



Survival outcomes of rectal and head and neck cancer patients receiving radio(chemo)therapy with a ketogenic diet. A post-hoc analysis from the KETOCOMP trial

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Abstract

Purpose Ketogenic diets (KDs) have been proposed to target glycolytic cancer metabolism and synergize with radio- and chemotherapy. We herein report survival outcomes of rectal and head and neck cancer (HNC) patients who followed a KD during radio(chemo)therapy.

Methods Thirty-five patients on a KD during radiotherapy and 46 patients on a standard diet were prospectively followed. Overall (OS), progression-free (PFS), and locoregional recurrence-free survival (RFS) were analyzed with the Kaplan–Meier method and by computing restricted mean survival times. Acute radiotherapy-induced side effects were compared using Fisher’s exact test. In an exploratory analysis, patients in the KD group were matched to control patients with propensity score matching, and survival analysis was performed.

Results Median follow-up was 77.4 (range 12.1–107.9; HNC) and 71.3 (1.5–127.1) months (rectal cancer), respectively. There were no significant differences in any survival outcome between the KD and control groups in either cohort. A numerically longer restricted mean RFS time for HNC patients did not reach the statistical significance threshold (KD: 100.5 months, 0 events; control group: 87.3 ± 7.0 months, 3 events; $p=0.059$). In the propensity score-matched HNC sample, patients on a KD exhibited numerically longer OS (log-rank test: $p=0.084$) and RFS ($p=0.064$); however, these differences were not statistically significant. Acute skin toxicity was less severe in HNC patients on a KD ($p=0.063$), which became significant in intention-to-treat analysis ($p=0.0495$); all other acute toxicities were without significant differences between the groups.

Conclusion Our analysis failed to detect a significant survival benefit of a KD during radio(chemo)therapy in HNC and rectal cancer patients, but provides further evidence for the safety of this approach.

Keywords Kaplan–Meier · Ketone bodies · Ketogenic metabolic therapy · Radiotherapy · Survival analysis

Introduction

For more than 100 years, an altered metabolism has been recognized as a defining hallmark of cancer. In the 1920s, Otto Warburg and his coworkers showed that compared to normal tissues, tumor tissue consumes large amount of glu-

cose and in turn excretes large amounts of lactate [1]. This phenomenon is now denoted the Warburg effect. Meanwhile, data have been obtained indicating that cancer cell mitochondria are frequently dysmorphic and dysfunctional, which would explain the compensatory upregulation of glucose fermentation to lactate and other fermentative pathways such as glutaminolysis to maintain the cancer cell’s necessary energy yield [2, 3]. In addition, cancer cells utilize glucose in the pentose phosphate pathway (PPP) to promote their proliferation. The PPP typically yields ribose for DNA and RNA synthesis but could also yield lactate plus acetyl-CoA for fatty acid synthesis in cancer cells that possess a mutated transketolase-like 1 (TKTL1) enzyme [4].

Trial registration: ClinicalTrials.gov identifier: NCT02516501; registered on August 06, 2015.

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Roughly 20 years after Otto Warburg's seminal studies, a German oncologist named Wilhelm Brünings conducted clinical trials in which he attempted to target the Warburg effect by cutting tumors from their glucose supply using a ketogenic diet (KD) in combination with maximally tolerable insulin injections [5]. This was the first clinical application of ketogenic metabolic therapy. Today, ketogenic metabolic therapy utilizes metabolic inhibitors, KDs, ketogenic supplements, and other applications targeting the weaknesses that emerge due to cancer cells' altered metabolism and the accompanied metabolic inflexibility [6]. Ketogenic diets are a central element of this therapeutic approach. Some authors have characterized KDs as an under-recognized tool empowering patients to contribute in a positive way to their own treatment outcomes [7]. However, due to the sparsity of clinical data with hard clinical endpoints, systematic reviews published in 2020 and 2021 came to inconsistent conclusions [8, 9]. Nevertheless, preclinical studies have shown promising results of applying KDs to treat various cancer entities [10, 11], which justifies further studies on ketogenic metabolic therapy.

In 2016, we initiated a controlled clinical trial to test the effects of a KD consumed during radiotherapy in patients with breast, head and neck (HNC) or rectal cancer [12–15]. While the main aim was to test the effects of the KD on body composition changes during radiotherapy, our prospective follow-up of patients allows us to conduct post-hoc survival analyses of clinical outcomes. These are reported herein for patients with HNC and rectal cancer.

Materials and methods

The KETOCOMP study was a monocentric nonrandomized controlled clinical trial performed at the Department of Radiotherapy and Radiation Oncology at the Leopoldina Hospital Schweinfurt, Germany [12]. Ethical approval was granted by the ethics committee of the Bavarian Medical Association (*Landesaerztekammer Bayern*), and the protocol was registered on August 6, 2015, under ClinicalTrials.gov identifier NCT02516501. In principle, patients with breast, HNC, or rectal cancer referred to our clinic for radiotherapy were eligible to participate, but only the latter two groups are analyzed here. Summarized briefly, recruitment was performed in two blocks. The first block of patients were enrolled into a control group consuming their usual standard diet (SD). The second block of patients were enrolled into the intervention group consisting of the switch to a KD (so as to minimize intergroup influencing in the waiting rooms, etc.). Patients who wanted to eat a KD were enrolled into the KD arm irrespective of the planned allocation to control or intervention arm, while patients not willing to consume a KD were offered the option to enroll

into the SD group instead (see [14, 15] for more details). The primary outcomes of interest were differences between both arms with respect to body composition changes assessed by weekly bioelectrical impedance analysis, which were published in separate papers for both tumor entities [14, 15]. Secondary outcomes were changes in blood parameters and several quality of life metrics that we have also published [16, 17]. However, we also followed most patients prospectively for at least 5 years or until the occurrence of locoregional or distant progression. This allowed us to test for any putative differences between both arms with respect to overall survival (OS), progression-free survival (PFS), and locoregional relapse-free survival (RFS) in a post-hoc analysis that was not specified in the original study protocol. We here report the results of survival analyses for the HNC and rectal cancer patient cohorts.

