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SSNC GESKES
Société Suisse de Nutrition Clinique
Gesellschaft für Klinische Ernährung der Schweiz
Società Svizzera della Nutrizione Clinica

Berner Symposium Ernährungsmedizin und GESKES-Zertifikatskurs

Onkologie: Ernährung im multimodalen Therapiekonzept – Nebensache oder doch mehr?

Federico Bozzetti

Do we feed the patient or the tumour?

Do we feed the patient or the tumour?

- which substrates does the tumor utilize and consequently is there a regimen which potentially privileges the host *vs* the tumor?
- does a nutritional intervention (normocaloric *vs* restricted diet) disproportionally affect the tumor growth?

just a premise

- The effects of feeding on the cancer cells may be measured in different ways: change of some proliferation markers or of the tumor mass or of the clinical outcome which are sometimes conflicting
- studies on tumor growth in cell cultures or animals are not always transferable to humans:
  - many experimental tumors grow about 0.6 mm/day and after 1 month tumor mass can account for 10-20% of the weight of the host
  - on the contrary most of the cancer patients die with cachexia when tumor burden is only 0.1% of the body weight
  - in many experiments, in contrast with clinical settings, nutritional modulation may last for ≈2/3 of the life span of the animal

TOPICS

- Few historical and biological musings
- Nutrients consumption by human tumors *in vivo*
- Effects of the nutritional status, of calorie restriction or nutrients administration (compared with baseline postabsorbitive status or no-PN controls) on tumor growth in cancer patients
- Biological and clinical effects of Ketogenic diets
- Effects of dietary restriction during the oncologic therapy
- Conclusions

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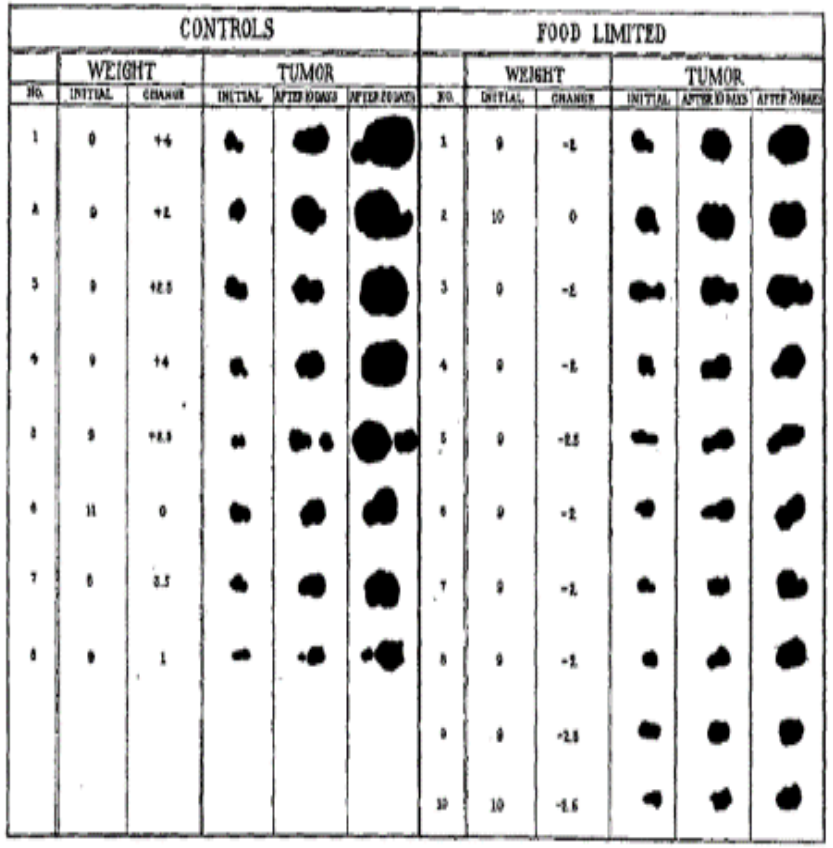
Calorie restriction to control the tumour growth

In 1914, P Rous first suggested that restricted food intake decreased tumour growth.

10 years later O Warburg observing that normal cells produce energy in the mitochondria and cancer cells produce energy in the cytosol, hypothesized that mitochondria were significantly impaired in cancer cells. He discovered the anaerobic glycolysis of cancer cells that is shifting energy derivation away from mitochondrial oxidative phosphorylation (*J Gen Physiol 1927;8:519-30*)



From P Rous, *J Exp Med 1914;20:433-51*

Locasale and Cantley *BMC Biology* 2010, 8:88
http://www.biomedcentral.com/1741-7007/8/88

BMC Biology
incorporating Journal of Biology

COMMENTARY Open Access

Altered metabolism in cancer

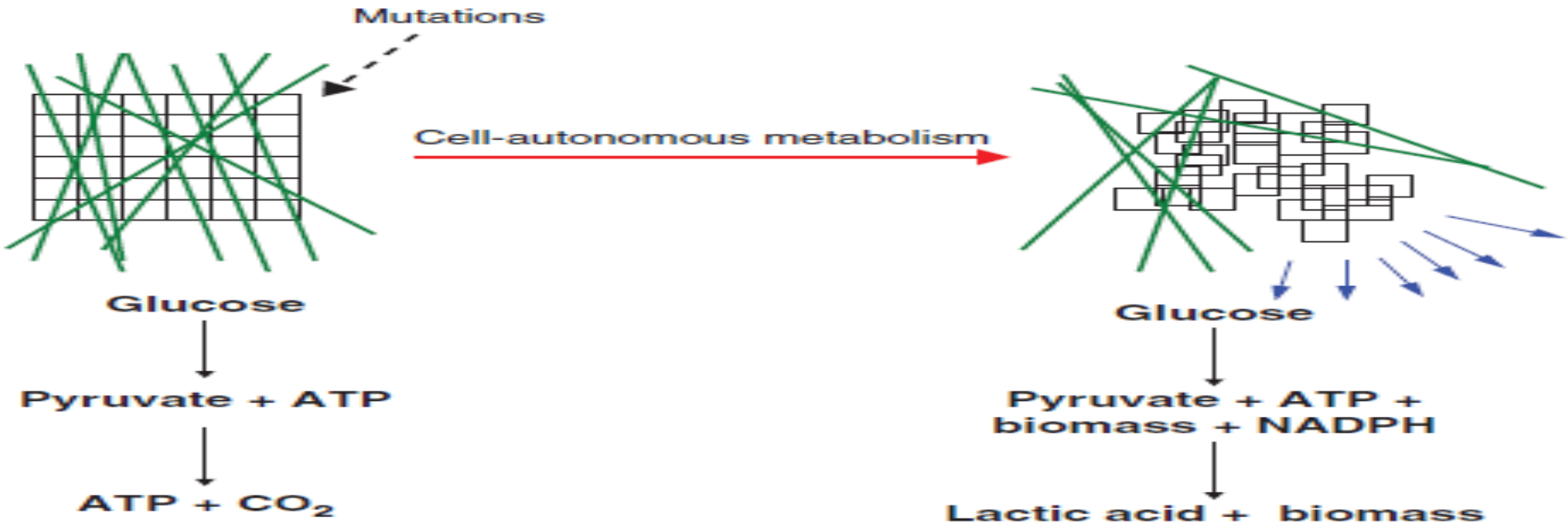


Figure 1. Cell-autonomous control of growth and metabolism are acquired upon cell transformation by mutation. Cells in a normal tissue (left-hand diagram) are constrained in their growth by their environment (depicted as green lines). During the development of a tumor (right-hand diagram), cells acquire mutations that allow growth outside the context of normal tissue development. As a result, metabolic pathways are reorganized and metabolism is altered to allow for cell-autonomous growth.

CHARACTERISTICS AND METABOLIC ADVANTAGES OF CANCER CELL AEROBIC GLYCOLYSIS

- Decrease of nutrient and oxygen availability in the center of the tumor
- Faster (but poorer) ATP production
- Reduced generation of ROS and preservation of cancer cell genoma
- Production of 5-phosphoribose-1-pyrophosphate, an intermediate product of the pentose phosphate pathway, which is used in the biosynthesis of purine and pyrimidine nucleotides
- Lactic acid build-up reduces cellular and extracellular pH and promotes genetic changes which impairs antitumor immune response, reduce adherence cell junction, facilitating detachment and metastases
- pyruvate kinase type M2 and hexokinase2, key enzymes in the glycolytic pathway of cancer cells, contribute to the invasive potential and metastatic ability

(*ME Cameron 2018*)

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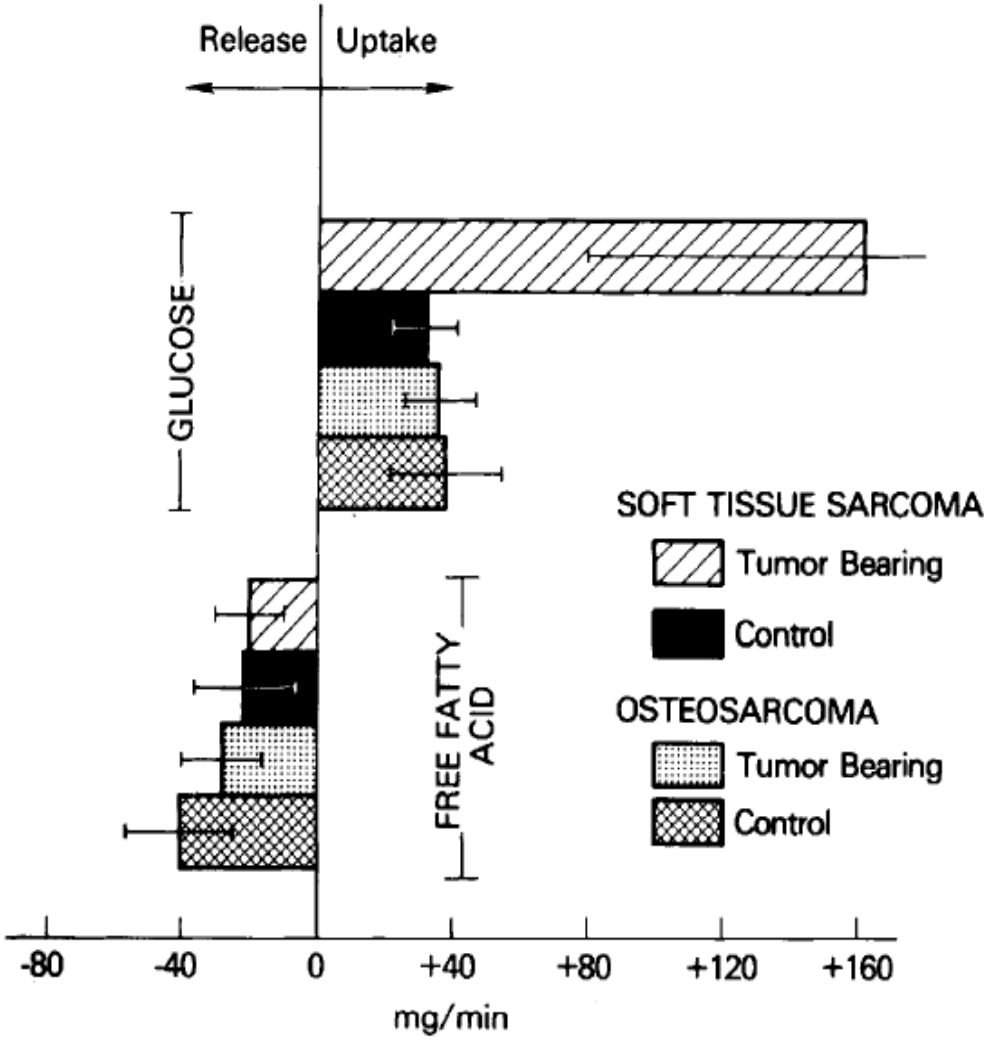
Norton *et al.* In vivo utilization of substrate by human sarcoma-bearing limbs.
Cancer 1980;45(12):2934-9.



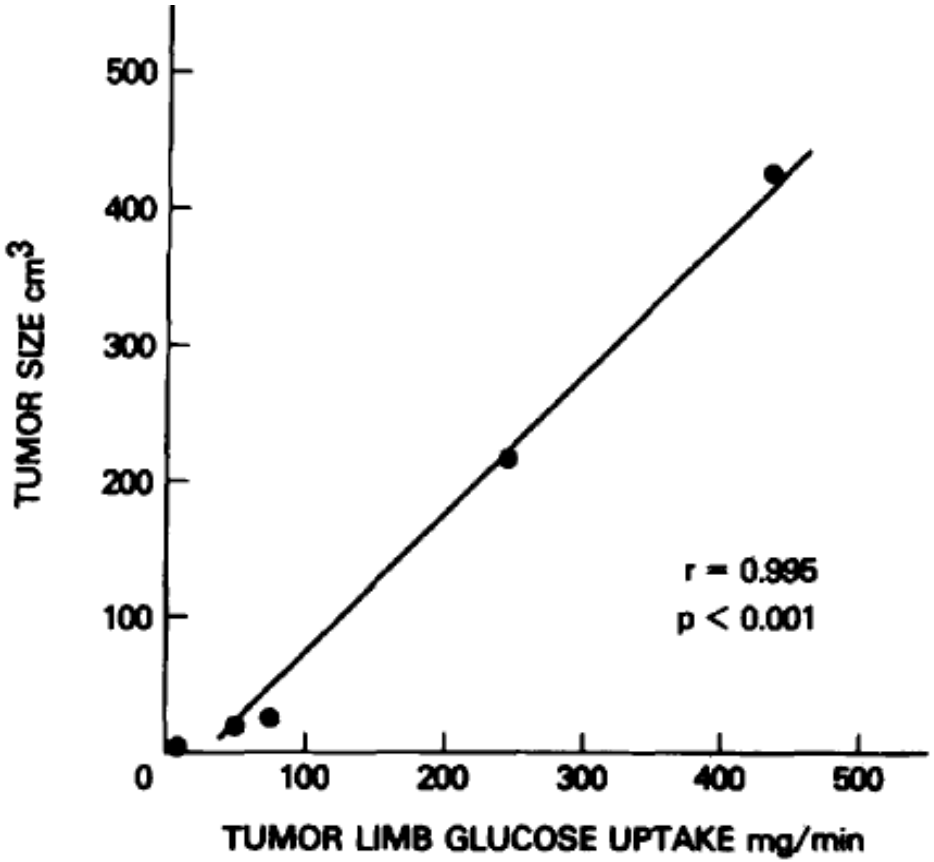


FIG. 2. Correlation of soft tissue sarcoma size with glucose uptake. The excised tumor volume of the soft tissue sarcomas in cu cm was proportional to the uptake of glucose by the *in vivo* sarcoma-bearing limb. (r = .995; $P < .001$).

