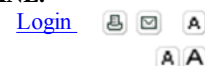




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Targeting energy metabolism in brain cancer through calorie restriction and the ketogenic diet

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> Abstract

Malignant brain tumors are a significant health problem in children and adults and are largely unmanageable. As a metabolic disorder involving the dysregulation of glycolysis and respiration (the Warburg effect), malignant brain cancer can be managed through changes in metabolic environment. In contrast to malignant brain tumors that are mostly dependent on glycolysis for energy, normal neurons and glia readily transition to ketone bodies (β-hydroxybutyrate) for energy in vivo when glucose levels are reduced. The transition from glucose to ketone bodies as a major energy source is an evolutionary conserved adaptation to food deprivation that permits the survival of normal cells during extreme shifts in nutritional environment. Only those cells with a flexible genome, honed through millions of years of environmental forcing and variability selection, can transition from one energy state to another. We propose a different approach to brain cancer management that exploits the metabolic flexibility of normal cells at the expense of the genetically defective and less metabolically flexible tumor cells. This approach to brain cancer management is supported from recent studies in orthotopic mouse brain tumor models and in human pediatric astrocytoma treated with calorie restriction and the ketogenic diet. Issues of implementation and use protocols are discussed.

Keywords: Angiogenesis, apoptosis, calorie restriction, glioma, inflammation, ketone bodies, metabolic control analysis, vascularity

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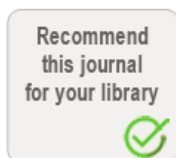


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Malignant brain cancer is a catastrophic disease of morbidity and mortality in adults and is the second leading cause of cancer death in children. [\[1\]](#),[\[2\]](#),[\[3\]](#),[\[4\]](#),[\[5\]](#),[\[6\]](#) Despite advances in imaging technologies, the standard therapies for malignant gliomas today are basically the same as they have been for over five decades and generally involve surgical resection followed by chemotherapy with or without radiation therapy. [\[2\]](#),[\[7\]](#),[\[8\]](#) While these therapies may manage glioma growth over a short term (weeks to months), they can facilitate glioma recurrence and enhance growth rate over the longer term. [\[9\]](#) Surgical resection induces wound-associated growth factor production, whereas radiation therapy produces oxidative tissue damage creating a microenvironment that facilitates aggressive tumor recurrence and formation of macrophage/tumor cell fusion hybrids. [\[9\]](#) Fusion hybrids are destabilized and invasive tumor cells representing the pinnacle of biological chaos. [\[9\]](#),[\[10\]](#),[\[11\]](#),[\[12\]](#) In view of the adverse biological consequences of conventional surgical and radiation therapies, it is remarkable that some glioblastoma patients can survive for as long as 2 years following these procedures. It is our opinion that the brain of glioma patients should rarely, be irradiated and that radiation therapy for brain cancer management does more harm than good. The calorically restricted ketogenic diet (CRKD, described below) will be more effective than radiation therapy for long-term brain cancer management and will not harm patients.

Conventional chemotherapy has faired little better than radiation therapy for the long-term management of malignant brain cancer. Brain tumor chemotherapy is often associated with severe adverse effects that diminish the length or quality of life. [\[8\]](#),[\[13\]](#) Indeed, bevacizumab and irinotecan therapy for malignant brain cancer management killed 6% of those taking the drug, while an additional 38% of patients had to discontinue the use due to toxicity issues. [\[13\]](#) Despite the severity of these adverse effects, the authors consider the response to this drug therapy superior to that of other available antiangiogenic drug therapies. Although temozolomide produced slight gains in glioblastoma patient survival, the absence of body weight controls in the original study makes it difficult to determine if these gains were primary effects of the drug or secondary effects of caloric restriction involving fatigue and weight loss. [\[14\]](#),[\[15\]](#) The therapeutic targeting of brain tumor-associated mutations, while conceptually appealing, may also be problematic as hundreds of mutations can be found in tumors and not all tumor cells express the same mutations. Targeted therapies suffer from the misconception that mutations cause cancer when, in fact, most tumor-associated mutations arise as epiphenomena of tumor progression, and their association with causality is far from clear. [\[9\]](#),[\[16\]](#),[\[17\]](#) Hence, new approaches are needed that can better manage malignant brain tumors while permitting a decent quality of life.

