Meeting nutritional needs of acute care patients

Fasting or feeding before chemotherapy

R. Caccialanza (IT)
Fasting or feeding before chemotherapy?

Riccardo Caccialanza

UOC Dietetica e Nutrizione Clinica
Fondazione IRCCS Policlinico San Matteo

r.caccialanza@smatteo.pv.it
Conflicts of interests: consulting for

- AKERN
- BAXTER
- B BRAUN
- ELI LILLY
- FRESENIUS KABI
- LEONARDO MEDICA
- NESTLE’ HEALTH SCIENCE
- NUTRICIA
Learning objectives:

• Know the animal evidence supporting fasting before chemotherapy

• Know the objective findings for fasting or feeding in human

• Know the risks of fasting in these cancer patients

• Know the potential alternatives to fasting in cancer patients to yield the same expected outcome
Investigation into the molecular mechanisms of autophagy performed over nearly two decades has greatly benefited research designed to improve human health. The role autophagy has in drug toxicity, pathophysiology and therapeutic outcomes, can be leveraged to design more effective treatment regimens. Methods for detecting and quantifying autophagy have immense potential in toxicological evaluations, and for the development of pharmaceuticals that specifically target autophagy for clinical applications. Autophagic function in cancer is complex, as autophagy is considered to have a tumor-suppressive function in healthy cells, but autophagy also promotes malignancy in tumor cells. As our knowledge of the autophagic process continues to grow, undoubtedly novel and innovative application of this information will serve to improve human health through the development of autophagy proteins as prognostic markers and drugs that target autophagy in pathologies.
Fasting: Molecular Mechanisms and Clinical Applications

Valter D. Longo¹,* and Mark P. Mattson²,³,*
Hunger Pains: Stimulating the Appetite of the Immune System for Cancer

Judson M. Engler* and Jonathan D. Powell†,*

Cancer cells

Normal Conditions

- Autophagy
- HO-1
- Apoptosis

Caloric Restriction

- Autophagy
- HO-1
- Apoptosis

Adenosine

ATP

Impaired Function

CD8

Treg

CD8

Treg
When less may be more: calorie restriction and response to cancer therapy

Clara H. O'Flanagan¹, Laura A. Smith¹, Shannon B. McDonell¹ and Stephen D. Hursting¹,²,³,⁴

Fig. 1 Mechanisms through which calorie restriction (CR) affects response to anticancer therapy. CR, fasting, or fasting-mimicking diets (FMDs) cause reduced Akt/mTOR and Ras signaling in normal cells, resulting in senescence, reduced growth, and protection from cytotoxic treatment, while in tumor cells, oncogenic signals remain and cells are sensitive to anti-mitotic therapies. CR, fasting, and FMD also reduce pro-inflammatory cytokines in the circulation and in the tumor microenvironment niche, as well as reduced leptin, insulin, IGF-1, and glucose. CR can reduce desmoplasia surrounding the tumor tissue, which may facilitate better therapeutic drug delivery to the tumor cells. CR can also aid in immunosurveillance of tumors by reducing Treg populations that inhibit cytotoxic CD8⁺ T cells. This figure has not been published elsewhere.
A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan

Sebastian Brandhorst,1,15 In Young Choi,1,15 Min Wei,1 Chia Wei Cheng,1 Sargis Sedrakyan,2 Gerardo Navarrete,1 Louis Dubbeu,3 Li Peng Yap,4 Ryan Park,4 Manlio Vinciguerra,6 Stefano Di Blasio,1 Hamed Mirzaei,1 Mario G. Mirisola,6 Patra Chidress,7 Lingyun Ji,3 Susan Groshen,3 Fabio Penna,8 Patrizio Odetti,10 Laura Perin,2 Peter S. Conti,4 Yuji Ikeno,11 Brian K. Kennedy,12 Pinchas Cohen,3 Todd E. Morgan,1 Tanya B. Dorff,1,15 and Valter D. Longo1,14,*

Rodent Diets

The FMD is based on a nutritional screen that identified ingredients that allow nourishment during periods of low calorie consumption (Brandhorst et al., 2013). The FMD consists of two different components designated as day 1 diet and day 2–4 diet that were fed in this respective order. The day 1 diet consists of a mix of various low-calorie broth powders, a vegetable medley powder, extra virgin olive oil, and essential fatty acids; day 2–4 diet consist of low-calorie broth powders and glycerol.

