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Nutritional Status and Interventions for Patients with Cancer

2nd Edition

Edited by
Nuno Borges, Fernando Mendes and Diana Martins

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Guest Editors

Nuno Borges
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Guest Editors

Nuno Borges
Faculty of Nutrition and Food Sciences
University of Porto
Porto
Portugal

Fernando Mendes
Coimbra Health School
Coimbra Polytechnic University
Coimbra
Portugal

Diana Martins
Coimbra Health School
Coimbra Polytechnic University
Coimbra
Portugal

Editorial Office
MDPI AG
Grosspeteranlage 5
4052 Basel, Switzerland

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About the Editors

Nuno Borges

Nuno Borges is a Nutritionist and currently an Associate Professor at the Faculty of Nutrition and Food Sciences, University of Porto, Portugal. He is presently researching the relationships between muscular function, nutritional status, and health outcomes in some diseases. Research interests also include pharmacology and drug–nutrient interactions.

Fernando Mendes

Fernando Mendes (FM) is working as a Coordinator Professor at the Biomedical Laboratory Sciences Scientific-Pedagogical Unit at Polytechnic University of Coimbra and is an effective member of the Health & Technology Research Center (H&TRC). He is also a researcher collaborator at the Center for Innovative Biomedicine and Biotechnology (CIBB) at the University of Coimbra. He finished his PhD in Medical Sciences in 2016 at the Faculty of Medicine of the University of Coimbra. For the past years, FM has been a member of a multidisciplinary team whose domain includes Oncology and Biophysics. He has published 30 full-text papers, 4 books, and 6 book chapters, more than 20 abstracts in periodic journals, more than 120 abstracts in conference proceedings, and 45 communications by invitation. He is a co-author of more than 200 posters in international scientific meetings. He was a supervisor of more than 60 bachelor's degree students, 6 master's theses, and 5 research projects in innovation and entrepreneurship, and is currently the supervisor of 2 PhD thesis. FM has 3 patents and more than 10 provisory patents submitted between Portugal and Brazil. In collaboration with Brazil, as an invited researcher, has more than 20 financed research projects. In recent years, he has given higher priority to the study of topics related to cancer treatment, namely using radiotherapy and immunotherapy. One of the subtopics that he has been studying aims to better understand the role of the immune system and the immune checkpoint inhibitors in cancer treatment, in prostate, bladder, and penile cancer among other cancers, which may contribute to increasing patients' life expectancy. He has been a reviewer of several journals, having reviewed more than 160 manuscripts. Has been awarded 10 prizes and distinctions.

Diana Martins

Diana Martins is an Associate Professor in the Biomedical Laboratory Sciences at Coimbra Health School. She is an effective member of the Health & Technology Research Center (H&TRC) research center and a collaborator in the Center for Innovative Biomedicine and Biotechnology (CIBB) at the University of Coimbra. A PhD in Pathology and Molecular Genetics at University of Porto and a Post doctoral grant in cancer research allow Diana to study the molecular mechanisms in breast and gastric cancer, focusing on biomarkers for cancer diagnosis and prognosis. Diana has published 36 full-text papers, 3 book chapters and 1 patent. Research interests include cancer, microenvironment, microbiome and cancer biomarkers.

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Article

The Effect of Nutritional Intervention in Nutritional Risk Screening on Hospitalised Lung Cancer Patients

Raquel Oliveira [1,2,3], Bruno Cabrita [1], Ângela Cunha [1], Sónia Silva [1], João P. M. Lima [4,5], Diana Martins [4,5,6,7] and Fernando Mendes [4,5,6,7,8,*]

1 Pulmonology Service, Centro Hospitalar de Leira, Rua das Olhalvas, 2414-016 Leiria, Portugal; raquel.oliveira@ulsrl.min-saude.pt (R.O.); bruno.cabrita@chleiria.min-saude.pt (B.C.); angela.cunha@chleiria.min-saude.pt (Â.C.); sonia.silva@ulsrl.min-saude.pt (S.S.)
2 ciTechCare—Center for Innovative Care and Health Technology, Health Innovation Hub | Politécnico de Leiria, Campus 5, Rua das Olhalvas, 2414-016 Leiria, Portugal
3 Higher School of Health, University of Algarve I University of Algarve—Campus de Gambelas, 8005-139 Faro, Portugal
4 H&TRC—Health & Technology Research Center, Coimbra Health School, Polytechnic University of Coimbra, 3045-043 Coimbra, Portugal; joao.lima@estesc.ipc.pt (J.P.M.L.); diana.martins@estesc.ipc.pt (D.M.)
5 Coimbra Health School (ESTeSC), Polytechnic University of Coimbra, 3046-854 Coimbra, Portugal
6 Biophysics Institute of Faculty of Medicine, Coimbra Institute for Clinical and Biomedical Research (iCBR) Area of Environment Genetics and Oncobiology (CIMAGO), University of Coimbra, 3000-548 Coimbra, Portugal
7 Center for Innovative Biomedicine and Biotechnology, University of Coimbra, 3000-548 Coimbra, Portugal
8 European Association for Professions in Biomedical Sciences, 1000 Brussels, Belgium
* Correspondence: fjmendes@estesc.ipc.pt

Abstract: Background: Lung cancer (LC) patients are prone to suffer from malnutrition. Malnutrition negatively affects patients' response to therapy, increases the incidence of treatment-related side effects, and decreases survival. Early identification of LC patients who are malnourished or at risk of malnutrition can promote recovery and improve prognosis. Objective: This study aimed to assess the risk and nutritional status of lung cancer patients who are hospitalised, as well as to evaluate the impact of nutritional intervention on the risk of malnutrition. Methods: From January 2022 to December 2023, 53 LC patients hospitalised in a pulmonology department had their nutritional risk (initial and final) and nutritional status (initial) assessed. All were selected for nutritional intervention. Nutrition counselling was the first intervention option, along with dietary changes with/without oral nutritional supplements. Results: At the time of hospitalisation, 90.6% of the patients were at nutritional risk, 45.3% were classified as moderately malnourished, and 35.8% were classified as severely underweight. After the hospitalisation, 73.6% were at nutritional risk at the time of discharge, suggesting a statistically significant decrease in the number of patients with nutritional risk. Conclusions: Most LC patients hospitalised presented an altered nutritional status. Our study suggests that a nutritional intervention must be implemented to reduce malnutrition risk, which may impact prognosis. The comprehensive nutritional problems experienced by LC patients require nutritional assessment and improved individually tailored nutritional support.

Keywords: nutrition assessment; nutrition therapy; lung cancer

1. Introduction

Lung cancer (LC) is the most commonly diagnosed cancer worldwide (12.4% of the total cases), followed by cancers of the female breast (11.6%), colorectum (9.6%), prostate

(7.3%), and stomach (4.9%). LC is also the leading cause of cancer death (18.7% of the total cancer deaths, over 1.8 million deaths worldwide) [1]. The disease is the leading cause of cancer death among men. The disease is second among women for both incidence and mortality, with male-to-female ratios for lung cancer incidence and mortality approximately 2:1. However, these ratios differ significantly by region, ranging from nearly equal in North America and Northern Europe to four-to-five-times higher in Northern Africa and Eastern Europe [1]. In Europe, LC is the leading cause of cancer mortality among men in all countries except Sweden and among women in 13 countries (one-third of the European nations). The disease has a more significant impact on men than on women, with a male-to-female incidence ratio varying from 3 to 10 [2]. Prostate (21%), colorectal (20%), and lung (12%) cancers are the most common cancers in men in Portugal, while in women breast cancer is the cancer with the highest incidence (28%), followed by colorectal cancer (16%) and LC (6%) [2]. LC is the leading cause of cancer mortality among men in Portugal and the third leading cause among women [2].

Depending on the disease stage and treatment modality, patients with LC are prone to malnutrition. Malnutrition negatively affects patients' response to therapy, increases the incidence of treatment-related side effects, and can contribute to a survival decrease. Malnutrition is a comorbidity frequently found in neoplastic patients, but it remains often underestimated and thus undertreated [3]. Early identification of patients who are malnourished or at risk of malnutrition can promote recovery and improve prognosis. In addition, early nutritional intervention is cost-effective, as it reduces complication rates and length of hospitalisation [4]. Malnutrition in people with LC is highly prevalent (35–70%) depending on the treatment type, stage of disease, and assessment method [4,5]. LC is one of the most common cancers worldwide; however, although malnutrition is frequent in LC patients, this aspect is underestimated and thus undertreated [6]. Malnutrition screening is the starting point for high-quality nutrition care. The systematic nutritional risk assessment in Portugal is mandatory for every hospital inpatient using the Nutritional Risk Screening 2002 [7,8].

Nutritional intervention is mandatory as an adjuvant to any treatment, as it improves nutritional parameters, body composition, symptoms, quality of life, and, ultimately, survival [3,8]. Risk factors for malnutrition have been described, such as nutritional deficiencies resulting from the disease per se, such as anorexia and nausea, and others resulting from therapeutic procedures during or before hospitalisation. Precipitating and/or aggravating causes of malnutrition during hospitalisation can be considered in situations such as the use of serums, prolonged fasting, skipping meals for tests, lack of control over intake, failure to record weight and its evolution, and delays in starting nutritional support [4,9].

Malnutrition changes the immunological, cardiovascular, respiratory, and gastrointestinal systems. These changes result in complications such as deterioration in physical and mental capacity, increased susceptibility to infections, and delayed wound healing, with the inherent risk of an increased length of hospital stay and morbidity and mortality [4,10–12]. Nutritional status is a significant clinical and prognostic indicator in evaluating lung cancer treatment. Malnutrition is linked to a poorer outcome in terms of overall survival, time to tumour progression, and quality of life in patients undergoing treatment for lung cancer [13].

All individuals previously identified as being at nutritional risk during screening should have their nutritional status assessed. This assessment is part of this comprehensive study, and good-quality care is given to hospitalised patients [10–12]. The purpose of evaluating nutritional status is to detect malnourished patients and their degree of malnutrition, identify patients who need nutritional support, program an appropriate dietary plan, and

assess the effectiveness of the nutritional support provided as part of the hospital treatment interventions [11,14].

It has been shown that the prevention and early treatment of malnutrition improves the quality of care in both clinical and economic terms. All strategies should be used to improve the nutritional status of hospitalised patients [12,15]. Several studies concluded that introducing nutritional support for malnourished patients significantly reduces hospitalisation time. Even though there are costs associated with the nutritional backing, these are offset by savings in hospitalisation time [3,15–17].

Insufficient food intake increases the prevalence and severity of malnutrition, with a concomitant increase in its complications. Therefore, all hospitalised patients must have a personalised nutritional care plan [8,9]. Dietary approaches, with a view to immediate nutritional intervention appropriate to the clinical situation, can take various forms, such as an oral diet enriched with nutritionally dense foods, diet changes (texture changes, inclusion of small intermediate meals), or even artificial oral feeding, enteral nutrition, or parenteral nutrition [16]. Dietary counselling should also be implemented as one of the first measures, and the patient should be involved in the nutritional care plan [11,14].

Many LC inpatients depend on hospital food, so it should be considered an integral part of individualised treatment, not just hospital routine. This means that assessing hospital food intake plays a vital role during hospitalisation. A patient with an adequate dietary intake will have a lower nutritional risk. 'Healthy' diets low in fats and sugars may be necessary for patients with coronary pathology or obesity, but most patients need diets fortified with energy and nutrients. Some actions should be implemented to change this scenario: food availability for intermediate meals and supplements can be used but should never be a substitute for regular food [17,18]. Once nutritional support has been implemented, monitoring is essential to assess its effectiveness and allow eventual corrections according to the patient's needs. Different interventions may be necessary during hospitalisation. Monitoring should include food intake, nutritional intervention tolerance, weight change, changes in laboratory parameters, etc. [8,12,18–21].

We aimed to assess the risk and nutritional status of hospitalised LC patients and evaluate the impact of nutritional intervention on the risk of malnutrition.

2. Materials and Methods

2.1. Type of Study

A prospective observational study was conducted in patients hospitalised with LC or lung metastasis, who were offered nutritional evaluation and support. This study was conducted in the Centro Hospitalar de Leiria between January 2022 and December 2023. Only patients with LC as a primary tumour or patients with lung metastasis (another primary tumour) were selected for this study. The exclusion criteria include patients with less than 18 years of age and patients with pulmonary nodules or consolidation that were not attributable to cancer.

The oncology treatment was intended to be provided according to national and international guidelines.

2.2. Data Collection

All the subjects were interviewed by the same two leading investigators responsible for this study. The collected data included a detailed clinical history and subjective and objective examinations. Biometric parameters were also collected to facilitate the Nutritional Risk Screening 2002 (NRS2002) calculation, at both admission and discharge, to evaluate nutritional risk. Nutritional status was assessed according to the Global Leadership Initiative on Malnutrition (GLIM) criteria [22–24].

Anthropometric measurements were taken according to the service's standard procedure:

Patients were weighed on the same scale (Seca 664 electronic wheelchair scale(Seca, CA, USA) under the same conditions. When it was not possible to weigh the patient, the weight reported by the patient or their family member or estimated by those responsible for this study was used (using the formula of Chumeal et al. (1988) [25]).

At the end of hospitalisation, the patients were weighed again, and the difference in weight compared to that recorded at the beginning of hospitalisation was calculated (except for patients who died). The height value reported by the patients or their relatives was used.

Data on food intake were collected from the patient's medical file. Food intake was assessed and recorded by the nursing team as a percentage of intake (0%, 25%, 50%, 75%, or 100%) in accordance with the service's usual procedure.

2.3. Statistical Analysis

Concerning data collection, the anonymisation was ensured. Patient characteristics were presented as the mean with standard deviation (±SD) regarding age and frequency (%) for gender and clinical characteristics of the cancer.

Continuous variables were assessed using *t*-tests when the normality of distribution was verified; otherwise, Mann–Whitney U tests were applied for non-normally distributed data. Categorical variables were evaluated using chi-square tests. A p-value ≤ 0.05 was considered the threshold for statistical significance. Statistical analyses were performed by using the Statistical Package for Social Sciences (SPSS) version 23 (IBM Corp., Armonk, NY, USA) on a Windows 11 platform.

2.4. Ethical Approval

This study was approved by the institutional Pulmonology and Nutritional Departments, Ethics Commission (nº 62/CECHL/2023), and the Administration Council of the Centro Hospitalar de Leiria at 9 August 2023, where this study was conducted.

This study respects the principles of the Declaration of Helsinki, ensuring maximum protection and confidentiality of the data obtained by the participants.

3. Results

3.1. Cohort Characterisation

This cohort included all patients hospitalised with LC between 2022 and 2023 and referred to nutritional evaluation. A total of 53 patients were included in our study for analysis, primarily males (38; 71.7%) and females (5; 28.3%) with a mean age of 64 ± 13 (Table 1). Most patients presented with an Eastern Cooperative Oncology Group (ECOG) Score of 1 (47.2%) (Table 2).

Table 1. Subject characterisation.

Variables	Results *n* (%)
Total of patients	53 (100)
Male patients	38 (71.7)
Age, mean years (SD)	64 (13)
Minimal age	39
Maximal age	89

Abbreviations: SD—standard deviation.

Table 2. Clinical characteristics of cancer.

Variables	Results *n* (%)
ECOG Score, *n* (%)	
0	0 (0)
1	25 (47.2)
2	2 (3.8)
3	18 (34)
4	8 (15.1)
Types of lung cancer, *n* (%)	
Adenocarcinoma	32 (60.4)
Squamous-cell carcinoma	8 (15.1)
Small-cell carcinoma	5 (9.4)
Undetermined/unknown	4 (7.5)
Metastasis	3 (5.7)
Large-cell carcinoma	1 (1.9)
Cancer stage, *n* (%)	
I	1 (1.9)
II	2 (1.9)
III	4 (7.5)
IV	45 (84.9)
Undetermined/unknown	2 (3.8)

Abbreviations: ECOG—Eastern Cooperative Oncology Group.

3.2. Types of Lung Cancer

Lung adenocarcinoma was the most common cancer: it was diagnosed in 32 patients (60.34%). Most patients (45; 84.9%) presented with cancer in an advanced stage (stage IV).

3.3. Hospitalisation

Patients were hospitalised due to multiple reasons; however, the most common reason was pneumonia (18; 34%), followed by cancer progression (6; 11.3%) and uncontrolled pain (n = 5; 9.4%). The mean hospitalisation was 16 ± 9 days, with a minimum of 2 and a maximum of 40 days.

3.4. Nutritional Assessment

Relevant nutritional symptoms were assessed, and the most significant symptom was anorexia, which was observed in 43 (81.1%) patients (Table 3). Other symptoms included obstipation and xerostomia. Three patients had no symptoms reported.

Table 3. Nutritional symptoms and characterisation of the nutritional status.

Variables	Results (t_0) *n* (%)	Results (t_1) *n* (%)	*p*-Value
Major nutritional symptoms			
Anorexia	43 (81.1)		
Dysphagia	4 (7.5)		
Other symptoms	3 (5.7)		
No symptoms	3 (5.7)		
NRS score, *n* (%)			
0	2 (3.8)	1 (1.9)	
1	0 (0)	1 (1.9)	
2	3 (5.7)	12 (22.6)	
3	26 (49.1)	21 (39.6)	
4	17 (32.1)	15 (28.3)	

Table 3. *Cont.*

Variables	Results (t_0) *n* (%)	Results (t_1) *n* (%)	*p*-Value
5	4 (7.5)	2 (3.8)	
6	1 (1.9)	1 (1.9)	
7	0 (0)	0 (0)	
Nutritional risk (NRS $\geq$ 3), *n* (%)	48 (90.6)	39 (73.6)	0.006
GLIM criteria, *n* (%)			
Nutritional risk	10 (18.9)		
Moderate malnutrition	24 (45.3)		
Severe malnutrition	19 (35.8)		

Abbreviations: t_0—at hospitalisation; t_1—at discharge; NRS—Nutrition Risk Screening; GLIM—Global Leadership Initiative on Malnutrition.

Forty-eight patients (90.6%) were at nutritional risk at hospitalisation, defined by an NRS score $\geq$3. According to the GLIM criteria, 24 (45.3%) and 19 (35.8%) patients had moderate and severe malnutrition, respectively.

At the time of discharge, after the nutritional intervention, there was a statistically significant decrease in the number of patients with nutritional risk ($p = 0.006$), with a change in the NRS score to <3.

3.5. Nutritional Intervention

All patients had a nutritional assessment, and the level of support and interventions was adjusted individually according to the nutritional risk/status.

Nutritional interventions included dietary counselling, changes in hospital diet (texture modification, salt addition, fibre addition), food supplements (such as yoghurts), and oral nutritional supplements.

For this analysis, patients were divided into two groups for direct comparison: patients with an NRS score improvement (group 1) and patients without improvement (group 2). The results are presented in Table 4.

Table 4. Characteristics of patients with Nutrition Risk Screening improvement.

Variables	Group 1 *n* (%)	Group 2 *n* (%)	*p*-Value
Total of patients	17 (100)	36 (100)	
Male patients	11 (64.7)	27 (75)	0.520
Female patients	6 (35.3)	9 (25)	
Age, median years (IQR)	61 (19)	66 (19)	0.153
Days of hospitalisation, median days (IQR)	12 (10)	15 (3)	0.335
ECOG, median (IQR)	2 (3)	3 (2)	0.556
Stage IV cancer, *n* (%)	17 (100)	28 (77.8)	0.044
NRS score t_0, median (IQR)	3 (1)	3 (1)	0.438
Severe malnutrition, *n* (%)	3 (17.6)	16 (44.4)	0.058
Nutritional intake, median %, (IQR)	75 (25)	50 (25)	0.040
Artificial nutrition, *n* (%)	10 (58.8)	16 (44.4)	0.328

Abbreviations: IQR—interquartile range.

Both groups had male patient prevalence, with no significant age ($p = 0.153$) or ECOG differences ($p = 0.556$). At the time of hospitalisation, there was no significant difference among initial NRS scores ($p = 0.556$).

Patients with stage IV cancer were associated with severe malnutrition ($p = 0.019$). However, they had significantly improved NRS scores ($p = 0.044$).

Patients with a higher nutritional intake also had improved NRS scores ($p = 0.04$).

A total of 26 patients (49.1%) were treated with artificial nutritional support, but no significant impact was observed in the NRS scores ($p = 0.328$).

4. Discussion

This study aimed to assess the risk and nutritional status of LC patients who are hospitalised, as well as to evaluate the impact of nutritional intervention on the risk of malnutrition. Most patients were conscious, collaborative, and autonomous, which is considered an added value for data collection, as it allowed for obtaining data more reliably and was also a facilitating element with regard to nutritional intervention.

From the analysis of the characteristics of the studied sample, it is worth mentioning that the majority of patients included in this sample are male, 38 (71.7%), which agrees with most studies on this type of cancer [1,2].

LC patients present a high frequency of malnutrition at the time of hospitalisation; the proportion of patients at nutritional risk at the beginning of hospitalisation found in this study aligns with what is reported in the literature for oncology patients [4,5].

All available literature emphasises that investments in nutritional support yield economic returns and improvements in the patient's quality of life [3,4,6,10]. The NRS2002 was used as a form of screening, as it is easy to use, quick to apply, and validated for the population focused on in this study (inpatient hospital) [6,7,12].

Nutritional status was only classified at the beginning of hospitalisation due to hospital service logistics. The literature supports using the GLIM in diagnosing malnutrition and predicting survival among LC patients [22–24].

According to the literature, insufficient food intake increases the prevalence and severity of malnutrition, with a concomitant increase in the associated complications, which is why every hospitalised patient should have a nutritional care plan that identifies their individual dietary needs and the corresponding treatment plan. Personalised nutritional interventions are key in helping to manage potential side effects of illness and treatments, such as anorexia and dysphagia. These data show that nutritional intervention for all patients has beneficial effects associated with reducing patients' nutritional risk [3,13,15,16].

Nutritional interventions can help patients maintain body weight by increasing food intake and by providing education on dietary strategies such as meals and snacks. Small, frequent meals and snacks can be helpful if appetite or intake is poor [9,15–17].

The significant positive aspect of this study is the reinforcement and validation of the multiple benefits a personalised nutritional intervention has to patients with LC, despite being hospitalised and in an advanced stage of the disease, by literature reports [13,15,20].

The length of stay did not influence the results of the NRS2002, which is why nutritional intervention must be considered regardless of the length of stay, and ideally from the beginning of hospitalisation [4,8,18,19].

To limit possible bias and inter-observer variation, all the data were collected by the same principal two investigators responsible for this study, and patients were selected from the same hospital department.

The selected cohort represents a specific group of patients hospitalised with LC. Therefore, it must fully describe the benefits of nutritional evaluation and support to patients with LC or others.

The nature of this research, which is not an experimental study, is a limitation. However, the randomisation of two groups, providing nutritional support to one group and none to the other, to better conclude the benefits of this intervention would certainly impose serious ethical issues. Other biases in this study were the variable length of hospitalisation, causes of hospitalisation, and nutritional intervention. Also, multiple types and stages

of cancer were included. Some patients were referred to nutritional support in the early stages, but others were referred later in the course of the disease.

Although we have only measured the impact of nutritional intervention by changes in nutritional risk, it is known that nutritional intervention in hospitalised lung cancer patients can offer several advantages [13,14,21,26]:

1. Improvement of nutritional status: adequate nutrition can help correct nutritional deficiencies common in cancer patients due to factors such as loss of appetite and side effects of treatments.
2. Increase muscle strength: proper nutrition can help preserve muscle mass, which is crucial for recovery and the patient's functional capacity.
3. Improvement in treatment tolerance: an adequate nutritional state can enhance tolerance to treatments such as chemotherapy and radiotherapy, reducing side effects.
4. Support for the immune system: essential nutrients can strengthen the immune system, helping the body to combat infections and other complications.
5. Quality of life: good nutrition can improve quality of life, alleviating symptoms such as fatigue and weakness.
6. Reduction in complications: nutritional intervention can help prevent malnutrition-related complications, such as infections and respiratory issues.
7. Individualisation of treatment: nutritional assessment allows for the personalisation of diet, tailoring it to the patient's specific needs while considering their clinical status and preferences.
8. Psychological support: nutrition can positively impact mental health, helping to enhance the patient's emotional well-being.

These advantages highlight the importance of a multidisciplinary approach in treating lung cancer patients, where nutrition plays a fundamental role in recovery and disease management [4,6,16,27–29].

With the findings of this study, the authors intend to promote early nutritional interventions in all hospitalised patients with lung cancer, even with advanced disease, and sensitise all healthcare professionals to the relevance of this therapeutic approach [28–30]. More studies with larger populations are required to validate other benefits, such as mortality and prognosis impact [4,6].

5. Conclusions

Most patients hospitalised with LC exhibit an altered nutritional status. Prompt nutritional screening using the NRS-2002 is strongly advised. If there is a risk of malnutrition, the patient should be swiftly referred to a clinical nutritionist for further assessment and nutritional therapy. In our study, the personalised nutritional intervention reduced the proportion of patients at nutritional risk, which is crucial for LC patients to mitigate the adverse effects of malnutrition in this population. Furthermore, based on our daily clinical experience, clinical nutritionists should be involved in tumour boards to provide nutritional support to lung cancer patients when necessary. Nutritional intervention should start with precise counselling and a personalised diet at the time of the diagnosis. However, more extensive studies are required to ascertain the prognostic impact of nutritional interventions.

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Informed Consent Statement: Informed consent was obtained from all subjects involved.

Data Availability Statement: Data are contained within this article.

Conflicts of Interest: The authors declare no conflicts of interest.

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A Plea for Monitoring Serum Selenium Levels in Breast Cancer Patients: Selenium Deficiency Is Rare during the First Year of Therapy, and Selenium Supplementation Is Associated with Elevated Risk of Overdosing

Laura Alicia Altmayer [1,*], Marina Lang [1], Julia Theresa Schleicher [1], Caroline Stuhlert [1], Carolin Wörmann [1], Laura-Sophie Scherer [1], Ida Clara Thul [1], Lisanne Sophie Spenner [1], Jana Alisa Simon [1], Alina Wind [1], Mert Tokcan [2], Elisabeth Kaiser [3], Regine Weber [3], Sybelle Goedicke-Fritz [3], Gudrun Wagenpfeil [4], Michael Zemlin [3], Erich-Franz Solomayer [1], Jörg Reichrath [5], Carolin Müller [1,6] and Cosima Zemlin [1]

[1] Department of Gynecology, Obstetrics & Reproductive Medicine, Saarland University, Campus Homburg, 66421 Homburg, Germany; lang.marina@gmx.de (M.L.); juliaschleicher@gmx.de (J.T.S.); caroline.stuhlert@gmail.com (C.S.); carowoer@aol.com (C.W.); laura-sophie.scherer@eurice.eu (L.-S.S.); ida.maier296@googlemail.com (I.C.T.); nelosa@spenner-me.de (L.S.S.); s8jssimo@teams.uni-saarland.de (J.A.S.); alinawind07@gmail.com (A.W.); erich.solomayer@uks.eu (E.-F.S.); carolin.mueller@uks.eu (C.M.); cosima.zemlin@uks.eu (C.Z.)

[2] Department of Internal Medicine III-Cardiology, Angiology and Intensive Care Medicine, Saarland University, Campus Homburg, 66421 Homburg, Germany; mert.tokcan@uks.eu

[3] Department of General Pediatrics and Neonatology, Saarland University, Campus Homburg, 66421 Homburg, Germany; elisabeth.kaiser@uks.eu (E.K.); regine.weber@uks.eu (R.W.); sybelle.goedicke-fritz@uks.eu (S.G.-F.); michael.zemlin@uks.eu (M.Z.)