> Metabolic Control Theory/Analysis



Metabolic control analysis evaluates the degree of flux in metabolic pathways and can be used to analyze and treat complex diseases. [\[18\]](#),[\[19\]](#),[\[20\]](#),[\[21\]](#),[\[22\]](#),[\[23\]](#),[\[24\]](#),[\[25\]](#),[\[26\]](#) The approach is based on findings that compensatory genetic and biochemical pathways regulate the bioenergetic potential of cells and ultimately the phenotype. [\[27\]](#) As rate-controlling enzymatic steps in biochemical pathways are dependent on metabolic environment, the management of disease phenotype depends more on the flux of the entire system than on any specific metabolic step or metabolite. In other words, complex disease phenotypes can be managed through self-organizing networks that display system-wide dynamics involving glycolysis and respiration. [\[28\]](#) Global manipulations of these metabolic networks can restore orderly adaptive behavior of widely disordered states involving complex gene-environmental interactions. [\[29\]](#),[\[30\]](#),[\[31\]](#)

Abnormal energy metabolism and biological chaos characterize brain tumors. [\[9\]](#),[\[32\]](#),[\[33\]](#),[\[34\]](#) Consequently, the general principles of metabolic control analysis can be effective for brain cancer management. This hypothesis is based on differences in energy metabolism between normal cells and neoplastic brain cells. As long as brain tumors are provided a physiological environment conducive for their glycolytic energy needs, they will survive; when this environment is restricted or abruptly changed, they will be either growth arrested or perish. [\[28\]](#) In this report, we describe how diet therapies, which lower circulating glucose and elevate ketone bodies (acetoacetate and β -hydroxybutyrate, β -OHB), can target brain tumors while enhancing the metabolic efficiency of normal neurons and glia. The success of this therapeutic strategy is also based on the principles of evolutionary biology involving adaptability and variability selection.

> Adaptability and Variability Selection



According to Richard Potts, the evolutionary success of our species has been due largely to the inheritance of traits that bestowed adaptive versatility. [\[35\]](#),[\[36\]](#) These traits were honed over millions of years and enabled humans to adapt rapidly to abrupt changes in the physical environment. The adaptability to abrupt environmental change is a property of the genome, which was selected for in order to ensure survival under environmental extremes. This hypothesis can be extended to the individual cells of the organism, which exist as an integrated society of cells. The success of the organism in dealing with environmental stress and disease is therefore dependent on the integrated action of all cells in the organism. Further, this integrated action depends on the flexibility of each cell's genome, which must respond to both internal and external signals. Environmental forcing

has therefore selected for those genomes most capable of adapting to change in order to maintain homeostasis. [\[35\]](#),[\[36\]](#)

In contrast to normal cells, which readily adapt to environmental stress through integrated genetic modifications, tumor cells have lost their adaptability due to accumulated genetic mutations and genomic rearrangements. These genetic defects generally involve the inactivation of tumor suppressor genes and activation of oncogenes or aneuploidy. The widely held notion that tumor cells are somehow hardy or tough and resistant to death (programmed or nonprogrammed) is a gross misconception. [\[28\]](#) How can tumor cells that express multiple types and kinds of genetic mutations be more fit and hardy than normal cells that possess a flexible genome with adaptive versatility? Reduced genomic flexibility will increase susceptibility to environmental stress and the likelihood of cell death. Regardless of when or how genomic defects become involved in the initiation or progression of tumors, these defects can be exploited for the metabolic destruction or management of the tumor according to the principles of evolutionary biology and metabolic control analysis. [\[28\]](#) Our recent findings using calorie restricted diets, that produce energy stress, provide direct support for this hypothesis. [\[14\]](#),[\[29\]](#),[\[37\]](#),[\[38\]](#),[\[39\]](#)