Norton's findings do not support the concept of substrates competition between tumor and host and consequently the importance of a CHO restriction

A 70-kg patient usually ingests 250-300 g CHO/d and has an endogenous glucose production of ≈ 200 g/d (from hepatic glycogen, lactate, glycerol, glycogenic AA).

His 500-g sarcoma would consumes ≈9.8 g CHO/d (Norton&Brennan 1980) that is 2% of total daily glucose disposal.

Holm *et al*. Substrate balances across colonic carcinomas in humans.

Cancer Res. 1995;15;55(6):1373-8.

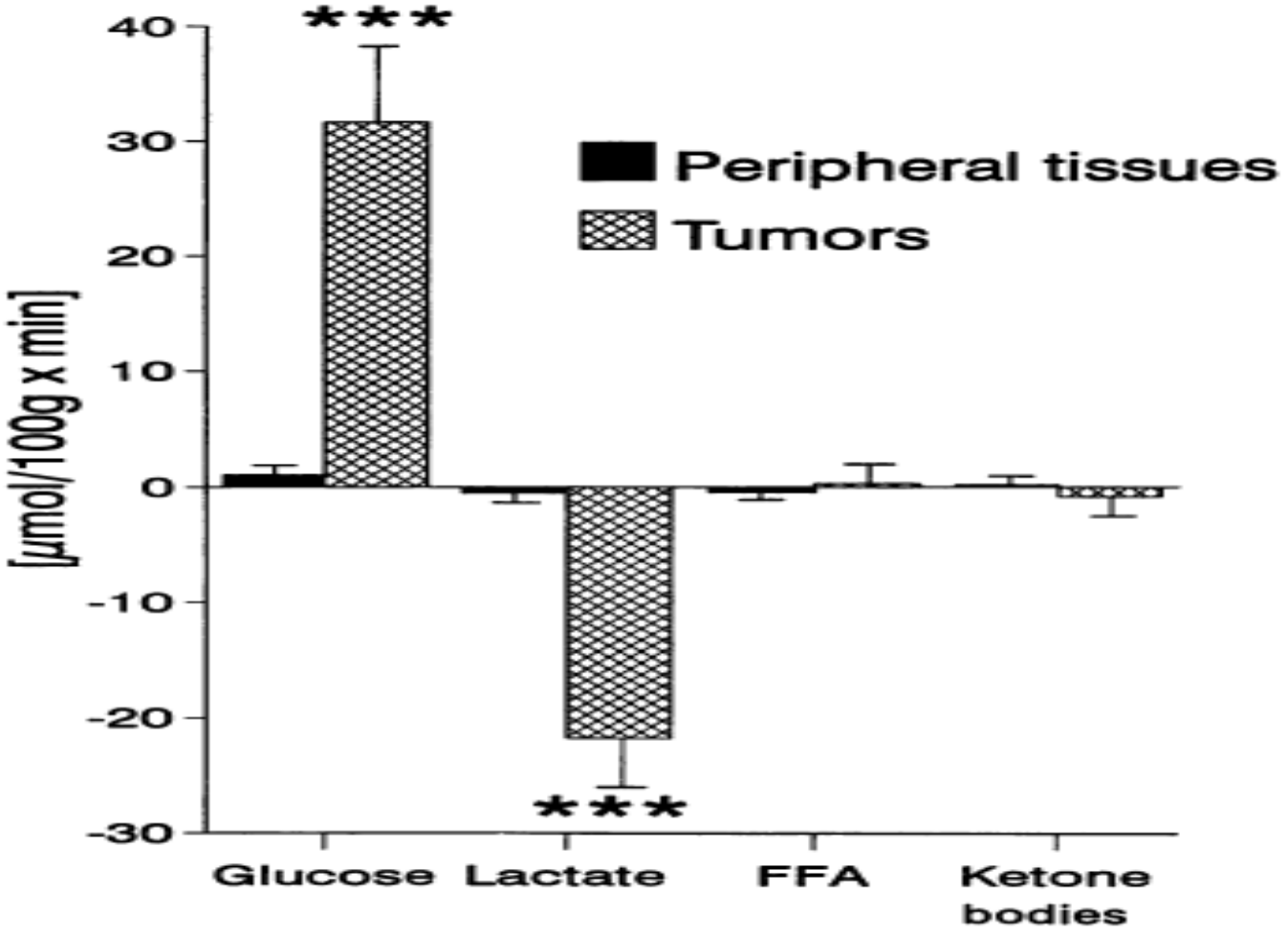


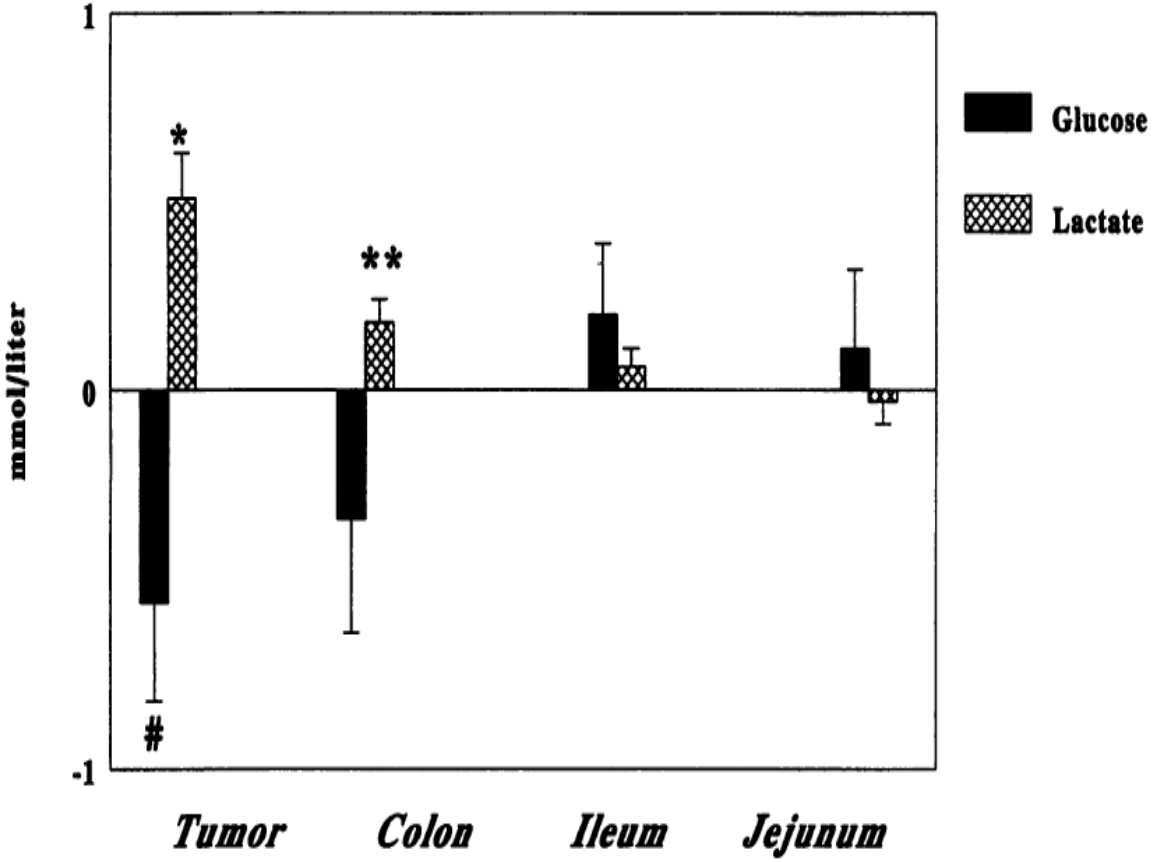
Fig. 2. Balances of energy-yielding substrates across both the peripheral tissues and the colonic tumors. *Columns*, mean; *bars*, SEM. ***, $P < 0.001$.

Glucose net uptake by the tumor exceeds peripheral glucose uptake by a factor of 30 and lactate output from the tumor was 43 times greater than peripheral release

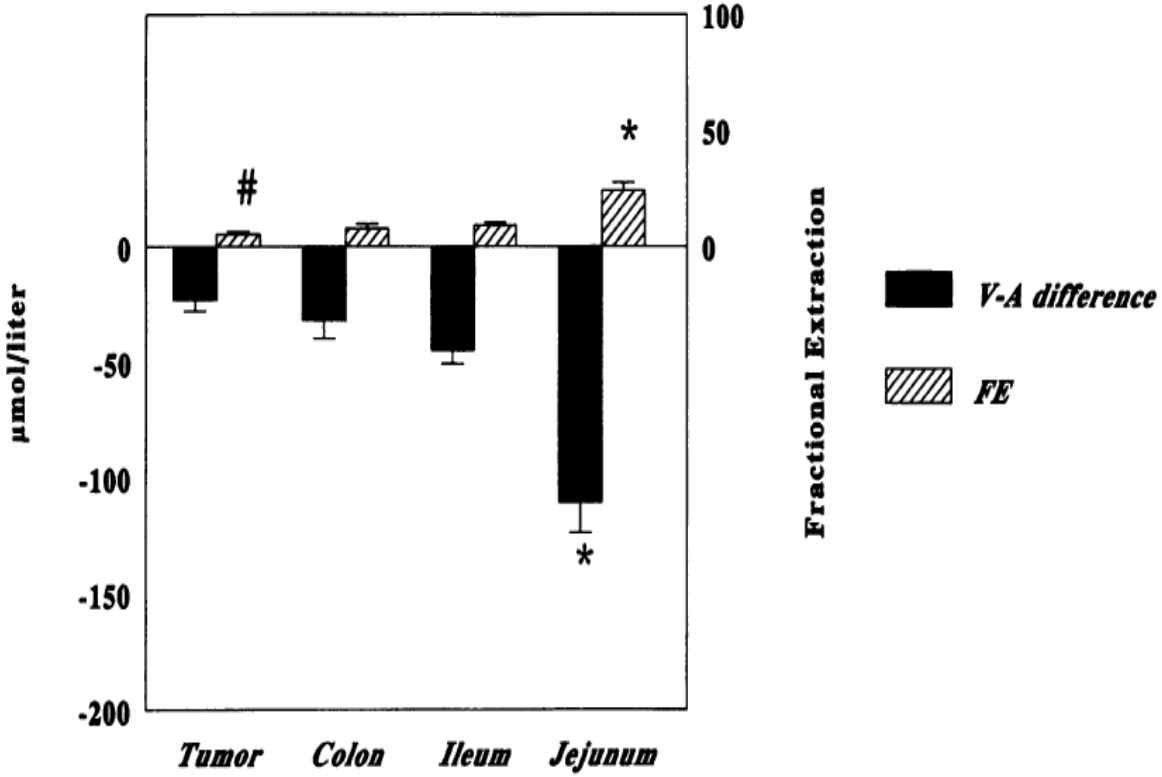
A net release of glutamine occurred in 7 pts and net retention in 10

van der Hulst *et al.* Glutamine extraction by the gut is reduced in depleted patients with gastrointestinal cancer.

Ann Surg. 1997; 225(1):112-21



Venous minus arterial balances for lactate and glucose across colon



Venous minus arterial differences and fractional extraction rate for glutamine across gut and tumor. Colon-containing tumor did not extract more glutamine than did nontumor-containing colon.

AA utilization by the human cancer

- High tumoral uptake of EAA and BCAA compared to a low peripheral release (*Norton 1980, Hagmuller 1995*)
- Glutamine retention is highly variable (*Holm 1993, Van der Hulst 1997*)

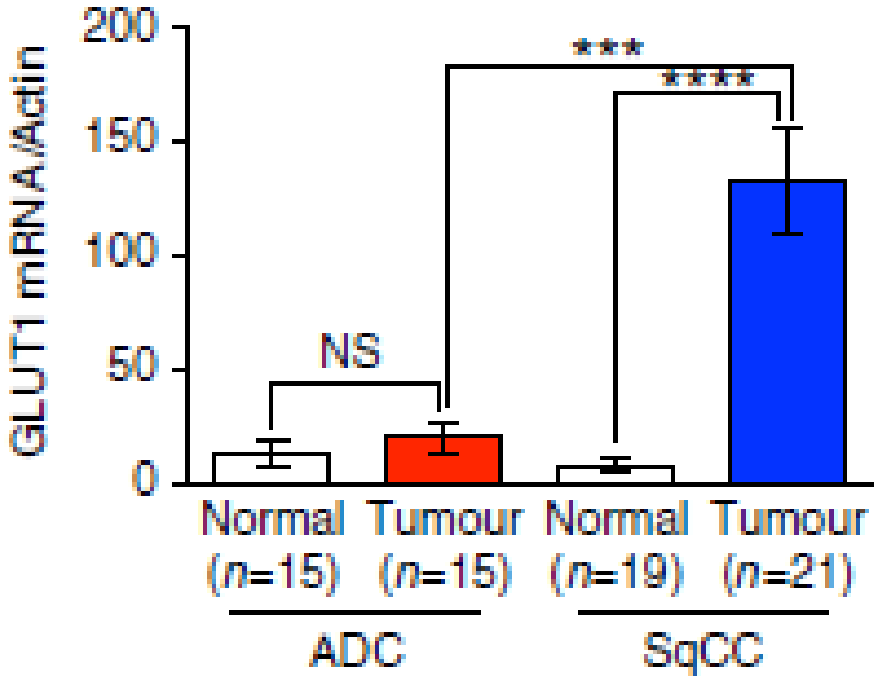
GLUCOSE UPTAKE and GLUCOSE TRANSPORTER

Tumor and host glucose consumption*

g/day per 100g tumour (ratio tumor/healthy tissue)