Intervention

Patients in the KD group received a thorough dietary consultation on the day of the baseline measurements. In addition, they received handouts including food choices and cooking recipes suitable for a KD. We advised patients to consume 75–80% calories from fat and to limit carbohydrates to 50g per day and 10g per meal. We promoted the consumption of an ad libitum wholefood KD including high-quality protein (meat, eggs, and fish) and micronutrient-dense foods (low-starch vegetables with every meal, organ meats, and bone broth), while industrial and processed foods, vegetable oils (except virgin coconut and olive oil), grains, and legumes were to be avoided. Patients had started the KD on a median of 2 days before the first radiotherapy treatment (range: 12 days before to 3 days after first irradiation). To check compliance with the KD, patients were asked to fill out a food diary for 2 days, measure urinary acetoacetate concentration daily by means of urinary ketone strips (Ketostix, Bayer Vital GmbH, Germany), and were regularly asked about the implementation of the diet. In addition, blood ketones and glucose were checked at least once weekly using the FreeStyle Precision device (Abbott Diabetes Care Ltd., Range Road, Witney, UK).

Patients in the SD group received no specific dietary advice; in the case that they requested dietary counselling, they were advised to follow the guidelines of the German Nutrition Society that promote the consumption of mostly unrefined plant foods (in particular wholegrains, vegetables, and fruits) and limitation of fats to 30–35% of the daily energy intake.

Patients

Details of patient enrollment and characteristics have been published previously [14, 15]. Briefly, 32 patients with

HNC and 49 patients with rectal cancer—all receiving neoadjuvant or adjuvant radio(chemo)therapy—were included in the study. Of those, 11 HNC and 24 rectal cancer patients were allocated to the KD group. One patient with rectal cancer who had followed a KD developed fatal Fournier’s gangrene and died a few days after completing radiotherapy due to septic shock [18]; this patient was kept in the analysis and treated as censored when analyzing PFS and RFS.

Recruitment began in November 2014 and ended in May 2021, due to slow recruitment of HNC patients and the impact of the COVID-19 crisis.¹ During radiotherapy, patients were seen at least once per week by the treating radiation oncologist and acute side effects were recorded according to Radiation Therapy Oncology Group (RTOG) criteria [19] in our digital patient data management system (Mosaik®, Elekta, Stockholm, Sweden). Recorded symptoms considered the skin, larynx, esophagus (dysphagia, dysgeusia), salivary glands, and mucous membranes in the HNC cohort and the skin, liver, urinary tract, and small and large intestines in the rectal cancer cohort. After treatment, prospective follow-up care of each patient was performed regularly. Briefly, the patients were admitted to our clinic for follow-up care a few weeks after therapy and then annually. Should they have lived too far away, regular follow-up letters were requested from the cooperating specialist clinics, where the patients continued to receive follow-up care. During April and May 2025, a final update of the study database was performed, with an attempt made to gather information from every patient from within the past year.

Statistical analyses

The primary outcomes of interest for this study were OS, PFS, and locoregional RFS, all calculated according to the Kaplan–Meier method. Overall survival was defined as the time from the start of radiotherapy until death from any cause. Progression-free survival was defined as the time from the start of radiotherapy until locoregional or distant tumor progression. Locoregional RFS was defined as the time from the start of radiotherapy until locoregional disease progression. In the case of no event, time-to-event data were censored at the last follow-up time or death. We also computed restricted mean survival times (RMSTs) in both the KD and SD groups, which could be useful for future meta-analyses [20]. The RMST is a measure of average sur-

vival up to a specified follow-up time, which distinguishes it from the mean survival time μ :

$$\mu = \int_0^{\infty} S(t) dt \quad (1)$$

$$\text{RMST}(t^*) = E[\min(T, t^*)] = \int_0^{t^*} S(t) dt \quad (2)$$

Here, $S(t)$ is the survival function, T the random time-to-event variable, and t^* a specified truncation time. The RMST thus measures the area under the survival curve up to the truncation time that we specified as

$$t^* = \min(t_{\max, \text{KD}}, t_{\max, \text{SD}}) \quad (3)$$

where $t_{\max, \text{KD}}$ and $t_{\max, \text{SD}}$ are the maximum follow-up times in the KD and SD groups, respectively, for the outcome of interest (i.e., OS, PFS, or RFS).

Survival analyses were performed for both the intention-to-treat (ITT) and per protocol (PP) populations. The ITT population was comprised of all patients starting the study and completing radiotherapy. The PP population is the subset of the ITT population ending the study without violating the protocol or voluntarily deciding to drop out. We also conducted exploratory survival analyses on propensity score-matched patients from the PP populations in order to achieve a better balance in measured baseline variables that could confound the outcomes of interest. Propensity score matching was performed by submitting the two datasets to a logistic regression analysis, predicting the intervention group “KD” vs. “SD” with the set of variables {age, BMI, chemotherapy} for HNC patients and {age, BMI, PTV, Karnofsky index} for rectal cancer patients (PTV denotes the planning target volume; BMI denotes body mass index). The consideration of chemotherapy for matching HNC patients was motivated by the expected impact of chemotherapy on outcomes, so that we wanted both groups to be balanced according to this variable. Among the rectal cancer patients, all but one had received chemotherapy, so both groups were naturally balanced with respect to this variable; however, we included the PTV and Karnofsky index in the logistic regression model because these variables were those most unbalanced in the original dataset (Table 1). For each patient from the KD group, one patient from the SD group was selected based on genetic matching, which is a robust method for achieving covariate balance [21]. Supplementary Table 1 shows that both cohorts were indeed well balanced after propensity score matching.

Qualitative data are described using frequency and percentage distributions and were compared between groups

¹ Three rectal cancer patients were recruited prior to the protocol registration as part of a case series study in order to first gain experience with the feasibility of the procedures [43].

