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Original article

Impact of a ketogenic diet intervention during radiotherapy on body composition: II. Protocol of a randomised phase I study (KETOCOMP)

Rainer J. Klement*, Reinhart A. Sweeney

Department of Radiation Oncology, Leopoldina Hospital, Schweinfurt, Germany

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SUMMARY

Background: We have found that a ketogenic diet (KD) during the course of radiotherapy (RT) was feasible and led to a preservation or favorable changes of body composition. Based on these observations and theoretical considerations, we initiated a study to investigate the impact of a KD or a ketogenic breakfast intervention in patients undergoing RT.

Methods: All patients presenting for curative RT with age between 18 and 75, body mass index between 18 and 34 kg/m^2 and a histologically confirmed cancer of the breast, colorectum or head and neck region are considered for inclusion. Exclusion criteria are Karnofsky index <70, pregnancy, metallic body parts that interfere with bioimpedance analysis (BIA), type I diabetes, known enzyme defects that contradict a KD and renal insufficiency. Randomization is achieved by all consecutive patients first entering the control group and then an intervention group 1 until both groups contain 15 breast, 15 colorectal and 5 head and neck cancer patients. Intervention group 1 will receive each radiotherapy fraction after an overnight fast and subsequently ingest a ketogenic breakfast consisting of (i) 50–250 ml of a medium-chain triglyceride drink (betaquick®, vitaflo, Bad Homburg, Germany) plus (ii) 5–15 g amino acids (MAP, dr. reinwald healthcare gmbh+co kg, Schwarzenbruck, Germany). If willing to undertake a complete KD for the duration of RT, patients are entered into intervention group 2. Intervention group 2 does not have to fast prior to RT fractions but will be supplemented with MAP analogous to intervention group 1. The control group will not receive dietary advice to follow a KD or reduce carbohydrate intake. The objective is twofold: (i) to test whether the ketogenic interventions are feasibly, as measured by the number of dropouts; (ii) to see whether intervention groups 1 and 2 attain a better preservation of BIA phase angle than the control group.

Endpoints: Primary endpoints are the feasibility of the interventions (measured through dropout rates), and changes in body weight and composition (measured through BIA). Secondary endpoints are changes in quality of life (EORTC questionnaires) and blood parameters as well as the occurrence and grade of toxicities and grade of regression after surgery in case of colorectal carcinomas.

Trial registration: Registered under ClinicalTrials.gov Identifier no. NCT00123456.

1. Background

It can be expected that a radio(chemo-)therapy (RT) has an impact on body composition, in consequence of reduced energy intake, increased energy turnover and inflammatory processes which could result in increased skeletal muscle breakdown, among other things. However, in many patient groups such changes are not systematically investigated, and it therefore remains unclear if putative changes are measurable and clinically significant. Furthermore, it is known that a tumor itself can impact metabolism and body composition in patients. For example, inflammatory cytokines from the tumor tissue are able to promote insulin resistance, resulting in decreased glucose uptake in peripheral tissues, particularly skeletal muscle, and providing a rationale for a metabolically adapted diet with increased fat content for cancer patients [1,2]. Through this, tumor regression during RT could also influence body composition changes.

It has been postulated that a specific dietary intervention during RT could have positive effects on body composition and

* Corresponding author. Tel.: +49 9721 7202761.
E-mail address: rainer_klement@gmx.de (R.J. Klement).