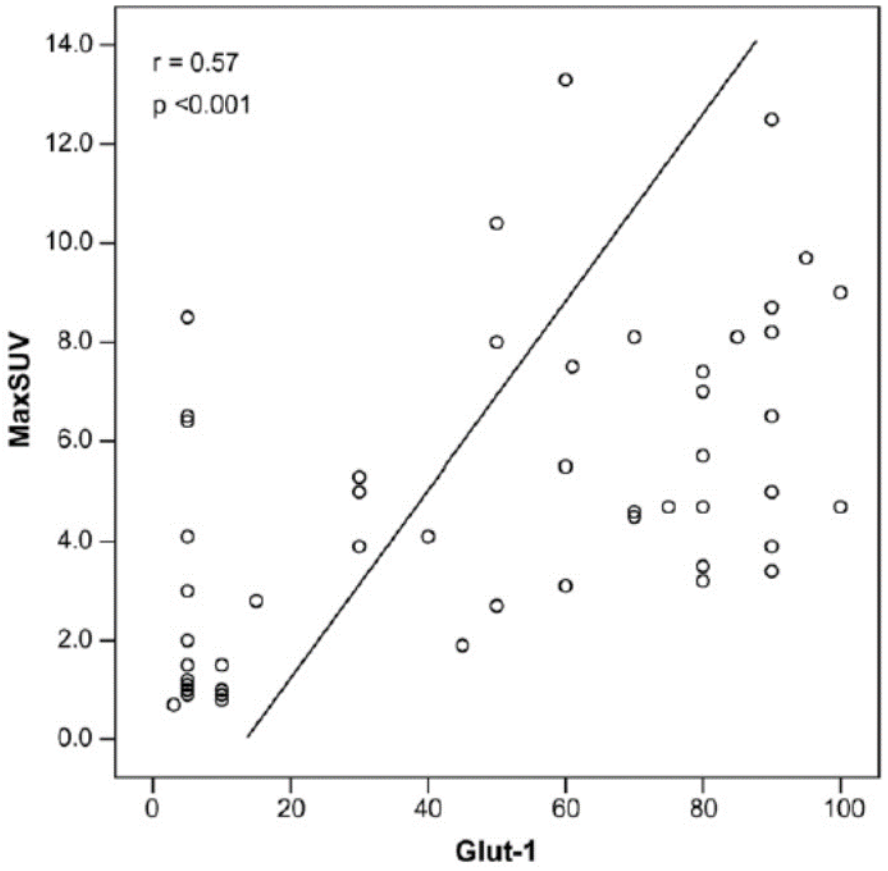
colon cancer 8.2	(x 4.3 tumor-free colon)
liver M+ from CR cancer	(x 3.2 tumor-free liver)
lung 4.1	(x 6.7 tumor-free lung)
limb soft tissue sarcoma	(x 1.8 tumor-free limb)

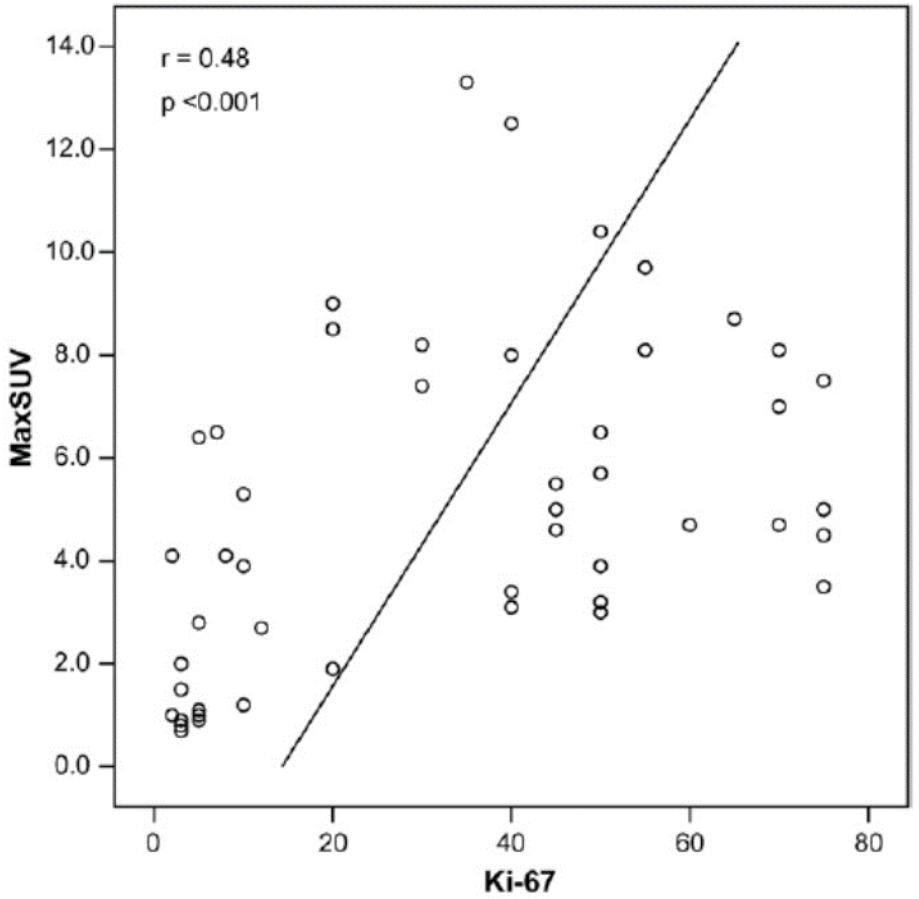
From Norton 1980, Hagmuller 1987, Nolop1995, Bozzetti 2004



from Goodwin 2017

Nguyen *XC et al.* FDG uptake, glucose transporter type 1, and Ki-67 expressions in non-small-cell lung cancer: correlations and prognostic values.
***Eur J Radiol. 2007; 62(2):214-9*.**





Vesselle *et al*. Relationship between NSCLC FDG uptake at PET, tumor histology, and Ki-67 proliferation index. *J Thorac Oncol. 2008; 3(9):971-8*

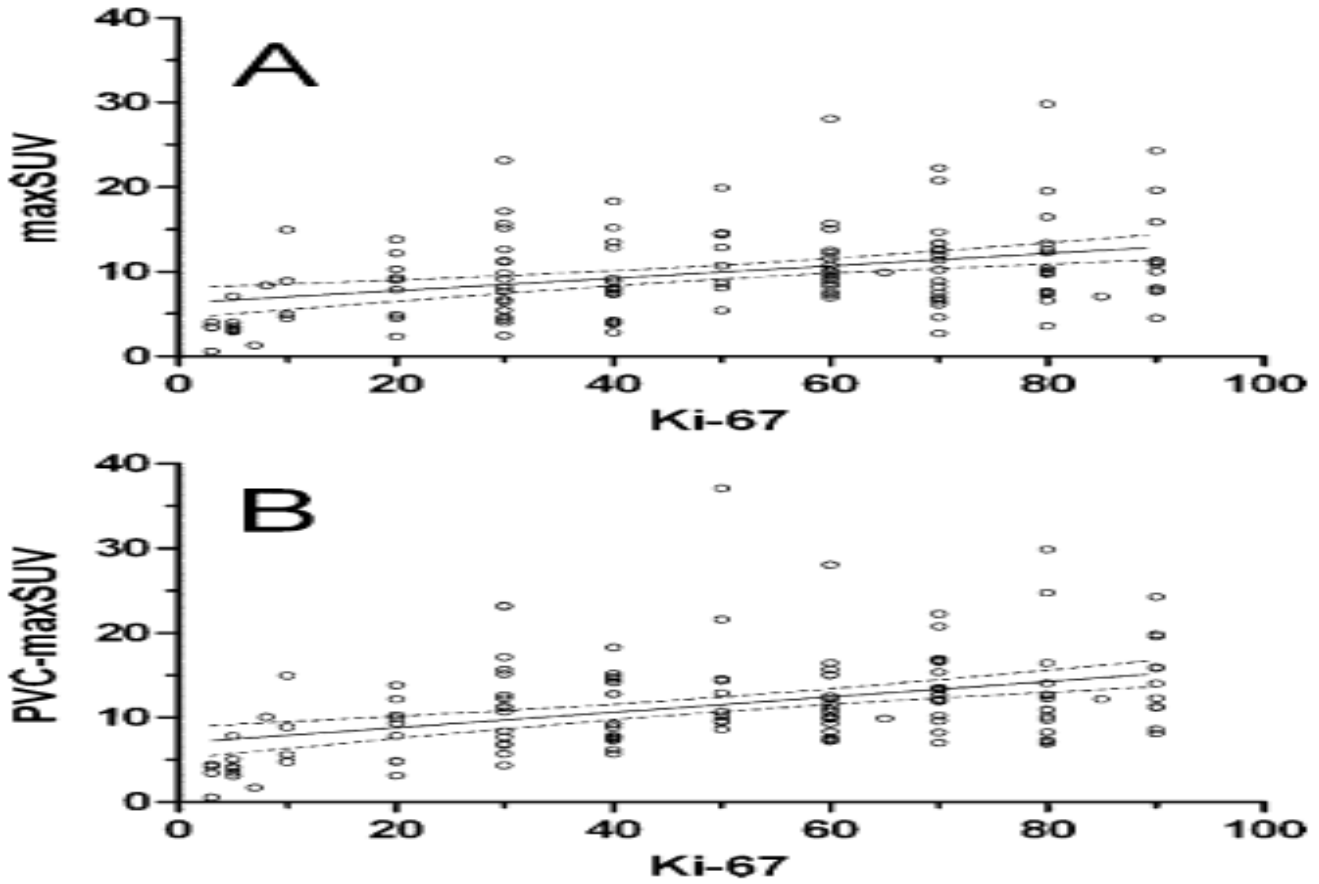
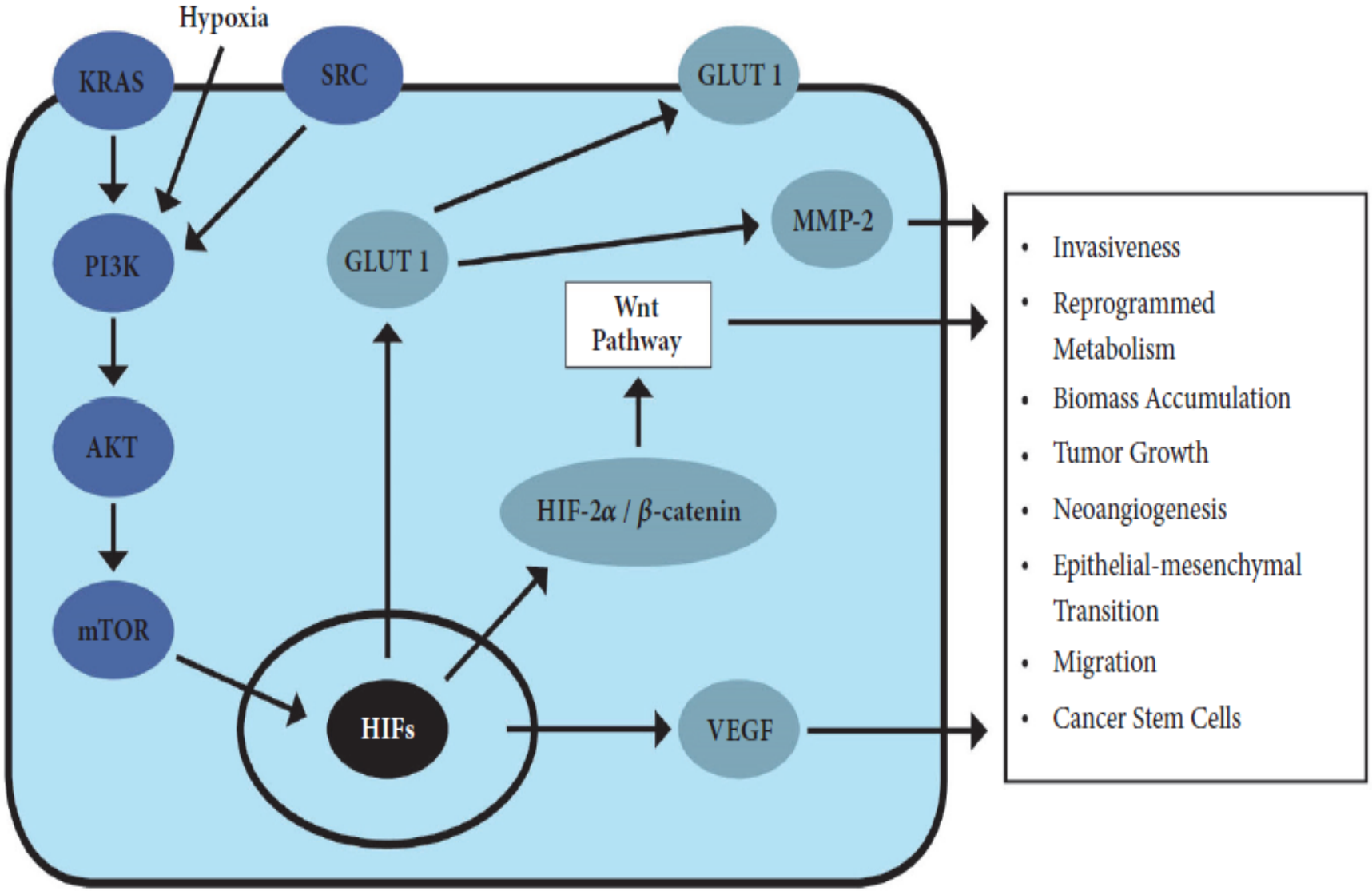


FIGURE 4. Correlations between Ki-67 score and maxSUV (A; Spearman's $\rho = 0.354$; $P < 0.0001$) and between Ki-67 score and PVCmaxSUV (B; Spearman's $\rho = 0.452$; $P < 0.0001$).