Table 1 Baseline characteristics of the intervention and control groups

Parameter	Head and neck cancer		Rectal cancer		p-value	p-value
	KD group (N= 11)	SD group (N= 21)	KD group (N= 24)	SD group (N= 25)		
<i>Gender</i>						
Male	8 (72.7%)	16 (71.4%)	15 (62.5%)	16 (64%)	1	1
Female	3 (27.3%)	5 (28.6%)	9 (38.5%)	9 (36%)		
<i>Age (years)</i>	63 (46–75)	63 (55–75)	56 (38–77)	65 (43–76)	0.647	0.105
<i>Karnofsky index</i>						
70	8 (72.7%)	7 (33.3%)	11 (45.8%)	4 (16%)	0.124	0.064
80	2 (18.2%)	10 (47.6%)	9 (37.5%)	11 (44%)		
90	1 (9.1%)	4 (19.0%)	3 (12.5%)	9 (36%)		
100	0	0	1 (4.2%)	1 (4%)		
<i>T stage</i>						
1	0	3 (14.3%)	0	0	0.699	0.657
2	7 (36.6%)	10 (47.6%)	1 (4.2%)	3 (12%)		
3	2 (18.2%)	4 (19.0%)	21 (87.5%)	19 (76%)		
4	2 (18.2%)	4 (19.0%)	2 (8.3%)	3 (12%)		
<i>N stage</i>						
0	2 (18.2%)	8 (31.1%)	7 (29.2%)	6 (24%)	0.550	0.817
1	1 (9.1%)	3 (14.3%)	12 (50%)	11 (44%)		
2	7 (36.6%)	9 (42.9%)	2 (8.3%)	2 (8%)		
3	1 (0.9%)	1 (4.8%)	0	0		
+	–	–	3 (12.5%)	4 (16%)		
X	–	–	0	2 (8%)		
<i>8th edition AJCC stage</i>						
II	2 (18.2%)	4 (19.0%)	4 (16.7%)	7 (28%)	0.423	0.456
III	2 (18.2%)	6 (28.6%)	1 (4.2%)	2 (8%)		
IIIA	–	–	1 (4.2%)	3 (1.5%)		
IIIB	–	–	15 (62.5%)	13 (52%)		
IIIC	–	–	2 (8.3%)	0		
IVA	5 (45.4%)	10 (47.6%)	1 (4.2%)	0		
IVB	2 (18.2%)	0	–	–		
IVC	0	1 (4.8%)	–	–		
<i>Body weight (kg)</i>	72.7 (55.2–109.7)	74.3 (47.9–99.4)	77.5 (55.9–111.3)	84.5 (52.1–111.8)	0.751	0.545
<i>BMI (kg/m²)</i>	23.7 (19.3–35.4)	24.8 (17.8–35.6)	25.3 (19.9–39.4)	27.5 (19.5–36.7)	0.389	0.503
<i>Phase angle (°)</i>	4.43 (3.98–5.03)	4.49 (3.96–5.70)	4.87 (3.74–6.59) ^a	4.71 (3.31–5.97)	0.612	0.216
<i>Diabetes</i>						
No	8 (72.7%)	18 (85.7%)	21 (87.5%)	19 (76%)	0.390	0.463
Yes	3 (27.3%)	3 (14.3%)	3 (12.5%)	6 (24%)		

Table 1 (Continued)

Parameter	Head and neck cancer		Rectal cancer		p-value	p-value
	KD group (N=11)	SD group (N=21)	KD group (N=24)	SD group (N=25)		
<i>Smoking status</i>						
No	2 (18.2%)	3 (14.3%)	14 (58.3%)	14 (56%)	0.276	1
Active	0	5 (23.8%)	2 (8.3%)	3 (12%)		
Formerly	9 (81.8%)	13 (61.9%)	8 (33.3%)	8 (32%)		
<i>Tobacco consumption (packyears)</i>						
PEG use	20 (0–60)	30 (0–55)	0 (0–49.5)	0 (0–90) ^a	0.782	0.723
No	8 (72.7%)	20 (95.2%)	–	–	0.106	–
Yes	3 (27.3%)	1 (4.8%)				
<i>Systemic therapy^b</i>						
No	4 (36.4%)	7 (33.3%)	0	1 (4%)	1	1
Yes	7 (63.6%)	14 (66.7%)	24 (100%)	24 (96%)		
<i>Radiation dose (Gy)</i>	60 (50–71)	63 (50.4–75)	50 (48.6–61.2)	50 (45–55.8)	0.888	0.259
<i>Radiation therapy fractions</i>	30 (25–38)	30 (28–36)	25 (25–31)	25 (25–31)	0.721	0.197
<i>PTV (cm³)</i>	821 (155–1542)	755 (132–1359)	1240 (904–1845)	1468 (950–2078)	0.532	0.0046*

Continuous and categorical variables are presented as median (range) and counts (frequencies), respectively

BMI body mass index, KD ketogenic diet, PTV planning target volume, SD standard diet, PEG percutaneous endoscopic gastrostomy, AJCC American Joint Committee on Cancer

^aData missing for two patients

^bSystemic therapy was cisplatin in all cases of head and neck cancer except in one patient in the SD group who had received cetuximab; rectal cancer patients received oral capecitabine

* $p < 0.05$

using Fisher's exact test. Quantitative data are described using their median and range or mean and standard deviation and were compared between groups using the Wilcoxon rank sum test or t-test, respectively. Kaplan–Meier survival curves were compared using the log rank test. Treatment side effects were compared using Fisher's exact test. Statistical significance was defined as p -values <0.05 . Given the post-hoc exploratory nature of the analysis, the absence of prespecified hypotheses, and the limited sample size, p -values should be interpreted descriptively rather than as confirmatory for any hypothesis.

All analyses were performed in R version 4.4.1 with the survival and survminer packages for survival analysis, the survRM2 package for computing RMSTs, and the MatchIt package for propensity score matching (thereby setting the pop.size parameter to 1000 [22]); for genetic matching, the MatchIt package calls functions from the Matching package [23].

Results

Patient characteristics

Table 1 summarizes the baseline characteristics of the ITT population. There were no statistically significant differences between the KD and SD groups, with the exception

that rectal cancer patients in the KD group had significantly smaller planning target volumes than rectal cancer patients in the control group ($p=0.0046$). When only the PP population was considered, this difference in PTV sizes remained statistically significant ($p=0.0045$), while all other differences between the KD and SD arms remained nominally non-significant (all $p \geq 0.05$; see [14] and [15]).

