Feeding patients with cancer: theory and practice

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The idea that a patient's outcome and quality of life could be influenced by their diet is hardly new and is almost axiomatic to most owners. However, the mechanisms by which diet might positively affect veterinary patients with cancer are poorly understood, and the efficacy in clinical patients barely studied at all. Nonetheless, owners and veterinarians alike, are interested in the possibilities, and there is a large amount of material available to owners, promoting a wide range of almost entirely unproven approaches, frequently accompanied by implausible claims (Heinze *et al.* 2012). In response, at least a quarter of owners will change their pet's diet in response to a cancer diagnosis (Rajagopaul *et al.* 2016). A holistic view of the nutritional aspects of cancer would not be complete without considering the mechanisms by which diet can both increase and decrease the risk of neoplasia. However, this talk is narrower, and will focus on the effect of diet once a cancer diagnosis has been made.

Tumour cell metabolism

In the early 20th Century, the biochemist Otto Warburg discovered that the majority of tumours (he assumed *all* tumours) produce ATP by anaerobic glycolysis (Warburg *et al.* 1927). Warburg noticed that, even when both oxygen and other fuels are available, tumour cells will predominantly, almost exclusively oxidise glucose to pyruvate, and then release lactate into the surrounding interstitium. This observation, which has been named the "Warburg effect", can be explained mechanistically, and causally.

Warburg postulated that the tumour cell mitochondria were defective, meaning that the cells had a metabolic requirement for anaerobic glycolysis. However, it has been shown that some tumours with the Warburg phenotype have mitochondria that can still process acetyl-CoA through the TCA cycle, and the electron transport chain is still functional and capable of utilising the NADH and FADH produced by the TCA cycle to synthesize ATP. So, although some tumours do have mutations in mitochondrial genes, not all do (Kozal *et al.* 2021). The adaptations that define the Warburg phenotype serve to increase the capacity for anaerobic glycolysis, and compensate for the lower efficiency of ATP production per molecule of glucose (Figure 1).

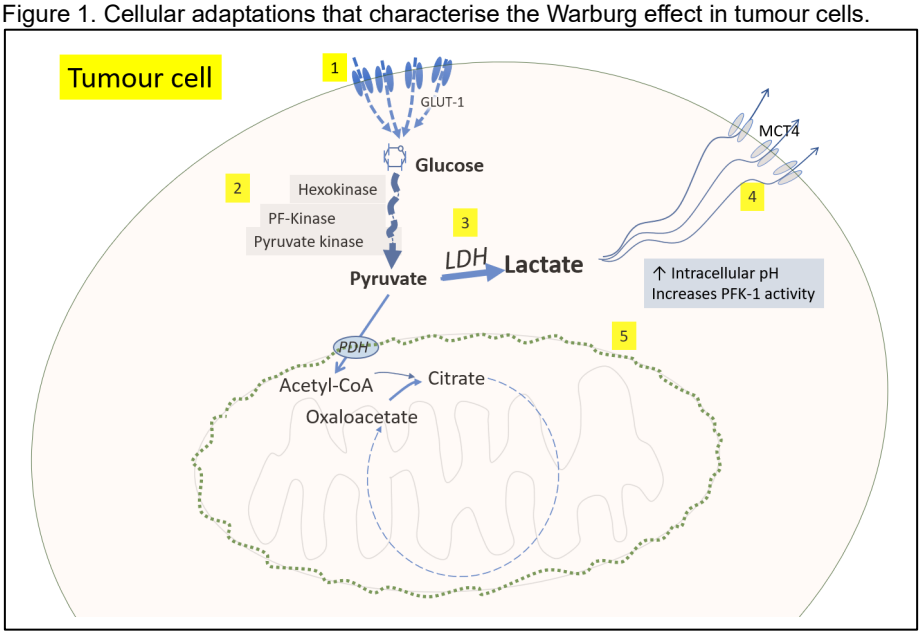
The first adaptation is the increased expression of cell-membrane glucose transporters (GLUT-1), which greatly increases the rate of glucose uptake. Next, the critical, rate limiting enzymes of glycolysis (hexokinase, PF-kinase, pyruvate kinase) are expressed in greater amounts. Then, to allow increased disposal of pyruvate, lactate dehydrogenase is over-expressed, leading to the increased production of lactate, which is exported efficiently from the cells through increased expression of the lactate transporter (MCT-4).