Day 1 diet contains 7.67 kJ/g (provided at ~50% of normal daily intake; 0.46 kJ/g protein, 2.2 kJ/g carbohydrate, 5.00 kJ/g fat); the day 2–4 diet is identical on all feeding days and contains 1.48 kJ/g (provided at ~10% of normal daily intake; 0.01 kJ/g protein/fat, 1.47 kJ/g carbohydrates).
A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan

Sebastian Brandhorst,¹,¹⁶ In Young Choi,¹,¹⁶ Min Wei,¹ Chia Wei Cheng,¹ Sargs Sodrakyan,² Gerardo Navarrete,¹ Louis Dubéau,³ Li Peng Yap,⁴ Ryan Park,⁴ Manlio Vinciguerra,⁵ Stefano Di Biase,¹ Hamed Mirzaei,¹ Mario G. Mirisola,⁶ Patra Childress,⁷ Lingyun Ji,⁸ Susan Groschen,⁹ Fabio Penna,¹⁰ Patrizio Odetti,¹⁰ Laura Perin,² Peter S. Conti,⁴ Yuji Ikeno,¹¹ Brian K. Kennedy,¹² Pinchas Cohen,³ Todd E. Morgan,¹ Tanya B. Dorff,¹,¹³ and Valter D. Longo¹,¹⁴,*

Human Diet

The human fasting mimicking diet (FMD) program is a plant-based diet program designed to attain fasting-like effects while providing micronutrient nourishment (vitamins, minerals, etc.) and minimize the burden of fasting. It comprises proprietary vegetable-based soups, energy bars, energy drinks, chip snacks, chamomile flower tea, and a vegetable supplement formula tablet (Table S4). The human FMD diet consists of a 5 day regimen: day 1 of the diet supplies ~1,090 kcal (10% protein, 56% fat, 34% carbohydrate), days 2–5 are identical in formulation and provide 725 kcal (9% protein, 44% fat, 47% carbohydrate).

<table>
<thead>
<tr>
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<tr>
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Starvation Promotes REV1 SUMOylation and p53-Dependent Sensitization of Melanoma and Breast Cancer Cells

Hong Seok Shim¹, Min Wei², Sebastian Brandhorst², and Valter D. Longo¹,²,³

Abstract

Short-term starvation or fasting can augment cancer treatment efficacy and can be effective in delaying cancer progression in the absence of chemotherapy, but the underlying molecular mechanisms of action remain elusive. Here, we describe the role of REV1, a specialized DNA polymerase involved in DNA repair, as an important signaling node linking nutrient sensing and metabolic control to cell fate. We show that REV1 is a novel binding partner of the tumor suppressor p53 and regulates its activity. Under starvation, REV1 is modified by SUMO2/3, resulting in the relief of REV1’s inhibition of p53 and enhancing p53’s effects on proapoptotic gene expression and apoptosis in breast cancer and melanoma cells. Thus, fasting in part through its effect on REV1 is a promising nontoxic strategy to increase p53-dependent cell death and to enhance the efficacy of cancer therapies. Cancer Res; 75(6): 1056–67. ©2015 AACR.
Fasting potentiates the anticancer activity of tyrosine kinase inhibitors by strengthening MAPK signaling inhibition

Irene Caffa¹, Vito D’Agostino², Patrizia Damonte¹, Debora Soncini¹, Michele Cea¹, Fiammetta Monacelli¹, Patrizio Odetti¹,³, Alberto Ballestrero¹,³, Alessandro Provenzani², Valter D. Longo⁴,⁵ and Alessio Nencioni¹,³

Tyrosine kinase inhibitors (TKIs) are now the mainstay of treatment in many types of cancer. However, their benefit is frequently short-lived, mandating the search for safe potentiation strategies. Cycles of fasting enhance the activity of chemo-radiotherapy in preclinical cancer models and dietary approaches based on fasting are currently explored in clinical trials. Whether combining fasting with TKIs is going to be potentially beneficial remains unknown. Here we report that starvation conditions increase the ability of commonly administered TKIs, including erlotinib, gefitinib, lapatinib, crizotinib and regorafenib, to block cancer cell growth, to inhibit the mitogen-activated protein kinase (MAPK) signaling pathway and to strengthen E2F-dependent transcription inhibition. In cancer xenografts models, both TKIs and cycles of fasting slowed tumor growth, but, when combined, these interventions were significantly more effective than either type of treatment alone. In conclusion, cycles of fasting or of specifically designed fasting-mimicking diets should be evaluated in clinical studies as a means to potentiate the activity of TKIs in clinical use.
Fasting Enhances the Response of Glioma to Chemo- and Radiotherapy

