment and 1/3 of the dogs failed to respond, the

owners and clinicians perceived the QOL of the dogs that received chemotherapy to be overall improved. This finding suggests that either the dogs benefited from the chemotherapeutic treatment in some manner not associated with clinical remission, or the symptoms of the neoplastic disease were improved even in cases that did not achieve complete remission. It is possible that both clinicians and owners projected a placebo effect into the animal's response, and they subjectively misperceived that the treatment benefited the animal.

Christiansen et al.¹⁷² reported that QOL assessment is necessary in veterinary medicine today. This is because it assists in the accurate evaluation of the efficacy of treatment and its implications for the small animal patients' QOL.¹⁷² We argue that using the QOL instrument developed for this study would assist in accurate evaluation of the efficacy and adverse effects of chemotherapeutic treatment in a veterinary oncology setting.

In conclusion, the QOL questionnaire developed for this study had several innovative aspects. To our knowledge this is the first QOL instrument developed in the field of veterinary medicine to assess, through longitudinal

evaluation, the QOL of canine cancer patients treated with chemotherapy, as perceived by both the owner and the attending clinician. A major finding of our study was that both owners and clinicians had statistically significant agreement regarding the QOL of each individual canine cancer patient when assessed over three consecutive visits. Our questionnaire is the first QOL instrument developed in the field of veterinary medicine to assess chemotherapy treated canine cancer patients that correlated the owner perceived QOL of the dog with level of stress of the owner. This represented the first attempt in veterinary medicine to address the concern for caregiver negative affect in QOL assessment. A significant finding of this study was that there was no statistical correlation between owner level of stress and dog's QOL parameters.

According to our study results, there were three statistically significant predictors of QOL of the chemotherapy treated canine cancer patient. These three factors were changes in play behaviors, exhibition of clinical signs of disease and canine "happiness" as perceived by the owner. This finding suggests that these three predictors would be valuable to be included in future studies regarding QOL assessment of canine cancer patients. Another unique aspect of this study is that it used the

same dog while healthy as an internal control of itself, rather than using individuals from a healthy matched population as control.

Our study also was unique in that we asked only the person closest to the dog to assess QOL throughout the duration of our longitudinal study. This minimized the potential for interference by differences in personal assessments, as well as obtaining observations from the most reliable source. The most proximate caregiver for the animal would be expected to have the best capability to observe changes in behavior and health status of the animal.

We found it feasible to use a QOL instrument addressed to the owner and to the attending clinician for 3 consecutive visits to the clinic. Furthermore, completion of our QOL questionnaire was considered to be a positive experience by the owners. Owners described the instrument to be easy to complete, and the owners reported that they enjoyed the opportunity to assess the QOL of their dog. The use of the QOL questionnaire greatly enhanced the perceived value of the cancer care provided by our clinic.

In future studies, it would be interesting to assess and compare the QOL of a group of dogs whose owners elect to pursue chemotherapy treatment with QOL of a group of

disease-matched dogs whose owners decline treatment. This approach would help to better define the natural history of the progressive disease process in question, and a placebo treated control group could help to better define the relative importance of any placebo effect in owner assessment of QOL. In order to assess repeatability of the results, it would be valuable to expand the use of the QOL questionnaire for canine cancer patients to a larger patient sample size. It would also be important to use the QOL questionnaire in studies with longer follow up than the 6-week evaluation period employed here. This would help to assess the sensitivity of the questionnaire in order to identify QOL changes when the canine cancer patients are improving or deteriorate throughout the treatment and disease process.

It would be interesting to assess how helpful a QOL questionnaire might be to facilitate client decision making around issues such as euthanasia counseling. Use of such a questionnaire might improve communication between the clinician and the owner. Appropriate use of QOL assessment could provide a level of emotional clarity to owners faced with difficult decisions such as whether or not to elect expensive or risky therapies. A well-designed QOL tool

might even help with closure for owners during the grief period after loss of a pet.

Furthermore, it would be interesting to evaluate owner perception of the QOL of companion dogs receiving care from other veterinary hospital services. Impact of other chronic disease processes may result in significantly different post-therapy perceived QOL, depending on the severity of debility of such other target diseases. Disease-specific questionnaires adjusted to evaluate the QOL of dogs affected by other chronic diseases, such as arthritis, heart diseases and diabetes should be created in the future. Use of QOL instruments to evaluate impact of therapy for disease of other domestic or companion species, such as pet cats, would also be useful.

It would also be interesting to evaluate the results of the same survey on a canine population visiting the hospital for annual wellness exam and vaccinations in order to assess the ability of the instrument to identify changes in health status of dogs over time.

Another important factor in evaluating the feasibility of a QOL instrument in a small animal clinical setting would be to develop a survey to assess the clinicians' perceptions regarding using a QOL survey instrument in veterinary clinics.

A major goal in veterinary QOL research is to develop truly objective scoring criteria to evaluate QOL. This would be invaluable for canine cancer patients, because such criteria would allow QOL assessment without using the owner's perceived QOL as the sole "gold standard".

In the future, if one were to design an improved QOL survey for dogs treated with chemotherapy as perceived by owners and clinicians, our results suggest that the survey should include questions regarding the dog's QOL 6 months before cancer diagnosis, assessing the following: behavior towards the owner, activity, appetite, playfulness, the overall QOL, signs of illness, pain/discomfort, dog's happiness, health, anxiety/fear, mobility problems, and the dog's favorite activity. These questions had high variability in responses in our study and they assessed important aspects of the 3 major domains of QOL (physical, psychological and social functioning) as discussed in Chapter 2. These questions are also important because they establish baseline values for each individual dog.