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protect normal tissue from ionizing radiation [1,3]. In a series of preclinical studies and human cases the research group of Valter Longo was able to show that fasting prior to chemo- and radiotherapy has opposite effects on normal and tumor tissue, such that the former gets protected while the latter sensitized to therapy-induced damage [4–6]. The fasting patients mainly profited from substantially reduced side-effects. Since a "fasting metabolism" is to a large part based on the *de facto* reduction in carbohydrates (CHOs) [7], CHO restriction could be considered an alternative to food abstention in oncological patients [8]. From the supply of exogenous amino acids and fat a better preservation of muscle mass would be expected without completely giving up the positive effects of fasting which are based on molecular mechanisms that can partly be activated by CHO restriction [3]. Furthermore it has been shown that the ketone bodies acetoacetate and β-hydroxybutyrate, whose concentrations rise with increasing fasting duration, have anti-tumor [9] and anti-cachectic [10] properties. While ketogenesis is classically promoted by fasting or a KD, recent data have shown that intake of medium-chain triglycerides (MCTs) can even then induce elevated ketone body levels when given within the context of a not necessarily CHO-restricted diet [11]. The reason is that due to their water solubility, after absorption in the gut MCTs are directly transported to the liver via the portal vein where they stimulate ketogenesis. Several studies on a KD in tumor patients have therefore specifically substituted with MCTs [12–14]. The administration of non-glucogenic amino acids could further make a valuable contribution to the diet of tumor patients without leading to increased hepatic glucose production and nitrogen waste. With a net nitrogen utilization of 99%, the Master Amino Acid Pattern (MAP) supplement fulfills these properties [15]. In theory, one gram of MAP should therefore only provide 0.04 kcal if the constituting amino acids are almost entirely used for building bodily proteins and not as substrates for gluconeogenesis. Indeed some institutions use MAP as part of a KD in the treatment of cancer patients, in particular to maintain the amount of muscle mass [16].

The effects of a dietary intervention during RT can be followed with bioimpedance analysis (BIA) measurements [17,18]. BIA provides an easy and fast method for assessing body composition; its results have been validated as prognostic factors for life expectancy of cancer and other critically ill patients. Already in 2004 the ESPEN considered BIA as a suitable and reproducible method for assessing fat free mass and total body water except in cases with extreme body weight or hydration status [17,18]. Reproducibly mainly seems to depend on whether the patient has eaten or is in a fasted state. By keeping to certain standards, the method therefore seems to have a high reproducibility [18].

The phase angle (PA) is a directly measurable parameter and appears because the voltage lags behind the current due the behavior of the cell membranes as capacities. Therefore, PA is established as a good indicator of cell wall integrity as well as body composition, particularly muscularity [19]. In oncological patients there was a significant correlation between low PA and poor prognosis [20,21]. A recently published prospective study has shown that a RT in the head and neck, abdominal and thoracic area was associated with a significant reduction of PA [22].

In a pilot case study of six patients, we have found that a KD during RT resulted in a preservation of PA in all but one patient. The KD was tolerated well, but some patients reported difficulties with its everyday practicability. Therefore we initiated a phase I study to investigate whether a strategic abstinence from CHOs only before and shortly after each RT fraction induces similar changes in PA and body composition measures as a complete KD conducted over the whole RT period, and whether these changes are different from those observed when no dietary intervention is made. According to the preclinical data, prolonging the nocturnal postabsorptive state until the RT fraction on the morning could induce a differential stress response between normal and tumor tissue such that only the former experiences protection against radiation. If radiation is then followed by a ketogenic breakfast this would minimize the postprandial rise of blood glucose levels, promote ketogenesis, and sustain or mimic a fasting metabolism for some time. By substituting with MAP, maintenance of muscle mass could be supported without producing excessive glucose through gluconeogenesis. If this intervention (RT after an overnight fast followed by a ketogenic breakfast with MAP) is feasible and has comparable effects on body composition as a complete KD, the ketogenic breakfast could provide a practicable option for patients not willing or able to undergo a complete KD.

2. Materials and methods

2.1. Objectives and endpoints

The study hypothesis is that morning irradiation after an overnight fast with subsequent ketogenic breakfast consisting of an MCT drink (10–50 g MCTs per serving) and 5–15 g MAP diminishes the expected decrease of PA during the course of RT. The exclusive ingestion of a KD plus MAP should have a similar or stronger effect.

The primary goal is the assessment of the feasibility of both ketogenic interventions (breakfast and complete KD) during RT. Furthermore it should be investigated whether these interventions have a positive influence on body composition.

Secondary goals are the recording of quality of life, relevant blood parameters and regression grade after surgery in case of colorectal carcinoma. A detailed description of all study endpoints is given in Table 1.

2.2. Study collective

2.2.1. Patient accrual

Eligible patients are those that present for primary RT with curative intent in our institution which is located within a community hospital. Of special interest in connection to CHO limitation

Table 1
Primary and secondary endpoints of the study.