Several signaling pathways lead to the expression of GLUT-1 in the cancer cell

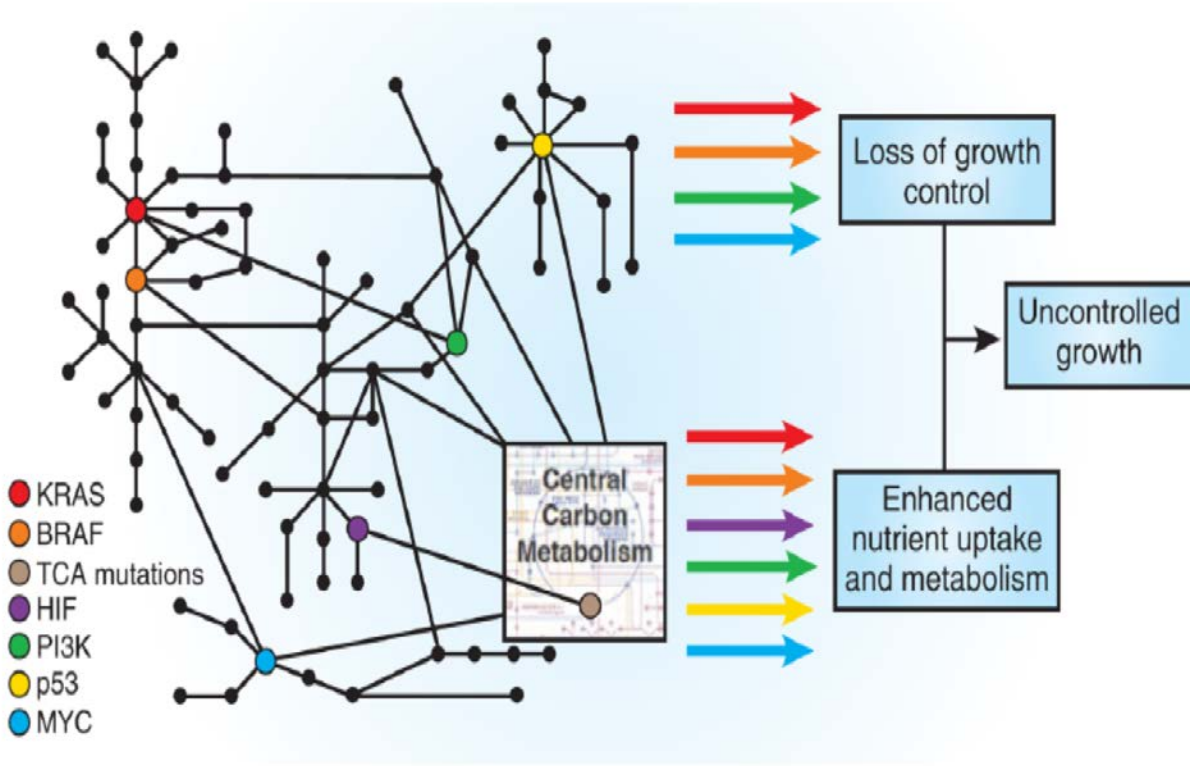


from Cameron ME 2018

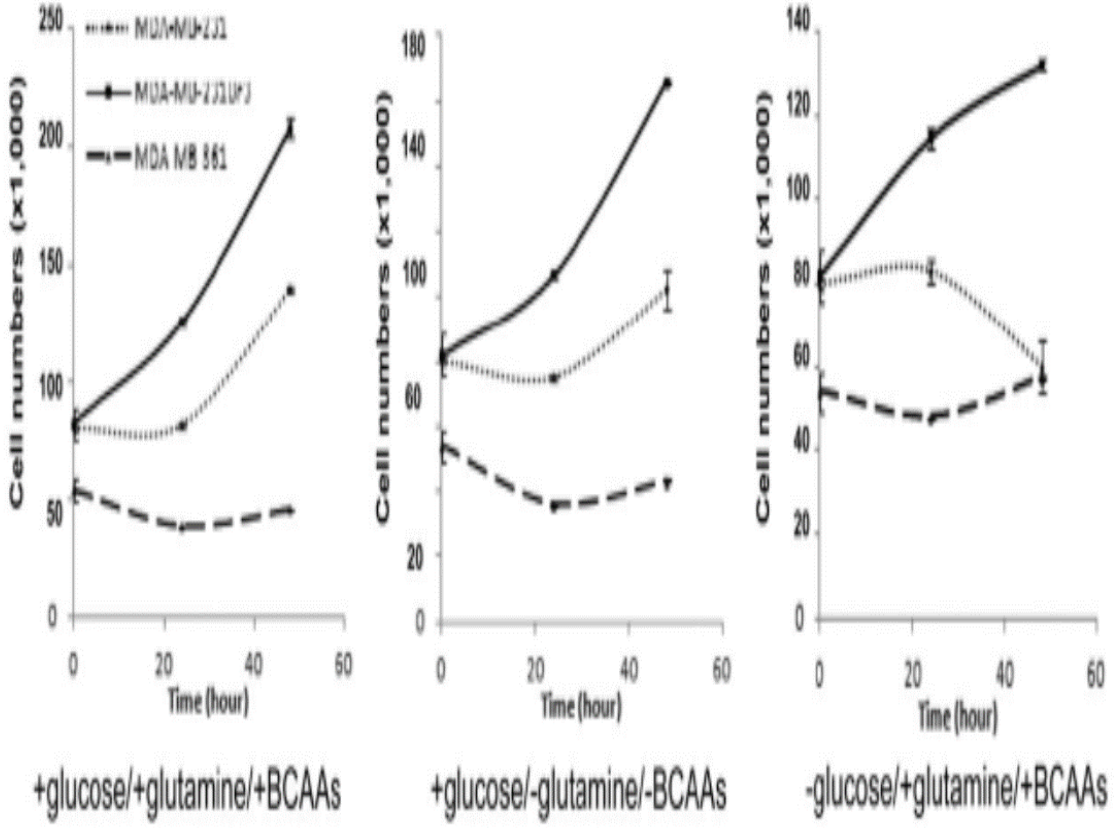
Table 1 Common genetic mutations in HNSCC and their implication for tumor cell metabolism

Gene	Frequency (%)[45]	Implications for metabolism
Loss of function mutations/deletions		
TP53	50-80	Loss of p53 leads to nuclear and mitochondrial DNA instability, increased oxidative stress, decrease of OXPHOS and up-regulation of glycolysis (reviewed in[46,47])
NOTCH1	14-15	Hypoactive Notch diminishes p53 levels and attenuates mitochondrial function, causing a switch to glycolysis and dependence on glucose[48]
PTEN	7	PTEN counteracts glycolysis by reversing the PI3K-mediated conversion of phosphatidylinositol1,4-biphosphate (PIP_2) to phosphatidylinositol1,4,5-triphosphate (PIP_3) that is required to activate Akt–mTOR signaling. Loss of PTEN therefore increases Akt activation. PTEN also counteracts glutaminolysis by reducing glutaminase levels through a PI3K-independent pathway[49]
Gain of function mutations/amplifications		
PIK3CA	6-20	PIK3CA encodes p110α, an isoform of the 110-kDa catalytic subunit of the class 1A phosphatidylinositol-3-kinase (PI3K). The PI3K–Akt–mTOR pathway is one of the most frequently hyperactivated signaling cascades in tumor cells. Enhanced Akt signaling induces a Warburg phenotype and increases the coupling of glycolysis to the mitochondrial citric acid cycle which yields intermediates for biosynthetic pathways and NADH as the primary electron donor for OXPHOS (reviewed in[50])
HRAS	4-5	HRAS encodes the small GTPase H-Ras, a member of the Ras superfamily of enzymes that become active when bound to GTP. Besides other pathways important for cell survival and proliferation, Ras-GTP directly acivates PI3K p110. Oncogenic H-Ras activation diminishes mitochondrial respiration, rendering transformed cells depend on glucose to fuel glycolysis[51]

Locasale&Cantley
Altered metabolism Cancer BMC Biol. 2010;25;8:88



In the full medium or in the medium devoid of glutamine/BCAAs, all types of cells could grow; in the absence of glucose only the brain metastatic cells grew and the MDA-MB231 cells (epithelial, human breast cancer cell line) do not (*Chen et al. 2015*)



Cancer cell does not utilize only glucose

Vol 458|9 April 2009|doi:10.1038/nature07782 nature

ARTICLES

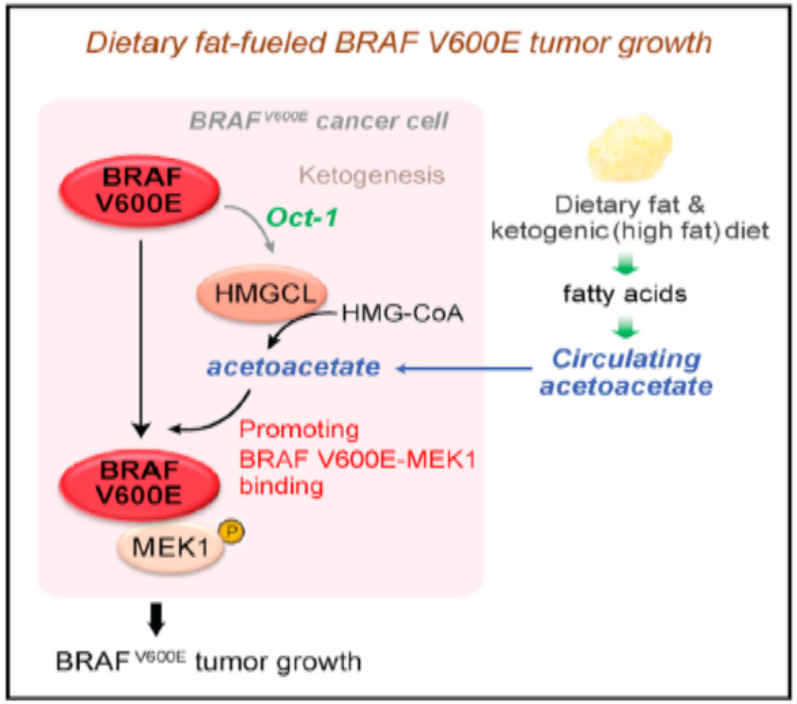
Tumours with PI3K activation are resistant to dietary restriction

Nada Y. Kalaany[1,2,3] & David M. Sabatini[1,2,3,4]

Dietary restriction delays the incidence and decreases the growth of various types of tumours, but the mechanisms underlying the sensitivity of tumours to food restriction remain unknown. Here we show that certain human cancer cell lines, when grown as tumour xenografts in mice, are highly sensitive to the anti-growth effects of dietary restriction, whereas others are resistant. Cancer cells that form dietary-restriction-resistant tumours carry mutations that cause constitutive activation of the phosphatidylinositol-3-kinase (PI3K) pathway and in culture proliferate in the absence of insulin or insulin-like growth factor 1. Substitution of an activated mutant allele of PI3K with wild-type PI3K in otherwise isogenic cancer cells, or the restoration of PTEN expression in a *PTEN*-null cancer cell line, is sufficient to convert a dietary-restriction-resistant tumour into one that is dietary-restriction-sensitive. Dietary restriction does not affect a *PTEN*-null mouse model of prostate cancer, but it significantly decreases tumour burden in a mouse model of lung cancer lacking constitutive PI3K signalling. Thus, the PI3K pathway is an important determinant of the sensitivity of tumours to dietary restriction, and activating mutations in the pathway may influence the response of cancers to dietary restriction-mimetic therapies.

Oncogenic BRAF V600E mutation

(from Xia et al. Cell Metabolism 2017)



- 50% of melanomas, 10% of colorectal cancer, 100% of hairy cell leukemia, 5% of multiple myeloma, some thyroid cancers

DOMINANT BIOENERGETIC PATHWAY

GLUCOSE

- Colon cancer
- Liver M+ from CR cancer
- NSCL
- Soft tissue sarcoma
- Glioma
- HCC
- BRAF-negative melanoma

Oncogenic KRAS may drive glycolytic activity in cancer cells

FAT

- Prostate adenocarcinoma
- Diffuse large B-cell lymphoma

If glucose or glutamine are limited, still tumor cells can utilize a wide variety of substrates to support the energetic needs including asparagine, leucine, arginine, methionine, valine, cysteine, lactate and acetate and through catabolizing both intracellular and extracellular macromolecules

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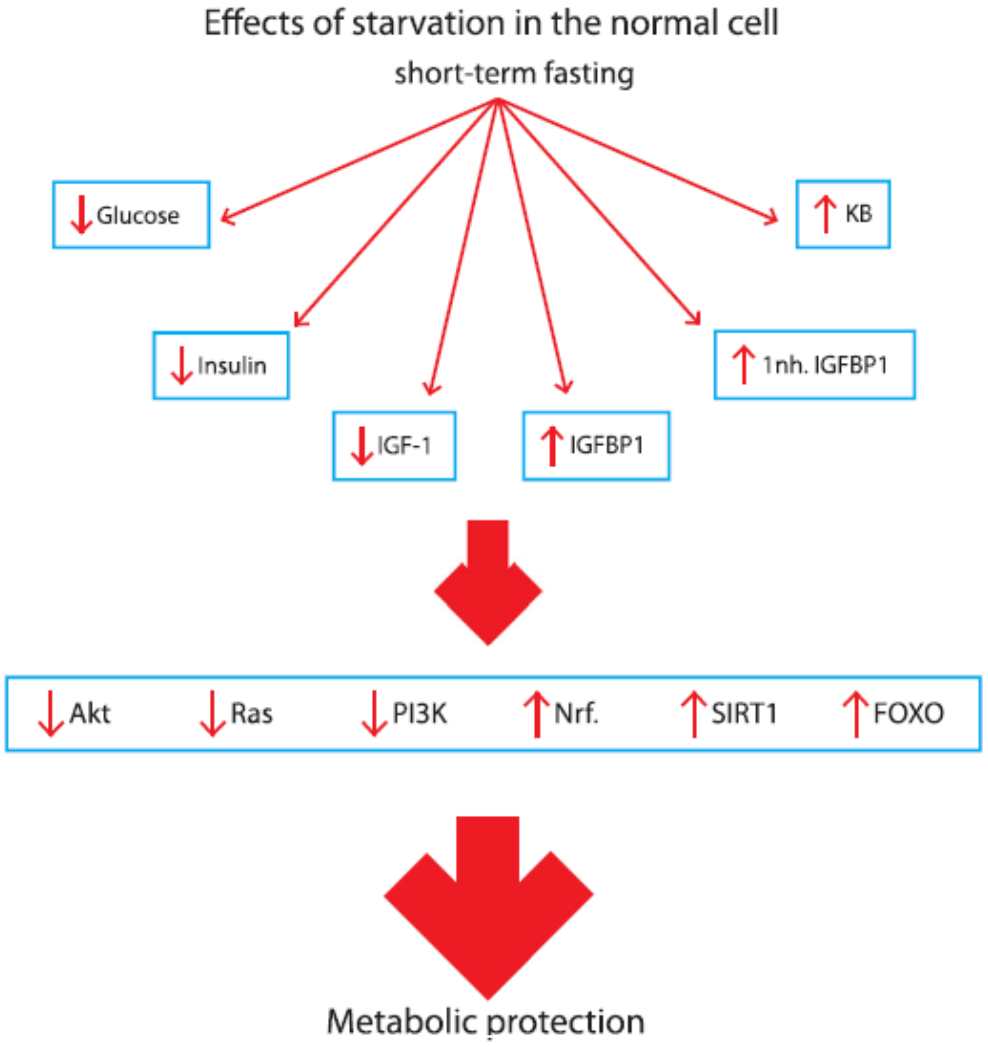
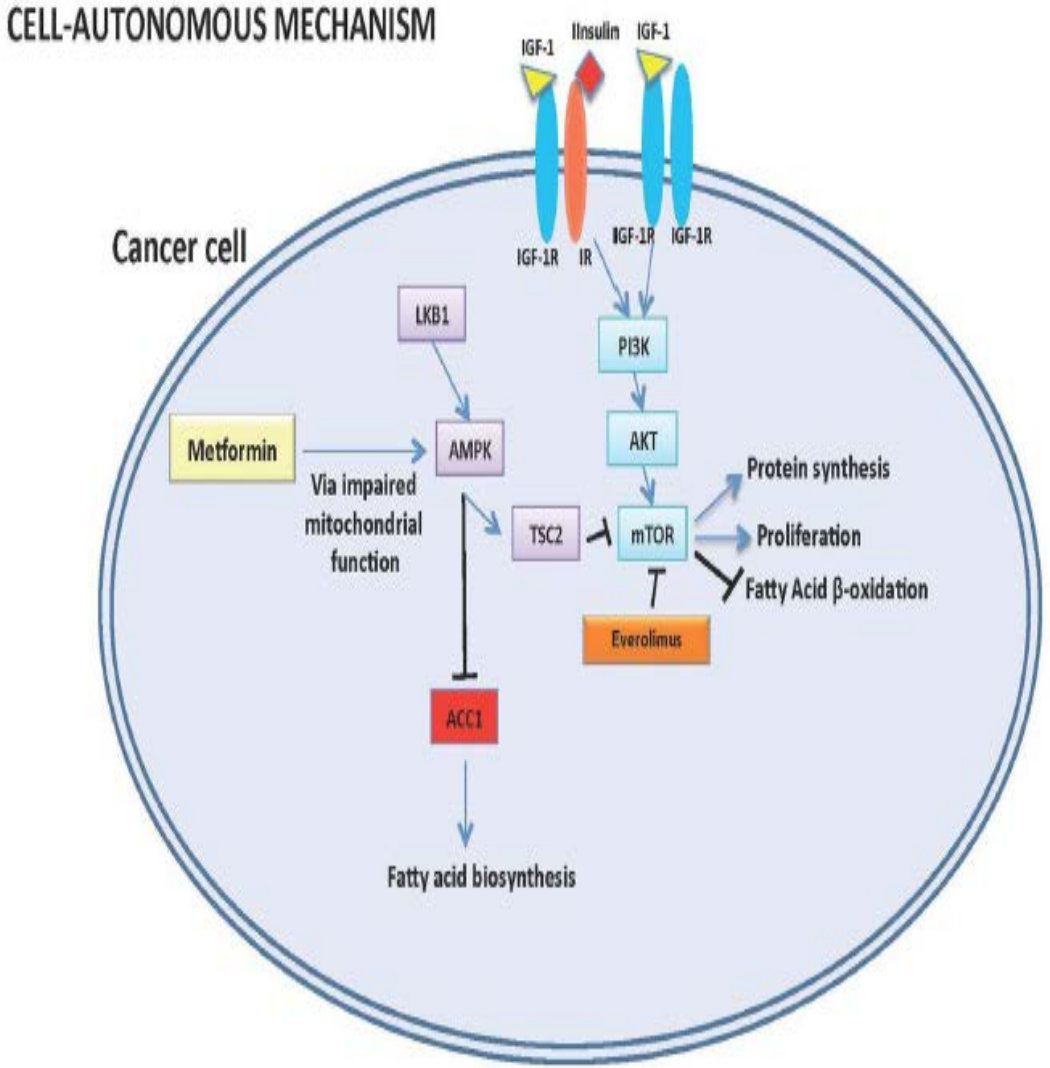
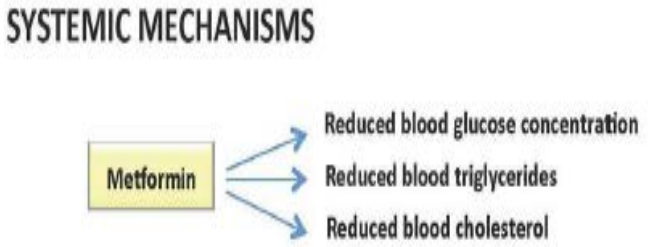


