

Nutritional Management of the Cancer Patient

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Few diseases evoke as much emotion as cancer. Cancer can have devastating effects, decreasing the length and quality of life of companion animals. Most pet owners have had or will have a personal experience with cancer, either in themselves, a family member or a close personal friend. Further, the popular press is filled with articles about cancer prevention and the promise of therapeutic breakthroughs, especially in the field of nutrition. Thus, pet owners have a heightened awareness of human cancer and are extending that awareness to their pets. Concurrently, an increasing number of pet owners view their pets as full-fledged family members; family members that are entitled to the best veterinary care possible. Quality of life is a central theme that guides pet owners and the veterinary health care team in all decisions about the medical care of pets. This is true throughout the life of the pet; however quality of life becomes of primary concern when an animal and its owner are faced with a life-threatening illness such as cancer. Nutritional management of the cancer patient empowers clients by giving them the ability to fight cancer with a positive force, and improve their pet's quality of life

Nutritional goals in the management of cancer include maintenance of optimal weight, addressing metabolic and treatment associated abnormalities, prevention of deficiencies/excess and improvement of patient outcomes including remission time and survival time.

Metabolic Alterations In Cancer

There are 4 phases of clinical and metabolic derangements in cancer patients.

Phase 1 is the preclinical silent phase. There are no overt clinical signs of disease. Despite normal appearance metabolic changes are already happening, with increased lactate and insulin levels and altered blood amino acid profiles.

Phase 2 is when early clinical signs appear; this is hopefully the time of initial presentation to the veterinary health care team. The patient may be anorexic or lethargic, with mild weight loss. During this phase animals are more susceptible to side effects from treatment. The same metabolic changes continue.

Phase 3 is cancer cachexia. Anorexia and lethargy continue, often with marked debilitation. Clinical signs of vomiting and diarrhoea, weakness and weight loss occur with end stage cancer. Similar but more profound metabolic changes continue.

Phase 4 is the recovery and remission stage. Metabolic changes persist, and other changes from chemotherapy, surgery and radiotherapy may occur, including changes in food intake.

Carbohydrate metabolism is dramatically altered in dogs with cancer. Metabolic alterations are suspected to occur in cats but there are no published reports to date¹. Altered metabolism occurs because tumours preferentially metabolize glucose for energy by anaerobic glycolysis, forming lactate as an end product. The host must then expend energy to convert lactate to glucose by the Cori cycle, resulting in a net energy gain by the

tumour and a net energy loss by the host. Animals normally metabolise glucose aerobically in the liver via gluconeogenesis (Kreb's cycle). This generates 38 molecules of ATP. Tumour cells preferentially metabolise glucose via anaerobic glycolysis for energy. Only 2 molecules of ATP are formed from this metabolism of glucose to lactic acid. Conversion of 2 molecules of lactate back to glucose (Cori cycle in liver), results in a net loss of 4 ATP and 2 GTP. The patient must expend energy to metabolize lactate. The host potentially loses $38 + 6 = 44$ high energy phosphate bonds for every 2 ATP's gained by the tumour per molecule of glucose utilized. The result is a net energy loss by the dog.

High carbohydrate diets effectively fuel the growth of tumours. Most commercial dog and cat foods are high in carbohydrate.

Dogs with malignancy have elevated resting lactate and insulin levels compared to controls. Glucose tolerance testing is abnormal. It's unknown whether elevated insulin levels precede cancer development. Vail et al² investigated alterations in carbohydrate metabolism in canine lymphoma patients. 14 client owned dogs with untreated lymphoma were compared to 10 various breed controls. Lactate and insulin levels were measured at baseline and at 5, 15, 30, 45, 60 and 90 minutes after I/V infusion of 500 mg/kg glucose. Serum lactate concentrations after glucose infusion were significantly increased in the lymphoma group compared to controls at all time points. ($P < 0.001$) This is thought to be due to increased anaerobic glycolysis of glucose for energy, and is seen in humans, laboratory animals and dogs. There was a significant increase in insulin levels in lymphoma patients Vs control at baseline, 5, 45, 60 and 90-mins post dextrose ($P < 0.001$). The same response is seen in humans with cancer cachexia, and is thought to be due to post-receptor non-responsiveness (insulin resistance)

The clinical significance of increased lactate levels is that energy requirements of the dog will increase due to energy loss through the Cori cycle, and that hydration fluids containing lactate (lactated Ringer's) may not be suitable for the cancer patient³

Altered carbohydrate metabolism occurs in different types of cancer and persists after remission. 27 dogs with lymphoma underwent a 90 minute I/V glucose tolerance test (GTT), both before and after treatment with doxorubicin⁴ and were compared to a group of controls who received one dose of chemotherapy. All dogs with lymphoma achieved complete remission. Lactate and insulin levels were higher than controls and did not improve with remission. 90 dogs with non-haematopoietic tumours (osteosarcoma, mammary and pulmonary adenocarcinomas) were also studied⁵ with an I/V GTT. They all had increased lactate, glucose and insulin compared to controls. The abnormal carbohydrate metabolism remained after surgical excision of the tumours. Abnormalities also persisted in 12 dogs with nasal carcinomas⁶ after radiation therapy, but these changes were reduced when dogs were fed a diet supplemented with omega-3 fatty acids and arginine, compared to a control diet which was supplemented with soybean oil. Dogs with osteosarcoma also demonstrated abnormalities in carbohydrate metabolism which persisted post surgery⁷. Even small amounts of tumour appear to be able to induce alterations in carbohydrate metabolism. The persistence of these changes after clinical

evidence of cancer is gone suggests that cancer causes a fundamental change in metabolism.