[4] Institute for Medical Biometry, Epidemiology and Medical Informatics (IMBEI), Saarland University Campus Homburg, 66421 Homburg, Germany; gudrun.wagenpfeil@uni-saarland.de

[5] Department of Dermatology, Venereology and Allergology, Saarland University, Campus Homburg, 66421 Homburg, Germany; joerg.reichrath@uks.eu

[6] Outcomes Research Consortium, Department of Anesthesiology, Cleveland Clinic, Cleveland, OH 44195, USA

* Correspondence: s8laaltm@stud.uni-saarland.de

Abstract: (1) Background: The role of selenium in cancer biology remains poorly understood. Our aim was to study the course of selenium serum levels and the use of selenium supplements during breast cancer therapy. (2) Methods: Serum selenium levels, clinical–pathological data, selenium supplementation, and lifestyle factors were monitored quarterly over one year. (3) Results: A total of 110 non-metastatic breast cancer patients were enrolled in the prospective observational "BEGYN-1" study. At baseline, 2.9% of patients were selenium-deficient (<50 ng/mL), 1.9% were overdosed (>120 ng/mL), and 6.4% received substitution. The median selenium level was 81.5 ng/mL and ranged between 78.7 and 84.5 ng/mL within the year. A total of 25.3% of the patients received supplementation, resulting in significantly higher selenium levels ($p < 0.05$). A total of 8.7–28.6% of the patients using supplements were overdosed. Selenium levels strongly correlated with mushroom consumption ($p = 0.003$), but no association was found with therapy or clinical characteristics. (4) Conclusions: Although selenium deficiency is rare, serum selenium levels should be assessed in breast cancer patients. Mushrooms and nuts should be preferred over supplements to correct selenium deficiency. Ruling out selenium deficiency helps prevent the risk of selenosis and avoid unnecessary, costly supplementation in patients who are often financially burdened due to their disease.

Keywords: selenium; breast cancer; nutrition; complementary medicine; body composition; antitumoral therapy

1. Introduction

Breast cancer is the most common cancer worldwide, with an estimated 2.3 million cases in 2020, and is the leading cause of cancer-related death in women [1,2]. Research is

underway to improve prevention, diagnosis, and treatment strategies. However, patients themselves also wish to contribute to the success of treatment. Despite questionable benefits, the use of dietary supplements by oncologic patients has increased in recent years because many patients believe that taking micronutrients or vitamins could improve their health [3]. The prevalence of supplement use among oncologic patients varies considerably, with estimates ranging from 30 to 90% in different studies. These patients often take supplements or presumed immunoprotective micronutrients without their physician's knowledge [3,4]. For instance, the SWOG 0221 study assessed the use of dietary supplements in 1467 breast cancer patients before diagnosis and during treatment [5]. A total of 48.1% of the study population were taking multivitamins prior to being diagnosed with breast cancer [5]. However, the efficacy or influence of multivitamins on oncological disease and treatment is controversial [3,6,7]. Furthermore, many patients take supplements without knowing whether they are deficient, resulting in the risk of overdosing. One micronutrient frequently used in this context is selenium. Selenium is a ubiquitous, nutritionally essential trace element in the human body. In the form of the amino acid selenocysteine, selenium is a component of numerous enzymes and proteins [8]. It plays an important role in protecting cells from oxidative stress and regulating cell growth and thyroid hormone metabolism [8–12]. Compared to other organs, the thyroid gland has the highest selenium content [12,13]. It is also thought to have an anti-inflammatory effect through its influence on eicosanoid metabolism [14].

Humans obtain selenium almost exclusively from food, and adequate selenium intake is possible through a balanced diet [8,15]. Protein-rich foods such as meat, fish, mushrooms, eggs, nuts, and cereals are particularly rich in selenium [8,16]. Milk, cheese, vegetables, and fruit also contain small amounts of selenium [8,16]. The amount of selenium in different foods can vary widely [8]. Brazil nuts are one of the richest sources of selenium, containing between 1 and 20 mg of selenium per kilogram [12,15]. Selenium is non-specifically incorporated into body proteins in the form of selenomethionine, particularly in organs with a high rate of protein synthesis, such as skeletal muscle, liver, or kidneys, where it is stored. By converting selenomethionine to selenocysteine, selenium can be mobilized for metabolic processes in the liver or kidneys [17].

The German Nutrition Society recommends a daily selenium intake of 60 µg for women and 70 µg for men [18,19]. A daily selenium intake of 300–450 µg for adults has been suggested by various institutions (Scientific Committee on Food, Expert Group on Vitamins and Minerals, Food and Nutrition Board of the U.S. National Academy of Sciences, Institute of Medicine) as a safe upper limit, at which no adverse effects should occur [8,12,15,20].

Selenium deficiency may occur if less than 20 µg of selenium per day is consumed over a prolonged period [8]. Toxic side effects can occur with a daily intake of 900 to 1200 µg [12,20,21]. Both persistent selenium deficiency and selenium overdose may be associated with non-specific health complaints [12,20,22]. These include gastrointestinal and muscular symptoms, fatigue, reduced performance, immune system, and thyroid dysfunction [8,12,22]. Acute selenosis caused by the ingestion of several grams of selenium can lead to heart failure, ventricular fibrillation, and death [15]. One common cause of selenosis is accidental or deliberate overuse of dietary supplements [23].

It is crucial to emphasize that chronic exposure to high selenium doses, often due to misformulated dietary supplements, can also result in selenium toxicity, selenosis symptoms, and adverse health effects [24,25].

It has been shown that chronic selenotoxicity can occur even at levels of selenium intake previously considered harmless, thereby increasing the risk of chronic disease [24]. This calls into question the widespread use of selenium supplements [24].

The causality between selenium deficiency and various diseases, as well as the anti-carcinogenic effect of selenium, have been discussed since the 1960s [26,27]. As a component of many enzymes, Selenium is considered to be of great functional importance in the human body. It is often used as a supportive measure in many diseases, including cancer,

because it is thought to have a tumor-protective and anti-proliferative effect, contributing to the inhibition of tumor growth and having an inhibitory effect on the development of metastases and recurrence [28–30].

In Europe, including Germany, healthy people have mean selenium serum levels of about 84 ng/mL (reference range 50–120 ng/mL [8]), whereas some studies observed lower selenium serum concentrations below 70 ng/mL in cancer patients [3]. Lower selenium levels have also been associated with poorer overall survival in breast cancer patients [31].

In strong contrast, a Cochrane review found that selenium supplementation had no effect on reducing the overall risk of cancer or the risk of certain types of cancer [32]. There was even evidence that selenium may increase the risk of high-grade prostate cancer, type 2 diabetes, and skin disorders [32]. A higher risk of breast cancer has also been found with increased selenium exposure [32]. The German S3 guideline on complementary medicine in oncology does not recommend selenium supplementation for breast cancer patients [7]. Further research has shown that the influence of selenoproteins changes both during the carcinogenic process and in a tissue-specific manner [33]. During the initiation phase, selenoproteins protect cells from oxidative DNA damage and thus appear to inhibit tumor development, while in existing tumor cells, selenoproteins support their growth [33].

Rodemann et al. described in their in vitro experiments that selenium has a radioprotective effect on healthy body cells but not on tumor cells [34]. Some studies observed a decrease in serum selenium levels after radiotherapy in breast cancer [35]. Selenium supplementation for chemoprevention reduced the risk of chromosome breaks in patients with BRCA1 mutations to the level of unaffected patients, thus preventing the risk of cancer [36].

It is also hypothesized that high selenium intake is associated with favorable body composition. Dietary intake of selenium is approximately 30% lower in obese patients than in normal-weight individuals. A dose-dependent inverse relationship has been found between selenium intake and BMI or total body fat [37,38].

Existing data on the role of selenium in tumor patients, particularly those with breast cancer, are contradictory [3,8,32]. Furthermore, the general occurrence of selenium deficiency and overdosage is not exactly known, as selenium testing is not part of the clinical routine [6,7]. In the present study, we aimed to analyze serum selenium levels during oncological therapies (e.g., chemotherapy, radiotherapy, endocrine therapy, HER2-targeted therapy) and how selenium supplementation, as well as lifestyle factors and nutrition, contributed to these changes during the first year after diagnosis of non-metastatic breast cancer.

2. Materials and Methods

2.1. Data Collection

From September 2019 to January 2022, the BEGYN-1 study prospectively observed 110 non-metastatic breast cancer patients at the Saarland University Medical Center. The study received approval from the Ethical Committee of the Medical Association of Saarland (study # 229/18, date of approval 6 November 2019). The study included female participants aged 18 years or older who had invasive non-metastatic breast cancer, possessed adequate German language skills to complete questionnaires and activity diaries, and had sufficient technical skills or support to use a smartphone and fitness tracker. In addition, all patients had to provide written informed consent. Patients were excluded if they had received oncological treatment prior to baseline, had non-invasive disease (e.g., carcinoma in situ), had a current history of other neoplasia, had a life expectancy of less than 12 months, were unable to perform treadmill spiroergometry, or were pregnant or breastfeeding.

Serum selenium levels were measured using atomic absorption spectrometry at the Medical Care Centre Laboratory Volkmann in Karlsruhe, Germany. Measurements were conducted at the baseline visit, prior to the start of any pharmacological, radiological, or surgical therapy, and subsequently every three months during the first year following the initial diagnosis. At each visit, patients were asked about supplementation of vitamins or

trace elements (including selenium). The supplementation and dosages of vitamins were then documented (at 0, 3, 6, 9, and 12 months). Patients received selenium substitution according to their test results.

Other laboratory values (including vitamin D serum levels, blood lipids, thyroid hormones, T cell subpopulations, and plasma cytokines) were collected every three months and analyzed in a routine clinical laboratory. At the quarterly visits, bioelectrical impedance analysis was performed using the TANITA BC-601 scale TM (Tanita Europe BV, Stuttgart, Germany). Moreover, patients underwent sprioergometry on a treadmill every three months, and information on physical activity was obtained using a fitness tracker and an activity diary. The results have previously been published [39].

Furthermore, information on clinicopathological data was retrieved from the hospital's digital documentation system (SAP, Walldorf, Germany). Nutritional data were obtained through a questionnaire administered during the baseline visit. The data collection process was previously described in detail in the BEGYN study protocol [40,41].

2.2. Statistics

Statistical analyses were performed using IBM® SPSS® (Statistical Package for the Social Sciences) Statistics, version 27.0 (International Business Machines Corporation, Armonk, NY, USA). Sample size calculation was previously presented in our published study protocol [40,41]: A sample size of 110 produces a two-sided 95% confidence interval with a distance from the mean to the limits that is equal to 2.835 when the estimated standard deviation is 15.0. A sample size of 110 produces a two-sided 95% confidence interval with a width equal to 0.187 when the sample proportion is 0.50.

Qualitative parameters are presented as absolute and percentage frequencies. All variables were tested for normal distribution using Kolmogorov–Smirnov or Shapiro–Wilk test. Some parameters were not normally distributed. Therefore, in the following, quantitative parameters are uniformly expressed as median with minimum and maximum, and non-parametric tests, i.e., Mann–Whitney U test or Kruskal–Wallis test, were uniformly used for comparisons between two or more independent groups. Correlations were calculated using Spearman's correlation. To investigate the influence of substitution in more detail, a univariate analysis with generalized estimating equations (GEE) was performed, considering repeated measurements.

3. Results

At baseline, BEGYN-1 enrolled 110 patients who were assessed every 3 months for one year (0 months = baseline, 3, 6, 9, and 12 months) after their breast cancer diagnosis. Nineteen patients withdrew from the study over the course of the year. Previously published data on tumor stage are available [40,41]. The median age of the patients was 55 years (minimum 26, maximum 81). There was no significant correlation between selenium level and age ($r = -0.15$; $p = 0.13$). Table 1 displays data on clinical characteristics, including tumor entity, UICC/AJCC stage, grading, tumor biology, progesterone receptor and estrogen receptor status, mutations, and menopause, and their association with serum selenium levels.

Prior to treatment, 95.2% of patients had serum selenium levels within the normal range, with a median of 81.5 ng/mL (44.4–123.2 ng/mL; Figures 1 and 2 and Table 2). Only 2.9% of patients suffered from a selenium deficiency of less than 50 ng/mL (minimum: 44.4 ng/mL), and 1.9% had an overdose of up to 123.2 ng/mL at baseline. Selenium substitution was administered to 6.4% of patients. At all five measurement points, more than 90% of patients had serum selenium levels within the recommended normal range of 50–120 ng/mL [8]. Selenium deficiency was most common three months after diagnosis, affecting 7.1% of patients, with a median serum level of 78.7 ng/mL (41.9–139.3 ng/mL). At 12 months, 24.7% of patients were receiving selenium supplementation, 4.4% had an overdose, and only 2.2% had a deficiency. None of the patients experienced a deficiency while on supplementation. Table 3 presents the amount of selenium substitution during

the year (0 months = baseline, 3, 6, 9, and 12 months). Patients who received selenium supplementation had significantly higher serum selenium levels than those who did not ($p < 0.05$), with 1.9 to 4.4% of patients per measurement showing a selenium overdose above 120 ng/mL. Substituting 1 µg of selenium per day increased selenium levels by 0.11 ng/mL ($p < 0.001$). This means that a patient who substituted 100 µg per day had an average increase in serum selenium levels of 11 ng/mL over time.

Table 1. Median serum selenium levels by clinical characteristics.

Clinical Characteristics		n	%	Serum Selenium Level (in ng/mL)	*p*-Value
Tumor entity	NST	91	82.7%	84.0 (44.4–123.2)	0.858
	Invasive lobular	12	10.9%	81.5 (52.0–108.7)	
	Others [1)]	7	6.4%	83.9 (62.2–110.3)	
UICC-/AJCC stage	I	46	41.8%	84.0 (44.4–123.2)	0.629
	II	56	50.9%	78.3 (52.0–120.8)	
	III	8	7.3%	82.4 (46.1–93.3)	
Grading	G1	10	9.2%	83.8 (62.2–110.3)	0.506
	G2	56	51.4%	80.6 (44.4–116.9)	
	G3	43	39.4%	84.2 (52.0–123.2)	
Tumor biology	Luminal A	48	43.6%	81.2 (44.4–110.3)	0.497
	Luminal B	24	21.8%	79.6 (57.3–123.2)	
	HER2/neu-positive	27	24.5%	78.3 (46.1–116.9)	
	Triple-negative	11	10.0%	85.9 (54.9–102.2)	
ER status	Positive	89	80.9%	81.5 (44.4–123.2)	0.811
	Negative	21	19.1%	81.1 (54.9–102.2)	
PR status	Positive	72	65.5%	80.4 (44.4–123.2)	0.325
	Negative	38	34.5%	84.2 (54.9.1–116.9)	
Mutations	No	30	71.4%	79.6 (44.4–114.6)	0.070 [2)]
	BRCA1/2	8	19.1%	89.0 (66.2–123.2)	
	CHECK/ATM	4	9.5%	69.6 (64.1–74.6)	
Menopause	No	33	30.0%	81.5 (52.0–120.8)	0.464
	Yes	77	70.0%	81.2 (44.4–123.2)	

n = absolute number of patients. % = percentage of patients. Serum selenium levels are given as median with minimum and maximum. For *p*-value, the Mann–Whitney U test was performed for two independent groups or the Kruskal–Wallis test was performed for more than two independent groups with a significance level of $p < 0.05$. [1)] Inflammatory, mucinous, tubular, metaplastic, mixed (NST, tubular). [2)] CHECK/ATM was excluded from the calculations due to the small group size ($n = 4$).

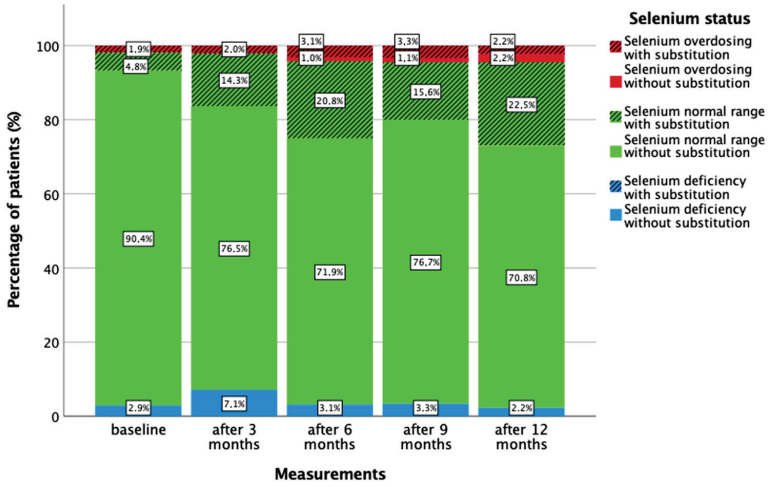

Figure 1. Serum selenium status throughout the year (0, 3, 6, 9, and 12 months), considering the substitution of selenium.

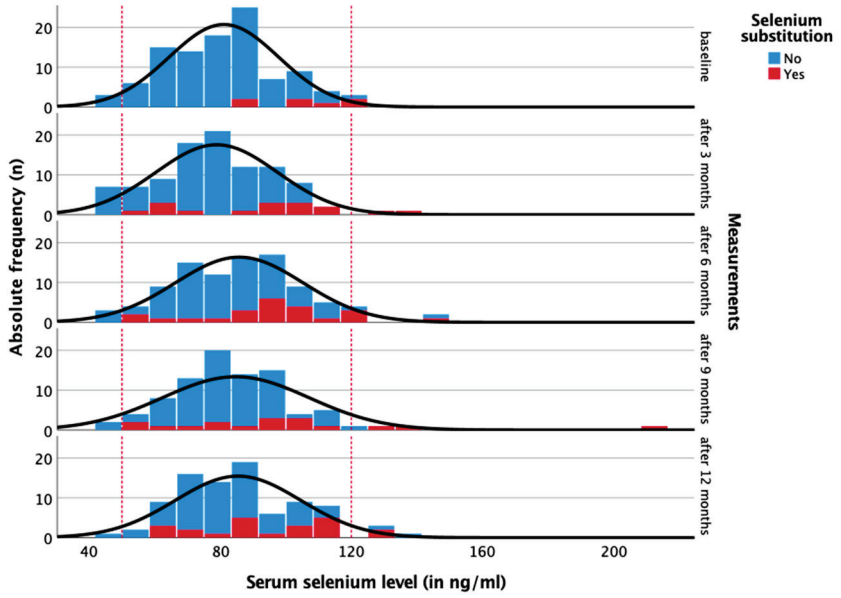

Figure 2. Serum selenium levels throughout the year (0, 3, 6, 9, and 12 months) considering the substitution of selenium. Reference range in dotted lines (50–120 ng/mL).

Table 2. Median serum selenium levels throughout the year (0, 3, 6, 9, and 12 months), frequency of substitution, and overdose with substitution.

Measurements	Serum Selenium Level in ng/mL	Frequency of Substitution	Overdose with Substitution
Baseline	81.5 (44.4–123.2)	7 of 110 (6.4%)	2 of 7 (28.6%)
After 3 months	78.7 (41.9–139.3)	17 of 101 (16.8%)	2 of 17 (11.8%)
After 6 months	84.5 (47.2–143.1)	23 of 96 (24.0%)	3 of 23 (13.0%)
After 9 months	82.4 (40.7–210.5)	17 of 90 (18.9%)	3 of 17 (17.6%)
After 12 months	84.3 (38.4–138.7)	23 of 91 (25.3%)	2 of 23 (8.7%)

Serum selenium levels are given as median with minimum and maximum.

Table 3. Dosage of selenium substitution throughout the year (0, 3, 6, 9, and 12 months).

Dosage	0 Months *n* = 7/110 (6.4%)	3 Months *n* = 17/101 (16.8%)	6 Months *n* = 23/96 (24.0%)	9 Months *n* = 17/90 (18.9%)	12 Months *n* = 23/91 (25.3%)
100 µg/day	0 (0.0%)	3 (17.6%)	3 (13.0%)	2 (11.8%)	3 (13.0%)
200 µg/day	1 (14.3%)	2 (11.8%)	4 (17.4%)	3 (17.6%)	5 (21.7%)
300 µg/day	1 (14.3%)	1 (5.9%)	6 (26.1%)	4 (23.5%)	7 (30.4%)
50 µg/day	0 (0.0%)	2 (11.8%)	2 (8.7%)	0 (0.0%)	1 (4.3%)
30 µg/day	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Variable, 100–300 µg/day	0 (0.0%)	1 (5.9%)	1 (4.3%)	1 (5.9%)	1 (4.3%)
35 µg/day LaVita juice (1 tbsp)	0 (0.0%)	2 (11.8%)	2 (8.7%)	3 (17.6%)	4 (17.4%)
113 µg Sinekrin (2 tablets)	1 (14.3%)	1 (5.9%)	1 (4.3%)	1 (5.9%)	2 (8.7%)
No information on exact dosage	4 (57.1%)	5 (29.4%)	6 (26.1%)	3 (17.6%)	1 (4.3%)

Regarding radiotherapy and chemotherapy, there was no significant association between selenium status and the number of days since the start or end of the respective therapy (Figures 3–6). In the case of endocrine therapy, it was observed that selenium levels decreased with the duration of the endocrine therapy in non-substituting patients. However, this observation was not significant (Figure 7).

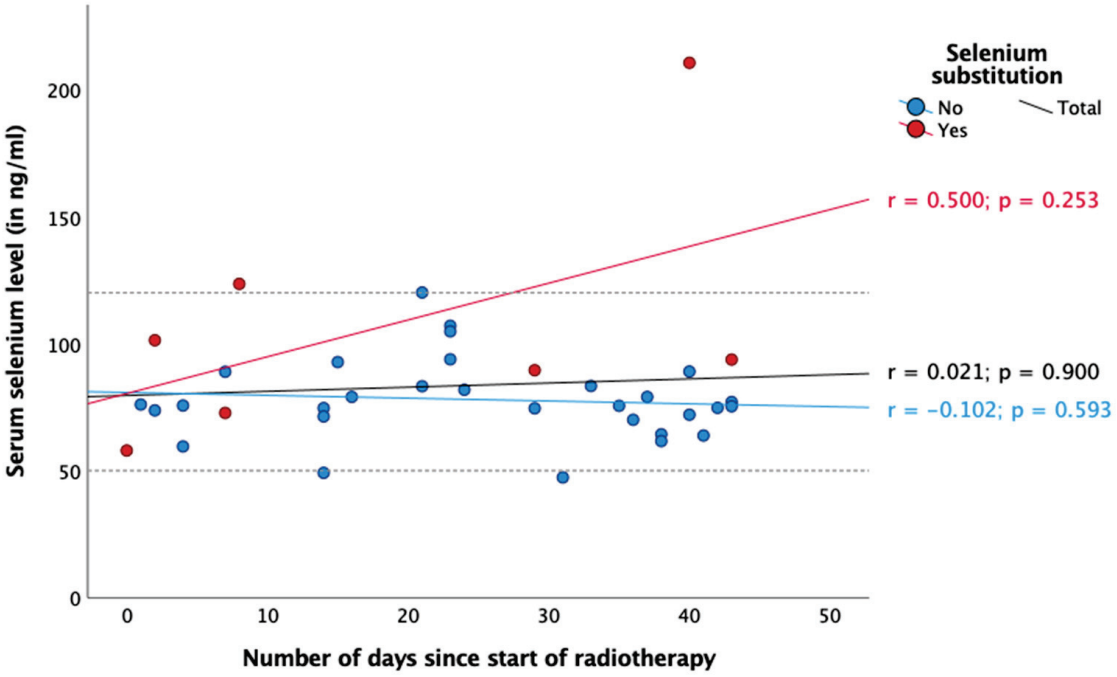

Figure 3. Serum selenium levels in patients receiving radiotherapy. Reference range in dotted lines (50–120 ng/mL). Spearman correlation was performed between serum selenium levels and number of days since the start of radiotherapy with r = correlation coefficient and with a significance level of $p < 0.05$.

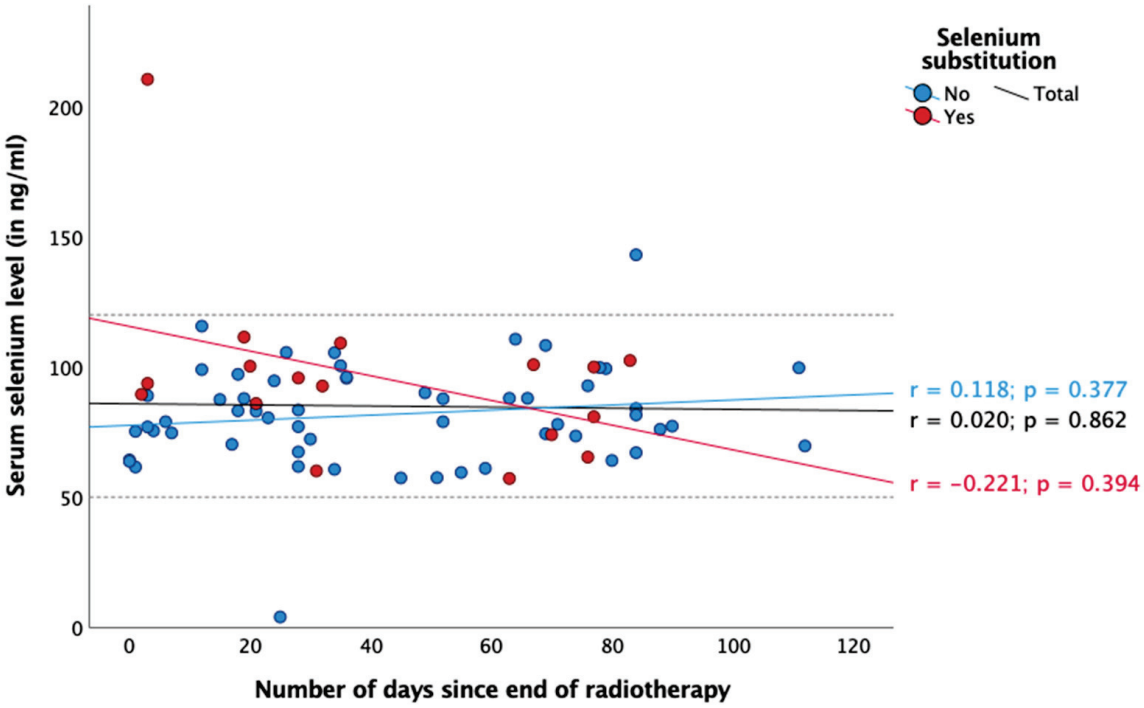

Figure 4. Serum selenium levels after all patients finished radiotherapy. Reference range in dotted lines (50–120 ng/mL). Spearman correlation was performed between serum selenium levels and number of days since the end of radiotherapy with r = correlation coefficient and with a significance level of $p < 0.05$.