While not all these questions were found to be statistically significant predictors for the dog's QOL, they contributed in total to a global assessment of the dog's QOL before being diagnosed with neoplastic disease. Several owners commented that they appreciated the

opportunity to reflect more deeply about the QOL of their pet and themselves through the process of cancer treatment. We feel that these questions helped to focus the owner's memories, to compare the dog's "normal" initial state with the dog's state after being diagnosed with neoplastic disease and during the different stages of treatment with chemotherapeutic agents. Serial assessment before and after such an experiment is a very important to ensure the veracity of findings.

The questions that pertained to the dog's QOL while healthy are repeated during the serial QOL assessment in order to help in identifying changes in QOL. In addition to the above-mentioned factors to be assessed during the 3 time points, we would continue to assess factors such as the impact of cancer on the dog, any changes in enjoying favorite activities, and any changes in sleeping/resting patterns. These questions had high variability of response in the current survey. We would also consider adding one question that specifically queries the incidence of vomiting, since gastrointestinal signs are commonly associated with chemotherapeutic treatment, and vomiting is a clinical sign that the owner can easily observe and identify. Vomiting is considered to severely compromise the QOL of human cancer patients and it is suggested that the

impact of this symptom on the patient's QOL would be better assessed with the use of an instrument that contains a separate item for vomiting.¹²

In all three questionnaires, we would reposition the question that specifically asks about the dog's current and past QOL to the end of the survey instrument. This question may be best answered after the owner has thought about all the individual factors that contribute to the dog's QOL individually. As a summary question, this would also help to clarify the comparison of current status with the dog's previous "normal" QOL status. Thus, this question needs to be answered as a conclusion to the reinforced process of reflection regarding the dog's QOL status.

In a new, improved survey, we would exclude questions that had a low variability among responses, such as when 90% of dog owners answered in the same way in our current study. Questions we found to have low variability included: if the dog enjoyed human interaction in the past, the dog's role in the household and the questions pertaining to information regarding time of ownership (Have you had your dog since it was a puppy?) Sixty-two percent of our responders failed to answer the question "How many years ago did you adopt the dog?" Thus, in order to avoid confusion but still be able to evaluate if the owner is

familiar with the dog sufficiently to accurately assess QOL, we would modify the survey to allow a yes or no response to "Have you owned your dog for at least 12 months?" According to Wojciechowska et al. 5 months of dog ownership was considered sufficient to allow an owner to accurately assess QOL and normal behaviors in his dog.¹⁴⁹ In our study we were asking information regarding the dogs QOL 6 months before cancer diagnosis in order to create a baseline of normal behaviors for this dog. We would consider a year of ownership optimum to allow accurate assessment of both normal behavior and the dog's QOL 6 months before cancer diagnosis, and upon subsequent diagnosis and treatment.¹⁴⁹

Questions that could be modified for increased clarity include the question regarding the dog's playfulness and activity level. The modified question would query only information regarding the dog's playfulness level, and we a separate question regarding the dog's activity level would be added in order to avoid the presence of "double-barreled" questions. Similarly, the question "How often did your dog experience signs of anxiety and fear (shivering, increased salivation, panting, whimpering, howling, barking and growling) or any other type of behavioral problems in

the past?" would be modified to exclude the part pertaining behavioral problems of the dog in the past. This would be assessed through a second question. Asking 2 different parameters in the same question (fear/anxiety versus behavioral problems) might cause confusion for the respondents. In the fear and anxiety question we would omit the parenthetical words "howling, barking and growling", as confusion may arise with regard to the underlying cause of such behaviors in dogs.

The similar question "How often does your dog experience signs of anxiety and fear (shivering, increased salivation, panting, whimpering, howling, barking and growling) during your visits to MSU VTH?" would be modified accordingly, with parenthetical descriptors of vocalization excluded. The question "How often is your dog vocalizing (whimpering, howl, bark, growl)?" which was repeated throughout the surveys, should be excluded because it was confusing for owners to discriminate causes of vocalization due to reasons other than pain and discomfort, such as excitement, guarding territory, and others. Owners reported confusion about the vocalization question in the feedback question: "Please comment how the survey can be improved?"

For the part of the survey that solicits information regarding the owners' QOL (caregiver's negative affect), we

would include all the current questions except the "Perception of others about me seeking advanced care for my pet." This question apparently made some owners feel uncomfortable, as determined by comments solicited about improving the survey. The rest of the domains and questions should remain in the questionnaire as discussed in Table 4. Even though these questions were not found to be statistically significant predictors of QOL, our sample was relatively small and the answers varied, so we cannot draw definitive conclusions. Caregiver's negative affect is of major importance in the area of proxy QOL questionnaires in pediatric medicine and is always considered as a factor contributing to the accuracy of a proxy QOL report.⁸⁵ Clearly, more attention to the important factor is warranted in veterinary QOL assessment.

Further studies regarding the impact of the dog's disease on the owners' QOL and judgment are needed. We would modify the question regarding rating "...the amount of worry your pet's QOL is causing you" to "...rate the amount of worry your pet's current QOL while receiving chemotherapeutic treatment is causing you." Based on owner feedback, altered phrasing of the question would help avoid confusion regarding the general concept of the dog's QOL versus the dog's QOL during chemotherapeutic treatment.

For the clinician's survey, we would continue to include all questions pertaining to the dog's QOL, the owners QOL, changes in both the owner's and the dog's QOL during the 3 serial assessments, and owners priorities in decision making. These questions should remain because QOL of the dog, and the owner (caregiver's negative affect) are critical aspects to evaluate. Also, the clinician should be cognizant of the owners' priorities in decision-making. Aside from the impact on QOL evaluation, improved client-clinician communication regarding the dog's QOL is a priority identified by owners in our study. However, the question regarding the dog's role in the household should be removed from the owner's version of the survey, and the question had a low variability while answered by the clinicians as well. This question would be removed from future clinicians' surveys as well.

