Perspective: Do Fasting, Caloric Restriction, and Diets Increase Sensitivity to Radiotherapy? A Literature Review

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ABSTRACT

Caloric starvation, as well as various diets, has been proposed to increase the oxidative DNA damage induced by radiotherapy (RT). However, some diets could have dual effects, sometimes promoting cancer growth, whereas proposing caloric restriction may appear counterproductive during RT considering that the maintenance of weight is a major factor for the success of this therapy. A systematic review was performed via a PubMed search on RT and fasting, or caloric restriction, ketogenic diet (>75% of fat-derived energy intake), protein starvation, amino acid restriction, as well as the Warburg effect. Twenty-six eligible original articles (17 preclinical studies and 9 clinical noncontrolled studies on low-carbohydrate, high-fat diets popularized as ketogenic diets, representing a total of 77 patients) were included. Preclinical experiments suggest that a short period of fasting prior to radiation, and/or transient caloric restriction during treatment course, can increase tumor responsiveness. These regimens promote accumulation of oxidative lesions and insufficient repair, subsequently leading to cancer cell death. Due to their more flexible metabolism, healthy cells should be less sensitive, shifting their metabolism to support survival and repair. Interestingly, these regimens might stimulate an acute anticancer immune response, and may be of particular interest in tumors with high glucose uptake on positron emission tomography scan, a phenotype associated with poor survival and resistance to RT. Preclinical studies with ketogenic diets yielded more conflicting results, perhaps because cancer cells can sometimes metabolize fatty acids and/or ketone bodies. Randomized trials are awaited to specify the role of each strategy according to the clinical setting, although more stringent definitions of proposed diet, nutritional status, and consensual criteria for tumor response assessment are needed. In conclusion, dietary interventions during RT could be a simple and medically economical and inexpensive method that may deserve to be tested to improve efficiency of radiation. *Adv Nutr* 2020;11:1089–1101.

Keywords: radiotherapy, fasting, caloric restriction, ketogenic diet, Warburg effect, immunity

Introduction

Background

The effect of conventional radiotherapy (RT) is mostly due to oxidative damage induced by reactive oxygen species (ROS) released during water radiolysis, in particular hydrogen peroxide (1). Oxygen is the best radiosensitizer, which favors ROS formation and oxidative stress–mediated damage (2). However, cancer tissues are often hypoxic (3). Therefore, to increase oxygen concentration in tumors, several pro-oxidative strategies have been proposed, such as hyperbaric oxygen therapy, blood transfusions, erythropoietin injection (4, 5), as well as hypoxia-inducible factor 1 (HIF-1) inhibitors (6) and oxygen mimetics compounds (7, 8). In recent times, there has been increasing interest by the general public in the use of natural products and diet regimens for cancer prevention and improvement in the efficacy and tolerability of cancer treatment.

However, the impact of dietary measures on response to radiation has been poorly elucidated. It has been reported that nutrient deprivation stimulates hydrogen peroxide production in cancer cells and promotes oxidative stress in response to RT (9, 10). However, since maintenance of an

appropriate BMI is a major determinant of RT efficacy (11–13), it may appear counterproductive to propose dietary restrictions during this period. In a recent review of >200 cancer patients consuming ketogenic diets (KDs) (14), it was concluded that the "probability of achieving an anti-tumor effect seemed greater with KDs than that of causing serious side effects." To clarify these issues, we conducted a systematic review examining the potential benefit of various nutritional interventions during RT, such as short fasting (SF), caloric restriction (CR), KD, and protein/amino acid restriction, to increase tumor response and survival.

Hallmarks of tumor cell metabolism

Cancer cells, even in presence of normal oxygen concentration, consume great amounts of glucose and release lactic acid, a phenomenon called the "Warburg effect" (15, 16). This metabolic anomaly is sustained by a complex interaction among different factors such as inactivation of onco-suppressor genes (p53), activations of oncogenic (MYC and RAS) and hypoxia-related (HIF-1) pathways, promotion of the proliferative signaling axis mediated by the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR), as well as loss of mitochondria, dysfunction of the tricarboxylic acid cycle (TCA) cycle, and of the respiratory chain (17,18). The large consumption of glucose and calories sustains biosynthesis while mitochondrial ATP, citrate and ROS production are maintained in adequate ranges for active proliferation (19). Lactate, released in the microenvironment, promotes invasiveness, suppresses immune response, and can fuel the oxidative metabolism of well-oxygenated cancer cells. This recycling pathway allows sparing of glucose for most hypoxic cancer cells (20). The presence of these metabolic features is in accordance with the observed correlation between a high uptake of ^{18F}-fluorodeoxyglucose (^{18}FDG) by tumors in positron emission tomography (^{18}FDG-PET) scan and a highly glycolytic metabolism, translating into increased resistance to chemotherapy (CT) and RT (21) and poor survival (22, 23).

Definition of dietary interventions

SF is a complete cessation of all caloric intake for a limited interval of time (24), while CR is usually defined as a reduction in calorie intake of ≥20–30%, without restriction of water (25). CR is usually limited to a maximum of 3 d; however, repeated cycles are possible (26,27). Severe and prolonged CR (<600–800 kcal/d) corresponds to a very low caloric intake. For instance, a low-caloric diet provides between 10 and 20 kcal/kg of "desirable" body weight, while a very-low-caloric diet provides ≤10 kcal/kg of desirable weight intake (28).