Finally, as stated above, some tumour cells do have mutations in mitochondrial genes, such as TCA cycle enzymes, particularly succinate dehydrogenase.

In addition, lactate normally circulates at levels of 1-2mm, but rises to 30-40mm in the tumour microenvironment (Santos *et al,* 2019). High lactate is an immunosuppressive and contributes to immune evasion by tumours.

Despite the shift towards anaerobic glycolysis, the tumour mitochondria are still metabolically active. The TCA cycle continues at a slower rate, and in part, by utilising amino acids, predominantly glutamine and glutamate. This dependence on glutamine, in particular, is referred to as the "glutamine addiction", and is the principle basis for the action of the enzyme asparaginase which, despite its name, hydrolyses glutamine and reduces the availability to dependant tumour cells (Chan *et al.* 2019).

Figure 1. Cellular adaptations that characterise the Warburg effect in tumour cells.



Importantly, not all tumours exhibit the Warburg phenotype. Some tumour cells can increase the rate of mitochondrial oxidative phosphorylation when glucose is limiting, and those cell types would not be expected to be clinically responsive to carbohydrate restriction. The oxygen availability of the environment in which the tumour initially develops appears to influence the phenotype. In rodent tumour-transplant models, oxidative phosphorylation is higher in tumours transplanted subcutaneously than those transplanted into the peritoneum. In addition, tumours vary in the degree of mitochondrial dysfunction. Some, such as those with succinate dehydrogenase mutations, have very little capacity for oxidative phosphorylation, whereas others appear fully functional. Thus, the Warburg phenotype may be present in the large majority but is not a universal feature of tumours (Martins Pinto *et al.* 2023).

Explanatory reasons for metabolic pathways risk teleology, just-so stories, or suggest tumour sentience and malignant intent. However, tumour cells are subject to evolutionary pressure in much the same way that whole organisms are. As such, cellular differences in tumours can be adaptations as much as causal oncogenic determinants.

Both normal and tumour cells respond to low oxygen availability by increasing their capacity for anaerobic glycolysis. In both types of cells, that includes up-regulation of the gamut of enzymes and transporters that characterise the Warburg phenotype. Similarly, in both cell types it is the same intracellular protein and transcription factor – hypoxia-inducible factor 1-α (HIF-1α) – that senses the low oxygen concentration and modulates the change in gene expression in response. The microenvironment within and around solid tumours is generally relatively hypoxic, and HIF-1α is essential for tumour adaptation and growth and is central to the development of the Warburg phenotype(Mathew *et al.* 2024). And in a positive feedback loop, intracellular lactate inhibits the normal degradation of HIF-1α, thus exaggerating the effect. Lastly, fumarate and succinate accumulate with succinate dehydrogenase mutations, and in high

intracellular concentrations, they activate HIF-1α. Unsurprisingly then, inhibitors of HIF-1α are a new type of chemotherapeutic adjuvants.

Glucose is not simply utilised for ATP production. In fact, the ATP requirement for cell division is less than that for the G0, or resting phase, and thus the high demand by tumour cells is only in part explained by glycolysis. Other uses of glucose include:

- Generation of NADPH through the pentose phosphate pathway (PPP) to regenerate glutathione for defence against the increased oxidative stress.
- Synthesis of dispensable amino acids such as serine
- Synthesis of ribose (through the PPP)

Insulin-mediated cell growth

We often think of insulin's actions very narrowly, considering only liver, muscle, and adipose tissue. However, we should remember that all mammalian cell types express insulin receptors, even erythrocytes, and insulin is a master regulator of cell growth. Hyperinsulinaemia is a risk factor for neoplasia, and the prognosis for cancer is increased reduced in type-2 diabetes. Several proteins activated by the insulin signalling pathway are prominent oncogenes, and the intensity of expression of the insulin receptor is negatively associated with survival in several tumour types in humans (Chen *et al.* 2023).