APPENDIX A

Table 1: Signs of pain regardless of species

Signs of pain regardless of species	Signs of acute pain	Signs of chronic pain
1. Attraction to the area of pain 2. Increased skeletal muscle tone 3. Altered electroencephalogram response 4. Increased blood pressure and heart rate 5. Pupillary dilation 6. Change in the respiratory pattern.	1. Protection of the painful part 2. Vocalization (especially on movement or palpation of the painful part) 4. Licking 5. Biting 6. Scratching or shaking of affected area 7. Restlessness 8. Pacing 9. Sweating 10. Increased rate of respiration	1. Limping 2. Licking of area affected 3. Licking of other areas if the painful part cannot be reached 4. Reluctance to move 5. Loss of appetite 6. Change in personality 7. Changes in eye brightness

Table 2: Medical record data obtained

Demographics and physical exam findings	Adverse events	Bloodwork
• Gender • Age • Breed of the canine patient • The type of neoplastic disease • Concurrent diseases and if they were being treated • The type of chemotherapeutic protocol used each time • Whether they were treated surgically for the neoplastic disease or other reasons while they received chemotherapy • Whether they were treated with radiation therapy • The presence of metastasis and the specific locations (lung, abdominal, other) • The dog's activity level • Pulse rate • Respiratory Rate • Body weight • Hydration level • Temperature	• Infection • Enteritis • Organ failure • Dysphagia • Anorexia • Diarrhea • Nausea • Vomiting • Constipation • Incontinence • CNS abnormalities • Musculoskeletal abnormalities • Reproductive abnormalities • Respiratory abnormalities • Cardiac abnormalities • Pneumothorax • Pleural effusion • Ascites • Vascular abnormalities • Bleeding disorders • Lethargy • Dermatological abnormalities	• Anemia (Yes/No) • Thrombocytopenia (Yes/No) • Neutropenia (Yes/No) • DIC (Yes/No) • Hypoalbuminemia (Yes/No) • White Blood Cell Count (Within Reference Limits/No) • ALP levels (Within Reference Limits/No) • ALT levels (Within Reference Limits/No) • Calcium (Within Reference Limits/No) • Creatinine (Within Reference Limits/No) • Bilirubin (Within Reference Limits/No) • Glucose (Within Reference Limits/No) • Potassium (Within Reference Limits/No)

Table 3: The 3 major domains of physical, psychological, and social functioning addressed in our study in order to assess the QOL of the canine cancer patient.

Physical functioning	Psychological functioning	Social functioning
Appetite: 1.Before cancer diagnosis: (SV1P2Q3) 2.At cancer diagnosis (SV1P3Q6) 3.At 2 nd visit: (SV2P2Q6) 4.At 3 rd visit (SV3P2Q6)	Anxiety and fear: 1.At cancer diagnosis: (SV1P3Q13) 2.At 2 nd visit (SV2P2Q13) 3.At 3 rd visit (SV2P2Q13)	Behavior towards owner: 1.Before cancer diagnosis: (SV1P2Q1) 2.At cancer diagnosis (SV1P3Q4) 3.At 2 nd visit (SV2P2Q4) 4. At 3 rd visit (SV3P2Q4)
Sleep changes: 1.At cancer diagnosis: (Sv1P3Q3) 2.At 2 nd visit: (Sv2P2Q3) 3.At 3 rd visit: (SV3P2Q3)	Play Behaviors: 1.Before cancer diagnosis (SV1P2Q5) 2.At cancer diagnosis (SV1P3Q8) 3.At 2 nd visit (SV2P2q8) 4.At 3 rd visit (SV3P2Q8)	Enjoyment of human interaction: 1.Before cancer diagnosis (SV1P2Q8) 2.At cancer diagnosis (SV1P3Q11) 3.At 2 nd visit (Sv2P2Q11) 4.At 3 rd visit (SV3P2Q11)
Physical activity: 1.Before cancer diagnosis (SV1P2Q2) 2.At cancer diagnosis: (SV1P3Q8) 3.At 2 nd visit (SV2, P2, Q8) 4.Physical activity at 3 rd visit (SV3P2Q8)	Dog Happiness: 1.Before cancer diagnosis (SV1P2Q9) 2.At cancer diagnosis (SV1P3Q12) 3.At 2 nd visit (SV2P2Q12) 4.At 3 rd visit (Sv3P2Q12)	Dog's role in the household: The dog's role in the household (SV1P2Q13)
Mobility: 1.Before cancer diagnosis (SV1P2Q12) 2.At 2 nd visit (SV2P3Q14) Mobility problems for 3 rd visit (SV3P3Q14)	Identification and enjoyment of favorite activities: 1.Identification of dog's favorite activities before cancer diagnosis (SV1P2Q14)	

Table 3 (cont'd)

Exhibition of clinical signs of illness: 1.Before cancer diagnosis (SV1P2Q2) 2.At cancer diagnosis (SV1P3Q9) 3.At 2 nd visit (SV2P2Q9) 4.At 3 rd visit (SV3P2Q9)	Enjoyment of favorite activities: 1.At cancer diagnosis (SV1P2Q2) 2. At 2 nd visit (SV2P2Q2) 3.At 3 rd visit (SV3P2Q2)	
Pain and discomfort: 1.Before cancer diagnosis (SV1P2Q9) 2.At cancer diagnosis (SV1P3Q10) 3.At 2 nd visit: (SV2P2Q10) 4.At 3 rd visit (SV3P2Q10)		
Dog's health status 6 months before diagnosis: Health before cancer diagnosis (Sv1P2Q10)		
Cancer impact: 1.At cancer diagnosis (SV1P3Q1) 2.At 2 nd visit (SV2P2Q1) 3.At 3 rd visit (SV3P2Q1)		
Vocalization consistent with pain (whimpering, howling, growling, barking): 1.At cancer diagnosis: (SV1P3Q5) 2.At 2 nd visit (SV2P2Q5) 3.At 3 rd visit (SV3P2Q5)		

Table 4: Domains that were assessed regarding the owner's QOL during the study. All questions are provided in the questionnaires: questionnaire of the 1st visit, section 4, and questionnaires of the 2nd and 3rd visit section 3.