Low-carbohydrate/lipid-rich diets have been proposed and popularized as KDs. There is no consensus on a definition of KDs: in general, fat intake accounts for >75% of energy intake. The traditional 4:1 ratio is composed, in total calories, of 90% lipids, 8% proteins, and 2% carbohydrates, respectively (26, 27). Less-strict KDs have recently emerged, with ratios of 3:1 and even 2:1, and thus many current "KDs" often contain more protein. Thus, some KDs mimic the so-called Atkins diet, which did not restrict consumption of calories or proteins and was historically tested for intractable epilepsy (29), or can contain more carbohydrates due to a high proportion of medium chain triglycerides, which promote liver ketone body synthesis (27). In cancer research, isocaloric KDs are mostly used in order to maintain weight, which is essential for cancer patients undergoing therapy, and should be distinguished from nonisocaloric KDs that combine this strategy with moderate CR.

Protein restriction (PR) is defined by a reduction in protein intake, representing <12.5% of total calories without CR (14). It should also be considered that, beyond their raw caloric value, dietary proteins are also a source of essential (not synthesized by eukaryotic organisms) and conditionally essential amino acids, whose synthesis can be limited under special pathophysiological conditions: an imbalance in the pool of amino acids absorbed through diet may have important metabolic implications in protein synthesis. For this reason, a dietary strategy based on selective amino acid deprivation may target specific metabolic patterns that are impaired in cancer cells (30).

Interplay of nutritional state with radiation sensitivity

Radiation induces oxidative stress by increasing ROS production, most notably superoxide ion released at the level of complex I and III of the respiratory chain. Thus, superoxide likely damages in first instance mitochondrial DNA, which is located in proximity of the respiratory chain and is not protected by histone proteins, as opposed to nuclear DNA (31). It is noteworthy that manganese superoxide dismutase (MnSOD)—converting superoxide to hydrogen peroxide, a less toxic compound—is located in mitochondria (31), suggesting that mitochondrial "dysfunction" (32, 33) has a major role in carcinogenesis through loss of mitochondria (34) and/or altered metabolism (35).

Delivery of an effective RT dose is limited by its toxicity on healthy tissues, especially on proliferating cells (bone marrow, gastrointestinal, hair follicles, and heart cells). Hence, it is of primary importance to selectively increase tolerance and recovery of normal cells. Unfortunately, radioprotective

The authors reported no funding received for this work.
Author disclosures: The authors report no conflicts of interest.
Supplemental Figure 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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Abbreviations used: AKT, protein kinase B; AMPK, AMP-activated protein kinase; CR, caloric restriction; CT, chemotherapy; FAO, fatty acid oxidation; HIF-1, hypoxia-inducible factor 1; IGF-I, insulin-like growth factor I; IGF-IR, insulin-like growth factor I receptor; KD, ketogenic diet; MnSOD, manganese superoxide dismutase; mTOR, mammalian target of rapamycin; OXPHOS, oxidative phosphorylation; PD-1, programmed death 1; PI3K, phosphatidylinositol 3-kinase; PR, protein restriction; ROS, reactive oxygen species; RT, radiotherapy; SCOT, succinyl-coenzyme A-3-ketoacid-CoA transferase; SF, short fasting; SIRT3, sirtuin-3; TBNC, triple-negative breast cancer; TCA, tricarboxylic acid cycle; TMZ, temozolomide; 3β-OHBD, 3β-hydroxybutyrate dehydrogenase; 3β-OHB, 3β-hydroxybutyrate; 18FDG-PET, 18F-fluorodeoxyglucose–positron emission tomography.

properties of natural antioxidants (e.g., glutathione, vitamin E, and analogs) or synthetic compounds (amifostine) are limited or questioned (36). Interestingly, SF, CR, and a KD could exert radioprotective effects because healthy cells would more efficiently adapt to glucose starvation than cancer cells, which led to a concept of a "differential stress resistance" (37–39) (**Supplemental Figure 1**).

The rational explanation supporting differential stress resistance is that metabolism of healthy cells is censored by suppressive control checkpoints [Rb, p53, p21, phosphatase and tensin homolog (PTEN), sirtuin-3 (SIRT3)], and is thus more flexible than cancer cell metabolism, which lacks censoring mechanisms (40, 41).

In healthy cells, glucose starvation induces a downregulation of the PI3K/AKT/mTOR proliferative pathway, resulting in the inhibition of the Warburg effect (42, 43), while activation of AMP-kinase (AMPK), the key energy sensor, activates fatty acid oxidation (FAO) and inhibits glycolysis (44). Of note, FAO is the most efficient catabolic pathway generating ATP and NAD. Both molecules, sustaining cell survival and repair, are regulated by p53, p21, the protein kinase forkhead box protein O3 (FOXO3), and the NAD+-dependent poly[ADP-ribose]polymerase 1 (PARP1) (45–47). Additionally, ROS neutralization is promoted by NAD+-dependent SIRT3, which upregulates MnSOD2 and also counteracts the Warburg effect (48–50).