In the PP population, median capillary β -hydroxybutyrate concentrations in the KD group were 0.7 mmol/L (0.2–3.2 mmol/L) for HNC [15] and 0.6 mmol/L (0.1–2.9 mmol/L) for rectal cancer patients [14]. Thereby, all patients in the KD group achieved at least one capillary or laboratory β -hydroxybutyrate measurement ≥ 0.4 mmol/L. Analyses of 2-day food diaries for 12 rectal cancer patients showed that the KDs included 37 g of carbohydrates per day on average (standard deviation 19 g, range 12–70 g), with average contributions of carbohydrates, protein, and fat to total energy intake of 8% (range 3.6–14.6%), 24% (17.7–31.4%), and 68% (54.7–76.4%), respectively [14]. Overall, these data provide evidence that patients tried to comply with the diet (the slight overconsumption of carbohydrates by some patients was no reason for removing a patient from the PP population).

Table 2 Survival statistics of the intention-to-treat (ITT) and per protocol (PP) populations of head and neck cancer patients

Parameter	Intention-to-treat population			Per protocol population		
	KD group ($N=11$)	SD group ($N=21$)	p -value	KD group ($N=7$)	SD group ($N=21$)	p -value
OS: follow-up time (months)	72.2 (12.4–102.2)	88.2 (12.1–107.9)	0.242	80.4 (12.4–102.2)	88.2 (12.1–107.9)	0.811
OS: RMST (months)	86.1 \pm 10.3 95% CI: [65.9, 106.3]	77.8 \pm 7.2 95% CI: [63.6, 91.9]	0.508	89.4 \pm 11.9 95% CI: [66.1, 112.7]	77.8 \pm 7.2 95% CI: [63.6, 91.9]	0.403
OS: RMST ratio	1.11 \pm 0.17 95% CI: [0.82, 1.49]		0.502	1.15 \pm 0.19 95% CI: [0.84, 1.58]		0.391
PFS: follow-up time (months)	61.4 (4.3–100.5)	74.4 (11.1–101.1)	0.405	77.3 (4.3–100.5)	74.4 (11.1–101.1)	0.832
PFS: RMST (months)	84.0 \pm 10.6 95% CI: [63.2, 104.7]	83.7 \pm 7.5 95% CI: [68.9, 98.5]	0.982	86.8 \pm 12.7 95% CI: [61.8, 111.7]	83.7 \pm 7.5 95% CI: [68.9, 98.5]	0.834
PFS: RMST ratio	1.00 \pm 0.16 95% CI: [0.74, 1.36]		0.982	1.04 \pm 0.18 95% CI: [0.74, 1.45]		0.833
RFS: follow-up time (months)	61.4 (9.9–100.5)	74.4 (6.2–101.1)	0.427	77.3 (12.4–100.5)	74.4 (6.2–101.1)	0.874
RFS: RMST (months)	100.5 \pm 0.0 95% CI: [100.5, 100.5]	87.3 \pm 7.0 95% CI: [73.6, 101.0]	0.059	100.5 \pm 0.0 95% CI: [100.5, 100.5]	87.3 \pm 7.0 95% CI: [73.6, 101.0]	0.059
RFS: RMST ratio	1.15 \pm 0.10 95% CI: [0.98, 1.35]		0.079	1.15 \pm 0.10 95% CI: [0.98, 1.35]		0.079

KD ketogenic diet, OS overall survival, PFS progression-free survival, RFS relapse-free survival, RMST restricted mean survival time as defined by Eq. 2, SD standard diet, CI confidence interval

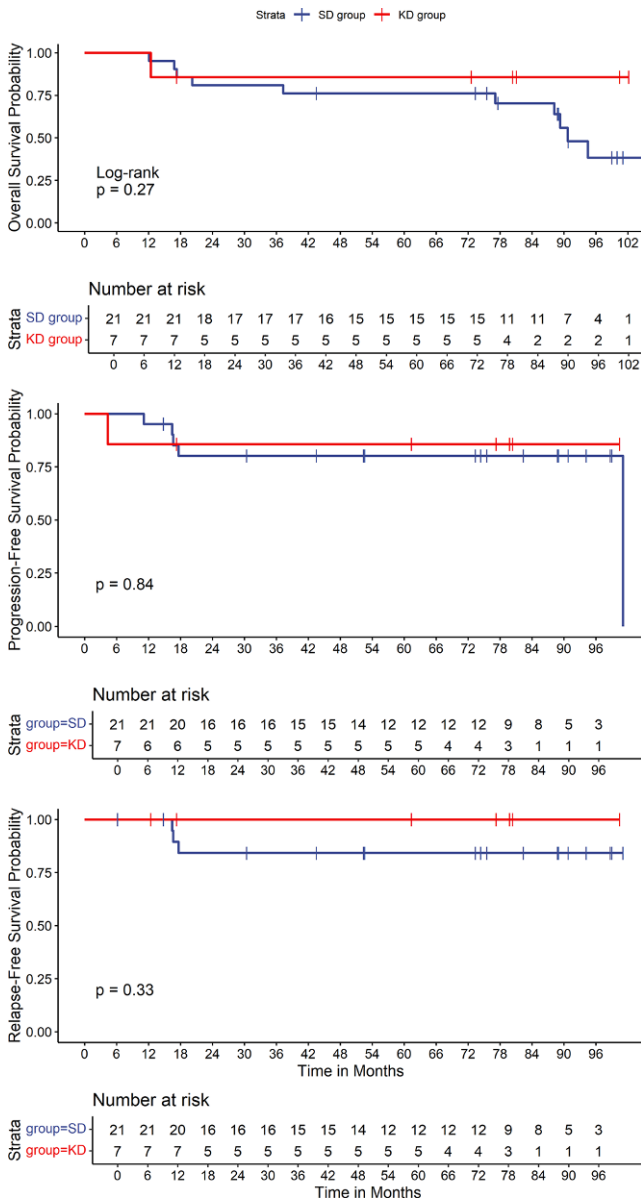


Fig. 1 Overall, progression-free, and relapse-free survival of head and neck cancer patients who finished the study regularly in the ketogenic diet (KD) and standard diet (SD) groups

Survival analysis for head and neck cancer patients

Table 2 shows the survival statistics for the HNC cohort. The length of follow-up was similar between the KD and SD groups for all three outcomes in both the ITT and the PP population. Notably, there were three locoregional relapses in the SD (14%) but none in the KD group; however, the difference in RMST for RFS was not statistically significant. The RMSTs for OS and PFS also did not significantly differ between the groups.