Both tumours and dogs have obligate protein requirements. If protein intake is less than requirements, imbalance occurs, resulting in decreased immune function, gastro-intestinal (GI) function and surgical wound healing. Starvation of a healthy animal results in 75% weight loss from fat, whereas in cancer cachexia equal losses of fat and body protein occur. Dietary protein intake in dogs with cancer should be increased to > 30% DMB to prevent negative nitrogen balance¹.

A study by Ogilvie and Vail (1990)⁸ suggests that cancer induces long lasting changes in protein metabolism as well as carbohydrate metabolism. Cancer bearing dogs had significantly lower plasma concentrations of threonine, glutamine, glycine, valine, cysteine and arginine, and significantly higher concentrations of iso-leucine and phenylalanine than did normal control dogs. The results were the same for different types of tumours, and the changes in amino acid profiles persisted after surgical removal of the tumours.

Arginine is a conditionally essential amino acid with immunomodulatory effects (T-cell mediated) and anti-tumour effects. A study of dogs with lymphoma⁹ showed that increased arginine intake, in conjunction with increased omega-3 fatty acids (FA), was positively correlated with survival time. Increased levels of arginine and omega-3 FA's fed to dogs undergoing radiation therapy for nasal carcinomas correlated with improved quality of life, and negatively correlated with inflammatory mediators and mucositis in irradiated areas⁶

The arginine intake in dogs with cancer should be increased to > 2% DMB¹ or > 500mg/100kcal

Tumour cells have variable capability to use fat for energy. Pets with cancer have decreased lipogenesis and increased lipolysis. This may result in depletion of body fat stores, weight loss and lipid profile abnormalities. Well differentiated tumours may retain ability to use FA as an energy source whereas undifferentiated tumours may have very limited capacity to, due to lack of the beta-oxidation enzyme.¹

There has been much research on the effects of omega -3 FA (EPA and DHA) in the pathogenesis and management of cancer in humans, dogs and laboratory animals¹⁰. These fatty acids are derived from cold water fish including anchovy, mackerel, sardine, and menhaden. There is epidemiological evidence of an inverse relationship between omega-3 FA intake and incidence of cancer, and this is the basis of research to evaluate the potential for prevention and therapy.

The recommendation to feed high levels on omega-3 FA to animals with cancer is based on in-vitro cell culture studies, extensive rodent model studies using various cancer types, clinical trials in humans with severe forms of cancer and clinical trials in dogs with lymphosarcoma and nasal tumours. Variables such as Vitamin E intake, antioxidant status and research methods can confound human studies.

The risks and side effects of high levels of dietary fatty acids are few. Soft faeces, overt diarrhoea, flatulence, vomiting and halitosis ("fishy breath")

are most commonly noted at typical levels of fatty acid supplementation. More serious potential side effects include haemorrhage due to reduced platelet function, decreased plasma vitamin E concentrations and increased susceptibility to oxidative injury. Haemorrhagic problems have not been recognized in dogs consuming levels of omega-3 FA found in pet foods and typical supplements; cats, however, appear to be more susceptible to haemorrhagic problems associated with fatty acid supplementation and caution should be used with high omega-3 FA intake in cats. A study by Saker¹¹ revealed decreased platelet aggregation and increased toenail or mucosal bleeding time in normal cats fed omega-3 FA-enriched foods. Because of the potential for serious bleeding problems, cats with cancer should be given foods with lower levels of fish oil or omega-3 FA than those levels recommended in dogs with cancer. Caution should also be exercised in pets taking other medications that affect platelet function and those with a history of pancreatitis coagulopathy.

Anti-oxidants

There are two opposing hypotheses on the use of anti-oxidants in cancer patients. One is that anti-oxidants may protect cancer cells from free radical damage by chemotherapy and radiation. The other thought is that anti-oxidant nutrients improve the efficacy of cancer therapy by improving immune function, decreasing toxicity to normal cells, and reversing metabolic changes e.g. less lactate. Prevention of cancer with anti-oxidants is a whole other story. Anti-oxidants reduce free radical damage to DNA so they are potentially useful in the prevention of cancer.

Cancer Cachexia is a process whereby weight loss occurs even in the face of apparently adequate nutrient intake. Prolonged altered metabolism results in accelerated starvation, with muscle wasting, weight loss, weakness and lethargy. This can result in decreased response to therapy, decreased wound healing, immuno-incompetence, anaemia, shortened survival time and decreased quality of life. Gastro-intestinal and cardiovascular compromise can also occur with cancer cachexia. If nutritional needs are not met by adequate food intake, the body will steal what it needs from body reserves. The cause of cancer cachexia is not known.