Treatment/ disease monitoring	Interference with owner's daily life	Disease outcome	Emotional impacts
Concerns for time and scheduling	Limitation that the dog's condition is causing to the owner	Worry because the disease is not curable	How worried the owners are about the dog's illness
Financial concerns	The dog urinating/ defecating / vomiting in the house	The pet's QOL	Perception of others about the owner seeking advanced care for the pet
Chemotherapy administration and side effects			

Figure 1: Multiple regression analysis, 1st visit, signs of illness. The relationship between the dog's QOL as perceived by the owner and potential predictor variables during the 1st visit was analyzed by multiple regression analysis. $R^2 = 0.8521$, [signs of illness] coefficient = 0.41, $p = 0.0001$). The solid line represents the best fit line, while the dotted lines represent the 95% confidence intervals (CI).

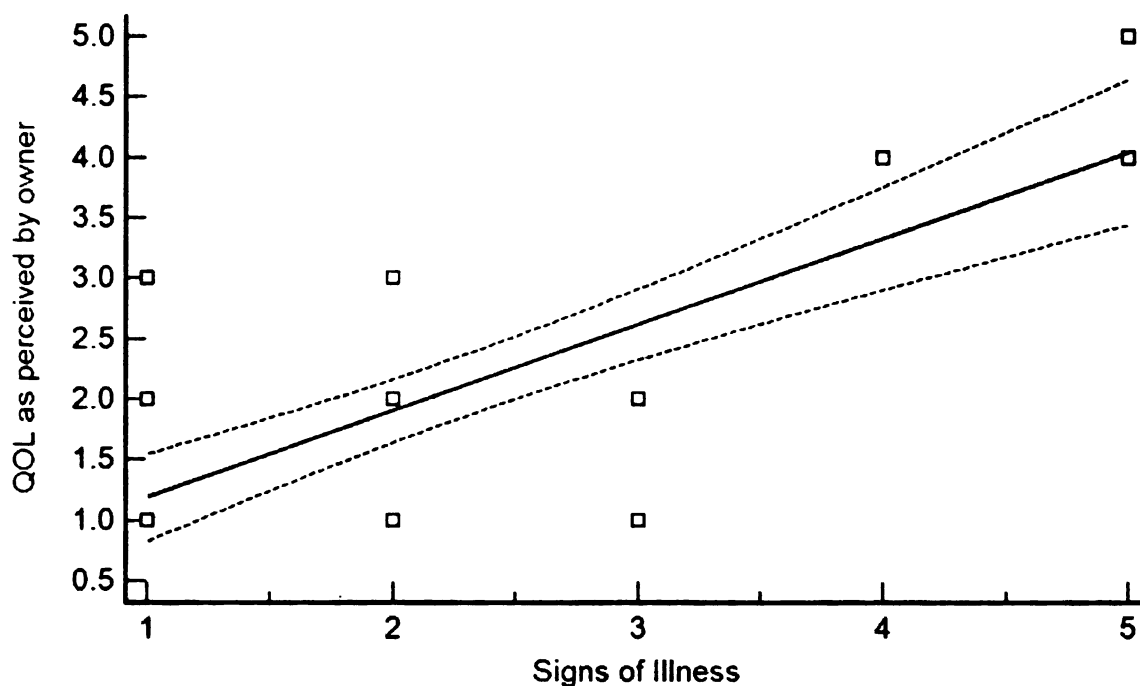


Figure 2: Multiple regression analysis, 1st visit, dog's playfulness. The relationship between the dog's QOL as perceived by the owner and potential predictor variables during the 1st visit was analyzed by multiple regression analysis. $R^2 = 0.8521$, [dog's playfulness] coefficient = 0.46, $p < 0.0001$). The solid line represents the best fit line, while the dotted lines represent the 95% CI.