Fernando Safdie\(^1\)\(^\circ\), Sebastian Brandhorst\(^1\)\(^,4\)\(^\circ\), Min Wei\(^1\), Weijun Wang\(^2\), Changhan Lee\(^1\), Saewon Hwang\(^1\), Peter S. Conti\(^3\), Thomas C. Chen\(^2\), Valter D. Longo\(^1\)\(^\circ\)

Abstract

**Background:** Glioma, including anaplastic astrocytoma and glioblastoma multiforme (GBM) are among the most commonly diagnosed malignant adult brain tumors. GBM is a highly invasive and angiogenic tumor, resulting in a 12 to 15 months median survival. The treatment of GBM is multimodal and includes surgical resection, followed by adjuvant radio-and chemotherapy. We have previously reported that short-term starvation (STS) enhances the therapeutic index of chemotherapies by differentially protecting normal cells against and/or sensitizing tumor cells to chemotoxicity.

**Methodology and Principal Findings:** To test the effect of starvation on glioma cells in vitro, we treated primary murine GL26, rat C6 and human U251, LN229 and A172 glioma cells with temozolomide in ad lib and starvation conditions. In vivo, mice with subcutaneous or intracranial models of GL26 glioma were starved for 48 hours or chemotherapies and the effects on tumor progression and survival were measured. Starvation-mimicking conditions sensitized murine, rat and human glioma cells, but not primary mixed glia, to chemotherapy. In vivo, starvation, which causes a significant reduction in blood glucose and circulating insulin-like growth factor 1 (IGF-1) levels, sensitizes both subcutaneous and intracranial glioma models to radio- and chemotherapy.

**Conclusion:** Starvation-induced cancer sensitization to radio- or chemotherapy leads to extended survival in the in vivo glioma models tested. These results indicate that fasting and fasting-mimicking interventions could enhance the efficacy of existing cancer treatments against aggressive glioma in patients.
Short-term calorie and protein restriction provide partial protection from chemotoxicity but do not delay glioma progression

Sebastian Brandhorst a,b, Min Wei a, Saewon Hwang a, Todd E. Morgan a,c, Valter D. Longo a,*

Short-term starvation (STS) protects normal cells while simultaneously sensitizing malignant cells to high-dose chemotherapeutic drugs in mice and possibly patients. The fasting-dependent protection of normal cells and sensitization of malignant cells depends, in part, on reduced levels of insulin-like growth factor-1 (IGF-1) and glucose. Calorie restricted diets with defined macronutrient (carbohydrate, protein, fat) ratios were evaluated for the effects on stress sensitization markers and protection in mice treated with high-dose chemotherapy. We show that short-term CR significantly reduced both glucose and IGF-1 levels, but when specific macronutrient deficiencies were tested, only the complete lack of proteins reduced IGF-1 levels. Short-term 50% CR combined with either severe protein-deficiency or ketogenic diets improved chemotoxicity resistance similarly to the standard 50% CR, but did not result in the high protection caused by STS. Notably, a high protein diet reversed the beneficial effects of short-term CR. In a subcutaneous mouse model of glioma, feeding a low protein (4% calories from protein) diet for more than 20 days did not delay tumor progression once the tumor became palpable. Also, cycles of short-term (3 days) 50% CR did not augment the chemotherapy efficacy of cisplatin in a murine breast cancer model. These results indicate that the protection from chemotoxicity and retardation of the progression of certain tumors achieved with fasting is not obtained with short-term calorie and/or macronutrient restriction.
Caloric restriction mimetics (CRMs) mimic the biochemical effects of nutrient deprivation by reducing lysine acetylation of cellular proteins, thus triggering autophagy. Treatment with the CRM hydroxycitrate, an inhibitor of ATP citrate lyase, induced the depletion of regulatory T cells (which dampen anticancer immunity) from autophagy-competent, but not autophagy-deficient, mutant KRAS-induced lung cancers in mice, thereby improving anticancer immunosurveillance and reducing tumor mass. Short-term fasting or treatment with several chemically unrelated autophagy-inducing CRMs, including hydroxycitrate and spermiding, improved the inhibition of tumor growth by chemotherapy in vivo. This effect was only observed for autophagy-competent tumors, depended on the presence of T lymphocytes, and was accompanied by the depletion of regulatory T cells from the tumor bed.