Cancer Therapy

Besides the effects of cancer itself, various treatment modalities (chemotherapy, radiation, surgery) may affect nutritional status. Many patients are already debilitated before treatment commences. Anorexia is often a cause for euthanasia, and is a consequence of the cancer as well as the therapy. Surgery to the head/neck may alter normal eating mechanisms, so the animal can't voluntarily eat. GI surgery such as intestinal resection may result in malabsorption/malassimilation, with concomitant increased energy requirements. Radiation to the head and neck can cause an alteration to taste and smell, difficulty swallowing, and mucositis. Chemotherapy can cause anorexia, nausea, vomiting, mucositis, damage to GI cells and bone marrow (myelosuppression involving rapidly dividing cells), and organ damage e.g. cardiotoxicity, nephrotoxicity.

Concurrent diseases also need to be considered. Conditions such as pancreatitis/lipid disorder, severe diarrhoea, gastric outflow obstruction, and gut motility abnormalities may impact on the animal's ability to tolerate a high fat diet. High protein levels may be counter-productive in the presence of renal or hepatic insufficiency. Raw foods should not be fed– many infections in animals with cancer are from food borne pathogens.

The individual nutritional plan should include a thorough assessment of the patient including a dietary history. Body condition scores should be done with particular attention to muscle mass in cats. Body weight should be measured every visit, using a sensitive scale for cats. The effects of surgery and chemotherapy should be anticipated, and concurrent/historical medical disorders (kidney, liver, pancreatitis, coagulopathy) should be considered when formulating a nutritional plan. Voluntary food intake should be assessed on a regular basis, and owners should be taught how to monitor their pet's food intake daily, and how to watch for signs of wasting. Total caloric needs should be reviewed regularly. In order to maximise oral intake and improve acceptance of the cancer diet, any change of diet should occur gradually over 7-14 days. New diets should be avoided in hospital to prevent aversion. Offer small, frequent meals that have been warmed to increase palatability. Anti-emetics or appetite stimulants may sometimes be useful. The need for feeding tubes should be discussed early.

Summary of Key Nutritional Factors for Canine Cancer

	Suggested Levels DM %	Hill's Prescription Diet™ n/d™ Canine
Carbohydrate	< 25	19.9
Protein	25-40	38
Fat	30-45	33.2
Omega- 3 fatty acids	> 5	7.29
Arginine	> 2.5	2.95

Several commercial foods provide some key nutrients in appropriate levels, but still require supplementation with omega-3 FA and arginine. Only one (Hill's Prescription Diet™ n/d™ Canine) has been clinically proven to improve the longevity and quality of life of dogs with naturally occurring cancer⁹.

In summary, underlying metabolic abnormalities have been documented in dogs with different tumour types. Nutritional support should be an integral part of the therapeutic plan. It should augment cancer management and provide an extended good quality life for the patient.

References

1. Saker KE and Selting KA. Cancer. In Hand et al, editors. Small Animal Clinical Nutrition. 5th edn. Mark Morris Institute, Kansas, 2010: 587-607
2. Vail D.M. et al Alterations in Carbohydrate Metabolism in Canine Lymphoma. J Vet Intern Med 1990; 4:8-11
3. Vail D.M et al Exacerbation of Hyperlactaemia by Infusion of Lactated Ringer's Solution in Dogs with Lymphoma. J Vet Intern Med 1990; 4:228-232
4. Ogilvie G.K. et al. Effects of Chemotherapy and Remission on Carbohydrate Metabolism in Dogs with Lymphoma. Cancer 1992; 69:233-238
5. Ogilvie G.K et al. Alterations in Carbohydrate Metabolism in Dogs with Nonhaematopoietic Malignancies. Am J Clin Res. 1997;58:277-281
6. Anderson C.R. Effect of Fish oil and Arginine on Acute Effects of Radiation Injury in Dogs with Nasal Tumours. Presented at the Veterinary Cancer Society/American College of Veterinary Radiology meeting, Chicago, Dec 1997
7. Mazzaferro E.M. et al. Metabolic alterations in dogs with osteosarcoma. Am J Vet Res 2001; 62:1234-1239
8. Ogilvie G.K. and Vail D.M. Advances in nutritional therapy for the cancer patient. Veterinary Clinics of North America: Small Animal Practice 1990; 20: 969-985
9. Ogilvie G. K. et al. Effect of fish oil, arginine and doxorubicin chemotherapy on remission and survival in dogs with lymphoma: a double blind, randomized, placebo-controlled study. Cancer, 88:1916-2000
10. Gleissman H. Omega-3 fatty acids in cancer, the protectors of good and the killers of evil? Experimental Cell Research 316, 2010;1365-1373
11. Saker K.E. et al. Manipulation of Dietary (n-6) and (n-3) Fatty Acids Alters Platelet Function in Cats. J Nutr. 128 1998. 2645S-2647S, 1998