The combination of peripheral insulin resistance and genetic susceptibility can explain a significant proportion of the development of some prominent tumours in humans. Once developed, hyperinsulinaemia and hyperglycaemia increase tumour replication, increase the rate of metastasis, and worsen the prognosis.

Limiting glucose availability

We can see that tumour cells may have a metabolic dependence on glucose availability, that increased lactate production may be beneficial for immune-evasion, and exaggerated insulin signalling may be integral in growth and metastasis. Therefore, there are several reasons for wanting to limit glucose availability in cancer patients.

The growth of cell types with the Warburg phenotype can be inhibited profoundly *in vitro* by either depriving them of glucose, or inhibiting glycolysis. As well as growth inhibition, the sensitivity to some chemotherapy drugs is increased – especially drugs that act through the generation of free-radicals such as the anthracycline agents (doxorubicin and danorubicin). But given the physiological mechanisms to prevent hypoglycaemia, through glucagon, cortisol, and adrenaline, can interstitial glucose be limited sufficiently to have an effect on tumour growth *in vivo*?

The answer is "yes". Unlike humans, neither dogs nor cats require dietary digestible carbohydrate, and can safely be fed carbohydrate-free diets. When dogs are fed diets with negligible amounts of digestible carbohydrate, interstitial glucose concentrations drop by 25%, without any impairment in the ability to exercise (Gal and Cave). Perhaps as importantly, insulin production is decreased. When combined with intermittent fasting, serum glucose and insulin are both significantly decreased relative to dogs fed conventional carbohydrate containing diets twice daily (Leung *et al.* 2019).

Ketones and cancer

It has long been known that ketones can produce a survival benefit in cancer. In mice with induced colonic adenocarcinoma, even small tumours produce a dramatic cachexia and weight loss, without a reduced loss of appetite. Exogenous insulin and βOHB both reduce with loss in

that model, however whilst the insulin administration predictably accelerates tumour growth, βOHB administration caused a reduction in the tumour mass (Tisdale and Beck 1990).

Once thought of as metabolic toxins, it is clear that ketones are essential fuel for neurons during prolonged fasting and are important metabolic signalling molecules. β-OHB, can influence a wide range of cells through several mechanisms:

- Activation of the HCAR2 receptors
- Activation of FFAR2 receptors
- Direct, and indirect inhibition of histone deacetylases, and provision of substrate for acetylation.

Of importance in cancer, is that β-OHB can inhibit class-1 histone deacetylases (Shimazu *et al.* 2013). Inhibition of deacetylases results in increased histone acetylation, and a more open chromatin structure that allows the expression of many more genes than otherwise was possible. This can increase the rate of cell-cycle arrest and apoptosis in tumour cells and increases the expression of molecules on the cell surface that increase susceptibility to T-cell mediated cytotoxicity. The net result in susceptible tumours is inhibition of tumour growth, increases susceptibility to chemotherapy and enhanced immune-mediated clearance.

There are many studies of the use of ketogenic diets in rodent cancer models, and most, though not all, show that the diet alone can be a potent therapy, reviewed in Weber *et al.* 2020. In almost 70% of properly controlled preclinical studies, rodents fed ketogenic diets experience delays in tumourigenesis, slowed tumour growth, prolonged the survival rates, and reduced or reversed cachexia. In addition, ketogenic diets appear to sensitise tumour cells to chemotherapy, reduce chemoresistance, and increase the efficacy of radiation.

Importantly, while the overall conclusion is the efficacy in rodent models, there is heterogeneity in the response between different tumours. Approximately 20% of studies have shown little to no effect, and up to 10% of studies suggested *pro*-tumour action. For example, in one study of melanoma in mice, cell proliferation was increased, and in a mouse model of renal cell carcinoma, mice fed the ketogenic diet exhibited marked weight loss and an undefined hepatopathy (Vidali *et al.* 2017, Xia *et al.* 2017).