> Energy Metabolism in Brain Tumors



While glucose is the preferred energy substrate of normal neurons and glia, these cells will metabolize ketone bodies (β -hydroxybutyrate and acetoacetate) for energy under fasting-induced reductions of blood glucose. This is a conserved physiological adaptation to prolonged food restriction and evolved to enhance survival and maintain adequate brain function while sparing proteins. [\[40\]](#),[\[41\]](#),[\[42\]](#),[\[43\]](#),[\[44\]](#),[\[45\]](#) In contrast to normal brain, which can oxidize either glucose or ketone bodies for energy, malignant brain tumors from either humans or animal models lack metabolic flexibility and are largely dependent on glucose for energy. [\[33\]](#),[\[39\]](#),[\[46\]](#),[\[47\]](#),[\[48\]](#),[\[49\]](#),[\[50\]](#),[\[51\]](#),[\[52\]](#),[\[53\]](#) Enhanced glycolysis produces excess lactic acid that can return to the tumor as glucose through the Cori cycle [More Details](#). [\[54\]](#) Although some neural tumors metabolize ketone bodies, this metabolism is largely for lipid synthesis rather than for energy production. [\[55\]](#),[\[56\]](#) Many brain tumors also have a reduced activity of succinyl-CoA: 3-ketoacid CoA transferase, the rate-controlling step for utilizing β -OHB as a respiratory fuel. [\[29\]](#),[\[57\]](#),[\[58\]](#),[\[59\]](#) Although glutamine may provide energy to some nonneural tumors, glutamine stimulates glycolysis in C6 rat glioma cells and may not serve as a direct respiratory fuel. [\[60\]](#) Considered together, these studies indicate that brain tumors either lack or have reduced capacity to metabolize β -OHB for energy and, like most malignant tumors, depend heavily on glycolysis for their metabolic energy.

In addition to glycolytic dependence, most tumors including brain tumors express abnormalities in the number and function of their mitochondria. [\[28\]](#),[\[50\]](#),[\[61\]](#) Such abnormalities would prevent the bioenergetic utilization of ketone bodies, which require functional mitochondria for oxidation. [\[62\]](#) Warburg originally emphasized that the high glycolytic rate of tumors resulted from diminished or disturbed respiration. [\[63\]](#),[\[64\]](#) While most cells die from damaged respiration, those cells that can enhance and modify their anaerobic glycolysis in response to respiratory damage will survive and form tumors. Later studies in a variety of neural and nonneural tumor systems showed that these respiratory disturbances could involve abnormalities in TCA cycle components, alterations in electron transport, and deficiencies in oxidative phosphorylation. [\[46\]](#),[\[65\]](#),[\[66\]](#),[\[67\]](#),[\[68\]](#) While mitochondrial DNA mutations might also diminish respiration, most described mutations are nonpathological and may result from methodological problems. [\[69\]](#),[\[70\]](#) Structural defects of the inner mitochondrial membrane, that would alter the proton motive gradient, could also prevent normal ATP production despite the appearance of oxidative metabolism, i.e., oxygen consumption and CO₂ production. [\[66\]](#),[\[71\]](#),[\[72\]](#) Uncoupled mitochondria could give the appearance of normal respiration. Considered together, these findings indicate that brain tumors suffer from reduced respiratory capacity coupled to an increased glycolysis and lactic acid production, i.e., the Warburg effect.