Primary endpoints	• Dropout rates as a measure of feasibility/tolerability in intervention groups 1 and 2 • Phase angle from BIA (measured at 1, 1.5, 2, 3, 5, 7.5, 10, 15, 20, 30, 50, 75, 100, 150, 200, 300, 500, 1000 kHz; main interest is in 5 and 50 kHz) • Body composition, a composite measure of several parameters obtained from the BIA scale (body weight, fat mass, fat free mass, total body water, extracellular water, intracellular water)
Secondary endpoints	• Quality of life (assessed using EORTC QLQ-C30 and site-specific questionnaires) • Blood parameters (composite measure including small blood count, glucose, albumin, urea, HbA1c, β-hydroxybutyrate, triglycerides, HDL and LDL cholesterol, creatinine, liver enzymes, insulin, IGF-1, TSH, free T3 and T4) • Regression grade after surgery (only for colorectal patients undergoing neoadjuvant RT: cTN status prior to and ypTN status after surgery) • Normal tissue toxicity after RT (evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0

Table 2
Rare metabolic disorders that pose exclusion criteria for this study.

Type of disorder	Example
Ketogenesis	Defects in medium-chain-acyl-CoA-dehydrogenase
Ketolysis	Deficiency in HMG-CoA-synthase
Gluconeogenesis	Deficiency in pyruvate-carboxylase
Fatty acid oxidation	Deficiency in acyl-CoA-dehydrogenase
Respiratory chain (except complex I defects)	

are those tumor entities that generally have a high glucose uptake (as known, e.g., from FDG-PET studies).

The detailed inclusion criteria are

- Carcinoma of the breast, colorectum, or head and neck region
- Histological confirmation of a malignant tumor
- Written informed consent
- Karnofsky index $\geq$70
- 18 kg/m^2 < BMI <34 kg/m^2
- Age between 18 and 75 years

The exclusion criteria are

- Palliative patients, in particular known metastases
- Type I diabetes
- Pregnancy
- Pacemaker and other metallic parts that influence BIA measurements
- Known defects in enzymes necessary for ketogenesis, ketolysis, fatty acid oxidation or gluconeogenesis (Table 2)
- Unable to speak or understand German
- Cognitive impairments or psychological disorders
- Renal insufficiency

Metformin-intake or type II diabetes pose no exclusion criteria. In case of patients with metformin prescription participating in the intervention groups lactate levels will be controlled in order to meet concerns about the risk for acidosis.

2.2.2. Patient number

For patient number estimation we take as the main outcome measure the absolute change of phase angle between the start and end of RT of intervention group 1 compared to the control group. In both groups it is assumed that PA is normally distributed with the same standard deviation. The differentiation between patients with different tumor entities will be neglected. The intervention is defined as successful if the PA, measured at 50 kHz, rises on average 0.3° more in intervention group 1 compared to the control group. It is assumed that the standard deviation of the change is 0.5°, corresponding to the age-independent standard deviation of the PA of German adults [23]. For sample size planning it is assumed that the-sided two-sample t-test can be used for evaluation. The level of significance should be 5%, the power 80%. Therefore a minimum of 35 patients are necessary in each of both groups [24]. Because of the less frequent presentation of head and neck cancer patients in our clinic the aim is to recruit 15 patients with breast cancer, 15 patients with colorectal cancer and 5 patients with head and neck cancer in the control and intervention group 1, so that a total of $2 \times (15 + 15 + 5) = 70$ patients gets recruited. For intervention group 2 the aim is at least 5 patients per tumor entity, but no maximum number is specified. Recruitment of this group runs parallel to the other groups and ends at the latest of three months after inclusion of the last patient into intervention group 1 (see below for more details).

2.2.3. Abortion criteria

Patients who demonstrably do not follow the dietary advice or who do not tolerate the dietary intervention end the study early and are counted as dropouts. The whole study will be ended premature of more than 50% of patients in intervention group 1 end the study early. The planned completion is 3 months after recruitment of the last patient into intervention group 1.

2.3. Study description

An overview of the study procedure is provided in form of a flow chart in Fig. 1.

The obligatory intervention for all patients – regardless of group membership – is RT, weekly BIA measurements, three blood withdrawals and three assessments of quality of life.

2.3.1. Intervention groups

The study follows a parallel assignment to groups. Two intervention groups will be investigated.