Glucose-starved cancer cells may escape these regulatory checkpoints, particularly when driven by strong oncogenic signals such as RAS/RAF, insulin-like growth factor I (IGF-I) axis, mitogen-activated protein kinase (MAPK), and c-Myc dictating an anabolic metabolism and forcing cells to replicate (51, 52), especially as suppressive controls are defectives. This can have important consequences for the metabolic assets of tumor cell, due to the dual-faceted activity of key regulator enzymes: for example, AMPK may shift from a profile characterized by a dominant activation β-subunit of AMPK, which promotes glycolysis and inhibits oxidative phosphorylation (OXPHOS) (44), to a prevalent activation of the α-subunit (53,54) under glucose starvation, thus forcing cancer cells to increase OXPHOS and generating more ATP with an increase in ROS production.

Similarly to SF and CR, KDs induce chronic glucose starvation since, in contrast with normal cells found in healthy tissues (in particular, the brain, heart, and muscle), cancer cells cannot catabolize either exogenous (supplied by dietary intake) fatty acids or endogenous ketone bodies (derived from FAO and released by the liver) to produce energy (55,56) because they lack catabolizing mitochondrial enzymes [i.e., 3β-hydroxybutyrate dehydrogenase (3β-OHBD) and succinyl-CoA:3-ketoacid CoA transferase (SCOT)] (56).

Concerning the interest of protein/amino acid restriction, it must be noted that biosynthesis and proliferation of various cancer cells lines can be supported by other nutrients than glucose (i.e., glutamine), especially in case of glucose starvation (57,58). Starvation in amino acids can inhibit tumor proliferation, as shown by arginine (59,60), serine, glycine (61), or methionine deprivation (62). Interestingly, cisplatin-resistant cells appear to be very sensitive to glutamine starvation (63). Arginine deprivation can counteract cancer development because the molecule is a precursor of polyamines, NO, and proline. An arginine diet could be effective in many cancers knowing that arginine-succinate synthetase 1 (ASS1) is commonly reduced or lost in liver cancer, metastatic melanoma, renal cell carcinoma, platinum refractory ovarian tumor, and in almost 90% of sarcomas regardless of their subtypes (60). In sarcoma, arginine deprivation with pegylated arginine deiminase induces cancer cell death if it is associated with chloroquine, an inhibitor of autophagy (60).

Current Status of Knowledge

Search methodology

A literary search was performed in PubMed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (64) using the following keywords: fasting, caloric restriction, ketogenic diet, protein restriction, amino-acid restriction, Warburg effect, and cancer and radiation. Evaluation of appropriateness was independently carried out by 2-author teams with expertise in radiation oncology and tumor metabolism (ML and MA, PI and LO). In case of inconsistency or disagreement, a final decision was formulated with a third author team (JT and PF). Thus, we identified 484 potentially eligible articles and checked their references for additional articles. Using this manual ad hoc checking, we found 7 additional articles. The progression of this methodology is summarized in **Figure 1**. After duplicates were removed, 90 articles remained. Among them, according to a consensus of all authors, we finally identified 26 eligible articles that reported data on RT and diets. In total, we found 9 original studies on cultured cells, 8 original studies in murine models, and 9 clinical studies including 2 case reports.

Preclinical experiences in SF and CR

In vitro experiments showed that near-complete SF increases cancer cell sensitivity to RT in various cancer cell lines (65,66). In a preclinical model of SF, hepatocellular carcinoma (HepG2), and hepatoblastoma cells (HuH6-clone5) were cultured in serum-free media for 6 to 24 h, showing increased sensitivity to RT (range: 0–10 Gy) correlated with activation of mTORC1, a critical pathway involved in ROS-mediated cell damage detection (via ATM) and repair (via modulation of autophagy) (65). Glucose starvation for 24 h increased DNA damage and double-strand-break DNA lesions induced by RT in the lung adenocarcinoma A549 cells and in the head and neck squamous cancer FaDu cells, while normal HSF7 fibroblasts were not affected by glucose starvation (66). Another model of glucose starvation, induced by inhibition of glucose uptake with 2-deoxyglucose, also increased sensitivity to radiation (2 Gy) in radioresistant rSCC-61 head and neck cancer cells (67).

In vivo experiments studying short-term SF and CR associated with RT on different mice models of cancers are