There are very few randomised controlled clinical trials of the efficacy of ketogenic diets in human patients, although there are many case reports, case series, and pilot or feasibility studies. However, the available evidence to date supports antitumour effects in humans with some types of cancer, as well as some positive metabolic effects in cases of cachexia. Ketogenesis can be initiated with intermittent fasting, and enhanced through feeding high fat, minimal digestible carbohydrate diets. When medium chain fatty acids (C8 to C12) are fed, they are absorbed through the portal veins, and enter the liver, unlike other fatty acids. As a result, they enter the hepatic mitochondria and induce the formation of ketone bodies, even in the fed state. Thus, the ideal ketogenic diet is free of carbohydrate, high in fat, and contains a significant content of medium chain triglycerides (at least 10% of total calories).

Specific dietary components

Antioxidants

Owners of animals with cancer should be discouraged from enriching diets with antioxidants. Several chemotherapy agents and radiation act, in part, through the generation of free-radicals which induce irreversible damage to DNA, proteins and lipids of cells. Enriching the diet with antioxidants has no benefit during treatment and may actually reduce the efficacy of therapy. Use of any antioxidant supplement (vitamins A, C, and E; carotenoids;coenzyme Q10) both

before and during treatment was associated with an increased hazard of recurrence and, to a lesser extent, death, in women treated for breast carcinoma (Ambrosone *et al.* 2020).

n-3 PUFA

Several epidemiological studies have suggested that the long chain n-3 PUFA DHA and EPA reduce the incidence of some types of cancer, enhance the efficacy of chemotherapy, and improve median survival times (Sahye-Pudaruth and Ma 2023). Some tumour cells have an increased uptake of free fatty acids, through increased expression of fatty-acid transport and binding proteins, and it can result in the development of cytosolic lipid droplets. When DHA and EPA accumulate, they are susceptible to oxidative damage, and can sensitise the cell to chemotherapy-induced free-radical damage.

One of the principal mechanisms is through inhibition of the production of PGE_2, which is why carcinomas appear to be more sensitive to the effects. However, not all carcinomas are dependent on PGE_2 production, and the replication of many other tumour types is completely independent. In fact, when all tumour types are considered, meta-analysis does not detect an overall effect (Zhang *et al.* 2014). Thus, whilst a diet rich in n-3 PUFA reduces the incidence of some types of cancer, and there may be some tumours that are sensitive to the effects of supplementation once developed, in humans at least, there is no generalised anti-tumour effect in patients with cancer.

However, n-3 PUFAs have been widely used to improve cancer-related complications such as cachexia, pain, depression, and some paraneoplastic syndromes. A reduction in the inflammatory response to a tumour can be beneficial in the advanced stages, and both EPA and DHA reduce muscle loss in cachexia, and improve quality of life and survival in a subset of patients (Jin *et al.* 2022). Since veterinary patients do not tend to be maintained through stages of advanced cachexia, it is uncertain what beneficial effect supplementation may have.

Gastrointestinal side effects

In methotrexate-induced enteritis, feeding a complex diet abrogated the proximal small intestinal atrophy and bacterial translocation associated with feeding an amino acid-based purified diet, and was associated with a marked attenuation of the clinical signs associated with the toxicity (Marks *et al.* 1997, Marks *et al.* 1999). Cats that were fed a complex diet did not vomit when given a toxic dose of methotrexate, whilst cats fed a purified diet did vomit.

It is now known what type or amount of fibre might alter the susceptibility to chemotherapy-induced enteropathy in dogs and cats. It is extremely likely that fermentable fibre will be both protective, help speed recovery, and reduce bacterial translocation, as it does in rodent models (Gallotti *et al.* 2021). However, it is possible that non-fermentable fibre, might exacerbate or even predispose to injury, as it does in dogs and cats with NSAID-induced enteropathy (Satoh *et al.* 2009, Satoh *et al.* 2016) .

Feeding patients

As with any other disease state, a non-negotiable prerequisite is to feed a complete and balanced diet. We should dissuade owners from excessive supplementation of balanced diets with single ingredients, unnecessary supplements, or treats. Always start with the premise that whatever the long diet is, it should meet their daily requirements.