**Significance**

Fasting can improve the efficacy of anticancer chemotherapy. We show here that this effect involves induction of autophagy in malignant cells, as well as an anticancer immune response. Fasting can be replaced by the administration of caloric restriction mimetics (CRMs), which—without causing weight loss—improve the efficacy of chemotherapy as well. The tumor growth-inhibitory effects of hydroxycitrate were epistatic to the inhibition of regulatory T cells. Altogether, our results reveal a common mechanism for the cancer protective properties of CRMs and point to the possibility of stimulating anticancer immune responses by inducing autophagy with well-tolerable CRMs in vivo.
Fasting inhibits hepatic stellate cells activation and potentiates anti-cancer activity of Sorafenib in hepatocellular cancer cells

Running title: Anti-fibrogenic and anti-cancer properties of fasting in liver cells

ORiana Lo Re1,2, Concetta Panebianco3, Stefania Porto4,5, Carlo Cervi5, Francesca Rappa6,7, Stefano Di Biase8, Michele Caraglia4,8,10, Valerio Pazienza3, Manlio Vinciguerra1,5

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RESULTS: Fasting decreased the proliferation and the activation of HSC. Repeated cycles of short-term starvation were safe in mice but did not improve fibrosis. Fasting synergized with Sorafenib in hampering HCC cell growth and glucose uptake. Finally, fasting normalized the expression levels of genes which are commonly altered by Sorafenib in HCC cells.

CONCLUSIONS: Fasting or fasting-mimicking diet diets should be evaluated in preclinical studies as a mean to potentiate the activity of Sorafenib in clinical use.
Safety and feasibility of fasting in combination with platinum-based chemotherapy

Tanya B. Dorff1, Susan Groshen2, Agustin Garcia1, Manali Shah1, Denice Tsao-Wei2, Huyen Pham3, Chia-Wei Cheng4, Sebastian Brandhorst4, Pinchas Cohen4, Min Wei4, Valter Longo4* and David I. Quinn1*

Abstract

Background: Short-term starvation prior to chemotherapy administration protects mice against toxicity. We undertook dose-escalation of fasting prior to platinum-based chemotherapy to determine safety and feasibility in cancer patients.

Methods: 3 cohorts fasted before chemotherapy for 24, 48 and 72 h (divided as 48 pre-chemo and 24 post-chemo) and recorded all calories consumed. Feasibility was defined as ≥ 3/6 subjects in each cohort consuming ≤ 200 kcal per 24 h during the fast period without excess toxicity. Oxidative stress was evaluated in leukocytes using the COMET assay. Insulin, glucose, ketones, insulin-like growth factor-1 (IGF-1) and IGF binding proteins (IGFBPs) were measured as biomarkers of the fasting state.

Results: The median age of our 20 subjects was 61, and 85% were women. Feasibility criteria were met. Fasting-related toxicities were limited to ≤ grade 2, most commonly fatigue, headache, and dizziness. The COMET assay indicated reduced DNA damage in leukocytes from subjects who fasted for ≥48 h (p = 0.08). There was a non-significant trend toward less grade 3 or 4 neutropenia in the 48 and 72 h cohorts compared to 24 h cohort (p = 0.17). IGF-1 levels decreased by 30, 33 and 8% in the 24, 48 and 72 h fasting cohorts respectively after the first fasting period.

Conclusion: Fasting for 72 h around chemotherapy administration is safe and feasible for cancer patients. Biomarkers such as IGF-1 may facilitate assessment of differences in chemotherapy toxicity in subgroups achieving the physiologic fasting state. An ongoing randomized trial is studying the effect of 72 h of fasting.

Trial registration: NCT00936364, registered prospectively on July 9, 2009.

Keywords: Fasting, Chemotherapy, Neutropenia, Oxidative stress, Insulin-like growth factor
The effects of short-term fasting on tolerance to (neo) adjuvant chemotherapy in HER2-negative breast cancer patients: a randomized pilot study

Stefanie de Groot, Maaike PG Vreeswijk, Marij JP Welters, Gido Gravesteijn, Jan JWA Boel, Anouk Jochems, Daniel Houtsma, Hein Putter, Jacobus JM van der Hoeven, Johan WR Nortier, Hanno Pijl and Judith R Kroep

Abstract

Background: Preclinical evidence shows that short-term fasting (STF) protects healthy cells against side effects of chemotherapy and makes cancer cells more vulnerable to it. This pilot study examines the feasibility of STF and its effects on tolerance of chemotherapy in a homogeneous patient group with early breast cancer (BC).

Methods: Eligible patients had HER2-negative, stage II/III BC. Women receiving (neo)-adjuvant TAC (docetaxel/doxorubicin/cyclophosphamide) were randomized to fast 24 h before and after commencing chemotherapy, or to eat according to the guidelines for healthy nutrition. Toxicity in the two groups was compared. Chemotherapy-induced DNA damage in peripheral blood mononuclear cells (PBMCs) was quantified by the level of γ-H2AX analyzed by flow cytometry.