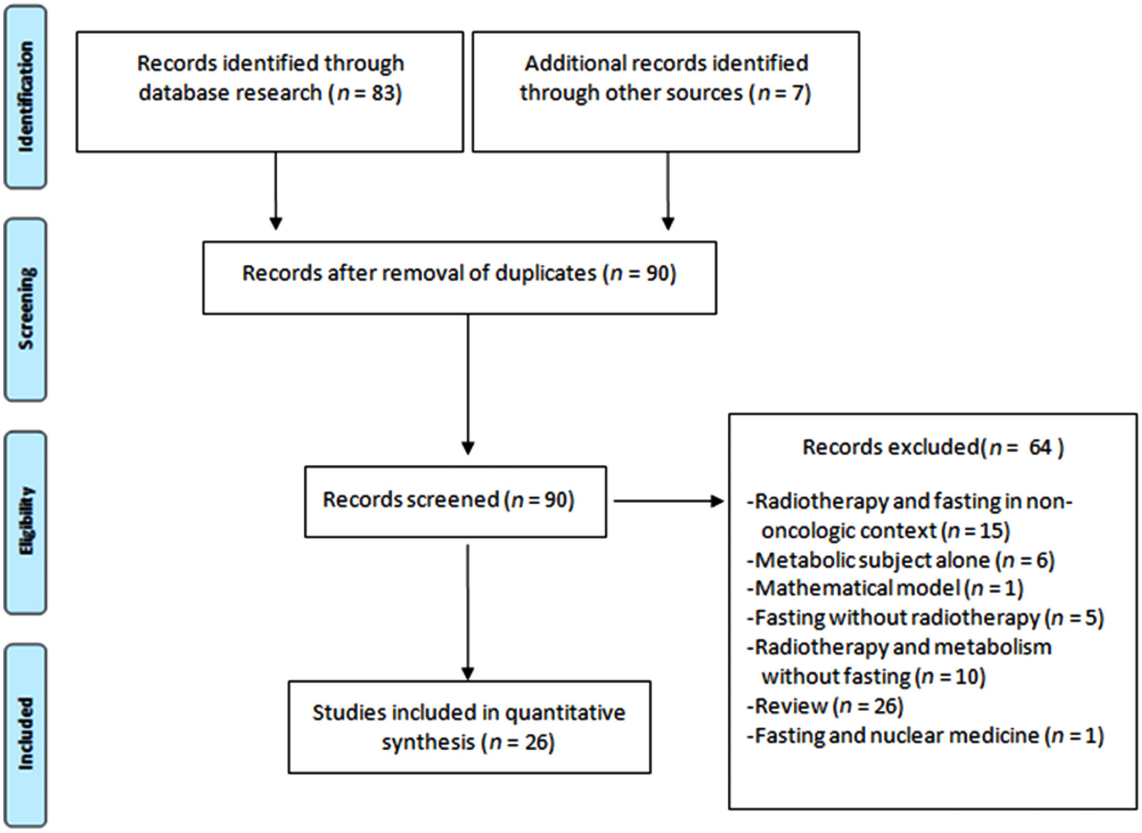

FIGURE 1 Flowchart for the literary search according to PRISMA. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

reported in **Table 1** (68–72). In summary, a CR of 30% increased tumor regression or delayed occurrence of metastases in 3 animal models of mammary tumors, including 2 models of triple-negative breast cancer (TNBC) (71, 72). The decrease in metastatic dissemination of tumor cells correlated with the downregulation of IGF-I receptor (IGF-IR), and PI3K/mTOR pathways, as well as the inhibition of the microRNA-17/20a cluster regulating expression of extracellular membrane proteins (72, 73). More pronounced caloric starvation (70% CR), coupled with low-dose irradiation (0.04 Gy) induced regression of spontaneous mammary cancers in C3H/He mice, associated with massive infiltration of cytotoxic $CD8^+$ T cells (69). SF for 48 h, prior to RT and temozolomide (TMZ) increased survival of mice bearing glioma tumors implanted subcutaneously or in the brain (68). Remarkably, in this study, SF as a single therapy significantly increased survival, decreased the size of subcutaneous glioma, and reinforced the effects of TMZ in intracranial tumors. A significant reduction in circulating blood glucose and IGF-I concentrations levels was also noticed.

We found no mature results from clinical studies evaluating RT with SF or CR. One clinical trial currently is evaluating the benefit of CR (∼25%) in patients with localized breast cancer undergoing surgery and RT (clinicaltrial.gov, NCT01819233): results are not yet available.

Preclinical experiences in KDs

In vitro, the administration of ketone body 3β-hydroxybutyrate (3β-OHB) at 3 mM concentration failed to induce additional inhibitory effects on the proliferation of 7 human breast cancer cells lines (BT20, BT474, HBL100, MCF-7, MDA-MB 231, MDA-MB 468, and T47D) exposed to various doses of RT (0, 2, 4, 6, and 8 Gy) in association with different cytotoxic agents (carboplatin, epirubicin, paclitaxel) and cultured in 5 mM glucose medium in response (74).

In vivo experiments (**Table 2**) (75, 76) showed slower tumor progression as well as increased survival in mice grafted with high-grade glioma, lung, or pancreatic cancer cells, when mice received a KD in association with RT (75–77).