Akt (protein-kinase B), PI3K (Phosphoinositide 3-Kinase)Ras (rat sarcoma) promote proliferative signals
Nrf (Nuclear factor-kB-repressing factor, Sirtuin1 promote mitochondrial function
FOXO (Forkhead box protein O) promotes cell cycle arrest and apoptosis





Pili R, Fontana L. Low-protein diet in cancer: ready for prime time?
Nat Rev Endocrinol. 2018 Jul;14(7):384-386.

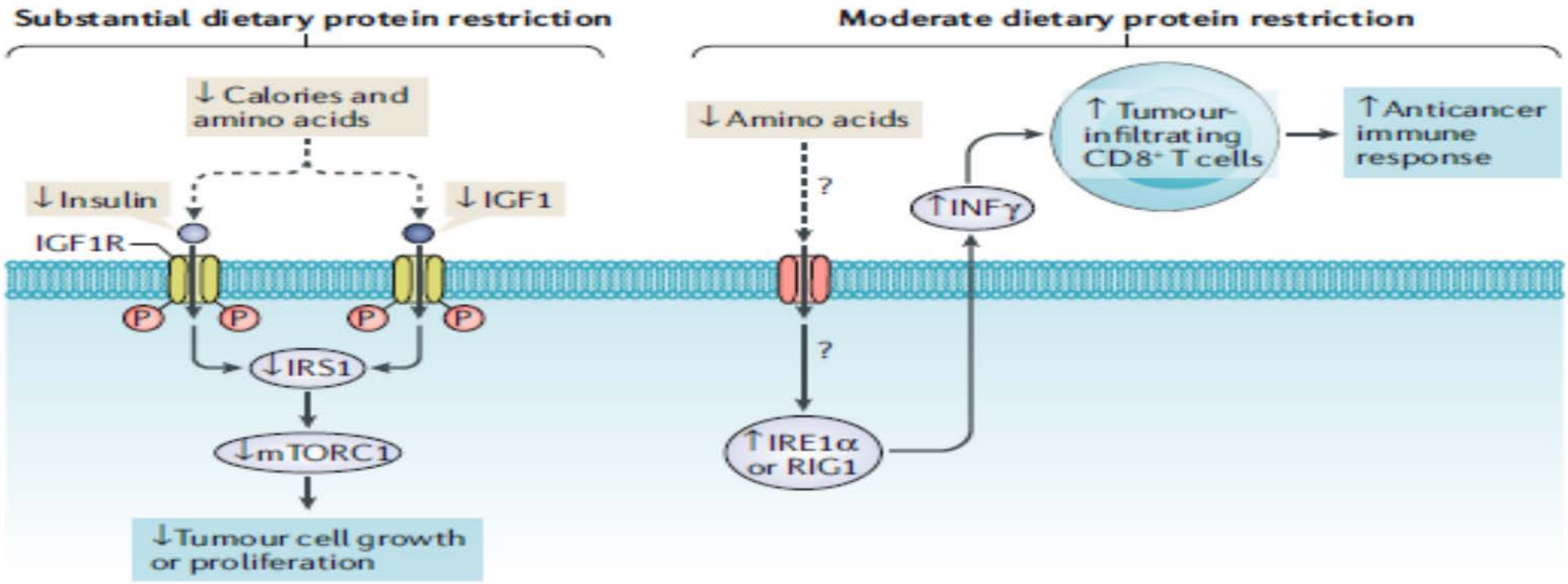


Fig. 1 | **Potential effects of different levels of dietary protein restriction.** A substantial protein and calorie restriction may directly inhibit tumour cell proliferation via the insulin–insulin-like growth factor 1 (IGF1)–insulin receptor substrate 1 (IRS1)–mammalian target of rapamycin complex 1 (mTORC1) axis. A moderate protein restriction may induce inositol-requiring protein 1α (IRE1α)–retinoic acid-inducible gene 1 protein (RIG1) expression in tumour cells, increase IFNγ secretion and subsequent recruitment of tumour-infiltrating $CD8^+$ T cells and induction of anticancer response.? and dashed arrows represent unknown receptor and mechanism. IGFR1, IGF1 receptor.

Tumori, 81: 1-6, 1995

RELATIONSHIP BETWEEN NUTRITIONAL STATUS AND TUMOR GROWTH IN HUMANS

Federico Bozzetti, Patrizia Boracchi, Aurora Costa, Luca Cozzaglio, Antonello Battista, Alberto Giori, Gaudenzio La Monica, and Rosella Silvestrini

Aims and background: There is considerable evidence from studies on tumor-bearing animals that nutritional support aimed at maintaining a good nutritional status can indeed promote tumor growth. Experience in humans, however, is scanty and controversial, this issue never having been extensively investigated. The purpose of this study was to analyze whether there exists a relationship between nutritional status and tumor growth in patients with non-Hodgkin's lymphoma. The hypothesis behind it was that if it is true than an abundant availability of substrates promotes tumoral growth, then the better the nutritional status the higher the tumor cell proliferation. *Methods:* Two hundred and forty six adult patients with non-Hodgkin's lymphoma were characterized according to nutritional status (percent of weight loss as compared to usual body weight, serum albumin, serum cholinesterase, number of lymphocytes) and rate of incorporation of ^{3}H thymidine labelling index in the tumor tissue. The values of serum albumin, serum cholinesterase and lymphocytes were subdivided into three classes adopting as cut-off points the tertile values of their distribution, while weight loss was scored as a "no" and a "yes". The association between nutritional parameters and labelling index was evaluated by a univariate analysis (X^2 test and Mantel-Haenszel X^2 test and the odds ratio) and by a logistic multiple regression model. *Results:* Results of the univariate analysis show a statistically significant association between "poor" nutritional status (depressed nutritional indexes) and "high" labelling index (increased tumoural growth), while the multiple regression analysis found that the only significant association was that between low serum cholinesterase and high labelling index. *Conclusions:* These data demonstrate for the first time in a large series of patients that maintenance of a good nutritional status does not have any deleterious effect on the tumor growth.

Key words: Nutritional status, tumor growth, artificial nutrition.

On a sample of 136 NHL there was a statistically significant association between poor nutritional status and high labelling indexes

1: J Thorac Cardiovasc Surg. 1964 Dec;48:984-90.

SPONTANEOUS REGRESSION OF BRONCHOGENIC CARCINOMA WITH FIVE YEAR SURVIVAL.

BELL JW, JESSEPH JE, LEIGHTON RS.

PMID: 14239988 [PubMed - OLDMEDLINE for Pre1966]

Aust. N.Z. J. Surg. 1987, 57, 375–379

PARENTERAL NUTRITION AND TUMOUR GROWTH IN THE PATIENT WITH COMPLICATED ABDOMINAL CANCER

M. L. RICE[1] AND A. M. VAN RIJ[1]

Department of Surgery, University of Otago Medical School, Dunedin, New Zealand

Parenteral nutrition has been advocated as an important adjunct in the treatment of the patient with cancer undergoing surgery, chemotherapy and radiotherapy. However there is universal agreement that parenteral nutrition does not have a stimulatory effect on tumour growth. Four cases are reported, in complicated abdominal cancer involving only surgery, in which a claim that acceleration of tumour growth by parenteral nutrition can be made.

Key words: abdominal cancer, complications, parenteral nutrition, surgery, tumour growth.

Introduction

Parenteral nutrition is an important adjunct in the management of patients with cancer. The advantages associated with the use of parenteral nutrition in these patients includes improved wound healing, sustained immunocompetence and the maintenance of weight as well as positive nitrogen balance.[1,2] The use of total parenteral nutrition (TPN) has also been advocated in both radiotherapy and chemotherapy to improve tolerance. Several studies of cancer patients have reported no evidence of accelerated tumour growth when TPN has been provided.[1–4] Studies in animal models have similarly supported the concept that total parenteral nutrition does not stimulate tumour growth.[5] However, in all these studies TPN administration is associated with the simultaneous administration of various anti-cancer treatments including chemotherapy or radiotherapy. It is less clear whether TPN influences tumour growth in the absence of anticancer treatments. It is possible that in these circumstances extra nutritional supplementation may enhance tumour growth to the detriment of the host. Such a possibility has been suggested in the experimental model. Conversely, the inhibitory effect of nutritional deficits on tumour growth is now recognized. In a variety of animal models protein depletion,[6] zinc deficiency[7] and the deletion of specific amino acids from the diet have been shown to inhibit tumour growth. The replenishment of these essential nutrients results in prompt return of the tumour growth characteristics. Indeed it has been suggested that the use of nutrient manipulation by creating a specific deficiency and, with subsequent replenishment, tumour susceptibility to other treatments such as chemotherapy might be enhanced.[5] The patient with cancer is often nutritionally depleted and in correcting this problem there may be a distinct disadvantage in terms of tumour growth enhancement.

In the cancer patient who develops complications following surgery nutritional support is often indicated for optimal care. In these circumstances chemotherapy or radiotherapy for the remaining disease is often inappropriate or impossible. If there is a remaining limited cancer mass it is possible that an aggressive nutritional repletion may have a stimulatory effect on the residual tumour. Although in the past it has been suggested that this is unlikely to occur, this has not been clearly demonstrated. What is not yet clear is whether or not TPN has an adverse effect on those who undergo surgery and sustain complications and who have residual tumour in which no adjuvant therapy is used.

Four cases are reported in which a note of caution should be recorded with regard to the possible deleterious effect that TPN had on the patient with stimulation of tumour growth.

Case Reports

CASE 1

A 44 year old female underwent excision of the transverse colon and greater curvature of the stomach for an invasive Duke's C adenocarcinoma of the colon on 22 September 1981. No macroscopic

[1] FRACS.

M. L. Rice, Department of Urology, Waikato Hospital, Hamilton, New Zealand.

Accepted for publication 18 December 1986.

Can the Growth of a Neuroblastoma Be Influenced by a Child's Nutritional State?

Observations in a Patient Treated for Kwashkiorkor and Later Given a Restricted Diet

Woodruff J. English, II, M.D., Robert Suskind, M.D., Damri Damrongsak, M.D., Panja Kulapongs, M.D., Robert E. Olson, M.D., Ph.D.

A 17-month-old Thai female with neuroblastoma presented with an abdominal mass and the classical findings of kwashiorkor. Concomitant with effective repair of the child's protein deficit, the mass enlarged dramatically and metastases were noted. This is the first known report of such an occurrence.

NEUROBLASTOMA comprises 6 to 8 per cent of all the malignancies of childhood.[1] It is a tumor which is frequently misdiagnosed.[2] The most common presenting sign is an abdominal mass which may be accompanied by low grade fever, anemia, weight loss, irritability, and hypertension.[3] Cases have also presented with intractable diarrhea, bone pain, proptosis of the eye,[4] or myasthenia gravis.[5] The case presented here is of interest because the neuroblastoma was associated with clinical signs of protein calorie malnutrition (PCM).

Case Report

A 17-month-old Northern Thai female was admitted to the Anemia and Malnutrition Research Center, Chiang Mai, Thailand, on March 31, 1972 with a one-month history of abdominal distention, recurrent diarrhea, anorexia, vomiting, weight loss, and intermittent fever. Five days earlier, swelling of the feet and legs had developed. An abdominal mass had not changed in size since birth.