Results: Thirteen patients were included of whom seven were randomized to the STF arm. STF was well tolerated. Mean erythrocyte- and thrombocyte counts 7 days post-chemotherapy were significantly higher ($P = 0.007$, 95% CI 0.106-0.638 and $P = 0.00007$, 95% CI 38.7-104, respectively) in the STF group compared to the non-STF group. Non-hematological toxicity did not differ between the groups. Levels of γ-H2AX were significantly increased 30 min post-chemotherapy in CD45 + CD3- cells in non-STF, but not in STF patients.

Conclusions: STF during chemotherapy was well tolerated and reduced hematological toxicity of TAC in HER2-negative BC patients. Moreover, STF may reduce a transient increase in, and/or induce a faster recovery of DNA damage in PBMCs after chemotherapy. Larger studies, investigating a longer fasting period, are required to generate more insight into the possible benefits of STF during chemotherapy.

Trial registration: ClinicalTrials.gov: NCT01304251, March 2011

Keywords: Early stage breast cancer, Chemotherapy, Short-term fasting, Toxicity, DNA damage
Fasting and Cancer Treatment in Humans: A Case series report

Fernando M. Safdie, Tanya Dorff, David Quinn, Luigi Fontana, Min Wei, Changhan Lee, Pinchas Cohen, and Valter D. Longo

Abstract: Short-term fasting (48 hours) was shown to be effective in protecting normal cells and mice but not cancer cells against high dose chemotherapy, termed Differential Stress Resistance (DSR), but the feasibility and effect of fasting in cancer patients undergoing chemotherapy is unknown. Here we describe 10 cases in which patients diagnosed with a variety of malignancies had voluntarily fasted prior to (48-140 hours) and/or following (5-56 hours) chemotherapy. None of these patients, who received an average of 4 cycles of various chemotherapy drugs in combination with fasting, reported significant side effects caused by the fasting itself other than hunger and lightheadedness. Chemotherapy associated toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI). The six patients who underwent chemotherapy with or without fasting reported a reduction in fatigue, weakness, and gastrointestinal side effects while fasting. In those patients whose cancer progression could be assessed, fasting did not prevent the chemotherapy-induced reduction of tumor volume or tumor markers. Although the 10 cases presented here suggest that fasting in combination with chemotherapy is feasible, safe, and has the potential to ameliorate side effects caused by chemotherapies, they are not meant to establish practice guidelines for patients undergoing chemotherapy. Only controlled-randomized clinical trials will determine the effect of fasting on clinical outcomes including quality of life and therapeutic index.
Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease

Min Wei,1* Sebastian Brandhorst,1* Mahshid Shelehchi,1 Hamed Mirzaei,1 Chia Wei Cheng,1 Julia Budniak,1 Susan Groshen,2 Wendy J. Mack,2 Esra Guen,1 Stefano Di Biase,1 Pinchas Cohen,1 Todd E. Morgan,1 Tanya Dorff,3 Kurt Hong,4 Andreas Michalsen,5 Alessandro Laviano,5 Valter D. Longo1,6†

Fig. 3. Post hoc analysis of metabolic variables in subgroups identified by severity of risk factors. Subjects from both study arms who completed three FMD
When less may be more: calorie restriction and response to cancer therapy

Clara H. O’Flanagan¹, Laura A. Smith¹, Shannon B. McDonell¹ and Stephen D. Hursting¹,²,³,⁴

Larger trials are currently underway to determine the potential for short-term fasting in reducing the side effects and efficacy of chemotherapies, and will likely be the launching point for future clinical trials with intermittent CR as a potential adjuvant therapy.
these interventions in the clinic. More preclinical studies are required to determine in which cancers, at which stage, and in what combinations CR mimetic drugs may prove most effective. Future studies should take into consideration (1) the risk of cachexia in a patient population, whereby those at high risk may benefit from a ketogenic diet or short-term fasting; (2) the immunologic state of the enrolled patients, when CR or rapamycin treatment may be detrimental to wound healing or inflammatory responses; and (3) the metabolic state of patients, with diabetic patients in particular being at risk of adverse effects during chronic CR or fasting regimens, whereby treatment with metformin or a ketogenic diet may be of benefit. While in the short-term studies will need to focus on the safety and added benefit to current therapies, future studies may also focus on the potential of CR in enhancing the response to lower doses of chemotherapy and radiation therapy. In summary, CR and its mimetics show promise as supportive anticancer therapies. Clinical studies are ongoing and will inform on the potential use of these dietary and drug treatments alongside conventional treatments.
Fasting vs dietary restriction in cellular protection and cancer treatment: from model organisms to patients