Whilst some patients do not have altered appetite, many have pronounced appetite suppression, and like humans, some may have altered taste and odour perception, as the result of the disease,

and the chemotherapy. In humans, alterations in perception are common, and are strongly associated with poor intake, weight loss, and hence poorer outcomes (Drareni *et al.* 2019). The recommendation to feed "highly palatable diets", seems sensible, but is essentially vapid, as attending veterinarians have no means to compare or measure palatability in general, and certainly not in an individual, other than by trial and error. However, we can attend to measures to prevent learned taste aversions, utilise the normal means of increasing palatability, and be attentive to weight loss and intervene early.

"The cancer diet"

It should be clear that there could be no one dietary type that would be suitable for all patients with cancer. In many cases, high quality maintenance diets are sufficient. Higher fat and protein contents may be beneficial when intake is low, such as growth or performance diets.

Recently, a RCT comparing a high-protein diet, supplemented with extra fibre and n-3 PUFA found that several measures of QoL, as assessed by owners, were improved by eight weeks of feeding the test diet.(Heinze *et al.* 2024) Although there were no differences in the rates of adverse events, nor in appetite or body condition score changes, and the trial was not long enough, nor designed to detect an effect on chemotherapy outcome, it is interesting several owner-identified parameters were improved. Only one study has evaluated an effect of diet on survival, which compared two high fat diets (57% fat, 27% protein, 15% carbohydrate as percentage ME) that differed only in the fat source (fish oil vs soybean oil) and arginine supplementation. The diets were fed to dogs treated with a CHOP protocol for lymphoma, and dogs fed the n-3 enriched diet had a longer disease free interval (181 vs. 136 days) and survival times (318 vs. 227 days).(Ogilvie *et al.* 2000)

Home-prepared diets are frequently more palatable and more digestible than commercial diets and have the advantage that they can be formulated using ingredients that the patient prefers and tailored to their particular needs. However, home-cooking is not for the faint-hearted or casually interested. Recipes for complete and balanced diets are often long, require specific supplements, and are not suitable for experimentation by the owners.

Predictably, I will always discuss nutrition with owners, and I find they are frequently, but not always interested in changing diets. For those owners most keen, I will recommend a home-prepared recipe, with the principle of *primum non nocere,* and a clear understanding of a lack of evidence. Dietary principles:

- No digestible carbohydrate. This will result in a relatively high fat, high protein diet. In patients with a reason to avoid high fat intake (e.g. hypertriglyceridaemia), or high protein intake (e.g. chronic kidney disease), this will be modified.
- Enriched with n-3 PUFA. I will aim for a ratio of linoleic acid+arachidonic acid: EPA+DHA of <0.5
- Source of MCT oil. This will be approximately 10% of calories.
- Rich in fermentable fibre, low in non-fermentable fibre. Purified fibre sources are easiest, such as wheat dextrin (Benefibre®). Gradual introduction, to a target of approximately 5% on a dry matter basis.
- Addition of extra palatants. This might be chicken or fish stock, Vegemite®, monosodium glutamate, or other stocks and broths.

At the moment, we have no controlled clinical trials of ketogenic diets in either cats or dogs with cancer. There is a case report of tumour regression following the introduction of restricted calorie, ketogenic diet to a dog with an unresectable facial mast cell tumour (Seyfried *et al.* 2023), and the author has had apparent success feeding ketogenic diets to cancer patients. However, it remains to be seen how effective such diets are in dogs and cats, what degree of

heterogeneity of response there will be, and whether there are certain tumour types, or certain patients, in which ketogenesis is harmful. Until proven otherwise, we should remain open to disappointment.

Conclusion

Most clients are interested in ways that they can participate in the treatment of their pet. Diet is the most common means by which they are motivated to do that. There is a desperate shortage of clinical trials evaluating *any* aspect of nutrition in feline and canine cancer patients. As with any other disease category, individualisation is critical, as actual nutritional and dietary requirements vary widely, and the patient's preference will often make the best intentions irrelevant. There is no evidence yet for a beneficial effect of ketogenic diets in dogs and cats with cancer, however, they have evolved consuming very low carbohydrate diets, have no physiological requirement, and there are very few cases where there is an argument for a benefit to including digestible carbohydrate.

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