On admission, the infant was apathetic, irritable, and weak. Significant findings included marked muscle wasting, edema of both feet, and distended abdomen with moderate ascites, a liver enlarged 5 cm below the right costal margin, a spleen tip palpable 4 cm below the left costal margin, and a nontender, mobile, superficial, 3 × 2 cm mass in the left upper quadrant. The blood Hbg was 8.5 gm, white blood count (WBC) 4,900 with 90 per cent PMNs, platelets 63,000, coagulation factors depressed (Table 1), Na^+ 129 mEq/l, K^+ 2.0, Ca^{++} 3.05, Mg^{++} 1.37, total protein 3.0 gm/100 ml, serum albumin 0.78 gm/100 ml, and globulin 2.22 gm/100 ml. A chest X-ray revealed bilateral perihilar infiltrates. A flat plate of the abdomen showed no abnormal soft tissue masses or calcifications. Pathogenic *E. coli* was recovered from the stool.

On admission, the patient was treated intravenously for pneumonia and sepsis with IV ampicillin 375 mg/kg and gentamicin 5 mg/kg, and her electrolyte balance was restored. Her diet was gradually increased to 100 calories and 1 gm protein/kg; this could not be raised further because of recurrent diarrhea. On day 26, although

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From the Anemia and Malnutrition Research Center, Faculty of Medicine, Chiang Mai University, St. Louis University School of Medicine, Chiang Mai, Thailand, and The Department of Biochemistry and Pediatrics, St. Louis University School of Medicine, St. Louis, Mo.

Correspondence to Robert Suskind, M.D., Departments of Nutrition and Food Sciences, Massachusetts Institute of Technology, Cambridge, Mass. 02139.

Calorie restriction and tumour growth in humans

Author	# pts	Primary	Regimen (weeks)	Comments
Zuccoli 2010	1	CNS	9.3 Kcal/kg/d, (8)	Radiochemotherapy: complete response
Fine 2012	10	mixed	17 Kcal/kg/d, KD (4)	Level of ketosis (not weight loss) correlated with PET response
Champ 2014	6	CNS	<21 Kcal/kg/d, CHO 36 g, KD, (28)	CR safe and well tolerated during RT&CT

Clinical Nutrition 28 (2009) 226–230

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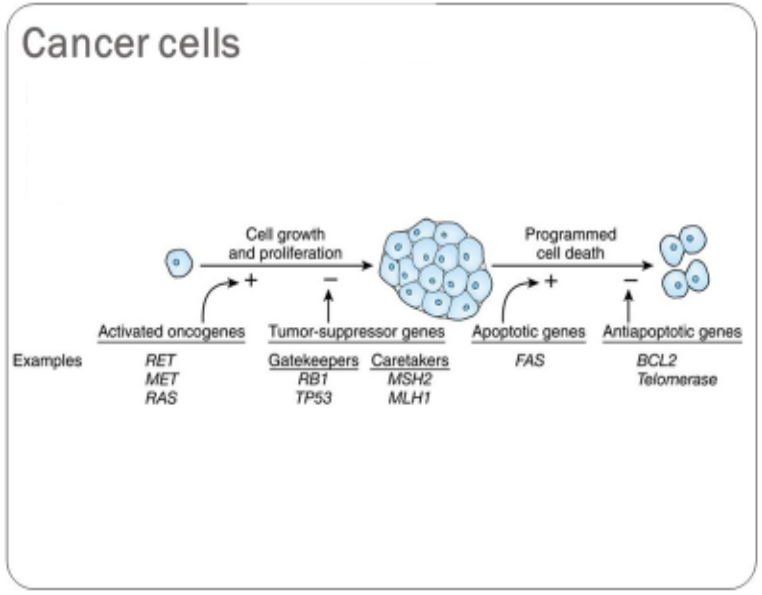
Review

Nutritional support and tumour growth in humans: A narrative review of the literature

Federico Bozzetti*, Valentina Mori

Indicators of tumor cells proliferation included the following:

- ornithine decarboxylase activity
- flow-cytometric DNA distribution
- labeling index with tritiated thymidine
- or bromodeoxyuridine incorporation
- DNA index
- DNA content and the % of cells in S phase



Bozzetti F, Mori V. Nutritional support and tumour growth in humans: a narrative review of the literature.
***Clin Nutr. 2009; 28(3):226-30*.**

Table 3
Clinical trials without control group.

Author	Duration (days)	No. of pts	Nutritional status	Nutritional support (kg/day)	Tumour growth
Ota[b]	8	16	MN	55 kcal; 2.6 g AA	↑ Statistically significant with TPN
Westin[a]	8	9	MN	31 kcal; 1.5 g AA	No change with TPN
Frank[a]	7	10	MN	H–B × 1.1	↑ Statistically significant with TPN
Cao[b]	5	7	?	26 kcal; 0.9 g AA	↑ Statistically significant with TPN

Bozzetti F, Mori V. Nutritional support and tumour growth in humans: a narrative review of the literature.

Clin Nutr. 2009;28(3):226-30.

Table 2

Comparative non-randomized clinical trials.

Author	Duration (days)	Controls		Fed		Tumour growth
		No. of pts	Daily nutritional hospital regimen	No. of pts	Daily nutritional support regimen	
Baron[a,c]	3–17	6	43 kcal/kg; 1.4 g/kg by mouth	8	59 kcal/kg and 1.9 g AA/kg as TPN	No change in controls, ↑ statistically significant in TPN
Rossi Fanelli[b,d]	15	9	Harris–Benedict × 1 and 1.5 g AA/kg by mouth	18	Harris–Benedict × 1 and 1.5 g AA/kg as TPN	No change in both arms
McNurlan[b,d]	1	7	Fasting	7	25 kcal/kg and 1.2 g AA[e]/kg by iv route	↑ Statistically significant in iv patients

Bozzetti F, Mori V. Nutritional support and tumour growth in humans: a narrative review of the literature.

***Clin Nutr. 2009;28(3):226-30*.**

Randomized clinical trials in malnourished patients.

Author	Duration (days)	Controls		Fed		Tumour growth
		No. of pts	Daily nutritional hospital regimen	No. of pts	Daily nutritional support regimen	
Edström[a]	6–8	13	<1000 kcal	13	Harris–Benedict × 1.2–1.5 as EN	No change in controls; significant increase in EN *versus* control pts
Dionigi[b]	8–18	7	19 kcal, 1.1 g AA/kg by mouth or iv	9	42 kcal/kg, 2.3 g AA/kg as TPN or EN	No difference in controls, no difference in fed *versus* control pts
Bozzetti[b]	10	9	Regular diet	10	Harris–Benedict × 1.5 as TPN	No change or ↓ in controls; no change or ↑ in TPN pts
Jin[b]	7	23	Not reported	23	35 kcal and 1.4 g AA/kg as TPN	No change in controls, ↑ significant in TPN pts, ↑ significant in TPN *versus* controls
Pacelli[b]	10–12	10	Standard hospital oral diet	10	30 kcal and 1.2 g AA/kg as TPN	No change in control or TPN pts

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Review

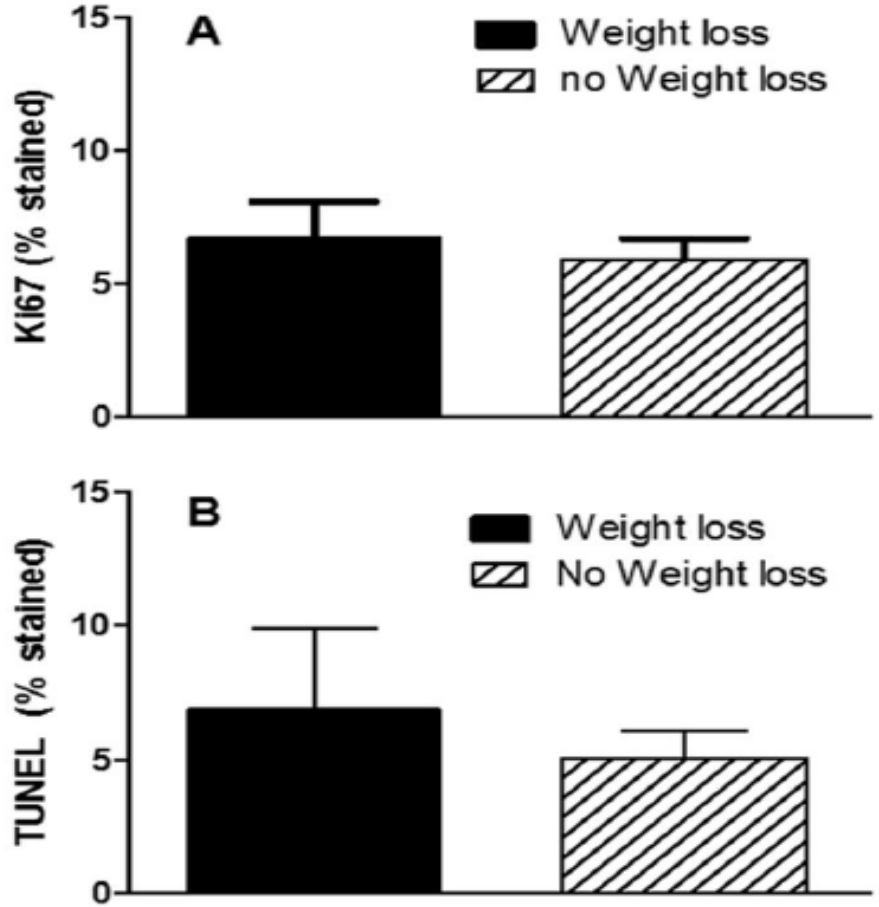
Nutritional support and tumour growth in humans: A narrative review of the literature

Federico Bozzetti*, Valentina Mori

…..in conclusion, on a total of 12 studies (150 patients on PN or EN and 90 controls) nutrition support seemed to stimulate tumor cells proliferation in 8 of them…

Henning SM et al. Phase II prospective randomized trial of weight loss prior to radical prostatectomy. ***Prostate Cancer Prostatic Dis. 2017. 10.1038/s41391-017-0001-1.***

Demark-Wahnefried W et al. Presurgical weight loss affects tumour traits and circulating biomarkers in men with prostate cancer. ***Br J Cancer. 2017:117:1303–13*****.**