Human noncontrolled/single-arm pilot studies and 2 case reports (in total, $n = 77$ patients) reporting RT and KD associations are presented in **Table 3** (70, 77–84). Isocaloric KDs were used in the 5 pilot studies, while a nonisocaloric approach combining KD + CR (660–900 kcal/d) was applied to the 2 case reports. Briefly, in these small cohorts of

TABLE 1 Short-term feed deprivation and caloric restriction associated with RT in mouse models of cancers: effects on tumor volume and survival[1]

Authors, year (ref)	Cancer model	Therapeutic protocol	Oncological effects
Kharazi et al., 1994 (69)	Female C3H/He mice, spontaneous mammary tumor	70% severe CR for 1 mo; RT, low dose: 0.04 Gy from a 6o Co source, 3 times/wk for 4 wk	70% RTV under CR + RT; T cells $CD8^+$ in tumors; no effect with RT or CT alone
Safdie et al., 2012 (68)	Glioma GL26 cells, subcutaneous or intracranial models	SF 48 h before TMZ ± RT ± RT: 7.5, 5, 2.5 Gy, at days 1, 15, and 22	DTG and IS
Saleh et al., 2013 (71)	TNBC (4T1 and 67NR cells)	30% CR + RT at initial burden; 6 Gy for 67NR cells, 8 Gy for 4T1 cells.	RTV
Simone et al., 2016 (72)	TNBC (4T1 cells)	30% CR at initial burden+ RT: 8 Gy	Lung metastases delayed (occurrence and number),IS

[1] CR, caloric restriction; CT, chemotherapy; DTG, delaying tumor growth; IS, increased survival; KD, ketogenic diet; ref, reference; RT, radiotherapy; RTV, regression of tumor volume; SF, short fasting; TMZ, temozolomide; TNBC, triple-negative breast cancer.

miscellaneous tumors (including glioma, breast, prostate, rectum, or small cell lung cancers), stabilization or regression of cancers was often reported. Concerning the 2 individual case reports, it was proposed that the rapid regression of glioma tumors after subtotal resection could be partially ascribed to the strict diet regimen (3-d SF followed by severe CR reducing the caloric intake to ∼60%, then a KD for several months) ,which was administered during the course of RT and TMZ (79, 83).

In both cases, no steroid medication was administered, and weight loss was maintained within 20% of baseline. In 1 case, despite initial major and rapid regression, a recurrence was observed at 9 mo, possibly in correspondence with suspension of the KD (79). In the second case, the patient ceased the KD at 9 mo and was still in good health at 20 mo, with a small, clinically stable residual disease (83).

As reported in **Table 4**, we list 15 clinical randomized trials testing RT with a KD. Results are not yet available.

Preclinical experiences in protein/amino acid restriction

Only in vitro models of amino acid restriction were identified in our search, while no studies of PR were identified. Arginine starvation induced massive apoptosis in 4 human epithelial cancer cell lines in 2D monolayer and 3D spheroid cultures and was remarkably efficient in association with RT (85). Pretreatment of cancer cells with arginase, an enzyme involved in arginine degradation, significantly enhanced the response to RT. The sensitivity to RT was reinforced by a low concentration of canavanine, a toxic arginine analog (86).

In a preclinical study, methionine starvation altered the metabolomic profile and significantly reduced tumor growth after a focal 20-Gy irradiation, in a mouse model of constitutively chemo- and radio-resistant human soft tissue sarcoma with mutated, KRAS, and p53-deficient cells (62). We found no other animal model or human clinical trials studying RT in association with either PR or amino acid restriction. Of note, despite 4 trials investigating PR in cancer in Clinicaltrials.gov, none address the question of the combination with RT.

Dietary interventions in association with RT

As shown by in vitro and in vivo studies (Table 1), SF potentially increases the radiosensitivity of glioma tumors (68), while 30% to 70% CR increased tumor sensitivity to RT + CT in several mammary cancer models (including TNBC) (71, 72). The increasing regression of tumors after short SF or CR associated with RT with or without CT has been correlated with the downregulation of the IGF-I/PI3K/mTOR pathway. Indeed, decreased glucose and IGF-I serum concentrations were observed during SF + RT (68), as well as reduced concentrations of IGF-IR (72) and downregulation of mTOR (71). This suppressive effect of CR or short SF on the IGF-I/PI3K/mTOR axis is extremely relevant considering the key role of this pathway in promoting the Warburg effect and tumor growth (87–89). It is noteworthy that IGF-IR is not counteracted by a dysfunctional or mutated p53 (87, 90) and is frequently overexpressed in various aggressive cancers (91). Interestingly, CR has been found, in a murine model, to reduce the risk of late occurrence of cancer after RT (92). This preventive role could rely on epigenetic processes and activation of immune surveillance. Concerning this latter aspect, SF also enhances the immune cytotoxic response against cancer cells (Table 1): a severe 70% CR during 1 mo associated with low-dose RT was shown to induce a massive cytotoxic response in a mammary cancer mouse model, albeit the uncombined treatment was not sufficient to induce this effect (69). Furthermore, intermittent 24-h SF for 2–3 wk increased tolerance to whole-body irradiation in mice and was associated with a better recovery of the leucocyte blood cell count following a sublethal dose of 5.26 Gy (93). Because cancer cells compete with lymphocytes and divert glucose for their own use (94), SF or CR associated with RT might likely activate an acute immune response by increasing glycolysis in $CD8^+$ T cells, while glycolysis in cancer cells is inhibited. Likewise, activation of glycolysis in effector T cells leads to inactivation of programmed death 1 (PD-1) ligand (PD-L1), resulting in their expansion and activation with release of IFN-γ (95).