Figure 1 displays the Kaplan–Meier curves for the PP population for all three outcomes. While the KD groups exhibited prolonged OS, PFS, and RFS, the survival curve

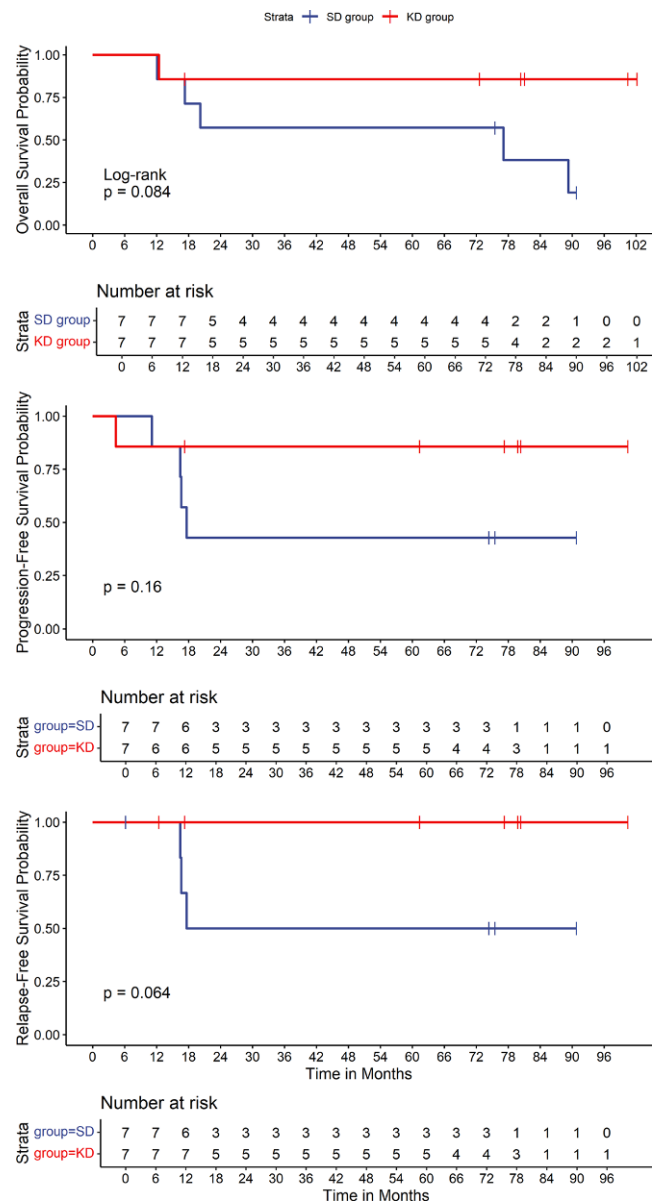


Fig. 2 Exploratory survival analyses of head and neck cancer patients after propensity score matching. KD ketogenic diet, SD standard diet

differences to the SD group were not statistically significant. When we matched the seven patients from the KD group who finished the study regularly to seven patients from the SD group (see “Materials and methods” section), the p -values for survival differences between both groups were 0.084, 0.16, and 0.064 for OS, PFS, and RFS, respectively (Fig. 2).

Survival analysis for rectal cancer patients

Table 3 shows the survival statistics for the rectal cancer cohort. The length of follow-up was significantly shorter in the KD than in the SD group for OS in the ITT population.

Table 3 Survival statistics of the intention-to-treat (ITT) and per protocol (PP) populations of rectal cancer patients

Parameter	Intention-to-treat population			Per protocol population		
	KD group (N=24)	SD group (N=25)	p-value	KD group (N=19)	SD group (N=23)	p-value
OS: follow-up time (months)	61.9 (1.5–127.1)	92.9 (16.5–122.4)	0.014*	61.7 (1.5–127.1)	99.2 (16.5–122.4)	0.037*
OS: RMST (months)	92.3 ± 8.7 95 % CI: [75.2, 109.4]	98.5 ± 7.3 95 % CI: [84.2, 112.7]	0.586	89.9 ± 10.0 95 % CI: [70.2, 109.6]	100.0 ± 7.5 95 % CI: [85.3, 114.7]	0.422
OS: RMST ratio	0.94 ± 0.11 95 % CI: [0.74, 1.19]		0.588	0.90 ± 0.12 95 % CI: [0.69, 1.17]		0.431
PFS: follow-up time (months)	57.7 (1.5–121.0)	62.0 (3.2–113.3)	0.535	59.0 (1.5–121.0)	62.0 (7.1–113.3)	0.696
PFS: RMST (months)	87.8 ± 8.6 95 % CI: [71.0, 104.7]	75.3 ± 8.8 95 % CI: [58.1, 92.5]	0.385	86.8 ± 9.7 95 % CI: [67.7, 105.8]	76.9 ± 8.8 95 % CI: [59.6, 94.2]	0.554
PFS: RMST ratio	1.14 ± 0.17 95 % CI: [0.85, 1.52]		0.388	1.11 ± 0.18 95 % CI: [0.81, 1.49]		0.553
RFS: follow-up time (months)	57.7 (1.5–121.0)	65.1 (15.5–112.2)	0.177	59.0 (1.5–121.0)	65.1 (15.5–112.2)	0.308
RFS: RMST (months)	99.2 ± 7.0 95 % CI: [85.5, 112.9]	92.2 ± 7.2 95 % CI: [78.1, 106.4]	0.487	96.2 ± 8.4 95 % CI: [79.8, 112.7]	90.8 ± 7.8 95 % CI: [75.8, 105.9]	0.633
RFS: RMST ratio	1.08 ± 0.11 95 % CI: [0.88, 1.32]		0.488	1.06 ± 0.13 95 % CI: [0.84, 1.35]		0.633

KD ketogenic diet, OS overall survival, PFS progression-free survival, RFS relapse-free survival, RMST restricted mean survival time as defined by Eq. 2, SD standard diet, CI confidence interval

* $p < 0.05$

Regarding the outcomes, there were no statistically significant differences between the groups in the RMSTs. There were also no statistically significant differences in the OS, PFS, or RFS curves between the groups in the PP population (Fig. 3) or in the propensity score-matched sample (Fig. 4).