C Lee and VD Longo

The dietary recommendation for cancer patients receiving chemotherapy, as described by the American Cancer Society, is to increase calorie and protein intake. Yet, in simple organisms, mice, and humans, fasting—no calorie intake—induces a wide range of changes associated with cellular protection, which would be difficult to achieve even with a cocktail of potent drugs. In mammals, the protective effect of fasting is mediated, in part, by an over 50% reduction in glucose and insulin-like growth factor 1 (IGF-1) levels. Because proto-oncogenes function as key negative regulators of the protective changes induced by fasting, cells expressing oncogenes, and therefore the great majority of cancer cells, should not respond to the protective signals generated by fasting, promoting the differential protection (differential stress resistance) of normal and cancer cells. Preliminary reports indicate that fasting for up to 5 days followed by a normal diet, may also protect patients against chemotherapy without causing chronic weight loss. By contrast, the long-term 20 to 40% restriction in calorie intake (dietary restriction, DR), whose effects on cancer progression have been studied extensively for decades, requires weeks–months to be effective, causes much more modest changes in glucose and/or IGF-1 levels, and promotes chronic weight loss in both rodents and humans. In this study, we review the basic as well as clinical studies on fasting, cellular protection and chemotherapy resistance, and compare them to those on DR and cancer treatment. Although additional pre-clinical and clinical studies are necessary, fasting has the potential to be translated into effective clinical interventions for the protection of patients and the improvement of therapeutic index.

Conflict of interest

Valter Longo founded L-Nutra, which develops diets for cancer patients.
Fasting-induced differential stress sensitization in cancer treatment

S. Di Biase\textsuperscript{a} and V. D. Longo\textsuperscript{a, b}

**ABSTRACT**
Most tumors are generated and evolve under high-nutrient conditions, yet therapy does not include dietary changes generating a hostile environment for cancer cells. Because fasting promotes the most drastic change in the levels of plasma macro- and micro-nutrients, and consequently in glucose and growth factors, it has the potential to maximize cancer cell sensitization.

The broad acting but highly coordinated differential effect of fasting on normal and cancer cells that is mediated by the levels of various factors including glucose, amino acids, and growth factors makes this approach not only highly effective in animal studies but also a candidate for successful translation into clinical applications (as shown in Fig. 1). Thus, fasting mimicking diets (FMDs), which are as effective as fasting in promoting the protection of normal cells, and cancer cell death, are candidates for clinical application in the near future.

**Disclosure of potential conflicts of interest**
VDL has equity interest in L-Nutra, a company developing fasting mimicking diets.
Review

Protective effects of short-term dietary restriction in surgical stress and chemotherapy

Sebastian Brandhorst\textsuperscript{a}, Eylul Harputlugil\textsuperscript{b}, James R. Mitchell\textsuperscript{b,\textsuperscript{**}}, Valter D. Longo\textsuperscript{a,\textsuperscript{c,\textsuperscript{*}}}

In cancer treatment, a few studies now begin to explore the fasting-induced protection against chemotoxicity-related side effects.

In cases where cancer progression could be monitored, no evidence was found that fasting interferes with chemotherapy efficacy or protects the tumors.

Despite the findings outlined above, it is noteworthy that data on humans remain limited and not confirmed in well-conducted and sufficiently large randomized clinical trials.
Dietary restriction: could it be considered as speed bump on tumor progression road?

Antonina Cangemi¹ · Daniele Fanale¹ · Gaetana Rinaldi¹ · Viviana Bazan¹ · Antonio Galvano¹ · Alessandro Perez¹ · Nadia Barraco¹ · Daniela Massihiñia¹ · Marta Castiglia¹ · Salvatore Vieni¹ · Giuseppe Bronte¹ · Mario Mirisola¹ · Antonio Russo¹

Since dietary approaches represent an easy tool in delaying aging, healing from damages, and preventing the onset of age-related diseases, they may become efficient allies for cooperating in the treatment of tumors, even though STS seems to be more tolerated by sick patients. It is essential to understand each change or hidden feature induced by the processes described above to reap the benefits related to fasting.