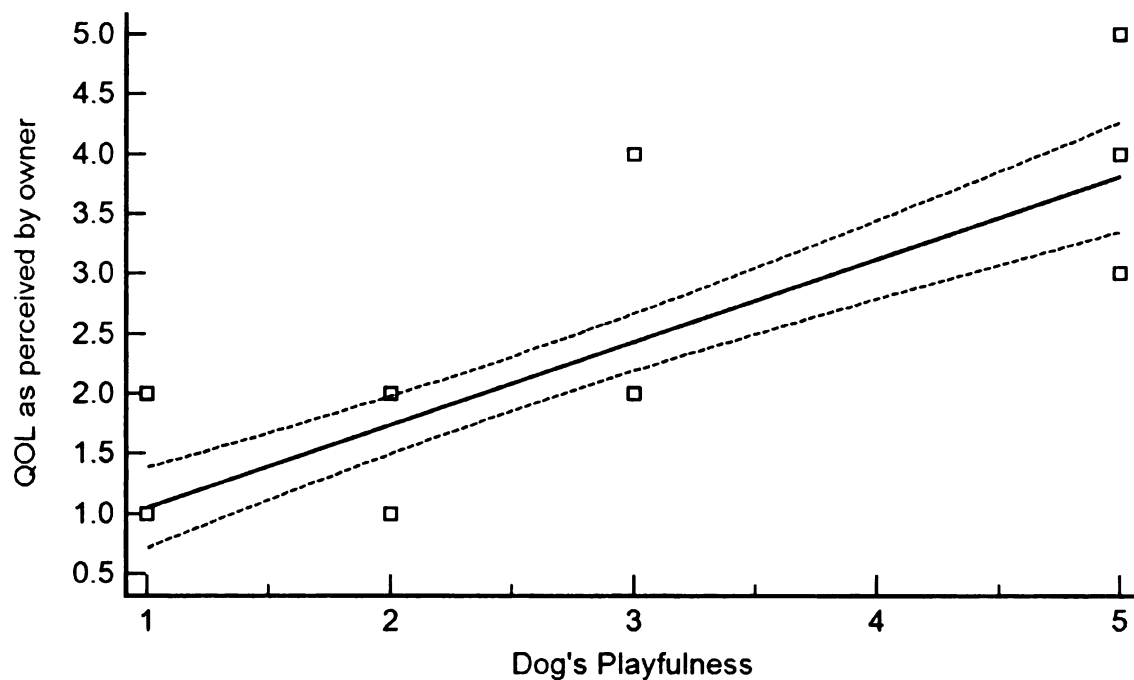


Figure 3: Multiple regression analysis, 2nd visit, dog's happiness. The relationship between the dog's QOL as perceived by the owner and potential predictor variables during the 2nd visit was analyzed by multiple regression analysis. $R^2 = 0.8256$, [dog's happiness] coefficient = 0.39, $p = 0.0169$). The solid line represents the best fit line, while the dotted lines represent the 95% confidence intervals (CI).

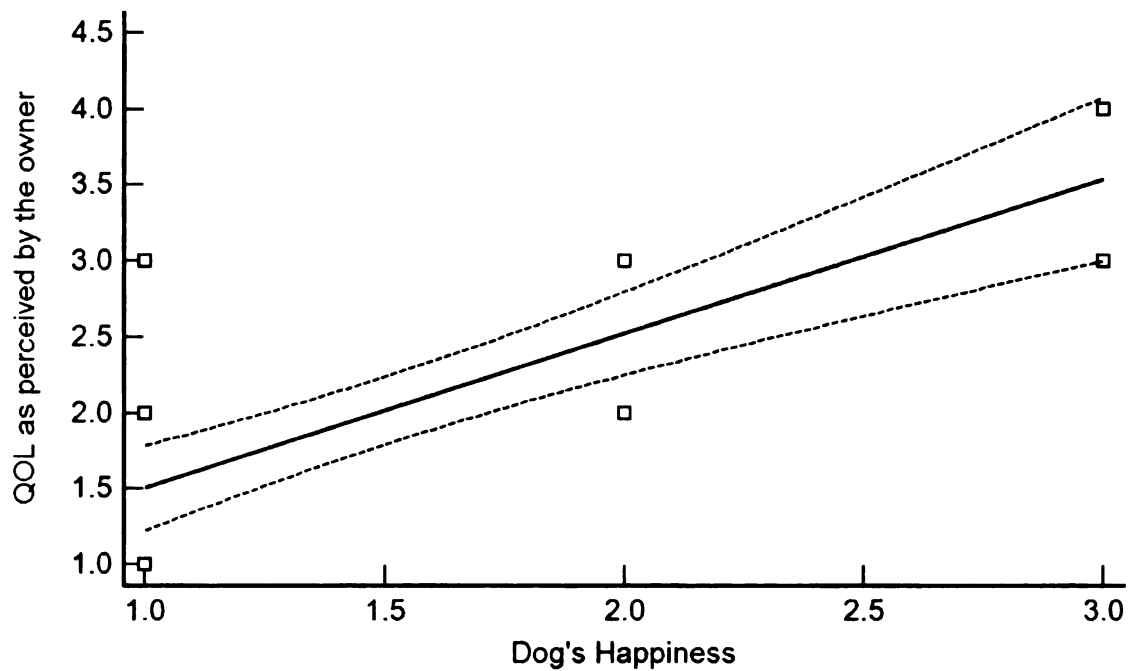


Figure 4: Multiple regression analysis, 2nd visit, dog's playfulness. The relationship between the dog's QOL as perceived by the owner and potential predictor variables during the 2nd visit was analyzed by multiple regression analysis. $R^2 = 0.8256$, [dog's playfulness] coefficient = 0.61, $p < 0.0001$). The solid line represents the best fit line, while the dotted lines represent the 95% confidence intervals (CI).