It is noteworthy that within the PP population, three male patients from the KD group had refused surgery; all of these patients developed disease progression (two locoregional relapses) and ultimately died. In contrast, only one patient from the SD group did not undergo surgery; he also developed locoregional disease progression but was still alive at the time of last follow-up (70.6 months).

Side effects

The comparison of acute side effects between the KD and SD groups in both cohorts are displayed in Tables 4 and 5. For HNC patients, skin toxicity was significantly less severe in the KD compared to the SD group in the ITT but not the PP population (Table 4). No other significant differences emerged for any side effect. In the rectal cancer patient cohort, side effects were generally mild, and no grade 3 toxicities occurred during radiotherapy. No statistically significant differences emerged between the KD and SD groups.

Discussion

Using prospective follow-up data from our KETOCOMP trial, we were able to conduct survival analyses of rectal and HNC patients who had consumed a KD during standard-of-care treatment with a median follow-up of more than 70 months. These analyses are important to investigate whether the beneficial short-term effects of a KD on body composition, quality of life, and blood parameters that we reported previously would translate into long-term survival benefits. However, we found no meaningful evidence that HNC or rectal cancer patients consuming a KD would have better survival outcomes than control patients on their SD. The greatest benefit of the KD intervention was a longer RFS time in the HNC cohort with $p = 0.059$ (Table 2). In an exploratory analysis using propensity score matching to obtain intervention and control groups that were more balanced, we obtained survival curve differences that were somewhat more pronounced in the HNC cohort but which were still not statistically significant (Fig. 2).

According to theoretical considerations, a KD could have the potential to improve clinical outcomes in HNC [24, 25] and rectal cancer [26, 27] patients. Schroeder et al. [28] showed that after a few days of switching to a KD, tumor lactate levels were reduced in HNC patients. Given that tumor lactate levels exert a radioprotective effect in HNC

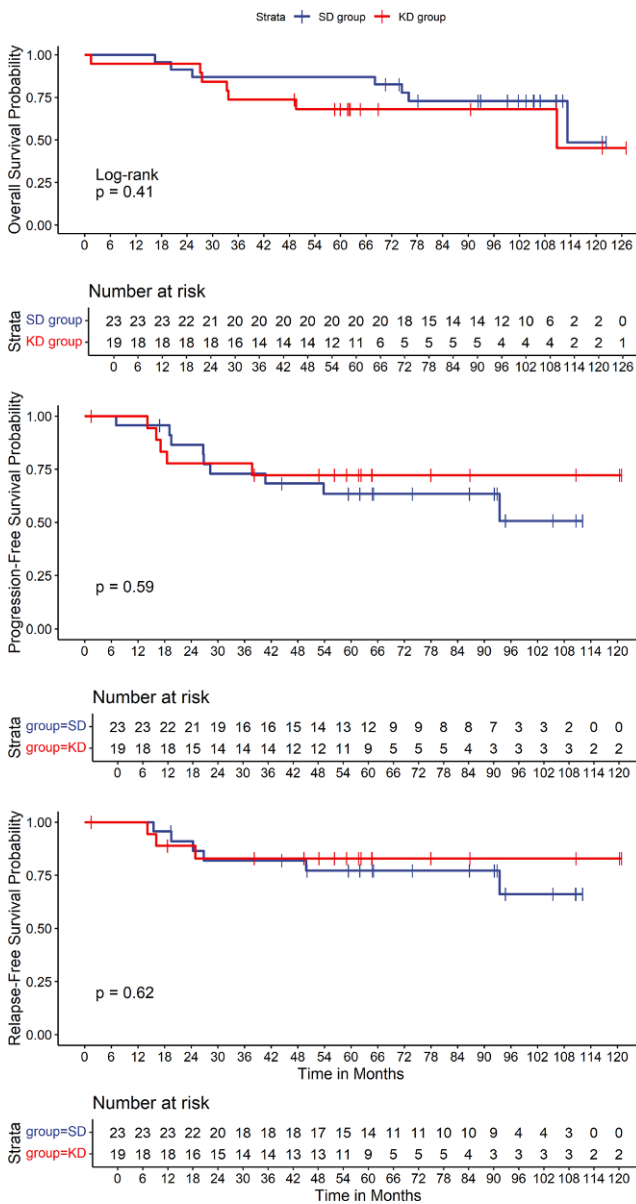


Fig. 3 Overall, progression-free, and relapse-free survival of rectal cancer patients who finished the study regularly in the ketogenic diet (KD) and standard diet (SD) groups

tumors [29], the numerically longer locoregional RFS time in the HNC cohort, although not statistically significant, is at least consistent with these findings. However, the rectal cancer cohort did not display any differences in OS, PFS, or RFS times. This is despite the fact that pathological responses after neoadjuvant radiochemotherapy were better in the KD group at the time of surgery [14]. Trials on neoadjuvant breast cancer treatment have shown that pathological complete response is only associated with disease-free survival or OS at the level of the individual patient and not at the level of a clinical trial [30, 31]. One explanation for these as well as our findings is that the pathological re-