The currently available data have associated the various dietary approaches to numerous biological processes (from cellular proliferation and vitality to inflammatory response) and to the response to the chemotherapy. Recent studies have reported that dietary restriction induces molecular changes in genes, including IGF-1 and its receptor, as well as downstream effectors. The modification regards also inflammatory cytokines and chemokines, such as IL-1β and TNF-α, and elements associated to apoptosis (Bax/Bcl-x). However, additional insights are needed. Moreover, it might be interesting to get more results in humans in order to ascertain the effect of fasting and create standard protocols that are able to correlate dietary approaches with chemotherapeutic treatments.
Change of Body Weight and Macrophage Inhibitory Cytokine-1 during Chemotherapy in Advanced Gastric Cancer: What Is Their Clinical Significance?

Zhihao Lu1,2, Li Yang3,4, Jingwei Yu1, Ming Lu1, Xiaotian Zhang1, Jian Li1, Jun Zhou1, Xicheng Wang1, Jifang Gong1, Jing Gao1, Jie Li1, Yan Li1, Lin Shen1*

Figure 2. Kaplan–Meier curves of overall survival (OS) of patients according to weight change before or during chemotherapy. A. OS curve of patients grouped by weight change trends during chemotherapy ($P=0.003$). B. OS curve of patients grouped by weight loss during chemotherapy ($P=0.000$). C. OS curve of patients with $>5\%$ weight loss before chemotherapy grouped by weight loss during chemotherapy ($P=0.004$). D. OS curve of patients with $\leq 5\%$ weight loss before chemotherapy grouped by weight loss during chemotherapy ($P=0.001$).
doi:10.1371/journal.pone.0088553.g002
Severe weight loss during preoperative chemoradiotherapy compromises survival outcome for patients with locally advanced rectal cancer

Junzhong Lin¹ · Jianhong Peng¹ · Aiham Qdaisat² · Liren Li¹ · Gong Chen¹ · Zhenhai Lu¹ · Xiaojun Wu¹ · Yuanhong Gao³ · Zhifan Zeng³ · Peirong Ding¹ · Zhizhong Pan¹

Fig. 3 Kaplan–Meier curve comparing 3-year overall survival (OS) rate by a baseline BMI classification, b BMI loss during preoperative chemoradiotherapy in patients with locally advanced rectal cancer
Loss of Lean Body Mass as an Independent Risk Factor for Continuation of S-1 Adjuvant Chemotherapy for Gastric Cancer

Toru Aoyama, MD\textsuperscript{1,2}, Taiichi Kawabe, MD\textsuperscript{1,2}, Hirohito Fujikawa, MD\textsuperscript{1,2}, Tsutomu Hayashi, MD\textsuperscript{1,2}, Takanobu Yamada, MD\textsuperscript{1,2}, Kazuhiro Tsuchida, MD\textsuperscript{1,2}, Norio Yukawa, MD\textsuperscript{2}, Takashi Oshima, MD, PhD\textsuperscript{2}, Yasushi Rino, MD\textsuperscript{2}, Munetaka Masuda, MD, PhD\textsuperscript{2}, Takashi Ogata, MD, PhD\textsuperscript{2}, Haruhiko Cho, MD\textsuperscript{3}, and Takaki Yoshikawa, MD, PhD\textsuperscript{1,2}

**FIG. 3** Comparison of the treatment continuation rates between patients who experienced a lean body-mass loss of $<5\%$ and those who lost more than $5\%$ of their lean body mass.
Finally, although recent animal model studies showed that pretreatment short-term starvation could improve chemotherapy (CT) efficacy and reduce toxicity by diminishing malignant cells’ resistance to drugs while protecting normal tissues (26), this hypothesis still needs to be confirmed in humans. Therefore, this practice is not recommended, particularly in malnourished patients and those at nutritional risk, since weight and lean body mass loss is associated with dose-limiting toxicity and mortality in patients undergoing CT.
ESPEN guidelines on nutrition in cancer patients

Jann Arends, Patrick Bachmann, Vickie Baracos, Nicole Barthelemy, Hartmut Bertz, Federico Bozzetti, Ken Fearon, Elisabeth Hütterer, Elizabeth Isenring, Stein Kaasa, Zeljko Krznaric, Barry Laird, Maria Larsson, Alessandro Laviano, Stefan Mühlebach, Maurizio Muscaritoli, Line Oldervoll, Paula Ravasco, Tora Solheim, Florian Strasser, Marian de van der Schueren, Jean-Charles Preiser

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<tr>
<td><strong>Level of evidence</strong></td>
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<tr>
<td><strong>Questions for research</strong></td>
<td>Effects of fasting or fasting mimicking diets on wanted and unwanted effects of anticancer agents</td>
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We recommend to not use dietary provisions that restrict energy intake in patients with or at risk of malnutrition.