In summary, preclinical experiments support the hypothesis that short SF and CR promote effectiveness of RT by

TABLE 2 The effects of a KD associated with RT in mouse cancer models[1]

Authors, year (ref)	Type of cancer model	Therapeutic protocol	KD, % of lipids/carbohydrates/proteins	RT administration	Oncological effects
Abdelwahab et al., 2012 (75)	Glioma(GL261-luc2 cells); intracranial implantation in albino mice	KD + RT vs SD + RT	72/3/15	Whole-brain irradiation: 2 × 4 Gy	RTV
Allen et al., 2013 (76)	Lung cancer(NCI-H292 and A549 cells)	KD ± RT ± CT (carboplatin)	90/1.6/8.4	34 times 1.8 Gy, 6 times 2 Gy; CON group: 2 times 6 Gy	RTV and ISKD alone; no effect
Zahra et al., 2017 (77)	Pancreas cancer(Mia-Paca-2 cells)	KD + RT	69/2.8/14.3	12 Gy: 6 × 2 Gy	RTV and IS

[1]CON group, control group; CT, chemotherapy; IS, increasing survival; KD, ketogenic diet; ref, reference; RT, radiotherapy (conventionally fractionated, 1.8–2 Gy; or hypofractionated (6 Gy) radiation as well as conventionally fractionated radiation); RTV, regression of tumor volume; SD, standard diet.

increasing cytotoxic stress, acute inflammation, and immune response; moreover, inhibition of the IGF-IR signaling pathway inactivates cancer cell proliferation and supports recovery of healthy cells.

Focusing on a KD, an increased response to RT in various animal models has been reported, consisting of delayed tumor progression, reduced occurrence of lung metastases, and prolonged survival, as seen in Table 2. In patients (Table 3), several studies suggested a possible benefit of KDs on tumor response.

It is noteworthy that, similarly to SF/CR, a KD may increase the immune response as shown in murine models of glioma by decreasing expression of immune inhibitory receptors PD-1 and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) as well as their inhibitory ligands (96). In accordance, immunosuppressive regulatory T cells and myeloid-derived suppressor cells (MDSCs) were depleted in another study (97).

In addition to these possible tumor-directed effects of a KD which could reinforce the efficiency of conventional treatment, especially in brain tumors (33), several studies have pointed out other beneficial effects of KDs on physical and mental condition. A KD is often well accepted and tolerated (98), in particular in children with brain tumor (78,84), despite frequent fatigue, constipation, and weight loss. An improvement in quality of life can be expected (99) and weight loss is likely dependent on the duration of the KD and extent of CR: weight decreased by a mean of 4% (0.0–6.1%) in 10 cancer patients receiving a KD with 35% ± 6% CR (100).

A better preservation of lean mass could be expected, since weight loss should mainly occur at the expense of body fat (26, 27). In a recent interim analysis reported by the KETOCOMP group, studying the benefit of a KD on RT in patients with rectal and breast cancers, 20 patients receiving a KD showed a loss of 0.5 and 0.4 kg fat mass/wk, with no significant changes in fat-free and skeletal muscle mass (70). This preservation of lean mass seems in line with the physiological regulation promoting gluconeogenesis in case of starvation, because this pathway is primarily sustained by glycerol provided by lipolysis and not by amino acids derived from proteolysis (101); this reduction in amino acid consumption delays proteolysis and loss of muscle resulting in sarcopenia, a process favored by a low baseline BMI reflecting poor fat reserves (102–104).

With regard to protein/amino acid restriction, the evidence in favor of a radiosensitizing effect of these interventions according to our analysis of the available literature is limited to single amino acid deprivation: for this reason, the impact of deprivation of simple amino acids cannot be differentiated from that caused by a reduction in the intake of whole proteins. This has important implication, since whole protein–restricted diets could be easier to prepare than diets based on single amino acids, considering, for example, that a vegan diet is low in methionine (105). Other than its exclusive metabolic implications, PR may be involved in modulation of immune antitumor response. Very recently, a

TABLE 3 Noncontrolled studies reporting results of RT associated with a KD in cancer patients[1]

Authors, year (ref)	Cancer types	Therapeutic protocol	KD, % of lipids/carbohydrates/proteins	Radiotherapy	Effects
Nebelling et al., 1995 (78)	Astrocytoma, advanced stage	RT + CT + KD	70/20/10	36 Gy on neuroaxis, 54 Gy on posterior fossa	Tumor response with possible increasing OS
Zuccoli et al., 2010 (79)	Glioblastoma	CR (660 kcal/d) + RT + TMZ + KD	75/15/10	60 Gy in 30 fractions of 2 Gy	TR, recurrence after diet suspension
Champ et al., 2014 (80)	Glioblastoma multiforme (n = 6)	RT + TMZ + KD	77/15/8	60 Gy in 30 fractions of 2 Gy	5 TP, 1 complete response
Klement et al., 2016 (81)	Breast, prostate, SCLC, and 2 rectal adenocarcinomas (n = 6)	RT + CT + KD	73/12/5	ST	1 TP (SCLC) and 5 TR
Kato et al., 2016 (82)	Invasive rectal cancers	RT + KD	40% kcal fat and CHO <100 g/d	ST	Reduced risk of cancer specific death?
Zahra et al., 2017 (77)	NSCLC (n = 7), pancreas (n = 2)	RT + CT + KD	90/2/8	ST	No difference in OS and PFS
Elsakka et al., 2018 (83)	Glioblastoma multiforme	RT + TMZ + CR (900 kcal/d) + KD + HOBT + MIX	70/15/15	30 times 2 Gy	TR
Van der Louw et al., 2019 (84)	Intrinsic Pontine glioma (n = 3)	RT + CT (TMZ or GCB) + KD 4:1 (for 3 mo)	Ketone levels >3 mmol/LKD with MCT emulsions	Fractionated RTup to 60 Gy	3 patients died
Klementet al., 2019 (70)	Colorectal, breast, head, and neck cancers (n = 81): 20 KD vs 61 control diet	SF + KD + RT ± CT	KD during RT: MCT + 10 g EAAs or full KD + 10 g EAAs	RT, RT + CT	Differential effects on weight fat and lean mass