Intervention group 1 (ketogenic breakfast) has to stay fasted until irradiation and subsequently receives a ketogenic breakfast consisting of a MCT-rich drink (betaquick®, vitaflo, Bad Homburg, Germany) plus a minimum of 5 g MAP (dr. reinwald gmbh + co. kg, Schwarzenbruck, Germany). The exact amount of MAP depends on the outcome of the first BIA measurement. It is 5 g, 10 g or 15 g, depending on whether the PA is above, within or below the age- and gender-specific normal range. For better tolerance the initial dose of the MCT drink will be 50 ml and increased by 10 ml daily until the maximum dose of 250 ml is reached, corresponding to 50 g MCTs. In case that prolonging an overnight fast until irradiation is unreasonable, for example on days with chemotherapy in the morning, the patient is allowed to ingest betaquick® before irradiation. After the ketogenic breakfast patients are free to eat and drink *ad libitum*.

Intervention group 2 (complete KD) only receives MAP after each RT fraction. Here breakfast and other meals are not controlled; instead patients are advised to follow a self-administered KD during the whole course of RT and to not count calories. To this aim, patients will be provided with brief information brochures and a popular book on KD during cancer therapy [25]. To help with practicability the substitution with betaquick® and other ketogenic drinks will be recommended. Furthermore patients are advised to keep track of daily urinary ketone body concentrations using ketone strips (Ketostix, Bayer Vital GmbH, Germany). A two-day food diary during the first two weeks of the intervention should allow for the possibility to help with further advise for the optimal realization of the KD with the aim of achieving stable ketosis (serum ketone body concentrations >0.3 mmol/l).

The *control group* will receive no dietary advice. In case of further inquiry patients will be advised to follow the standard recommendations for a heathy diet provided by the German Society for Nutrition (DGE).

2.3.2. Recruitment

The recruitment begins with the control group in which all consecutive patients who fulfill the inclusion criteria will be included. As soon as the required number of patients in the control group has been reached for one tumor entity, all further patients with that tumor entity will be offered to enter intervention group 1. This has the purpose of avoiding interaction between patients who receive no dietary advice (control group) and those receiving the dietary intervention, since in our experience patients frequently exchange notes about dietary measures such as specific diets or supplements. Accrual of intervention group 2 occurs parallel to that of the other two groups; the patients recruited for this group consist of those who either show