Although aerobic glycolysis characterizes many tumors, Warburg considered these phenomena too labile or too dependent on environmental conditions to be reliable indicators of tumor metabolism. [\[64\]](#) Rather, he emphasized the importance of defects in the coordination of glycolysis with respiration. The latency between tumor initiation and progression was considered the period necessary to disconnect respiration from glycolysis. Considerable effort is underway to explain the Warburg effect. [\[73\]](#),[\[74\]](#),[\[75\]](#),[\[76\]](#),[\[77\]](#),[\[78\]](#),[\[79\]](#),[\[80\]](#),[\[81\]](#),[\[82\]](#),[\[83\]](#),[\[84\]](#),[\[85\]](#),[\[86\]](#) Regardless of how the Warburg effect becomes established in tumor cells, a dependence on glucose for survival together with multiple types of mutations and mitochondrial defects makes most tumors vulnerable to management through principles of evolutionary biology and metabolic control analysis as we recently described. [\[28\]](#) Our recent studies with caloric restriction and the ketogenic diet provide support for this hypothesis. [\[14\]](#),[\[29\]](#)

Dietary energy metabolism and brain cancer

The ketogenic diet

In 1995, Nebeling and coworkers attempted the first nutritional metabolic therapy for human malignant brain cancer using the ketogenic diet. [\[87\]](#) The ketogenic diet (KD) is a high-fat low-carbohydrate diet that has been used for decades as an effective therapy for refractory seizures in children. [\[28\]](#),[\[88\]](#),[\[90\]](#) The objective of the study was to shift the prime substrate for energy metabolism from glucose to ketone bodies in order to disrupt tumor

metabolism while maintaining the nutritional status of patients. [87] The patients in this landmark clinical study included two female children with nonresectable advanced stage brain tumors (anaplastic astrocytoma stage IV and cerebellar astrocytoma stage III). A measurable tumor remained in both subjects following extensive radiation and chemotherapy. Although severe life-threatening adverse effects occurred from the radiation and chemotherapy, both children responded remarkably well to the KD and experienced long-term tumor management without further chemo- or radiation therapy. Indeed, one of the patients was still alive at the time of this writing (Nebeling, personal communication). Positron emission tomography with fluoro-deoxy-glucose (FDG-PET) also showed a 21.8% reduction in glucose uptake at the tumor site in both subjects on the KD. [87] These findings indicated that the calorically restricted diet, which lowered glucose and elevated ketone bodies, reduced glycolytic energy metabolism in these brain tumors. The KD is also most effective for seizure management when given in calorically restricted amounts. [31]

Despite the efficacy of this therapeutic approach together with the absence of adverse side effects, no further human studies or clinical trials have been conducted on the therapeutic efficacy of the calorie restricted ketogenic diet (CRKD) for brain cancer in either children or adults. The reason for this is not clear but appears to reflect a preference by the North America Brain Tumor Collaborative for using "hand-me-down" drug therapies from other cancer studies rather than exploring less costly and more effective alternative approaches. [8], [13] This is unfortunate as our recent findings in brain tumor animal models show that the therapeutic potential of the CRKD, involving reduced glucose and elevated b-OHB is likely to be greater than that for any current brain tumor therapy. [14], [29] Moreover, the CRKD would eliminate or greatly reduce the need for adjuvant anticonvulsant and steroidal medications for brain tumor patients as the CRKD was designed as an antiepileptic therapy and, when administered in restricted amounts, will naturally elevate circulating glucocorticoid levels. [88], [90], [91], [92], [93], [94] These findings indicate that the CRKD would be an effective multifactorial diet therapy for malignant brain cancer and should be considered seriously as a therapeutic option. [28], [29]

Dietary energy restriction

We recently confirmed the findings of the Nebeling group in a series of orthotopic mouse brain tumor models treated with the CRKD and dietary energy restriction [14], [29], [37], [38], [39] [Figure 1]. As with the KD, dietary restriction (DR) reduces glucose and elevates ketone bodies. [30], [31] The DR-induced inhibition of brain tumor growth is directly correlated with reduced levels of glucose and elevated levels of ketone bodies. [39] The gradual transition from glucose to ketone bodies as an energy source is the key to the long-term management of brain tumors. DR is produced from a total restriction of dietary nutrients and differs from starvation in that DR reduces total caloric energy intake without causing anorexia or malnutrition. [20], [95], [96], [97], [98], [99] As a natural dietary therapy, DR improves health, prevents tumor formation, and reduces inflammation. [20], [97], [100], [101], [102], [103]