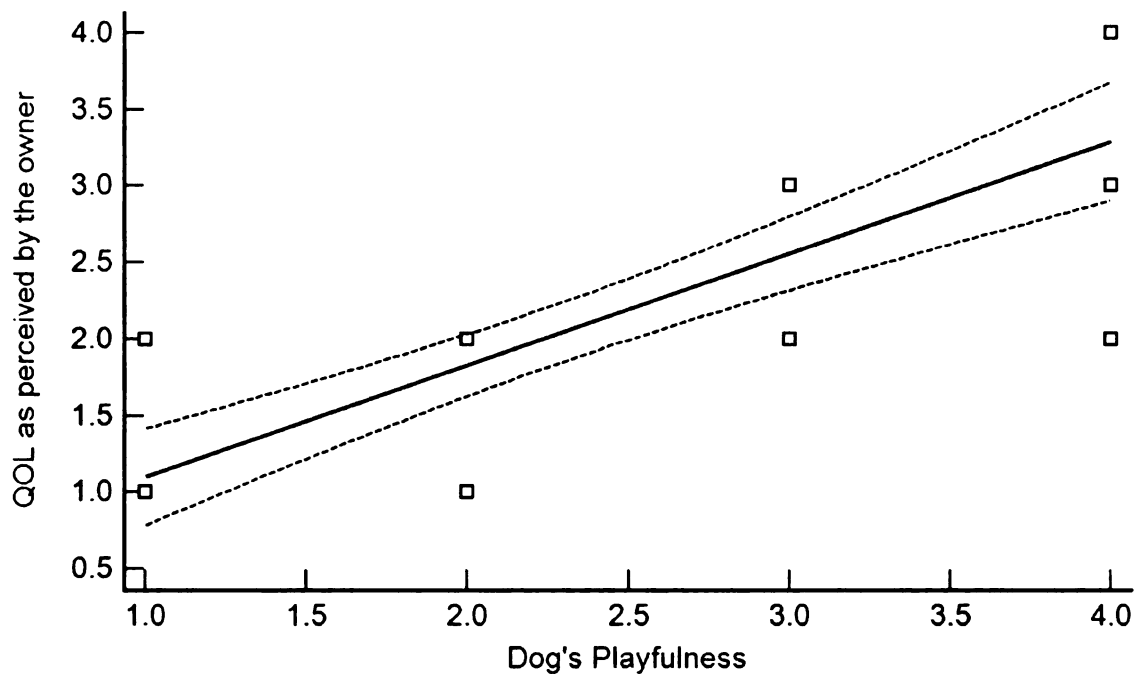


Figure 5: Multiple regression analysis, 3rd visit, signs of illness. The relationship between the dog's QOL as perceived by the owner and potential predictor variables during the 3rd visit was analyzed by multiple regression analysis. $R^2 = 0.5553$, [signs of illness] coefficient = 0.33, $p = 0.0145$). The solid line represents the best fit line, while the dotted lines represent the 95% confidence intervals (CI).

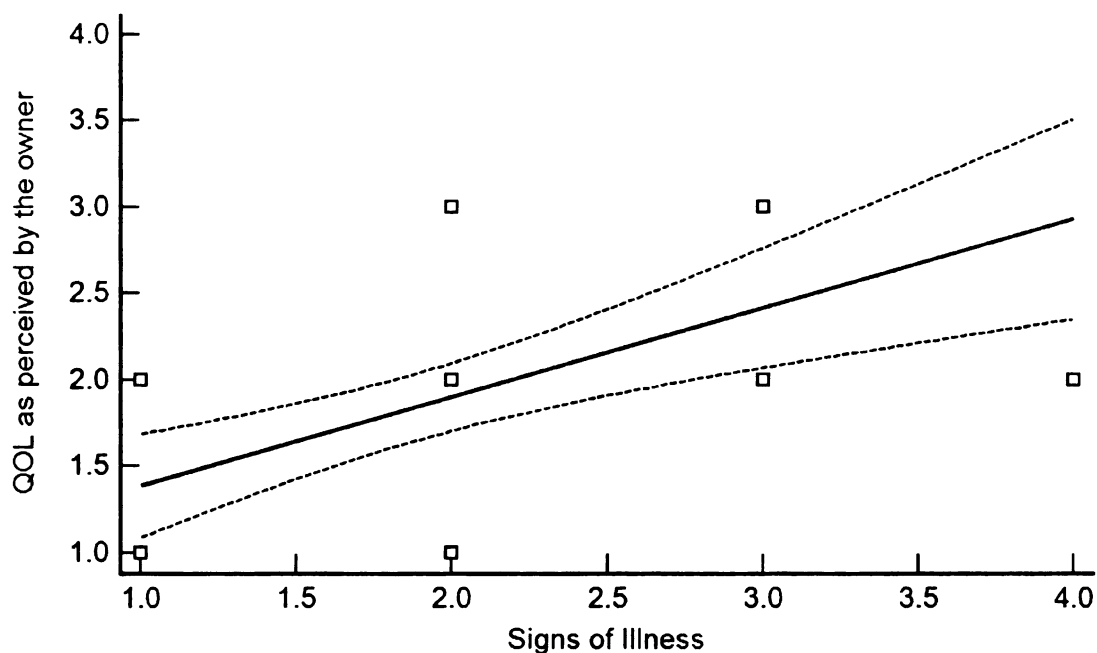
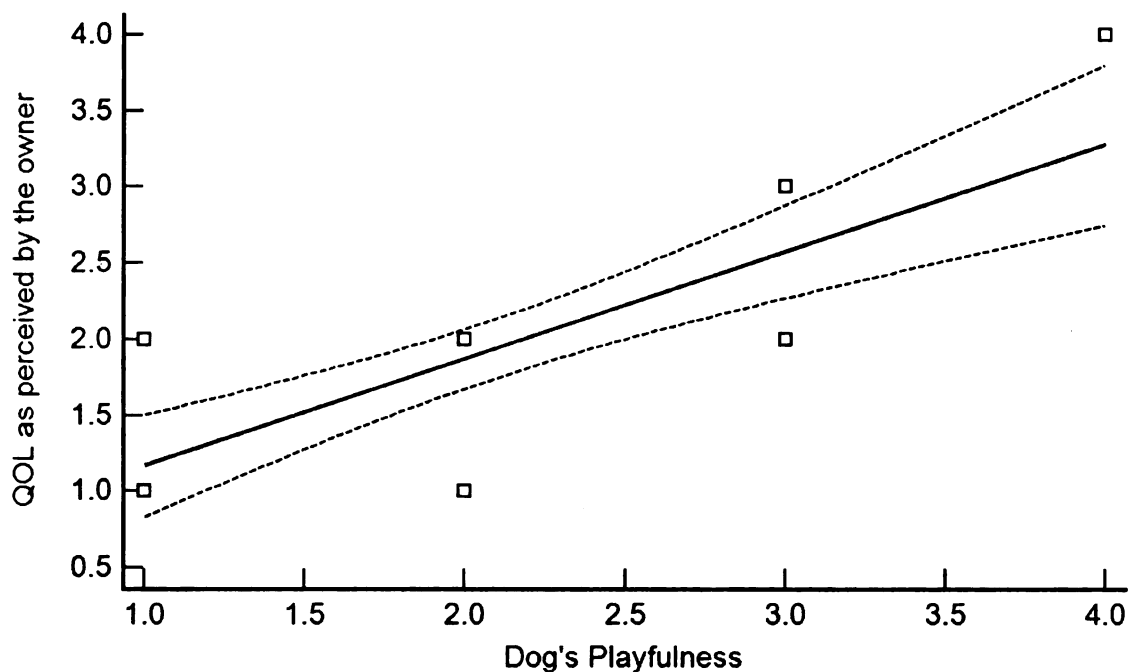


Figure 6: Multiple regression analysis, 3rd visit, dog's playfulness. The relationship between the dog's QOL as perceived by the owner and potential predictor variables during the 3rd visit was analyzed by multiple regression analysis. $R^2 = 0.5553$, [dog's playfulness] coefficient = 0.44, $p = 0.0058$). The solid line represents the best fit line, while the dotted lines represent the 95% confidence intervals (CI).