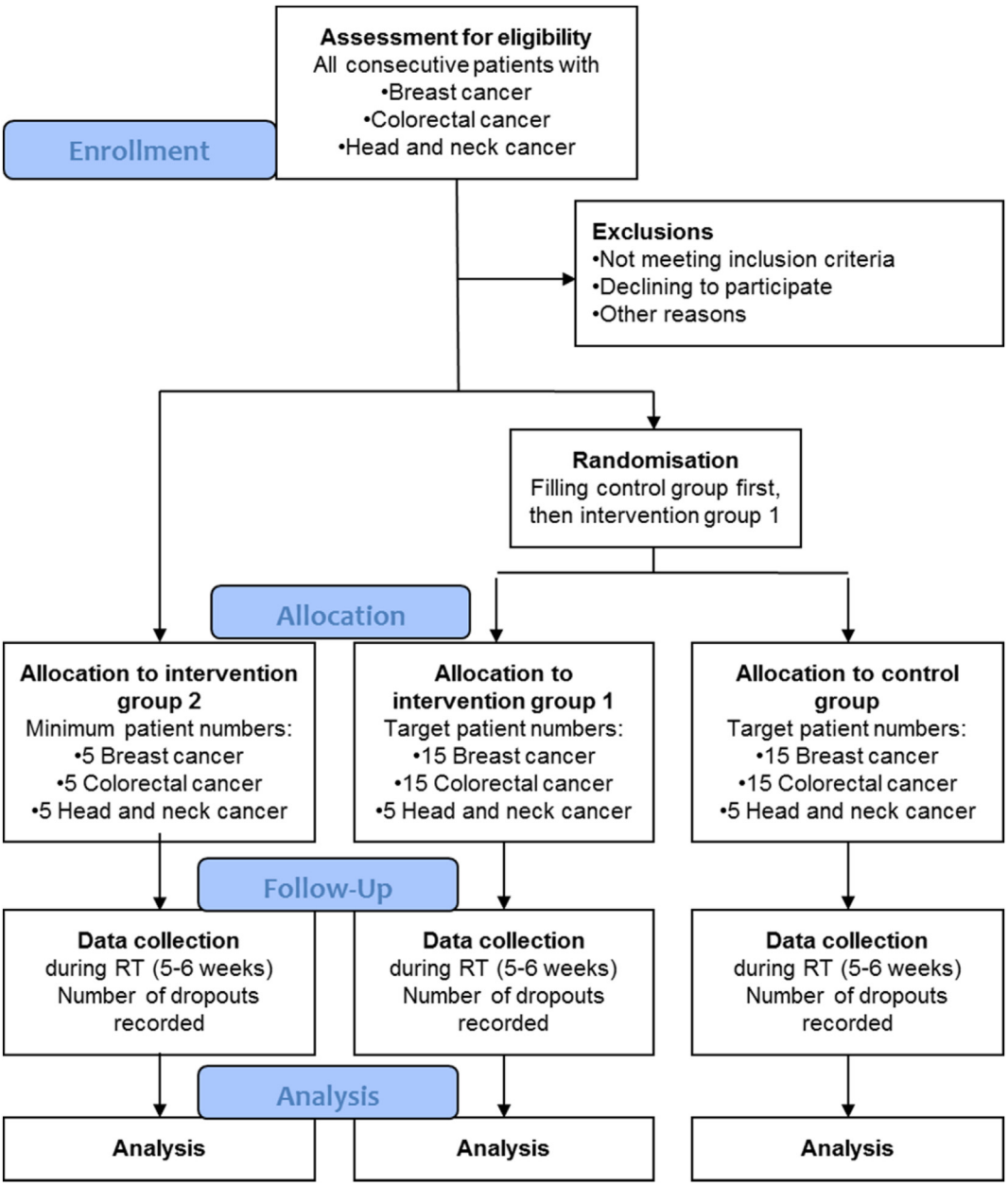

Fig. 1. Flow chart of the planned study.

large interest in a KD during the initial consultation, started a KD from their own initiative or those considered for intervention group 1 but who agreed to try a complete KD during the study consultation.

This recruitment procedure can be considered as randomized in so far as the individual groups are filled by consecutive patients without preselection. In this way we mainly try to prevent the interaction between patients from intervention group 1 and the control group in order to not influence the diet of the latter.

2.3.3. Bioimpedance measurements

BIA and body weight measurements are made on a seca 515/514 medical Body Composition Analyzer (mBCA; seca Deutschland, Hamburg, Germany), a combination between scale and BIA device. The device has a CE certificate and complies with the 93/42/EWG guidelines about medical devices. Its construction allows a high reproducibility of patient positioning which was partly made responsible for the good individual agreement between the seca mBCA results and those obtained by gold standard reference methods [26]. To further optimize the reproducibility of BIA results, all measurements are performed after an overnight fast, without having drunk for at least 10 h, and with an empty bladder as recommended by the ESPEN guidelines [18]. The mBCA device has a standing platform with an integrated scale and a handrail system, with one pair of electrodes for each hand and foot (eight-electrode BIA). A current of 100 μA and a total of 19 frequencies between 1 kHz and 1000 kHz are used to obtain impedance measurements. Instrumental precision is specified as 100 g for BW between 50 kg and 200 kg and 5 Ω for impedance of the left and right half of the body. Following the manufacturer's instructions, body height is measured to within the closest 5 mm with a seca 231 stadiometer before each BIA measurement.

The first BIA measurement serves to define the baseline status and is performed in the week prior to the first RT fraction. All consecutive measurements take place at least once weekly, in

general in the morning prior to irradiation. Patient appointments will be preferentially scheduled in the morning between 7:30 and 9:30. The final measurement takes place in the last week of RT.

2.3.4. Blood withdrawals

The first blood withdrawal is performed together with the first BIA measurement in the week prior to the first RT session. Further blood withdrawals are scheduled according to the treating physician's decision, but at least once during RT (after an expected time of three weeks into treatment). The final blood withdrawal is taken within the last week of RT. A regular control of ketone body and blood glucose levels in the intervention groups is performed once weekly on days of BIA measurements, either by the clinical laboratory or through finger-pricktests with a FreeStyle Precision device (Abbott Diabetes Care Ltd., Range Road, Witney, UK).