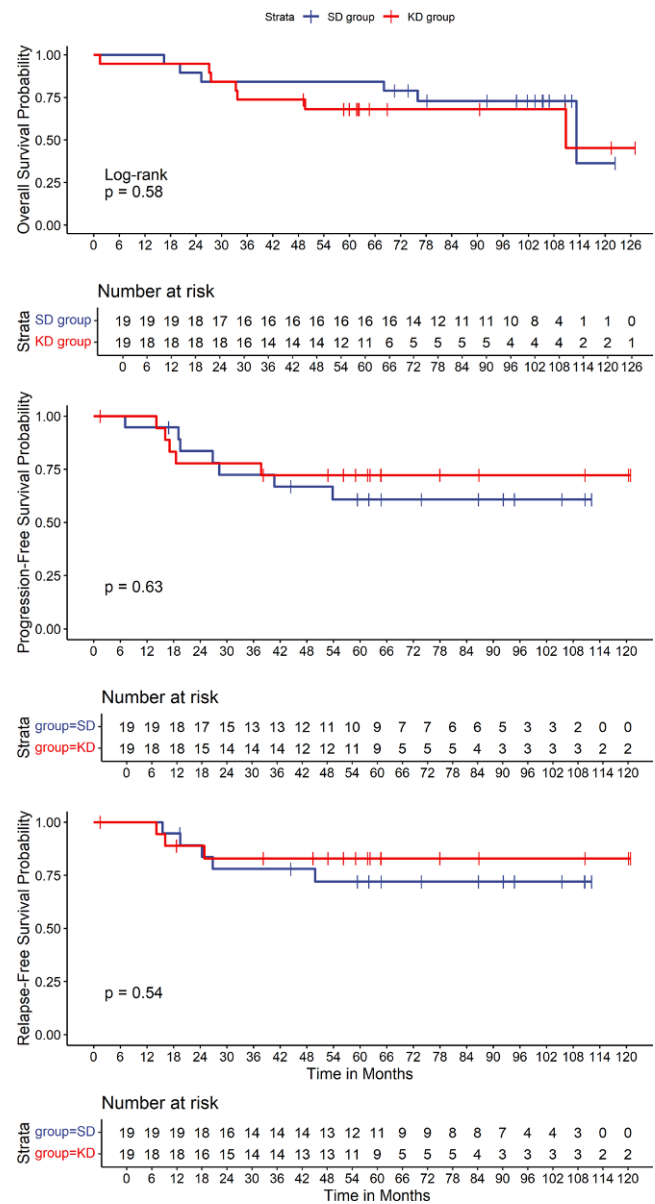


Fig. 4 Exploratory survival analyses of rectal cancer patients after propensity score matching. KD ketogenic diet, SD standard diet

sponse of the primary tumor does not reflect the therapeutic effects on micrometastases. Furthermore, after surgery had been performed, the odds of developing locoregional recurrence would have been equal in both groups regardless of the response to neoadjuvant therapy. This is because the great majority of our patients discontinued the KD after study termination, so that any putative antitumor mechanism of the KD could no longer operate. The larger number of patients receiving no surgery after radiochemotherapy in the KD group (three versus one) and the one patient dying due to Fournier's gangrene a few days after radiotherapy [18] could further have contributed to a distortion of the

Table 4 Acute radiotherapy side effects in the intention-to-treat (ITT) and per protocol (PP) populations of head and neck cancer patients according to RTOG criteria

Parameter	Intention-to-treat population			Per protocol population		
	KD group (N= 11)	SD group (N=21)	p-value	KD group (N=7)	SD group (N=21)	p-value
Skin toxicity	0: 1 (9.1 %)	0: 0	0.0495*	0: 1 (14.3 %)	0: 0	0.063
	1: 6 (54.5 %)	1: 7 (33.3 %)		1: 4 (57.1 %)	1: 7 (33.3 %)	
	2: 3 (27.3 %)	2: 14 (66.7 %)		2: 2 (28.6 %)	2: 14 (66.7 %)	
	3:1 (9.1 %)	3: 0		3:0	3: 0	
Dysphagia	0: 1 (9.1 %)	0: 0	0.334	0: 1 (14.3 %)	0: 0	0.089
	1: 4 (36.4 %)	1: 9 (42.9 %)		1: 4 (57.1 %)	1: 9 (42.9 %)	
	2: 2 (18.2 %)	2: 8 (38.1 %)		2: 0	2: 8 (38.1 %)	
	3: 4 (18.2 %)	3: 4 (19.0 %)		3: 2 (28.6 %)	3: 4 (19.0 %)	
Dysgeusia	0: 1 (9.1 %)	0: 1 (4.8 %)	0.661	0: 1 (14.3 %)	0: 1 (4.8 %)	0.400
	1: 3 (27.3 %)	1: 9 (42.9 %)		1: 3 (42.9 %)	1: 9 (42.9 %)	
	2: 5 (45.5 %)	2: 6 (28.6 %)		2: 3 (42.9 %)	2: 6 (28.6 %)	
	3: 2 (18.2 %)	3: 5 (23.8 %)		3: 0	3: 5 (23.8 %)	
Mucous membrane	0: 1 (9.1 %)	0: 3 (4.8 %)	0.364	0: 1 (14.3 %)	0: 3 (4.8 %)	0.435
	1: 6 (54.5 %)	1: 8 (38.1 %)		1: 5 (71.4 %)	1: 8 (38.1 %)	
	2: 2 (18.2 %)	2: 9 (42.9 %)		2: 1 (14.3 %)	2: 9 (42.9 %)	
	3: 2 (18.2 %)	3: 1 (4.8 %)		3: 0	3: 1 (4.8 %)	
Salivary glands	0: 0	0: 1 (4.8 %)	1	0: 0	0: 1 (4.8 %)	1
	1: 6 (54.5 %)	1: 7 (33.3 %)		1: 3 (42.9 %)	1: 7 (33.3 %)	
	2: 2 (18.2 %)	2: 12 (57.1 %)		2: 4 (57.1 %)	2: 12 (57.1 %)	
	3: 2 (18.2 %)	3: 1 (4.8 %)		3: 0	3: 1 (4.8 %)	

KD ketogenic diet, SD standard diet, RTOG Radiation Therapy Oncology Group
 *p<0.05

Table 5 Acute side effects during radiotherapy in the intention-to-treat (ITT) and per protocol (PP) populations of rectal cancer patients according to RTOG criteria