APPENDIX B

EVALUATION OF QUALITY OF LIFE (QOL) IN SMALL ANIMAL PATIENTS OF THE MSU CENTER OF COMPARATIVE ONCOLOGY

Informed consent for the owner
Companion animal owners

Principal investigator:
Study location: Michigan State University Veterinary
Teaching Hospital

Participant Name:

Participant Initials:

Pet name:

A. Introduction and Purpose

You are being asked to allow your pet to participate in a veterinary clinical research study sponsored by the Michigan State University Center for Comparative Oncology. The medical treatment of dogs with cancer is largely palliative. Decisions made about the types and length of treatment often requires the veterinarian and the owner need to discuss the quality of life (QOL) of the patient. This discussion is usually done in an impressionistic manner, which may or may not be true reflection of the dog's status. Thus, it is important to have an efficient tool to assess QOL of the companion animal cancer patient. The goal of this study is to write a questionnaire to help owners and veterinarians make more accurate decisions about pet quality of life during cancer treatment.

B. Procedure

- Thirty canine patients will be part of the study. Dogs can be included if they have disseminated metastatic cancer of any kind that requires chemotherapy as treatment (i.e. lymphoma, metastatic carcinoma, metastatic sarcoma). Dogs with acute leukemia, or dogs with non-neoplastic life-limiting diseases will not be part of the study at this time.
- Patients will be evaluated both by you (owner) and the attending veterinarian at the time of your first visit

to the oncology clinic. Your dog also will be evaluated at 3 and 6 weeks after the start of chemotherapy. Two different questionnaires will be used; one for you (the owner) and one for the veterinarian. The survey questions will have answers choices for you to use to rate your dog's quality of life (for example you may be asked to rate your dog's appetite between 1 and 5 with 1. =excellent, 2. = very good, 3. = good, 4. =fair, 5. =poor).

- Initial evaluation (time 0):

The study purpose and procedures will be explained to you at the first visit to the Oncology Clinic. You will be asked to read and sign a consent form to be included in the study. At the first visit you will be given a questionnaire asking information about your dog's current and past quality of life. The veterinarian you will see also will be given a survey to answer about meeting you and your dog (you have the right to see the veterinarian survey if you would like to). And your dog's relevant medical record information will be recorded.

- Second evaluation (3 weeks):

Three weeks later, you and the veterinarian treating your dog will make a second evaluation. Again you will be asked to answer a similar but shorter questionnaire about your dog's quality of life since the first visit. The veterinarian will also answer a questionnaire with questions similar to the first visit.

- Third evaluation (6 weeks):

Six weeks after the first visit, you and the veterinarian treating your dog will make a third evaluation. At this visit your dog will be reevaluated about its response to cancer treatment. Again you will be asked to answer a similar but shorter questionnaire about your dog's quality of life since the first visit. The veterinarian will also answer a questionnaire with questions similar to the first visit.

- Your pet will be assigned a study identification number, which will appear on the survey and on the information collected from the medical record. Your name and your pet's name will appear on the questionnaire, but it will not be part of the research. Only the code numbers will be used.

- There is no anticipated risk to human participants and animal subjects enrolled in this study.
- Participation is voluntary. You may choose not to participate at all. You have the right to withdraw from the study or stop participating at any time without penalty. Signing and dating this consent form, indicates your agreement to participate in this research and complete the questionnaires provided.

C. Benefits

If you do not want to be part of this research your pet will still receive the same high quality care as other pets treated at the MSU Oncology clinic.

There is no direct benefit to you or your pet by participating in this study. Information from this study may help us create a questionnaire to help veterinarians understand QOL of your pet as cancer patient. This research may help other owners with the difficult process of decision making for a beloved pet. Human medicine recognizes the need to assess the impact of cancer and cancer treatment on the patients QOL.

If you request it, the results of QOL study will be available to you after the research has been completed.

D. Confidentiality

All information collected about you or your pet during this study will be kept confidential to the extent permitted by law. Only a code number will identify your pet during the research process.

Information that identifies you or your pet will not be released. The Michigan State University Biomedical and Health Sciences Institutional Review Board (BIRB) may review research records.

Results of this study may be published, but your identity, your pet's identity and questionnaire answers will be kept confidential in any publications. Your privacy will be protected to the maximum extent allowed by the law.

E. Questions

If you have any questions about this study, such as scientific issues, how to do any part of it, or to report an injury, please contact the researcher, Barbara E. Kitchell, director of Comparative Oncology center at: D211

VET MEDICAL CTR EAST LANSING MI 48824-1314 Office: Small
Animal Clinical Sciences (mailing address),
517-353-5420 (phone number)
kitchel2@msu.edu (e-mail address)

If you have any questions about your role and rights as a research participant, or would like to register a complaint about this study, you may contact, anonymously if you wish, the Director of MSU's Human Research Protection Programs, Dr. Peter Vasilenko, at 517-355-2180, FAX 517-432-4503, or e-mail irb@msu.edu, or regular mail at: 202 Olds Hall, MSU, East Lansing, MI 48824.