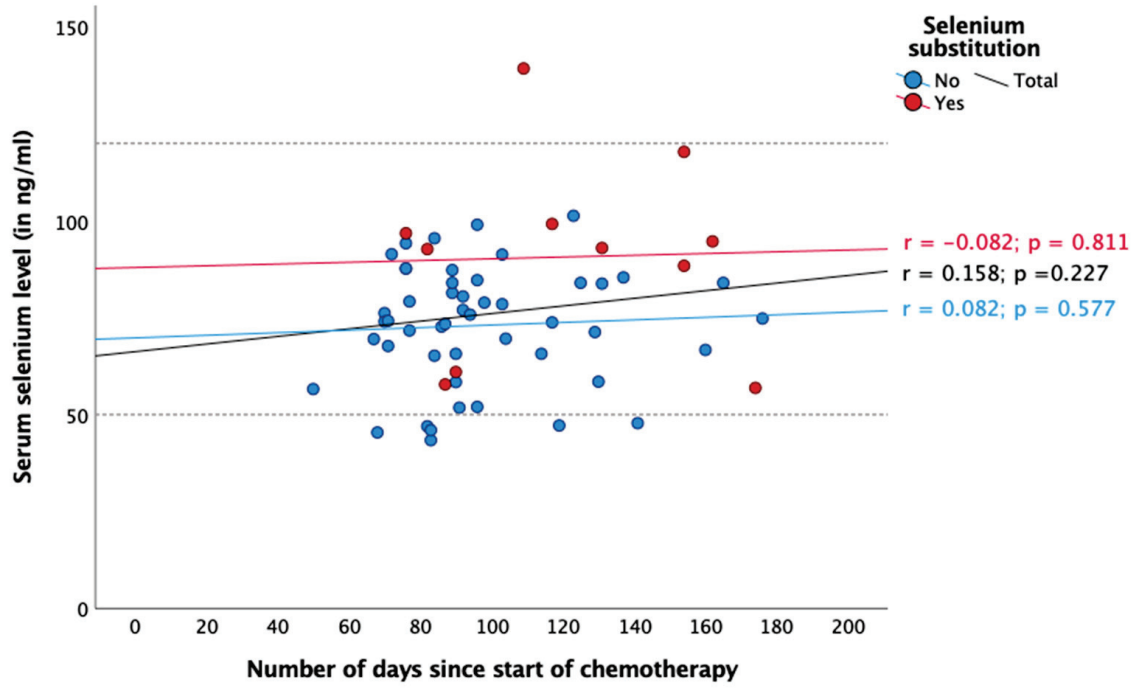

Figure 5. Serum selenium levels in patients receiving chemotherapy. Reference range in dotted lines (50–120 ng/mL). Spearman correlation was performed between serum selenium levels and number of days since the start of chemotherapy with r = correlation coefficient and with a significance level of $p < 0.05$.

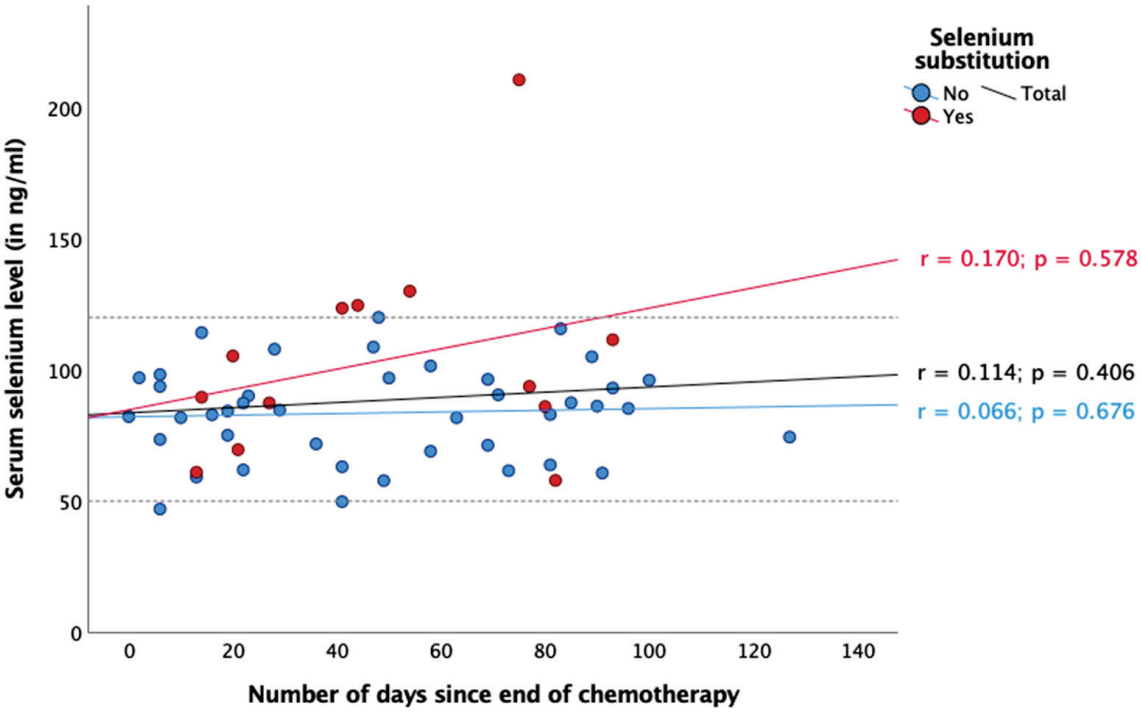

Figure 6. Serum selenium levels after chemotherapy. Reference range in dotted lines (50–120 ng/mL). Spearman correlation was performed between serum selenium levels and number of days since the end of chemotherapy with r = correlation coefficient and with a significance level of $p < 0.05$.

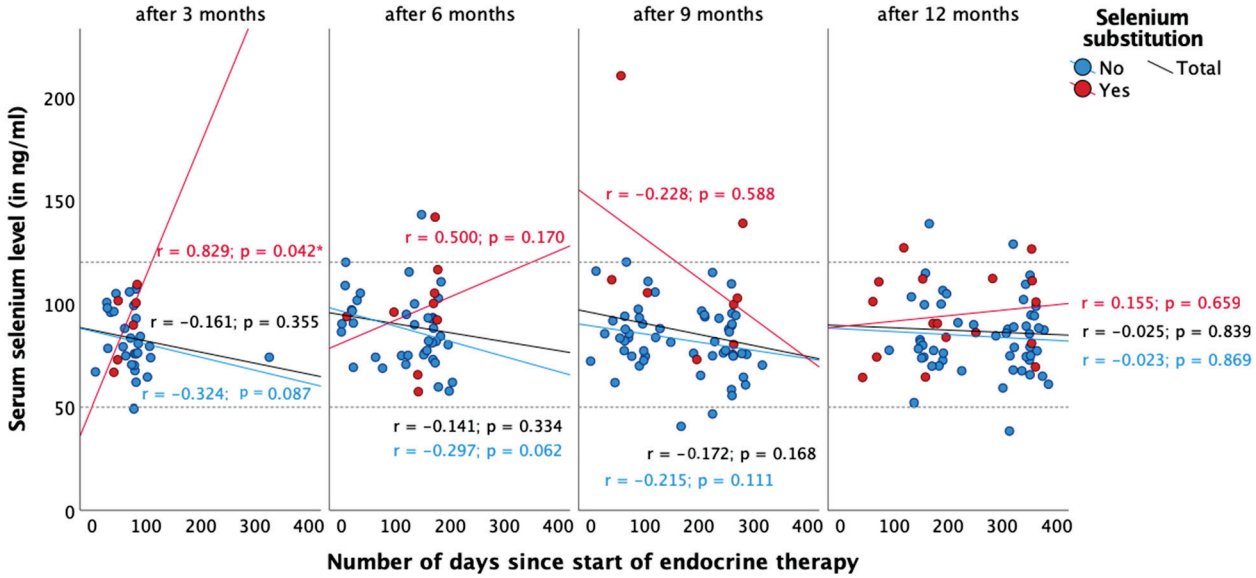

Figure 7. Course of serum selenium levels in patients receiving endocrine therapy. Reference range in dotted lines (50–120 ng/mL). Spearman correlation was performed between serum selenium levels and the number of days since the start of endocrine therapy with r = correlation coefficient and with a significance level of $p < 0.05$. * = $p < 0.05$.

Additionally, during the baseline visit, patients were questioned about their dietary habits, as shown in Table 4. A significant positive correlation was found between selenium levels and mushroom consumption (r = 0.324, $p = 0.003$). However, no significant correlation was observed between selenium levels and the consumption of fish, eggs, milk products, cheese, or butter.

Table 4. Dietary habits and selenium content in various food products.

Various Food Products	Dietary Intake (in Days per Month)	Selenium Content (in µg/kg)	Spearman Correlation
Herring/trout/salmon	3.0 (0–12)	250–430	r = 0.044 $p = 0.694$
Mackerel/tuna	1.0 (0–8)	390–820	r = 0.132 $p = 0.239$
Eggs/margarine	12.0 (0–28)	Eggs: 100–200 Margarine: no data available	r = 0.104 $p = 0.355$
Cream/gouda/butter	20.0 (0–28)	No data available	r = 0.003 $p = 0.978$
Whole milk/quark/yogurt	20.0 (0–28)	5–20	r = 0.156 $p = 0.166$
Chanterelles/champignons/ porcini mushrooms	3.0 (0–28)	10–1800	r = 0.324 $p = 0.003$
Beef/veal liver	0 (0–5)	20–200	r = 0.198 $p = 0.077$

Dietary intake is given as median with minimum and maximum. Spearman correlation was performed between serum selenium levels and dietary intake of different foods with r = correlation coefficient and with a significance level of $p < 0.05$. Patients with selenium substitution were excluded.

Table 5 displays the correlation between serum selenium levels and body composition measured by bioelectrical impedance analysis. No significant correlation was found between selenium and body composition, including weight, BMI, body fat percentage, visceral fat, muscle mass, and bone mass.

Table 5. Spearman correlation between serum selenium level and body composition at different points in time within one year after breast cancer diagnosis.

Body Composition	Selenium Level at Baseline	Selenium Level after 3 Months	Selenium Level after 6 Months	Selenium Level after 9 months	Selenium Level after 12 Months
Weight	r = −0.06 *p* = 0.52	r = 0.05 *p* = 0.63	r = 0.07 *p* = 0.49	r = 0.10 *p* = 0.35	r = 0.06 *p* = 0.61
Body Mass Index	r = −0.12 *p* = 0.24	r = −0.01 *p* = 0.89	r = 0.11 *p* = 0.30	r = 0.12 *p* = 0.26	r = 0.07 *p* = 0.50
Muscle mass	r = 0.04 *p* = 0.677	r = 0.04 *p* = 0.69	r = −0.01 *p* = 0.94	r = −0.08 *p* = 0.44	r = 0.06 *p* = 0.60
Body fat percentage	r = −0.14 *p* = 0.16	r = 0.07 *p* = 0.52	r = 0.15 *p* = 0.16	r = 0.20 *p* = 0.06	r = 0.07 *p* = 0.54
Visceral fat	r = −0.17 *p* = 0.08	r = −0.02 *p* = 0.84	r = 0.14 *p* = 0.18	r = 0.09 *p* = 0.40	r = 0.09 *p* = 0.41
Bone mass	r = 0.05 *p* = 0.63	r = 0.05 *p* = 0.61	r = −0.02 *p* = 0.85	r = −0.09 *p* = 0.40	r = 0.02 *p* = 0.84

Spearman correlation was performed between serum selenium levels and body composition with r = correlation coefficient and with a significance level of $p < 0.05$.

Additionally, Table 6 shows no significant association between selenium and thyroid hormones (TSH, T3, and T4).

Table 6. Spearman correlation between serum selenium level and thyroid hormone levels at different points in time within one year after breast cancer diagnosis.

Thyroid Hormones	Selenium Level at Baseline	Selenium Level after 3 Months	Selenium Level after 6 Months	Selenium Level after 9 Months	Selenium Level after 12 Months
TSH	r = −0.07 *p* = 0.51	r = −0.13 *p* = 0.26	r = −0.09 *p* = 0.43	r = 0.02 *p* = 0.88	r = 0.00 *p* = 0.98
T3	r = 0.11 *p* = 0.30	r = −0.14 *p* = 0.20	r = 0.05 *p* = 0.65	r = 0.11 *p* = 0.37	r = 0.01 *p* = 0.95
T4	r = 0.05 *p* = 0.67	r = 0.15 *p* = 0.17	r = 0.15 *p* = 0.20	r = −0.03 *p* = 0.82	r = −0.04 *p* = 0.77

Spearman correlation was performed between serum selenium levels and thyroid hormones with r = correlation coefficient and with a significance level of $p < 0.05$.

4. Discussion

In the present study, the median serum selenium level of patients was 81.5 ng/mL. The majority of patients (95.2%) had selenium levels within the recommended reference range of 50 to 120 ng/mL [8]. In other observational and case–control studies in breast cancer patients, a mean selenium level of 86.2 ng/mL [31] and 81.1 ng/mL [42] was measured. Compared with the healthy European general population (84 ng/mL) [3] and the German general population (70–80 ng/mL) [8], the level does not appear to be substantially different [3]. Thus, our study does not support the hypothesis that the risk for breast cancer would be associated with lower serum selenium levels.

At baseline, 6.4% of patients were using selenium supplements. During the first year, this percentage increased remarkably to 25.3%. This increase may be attributed to recommendations from physicians, friends, or relatives [43], as well as increased advertising by the pharmaceutical industry regarding the importance of taking selenium after a cancer diagnosis.

Most patients without substitution were within the normal range during treatment. In accordance with the recommendation of the German S3 guideline on oncology-complementary

medicine [7], general substitution during therapy is not recommended for breast cancer patients. Instead, it might be beneficial to assess serum selenium levels at diagnosis of breast cancer as patients with normal selenium levels can be reassured that substitution is unnecessary and should be avoided to prevent overdosing and selenosis. Patients with selenium deficiency may benefit from substitution or a dietary modification to include selenium-rich food such as mushrooms or nuts. Moreover, an overdose of selenium could be identified by a routine control of serum selenium levels at diagnosis of breast cancer. In the present study, some patients who took selenium supplements, and even some who reported not taking selenium supplements, had a selenium overdose. It is therefore reasonable to assume that unnecessary selenium supplementation may lead to selenium overdose and undesirable side effects [8,12,22]. In our opinion, it seems sensible to recommend a determination of baseline selenium level at diagnosis of breast cancer. In contrast, only patients with selenium deficiency or overdose should undergo regular laboratory tests until their levels normalize.

Some patients were observed who had a low selenium baseline value in the deficiency range and whose selenium levels rose into the normal range after supplementation. However, the selenium deficiency reoccurred after supplementation was discontinued. This suggests that selenium levels should be monitored, especially in patients who have previously been diagnosed with selenium deficiency. Lifelong supplementation or a change in diet may be necessary. However, even a sufficient selenium baseline value does not guarantee that selenium levels will not fall into the deficiency range. It seems that tests could help to detect selenium deficiency in specific indications, and a diet rich in selenium, such as mushrooms and nuts (in moderation), could be useful in preventing selenium deficiency.

Three months after diagnosis, the proportion of patients with selenium deficiency increased from 2.9% to 7.1%, and the median selenium level fell from 81.5 to 78.7 ng/mL ($p = 0.360$). However, the number of patients who have substituted had increased (0 months: 6.4%, 3 months: 16.8%). Over the course of the year, the median serum selenium levels increased to 84.3 ng/mL after one year. The changes did not reach statistical significance ($p = 0.078$). Nevertheless, we sought to identify potential explanations for the observed changes in serum selenium levels. With regard to radiotherapy, chemotherapy, and endocrine therapy, no significant association was observed between selenium status and the number of days since the start and end of therapy, respectively (Figures 4–7).

It is noteworthy that the mean selenium concentration exhibited a slight increase during chemotherapy (Figures 5 and 6), whereas during radiotherapy, data were inconsistent (Figures 3 and 4). None of our observations showed any significance. Nevertheless, a potential explanation for this phenomenon could be that patients consumed foods containing selenium (e.g., Brazil nuts) during chemotherapy, either in accordance with their physician's advice or on their own initiative, which could explain the observed increase in selenium levels.

During endocrine therapy, patients without selenium supplementation had lower selenium levels over the year (Figure 7). There is currently no scientific evidence of a relationship between selenium and endocrine therapy. Patients receiving selenium supplementation showed inconsistent courses, probably due to the very small number of cases and due to outliers. A possible explanation for the inconsistent serum selenium levels could also be that patients consumed different foods containing selenium (e.g., Brazil nuts) and unknown supplements during therapy, which could explain the changes in serum selenium levels. Therefore, examining the selenium level can be useful.

In a randomized controlled trial, some participants received a total of 13 g of defatted, granulated Brazil nuts per day, equivalent to approximately four Brazil nuts and approximately 227.5 µg of selenium per day [44]. The intake of Brazil nuts resulted in a significant increase in selenium levels from 87.0 ± 16.8 to 180.6 ± 67.1 ng/mL (an increase of 119%) within 12 weeks [44]. From this, it can be concluded that a deficiency can be easily corrected through a simple change in diet by adding, e.g., two Brazil nuts per day [15,45]. On the other hand, patients whose serum selenium levels are within the normal range can be

reassured that supplementation is not necessary, thus preventing them from spending money unnecessarily, as they are often already financially burdened by the disease.

According to our results, patients who consumed mushrooms on more days per month had higher selenium levels than those who consumed little or no mushrooms (r = 0.324, p = 0.003). Mushrooms are known to be rich in selenium [8]. Eating foods that contain selenium, such as mushrooms and Brazil nuts, can help maintain selenium levels in the normal range or increase the selenium level from the deficiency range to the normal range. This means that supplementation may not be absolutely necessary in cases of selenium deficiency and that a deficiency could be corrected more naturally by dietary changes. Therefore, patients would often save huge amounts of money. It is known that approximately 25 to 33% of gynecological patients suffer from financial problems [46,47]. Cancer can reduce people's ability to work, leading to reduced working hours, job loss, or early retirement [48]. On average, cancer patients in Germany lose 26% of their income [48]. This can lead to financial strain and financial toxicity, which can have a considerable impact on quality of life and possibly also on the prognosis of the disease [48]. The purchase of dietary supplements is associated with additional costs for patients who are already financially burdened.

The producers heavily promote their pharmaceutical products. They argue that they can help improve the patients' wellbeing and sell them as absolutely necessary. Notably, research has shown that the pharmaceutical industry spends twice as much money on advertising as it does on research [49]. Furthermore, the advertising strikes a fertile ground as patients attempt to regain lost control over their health condition. Critical examination of pharmaceutical industry advertising and raising awareness of this issue among patients and physicians should be at the forefront. It is time to enforce regulations that prevent misleading advertising of supplements with unknown effects.

We hypothesize that it is more beneficial to obtain selenium from the diet than from expensive supplements. Further randomized controlled trials comparing a selenium-rich diet with selenium supplements should be conducted.

Overall, we could not find a link between breast cancer and selenium. We cannot confirm the suggestion that the change in serum selenium concentration in women with breast cancer is most likely a consequence rather than a cause of the disease or therapeutic interventions [42]. According to our results, a change in selenium concentration is neither a cause nor a consequence of the disease. It should be emphasized that only mild selenium deficiency was found in the present study. The lowest selenium value was 38.4 ng/mL, and all other values in the selenium deficiency range were between 40 and 49.9 ng/mL. The overall change is rather small, and at all five time points, more than 90% of the patients were within the recommended selenium range. The percentage of selenium deficiency is therefore low and not necessarily due to breast cancer but can also be explained by diet. It can be assumed that there is also a small proportion of patients with selenium deficiency or excess in the general German population. In addition to studies examining selenium intake in the general population, more studies should be conducted to determine selenium status in serum.

One of the limitations of the study is that selenium levels were measured independently of therapy. Additionally, compliance and patients' self-reported information on supplementation and dietary habits cannot be independently verified, e.g., some patients take mixed preparations, including selenium, without knowing exactly which active ingredients they contain. Despite careful investigation and the development of a relationship of trust, it cannot be ruled out with 100% certainty that patients were taking selenium supplementation without our knowledge. Furthermore, we did not explicitly ask for the patients' consumption of Brazil nuts or other nuts. In addition to patients' self-reports, varying selenium levels in different food sources may also have caused inaccuracies. Selenium is naturally present in soil, influencing the selenium content of plant-based foods. In regions with sufficient soil selenium levels, excellent organic sources of selenium include Brazil nuts, green vegetables, and button mushrooms [8,12,15,16]. Moreover, the absorption

rate of selenium by plants is crucial and is determined by a number of factors, including plant type, soil pH levels, soil composition, rainfall patterns, microbial activity, and other biogeochemical elements [50]. For this reason, not only diet and reported dietary habits but also food per se plays a crucial role in determining selenium levels in patients. Which foods (from which manufacturer, etc.) the patients consumed and how much selenium the individual foods actually contained were not analyzed as part of the BEGYN-1 study. Therefore, dietary inaccuracies might have influenced our research results. Overall, research on selenium and cancer is complicated by the existence of a large number of organic and inorganic selenium compounds, each with different biological properties, as well as various lifestyle and dietary factors that are difficult to objectify [32]. Furthermore, genetic predispositions or environmental exposures that might have an influence on selenium serum levels were not assessed within the BEGYN-1 study.

5. Conclusions

Although selenium deficiency is rare in breast cancer patients, we recommend monitoring the selenium levels in newly diagnosed breast cancer patients. A deficiency can be easily corrected through nutritional supplements or a change in the diet by adding, e.g., two Brazil nuts per day [15,44,45]. On the other hand, patients with serum selenium levels within the normal range can be reassured that supplementation is unnecessary and should be avoided to prevent overdosing and selenosis. This reduces their financial burden and encourages cancer patients to focus on more important therapies, such as physical activity. Further studies with larger sample sizes are needed to investigate the effects of selenium deficiency in breast cancer patients and during oncological treatment, considering the influence of various forms of supplementation, lifestyle, genetic predisposition, and dietary factors in particular.

Author Contributions: C.Z. wrote the study conception and design. C.Z. implemented the study in the clinic, recruited the patients, and supervised the study. E.-F.S., M.Z. and J.R. gave advice for the study design and supervised the study. Material preparation and data collection were performed by L.A.A., C.S., J.T.S., C.W., M.L., L.-S.S., I.C.T., L.S.S., J.A.S., A.W., E.K., R.W., S.G.-F., M.T. and C.M. The data analysis was performed by L.A.A. and G.W. The first draft of the manuscript was written by L.A.A. and C.Z. All authors commented on previous versions of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study is carried out at the Department for Gynecology, Saarland University Medical Centre, and has been approved by the Ethics Committee of the Medical Association of Saarland with an unqualified ethics vote on 6 November 2019 (study # 229/18). Written informed consent is obtained from all patients in accordance with the Declaration of Helsinki. This study is registered at the German Clinical Trials Register (DRKS) (DRKS00024829). Patient recruitment took place between September 2019 and January 2021, and data collection continued until March 2022.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets generated during the current study are available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

BMI	body mass index
ER	estrogen receptor
PR	progesterone receptor
HER2	human epidermal growth factor 2
GEE	generalized estimating equations analysis
NST	no special type
UICC/AJCC	Union for International Cancer Control/American Joint Committee on Cancer

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Assessment of the Dietary Intake Changes in Patients with Head and Neck Cancer Treated with Radical Radiotherapy

Agnieszka Surwiłło-Snarska [1,*], Aleksandra Kapała [1,2] and Dorota Szostak-Węgierek [3]

[1] Department of Clinical Nutrition, Maria Sklodowska-Curie National Research Institute of Oncology, 02-781 Warsaw, Poland; aleksandra.kapala@nio.gov.pl
[2] Department of Oncology Diagnostics, Cardio-Oncology and Palliative Medicine, Maria Sklodowska-Curie National Research Institute of Oncology, 02-781 Warsaw, Poland
[3] Department of Clinical Dietetics, Faculty of Health Sciences, Medical University of Warsaw, E Ciołka 27, 01-445 Warsaw, Poland; dorota.szostak-wegierek@wum.edu.pl
* Correspondence: agnieszka.surwillo-snarska@nio.gov.pl

Abstract: Background: Patients during radiotherapy due to head and neck cancers experience a lot of side effects which may have a considerable impact on the patients' ability to meet individual daily energy demands by means of oral diet. Methods: The study included 104 head and neck cancer patients who qualified for radical radiotherapy. Radical treatment takes 6 weeks and every week the patients were assessed for dietary intake. The subjects were covered with the constant care of a dietician, received FSMP (food for special medical purposes), and, if necessary, enteral nutrition. Results: In the first week of treatment, the patients, from the kitchen diet alone, met 91.5% of the energy demand, while in the last week of treatment, only 40.9%. After introducing the FSMP or enteral nutrition, the patients met 120% of the demand in the first week of therapy and 95% in the last week, respectively. The patients who followed the dietary recommendations were characterized by significantly lower weight loss (3.07 kg) compared to non-adherent patients (5.56 kg). Conclusions: The used therapy significantly contributed to decreasing nutritional intake in the subsequent weeks of treatment. On the other hand, incorporating FSMP in the diet and enteral nutrition with industrial diets significantly increased the fulfilled energy demand of patients.

Keywords: head and neck cancers; radical radiotherapy; nutritional assessment; malnutrition; clinical nutrition; dietary counseling

1. Introduction

The term "tumors of the head and neck area" refers to a group of cancers originating in the following organs: mouth, lip, pharynx (oral, laryngeal, and nasal parts), nasal sinuses, nasal cavities, salivary glands, and ear. The most common histological type of head and neck organ tumors is squamous cell carcinoma, which develops from mucosal epithelium [1,2].

Head and neck cancers account for 5–6% of all the malignant tumors in Poland. According to the National Cancer Registry Report, they affect men more often than women, with an increase in incidence in people over 50. The exception is nasopharyngeal squamous cell carcinoma, where the highest incidence is in young people (20–35 years of age). The most common cancer of the head and neck is the cancer of the larynx [3].

Risk factors for developing head and neck cancer are well known. These include cigarette smoking, both active and passive, and alcohol consumption. These are responsible for 70% of the incidence. Other risk factors include a lack of proper oral hygiene, mechanical irritation of the oral mucosa (e.g., through ill-fitting dentures), and viral infections, mainly human papilloma virus (HPV) and Epstein–Barr virus (EBV). Dietary factors that increase the risk of developing head and neck cancer include low consumption of fruits and vegetables [4,5].

Radical treatment options for patients diagnosed with head and neck cancer include surgery or radiation therapy. These methods are also used as combined treatment with radiotherapy complementing surgery. Additionally, in patients with more advanced disease (locally and/or regionally), radiotherapy is used in combination with chemotherapy. Radical radiotherapy (alone or in combination with chemotherapy) is a long-term treatment, usually carried out in 28–30 fractions, so it usually lasts 6 to 7 weeks. Radical radiotherapy (ionizing) is carried out using 3D conformal irradiation technology, with a preference for IMRT (intensity-modulated beam irradiation). The treatment of head and neck cancer is fraught with high toxicity; therefore, nutritional intervention is an integral part of it [1,2].

Ionizing radiation used in diagnosis and cancer radiotherapy is well known and has both beneficial and harmful effects on biological systems. The method by which radiation interacts with a biological system may be direct or indirect. Damage can occur due to the direct ionization of the DNA molecule itself or indirectly through the formation of toxic products, such as free radicals, hydrogen peroxide, hydroperoxy radicals, and hydroperoxy ions, that diffuse from the site of formation and interact with any molecules in their path. The risk of radiation damage to normal tissues increases with the number of radiotherapy fractions, the total dose, and the volume of tissues that have been irradiated. The main challenge is to select the appropriate maximum doses of radiation reaching the cancer cells while minimizing the damage to healthy tissue [6,7].

The appearance of radiation reaction in the mucous membranes and skin in the irradiated area translates into the development of swallowing disorders ranging from dysphagia and odynophagia to aphagia. A consequence of salivary gland damage is the development of xerostomia. In addition, patients experience anorexia, nausea and vomiting; trismus; and an increased risk of aspiration during treatment. As early as the 3rd week of treatment, the discomfort worsens, and patients report three or more problems with their ability to eat efficiently, which directly translates into weight loss [8,9].

The problems described above often prevent patients from receiving effective oral nutrition, and it is necessary to incorporate enteral feeding via artificial access (a percutaneous endoscopic gastrostomy created before treatment or a nasogastric tube inserted during therapy). Patients require the care of a nutritionist, speech therapist, physical therapist, psychologist, nurse, and social worker during treatment. The goal of multispecialty teams is not only to improve treatment outcomes, but also to improve the patient's quality of life [10].

The main purpose of this study was to evaluate in detail the intake of energy, protein, and other macro- and micronutrients during each successive week of radiation therapy. To the authors' best knowledge, these are data that are limited in the literature.