Short-term (24–72 h) fasting before, during and after the application of anticancer agents has been suggested to possibly increase the effectivity and tolerability of cytotoxic treatment [180–184]. A small observational series and a small randomized trial reported good tolerability of this approach in humans [185,186]. Further trials are ongoing (NCT00936364, NCT00175837, NCT01802346, NCT02126449). Because of the risks of malnutrition and because patients might be tempted to prolong fasting episodes, without firm evidence of a benefit fasting during chemotherapy cannot be recommended.
Disinformation is a critical point with regard to nutrition for patients with cancer. Despite the lack of evidence-based data, hundreds of books and websites promote anticancer diets and nutritional supplements.
Fasting may be the best way to combat cancer. It boosts treatment, tests on mice show chemotherapy does not harm fetuses.
Overall Survival
Treatment Response
Toxicity
Progression-free Survival
Quality of Life
Treatment Tolerance
Nutritional support for cancer patients: still a neglected right?

1. Right to correct information and nutritional counseling: every cancer patient has the right to comprehensive evidence-based clinical information on her/his nutritional status, possible associated consequences and available nutritional therapeutic options; nutritional counseling to adapt her/his diet to suit ensuing medical, surgical or radiotherapeutic treatment.

Table 1 Cancer Patients’ Bill of Rights for appropriate and prompt Nutritional Support

1. Right to correct information and nutritional counseling: every cancer patient has the right to comprehensive evidence-based clinical information on her/his nutritional status, possible associated consequences and available nutritional therapeutic options; nutritional counseling to adapt her/his diet to suit ensuing medical, surgical or radiotherapeutic treatment.

2. Right to nutritional screening and assessment: every cancer patient has the right to nutritional screening to reduce the risk of malnutrition, using validated tools, both at diagnosis and at regular time points, while ensuring that the cancer type and stage are taken into account along with any treatment likely to affect nutritional status. Every cancer patient at nutritional risk has the right to prompt referral for comprehensive nutritional assessment and support to Clinical Nutrition Services or to medical personnel with documented skills in clinical nutrition. Nutritional assessment must be an integral part of any diagnostic-therapeutic regimes developed by Oncology Units.

3. Right to dietary prescriptions: every cancer patient at nutritional risk or malnutrition has the right to receive personalized dietary prescriptions by medical personnel with documented skills in clinical nutrition.

4. Right to oral nutritional supplements: every cancer patient at nutritional risk has the right, according to clinical conditions and specific nutrient deficiencies, to receive oral nutritional supplements, including vitamins and minerals.

5. Right to appropriate and prompt artificial nutrition: artificial nutrition is a complex therapeutic procedure that requires specific medical skills, as it may be associated with severe complications if not carried out according to evidence-based standard operating protocols. Every cancer patient at nutritional risk who is unable to maintain an adequate nutritional status despite nutritional counseling and oral nutritional support, has the right to receive appropriate and swift artificial nutrition in every healthcare setting, as part of continuing care.

6. Right to appropriate and safe home artificial nutrition: every cancer patient, who needs to continue artificial nutrition after hospital discharge, has the right to receive appropriate and safe home artificial nutrition, prescribed by Clinical Nutrition Services or medical personnel with documented skills in clinical nutrition.

7. Right to nutritional support monitoring: every cancer patient requiring nutritional support has the right to periodic reassessment of treatment adequacy and efficacy using established integrated health care regimes which ensure the collaboration of both Oncologists and Clinical Nutritionists.

8. Right to treatment for overweight-related health problems during or after cancer treatment: every cancer patient has the right to be referred to Clinical Nutrition Services, during or after oncologic rehabilitation programs, so that ideal body weight can be recovered or maintained, to avoid the negative impact of increased weight on prognosis and the clinical course of many cancer types.

9. Right to psychological support: malnutrition and overweight considerably affect body image and can cause problems within families. Any patient likely to experience such problems has the right to receive appropriate and swift psychological support.

10. Right to participate in clinical nutrition trials: every cancer patient has the right to be enrolled in clinical studies on nutritional support at different stages of the disease.
Chemolieve® è un protocollo dietetico Mirna Digiuno da seguire in 4 giorni studiato appositamente per il paziente oncologico per ridurre i numerosi effetti collaterali della chemioterapia e aumentare la morte delle cellule cancerose.

"I want you to take one of these every day until I think of something else."

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“I HOPE TO STAND FIRM ENOUGH TO NOT GO BACKWARD, AND YET NOT GO FORWARD FAST ENOUGH TO WRECK THE COUNTRY'S CAUSE.”

ABRAHAM LINCOLN