[1] CHO, carbohydrate; CR, caloric restriction; CT, chemotherapy; EAA, essential amino acid; GCB, gemcitabine; HOBT, hyperbaric oxygen therapy; KD, ketogenic diet; MCT, medium-chain triglyceride; MIX, metformin, methylfolate, chloroquine, epigallocatechin gallate, and levetiracetam; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; ref, reference; RT, radiotherapy; SCLC, small cell lung cancer; SF, short fasting; ST, standard treatment; TMZ, temozolomide; TP, tumor progression; TR, tumor response.

TABLE 4 Current clinical trials associating a KD and RT[1]

Study number	Study	Protocols
NCT01975766	KD phase 1 in head and neck cancer	RT + CT ± KD
ACTRN12614001056684	Pilot study evaluating progression-free survival in glioma cancers under standard treatment (CT + RT) associated with KD	RT + CT ± KD
NCT01092247	Effect of KD, CR, and IF cancer recurrence and progression (ARTZI 2017)	RT ± KD + CR and IF
NCT01754350	KD, CR, and IF during re-irradiation of recurrent GBM (ERG02)	RT ± KD + CR and IF
NCT01819233	CR in breast cancer undergoing surgery and RT	RT + CT + CR 25%
NCT02046187	KD as adjunctive treatment of RT and CT in newly diagnosed glioma	RT = CT ± KD
NCT02302235	KD as adjunctive treatment of RT and CT in glioma	RT + CT ± KD
NCT02149459	Metabolic manipulation combined with RT as treatment of recurrent brain tumors (smc0712–13)	RT + KD + metformin
NCT02516501	Impact on body composition of KD during RT (KETOCOMP)	RT ± KD
NCT03278249	Feasibility study of modified Atkins KD in treatment of newly diagnosed glioma	RT + CT ± KD
NCT01419483	KD with concurrent chemoradiation in pancreatic cancer	RT + CT + KD
NCT01419587	KD with concurrent chemoradiation in non–small cell lung cancer.	RT + CT + KD
NCT01754350	CR with IF and KD with concurrent RT in recurrent glioma	RT + CR + IF + KD
NCT02302235	KD as adjunctive treatment of RT and CT in glioma	RT + CT ± KD
NCT02149459	Metabolic manipulation combined with RT as treatment of recurrent brain tumors (smc0712–13)	RT + KD + metformin

[1] CT, chemotherapy; CR, caloric restriction; IF, intermittent fasting; KD, ketogenic diet; RT, radiotherapy.

low-protein (< 5%) isocaloric diet reduced tumor growth in 3 independent mouse cancer models (lymphoma, melanoma, and colon cancer); the anticancer effect of this moderate-protein starvation was mediated by activation of $CD8^+$ T-cell immune response. In contrast, a low-carbohydrate diet had no effect in these mouse models (106).

Controversies

It has been reported that ketone bodies may be used by tumor cells as a substrate for energy metabolism as shown by in vitro and in vivo experiments (107, 108). For instance, 3β-OHB did not influence proliferation and response to CT and RT of several breast cancer cell lines cultured in low-glucose medium (5 mM) (74), but accelerated tumor growth in an acute myeloid leukemia xenograft model (109) as well as some breast cancer models (110, 111). In mice bearing MMTV-NEU-NT mammary tumors, 3β-OHB increased ATP production in cancer cells (measured by spectrometer) and promoted tumor growth, while demonstrating no effect on histone acetylation (108). In fact, very few studies have been conducted on cell lines supporting the "paradigm" that cancer cells lack 3β-OHBD and SCOT (55, 112–114). Several authors reported the capability of cancer cells to utilize fatty acids, especially when they grow in rich adipocyte tissues or atmosphere (115–118). Tisdale and Brennan (55) studied 10 murine cell lines, including 5 hematopoietic cells lines: 1 sarcoma cell line, 1 carcinosarcoma cell line, 1 "rat" cell line, and 2 bladder cell lines. While SCOT activity was reduced in these tumor cells in comparison with normal tissues, 3β-OHBD activity levels were quite similar. Moreover, in 4 cells lines cultured with 2 mM of 3β-OH for 7 d, the decrease in 3β-OH over this period ranged from 14% to 44%, thus demonstrating significant consumption of the ketone bodies.