2. Materials and Methods

The study was conducted between 2018 and 2019. It was designed as an observational clinical trial involving 104 adult patients diagnosed with primary head and neck organ cancer who were qualified for radical treatment: radiotherapy alone or radiochemotherapy or radiotherapy with cetuximab. Consecutive hospitalized patients treated at the Head and Neck Cancer Department at the National Research Institute of Oncology in Warsaw were included in the study. The study received a positive opinion from the Bioethics Committee (No. 4/2018) at the National Research Institute of Oncology in Warsaw.

2.1. Inclusion Criteria

Inclusion criteria for the study included diagnosed cancer of the organs of the head and neck qualified for treatment with radical radiation therapy, hospitalization for the duration of the entire treatment, and patient consent to participate in the study.

Exclusion criteria for the study included palliative treatment, prior radiation therapy in the head and neck region, other concurrent malignant neoplasm, outpatient treatment, and the lack of patient consent to participate in the study.

2.2. Scheme of Implementation of the Survey

The study lasted 6 weeks and was carried out using a prospective observational method with the tools detailed below. Throughout the period of radical treatment, the patients underwent weekly dietary assessments. In addition, each patient had an individual dietary consultation.

2.3. Dietary Assessment

The assessment of dietary intake and intake of macro- and micronutrients was carried out using the 24 h dietary interview method. During the dietary consultation, the patient was asked what products, foods, and drinks and in what quantities (in home measures) he/she had consumed the previous day. The Food and Nutrition Institute's "Photo Album of Products and Foods" was used to assess portion sizes [11].

Information was also collected on the oral use of Food for Special Medical Purposes (FSMP) and the amount and type of enteral nutrition (if the patient was receiving nutrition in this way); in addition, an intravenous glucose supply was included.

The 24 h dietary interview method is a retrospective, questionnaire-based, qualitative–quantitative method that provides accurate information on the amount and type of food and beverages consumed. The method determines current consumption [12]. The data obtained were entered into the DIETA 6.0 computer program developed by the Institute of Food and Nutrition in Poland, which made it possible to estimate the intake of energy and the main nutrients, i.e., protein, fat, and carbohydrates, as well as selected vitamins and minerals. The values obtained were reduced by technological and plate losses.

The analysis also identified the patients who were not consuming the recommended amount of energy, which was the basis for implementing an appropriate dietary intervention to increase energy supply through the use of fortified foods, oral application of FSMP, or enteral nutrition (EN). It was assumed that the daily energy requirement for normal-weight and malnourished patients was 30 kcal/kg/d of current body weight, while for overweight and obese patients, the caloric requirement was converted to due body weight [10,13].

2.4. Dietary Consultation

The patients included in the study received regular care from a dietitian throughout the treatment period. The first dietary consultation was held on the first day of radical radiotherapy, subsequent consultations were held at the beginning of the second, third, fourth, and fifth weeks of treatment, and the sixth consultation was held on the last day of treatment. If nutritional problems arose, the patients could receive an additional dietary consultation at any time during treatment. The dietitian's consultation consisted of a detailed history in accordance with the established practice, the estimation of individual energy requirements, and the selection of a dietary supply route depending on the patient's current clinical condition. On the day of the start of radiation therapy, each patient received in writing detailed guidelines for the selection of foods and the principles of diet composition.

From the first day of radiation therapy, each patient, regardless of the baseline nutritional status, received special medical nutrition (2 packs per day of a high-protein or high-energy diet, which translated into providing 600–800 kcal/d and 36 protein/d in addition to the baseline diet). In the case of pre-treatment weight loss greater than 10% of the baseline body weight, the patients additionally received a fat supplement providing 400 kcal/d.

With regular medical and dietary supervision, the patients whose oral food intake fell below 60% of the energy requirements were ordered enteral nutrition via PEG or nasogastric tube insertion. The diets routinely used for enteral nutrition are high-energy or high-protein industrial diets. In the case of special clinical situations, such as diabetes mellitus, liver failure, and intolerance to polymeric diets, there was the possibility of individual selection of the diet composition to suit the patient's current condition.

The patients included in the study also benefited from nursing care (this was especially true of care for access to nutrition, and the delivery of oral and enteral formula), and had the opportunity to receive care from a speech therapist, physiotherapist, and psychologist.

For the purposes of the study, medical data were additionally collected from the patient's medical history regarding comorbidities, medications used, the length of hospitalization, and the complications of treatment. A history was taken, based on which the presence of gastrointestinal symptoms accompanying the underlying disease and its treatment (including nausea, vomiting, constipation, and diarrhea) was noted.

2.5. Statistical Analysis

The mean (M), standard deviation (SD), median (Me), and minimum (min.) and maximum (max.) values were used for descriptive statistics. The Shapiro–Wilk test was used to assess the normality of the data distribution. To assess the statistical significance of changes, the Student's *t*-test was used for the variables whose distribution approximated a normal distribution, while the Wilcoxon test was used for the variables whose distribution deviated from a normal distribution. If the assumptions allowing the use of parametric tests were not met (a lack of normality of the distributions of the variables confirmed by the Shapiro–Wilk test, or a lack of sphericity of the variables confirmed by the Mauchly test), comparisons were made using Friedman's non-parametric ANOVA test. To determine the strength and direction of the relationship between the parameters analyzed in the study, Pearson's linear correlation coefficient was used (in the case of conformity to a normal distribution), in the case of non-normality of the distribution, the rho-Spearman correlation coefficient was tested. The significance level was taken as $\alpha < 0.05$. The statistical analyses were performed using the Jamovi software version 1.2.22.

3. Results

3.1. Characteristics of the Study Group

The table below (Table 1) presents the characteristics of the study group.

Table 1. Basic characteristics of the study group.

Variable	Feature	N	%	*p* *
Sex	man	78	75.0	<0.001
	woman	26	25.0	
Age (years)	20–29	3	2.9	<0.001
	30–39	6	5.8	
	40–49	10	9.3	
	50–59	26	25.0	
	60–69	47	45.2	
	70–79	12	11.5	
	80+	0	0	
Body weight (kg)	<45	0	0	<0.001
	45–54	5	4.8	
	55–64	22	21.2	
	65–74	31	29.8	
	75–84	15	14.4	
	85–94	19	18.3	
	≥95	12	11.5	
BMI $(kg/m)^2$	<18.5	2	1.9	<0.001
	18.5–24.9	48	46.2	
	25–29.9	35	33.7	
	≥30	19	18.3	
Operation	yes	39	37.5	0.011
	not	65	62.5	

Table 1. *Cont.*

Variable	Feature	N	%	*p* *
Induction chemotherapy	yes	34	32.7	<0.001
	not	70	67.3	
Type of therapy	rth	39	37.5	<0.001
	rth-chth	61	58.7	
	rth-Cetuximab	4	3.8	
The manufacture of a PEG before treatment	yes	29	27.9	<0.001
	not	75	72.1	
Alternative supplementation or diet without medical indication	yes	5	4.8	<0.001
	not	99	95.2	

rth—radiotherapy; rth-chth—radiochemotherapy; rth-Cetuximab—radiotherapy with Cetuximab; PEG—percutaneous endoscopic gastrostomy; * χ^2 test.

The mean age of the patients was 58.5 ± 10.8 years. The mean weight of the patients at the beginning of treatment was 74.6 ± 14.0, and BMI was 25.65 ± 4.34 kg/m^2.

3.2. Effects of Treatment on Energy and Macro- and Micronutrient Dietary Intake

Data on the average daily intake of energy, macronutrients, and micronutrients in the following weeks of treatment, excluding FSMP and enteral nutrition, are shown in the table (Table 2).

Table 2. Average intake of energy and macro- and micronutrients of the diet without FSMP.

Component	Unit	T2	T3	T4	T5	T6	T6 as % of T2	*p*
Energy	kcal	1847.01	1467.76	1221.29	993.33	809.47	43.83%	<0.001
Total protein	g	70.31	60.87	53.73	44.51	36.55	51.99%	<0.001
Animal protein	g	38.00	35.21	33.05	27.00	22.54	59.32%	<0.001
Plant protein	g	31.52	24.94	19.97	16.97	13.46	42.69%	<0.001
Grease	g	49.98	39.61	34.80	26.89	22.54	45.09%	<0.001
Total carbohydrates	g	290.05	226.32	180.77	149.63	120.23	41.45%	<0.001
Sodium	mg	4060.48	3617.95	2957.83	2576.32	1996.97	49.18%	<0.001
Potassium	mg	2791.74	2442.03	2160.15	1822.65	1476.05	52.87%	<0.001
Calcium	mg	504.32	526.58	591.74	483.52	393.49	78.02%	0.001
Phosphorus	mg	1181.67	1043.87	987.71	819.72	674.41	57.07%	0.001
Magnesium	mg	312.48	268.66	236.14	206.18	162.11	51.88%	<0.001
Iron	mg	10.40	8.67	7.15	6.06	4.89	47.05%	<0.001
Zinc	mg	9.15	7.79	6.55	5.58	4.56	49.81%	<0.001
Copper	mg	1.16	0.94	0.81	0.67	0.53	45.73%	<0.001
Manganese	mg	3.78	3.36	2.98	2.48	2.05	54.18%	<0.001
Vitamin A (retinol eq.)	µg	1622.90	1299.49	1116.05	855.76	679.38	41.86%	<0.001
Vitamin E (alpha-tocopherol eq.)	mg	5.08	4.20	3.77	2.75	2.29	45.07%	<0.001
Thiamine	mg	1.22	0.94	0.82	0.69	0.55	44.94%	<0.001
Riboflavin	mg	1.41	1.26	1.28	1.02	0.84	59.72%	<0.001
Niacin	mg	15.34	11.09	9.35	7.75	6.16	40.15%	<0.001
Vitamin B6	mg	1.83	1.52	1.29	1.09	0.88	48.04%	<0.001
Vitamin C	mg	50.94	44.03	36.22	29.74	22.47	44.12%	<0.001
Fatty acids: total saturated	g	24.64	19.28	16.45	13.46	11.24	45.63%	<0.001
Fatty acids: total monounsaturated.	g	15.05	12.39	11.00	8.09	6.92	45.96%	<0.001
Fatty acids: total polyuns.	g	6.29	4.80	4.69	3.28	2.60	41.31%	<0.001
Cholesterol	mg	284.49	211.80	169.15	137.37	126.64	44.51%	<0.001
Dietary fiber	g	22.06	18.78	14.84	12.53	10.20	46.24%	<0.001

Table 2. *Cont.*

Component	Unit	T2	T3	T4	T5	T6	T6 as % of T2	*p*
Folates	µg	228.21	197.60	170.96	146.28	114.73	50.27%	<0.001
Vitamin B12	µg	3.43	2.57	2.62	2.18	1.81	52.75%	<0.001
Vitamin D	µg	2.53	1.29	1.21	0.86	0.81	32.24%	<0.001
Iodine	µg	169.84	162.06	141.98	129.09	95.40	56.17%	<0.001
Long-chain polyunsaturated fatty acids	g	0.44	0.14	0.14	0.12	0.10	23.39%	<0.001
Omega-6 fatty acids	g	4.54	3.78	3.51	2.47	2.07	45.60%	<0.001
Omega-3 fatty acids	g	1.75	1.01	1.18	0.81	0.53	30.14%	<0.001
Percentage of energy from protein	%	15.82	16.93	14.15	15.83	14.04	88.77%	n/a
Percentage of energy from fat	%	23.79	23.21	24.15	20.84	18.22	76.60%	n/a
Percentage of energy from carbohydrates	%	57.13	54.54	52.23	45.50	38.27	66.99%	n/a

T2—second week of the study; T3—third week of the study; T4—fourth week of the study; T5—fifth week of the study; T6—sixth week of the study; n/a—not applicable.

The average daily value of energy and nutrient intake in the following weeks of the patients' treatment was significantly reduced in the vast majority of cases. The average value of energy consumed after the first week of the patients' treatment was 1847.01 kcal per day. By the final week, this average had dropped to just 809.47 kcal per day, which was 43.8% of the value from T2. The changes that occurred in the overall energy intake during the following weeks of treatment are shown in the following figure (Figure 1).

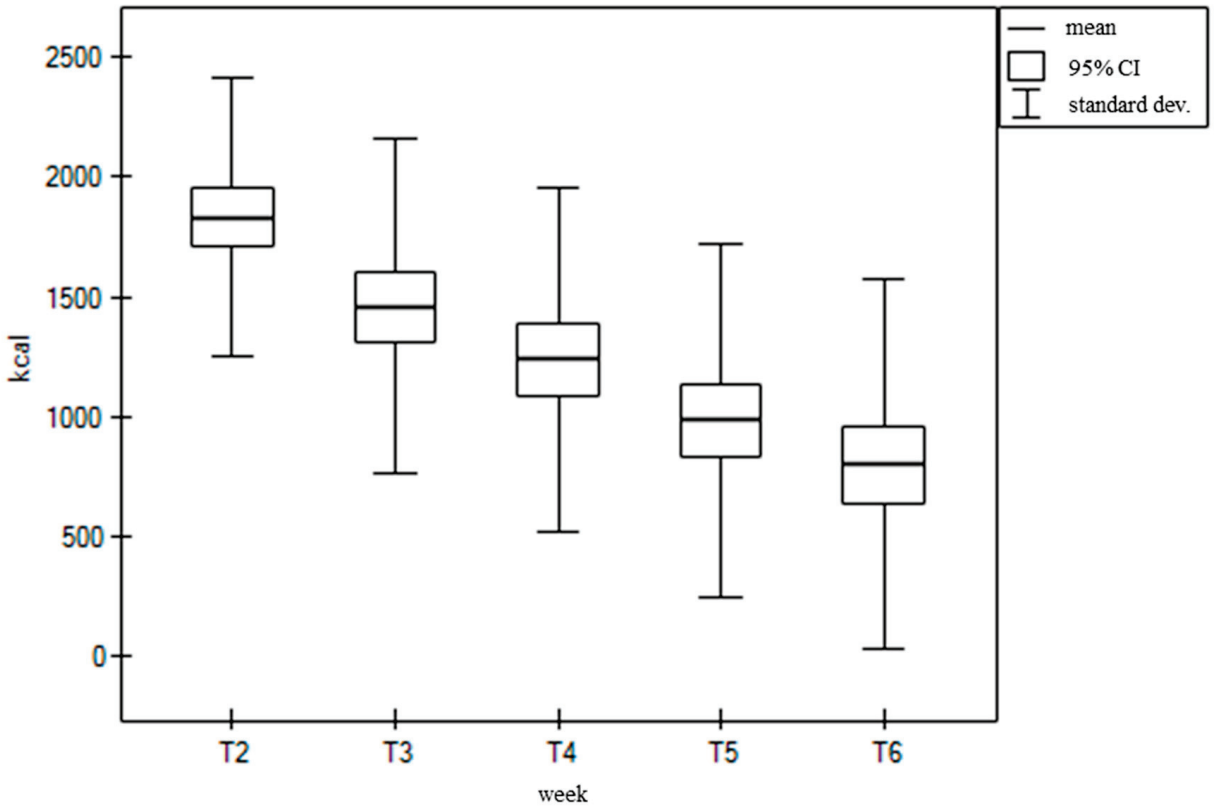

Figure 1. Daily dietary energy value (kcal) for consecutive weeks of treatment (from T2 to T6).

Data on energy, macronutrient, and micronutrient intake for each week of treatment, together with FSMP and enteral nutrition, are shown in the table below (Table 3).

Table 3. Average intake of energy and macro- and micronutrients of the diet including FSMP and enteral nutrition.

Component	Unit	T2	T3	T4	T5	T6	T6 as % of T2	*p*
Energy	kcal	2432.21	2111.24	1943.32	1860.67	1889.87	77.7%	<0.001
Total protein	g	100.00	92.75	89.51	87.82	92.43	92.4%	0.002
Animal protein	g	38.00	35.21	33.05	27.00	22.54	59.3%	<0.001
Plant protein	g	31.52	24.94	19.97	16.97	13.46	42.7%	<0.001
Grease	g	79.48	73.04	73.54	74.26	78.98	99.4%	0.149
Total carbohydrates	g	339.62	279.22	237.25	214.99	205.18	60.4%	<0.001
Sodium	mg	4174.30	3751.54	3119.55	2786.50	2341.84	56.1%	<0.001
Potassium	mg	3068.63	2761.17	2544.38	2322.49	2238.41	72.9%	<0.001
Calcium	mg	1196.88	1260.67	1397.85	1438.53	1589.70	132.8%	<0.001
Phosphorus	mg	1747.47	1633.09	1607.98	1521.39	1518.64	86.9%	<0.001
Magnesium	mg	419.35	381.13	358.11	347.27	342.61	81.7%	<0.001
Iron	mg	15.36	14.23	14.03	15.04	17.86	116.3%	0.051
Zinc	mg	14.34	13.46	13.12	13.75	15.69	109.4%	0.008
Copper	mg	172.83	253.71	517.46	866.66	1484.95	859.2%	0.214
Manganese	mg	5.11	4.81	4.67	4.56	4.89	95.7%	0.213
Vitamin A (retinol equiv.)	µg	2173.28	1896.09	1805.08	1710.40	1809.62	83.3%	0.002
Vit. E (alpha-tocopherol equiv.)	mg	13.62	13.67	14.82	16.74	21.20	155.7%	0.085
Thiamine	mg	2.16	1.94	1.94	2.03	2.28	105.9%	0.012
Riboflavin	mg	2.45	2.38	2.59	2.63	2.98	121.3%	0.416
Niacin	mg	22.28	18.37	17.17	16.68	17.66	79.3%	<0.001
Vitamin B6	mg	2.97	2.76	2.70	2.83	3.18	107.1%	0.073
Vitamin C	mg	112.24	109.57	108.83	116.31	134.11	119.5%	0.210
Fatty acids: total saturated	g	28.72	24.30	23.79	24.05	26.53	92.4%	0.003
Fatty acids: total monounsaturated.	g	15.83	13.57	13.45	12.13	14.69	92.8%	0.004
Fatty acids: total polyuns.	g	7.15	6.05	7.25	7.58	9.86	137.9%	0.016
Cholesterol	mg	284.49	211.80	169.15	137.37	126.64	44.5%	<0.001
Dietary fiber	g	22.65	19.56	15.31	12.91	10.57	46.7%	<0.001
Folates	µg	228.21	197.60	170.96	146.28	114.73	50.3%	<0.001
Vitamin B12	µg	5.65	4.93	5.28	5.39	5.88	104.2%	0.144
Vitamin D	µg	3.99	3.37	4.66	6.42	9.48	237.3%	<0.001
Iodine	µg	265.43	265.15	262.00	278.16	291.72	109.9%	0.363
Long-chain polyunsaturated fatty acids	g	0.44	0.14	0.14	0.12	0.10	23.4%	<0.001
Omega-6 fatty acids	g	4.54	3.78	3.51	2.47	2.07	45.6%	<0.001
Omega-3 fatty acids	g	1.75	1.01	1.18	0.81	0.53	30.1%	<0.001

T2—second week of the study; T3—third week of the study; T4—fourth week of the study; T5—fifth week of the study; T6—sixth week of the study.

The intake of energy and macro- and micronutrients in the diet, including FSMP and enteral nutrition, shows a much smaller range of decreases than when they were consumed with the kitchen diet alone. In many cases, the intake levels were higher at T6 compared to T2. This includes calcium (132.8%), iron (116.3%), vitamin E (155.7%), and vitamin C (107.1%). The daily energy value of the diet, however, dropped from an average of 2432.2 kcal at T2 to 1889.97 kcal at T6. Changes in the energy intake during the following weeks of treatment are shown in the figure (Figure 2).

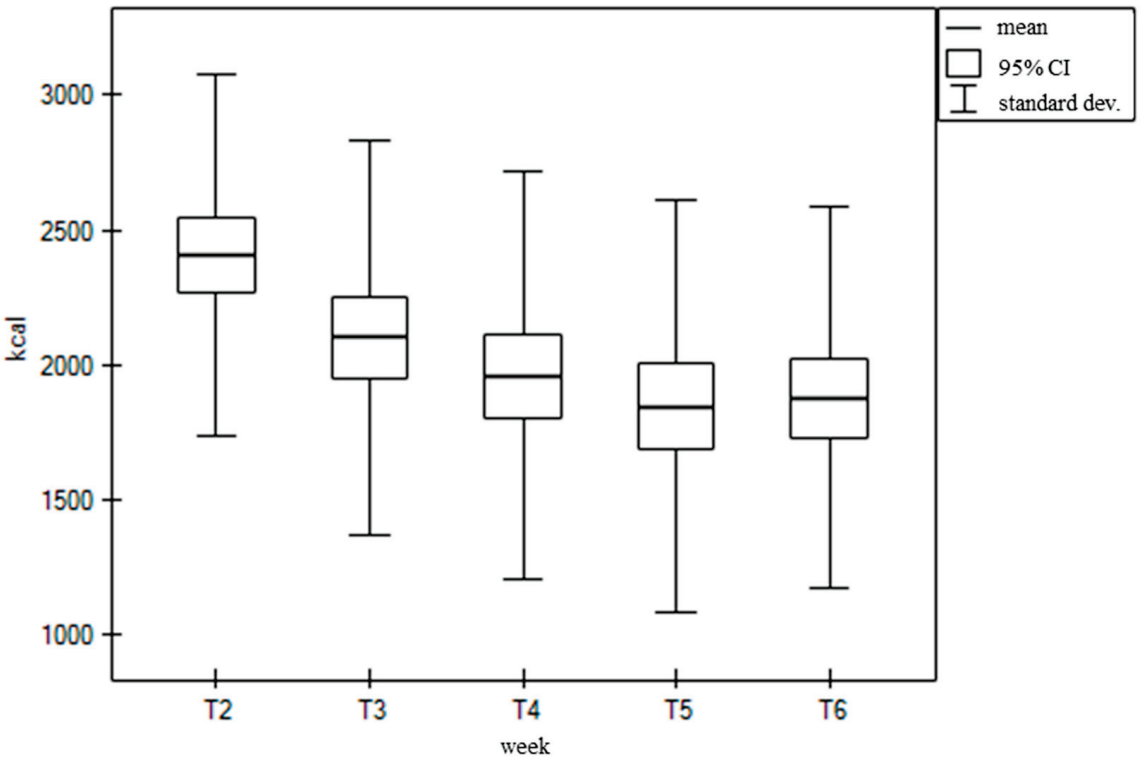

Figure 2. Daily dietary energy value (kcal), together with FSMP and EN, in consecutive weeks of treatment (from T2 to T6).

3.3. Energy Consumption vs. Individual Energy Needs

Data on the energy consumed by the patients, compared to the average daily energy requirements, are shown in the following table (Table 4).

Table 4. Comparison of average daily energy intake (kcal) to energy requirements in consecutive weeks of treatment.

		T2	T3	T4	T5	T6
Energy requirement	kcal	2019.1	2009.0	1998.9	1993.0	1978.1
Consumption without FSMP and EN	kcal	1847.0	1467.8	1221.3	993.3	809.5
	% of demand	91.5	73.1	61.1	49.8	40.9
	p	0.023	<0.001	<0.001	<0.001	<0.001
Consumption with FSMP and EN	kcal	2432.2	2111.2	1943.3	1860.7	1889.9
	% of demand	120.5	105.1	97.2	93.4	95.5
	p	<0.001	0.107	0.628	0.171	0.408

T2—second week of the study; T3—third week of the study; T4—fourth week of the study; T5—fifth week of the study; T6—sixth week of the study.

There was a significant decrease in energy intake during the subsequent weeks of the patients' treatment. At T2, the average intake without FSMP and EN accounted for 91.5% of the patients' average requirements, while at T6, this ratio dropped to only 40.9% of the requirements. For intake with FSMP and EN, in the second week, the average energy value of the meals consumed was 120.5% of the requirement. In the last week of treatment, intake from FSMP and EN accounted for 95.5% of the energy requirements. These data are presented in the figure (Figure 3).

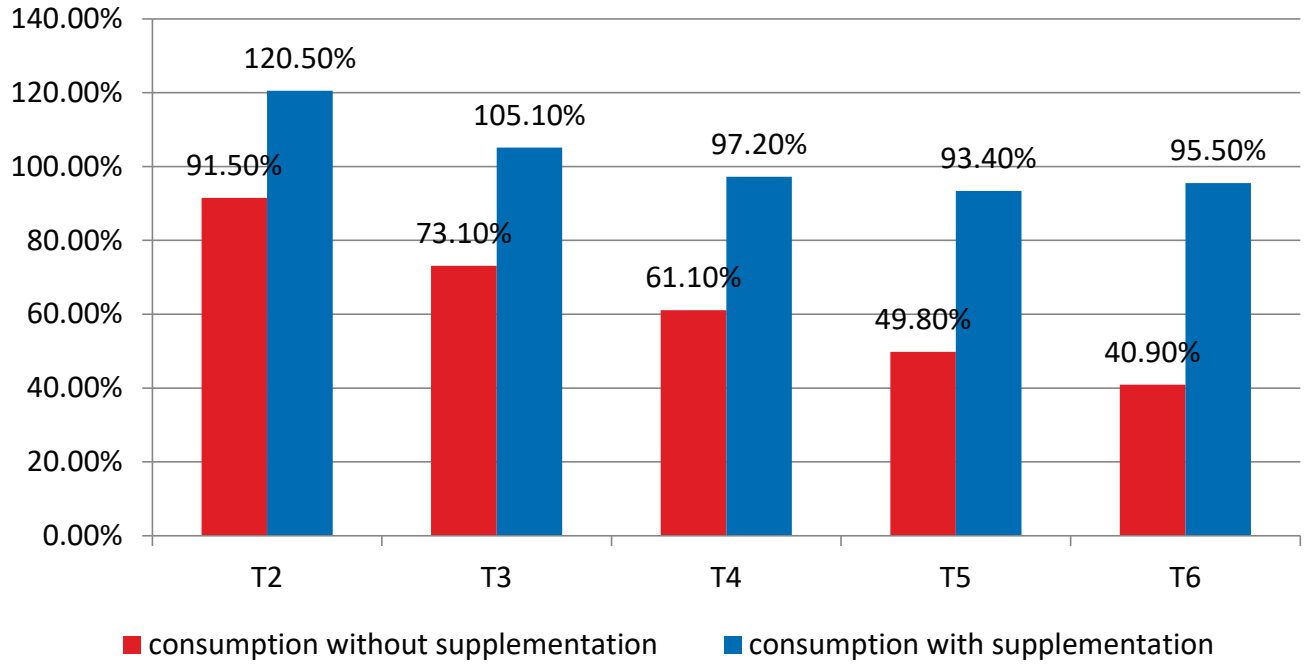

Figure 3. Energy intake with and without FSMP and EN in consecutive weeks of treatment, as a percentage of daily energy requirements.

The therapy used significantly contributes to the reduction in oral food intake in the following weeks of treatment. In the last week of treatment, the patients realized only 40.9% of their energy requirements. In contrast, the inclusion of FSMP and enteral nutrition in the diet significantly increased the degree of the realization of the patients' energy requirements.

3.4. The Stage of Treatment at Which the Inability to Maintain Daily Food Intake by Oral Route above 60% of Daily Energy Requirements Appears, Which Is an Indication for the Inclusion of Enteral Nutrition by Artificial Route (Tube or PEG)

The table shows the percentage of the subjects consuming by oral route more than 60% of their daily energy requirements in the following weeks of treatment (Table 5).

Table 5. Share of people consuming by oral route more than 60% of daily energy requirements, not including FSMP and enteral feeding.