F. Consent to Participate in a Research Trial:

To voluntarily agree to participate yourself and have your pet take part in this study, you must sign on the line below. If you choose to participate and to have your pet take part in this study, you may withdraw at any time. You are not giving up any of your legal rights by signing this form. Your signature below indicates that you have read, or had read to you, this entire consent form, including the risks and benefits, and have had all your questions answered. You will be given a copy of this consent form.

I voluntarily agree to participate myself and have my pet participate in this study.

Signature of Study Participant Owner Date

Printed Name of Study Participant Owner Date

Signature of Witness Date

Signature of Investigator/Designee Obtaining Informed
Consent Date

EVALUATION OF QUALITY OF LIFE (QOL) IN SMALL ANIMAL
PATIENTS OF THE MSU CENTER OF COMPARATIVE ONCOLOGY

Informed consent for the clinician

Principal investigator:

Study location: Michigan State University Veterinary
Teaching Hospital

Participant Name:

Participant Initials:

Pet name:

D. Introduction and Purpose

You are being asked to participate in a veterinary clinical research study at the Michigan State University. The goal of this pilot study is to develop a survey instrument that will allow a more objective assessment of the quality of life (QOL) that will be of value to the animals, their owners and the veterinary professionals.

Decisions made for the choice and duration of treatment in veterinary oncology often require that the clinician and the owner assess the quality of life (QOL) of the patient. Thus, it is important to have an effective and objective tool to assess QOL of the companion animal cancer patient. Your participation in this survey will help us develop such a tool.

E. Procedure

- Thirty canine patients will be recruited to the study. Inclusion criteria: Dogs with disseminated metastatic cancer of any kind that requires chemotherapy as treatment (i.e. lymphoma, metastatic carcinoma, metastatic sarcoma). Exclusion criteria: Dogs with acute leukemia, or dogs with non-neoplastic life-limiting diseases.

- Patients will be evaluated both by the owner and you (attending clinician) at the time of your initial visit to the clinic, and then at 3 and 6 weeks after the initiation of chemotherapy. Two different survey forms will be used; one for you (attending clinician) and one for the owner. The survey questions will have

answers that would be rated on a 1-to-5-response scale (1. =excellent, 2. = very good, 3. = good, 4. =fair, 5. =poor).

- Initial evaluation (time 0):

The study objectives and methods will be presented to the clients and a consent form will be signed. Action taken at the initial visit will include:

1. An initial survey form addressed to the owner.
2. An initial survey form addressed to the attending clinician.
3. The patient's relevant medical record information will be recorded.

- Second evaluation (3 weeks):

During that visit a very similar format of the initial survey form will be distributed in order to assess changes occurring in the past 3 weeks. Surveys will be distributed again to both you (attending clinician) and the owner and the patient's medical record information will be recorded.

- Third evaluation (6 weeks):

Six weeks after the initial visit, the animal is being reevaluated by the attending clinicians for its response to treatment. Based on this reevaluation, changes in treatment plan might be implemented. At that time the same survey format distributed during the second evaluation will be redistributed to both you (attending clinician) and the owner in order to assess further changes in your pet's QOL. The patient's medical record information will be recorded.

- Your patient will be assigned a study identification number, which will appear on the survey and on the data collected from the medical record. Your name, your client's and your patient's name will not be used during data analysis. Only the code number will be used.
- There is no anticipated risk to human and animal subjects enrolled in this study.
- Participation is voluntary. You may choose not to participate at all. You have the right to discontinue

your participation at any time without penalty. Signing and dating this consent form, indicates your agreement to participate in this research by completing the survey instruments provided.

C. Benefits

There may be no direct benefit to you or your client and patient by participating in this study; however, information from this study may lead to the development of an efficient tool to assess QOL of the companion animal cancer patient and may help significantly other owners and clinicians in the difficult and painful process of decision making for their beloved pet. Upon request, the results of QOL survey will be available to you after the study has been completed.

D. Confidentiality

All information collected about you or your client and patient during the course of this study will be kept confidential to the extent permitted by law. Only a code number will identify your patient in the research records.

Information that identifies you personally or your client and patient will not be released without your written permission; however, the Michigan State University Biomedical and Health Sciences Institutional Review Board (BIRB) may review research records.

Information from this study may be published, but your identity and your client's and patient's identity will be kept confidential in any publications.

E. Questions

If you have any questions about this study, such as scientific issues, how to do any part of it, or to report an injury, please contact the researcher, Barbara E. Kitchell, director of Comparative Oncology center at: D211 VET MEDICAL CTR EAST LANSING MI 48824-1314 Office: Small Animal Clinical Sciences (mailing address), 517-353-5420 (phone number) kitchel2@msu.edu (e-mail address)

If you have any questions about your role and rights as a research participant, or would like to register a complaint about this study, you may contact, anonymously if you wish, the Director of MSU's Human Research Protection Programs, Dr. Peter Vasilenko, at 517-355-2180, FAX 517-432-4503, or

e-mail irb@msu.edu, or regular mail at: 202 Olds Hall, MSU,
East Lansing, MI 48824.

F. Consent to Participate in a research trial:

To voluntarily agree to participate in this study, you must sign on the line below. If you choose to participate in this study, you may withdraw at any time. You are not giving up any of your legal rights by signing this form. Your signature below indicates that you have read, or had read to you, this entire consent form, including the risks and benefits, and have had all your questions answered. You will be given a copy of this consent form.

I voluntarily agree to participate myself and have my patient participate in this study.

Signature of Study Participant Assigned Clinician Date

Printed Name of Study Participant Assigned Clinician
Date

Signature of Witness Date

Signature of Investigator/Designee Obtaining Informed
Consent Date

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