Previous studies showed that the antitumor effects of DR result from caloric restriction *per se* and not from the restriction of any specific dietary component such as proteins, vitamins, minerals, fats, or carbohydrates. [39], [98], [99], [104] Calorie restriction, that lowers glucose and elevates ketone bodies, [30], [31] improves the mitochondrial respiratory function and glutathione redox state in normal cells. [105], [106] Ketone bodies can also protect normal neurons and glia from damage associated with aggressive tumor growth through a variety of neuroprotective mechanisms. [43], [62], [107], [108], [109], [110], [111] Although elevated ketone bodies are often associated with diabetic states, ketone body elevation in people with normal physiology is considered "good medicine" and therapeutic for a broad range of neurological and neurodegenerative diseases. [23], [41], [43], [112] Thus, DR naturally inhibits glycolysis and tumor growth by lowering glucose while, at the same time, enhancing the health and vitality of normal cells and tissues through ketone body metabolism.

Dietary restriction is antiangiogenic and proapoptotic

Rous first suggested in 1914 that DR might inhibit tumor growth by delaying tumor vascularity (angiogenesis) from the host. [113] Angiogenesis involves neovascularization or the formation of new capillaries from existing blood vessels and is associated with the processes of tissue inflammation, wound healing, and tumorigenesis. [114], [115], [116] A significant literature suggests that vascularity is rate limiting for the formation of solid tumors, including brain tumors. [117], [118], [119], [120] The malignancy and invasiveness of brain tumors is also correlated with the degree of their vascularity since prognosis is generally better for tumors that are less vascular than for those that are more vascular. [117], [121], [122] The inhibition of vascularity is therefore considered an important therapeutic strategy for managing brain tumors. [13], [123], [124], [125] The challenge is to target tumor angiogenesis without harming patients or reducing the quality of life.

We recently corroborated the Rous hypothesis in our mouse and human brain tumor models by showing that DR is antiangiogenic [Figure 2]. DR also reduces angiogenesis in prostate and breast cancer. [104], [126] As DR targets brain tumor angiogenesis naturally, while also enhancing the health and vitality of normal brain cells, we suggest that the antiangiogenic effects of DR or CRKDs will be greater than that of any known antiangiogenic drug therapy for brain tumors including those involving metronomic applications. [14], [29], [38] Clinical trials with glioblastoma patients could support our hypothesis.

Our findings with mouse brain tumor models show that the antiangiogenic effects of DR arise from reduced tumor energy metabolism due to DR. This is important since the angiogenic properties of most human gliomas are

closely linked to the metabolic activity. [\[127\]](#) DR or therapeutic fasting can also reduce cerebral blood flow and oxygen consumption that would further stress brain tumor cells already weakened from reduced glucose levels. [\[41\]](#) Besides reducing angiogenesis, DR also significantly increases brain tumor apoptosis. [\[37\],\[38\]](#) This was associated with enhanced caspase-3 activation and poly(ADP-ribose) polymerase cleavage in mouse brain tumors. The proapoptotic effects of DR occur in large part from reduced glycolytic energy that most tumors rely upon for growth. [\[52\],\[128\]](#) This could kill tumor cells by depleting available energy or by creating oxidative stress through glucose deprivation. [\[28\],\[129\]](#)

Reduced glycolytic energy would also reduce lactate levels. This is important since lactate can enhance tumor inflammation. [\[130\],\[131\],\[132\],\[133\]](#) Previous studies show that DR also reduces inflammation and the inflammatory properties of macrophages, while enhancing their phagocytic activities. [\[102\],\[134\],\[135\]](#) An uncoupling of the detrimental inflammatory properties of tumor-associated macrophages from their beneficial phagocytic properties (to remove tumor cell corpses) is considered essential for the eventual management of brain cancer. [\[9\]](#) Hence diet therapies, which lower glucose availability and elevate ketone bodies, can reduce brain tumor growth through integrated anti-inflammatory, antiangiogenic, and proapoptotic mechanisms.