	T1	T2	T3	T4	T5	T6
N	104	104	104	104	104	104
N yes	98	88	68	49	42	31
% Yes	94.2	84.2	66.0	47.4	40.6	29.7
N no	6	16	36	55	62	73
% No	5.8	15.8	34.0	52.6	59.4	70.3

T1—first week of study; T2—second week of study; T3—third week of study; T4—fourth week of study; T5—fifth week of study; T6—sixth week of study.

The proportion of the patients consuming orally more than 60% of their daily energy requirements declined steadily in the subsequent weeks of the therapy administered. In the first week, 94.2% of the patients met this criterion, while in the last week (T6) only 29.7% of the patients did. The weighted average of the time elapsed before the onset of the inability to consume 60% of the daily energy requirements was 4.5 weeks. Differences in the percentage of the patients realizing an energy intake above 60% of the requirements in successive weeks of treatment proved to be statistically significant (<0.001). The changes occurring in this regard are shown in the figure (Figure 4).

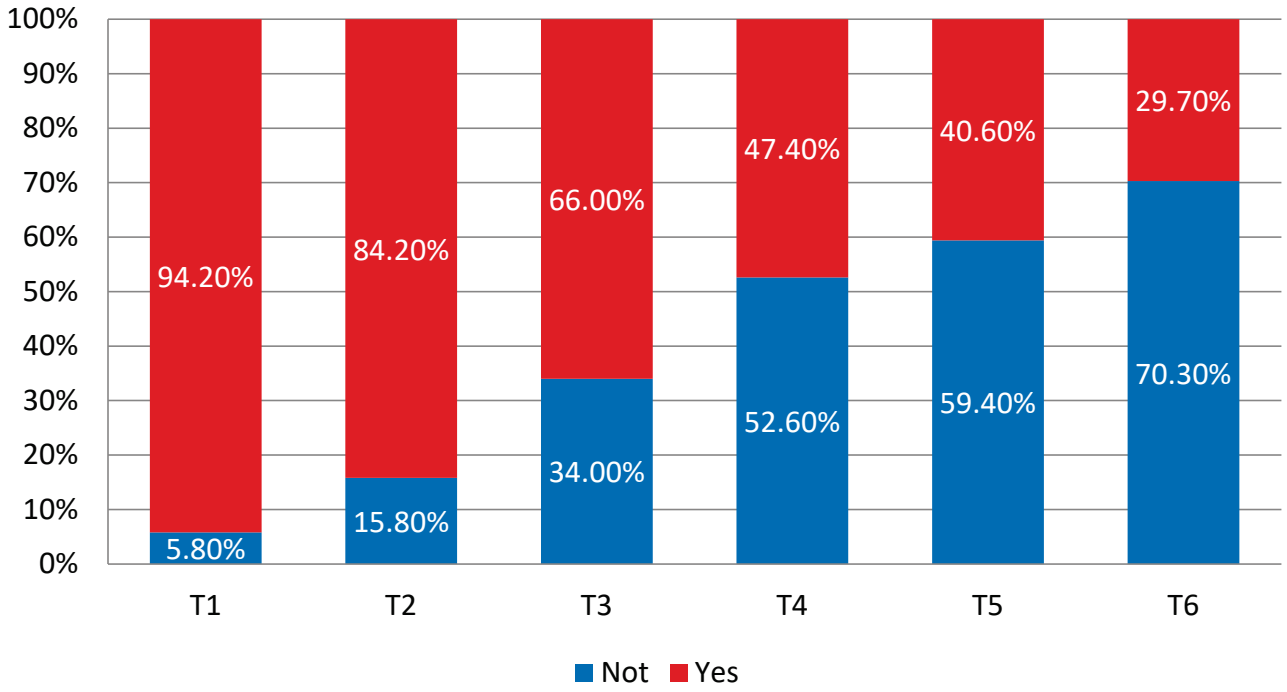

Figure 4. Realization of oral intake of 60% of energy requirements by patients.

3.5. Degree of Patient Adherence to Dietary Recommendations

The table shows the data on the daily energy value of the recommended food for special medical purposes (FSMP) and enteral nutrition (EN); the daily energy value of the FSMP and EN preparations actually taken, and the difference between these values in the subsequent weeks of treatment (Table 6).

Table 6. Daily energy values of recommended and actual FSMP intake and EN (kcal), and the difference between these values in subsequent weeks of treatment (kcal) (n = 104).

T	M/SD	Energy Value Recommended FSMP/EN [kcal]	Energy Value Taken FSMP/EN [kcal]	Difference between the Energy Value of the Recommended and Taken FSMP/EN [kcal]	*p*
T2	M SD	749.7 332.70	595.8 420.34	153.0 291.59	<0.001
T3	M SD	793.8 343.76	662.4 424.08	137.7 273.69	<0.001
T4	M SD	947.8 416.46	733.80 481.24	214.0 317.44	<0.001
T5	M SD	1141.5 511.94	893.2 541.19	248.4 357.15	<0.001
T6	M SD	1340.4 545.2	1096.8 579.47	243.7 465.60	<0.001

FSMP—food for special medical purposes; EN—enteral nutrition; T—study week; T2—second study week; T3—third study week; T4—fourth study week; T5—fifth study week; T6—sixth study week.

During the following weeks of the patients' treatment, the average daily energy value of the prescribed FSMP and EN preparations increased. At the beginning of treatment, it was 749.7 kcal (SD = 332.7), while in the last week, it was already 1340.4 kcal (SD = 572.82). The energy values of FSMP and EN taken by the patients in the following weeks also gradually increased. In the second week, the patients consumed an average of 595.8 kcal

per day (SD = 420.34) in this form, while in the last week, they consumed 1096.8 kcal (SD = 579.47). The increase between T2 and T6 was thus 84.1%.

During the following weeks of treatment, there was a trend toward an increase in the difference between the energy value of the recommended FSMP and EN preparations and that actually taken. At T2, the average difference was 153.0 kcal (SD = 291.59), while at T6 it was already 243.7 kcal (SD = 465.60). This represents an increase between T2 and T6 of 59.3%. Differences between the daily energy values of the recommended and actual FSMP and EN intake in the successive weeks of treatment proved to be statistically significant ($p < 0.001$).

3.6. Reasons for Non-Compliance with FSMP Application Recommendations

The patients gave up taking the recommended food for special medical purposes mainly due to a feeling of fullness (35.7%), nausea (33.3%), and a lack of taste acceptance (28.6%). Less frequently, the reason for non-adherence was diarrhea (2.4%).

3.7. Degree of Implementation of Recommendations

Those completing at least 75% of the recommended dose of FSMP or enteral nutrition were counted as adhering to dietary recommendations. Sixty-one percent of the patients adhered to the dietary recommendations. Below the established threshold were 38.5% of the study participants.

Data on weight loss between T1 and T6, depending on adherence to dietary recommendations, are shown in the following table (Table 7).

Table 7. Weight loss (kg) from T1 to T6 in patients according to adherence to dietary recommendations.

	N	**M**	**Me**	**SD**	***p***
Total	104	4.03	4.00	3.03	
Compliant	64	3.07	3.00	2.32	$p < 0.001$
Non-compliant	40	5.56	5.25	3.40	

Those who followed the dietary recommendations lost an average of 3.07 kg (SD = 2.32) during the treatment period, while those who did not follow the recommendations lost 5.56 kg (SD = 3.40). The average compliance rate with dietary recommendations was 78.0% (SD = 28.6%).

4. Discussion

When analyzing the clinical situation of patients with head and neck cancer, it is impossible to ignore the impact of the acute and late side effects of radical radiotherapy, which include oral mucositis, xerostomia, dysphagia, odynophagia, taste and smell disorders, a loss of appetite, and nausea. The development of the aforementioned ailments directly translates into a worsening of an already mostly abnormal nutritional state [14–17].

One of the determinants of nutritional status is nutrition, both quantitative and qualitative. The ability for efficient oral nutrition in patients with head and neck cancer is mainly determined by the location and stage of the disease and the stage of radical treatment (the severity of dysphagia and oral mucositis play an important role). Due to the problems described, food intake is often reduced, leading to weight loss. It should be noted that the side effects of radiation therapy worsen with each successive week of treatment despite the use of modern drugs designed to alleviate them. They adversely affect the quantity and quality of food consumed and nutritional status. Therefore, it is extremely important to match dietary advice with the current complaints reported by the patient [17,18].

It is estimated that an energy intake of less than 25 kcal/kg/day is associated with a high risk of malnutrition. Nutrition assessment should be conducted regularly so that the optimal dietary intake can be determined and adapted to the current clinical situation [19,20]. According to the "NutritionDay" multicenter study conducted by means of a

one-day nutritional assessment in more than 300 European hospitals, hospital meals do not cover the energy needs of hospitalized patients. The authors of the study report that energy intake in 43% of the subjects did not exceed 1500 kcal per day [21].

Given the poor quality of hospital meals, patients' aversion to food served in hospitals, and the undeniable impact of radical radiotherapy on the ability to eat orally, our study analyzed data on oral food intake. During the first week of radiotherapy, considering only oral diet, the patients took in an average of 1847 kcal and 70.3 g of protein per day. With each subsequent week of radiotherapy, energy and protein intake successively decreased shaping up in the last week of treatment at only 809.5 kcal and 36.5 g of protein per day. The percentage of the realization of energy requirements during the treatment decreased from 91.5% to 40.9%. The changes described above were statistically significant. A similar relationship was observed by van Berg et al. [22]. The energy intake of the patients treated with radiochemotherapy on the day of the completion of therapy was lower by 1234 kcal compared to baseline, which translated into a supply of only 19 kcal/kg/d.

In our study, the supply of other nutrients also successively decreased with the duration of radiotherapy. A decrease in the average intake of total fat, long-chain polyunsaturated fatty acids, carbohydrates, sodium, iron, zinc, copper, vitamin A, vitamin E, thiamin, niacin, vitamin B6, vitamin C, and vitamin D was observed. During the last week of radiotherapy, the average intake of energy; protein; carbohydrates; total fat; vitamins A, E, C, D, and B12; thiamin; riboflavin; magnesium; zinc; iron; copper; potassium; and iodine was lower than the recommended standard. Our own results regarding the successive decrease in oral food intake are consistent with those obtained by other authors [22–24]. In one study, on the day of radiotherapy initiation, 96.3% of the patients consumed more than 50% of the volume of meals administered, while on the day of the completion of radiotherapy, this percentage dropped to 38.9%. The patients who reported consuming less than 50% of their meal volume were characterized by a greater degree of malnutrition compared to the patients who took in more than 50% of their due portion of food [8].

In the available literature, there are few papers devoted to a detailed quantitative and qualitative analysis of the oral diet of head and neck cancer patients treated with radical radiotherapy. The present study not only attempted such an analysis, but also compared the effect of the addition of FSMP and enteral nutrition (as indicated) to the daily oral diet on the ability to meet daily energy requirements. The patients, due to the implementation of the recommendations at the beginning of therapy, took 585 kcal/d additionally to the oral diet, which translated into a total energy intake of 2432 kcal/d on average, while at the end of treatment, they took an additional 1080 kcal/d, resulting in a total average energy intake of 1890 kcal/d. With the inclusion of FSMP and enteral nutrition as indicated, the decrease in energy intake over the course of treatment was not as steep and drastic compared to the energy intake from the diet alone (a deficit of 543 kcal vs. 1038 kcal, respectively). Due to the fact that the patients received individually selected supplementation, they realized as much as 95.5% of their energy requirements in the last week of treatment, while from the oral diet alone the realization remained at only 40.9%. The inclusion of supplementation in the diet also improved the daily intake of protein (an additional 30 g of protein at the beginning of therapy and 56 g of protein at the end of therapy) and other macronutrients, as well as vitamins and minerals. Also of note in our study is the dynamic decline in the patients' ability to eat orally. At the beginning of treatment, 94% of the patients were eating completely by the oral route; on the day of the end of therapy, only 49% were doing so. Due to aphagia, almost 30% of the patients on the day of the end of therapy were unable to take even a small amount of fluids by the oral route. This is in line with the results presented in the study by Citak et al. [8], in which 87% of patients were fed by the oral route at the beginning of therapy, and at the end of therapy this percentage dropped to 35.2% (statistically significant change).

According to our own research and a systematic review of the literature by Nugent et al. [25], relying solely on oral diets in the nutrition of head and neck cancer patients undergoing radical radiotherapy does not ensure that individual energy and protein requirements are

met. The literature data confirm the positive effect of dietary intervention with special medical use foods on the nutritional status of patients treated with radiation therapy [8,25–29]. Ravasco et al. [30] showed that both dietary consultation and the use of FSMPs have a positive effect on ensuring the maintenance of adequate energy and protein intake in head and neck cancer patients treated with radical radiotherapy. In a study conducted by other authors, 13% of the patients were already on industrial diets at the start of therapy, and this percentage increased to 65% during therapy (FSMP -57.5%, industrial diet administered by nasogastric tube—7.5%). Patients who did not receive additional support using FSMP or enteral nutrition were statistically significantly more likely to be malnourished than those receiving FSMP or enteral nutrition [8]. Thus, the use of properly selected and well-managed supplementation with foods for special medical purposes and enteral nutrition with industrial diets may be helpful in improving the nutritional status of head and neck cancer patients treated with radical radiotherapy [25–28].

In order to improve the realization of daily energy requirements in patients with head and neck cancer, it seems reasonable to calculate individual energy requirements and fill the energy gap with FSMP and enteral nutrition, rather than following a general scheme, e.g., "two FSMPs for each patient for the entire treatment period".

In a large proportion of head and neck cancer patients, despite the use of dietary counseling supported by FSMP at a certain stage of therapy, due to the severity of dysphagia, nutrition by oral route becomes insufficient or completely impossible and the patient requires the inclusion of enteral nutrition through artificial access. The criterion for choosing the type of enteral feeding access is the planned feeding time. If the planned period of enteral feeding is longer than 30 days, a PEG should be inserted according to established practice. When the planned duration of enteral feeding is less than 30 days, the access of choice is a nasogastric tube. The use of PEGs undoubtedly has more advantages over the use of tubes. These include the aforementioned possibility of longer, essentially indefinite enteral feeding, and as practice shows, patients often require enteral feeding for several more months after the end of radiotherapy. In addition, it is a more comfortable access for the patient, possible to hide under clothes, not stigmatizing the patient. By creating a PEG prior to treatment, it is possible to start feeding the patient at the exact moment when treatment toxicity begins to significantly result in reduced oral intake, without waiting for the access to be established and the location confirmed, as with the use of tubes [31,32]. Gavages, due to the risk of sores in the gastrointestinal tract, are removed approximately four weeks after insertion. Other complications associated with the use of gavages include changes in the nasal wing, chronic sinusitis, gastroesophageal reflux, and aspiration pneumonia. Furthermore, it is quite easy to have an untargeted gavage removed, and the time until the next probe is inserted is when no food can be administered, which is tantamount to starving the patient [31,32]. Prophylactic PEG insertion is practiced in head and neck cancer patients scheduled for treatment with radical radiation therapy, but it is not routine. At the National Institute of Oncology in Warsaw, where this study was conducted, according to established practice, most patients are offered prophylactic PEG insertion prior to radical radiotherapy. However, a significant number of patients refuse to have the access inserted. It should be noted that due to numerous complications, including death, a PEG is not inserted during treatment with radical radiotherapy. In a situation where a patient requires the initiation of enteral feeding during radical radiotherapy, and has not had a PEG created prior to treatment, the only option left is to insert a tube.

In the success of dietary intervention, a large role is played by the so-called compliance, i.e., the degree to which the patient adheres to the recommendations of medical personnel. In our study, those adhering to dietary recommendations (realizing at least 75% of the recommended dose of FSMP supplementation or enteral nutrition) had a statistically significantly lower mean weight loss compared to those not adhering to dietary recommendations (3.07 kg vs. 5.56 kg). The average compliance rate with dietary recommendations was 78%. In addition, there was a statistically significant negative association between weight loss during the course of radiation therapy and the degree of the imple-

mentation of recommendations. The increase in the implementation of recommendations was accompanied by a significant decrease in weight loss. The patients adhering to the recommended intake of the recommended amount of FSMP and enteral nutrition had less weight loss because they had a higher realization of daily energy, protein, and other macronutrient and micronutrient requirements compared to the patients not adhering to the recommendations. This is consistent with the results presented by Hubbard et al. [33], who conducted a meta-analysis of 46 studies and found that the clinical effect of taking FSMPs depends on the degree of patients' compliance with the recommendations. The level of compliance with recommended FSMP supplementation in patients overall (inpatients and nursing home residents) was 78%, while it was 67% in hospitalized patients. The highest compliance with recommendations was observed in patients using liquid formulas, which are less filling and easier to ingest compared to other forms of administration, and high-energy formulas, which are lower in volume compared to isocaloric formulas. Clinical benefits were noted when energy intake from nutritional supplements was in the range of 250–600 kcal/d and the duration of use was at least 5 weeks. On the other hand, Hopanci et al. [27] reported that parameters such as BMI value, body weight, fat mass, and muscle mass significantly decreased during treatment in the group of patients who did not adhere to dietary recommendations and FSMP supplementation compared to the adherent group. In addition, severe oral mucositis was observed less frequently in the compliant patients (11.1%) compared to the non-compliant patients (88.9%).

The reasons for patients' non-adherence to recommended FSMP supplementation and enteral nutrition remain under discussion. In our own study, the patients cited feelings of fullness (35.7%), nausea (33.3%), and taste disapproval (28.6%) as reasons for not adhering to the recommended supplementation. In contrast, in a study by Orell et al. [34], the most common included nausea (22% of the subjects), early satiety (12% of the subjects), loss of motivation (9% of the subjects), or others including diarrhea, financial problems, and weakness (21% of the subjects). Thus, it is extremely important to have a dietitian's constant supervision over the amount of FSMPs taken and the implementation of enteral nutrition.

5. Limitations of the Study

In planning the methodology of the study, a prospective study using a control group was abandoned. In view of the knowledge regarding the impact of the negative effects of malnutrition on the patient's general condition and the effectiveness of cancer therapy, it would have been unethical to isolate a group of patients who did not receive dietary counseling.

In the study, a historical control group was selected; however, the only parameter available from the area of nutritional status was body weight and information on whether there was any nutritional support (dietary consultation, FSMP, or enteral nutrition). The other parameters that were analyzed in the study group were not determined or information about them was incomplete in the analyzed medical records of patients in the historical control group.

6. Conclusions

Radical radiotherapy resulted in a systematic decrease in the average daily intake of energy and macro- and micronutrients in the following weeks of treatment.

The inclusion of FSMP and enteral nutrition in the diet significantly increased the percentage of meeting the patients' energy requirements.

The fourth week of radiotherapy is the critical moment of treatment, when the greatest weight loss occurs along with the inability to consume 60% of the daily energy requirements.

The patients' adherence to dietary recommendations (FSMP supplementation and enteral nutrition) was associated with decreased weight loss during radical radiotherapy.

Regular supervision by a dietitian (including the use of FSMP and enteral nutrition as indicated) of head and neck cancer patients undergoing radical radiotherapy should be routine during anticancer treatment.

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Informed Consent Statement: Informed consent was obtained from all the subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy reasons.

Conflicts of Interest: The authors declare no conflicts of interest.

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Article

Prevalence of Dietary Modification and Supplement Use in Patients with Metastatic Renal Cell Carcinoma Receiving Systemic Therapy

Hedyeh Ebrahimi [1], Dena Battle [2], Nicholas J. Salgia [3,4], Zeynep B. Zengin [1], Nazli Dizman [5], Luis Meza [1], Cristiane D. Bergerot [6], Regina Barragan-Carrillo [1], JoAnn Hsu [1], Daniela Castro [1], Benjamin Mercier [1], Neal Chawla [1], Xiaochen Li [1], Abhishek Tripathi [1], Sandy T. Liu [7], Alex Chehrazi-Raffle [1], Ulka Vaishampayan [8], Michael D. Staehler [9] and Sumanta K. Pal [1,*]

[1] Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA 91010, USA; hebrahimi@coh.org (H.E.); zeynepbusrazengin@gmail.com (Z.B.Z.); luis.mezacontreras@yale.edu (L.M.); rbarragancarril@coh.org (R.B.-C.); johsu@coh.org (J.H.); dacastro@coh.org (D.C.); bmercier@coh.org (B.M.); nchawla@coh.org (N.C.); xiaoli@coh.org (X.L.); atripathi@coh.org (A.T.); achehraziraffle@coh.org (A.C.-R.)
[2] Kidney Cancer Research Alliance (KCCure), Alexandria, VA 22314, USA; dena@kccure.org
[3] Department of Immunology, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14203, USA; nicholas.salgia@roswellpark.org
[4] Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY 14203, USA
[5] Department of Internal Medicine, MD Anderson Cancer Center, Houston, TX 77030, USA; ndizman@mdanderson.org
[6] Oncoclinicas&Co—Medica Scientia Innovation Research (MEDSIR), Sao Paulo 04543906, Brazil; crisbergerot@gmail.com
[7] City of Hope Orange County Lennar Foundation Cancer Center, Irvine, CA 92618, USA; sanliu@coh.org
[8] Department of Medicine/Oncology, Rogel Cancer Center, University of Michigan, Ann Arbor, MI 48109, USA; vaishamu@med.umich.edu
[9] Department of Urology, University Hospital Munich-Grosshadern, Ludwig-Maximilian University, 80539 Munich, Germany; michael.staehler@med.uni-muenchen.de
* Correspondence: spal@coh.org; Tel.: +1-626-256-4673; Fax: +1-626-301-8233

Abstract: Many patients diagnosed with cancer adopt dietary changes and supplement use, and a growing body of evidence suggests that such modifications can affect outcomes to cancer therapy. We sought to assess the prevalence of these practices and the surrounding physician-patient dialogue among patients with metastatic renal cell carcinoma. An online survey was administered by Kidney Cancer Research Alliance (KCCure), interrogating dietary modification patterns, supplement usage, out-of-pocket expenditure related to supplements, and patients' views toward alternative medicine practices. Patients with metastatic renal cell carcinoma receiving combination therapy were actively solicited. In total, 289 unique responses were collected. The most common first-line treatments were nivolumab/ipilimumab (32.4%) and axitinib/pembrolizumab (13.1%). Within the cohort, 147 (50.9%) started using supplements following diagnosis of renal cell carcinoma; the most utilized supplements were probiotics, cannabidiol (CBD) oil/marijuana, and Vitamin C, reported by 70 (47.6%), 61 (41.4%), and 54 (36.7%), respectively. Dietary modifications following cancer diagnosis were reported by 101 (34.9%) respondents, of which 19.8% followed the Mediterranean diet and 18.8% adopted a ketogenic diet. Most respondents (71.3%) noted that they consistently report supplement usage to their physicians. A substantial proportion of patients with metastatic renal cell carcinoma utilize dietary modification and supplements as an adjunct to antineoplastic therapy. Considering the widespread adoption of these practices and the reported effects on cancer treatment, it is crucial for healthcare providers to engage in discussions with patients regarding supplement use.

Keywords: renal cell carcinoma; dietary supplements; probiotics; diet therapy

1. Introduction

The prognosis of metastatic renal cell carcinoma (mRCC) has improved markedly over the course of the past several decades, owing largely to the advent of two classes of therapies: (1) vascular endothelial growth factor (VEGF)-directed agents, and (2) immune checkpoint inhibitors [1]. VEGF-directed therapies either abrogate signaling through binding of circulating VEGF (bevacizumab) or through inhibition of its cognate receptor (cabozantinib, lenvatinib, axitinib, and others) [2–4]. Commonly used checkpoint inhibitors in mRCC block signaling through either programmed death-1 (PD-1) or cytotoxic T-lymphocyte antigen 4 (CTLA4) [5]. Ahead of the introduction of these therapies, the median survival of mRCC was often quoted at approximately 1 year [6]. In contemporary studies using front-line combinations of VEGF-directed agents with checkpoint inhibitors or dual checkpoint inhibitor therapy, a median survival in excess of 4 years has been observed [7,8].

While improved prognosis and expanding treatment options for mRCC is a source of inspiration for many patients, the disease remains terminal for the majority. As a consequence, many patients turn to alternative strategies in the hopes of enhancing their outcomes. Such alternative strategies may encompass non-pharmacologic methods (e.g., exercise, meditation, and acupuncture) or pharmacologic approaches (e.g., herbs, vitamins, and minerals). We use the term "dietary supplements" herein to encompass the latter. The use of dietary supplements is pervasive not just among cancer patients but among healthy patients as well. The benefit in cancer outcomes is suspect. In the US-based National Health and Nutrition Examination Survey (NHANES) study, 30,958 adults were surveyed regarding dietary habits [9]. The majority of respondents (51%) reported use of dietary supplements, with 38% reporting use of multivitamins. With 6 years of follow-up, there was no reduction in cancer-related mortality: in fact, among patients taking calcium supplements, mortality was increased (hazard ratio [HR] 1.62, 95% CI, 1.07–2.45).

The literature around dietary supplement use among cancer patients is complex. A meta-analysis encompassing 32 large studies suggested that between 64 and 81% of cancer survivors use dietary supplements, with 14–32% of patients initiating these agents after a cancer diagnosis [10]. Rates of utilization were highest among patients with breast cancer, and multiple studies cite a higher rate of use among women as compared to men [11–13]. While questionnaire studies among patients consistently show high rates of dietary supplement use, up to 68% of treating physicians may be unaware of the practice, an alarming statistic [10]. Without systematic review and characterization of dietary supplements in the clinic, prior studies have shown that patients may experience harmful drug–supplement interactions or be taking agents that could compromise their long-term outcome [14].

Unlike in more prevalent cancer types (e.g., breast, lung, or prostate cancer), to our knowledge, there has been limited formal study of dietary intervention and supplement use among patients with RCC. To address this, we performed a survey study of a large online patient community of patients with RCC. Our results are focused specifically on those patients with metastatic disease on active systemic therapy.

2. Materials and Methods

The survey was developed by the Kidney Cancer Research Alliance (KCCure), a US-based non-profit patient advocacy forum, with multidisciplinary representation from a surgeon (MS), medical oncologist (UV), and patient advocate (DB). A committee with specific interest in microbiome research added questions pertaining to dietary habits and supplement usage (SKP, ND). A separate group of patient advocates initially evaluated the survey for ease of interpretability. The survey contained questions regarding patient demographics, including sex, age, race, country of residence, living area, and education level. Next, patients were asked about treatment-related information, consumption of supplements following cancer diagnosis, types of supplements utilized as a result of cancer diagnosis, dietary modifications following cancer diagnosis, views toward alternative

medicine, frequency of sharing information about supplement use with their physician, and monthly out-of-pocket costs for supplements (see Appendix A for full survey).

The survey was distributed between July and September 2022 to a patient mailing list maintained by the KCCure and through online social media platforms (specifically, Facebook and Twitter). The system prohibited multiple responses from the same patient via anonymized IP address tracking. Responses from patients who (1) self-reported an mRCC diagnosis and (2) were receiving a checkpoint inhibitor-based systemic therapy regimen at the time of the survey were included for analysis.

Statistical Analysis

Throughout this work, qualitative variables are provided as the number (percentage), and age is reported as the median (range: minimum–maximum). Descriptive statistics were used to report the frequency. The Student's *t*-test and Chi-square test were used to compare sociodemographic characteristics between participants. Statistical analyses were conducted using R Statistical Software, version 4.3.0. (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and an alpha level of 0.05 was considered for statistical significance.

3. Results

3.1. Characteristics of Patients

The survey was distributed to 1532 individuals, of which 1062 patients with RCC completed the survey. Among participants, 289 (27.2%) met the inclusion criteria of undergoing systemic therapy with a combination of dual checkpoint inhibitors or checkpoint inhibitors plus VEGF-directed agents for metastatic disease. Thus, our study population consisted of 143 (49.5%) females and 145 (50.2%) males, while 1 (0.3%) respondent preferred not to disclose their sex. The median age of the total inclusion cohort was 61 (range: 20–85 years). The majority (86.9%) of patients were residents of the United States, followed by Canada (3.1%). In this study, 269 (91.0%) respondents identified as white and 153 (52.9%) respondents had completed a bachelor's degree or higher. The most commonly reported first-line treatments were nivolumab/ipilimumab (32.4%) and axitinib/pembrolizumab (13.1%). Detailed characteristics of respondents are presented in Table 1.