2.3.5. Questionnaires

QoL will be assessed before, once during and at the end of RT using the EORTC QLC-C30 questionnaire version 3.0 together with its disease-specific modules [27]. At termination of RT, each patient in intervention group 2 will receive a short non-validated questionnaire addressing several aspects of their subjective feeling with regard to the KD that we used in an initial case study.

3. Discussion

As preclinical data accumulate showing positive effects of KD interventions in tumor-bearing animals the question whether these effects translate to humans can only be addressed with human data, preferentially randomized clinical trials. There are currently several ongoing clinical trials testing the feasibility and efficacy of a KD combined with standard treatment [Table 1 in 8], and one study tests the feasibility of a KD and its impact on quality of life, physical performance and body composition in breast cancer patients during the rehabilitation phase (the KOLIBRI study; NCT02092753).

In a pancreatic cancer model ketone bodies exhibited anti-cachectic effects [10]. Other studies in rats provided evidence that physiological levels of ketone bodies inhibit oxidation of the branched chain amino acids in muscle [28] and decrease the release of the gluconeogenic amino acid alanine [29]. From an evolutionary standpoint, the muscle-sparing effect of ketosis should have been essential for surviving longer periods of starvation [30].

A KD requires abstinence from certain foods and may therefore not be suited for every patient. It would be good to find that part-time ketosis has similar effects to a complete KD. Therefore this study will investigate whether a ketogenic breakfast is sufficient to induce positive effects on body composition in patients undergoing RT. In one cancer patient we have found that the MCT drink beta-quick® significantly elevated ketone body levels from 0.4 to 1.1 mmol/l 1 h after ingestion. Furthermore Courchesne-Loyer et al. showed that MCT supplementation to a not CHO restricted diet induced a mild state of ketosis [11]. Therefore, if ketone bodies mediate anti-cachectic and muscle-sparing effects as indicated by preclinical data, this intervention could be valuable for cancer patients undergoing RT, especially those at high risk of weight loss such as head and neck cancer patients, in particular if they have to ingest their ketogenic breakfast under supervision. The provision of MAP provides the amino acids for this breakfast. Given that MAP has bee shown to have a net nitrogen utilization of 99% in healthy subjects [15], this seems to be an ideal amino acid source for a ketogenic intervention in cancer patients.

Limitations of this study lie mostly in the compliance of the intervention groups. In intervention group 1 the ketogenic breakfast will be provided immediately after each RT fraction by our staff, ensuring adherence to the prescription. However, dietary intake in intervention group 2 will be much less controlled, with ketone monitoring being the main indicator of whether the diet is ketogenic or not. However, we are planning to employ an registered dietician for this study in order to ensure compliance to the KD.

The risk associated with both dietary interventions is judged as small. Hypoglycemia could occur in both intervention groups with associated symptoms such as lightheadedness. In intervention group 2, the first 2–3 weeks of the KD could induce some adaption symptoms such as headache, nausea, anorexia and digestive problems. In general such symptoms improve during a few weeks. Intestinal problems can also occur after consuming the MCT drink, but by increasing the doses carefully we hope to minimize these problems. Due to the restriction of the intervention period to a maximum of approximately 6 weeks RT, no long term negative effects are expected.

In summary, this study is going to collect data on the feasibility of a ketogenic diet intervention in the form of a MCT and amino acid-rich ketogenic breakfast. The effects of the intervention on body composition, as well as blood parameters and quality of life, will be evaluated against those on a complete KD or an unspecified non-ketogenic control diet. If the ketogenic breakfast intervention shows its feasibility and efficacy this would provide a good and less restrictive alternative to a complete KD as a supportive option during RT.

List of abbreviations

BIA	bioimpedance analysis
BMI	Body mass index
CHO	carbohydrate
MCT	Medium chain triglyceride
KD	ketogenic diet
PA	phase angle
RT	Radio(chemo-)therapy

Statement of authorship

RJK and RAS designed the study and wrote the protocol. Both authors read and approved the final manuscript.

Conflict of interest statement and funding sources

Both authors declare that they have no conflicts of interest. The study will be funded solely by our clinic.

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