> Complicating Issues for Implementing Diet Therapy for Malignant Brain Cancer



Several complicating issues can arise in attempting to implement calorically restricted diets for brain cancer management. The first issue is the nonconventional and nonpharmacological nature of the diet therapy. Modern medicine does not look favorably on diet therapies for complex diseases especially when well-established parameters for acceptable clinical practice are available, regardless of their poor efficacy. In the case of brain cancer management, these approved practices generally involve surgical resection followed a few weeks later by either radiation therapy or radiation and chemotherapy. The type of therapy will usually depend on the age and health status of the patient. However, the number of older GBM patients who are either offered no therapy or who choose no therapy appears to be increasing. [\[3\]](#) On the other hand, a significant neurological damage often occurs in those children who survive malignant brain cancer. [\[136\],\[137\],\[138\],\[139\]](#) These situations are unacceptable and highlight the inadequacies of conventional approaches to malignant brain cancer management in adults or children. Indeed, healthy long-term survivors of these conventional practices are generally the exception rather than the rule.

Despite this bleak situation, the brain tumor field continues with clinical trials using new combinations of radiation and toxic drug therapies in the hope of finding a therapeutic approach with an improved efficacy. More than 50 years of research, however, indicates that such approaches are largely ineffective in extending survival or improving quality of life. It is our opinion that therapeutic approaches to brain cancer management, which produce adverse effects and reduce quality of life, should not be pursued, especially when more effective and less toxic alternative therapies are available. As most brain cancer therapies are highly toxic to cells and tissues, toxicity has become the norm rather than the exception for new cancer therapies. The problem is in recognizing the existence and scientific basis for effective, nontoxic, alternative dietary approaches and whether these approaches can become part of the standard clinical practice in the field.

A second issue in implementing calorically restricted diets for brain cancer management is the simplicity of action. How can the process of simply lowering blood glucose while elevating ketone bodies through DR be so effective in managing malignant brain cancer? The simplicity of action is based on the Warburg effect, a well-established scientific fact which makes tumor cells dependent on glucose metabolism for their survival and reduces the tumor cell's ability to use ketone bodies as an alternative metabolic fuel. [\[29\]](#) How can a diet therapy, which reduces food intake and body weight, be recommended to patients who are already losing body weight because of cancer cachexia? By killing glycolytically active tumor cells, the diet therapies will reduce tumor cachexia, which depends on the release of cachexia-enhancing molecules from the tumor cells. [\[39\],\[54\]](#) In contrast to most conventional brain tumor therapies, which indiscriminately target both normal cells and tumor cells, DR and particularly CRKD are the only known therapies that can target brain tumor cells while enhancing the health and vitality of normal brain cells. [\[28\],\[29\],\[87\]](#) In this regard, calorie restricted diet therapies are superior in concept and efficacy to all current conventional brain cancer therapies. Support for our position on this issue can be established through randomized controlled trials.

A third difficulty with calorically restricted diets for brain cancer management is the lack of a standardized use protocol. In other words, how is the diet implemented? This is a legitimate concern, which hinders applicability to a broad range of patients. Similar concerns are often raised for implementing the ketogenic diet as a therapy for epilepsy. Fortunately, several medical groups have established protocols and menus for implementing the ketogenic diet or low glycemic diets in children. [\[140\],\[141\]](#) Clinicians could adapt these protocols and menus for their brain cancer patients. Nebeling and Lerner also provided a protocol for using the medium-chain triglyceride ketogenic diet for brain cancer management. [\[142\]](#) Since most reasonably healthy adults can tolerate more DR than children, adults have greater flexibility than children in using calorically restricted diet therapies for brain cancer management.