Table 1. Patient characteristics.

Demographic Characteristics (*n* = 289)		
Age: median (range)		61 (20–85)
Sex: number (%)	Female	143 (49.5%)
	Male	145 (50.1%)
	Prefer not to disclose	1 (0.3%)
Race: number (%)	White	263 (91.0%)
	Hispanic	11 (3.8%)
	Other	15 (5.2%)
Living area: number (%)	Urban	61 (21.1%)
	Suburban	133 (46.0%)
	Rural	94 (32.5%)
Education level: number (%)	High school degree or less	47 (16.3%)
	Some college without a degree	89 (30.8%)
	Bachelor's degree or above	153 (52.9%)

3.2. Supplement Use in Patients with Metastatic Renal Cell Carcinoma

Within the studied cohort, 147 (50.9%) respondents started using supplements following the diagnosis of mRCC. There were no statistically significant associations between the initiation of supplements following cancer diagnosis and age, sex, living area, or education. Among patients who began using supplements, 70 (47.6%) started using probiotics and 61 (41.4%) initiated cannabidiol (CBD) oil or marijuana subsequent to their cancer diagnosis. Table 2 presents the type and frequency of supplement use amongst respondents.

Table 2. Supplement use pattern secondary to RCC diagnosis among the survey respondents.

Supplement	Female: Number (%)	Male: Number (%)	*p*-Value
Probiotics	31 (21.7%)	39 (26.9%)	0.3
Cannabidiol (CBD) oil or Marijuana	24 (16.8%)	37 (25.5%)	0.07
Vitamin C	20 (14.0%)	34 (23.4%)	0.04
Turmeric or Curcumin	18 (12.6%)	22 (15.1%)	0.5
Vitamin E	11 (7.7%)	11 (7.6%)	0.9

Furthermore, 101 (34.9%) patients reported dietary modification after diagnosis of mRCC. The Mediterranean diet was the most common (19.8%) newly adopted regimen among patients, followed by the ketogenic diet (18.8%%) (Figure 1).

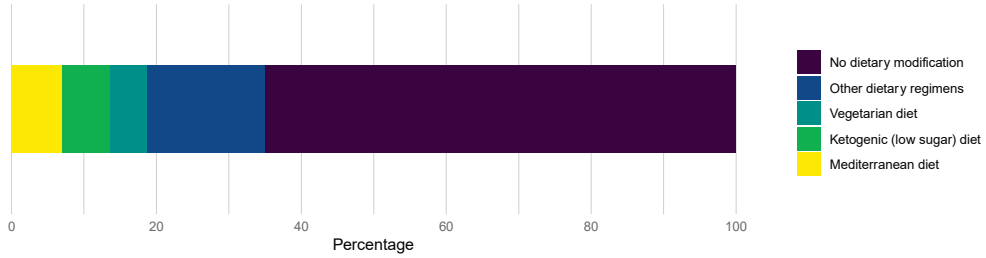

Figure 1. Dietary modification following the diagnosis of RCC.

When patients were asked about the frequency of sharing information about supplement use with their physician, 206 patients (71.3%) indicated they always shared relevant information with their physician, 33 patients (11.4%) reported they usually/sometimes did so, and 8 patients (2.8%) reported rarely or never sharing information on supplement use with their provider. Notably, 42 patients (14.5%) preferred not to respond to this question. Survey prompts also assessed the out-of-pocket cost attributed to supplements and over-the-counter products not covered by insurance for patients with mRCC. Among the respondents, 103 patients (35.6%) spent less than $100 per month, 41 patients (14.2%) spent between $100 and $250 per month, and 24 patients (8.3%) spent more than $250 per month for supplements and over-the-counter products following mRCC diagnosis.

Additionally, participants' views toward alternative medicine were interrogated in this study. Notably, 111 patients (38.4%) indicated that they have tried or would try alternative medicine approaches to help alleviate the side effects of their systemic treatment or increase their quality of life. While 104 respondents (36.0%) were skeptical toward alternative medicine, 27 (9.3%) mentioned that they have tried or would try alternative medicine to assist their cancer shrinkage instead of using approved treatments. Detailed results of respondents' views toward alternative treatment are presented in Figure 2.

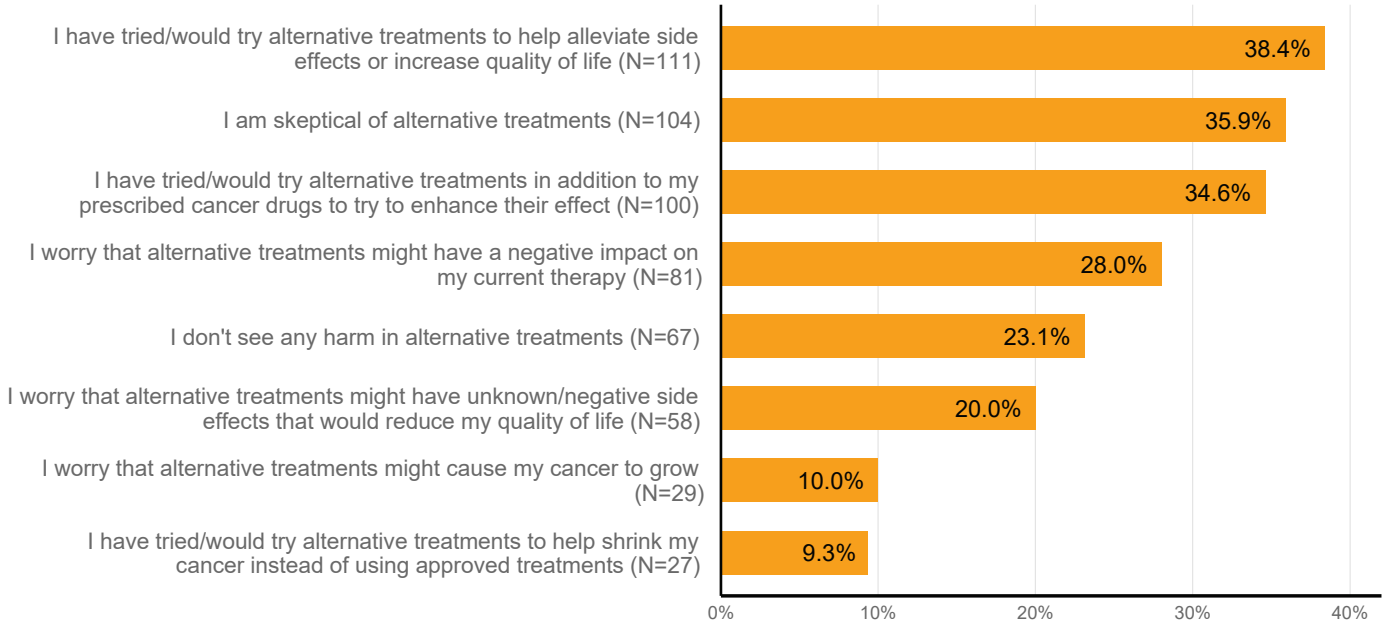

Figure 2. Respondents' perspectives on supplements and alternative medicine.

4. Discussion

To our knowledge, the results herein represent the first study to systematically characterize the practice of supplement use within a population of patients diagnosed with mRCC. Our study identifies that most patients with mRCC use dietary supplements alongside formally prescribed anti-cancer therapy. Use of dietary supplements was prompted by the diagnosis of cancer in most cases, and the most frequently utilized dietary supplements included probiotics, cannabinoids, and vitamin C. Perspectives on dietary supplements varied among those surveyed, with roughly similar proportions of patients expressing optimism around improved clinical outcome and, on the contrary, concern around potential side effects. Reassuringly, most patients appear to maintain open communication with their treating physicians surrounding supplement use.

In the context of mRCC, the clinical impact of most dietary supplements is poorly understood. With the cornerstone of front-line therapy being immune checkpoint inhibitors, there is an emerging literature around how certain dietary interventions may impact patient outcomes in RCC and other tumor types with this class of therapy. Spencer and colleagues performed a detailed assessment of 128 patients with melanoma receiving checkpoint inhibitors: in this population, a high-fiber diet and no use of probiotics were associated with improved outcomes [15]. In preclinical models, the authors also demonstrated that low fiber intake or untailored probiotics were associated with impaired response to anti-PD-1 therapy and posit that such findings are driven by decreases in interferon-γ-expressing T cells in the tumor microenvironment. While untailored probiotics may hinder outcomes with checkpoint inhibitors, prospective trials combining live bacterial products (LBPs) with immune checkpoint inhibitors have been undertaken by our group and others, specifically with the intent of augmenting immunotherapy responses. The LBP CBM588 is a strain of *Clostridium butyricum*: once ingested, this LBP propagates in the lower gastrointestinal tract and prompts the release of butyrate, a short-chain fatty acid postulated to increase the recruitment of Th17 cells and other anti-tumor immune populations to the tumor microenvironment [16,17]. In two separate, phase I randomized trials, CBM588 has been shown to augment the activity of both cabozantinib/nivolumab and nivolumab/ipilimumab [18,19]. It is thus foreseeable that an evidence-based approach could be used to augment therapy via dietary supplementation, although further study is needed to validate this.

Furthermore, clinical anecdotes and preclinical studies have identified the potential for nutritional supplements to enhance immunotherapy outcomes in patients with cancer.

Camu camu, for example, is a fruit native to Brazil and Peru, of which the active compound is castalagin. Recent work demonstrated that oral supplementation of castalagin enriched for bacterial species previously associated with immunotherapy response, improved the ratio of effector-to-regulatory T cells in the tumor microenvironment, and induced systemic metabolic changes, all of which associated with a biological program sufficient to bypass resistance to anti-PD1 immunotherapies in human xenograft models [20] Clinically, a recent report has also identified two patients with immunotherapy-refractive metastatic melanoma who went on to achieve durable responses to immunotherapy rechallenge after the addition of a camu camu prebiotic supplement [21]. Based on these compelling data, our group has initiated a randomized phase I trial to test camu camu in combination with nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA-4) compared to nivolumab/ipilimumab alone for patients with treatment-naïve metastatic renal cell carcinoma [22].

While the literature around microbiome modulation is scant, there is even less literature to support the use of cannabinoids or vitamins in mRCC. In a study including 140 patients receiving nivolumab for mRCC, 51 patients (36%) were noted to have concurrent use of cannabis [23]. Interestingly, cannabis use was associated with an impaired response rate on multivariate analysis (38% versus 16%; $p = 0.016$), but no impact on progression-free survival (PFS) or overall survival (OS) was observed. Although the pathogenesis of this is unclear, several preclinical studies do point to both cannabinoid receptors 1 and 2 as being associated with RCC progression [24,25]. The recent announcement by the United States Drug Enforcement Administration to reclassify marijuana from a Schedule I to a Schedule III compound will allow for improved study of the interactions between cannabinoids and tumors, including RCC. Conflicting evidence exists around the role of vitamin C in RCC (the most commonly used vitamin supplement in our survey). Although meta-analyses point to an inverse relationship between vitamin C intake and the development of RCC, there is no data addressing the impact on metastatic disease [26]. Thus, future work on Vitamin C's impact on RCC tumor growth and progression, alongside its interaction with anti-cancer therapies utilized in RCC, is imperative.

A modest proportion of patients in our series expressed concern over harm from alternative treatments. These concerns are warranted: for instance, a survey of 1081 cancer survivors from France identified that 18% of individuals taking dietary supplements had potentially harmful patterns of intake [14]. These practices included the consumption of phytoestrogens among patients with hormonally driven cancers (e.g., breast or prostate cancer) or the use of vitamin E with anticoagulants or antiplatelet agents (thereby enhancing bleeding risk). Studies evaluating the rates of drug interactions between dietary supplements and prescription medications in cancer patients have produced varying results, suggesting that interactions may occur in the range of 12 to 60% of patients [27,28]. These datasets highlight the importance of reviewing dietary supplement use with healthcare providers. Although some studies have pointed to low rates of information sharing between patients and providers, our study suggested that the majority of patients were open to discussing supplement use with their physicians [10].

Our study has multiple limitations. First, the survey was administered via online platforms and was open to any patients with a self-reported diagnosis of RCC. Thus, it is challenging to define an absolute denominator of patients to whom the survey was available. The population of respondents was representative of a typical RCC population based on many demographic features (i.e., age), but the gender distribution was equal (whereas RCC tends to have a 2:1 male predominance at the population level), and the declared race was largely white (91%), with relatively few minorities represented [29]. Patients were highly educated, with the majority of patients achieving a bachelor's degree; the socioeconomic factors attached to this could have implications for the patterns of dietary supplement use observed (e.g., more affluent patients may have more resources to purchase these products). Reliance on self-reporting also makes it challenging to verify certain clinical characteristics, such as clinical stage or treatment status. Although our survey was quite detailed, we did not have the ability to capture certain detailed elements

like supplement dose; therefore, although we presume that certain dietary supplements (e.g., vitamin C or E) might be used in excess, it is possible that patients are simply adhering to recommended daily values.

5. Conclusions

The data provided herein provide a first glimpse at dietary supplement use among patients with mRCC. Among nearly 300 patients with mRCC profiled herein, the majority of patients noted nutritional supplement use in addition to their checkpoint inhibitor-based systemic therapy. Furthermore, most patients maintained an open dialogue regarding supplement use with their providers. Given the prevalence of supplement use in the mRCC patient population and the potential risks posed by it, this dialogue between oncology providers and patients around dietary supplement use is critical to ensure patient safety and optimize positive therapeutic outcomes. Further work will seek to expand on these conversations to better understand both patient and provider perspectives on supplement use as an adjuvant to systemic anti-cancer therapies. The interest that patients express in dietary supplements is also justification for more formal study of their use, an avenue of research exploration that has only recently emerged. Together, our results represent the first interrogation of supplement use in a cohort of patients with mRCC receiving systemic therapy and open multiple avenues for future study to best optimize nutritional supplements and their interactions with anti-cancer therapy with the goal of improving patient outcomes in this aggressive disease setting.

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Institutional Review Board Statement: Not applicable. Data utilized in the current study was obtained in a completely anonymized fashion by KCCure, with no transmittal of personal health information (PHI) to the study principal investigators (HE, SKP).

Informed Consent Statement: Formal patient consent was waived due to the voluntary nature of survey initiation and completion.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Conflicts of Interest: Hedyeh Ebrahimi, Dena Battle, Zeynep B. Zengin, Luis Meza, Cristiane D Bergerot, Regina Barragan-Carrillo, Daniela Castro, Benjamin Mercier, Ameish Govindarajan, Neal Chawla, Abhishek Tripathi, Sandy T. Liu, and Sumanta K. Pal declare no conflicts of interest. Nicholas J. Salgia received funding support from NCI T32CA085183. Nazli Dizman, MD: Consulting—Vivreon Biosciences. Alex Chehrazi-Raffle, MD: Consultant: Tempus Labs, Inc; Honoraria: Exelixis, Inc., AVEO. Ulka Vaishampayan, MD: Research Support: Merck and OncoC4, Consultant and Honoraria: BMS, Merck, Pfizer, Gilead, Sanofi, Bayer, Exelixis Inc. Michael D. Staehler, MD: Consultant: Pfizer, GlaxoSmithKline, Novartis, Bayer, Roche, Aveo, EUSAPharm, Astellas, Ipsen, Exelixis, Pelloton, EISAI, BMS, MSD, Apogepha, Oncorena, Jansen; Honoraria: Pfizer, GlaxoSmithKline, AVEO, Novartis, Bayer, EUSAPharm, Astellas, Ipsen, Exelixis, Pelloton, EISAI, BMS, MSD, Apogepha; Research Funding: Pfizer, GlaxoSmithKline, AVEO, BMS, Novartis, Bayer, Roche/Genentech, Immatics, Wilex, Ipsen, Exelixis, EISAI.

Appendix A

Survey Questionnaire

Q1 How do you describe your gender identity?

- ○ Female
- ○ Male
- ○ I prefer not to answer
- ○ Non-binary
- ○ Transgender

Q2 Which option best describes your ethnic group or background?

- ○ White
- ○ Black or African-American
- ○ Asian
- ○ American Indian or Native American
- ○ Hispanic or Latino
- ○ Middle Eastern or North African
- ○ Pacific Islander
- ○ Prefer not to disclose
- ○ Other

Q3 Which best describe where you live?

- ○ Urban
- ○ Suburban
- ○ Rural

Q4 What country do you live in?

- ○ Drop down menu with full list of countries

Q5 What is the highest level of school you have completed or the highest degree you have received?

- ○ Less than high school degree
- ○ High school degree or equivalent (e.g., GED)
- ○ Some college but no degree
- ○ Associate degree
- ○ Bachelor degree
- ○ Graduate degree

Q6 Which of the following treatments have you had? Please specify the order that you received them.

	1st Treatment	2nd Treatment	3rd Treatment	4th Treatment	5th Treatment	6th Treatment	7th Treatment	8th Treatment	9th Treatment	10th or Later Treatment	
Opdivo + Yervoy (nivolumab + ipilimumab)	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→
Keytruda + Inlyta (pembrolizumab + axitinib)	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→
Opdivo + Cabometyx (nivolumab + cabozantinib)	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→
Keytruda + Lenvima (pembrolizumab + lenvatinib)	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→
Bavencio + Inlyta (avelumab + axitinib)	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→
Cabometyx (cabozantinib) single agent	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→
Lenvima + Afinitor (lenvatinib + everolimus)	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→
Fotivda (tivozanib)	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→
Inlyta (axitinib) single agent	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→
Sutent (sunitinib) single agent	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→
Votrient (pazopanib) single agent	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→
Afinitor (everoliumus) single agent	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→
Other (specify in box below)	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→	○→

Q7 How long following the discovery of metastatic cancer did you start systemic therapy (drug treatment)?

- ○ Within 2 weeks
- ○ Within 4 weeks
- ○ Within 3 months
- ○ Within 6 months
- ○ More than 6 months

Q8 How much money do you spend per month on health related products that are not covered by insurance, such as supplements, vitamins, over the counter medicines.

- ○ Nothing
- ○ <$20
- ○ $20–$50
- ○ $50–$100
- ○ $100–$250
- ○ $250–$500
- ○ >$500

Q9 Have you taken any of the following alternative supplements as a result of your cancer diagnosis?

- ○ Marijuana
- ○ Rick Simpson Oil (RSO)
- ○ CBD oil
- ○ Vitamin C
- ○ Turmeric/Curcumin
- ○ Fenbendazole
- ○ Ivermectin
- ○ Probiotics
- ○ Vitamin E
- ○ Other (please specify)

Q10 What statements most accurately reflect your views/experience related to alternative treatments. (Check all that apply).

- ○ I have tried/would try alternative treatments to help shrink my cancer instead of using approved treatments
- ○ I have tried/would try alternative treatments in addition to my prescribed cancer drugs to try enhance their effect
- ○ I have tried/would try alternative treatments to help alleviate side effects or increase quality of life
- ○ I don't see any harm in trying alternative treatments
- ○ I am skeptical of alternative treatments
- ○ I worry that alternative treatments might cause my cancer to grow
- ○ I worry that alternative treatments might have a negative impact on my current therapy
- ○ I worry that alternative treatments might have unknown/negative side effects that would reduce my quality of life

Q11 Do you tell your doctor about supplements you are taking?

- ○ Always
- ○ Usually
- ○ Sometimes
- ○ Rarely
- ○ Never

Q12 Have you adopted a different diet as a result of your cancer diagnosis?

- ○ Ketogenic (low sugar) diet
- ○ Vegan diet
- ○ Vegetarian diet
- ○ Mediterranean diet
- ○ Other (please specify)

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Article

Nutritional Status as a Prognostic Factor for Survival in Palliative Care: A Retrospective Observational Analysis of Home Parenteral Nutrition in Cancer Patients with Inoperable Malignant Bowel Obstruction

Karolina Tenderenda [1,*], Aleksandra Gierczak [1], Mariusz Panczyk [2], Jacek Sobocki [3,†] and Zuzanna Zaczek [3,4,†]

[1] Student Research Association for Clinical Nutrition of Medical University of Warsaw, Department of General Surgery and Clinical Nutrition, Centre of Postgraduate Medical Education, 00-401 Warsaw, Poland
[2] Department of Education and Research in Health Sciences, Faculty of Health Sciences, Medical Univeristy of Warsaw, 00-518 Warsaw, Poland; mariusz.panczyk@wum.edu.pl
[3] Department of General Surgery and Clinical Nutrition, Centre of Postgraduate Medical Education, 00-401 Warsaw, Poland; zuzanna.zaczek@wum.edu.pl (Z.Z.)
[4] Department of Human Nutrition, Faculty of Health Sciences, Medical University of Warsaw, Erazma Ciołka 27, 01-445 Warsaw, Poland
* Correspondence: karola.tenderenda@gmail.com
† These authors contributed equally to this work.

Abstract: Palliative care patients with malignant bowel obstruction are particularly at risk of developing malnutrition, which in turn directly shortens survival time and worsens quality of life (QoL). According to the available data, the survival time in this patient group is often less than three months. To avoid further complications related to malnutrition and poor outcomes in oncological therapy, nutritional therapy such as home parenteral nutrition (HPN) is offered. The aim of this study was to investigate whether nutritional status is a prognostic factor for survival in palliative care patients with malignant inoperable bowel obstruction qualified for home parenteral nutrition and which nutritional assessment tool has the most accurate prognostic value. This retrospective observational analysis included 200 patients with malignant bowel obstruction referred for home parenteral nutrition between January 2018 and August 2023. The analysis included laboratory test results, body mass index (BMI), Subjective Global Assessment (SGA), Nutritional Risk Index (NRI), Geriatric Nutritional Risk Index (GNRI), Prognostic Nutritional Index (PNI) and malnutrition as defined by the Global Leadership Initiative on Malnutrition (GLIM). The average survival time of the patients was 75 days. Patients with higher NRI and PNI scores were more likely to survive (NRI: $p < 0.001$; PNI: $p < 0.001$). The GLIM criteria, SGA scores and BMI values did not prove to be good prognostic factors for survival (GLIM $p = 0.922$, SGA $p = 0.083$, BMI $p = 0.092$). The results suggest that the use of NRI and PNI may be helpful in prognosing survival in these patients and that prevention of the development of malnutrition through earlier nutritional assessment and intervention should be considered in this patient group.

Keywords: palliative care patients; malignant inoperable bowel obstruction; home parenteral nutrition; malnutrition; survival time

1. Introduction

The World Health Organization (WHO) defines palliative care as an approach that improves the quality of life of patients and their families facing problems associated with an untreatable illness [1]. If the treatment administered is ineffective and the patient's recovery is prevented, palliative therapy should be considered. Palliative patients with disseminated abdominal and pelvic cancer are particularly susceptible to impairment of gastrointestinal function caused primarily by the disease but also by the treatment.

Attention should also be paid to malignant bowel obstruction (MBO), which occurs in 6–13% of patients with gastric cancer [2] and 20–50% of patients with ovarian cancer, as well as in patients with colorectal [3] and pancreatic cancer, but may be a result of primarily extra-abdominal malignancy as well. Malignant bowel obstruction leads to complications such as chronic pain, bloating, nausea and vomiting, as well as the inability to eat [3]. This impairs the absorption of nutrients and leads to the deterioration of nutritional status and malnutrition. The consequences of malnutrition and not the disease itself are the cause of death in 10–20% of cancer patients [4]. MBO worsens the patient's prognosis and makes palliative oncological treatment impossible. Moreover, water retention in palliative cancer patients disturbs several parameters, i.e., body mass and body mass index (BMI), and has a negative impact on survival [5]. In addition to chemotherapy, which is proven as a palliative therapy [6] to prolong survival [7], nutritional support should also be provided, giving a synergistic effect. In patients with malignant bowel obstruction, parenteral nutrition (PN) can be an effective method to improve the patient's nutritional status, preferably administered as home parenteral nutrition. HPN improves prognosis and quality of life, and, in the majority of cases, makes oncological treatment reasonable [5]. Although HPN can be helpful in patients with malignant bowel obstruction, it should be borne in mind that patients qualified to receive this procedure require hospitalisation for days or weeks, during which the patient's medical status is optimised, a central intravenous access is inserted, adequate training is conducted, and the composition of the nutritional admixture is adapted to the patient's needs. The ESPEN guidelines [8] recommend that parenteral nutrition should be considered if survival is estimated to be greater than 2–3 months. However, this guideline is controversial due to the difficulty in estimating patient survival time. The question arises as to how accurately specialists can really determine the survival time of patients and whether there are tools that could facilitate this. In this study, attention was focused on nutritional status and nutritional risk assessment tools such as the Subjective Global Assessment (SGA) scale, laboratory tests, the Nutritional Risk Index (NRI), the Geriatric Nutritional Risk Index (GNRI) and the Prognostic Nutritional Index (PNI) to consider them as factors of survival for better assessment and decision making on possible nutritional treatment in palliative care patients with malignant bowel obstruction.

2. Materials and Methods

2.1. Setting and Study Design

This study was conducted at the Polish national reference centre for home parenteral nutrition (HPN) between January 2018 and August 2023. The research employed a retrospective observational review design, where data were collected from hospitalisation records during the HPN qualification and from all medical records of outpatient visits to the HPN centre. The study protocol received approval from the Ethics Committee of the Medical University of Warsaw (AKBE/348/2023), ensuring compliance with ethical standards in research.

2.2. Sample

Participants included in this study were all consecutive adult palliative cancer patients with malignant bowel obstruction who were qualified for HPN treatment at the reference centre between January 2018 and August 2023. Eligibility for inclusion required that patients' cancers were a direct cause of the qualification for home parenteral nutrition, with conditions not amenable to curative treatment due to advanced tumour progression and significant impairment of gastrointestinal function. Patients were excluded if their cancers had not spread, were not the primary cause of HPN qualification, or were not directly related to gastrointestinal function impairment. After applying these criteria, a total of 200 patients formed the study cohort. The detailed process of qualifying patients for the study is shown in Figure 1.

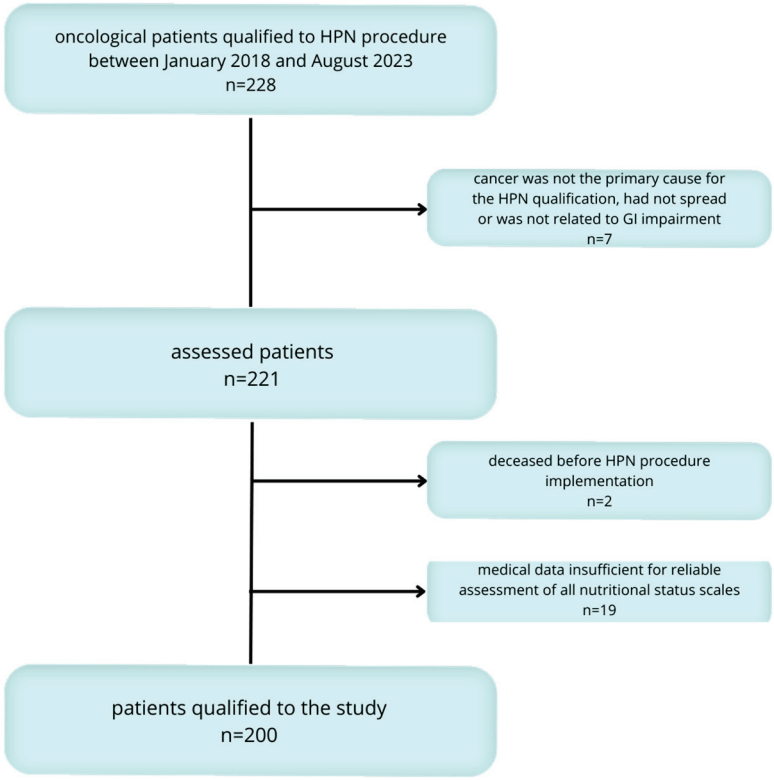

Figure 1. Flow chart: patients who met the inclusion criteria and qualified for the study group.