Parameter	Intention-to-treat population			Per protocol population		
	KD group (N= 24)	SD group (N=25)	p-value	KD group (N= 19)	SD group (N=23)	p-value
Skin toxicity	0: 13 (54.2 %)	0: 15 (60 %)	0.794	0: 11 (57.9 %)	0: 14 (60.9 %)	1
	1: 7 (29.2 %)	1: 5 (20 %)		1: 4 (21.1 %)	1: 4 (17.4 %)	
	2: 4 (16.7 %)	2: 5 (20 %)		2: 4 (21.1 %)	2: 5 (21.7 %)	
Small intestine	0: 19 (79.2 %)	0: 15 (60 %)	0.217	0: 16 (84.2 %)	0: 14 (60.9 %)	0.169
	1: 5 (20.8 %)	1: 10 (40 %)		1: 3 (15.8 %)	1: 9 (39.1 %)	
Large intestine	0: 6 (25 %)	0: 5 (20 %)	0.656	0: 4 (21.1 %)	0: 4 (17.4 %)	0.428
	1: 10 (41.7 %)	1: 14 (56 %)		1: 8 (42.1 %)	1: 14 (60.9 %)	
	2: 8 (33.3 %)	2: 6 (24 %)		2: 7 (36.8 %)	2: 5 (21.7 %)	
Liver	0: 23 (95.8 %)	0: 22 (88 %)	0.609	0: 18 (94.7 %)	0: 20 (87.0 %)	0.614
	1: 1 (4.2 %)	1: 3 (12 %)		1: 1 (5.3 %)	1: 3 (13.0 %)	
Urinary tract	0: 18 (75 %)	0: 13 (52 %)	0.172	0: 16 (84.2 %)	0: 13 (56.5 %)	0.090
	1: 5 (20.8 %)	1: 11 (44 %)		1: 2 (10.5 %)	1: 9 (39.1 %)	
	2: 1 (4.2 %)	2: 1 (4 %)		2: 1 (5.3 %)	2: 1 (4.3 %)	

KD ketogenic diet, SD standard diet, RTOG Radiation Therapy Oncology Group

survival statistics to the disadvantage of the intervention group. Finally, some clinical data indicate that the OS of cancer patients consuming a KD is positively associated with the duration of the KD [32, 33]. The KD duration in our patients was relatively short compared to the follow-up time (no patient had started the KD more than 12 days

prior to the first irradiation), which could also be a reason for why we did not observe statistically significant differences in OS.

A meta-analysis of mouse studies has shown that among 15 cancer types, pancreatic cancer, glioblastoma, stomach cancer, and HNC had the highest evidence for synergistic

antitumor effects of a KD combined with oncological therapies [11]. While evidential support for antitumor effects of a KD in colon cancer was also strong when used as monotherapy, the evidence for synergistic effects was not significant. Assuming biological similarity between colon and rectal cancer, the results of this preclinical meta-analysis would be consistent with our findings that HNC patients responded better to synergistic treatment in terms of PFS improvements than rectal cancer patients. Only a few other studies have investigated the application of a KD during treatment of HNC or rectal cancer patients. Ma et al. conducted a phase I clinical trial in patients with locally advanced HNC undergoing radiochemotherapy with or without a KD, but no survival analyses could be performed due to small patient numbers [25]. İyikesici presented the preliminary results of combining a KD with metabolically supported chemotherapy, hyperthermia, and hyperbaric oxygen therapy in stage II–IV rectal cancer patients [34]. While he concluded that the survival data were promising for this combinatorial protocol, a control group not following a KD was lacking, so that no conclusions can be drawn regarding putative anticancer effects of the KD. A retrospective analysis from Detroit, USA, found that rectal cancer patients consuming $\geq 40\%$ energy from fat and $< 100\text{g}$ carbohydrates/day had an approximately 50% reduced risk of cancer-specific death after radiotherapy, a result that approached the threshold for statistical significance (HR 0.49, 95% CI 0.23–1.02) [35].

Findings from clinical trials investigating a KD as a complementary treatment in other tumor entities are mixed. A recently published phase II trial found evidence for synergistic effects of a KD combined with chemotherapy in pancreatic cancer patients, with improved PFS and OS in the KD group [36]. A study conducted in Tehran, Iran, found that a KD in addition to neoadjuvant chemotherapy significantly prolonged the survival of breast cancer patients, although no such effect was found for patients with metastasized breast cancer receiving chemotherapy [37]. The majority of clinical trials reporting survival outcomes have focused on patients with high-grade gliomas, but their findings are inconclusive, either because a control group was lacking [38–40] or because survival outcomes were not statistically different between the KD and control groups [41]. Therefore, our study adds important data to the field of KD and cancer research.

Besides evidence for antitumor effects of KDs from preclinical research, mechanisms have been identified that hint towards a protective role of ketone bodies, in particular β -hydroxybutyrate, concerning normal tissue tolerance to radio- and chemotherapy [42]. Consistent with this, we detected a significantly lower rate of high-grade skin toxicity in the KD compared to the SD group in the HNC ITT population. However, no other significant differences were

found for the remaining toxicities included in our evaluation. This could be due to the small sample sizes, which represent the main limitation of our study. Unfortunately, other studies comparing radiotherapy side effects between a KD and control group are lacking, so we cannot interpret our findings within the context of other clinical trials.

The KETOCOMP study was performed in a community hospital without financial support from industry or other sources, and we believe that larger institutions would be better suited to perform larger trials in the future. A second limitation is that the great majority of our patients quit the KD after study termination, which could have negatively impacted survival statistics. We also did not track or control for other lifestyle factors such as physical exercise that could have influenced the course of the disease after radiotherapy. Another limitation is that the degree of ketosis and the ratio between glucose and ketone body concentrations, which is proposed as a surrogate measure to track the effects of ketogenic metabolic therapy [6], were also not accounted for in this analysis. Finally, only 79 and 64% of the rectal and HNC cancer patients, respectively, adhered to the KD and finished the study regularly. Nevertheless, these numbers are higher than average adherence rates reported in the literature [9, 25].

A strength of this study is that we systematically collected data on acute side effects and prospectively followed patients for long periods that, for most patients without clinical events of interest, exceeded 5 years. It is therefore one of the clinical trials with the longest follow-up of cancer patients who followed a KD in conjunction with their standard-of-care therapy. The results, indicating the potential of antitumor effects of KDs and radiotherapy in select patient cohorts, could guide the design of future trials and could be used in future meta-analyses.

In conclusion, our analysis found no statistically significant differences in OS between rectal and HNC patients consuming a KD and those on a SD during radiotherapy. However, the KD was associated with slightly prolonged RFS times ($p=0.059$) and less severe skin toxicity ($p=0.0495$) in the HNC ITT population. Because we did not observe any detrimental effect of the KD on any of the three survival outcomes, our study adds to the growing literature confirming the safety of ketogenic metabolic therapy.

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Data Availability Statement Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Conflict of interest R.J. Klement occasionally consumes a ketogenic diet. R.A. Sweeney declares that he has no competing interests.

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