> Guidelines for Implementing Dietary Management of Malignant Brain Cancer



We suggest a sequential series of therapeutic phases for the dietary management of malignant brain cancer. Phase I would gradually lower circulating glucose levels and elevate circulating β -OHB levels over several weeks using CRKDs or therapeutic fasting. [\[29\]](#),[\[112\]](#) Blood glucose ranges between 3.0 and 3.5 mM (55-65mg/dl) and β -OHB ranges between 4 and 7 mM should be effective for tumor management. These values are well within normal physiological ranges of glucose and ketones and will have antiangiogenic and proapoptotic effects causing metabolic isolation and a significant growth arrest. The importance of maintaining low blood glucose levels cannot be overemphasized. Caloric restriction provides an effective means to maintain low blood glucose levels. Consequently, the diet therapy will require considerable personal discipline, as water-only fasting will occasionally be required to lower glucose and elevate ketone bodies. The CRKD can reduce the feeling of hunger while maintaining low glucose and elevated ketone body levels. Glucose levels can be monitored several times/day with any standard glucose-meter, while blood ketone levels can be monitored once/week with either a ketone-meter or with an enzyme assay as we described. [\[30\]](#) A clinical chemistry laboratory would be needed to measure blood ketone levels using the enzyme assay. It is better to measure ketone levels in blood than in urine, as urine values may not reflect ketone body availability for energy. It is imperative that daily records be kept of the blood glucose levels and weekly records for ketone measurements. Brain tumor imaging analysis can be used to assess the efficacy of the diet therapy in tumor progression. [\[143\]](#) Tumor imaging using PET may be a problem, however, especially if the diet reduces glucose uptake. This would actually be a favorable outcome and suggestive of diet efficacy. Additionally, CRKDs would eliminate the need for antiepileptic drugs or steroidal medications for reasons described above. The use of steroids is not recommended during diet therapy as steroids can increase blood glucose values, which would contribute to tumor recurrence.

Phase II of the therapy would involve surgical resection. We suggest surgical resection as an option after first implementing the diet therapy. The diet should halt progression and more clearly delineate tumor tissue from surrounding normal brain tissue. Neurosurgeons should recognize that smaller brain tumors with reduced vascularity and clearly circumscribed boundaries should be easier to resect than larger brain tumors with poorly circumscribed boundaries and extensive vascularization. This would also insure greater debulking thereby increasing the likelihood long-term survival. The diet therapy could also be continued following surgery to facilitate healing and to maintain metabolic pressure on any surviving tumor cells.

Finally, phase III could involve carefully executed weight cycling strategies to maintain metabolic pressure on surviving tumor cells. [\[28\]](#),[\[144\]](#) Weight cycling for humans could include weekly transitions from ketogenic diets to nutritious low-calorie, low glycemic diets. While several investigators have suggested using glycolysis inhibitors to target tumor energy metabolism, these inhibitors will target glycolysis in both tumor cells and normal cells, thus potentially producing adverse effects. [\[85\]](#),[\[145\]](#),[\[146\]](#),[\[147\]](#),[\[148\]](#),[\[149\]](#),[\[150\]](#) An interesting therapeutic strategy could also involve low doses of glycolysis inhibitors combined with the CRKD. With this approach, ketone bodies could protect normal cells from the adverse effects of low glucose while more effectively targeting the energy metabolism of the tumor cells. Studies are in progress to examine this possibility.





> Conclusions

We provide information on a new, alternative approach to brain cancer management using calorically restricted diets. The objective of this new therapeutic approach is to change the metabolic environment of the tumor and the host. Only those cells with a normal flexible genome, honed through millions of years of environmental forcing and variability selection, are expected to survive extreme shifts in metabolic environment. [\[28\]](#) Indeed, extreme conditions of survival and fitness will test the limits of a cell population's persistence in any given location over time. [\[35\]](#),[\[36\]](#) In other words, it is the theory of Potts applied with sustained pressure to the entire population of normal and neoplastic brain cells. This therapeutic approach, illustrated with calorically restricted diets, will be more efficacious than current approaches for brain cancer management because it is based on the principles of evolutionary biology and metabolic control theory.

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Figures

[\[Figure 1\]](#), [\[Figure 2\]](#)

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