2.3. Approach to Home Parenteral Procedure

The criteria for eligibility for HPN included intestinal failure, the possibility of using parenteral nutrition (possibility of central venous access, care, patient co-operation), potential survival of more than 2 months, absence of treatment requiring hospitalisation (e.g., advanced pain management), and ethical reasons for further therapy (mainly quality of life).

Qualification for home parenteral nutrition included a nutritional assessment, education and training of caregivers, a physical examination, blood tests, a prescription, and adjustment of a parenteral formula. If the patient did not already have a central intravenous access, a vascular port or tunnelled central venous catheter (CVC) was implemented. A parenteral nutrition formula was prepared individually by the hospital pharmacy or the patient's caregiver according to the medical prescription. Ready-to-use (RTU) formulas were prescribed only to individual patients.

The nutritional assessment included measurements of body weight and height, a full medical examination and screening of nutritional status based on the Subjective Global Assessment (SGA) and was performed by a trained clinical dietitian in the first 24 h after admission to the clinical nutrition unit. After discharge from hospital, patients had mandatory follow-up visits to the outpatient clinic every three months, or more frequently if adverse symptoms or complications arose.

2.4. Data Collection and Nutritional Status Evaluation

Data collected included gender, age at the time of qualification for HPN, date of HPN commencement, date of death or withdrawal of HPN, type of cancer and stage of progression, anthropometric measurements (weight, height), BMI, unintentional weight loss in the 6 months prior to starting nutritional treatment, laboratory tests (serum albumin level, lymphocytes, leucocytes, total protein and C-reactive protein), data from the Subjective Global Assessment, information on the nutritional programme and the content of nutritional admixtures such as volume (mL), energy (kcal), osmolality, amino acids (g), fat (kcal), volume of fat emulsion (mL) and non-protein energy (kcal).

BMI categories for patients < 65 years were classified according to the CDC criteria [9]: BMI < 18.5 kg/m^2—underweight; BMI $\leq$ 25 kg/m^2—normal weight; BMI $\geq$ 25 kg/m^2—overweight. For patients over 65 years, Lipschitz criteria [6] were used: BMI < 22 kg/m^2—underweight; BMI $\leq$ 27 kg/m^2—normal weight; BMI $\geq$ 27 kg/m^2—overweight. The results of the Subjective Global Assessment were interpreted as follows: A—well nourished; B—moderately (or suspected of being) malnourished; C—severely malnourished; D—high risk of malnutrition.

In addition to analysing the results of the SGA scale and BMI classification, the criteria of the Global Leadership Initiative on Malnutrition (GLIM) were used to assess the nutritional status of patients [10]. The loss of muscle mass was assessed using the physical examination data in the SGA scale and the decrease in the functional capacity of muscle mass (physical condition and abilities of the patients). The presence of inflammation was determined when the C-reactive protein (CRP) level exceeded 10 mg/L.

All of the following nutritional indexes were calculated during data collection and analysed by a second clinical dietitian.

Based on serum albumin level, body weight and ideal body weight, the Nutritional Risk Index was calculated. Ideal body weight was calculated based on the Lorentz formula [11]:

$$\text{Ideal body weight men} = (\text{height [cm]} - 100 - ((\text{height} - 150)/4)$$

$$\text{Ideal body weight women} = (\text{height [cm]} - 100 - ((\text{height} - 150)/2)$$

The Nutritional Risk Index was calculated using the following formula [12]:

$$\text{NRI} = (1.519 \times \text{serum albumin})\ (\text{g/L}) + 41.7 \times (\text{present weight/ideal body weight})$$

The patients with an NRI score > 100 were considered to be at no nutritional risk, 97.5–100 as at mild risk, 83.5–97.5 at moderate and <83.5 at major nutritional risk.

For patients who were over 65 years old, the Geriatric Nutritional Risk Index was calculated. The GNRI was calculated based on the formula proposed by Bouilanne et al. [13]:

$$\text{GNRI} = (1.489 \times \text{serum albumin})\ (\text{g/L}) + 41.7 \times (\text{present weight/ideal bodyweight})$$

The patients with a GNRI score > 98 were at no nutritional risk, $\leq$98 at low risk, 82 to <92 at moderate risk and <82 at major risk.

Also, the Prognostic Nutritional Index was calculated based on the following formula [14]:

$$\text{PNI} = 10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total peripheral lymphocyte count (mL)}$$

The cut-off points for PNI were set as follows: PNI < 35—severe risk; PNI < 38—moderate risk; PNI > 38—normal risk.

2.5. Statistical Analysis

Statistical analyses were conducted using STATISTICA version 13.3 (TIBCO Software, Palo Alto, CA, USA). Descriptive statistics summarised the demographic and clinical characteristics of the study population, with means and standard deviations (SDs) calculated for continuous variables like age, height, weight, and BMI, and the median (Mdn) and semi-interquartile range (IQR/2) reported where appropriate. Similar descriptive methods were applied for laboratory test results (including serum albumin, lymphocytes, leukocytes, CRP, and total protein) and for summarising data on patients' nutritional programs (volume, energy, osmolarity, amino acids, fat content). The risk of malnutrition was assessed using indices such as SGA, NRS, PNI, Total Lymphocyte Count, NRI, and GNRI, presented in percentage format. Survival analysis utilised the Kaplan–Meier method, calculating survival time from the start of home parenteral nutrition. Multivariate Cox regression anal-

ysis explored predictors of patient survival, such as PNI and NRI/GNRI scores. Receiver Operating Characteristic (ROC) curves, utilising the Youden Index to establish the optimal cut-off points, determined these indices' predictive accuracy for patient survival.

All tests were two-sided, and a *p*-value of less than 0.05 was considered statistically significant.

3. Results

A total of 200 patients met the inclusion criteria for this study. The mean age of the group was 58.9 ± 13 years (women 57.09, men 62.77; $p = 0.004$). The majority of patients included in the study were women—67.5%. All patients were classified according to tumour location as follows: 32.5% ($n = 65$) gynaecological cancers, 32.0% ($n = 64$) upper digestive tract cancers, 24% ($n = 48$) lower gastrointestinal tract cancers and 11.5% ($n = 23$) other cancers with a different or unknown origin. Detailed characteristic of the group, including age at qualification, height, weight, and body mass index, is presented in Table 1.

Table 1. Characteristics of the study group including age, height, weight, and body mass index (BMI).

	N	M	SD	Mdn	IQR/2	Min	Max	CV [%]
Age at qualification	200	58.9	13.0	61.0	9.0	19.0	88.0	22.1
Height (cm)	200	166.9	9.1	165.0	7.0	145.0	190.0	5.4
Weight (kg)	200	56.6	11.7	55.0	8.5	30.4	86.0	20.7
BMI	200	20.3	3.9	19.8	2.4	12.7	32.8	19.4

M—mean; SD—standard deviation; Mdn—median; IQR/2—semi-interquartile range; CV—coefficient of variation.

In addition to the anthropometric examinations, the results of the laboratory tests were also taken into account, including serum albumin levels, lymphocytes, leucocytes, C-reactive protein and total protein, which are listed in Table 2. All laboratory tests were performed prior to the start of nutritional therapy at the patient's admission. The C-reactive protein values showed that the majority of patients (93.0%) had severe inflammation on admission to hospital. The majority of them had a subclinical infection of the vascular port.

Table 2. Characteristics of the study group including albumin level, lymphocytes, leukocytes, C-reactive protein (CRP) and total protein.

	N	M	SD	Mdn	IQR/2	Min	Max	CV [%]
Serum albumin (g/dL)	200	2.67	0.78	2.60	0.59	1.25	5.40	29.06
Lymphocytes (tys/μL)	200	1.28	0.66	1.17	0.39	0.16	4.56	51.71
% Lymphocytes	200	18.30	11.50	15.76	7.10	1.93	68.51	62.87
Leukocytes (tys/μL)	200	8.70	4.99	7.71	2.57	1.90	36.80	57.31
C-reactive protein (mg/L)	200	69.51	76.15	43.2	45.96	0.40	497.44	109.5
Total protein (g/dL)	198	6.41	1.04	6.40	0.72	3.10	8.90	16.20

M—mean; SD—standard deviation; Mdn—median; IQR/2—semi-interquartile range; CV—coefficient of variation.

All patients had individually compiled All-in-One (AIO) nutritional admixtures. One hundred and ninety-five patients (88.5%) received their nutritional admixture prepared and premixed in the hospital pharmacy. The data on the nutritional programme are shown in Table 3.

Table 3. Characteristics of the study group including data related to the nutrition programme (volume, energy, osmolality, amino acids, calories of fat, volume of fat emulsion, non-protein energy).

	N	M	SD	Mdn	IQR/2	Min	Max	CV [%]
Volume (mL)	200	2452.8	377.7	2600.0	250.0	1000.0	3600.0	15.4
Energy (kcal)	200	1356.9	138.7	1360.0	59.3	715.0	1915.0	10.2
Mosm/L	200	844.0	131.2	824.0	58.9	145.0	1450.0	15.6
Amino acids (g)	200	49.1	7.7	50.0	7.3	17.0	62.5	15.6
Fat (kcal)	200	242.9	61.4	200.0	50.0	100.0	600.0	25.3
Volume of fat emulsion (mL)	200	129.9	35.6	100.0	25.0	50.0	300.0	29.0
Non-protein energy (kcal)	199	1155.6	145.8	1166.0	66.0	132.0	1665.0	12.6

M—mean; SD—standard deviation; Mdn—median; IQR/2—semi-interquartile range; CV—coefficient of variation.

Assessment of nutritional status according to GLIM criteria showed that 88% (n = 176) of patients were malnourished on hospital admission. The results of the assessment of nutritional status and nutritional risk, assessed with SGA, PNI, Total Lymphocyte Count (TLC), NRI and GNRI, are shown in Table 4.

Table 4. Summary of SGA, PNI, TLC, NRI and GNRI results.

Variable		N	%
SGA (n = 200)			
	A	1	0.50
	B	73	36.50
	C	16	8.00
	D	110	55.00
PNI (n = 200)			
	normal	57	28.50
	moderate risk	24	12.00
	severe risk	119	59.50
Total lymphocyte Count (n = 200)			
	nourished	29	14.50
	moderate malnutrition	125	62.50
	severe malnutrition	46	23.00
NRI (n = 122)			
	no risk	4	3.28
	mild risk	21	17.21
	moderate risk	97	79.51
GNRI (n = 78)			
	normal	5	6.41
	low risk	4	5.13
	moderate risk	17	21.79
	high risk	52	66.67

Patients who were classified as "A" using the SGA (n = 1), "no risk" using the NRI (n = 4) and "normal" using the GNRI (n = 5) were not included in further analysis, and only patients who were at high risk of malnutrition or malnourished on admission to hospital were included.

The overall survival (OS) curve for the study group is shown in Figure 2 and detailed data is presented in Table 5.

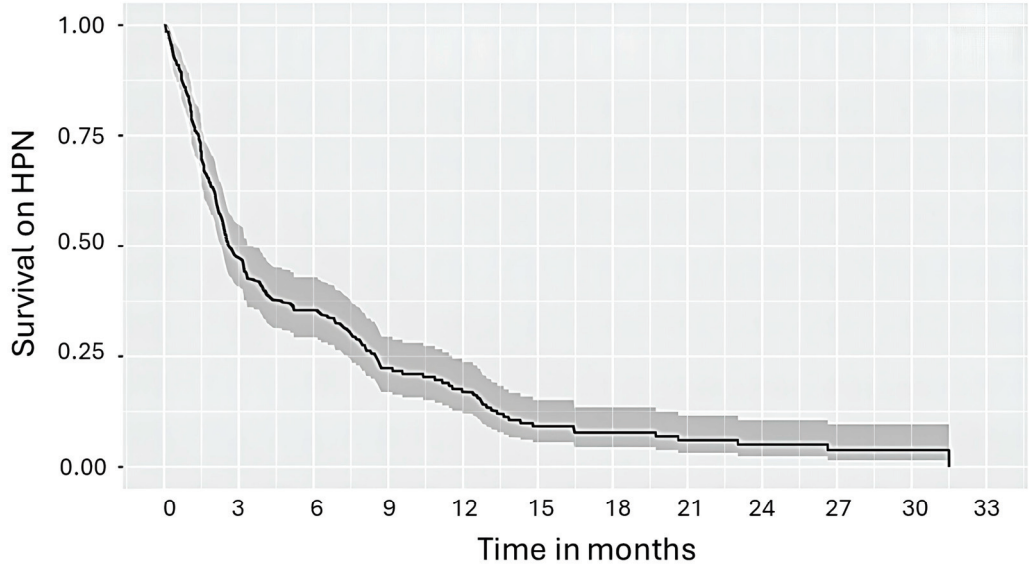

Figure 2. Kaplan–Meier curve for overall survival in palliative oncological patients with malignant bowel obstruction.

Table 5. Details for Kaplan–Meier curve including 3–6–9–12-month survival.

				95% Confidence Interval	
Time	**Number at Risk**	**Number of Events**	**Survival**	**Lower**	**Upper**
3	89	104	47.3 %	40.8 %	54.9 %
6	61	22	35.5 %	29.3 %	42.9 %
9	34	21	22.3 %	16.9 %	29.5 %
12	24	8	16.9 %	12.1 %	23.7 %

The mean survival time of the patients was 75 days. The probability of survival was also assessed using PNI and NRI/GNRI scoring as possible predictors of patient survival. The results of multivariate Cox regression analysis showed that the Prognostic Nutritional Index score was positively associated with the risk of death ($p < 0.001$, HR = 0.950; 95%CI, 0.932–0.968).

Figure 3 shows the probability of survival as a function of the Prognostic Nutritional Risk Index. The survival time in all figures is given in days.

As ESPEN states that the estimated survival time for patients included in the HPN procedure should be at least 90 days (three months), the relationship between the PNI score and the three-month survival time was investigated. The probability of three-month survival was 77.9% for patients classified with a "normal" PNI, 57.6% for "moderate risk" and 31.1% for "severe risk".

As the Nutritional Risk Index and Geriatric Nutritional Risk Index are age-dependent indicators of the risk of malnutrition, the analysed group was divided as follows: NRI, patients < 65 years old ($n = 122$); GNRI ≥ 65 years old ($n = 78$). NRI/GNRI scoring was also positively related to the risk of death ($p < 0.001$, HR = 0.979; 95%CI 0.969–0.990). Figure 4 shows the probability of survival as a function of the Nutritional Risk Index or Geriatric Nutritional Risk Index.

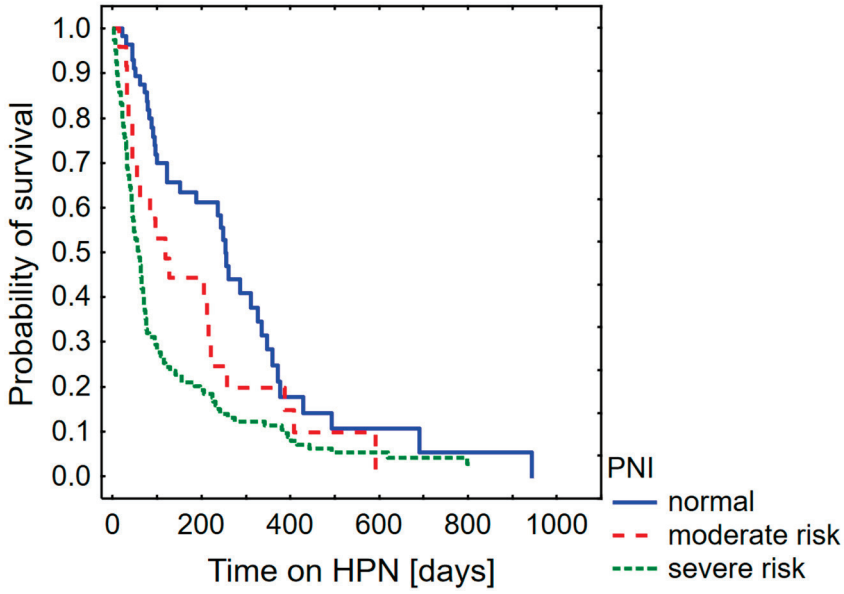

Figure 3. Probability of survival in palliative oncological patients with malignant bowel obstruction considering Prognostic Nutritional Index (PNI).

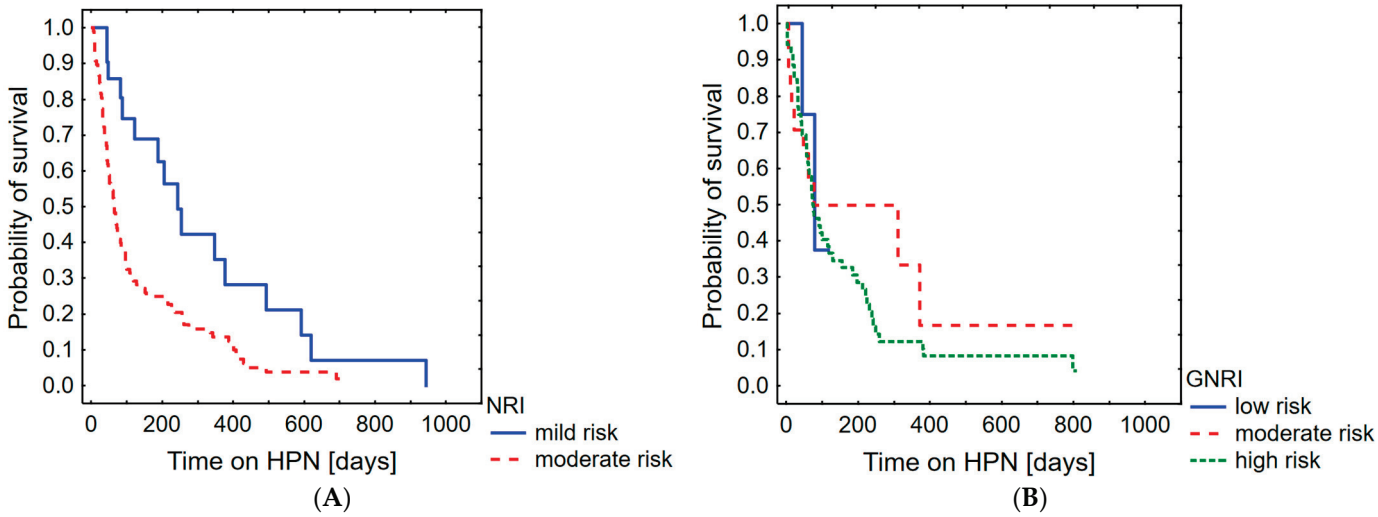

Figure 4. Probability of survival in palliative oncological patients with malignant bowel obstruction including NRI (**A**) and GNRI (**B**).

There was no significant correlation between the Geriatric Nutritional Risk Index values and the probability of survival; however, for the Nutritional Risk Index, the results showed that the "moderate" group had a significantly lower probability of survival than the "mild" group ($p = 0.001$). The probability of surviving three months was 74.6% in the mild-risk group and 38.8% in the moderate-risk group.

The presence of a relationship between nutritional status, taking into account criteria such as GLIM, SGA, BMI and survival time on home parenteral nutrition, was also analysed. The results for these criteria are shown in Figure 5. There was no significant difference between the groups; GLIM $p = 0.922$, SGA $p = 0.083$, BMI $p = 0.092$.

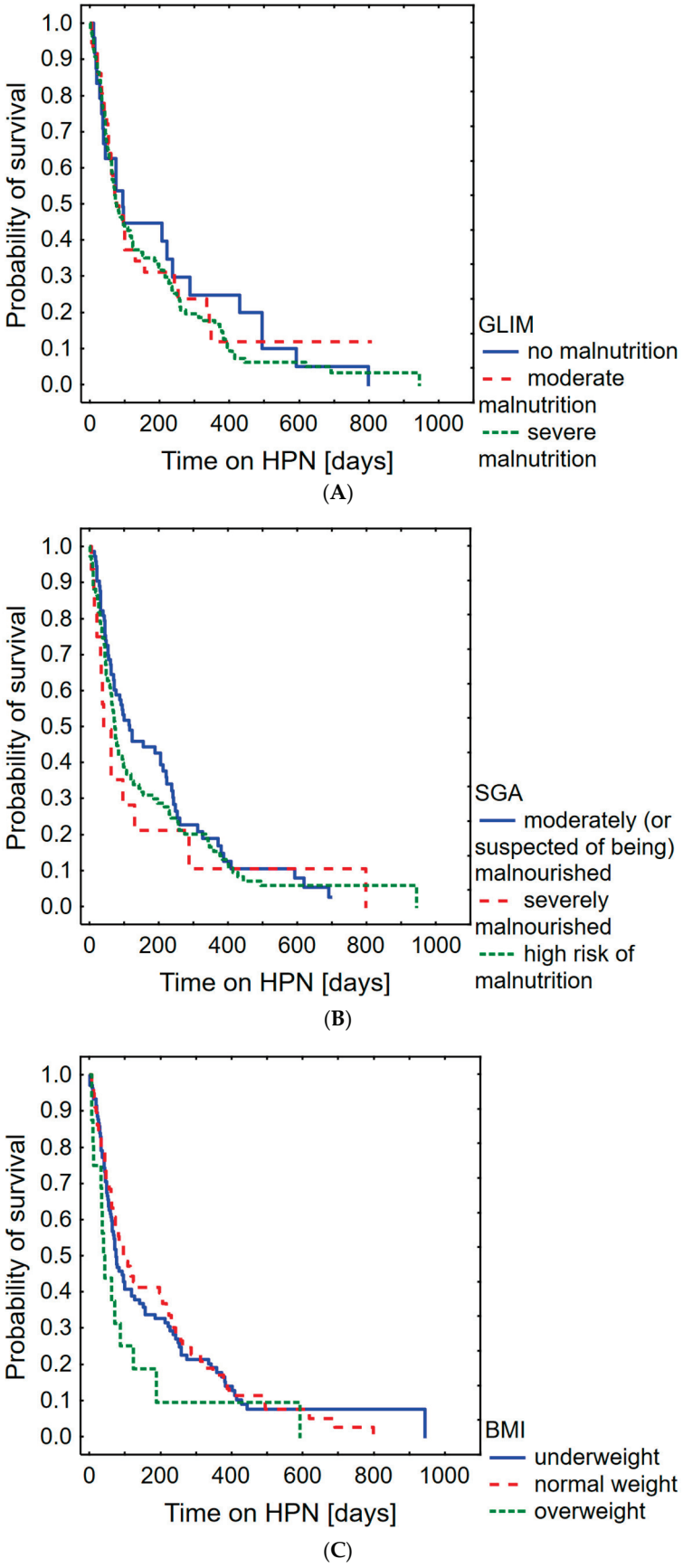

Figure 5. Probability of survival in palliative oncological patients with malignant bowel obstruction depending on GLIM (**A**), SGA (**B**) and BMI (**C**).

The ROC curves showed the best cut-off points for the Prognostic Nutritional Index and the Nutritional Risk Index, which are presented in Figure 6. For the PNI, the cut-off point was 35.25: $p < 0.001$ (AUC = 0.681; 95%CI 0.605–0.756). At this cut-off point, the test was shown to have a moderate ability to detect disease states (3-month survival) and a good ability to detect non-disease states (no 3-month survival). Further details on the ROC parameters can be found in Table 6.

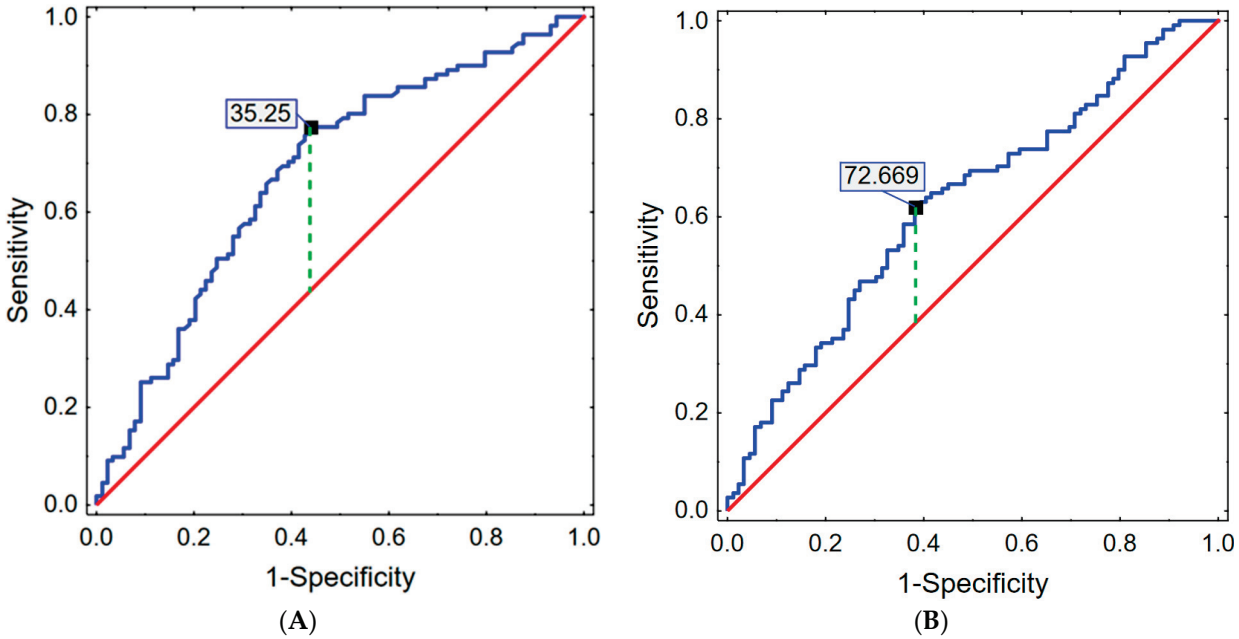

Figure 6. Receiver Operating Characteristic (ROC) curve for PNI (**A**) and NRI (**B**) scoring.

Table 6. Parameters of ROC curve for Prognostic Nutritional Index (cut-off point = 35.25).

True Positives	False Positives	False Negatives	True Negatives	Sensitivity	Specificity	Accuracy	PPV	NPV	LR (+)	LR (−)	Youden Index
51	27	43	96	0.543	0.780	0.677	0.654	0.691	2.472	0.586	0.323

PPV—Positive Predictive Value; NPV—Negative Predictive Value; LR (+)—Positive Likelihood Ratio; LR (−)—Negative Likelihood Ratio.

For NRI, the cut-off point was 72.67: $p = 0.001$ (AUC = 0.626; 95%CI 0.549–0.704). Detailed data are presented in Table 7.

Table 7. Parameters of ROC curve for Nutritional Risk Index (cut-off point = 72.67).

True Positives	False Positives	False Negatives	True Negatives	Sensitivity	Specificity	Accuracy	PPV	NPV	LR (+)	LR (−)	Youden Index
56	43	35	71	0.615	0.623	0.620	0.566	0.670	1.631	0.618	0.238

PPV—Positive Predictive Value; NPV—Negative Predictive Value; LR (+)—Positive Likelihood Ratio; LR (−)—Negative Likelihood Ratio.