It could be inferred that specific brain tumors (e.g., astrocytoma, schwannoma, and craniopharyngioma) may have significantly lower concentrations of enzymes catabolizing ketone bodies (in particular, SCOT), in comparison with normal brain; however, a panel of 7 glioblastoma multiforme exhibited a wide range of enzymatic activities (112). More recently, gene expression of 3β-OHBD and SCOT has been found to be lower in malignant astrocytoma (CT-2A) and human malignant glioma (U87-MG) cells lines implanted in the brain of mice (113), as well as in human neuroblastoma (SK-N-AS) cell lines (112–114) in comparison with normal brain. It is noteworthy that, in 2 patients with glioblastoma showing little benefit from a KD, in both cases tumors expressed mitochondrial 3β-OHBD and SCOT (119). Furthermore, even if SCOT is deficient, acetoacetate could promote tumor growth as shown in mice bearing human melanoma xenografts with BRAF V600E expression, the binding of acetoacetate to BRAF protein promoting growth (107).

Of note, the small numbers of patients in these cohorts and the absence of control groups hinder any definitive conclusions. Furthermore, in 3 studies, a KD was not the only variable associated with response to RT but was frequently combined with other therapeutic measures such as chemotherapy (70,77–80), SF (70) or CR (79, 83). With regard to the latter, it should be noted that unintended CR may occur in patients receiving an isocaloric KD (100), resulting in additional confounding bias.

Hence, the presence of multiple confounders is a serious limitation in defining the individual impact of a KD in retrospective experiences, as proposed by some authors (120), while results from 15 clinical randomized trials testing a KD and RT are not yet available (Table 4).

It should be pointed out that numerous cancer cells are not inherently glycolytic but rely on a predominant oxidative metabolism or an intermediate functioning (121, 122). Thus, as remarked by Rodrigues et al. (108), the "butyrate paradox"

is likely related to the capability of 3β-OHBD acting as an energy source in cells supported by an oxidative metabolism, and as an epigenetic factor inhibiting cancer growth in cells relying on the Warburg effect (123). Under glucose deprivation (0.5-mM concentration) cancer cells carrying KRAS and BRAF mutations can also increase the expression of glucose membrane transporter GLUT1, a carrier that has a high avidity for glucose (124). Thus, stress conditions may select resistant cancer cells capable of adapting to changes in their microenvironment by modifying their metabolism, epigenome, and genomes.

Diets based on a single amino acid may have dual effects: for example, a protein-deficient diet, in particular with reduced methionine, can promote hepatocarcinogenesis in animals (125, 126), while arginine supplementation antagonizes both in vitro and in vivo the malignant transformation of mammary epithelial cells (59). Of note, arginine supplementation could also improve the performance status and Karnofsky index of patients with esophageal cancers (127) and reduces (in association with glutamine and fish oil) the incidence of severe hematologic toxicities occurring during CT and RT (128).

Concluding Remarks

In conclusion, our literature review offers preliminary evidences that SF before RT and CR during RT sessions may improve tumor response to radiation. Repeated sessions may increase the efficiency of RT administration and might exert a radioprotective effect on healthy tissues. This nutritional strategy might be of interest for tumors displaying high glucose uptake on PET scan, a feature associated with poor survival that may be related to Warburg metabolism functioning (22, 23).

Other interventions, such as KDs, may be more hazardous, considering the contradictory results of preclinical studies, and some authors have advised against their use in cancer patients (120). Even if preclinical studies and limited clinical experiences argued in favor of a possible beneficial synergistic effect of KDs and RT in high-grade cancers (in particular for TNBC and brain tumors) (27, 33, 98, 119), more robust data are needed.

Only evidence-based data from randomized clinical trials can evaluate the impact of dietary interventions on response to cancer treatments (129). It should be pointed out that, even if the majority of animal studies (~70%) provide evidence of an antitumor effect of KDs (130), preclinical models give often discordant results and do not reflect the clinical situation, since the metabolic rate in mice is 7-fold higher than in humans (131).

Human trials should strictly define daily caloric intake, composition of diets, placebo diets, biological parameters assessing glucose starvation and ketosis (132), as well as prespecified criteria for the evaluation of tumor response. To assess which nutritional strategies should be favored, a deeper knowledge of the specific biological vulnerabilities of each cancer type should be obtained. For that purpose, assessment of various proteins (IGF-I) and metabolite profiles on liquid samples (133) and expression analysis of enzymes and membrane transporters on tumor biopsies (134) could be performed to identify the metabolic profile involved in a specific clinical situation (20, 135, 136).

Finally, modulation of nutrition during RT could be a simple and medically economical and inexpensive method that may deserve to be tested to improve efficiency of RT by exploiting increased radiosensitivity of tumor cells while reducing radiation-related injury to healthy tissues.

Acknowledgments

We acknowledge Gilles Girault (Centre Francois Baclesse, Caen, France) for his technical assistance in the research of references. The authors' responsibilities were as follows—PI and JT: designed the manuscript; PI and LO: wrote the manuscript; JT: entered references; ML, PF, JO, and MA: prepared the figures or commented on the text; LF: contributed to comments, literature review, and editing; and all authors: read and approved the final manuscript.

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