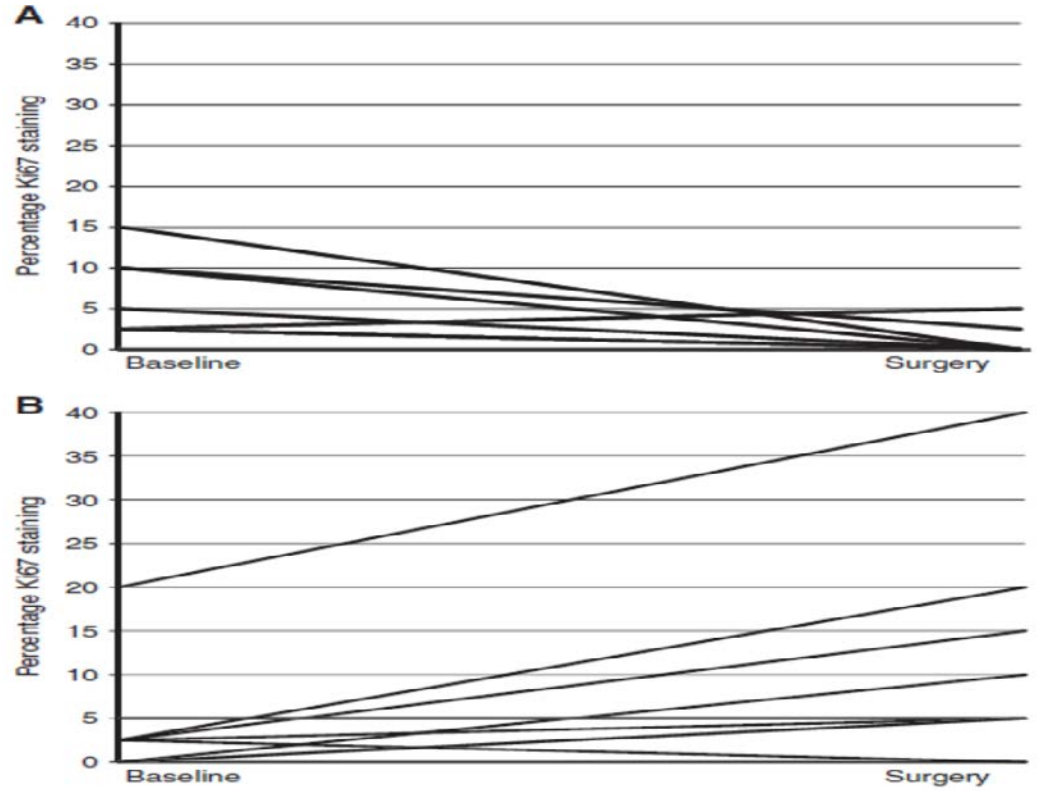
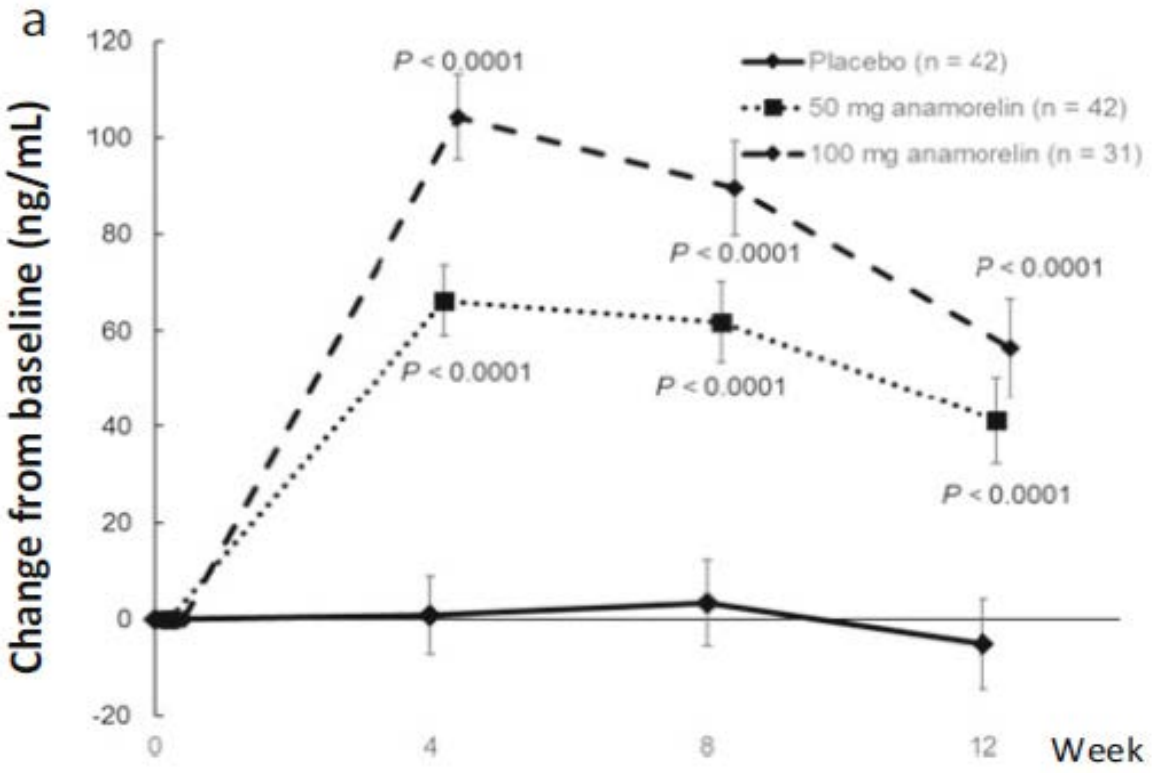
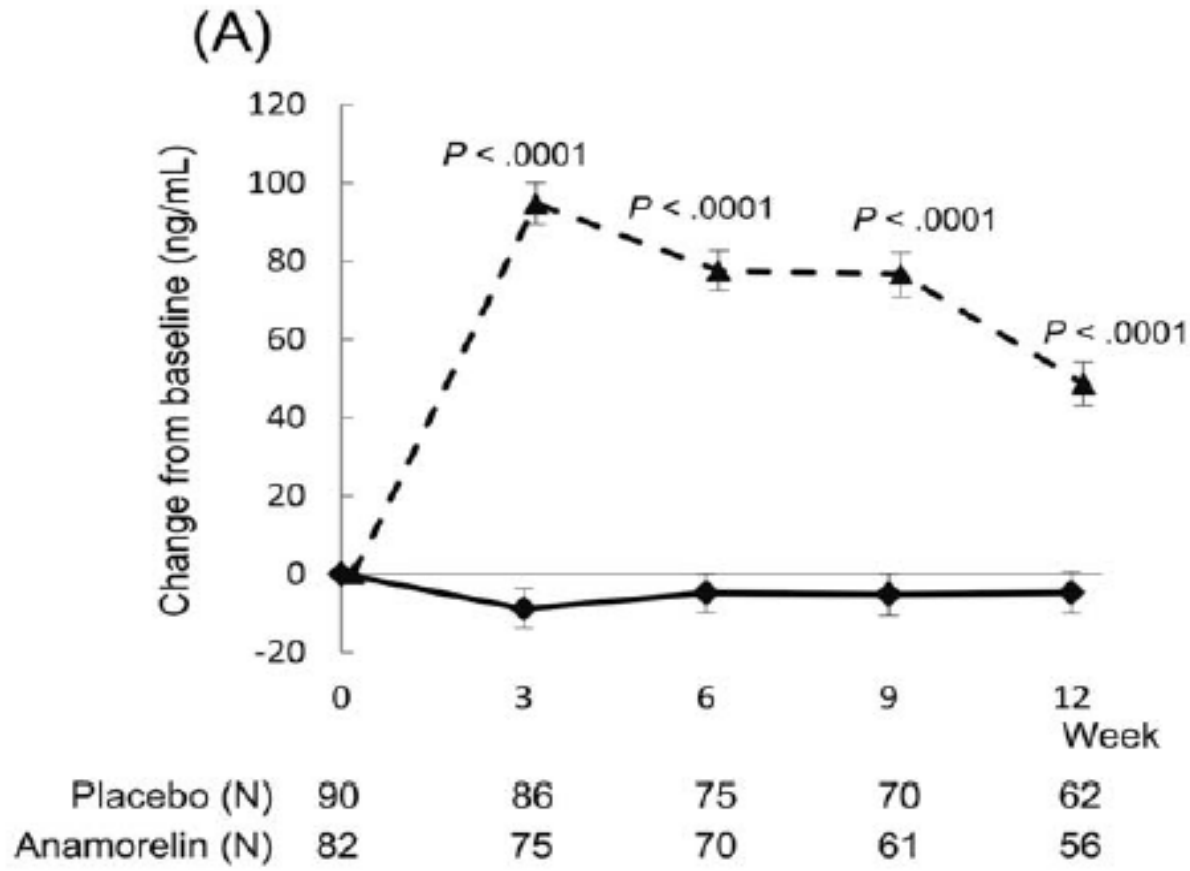


Figure 2. Tumour Ki67 for controls (A) and weight loss group (B) at biopsy and surgery ($P = 0.0298$ controls baseline-to-surgery; $P = 0.0128$ weight loss group baseline-to-surgery).

INCREASE OF ILGF-1 DUE TO ANAMORELIN ADMINISTRATION DOES NOT IMPACT ON SURVIVAL



from Takayama et al. 2016



from Katakami et al. 2017

TOPICS

- Few historical and biological musings
- Nutrients consumption by human tumors *in vivo*
- Effects of the nutritional status and of calorie restriction or nutrients administration (compared with postabsorbitive status or no-PN controls) on tumor growth in cancer patients
- Biological and clinical effects of Ketogenic diets
- Effects of dietary restriction during the oncologic therapy
- Conclusions

DIETARY MANIPULATIONS INDUCING THE KETOGENIC STATE

- Total starvation (KB levels 3-7 mM)
- Semistarvation KG diets (<800 kcal/d) with only protein and <50 g CHO (KB levels 0.5-1 mM)
- Mildly hypocaloric-eucaloric KG diets without caloric restriction (70%-80% fat calories, few proteins and < 50 g CHO)

RATIONALE FOR THE KETOGENIC DIET

- **Many tumors are dependent on glucose for energy support** because of
  a. activation of growth factor receptor/PI3 kinase/Akt signaling and
  b. loss of p53 wild-type activity and reduced expression of synthesis of cytochrome oxidase 2 necessary for the function of the mitochondrial respiratory chain and
  c. loss of tp53-induced glycolysis and apoptosis regular (TIGAR), which suppresses glycolysis
  d. tumor hypoxia might stimulate accumulation of HIF-1α and subsequent expression in the suppression of oxidative phosphorylation
- **Many cancer cells lack of ketolytic enzymes**
- **β-hydroxybutyrate**, is an endogenous histone deacetylase inhibitor, which **induces cell cycle arrest, differentiation and/or apoptosis**
- **KB may improve mitochondrial function**
- **KB are efficient in several rodent tumor models**

Schroeder *et al.* Decline of lactate in tumor tissue after ketogenic diet: in vivo microdialysis study in patients with head and neck cancer.

Nutr Cancer. 2013;65(6):843-9

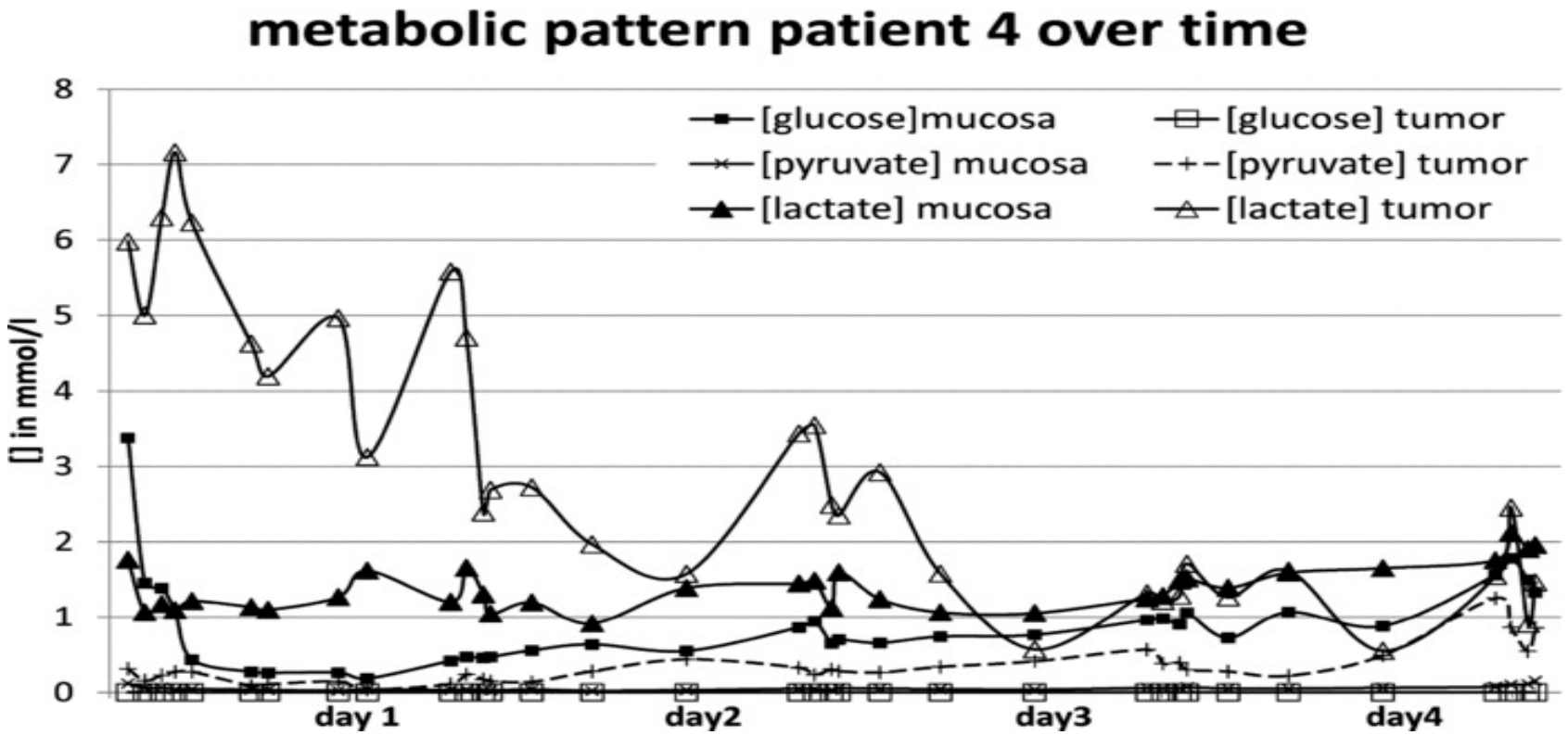
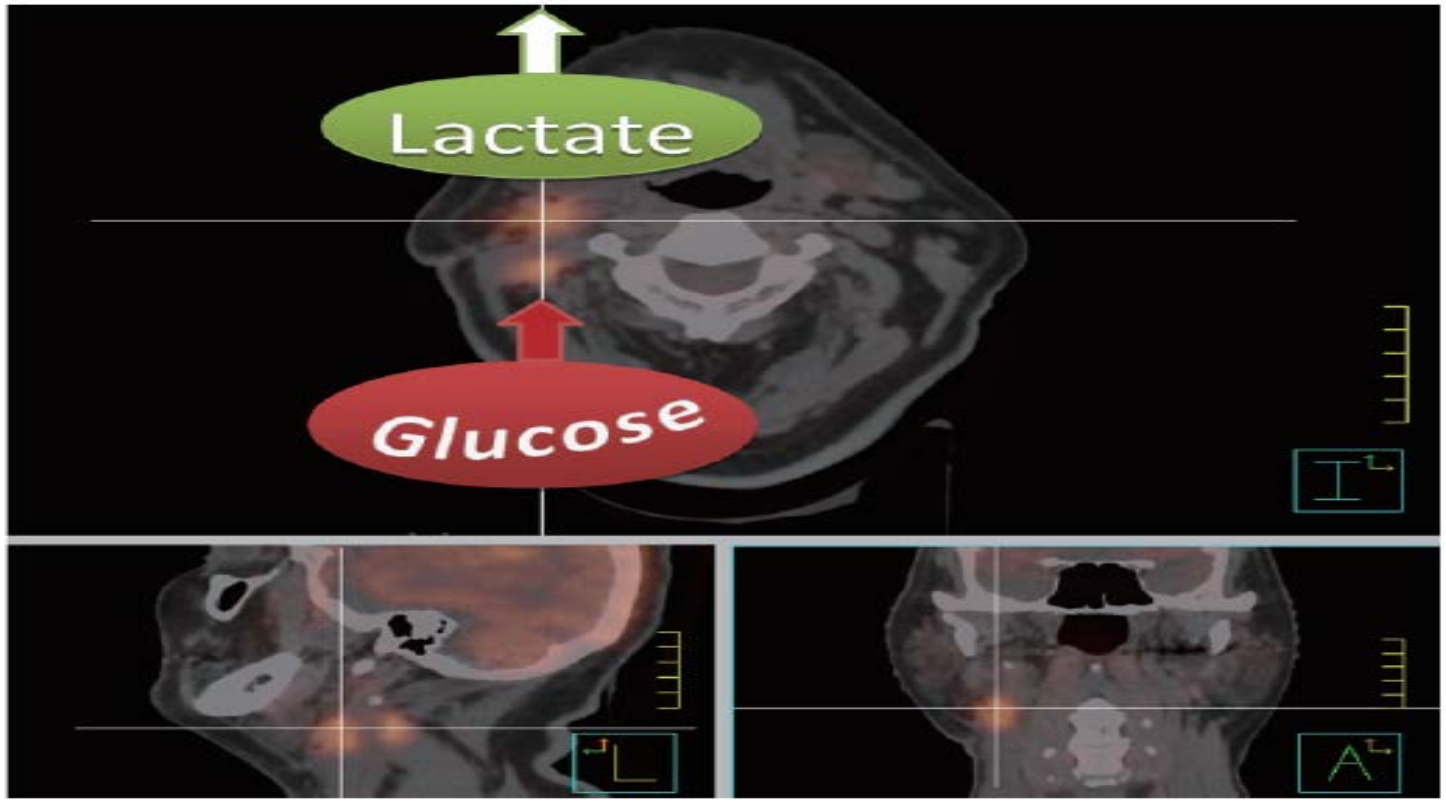


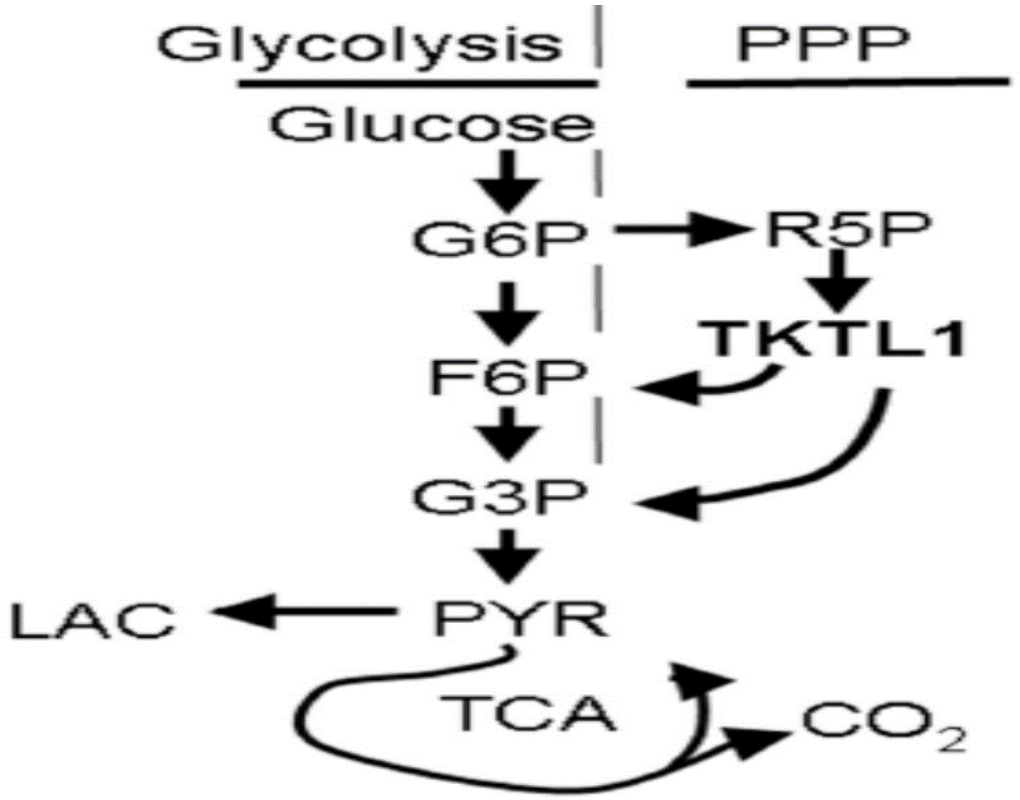
FIG. 2 Concentrations of glucose, lactate and pyruvate over time (Day 2–5 ketogenic diet) in patient No. 4 with the µD-catheter in the N3 lymph-node metastasis. y-axis: Concentrations of glucose, lactate and pyruvate; x-axis: time in days.

Klement R. Restricting carbohydrates to fight head and neck cancer-is this realistic? ***Cancer Biol Med. 2014;11(3):145-61.***



Jansen N, Walach H. The development of tumours under a ketogenic diet in association with the novel tumour marker TKTL1: A case series in general practice. *Oncol Lett. 2016; 11(1):584-592*.

TKTLI ENHANCES THE PRODUCTION OF GLUCOSE-6-P AND GLYCERALDHEIDE-3-P



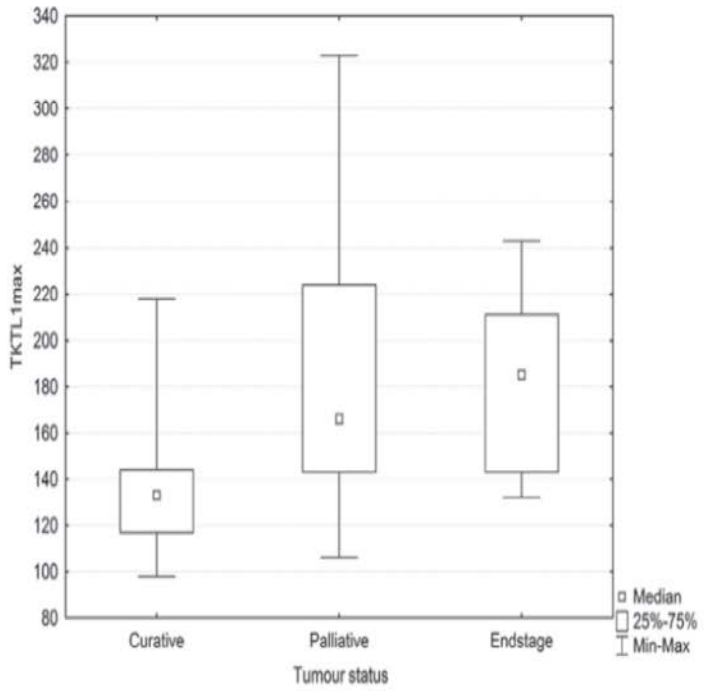


Figure 1. Maximum values of TKTL1 (TKTL1 max) according to tumour status. Box plot of the median, interquartile and full range by group. Significant differences were observed between the groups (Kruskal-Wallis test, P=0.0002). TKTL1, transketolase-like-1; min, minimum; max, maximum.

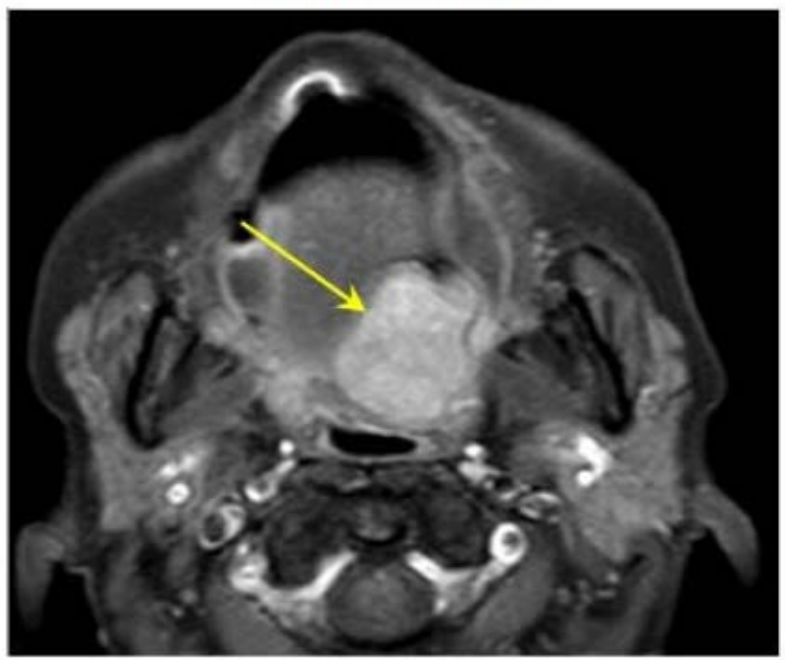
American Journal of Medical Case Reports, 2016, Vol. 4, No. 8, 288-292
Available online at http://pubs.sciepub.com/ajmcr/4/8/8

DOI:10.12691/ajmcr-4-8-8

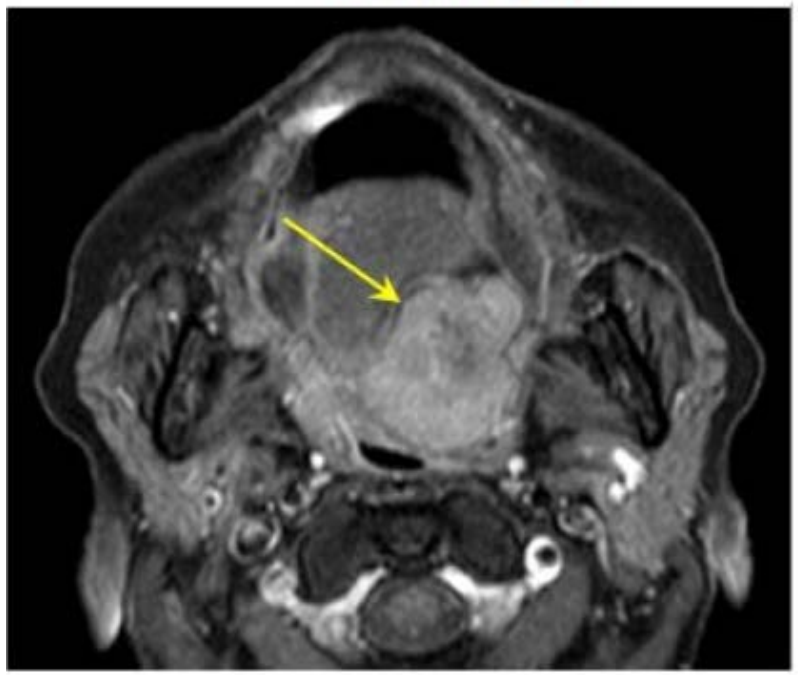
Halted Progression of Soft Palate Cancer in a Patient Treated with the Paleolithic Ketogenic Diet Alone: A 20-months Follow-up

Csaba Tóth[1], Zsófia Clemens[1,2,*]

20 Dec 2014



12 Jan 2016



Bozzetti F, Gavazzi C, Mariani L, Crippa F.
Glucose-based total parenteral nutrition does not stimulate glucose uptake by humans tumours. *Clin Nutr. 2004;23:417-21*

STANDARDIZED UPTAKE VALUE of FDG in FASTING CONDITION			
CR LIVER M+	LIVER	METASTASIS	METASTASIS/LIVER ratio
12 patients	435.1	1433.2	3.2

Bozzetti F, Gavazzi C, Mariani L, Crippa F.
Glucose-based total parenteral nutrition does not stimulate glucose uptake by humans tumours. Clin Nutr. 2004;23:417-21

STANDARDIZED UPTAKE VALUE (SUV) of FDG				
PATIENTS	**NORMAL LIVER**		**METASTASIS**	
	Fasting	**After load**	**Fasting**	**after load**
GLUCOSE PN *4 mg/kg/min* **(6 patients)**	**245.1**	**391.6 (+ 60%)**	**745.9**	**788.6 (+ 5%)**
LIPID PN *2 mg/kg/min* **(6 patients)**	193. 9	210.4 (+ 8%)	687.3	649.6 (- 6%)

Overview of normo-caloric ketogenic dietary regimes applied to oncology patients: case reports

AUTHOR	# PTS	PRIMARY	KD REGIMEN	DURATION	OUTCOME
Nebeling 1995	2	astrocytoma	60% MCT oil 10% LCT-based KD	?	After 8 weeks ↓ 21% FDG Healthy after 4 years
Bozzetti 1996	1	desmoid	Lipid-based TPN, 40 g CHO x os	5 mos	unchanged tumor mass
Branca 2015	1	breast	Self-administered KD	3 wks	
Klement 2016	6	mixed	Fat 73%, CHO 40 g	1-2.5 mos	No adverse effects, weight loss

mod. from Erickson et al. 2017

KD regimes: effects on tumor outcome patients without oncologic therapy

AUTHOR	PTS	PRIMARY	KD REGIMEN	DURATION	OUTCOME
Rossi Fanelli 1991	9 vs 27	GI	FAT vs CHO PN vs oral diet (EUCAL)	2 wks	= Labeling Index
Bozzetti 2004	12	CR liver M+	FAT vs CHO PN (EUCAL)	During infusion	ns↓ in FDG uptake
Schroeder 2013	20	Head-neck	nd	4 days	↓ tumor lactate
Chu-Shore 2010	4	Tub Scler C	EUCAL	3 mos-5 yrs	= tumor mass
Fine 2012	10	miscellanea	EUCAL	28 days	↓/= tumor mass in 6/10
Schmidt 2013	16	miscellanea	<70 g CHO (HYPO.EUCAL)	3 mos	= tumor mass in 7/11
Rieger 2014	17	glioblastoma	60 g CHO	6 weeks	↓ 0/17
Schwartz (2015)	2	glioblastoma	EUCAL	3-12 mos	↓ tumor mass in 0/2
Jansen 2016	7	miscellanea	HYPO/EUCAL	5 mos?	↓ tumor mass in 3/11
Tan-Shalaby 2016	14	miscellanea	20-40 g CHO (EUCAL)	4 mos	↓tumor mass in 7/7

THE FUTURE BEYOND THE KETOGENIC DIET IN HIGHLY GLYCOLYTIC CANCERS (SUV > 5) *

- REDUCING PHARMACOLOGICALLY BLOOD GLUCOSE: In vitro tests showed that blood glucose reduction to 36 mg/L for 180 min through insulin adminstration can reduce tumor cells growth (Mathews 2013)
- POTENTIATING KETOSIS: addition of exogenous ketone supplements (MCT, ketone salts and/or esters) to KG diet
- ADDING METFORMIN (500 mg/d): it decreases basal glucose by suppressing hepatic gluconeogenesis and glycogenolysis, as well as by increasing glucose uptake in muscle tissue
- ADDING ATENOLOL (50 mg/d) to suppress glucose counter-regulation
- ADJUSTING DOSES to maintain a GKI value of less than 2.0 (preferably 1.0)

* *from Mathews 2018*

TOPICS

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- Biological and clinical effects of Ketogenic diets
- Effects of dietary restriction during the oncologic therapy
- Conclusions

Shingler et al. Dietary restriction during the treatment of cancer: results of a systematic scoping review.
BMC Cancer. 2019;15;19(1):811

- Ketogenic Diet:10 studies
- Fasting: 4 studies
- Protein restriction: 5 studies
- Combined interventions: 4 studies

Conclusions

Future research with adequately powered studies is required to test the effects of each DR intervention on treatment toxicities and outcomes. Further research into improving adherence to DR may improve the feasibility of larger trials.

CONCLUSION (I)

- Nutrients consumption by human tumors *in vivo:*
  - *most human tumors utilize glucose*
- Effects of the nutritional status and of calorie restriction or nutrients administration on tumor growth
  - *good nutritional status is not associated with higher tumor proliferation, on the contrary losing weight may be associated with faster proliferation*
  - *some studies on pts on PN showed increased «proliferative» markers but long-term studies showed that increasing food intake and consequent ↑IGF-1 is not associated with poor outcome*

CONCLUSION (II)

- Biologic and clinical effects of ketogenic diets
  - *in glycolytic tumors, short-term studies would indicate a metabolic interference of the KD on glucose utilization, long-term studies would suggest a check on tumor growth in about 50% of patients.*
  - *High SUV, high level of TKTL1, BRAF and Kras status could address the use of KG diet*
- Effect of dietary restriction during the oncologic therapy
  - *data are quite preliminary and would suggest some benefit on early compliance with chemotherapy*

…knowledge is the enemy of disease…

Federico Bozzetti gave indipendent lectures at scientific and educational events also sponsored by nutritional industries. There is no conflict of interest