4. Discussion

The main objective of the present study was to investigate whether the nutritional status of palliative cancer patients receiving home parenteral nutrition can be used as a prognostic factor for survival. According to a recent scoping review [15], clinical practice guidelines for nutritional assessment are not uniform with regard to the choice of specific tools and criteria. In this study, both the most commonly used tools, i.e., the body mass

index and the Subjective Global Assessment, and those less commonly used in clinical practice, such as the GLIM criteria, the Nutritional Risk Index, the Geriatric Nutritional Risk Index and the Prognostic Nutritional Risk Index, were considered. The use of these indicators enabled not only an accurate assessment of the nutritional status of patients but also a review of whether they can be used as a tool to better estimate patient survival in the context of initiating nutritional therapy.

In this study, 99.5% of patients were malnourished or at high risk of malnutrition according to the results of the SGA scale, and 88% of patients were malnourished based on the GLIM criteria. In the meta-analysis presented by Matsui et al. [10], which focused on treatment outcomes in cancer patients and was based on the GLIM criteria for malnutrition, the prevalence of malnutrition ranged between 30 and 40% in most studies.

The ESPEN guideline (No. 7) for clinical nutrition in cancer stated that nutritional therapy should be implemented when patients are not yet severely malnourished [4]. This indicates an urgent need for more rapid nutritional interventions focusing on the assessment of nutritional status, particularly in the context of the impact of malnutrition on the treatment process. Another ESPEN recommendation (No. 4) states that parenteral nutrition should be implemented in patients with an estimated survival time of more than one to three months [16]. A meta-analysis by Naghibi et al. [17], which included patients with palliative malignancy and inoperable bowel obstruction (n = 244), found a mean survival time of 116 days. However, in our study, the median survival of patients with disseminated cancer in a palliative state was only 75 days, which does not meet the ESPEN criteria.

It is also important to consider how we can improve the accuracy of survival time estimates. This study shows that neither BMI values nor Subjective Global Assessment scores are good tools for estimating survival time in the analysed patient group (BMI: p = 0.092, SGA: p = 0.083). Similar results for BMI were reported by Nazari et al. [18] and Przekop et al. [19] in patients with head and neck cancer. On the other hand, Chong et al. [20] reported that the modified Patient-Generated Subjective Global Assessment (mPG-SGA) is a valuable tool for survival prognosis in patients with malignant cancer involving two or more organs. This is consistent with the findings of Carvalho et al. [21], who reported that Patient-Generated SGA (PG-SGA) scores are directly related to survival in palliative cancer patients. The results of Huo et al. [22] show that the modified version has similar predictive power for survival in patients with lung cancer as the PG-SGA and the GLIM, suggesting that all three instruments are applicable in this patient group. This may suggest that the Patient-Generated Subjective Global Assessment (both basic and modified) is more suitable than the Subjective Global Assessment for prognosing survival prediction in the oncological population. Nevertheless, the study by Crestani et al. [23] showed that the SGA has good accuracy and sufficient specificity (>80%) in the diagnosis of malnutrition compared to the PG-SGA, demonstrating its usefulness in clinical practice.

The Global Leadership Initiative on Malnutrition criteria were also not found to be a good tool for predicting patient survival (p = 0.922). However, as shown in a meta-analysis by Yin et al. [24], GLIM-defined malnutrition has an impact on all-cause mortality in the oncological population, and these criteria are highly recommended for the assessment of nutritional status due to the use of both phenotypic and aetiological criteria [25], making them highly relevant in daily clinical practice.

Although albumin levels are not a good indicator of nutritional status [26,27], they proved useful in this study as they were used to calculate indicators of nutritional status such as the Nutritional Risk Index, the Geriatric Nutritional Risk Index and the Prognostic Nutritional Index. This study showed significant results with regard to the NRI. Patients classified in the "moderate" group had a lower probability of survival than those classified as "mild risk" ($p < 0.001$). Similar conclusions were reached by Chaufour-Andre et al. [28] and Zhou et al. [29]. Both studies found that a low NRI was associated with poorer patient outcomes. A paper by Chen et al. [30], which focused on patients with breast cancer, highlighted that overall survival in this group was remarkably longer when the NRI was

higher. It is therefore worth considering incorporating the Nutritional Risk Index into daily clinical practice, although it should be borne in mind that it only applies to patients under the age of 65.

Particular attention should be paid to the Prognostic Nutritional Index, which is not used in daily practice. The analysis showed that patients with a "normal" PNI score had a 75.2% chance of surviving for three months. Zhang et al. [31] showed in their study of patients with gastrointestinal cancer that those with a higher PNI score had a higher survival rate ($p < 0.001$). Similar conclusions were drawn in Bullock et al.'s [32] paper, which focused on elderly patients (>70 years) with cancer. This suggests that the Prognostic Nutritional Index can be used to estimate patient survival with a lower margin of error. It should also be emphasised that the Prognostic Nutritional Index is a universal indicator compared to the Nutritional Risk Index, as it is applicable to any age group of adult patients. The use of NRI and PNI as indicators in the context of deciding whether to refer a patient for home parenteral nutrition should be considered, as this may minimise the risk of underdiagnosis and overtreatment.

It is generally recognised that the primary aim of nutritional therapy is to improve the patient's nutritional status to such an extent that it also has a positive effect on the treatment outcome and QoL. However, it should not be forgotten that this is still a medical procedure that not only places a physical but also a psychological burden on the patient, requires hospitalisation to prepare for the procedure, and can be associated with complications that just as often end in hospitalisation and reduce the quality of life remaining [33]. It is also important to make an assessment after optimising the patient's condition and to plan the optimal method of parenteral nutrition (especially AIO). The use of RTU admixtures and additional fluids leads to poorer outcomes as RTU is sub-optimally balanced and contains too much fat, and the separation of the nutritional mixture from the fluids shortens the infusion time and accelerates the water infusion time, leading to poorer bioretention and metabolism of macronutrients and having a tendency to cause oedema and water retention as a result of rapid fluid infusion.

Ultimately, the question arises as to where the ethical line is drawn between using nutritional therapy to improve the patient's condition and another medical intervention that may shorten the patient's final days.

Our study had some limitations. Due to its retrospective design, we did not have access to detailed medical records from other medical institutions that included the date of diagnosis and the treatment given. In addition, some patients were transferred to hospice and were no longer in the care of the HPN centre (they were classified as weaned from HPN), so we had no current information on their survival.

5. Conclusions

This study has shown that there is a high need for early nutritional intervention, particularly in relation to the consequences of malnutrition, which directly increases the risk of poorer prognosis and death.

The nutritional status of the patient can be one of the most important elements in the assessment of estimated survival time and should be carried out with validated instruments.

The Nutritional Risk Index and Prognostic Nutritional Index have been shown to be good indicators for assessing the nutritional status of patients in relation to their survival time, although the PNI may prove to be the more versatile tool due to the lack of age restriction.

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Informed Consent Statement: This study was conducted retrospectively.

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Assessing Nutritional Status in Gastric Cancer Patients after Total versus Subtotal Gastrectomy: Cross-Sectional Study

Fawzy Akad [1,2], Bogdan Filip [3,*], Cristina Preda [4], Florin Zugun-Eloae [2,5], Sorin Nicolae Peiu [6], Nada Akad [7], Dragos-Valentin Crauciuc [2], Ruxandra Vatavu [2], Liviu-Ciprian Gavril [2], Roxana-Florentina Sufaru [2] and Veronica Mocanu [1,8,*]

1 Center for Obesity BioBehavioral Experimental Research, "Grigore T. Popa" University of Medicine and Pharmacy, 700115 Iasi, Romania; fawzy_akad@umfiasi.ro
2 Department of Morpho-Functional Sciences I, "Grigore T. Popa" University of Medicine and Pharmacy, 700115 Iasi, Romania; eloae.zugun@umfiasi.ro (F.Z.-E.); dragos.crauciuc@umfiasi.ro (D.-V.C.); ruxandra-vatavu@umfiasi.ro (R.V.); liviu.gavril@umfiasi.ro (L.-C.G.); roxana-florentina.sufaru@umfiasi.ro (R.-F.S.)
3 Department of Surgery I, "Grigore T. Popa" University of Medicine and Pharmacy, 700115 Iasi, Romania
4 Department of Medical Sciences II (Endocrinology), "Grigore T. Popa" University of Medicine and Pharmacy, 700115 Iasi, Romania; cristina.preda@umfiasi.ro
5 Transcend Research Center, Regional Oncology Institute, 700483 Iasi, Romania
6 Department of Vascular Surgery, "Grigore T. Popa" University of Medicine and Pharmacy, 700115 Iasi, Romania; sorin-nicolae.peiu@umfiasi.ro
7 Department of Medical Sciences II (Nephrology), "Grigore T. Popa" University of Medicine and Pharmacy, 700115 Iasi, Romania; akad_nada@d.umfiasi.ro
8 Department of Morpho-Functional Sciences II, "Grigore T. Popa" University of Medicine and Pharmacy, 700115 Iasi, Romania
* Correspondence: bogdan.filip@umfiasi.ro (B.F.); veronica.mocanu@umfiasi.ro (V.M.)

Abstract: Gastric cancer (GC) remains a significant global health concern, ranking as the third leading cause of cancer-related deaths. Malnutrition is common in GC patients and can negatively impact prognosis and quality of life. Understanding nutritional issues and their management is crucial for improving patient outcomes. This cross-sectional study included 51 GC patients who underwent curative surgery, either total or subtotal gastrectomy. Various nutritional assessments were conducted, including anthropometric measurements, laboratory tests, and scoring systems such as Eastern Cooperative Oncology Group/World Health Organization Performance Status (ECOG/WHO PS), Observer-Reported Dysphagia (ORD), Nutritional Risk Screening-2002 (NRS-2002), Patient-Generated Subjective Global Assessment (PG-SGA), and Simplified Nutritional Appetite Questionnaire (SNAQ). Serum carcinoembryonic antigen (CEA) levels were significantly higher in the subtotal gastrectomy group. Nutritional assessments indicated a higher risk of malnutrition in patients who underwent total gastrectomy, as evidenced by higher scores on ORD, NRS-2002, and PG-SGA. While total gastrectomy was associated with a higher risk of malnutrition, no single nutritional parameter emerged as a strong predictor of surgical approach. PG-SGA predominantly identified malnutrition, with its occurrence linked to demographic factors such as female gender and age exceeding 65 years.

Keywords: gastric cancer; gastrectomy; malnutrition; nutritional assessment; Nutritional Risk Screening-2002; Patient-Generated Subjective Global Assessment

1. Introduction

Gastric cancer (GC) poses a substantial global public health challenge, ranking as the third leading cause of cancer-related deaths, even though its incidence has decreased over the past five decades. The occurrence of GC exhibits regional variations, and this diversity is linked to a range of factors, including infectious, environmental, and genetic

characteristics [1]. It is a tumor often linked to malnutrition and various nutritional deficiencies. The identification and effective management of these nutritional issues can play a crucial role in enhancing the quality of life and increasing the survival rates of affected patients [2]. The studies have found the prevalence of malnutrition in GC to be around 60%, although it varies widely depending on the tumor stage, type of treatment received, and the nutritional assessment (NA) tool used. Malnutrition in these patients, as with other oncological processes, results in a worse prognosis and quality of life, as well as a negative clinical impact (higher rates of infections, toxicity of treatments, complications, hospital stay, etc.) and financial impact [2,3]. The standard treatment for GC involves curative resection and perioperative adjuvant treatment. The surgical approach for GC is either total gastrectomy (TG) or subtotal gastrectomy (SG). These surgical procedures can alter the gastrointestinal anatomy and physiological function of patients, impacting nutrient absorption and giving rise to gastrointestinal symptoms [4]. Despite improvements in prognosis, over half of the patients experience recurrent disease. Identifying useful prognostic factors is crucial to enhance outcomes. The perioperative nutritional and inflammatory status influences short-term and long-term oncological outcomes, impacting complications and treatment continuation.

Following surgery, patients commonly encounter reduced appetite, early satiety with minimal food intake, or gastroesophageal reflux. They may also manifest symptoms like nausea, vomiting, bloating, abdominal discomfort, and diarrhea or encounter difficulties with swallowing, known as dysphagia [5]. Intense symptoms can contribute to heightened psychological distress and have an adverse effect on the patient's dietary intake. Emotional distress, symptom disturbance, and inflammation associated with cancer can contribute to protein-energy wasting, resulting in a decrease in overall body weight [6]. The distinction between weight loss and cancer cachexia is essential to make, the latter being represented by loss of skeletal muscle mass and reduced energy intake. Cancer cachexia cannot be completely reversed by standard nutritional support and results in a gradual decline in physical function. Its pathophysiology involves a disturbance in protein and energy balance, typically caused by a combination of reduced food intake and abnormal metabolism [7].

Various NA tools have been developed for patients with GC, offering clinical advantages like accessibility and cost-effectiveness. However, understanding the characteristics of each tool is essential for informed clinical use [8]. Most frequently, these systems relied on objective measurements like oral energy intake, body weight, weight loss over time, subcutaneous fat loss, muscle wasting, serum protein levels, and immune competence. Subjective NA scoring systems, incorporating a variety of measurements, have been developed to enhance the sensitivity and specificity of nutritional status assessments [9]. The most used NA tools used are the Eastern Cooperative Oncology Group/World Health Organization Performance Status (ECOG/WHO PS), Observer-Reported Dysphagia (ORD), Nutritional Risk Screening-2002 (NRS-2002), Patient-Generated Subjective Global Assessment (PG-SGA) and Simplified Nutritional Appetite Questionnaire (SNAQ). While body mass index (BMI) is well-suited for population-level studies, its use can lead to inaccuracies in assessing adiposity. This is because the calculation does not differentiate between lean muscle mass and fat mass [10].

This research aimed to assess the frequency of postoperative malnutrition among individuals with GC who underwent either total or subtotal gastrectomy. Additionally, it examined the associations between measurable factors like laboratory results and subjective scoring systems used to evaluate nutritional status during the postoperative recovery phase.

2. Materials and Methods

2.1. Study Design and Patients

The study was conducted prospectively and included a total of 51 patients who had undergone curative surgery for GC. Within this cohort, 22 patients underwent total gastrectomy, while 29 patients underwent subtotal gastrectomy. The enrolled patients were provided with standard nutritional supplements from the hospital throughout both the

perioperative and postoperative periods. The participants were recruited from hospitalized patients at the Regional Institute of Oncology in Iasi. The patient selection was based on criteria to enhance homogeneity (age, gender, body mass index).

The project plan required a group of cooperative patients, with the diagnosis of GC being a crucial criterion for participation in the study.

2.2. Serological Measurements

Blood samples were drawn from the cubital vein for testing, which encompassed the analysis of serum protein, albumin, cell blood count, serum electrolytes Na^+, K^+, urea, creatinine, tumoral markers carcinoembryonic antigen (CAE), and carbohydrate antigen 19-9 (CA 19-9). Standard laboratory techniques were employed to gather the laboratory data.

2.3. Nutritional Assessments

The patients underwent evaluations on the following parameters: anthropometric measurements, laboratory data, the Eastern Cooperative Oncology Group/World Health Organization Performance Status (ECOG/WHO PS), Observer-Reported Dysphagia (ORD), Nutritional Risk Screening-2002 (NRS-2002), Patient-Generated Subjective Global Assessment (PG-SGA), and Simplified Nutritional Appetite Questionnaire (SNAQ).

2.3.1. Eastern Cooperative Oncology Group/World Health Organization Performance Status

ECOG/WHO PS is a scale that ranges from zero ("fully active") to three ("capable of only limited self-care") and up to five ("dead"). Recognizing the significant insights functional status information can offer for cancer research populations, there is global interest in integrating performance measures like ECOG/WHO PS into routine follow-ups.

2.3.2. Dysphagia Score

ORD was scored by the physician treating the patient. It is scored 0–4 (a score of 0 denotes no dysphagia; a score of 1: symptomatic, able to eat regular diet; a score of 2: symptomatic, altered eating/swallowing, I.V. fluids indicated < 24 h; a score of 3: symptomatic, severely altered eating/swallowing with inadequate caloric or fluid intake, I.V. fluids or FT indicated > 24 h; and a score of 4: life-threatening, due to obstruction or perforation).

2.3.3. Nutritional Risk Screening-2002

The NRS-2002 was endorsed by the European Society of Parenteral and Enteral Nutrition as the preferred screening and assessment method for hospital patients. It reflects the imbalance between the metabolic stress demand and normal nutritional intake. It includes the following components: assessment of food intake, anthropometric indicators, general health assessment, acute assessment, and assessment of involuntary weight loss. It also includes an age adjustment for patients aged over 70 years (+1). The questionnaire uses these items to calculate the overall nutritional risk score. Thus, the NRS-2002 questionnaire in GC aims to detect and manage malnutrition and nutritional deficiencies, contributing to the improvement of treatment outcomes and quality of life for patients. A score $\geq$3 is suggestive that the patient is at risk of malnutrition and a nutritional plan is to be followed.

2.3.4. Patient-Generated Subjective Global Assessment

PG-SGA is widely acknowledged in clinical research as the standard method for evaluating the nutritional status of cancer patients, representing a modified iteration of the nutritional assessment tool, Subjective Global Assessment. The initial section of PG-SGA is filled out by the patients and is employed as a screening tool for nutritional risk/deficiency, commonly known as PG-SGA Short Form.

2.3.5. Simplified Nutritional Appetite Questionnaire

SNAQ is a concise four-item instrument that includes items 1, 2, 4, and 6 from the Comprehensive Nutritional Assessment Questionnaire (CNAQ). These specific items evaluate appetite, satiety, taste of food, and the number of meals per day, respectively. The SNAQ was designed as a self-assessment screening tool, aiming for a quick and straightforward administration without the necessity for trained assessors or laboratory measurements. The total score ranges from 4 to 20. Previous validation studies propose a cutoff of $\leq$14 to indicate malnutrition and involuntary weight loss.

2.4. Statistical Analysis

The data underwent analysis using the statistical software "Statistical Package for Social Science (SPSS)" version 20.0 for Windows. Variations between independent groups were examined through Student's *t*-test and one-way analysis of variance. Spearman's rank correlation coefficients were computed to assess the association between the scores and variables. Data are presented as mean $\pm$ SD. Significance was determined at $p < 0.05$. The agreement between the two assessment methods was evaluated using the Chi2 statistic. The Chi2 value ranges from 0 to 1; a value of 0.4 or less suggests that chance alone can explain the observed agreement, while a value of 1 signifies perfect concordance. Comparison between group means was performed with ANOVA. The coefficient of variation (CV%) highlights the percentage deviation between the two means, providing insights into the homogeneity of the value series. Additionally, if the examined variable comprises continuous values, the skewness test ($-2 < p < 2$) is applied to validate the normality of the value series. Using the ROC curve, the balance of specificity/sensitivity as a prognostic factor was represented.

3. Results

3.1. Demographic Characteristics

The demographic characteristics are shown in Table 1.

Table 1. Demographic characteristics of the patients.

	Gastrectomy		Both Groups (N = 51)	*p*-Value
	Total (N = 22)	Subtotal (N = 29)		
Sex				
Male	16 (72.7%)	18 (62.1%)	34 (66.7%)	0.421
Female	6 (27.3%)	11 (37.9%)	17 (33.3%)	
Age (years)				
Mean $\pm$ SD	66.91 $\pm$ 12.68	65.62 $\pm$ 13.32	66.18 $\pm$ 12.93	0.728 [#]
median/limits	66/35–82	65/34–82	66/34–82	
Age groups				
<65 years	9 (40.9%)	11 (37.9%)	20 (39.2%)	0.829
$\geq$65 years	13 (59.1%)	18 (62.1%)	31 (60.8%)	
Environment				
Urban	13 (59.1%)	16 (55.2%)	29 (56.9%)	0.779
Rural	9 (40.9%)	13 (44.8%)	22 (43.1%)	

[#] Student's *t*-test.

Distribution by gender highlighted a higher frequency of male cases (66.7%), with a male/female ratio of 2/1 in both study groups (72.7% vs. 62.1%; $p = 0.421$). The average age in the GT group was slightly lower compared to the SG group (65.62 vs. 66.91 years; $p = 0.728$). In terms of age groups, it is noteworthy that 59.1% of patients in the TG group and 62.1% in the SG group were over 65 years old ($p = 0.829$), making 65 years a chosen threshold for subsequent comparisons. In terms of origin, it is notable that 55.3% of patients in the TG group and 53.5% in the SG group were from urban areas ($p = 0.749$).

Regarding lab work, only CEA differed significantly between the analyzed groups; in the SG group, it was significantly higher (1.85 vs. 3.97 U/mL; $p = 0.027$) (Table 2).

Table 2. Biochemical parameters compared between the two groups.

Parameters	Gastrectomy		*p*-Value
	Total (N = 22)	Subtotal (N = 29)	
Hemoglobin, g/dL	10.43 ± 2.81	11.36 ± 2.41	0.209
Hematocrit, %	32.57 ± 7.65	34.97 ± 6.07	0.217
PLT, $\times 10^3/\mu L$	330.59 ± 131.43	337.76 ± 120.98	0.841
WBC, $\times 1000/\mu L$	7.59 ± 2.04	8.11 ± 2.84	0.474
Lymphocytes/μL	9.25 ± 9.28	7.64 ± 10.32	0.567
PLT/Lymphocytes	109.13 ± 97.39	137.42 ± 93.71	0.299
Serum protein, g/dL	7.13 ± 0.71	6.96 ± 0.96	0.482
Albumin, g/dL	4.22 ± 0.63	4.40 ± 0.61	0.325
Na^+, mmol/L	138.68 ± 3.24	139.90 ± 3.71	0.228
K^+, mmol/L	4.53 ± 0.38	4.41 ± 0.44	0.345
Urea, mg/dL	40.0 ± 11.69	43.18 ± 15.53	0.426
Creatinine, mg/dL	0.99 ± 0.21	1.01 ± 0.23	0.783
CEA, U/mL	1.85 ± 2.27	3.97 ± 1.63	0.027
CA19-9, U/mL	53.55 ± 32.80	43.03 ± 26.69	0.803

3.2. Nutritional Assessment

A registered dietitian conducted nutritional evaluations. It is worth noting that no comparative analysis of nutritional supplements was conducted, thus hindering the identification of the most effective option.

3.2.1. WHO/ECOG Score

The value series for the WHO/ECOG score was homogeneous, suggesting that statistical significance tests can be applied: variations within the range of 0–3; group mean 0.86 ± 0.92; median = 1; skewness test result $p = 0.930$.

The WHO/ECOG score of 3 (patient capable of limited self-care, spending over 50% of the time in bed or chair) was recorded in a small number of patients: 13.6% in the GT group and only 3.4% in the GS group. Approximately 80% of patients were physically active or capable of short-duration physical activities ($p = 0.305$).

Patients with an ECOG score of 2 (patients capable of self-care but struggling with relatively easy physical activities) were all over 65 years old ($p = 0.001$), with 2/3 originating from urban areas ($p = 0.661$). Those with a WHO/ECOG score of 3 (patients capable of limited self-care) were all over 65 years old ($p = 0.001$), and 3/4 were female ($p = 0.018$) (Table 3).

Table 3. Distribution of cases based on ECOG/WHO PS scores and demographic characteristics.

ECOG/ WHO PS		0 N = 21 (41.2%)	1 N = 20 (39.2%)	2 N = 6 (11.8%)	3 N = 4 (7.8%)
Surgical treatment	SG (N = 29)	12 (41.4%)	11 (37.9%)	5 (17.2%)	1 (3.4%)
	TG (N = 22)	9 (40.9%)	9 (40.9%)	1 (4.5%)	3 (13.6%)
Sex	Male	17 (80.9%)	13 (65%)	3 (50%)	1 (25%)
	Female	4 (19.0%)	7 (35%)	3 (50%)	3 (75%)
Age	<65 years	17 (80.9%)	4 (20%)	0	0
	≥65 years	5 (23.8%)	16 (80%)	6 (100%)	4 (100%)
Environment	Urban	10 (47.6%)	13(65%)	4 (66.6%)	2 (50%)
	Rural	11 (52.3%)	7(35%)	2 (33.3%)	2 (50%)

SG = subtotal gastrectomy; TG = total gastrectomy. 0 = asymptomatic; 1 = symptomatic but completely ambulatory; 2 = symptomatic, <50% in bed during the day; 3 = symptomatic, >50% in bed but not bedbound.

3.2.2. Dysphagia Score

The value series for the dysphagia score was homogeneous, indicating that statistical significance tests can be applied: variations within the range of 0–2, group mean 0.51 ± 0.78, median = 0, skewness test result $p = 1.132$ (Table 3).

A dysphagia score of 2 (capable of swallowing only semi-solid foods) was recorded in 18.2% of patients in the TG group and 17.2% in the SG group ($p = 0.940$). The TG group exhibited a more pronounced dysphagia score compared to the SG group.

Patients with a dysphagia score of 2 (capable of swallowing only semi-solid foods) were 3/4 female ($p = 0.006$), 88.9% were over 65 years old ($p = 0.011$), and 2/3 came from urban areas ($p = 0.073$) (Table 4).

Table 4. Distribution of cases based on dysphagia scores and demographic characteristics.

Dysphagia Score		**0 N = 34 (66.7%)**	**1 N = 8 (15.7%)**	**2 N = 9 (17.6%)**
Surgical treatment	SG (N = 29)	19 (65.5%)	5 (17.2%)	5 (17.2%)
	TG (N = 22)	15 (68.2%)	3 (13.6%)	4 (18.2%)
Sex	Male	27 (79.4%)	5 (62.5%)	2 (22.2%)
	Female	7 (20.6%)	3 (37.5%)	7 (77.7%)
Age	<65 years	18 (52.9%)	1 (12.5%)	1 (11.1%)
	≥65 years	16 (47.0%)	7 (87.5%)	8 (88.8%)
Environment	Urban	16 (47.0%)	7 (87.5%)	6 (66.6%)
	Rural	18 (52.9%)	1 (12.5%)	3 (33.3%)

SG = subtotal gastrectomy; TG = total gastrectomy. 0 = no dysphagia; 1 = symptomatic, able to eat a regular diet; 2 = symptomatic, altered eating/swallowing.

3.2.3. Nutritional Risk Screening-2002

The value series for the NRS score was homogeneous, suggesting that statistical significance tests can be applied: variations within the range of 0–3; group mean 0.25 ± 0.74; median = 0; skewness test result $p = 1.879$.

An NRS score of 2 (moderate imbalance) was recorded in 9.1% of patients in the TG group and 3.4% in the SG group, while an NRS of 3 (severe imbalance) was recorded in 4.5% of patients in the TG group and 3.4% in the SG group ($p = 0.603$). A higher prevalence of malnutrition was observed in the group of patients who underwent TG.

Patients with an NRS score of 2 (moderate imbalance) were all female ($p = 0.019$), over 65 years old ($p = 0.049$), and 1/2 from urban areas ($p = 0.725$). Those with an NRS score of 3 (severe imbalance) were 1/2 female ($p = 0.019$), all over 65 years old ($p = 0.049$), and 1/2 from urban areas ($p = 0.725$) (Table 5).

Table 5. Distribution of cases based on NRS-2002 scores and demographic characteristics.

NRS-2002 Score		**0 N = 44 (88.2%)**	**1 N = 1 (2%)**	**2 N = 3 (5.9%)**	**3 N = 2 (3.9%)**
Surgical treatment	SG (N = 29)	26 (89.7%)	1 (3.4%)	1 (3.4%)	1 (3.4%)
	TG (N = 22)	19 86.4%	0	2 (9.1%)	1 (4.5%)
Sex	Male	33 (73.3%)	0	0	1 (50%)
	Female	12 (26.7%)	1 (100%)	3 (100%)	1 (50%)
Age	<65 years	20 (44.4%)	0	0	0
	≥65 years	25 (55.5%)	1 (100%)	3 (100%)	1 (100%)
Environment	Urban	25 (55.5%)	1 (100%)	2 (66.6%)	1 (50%)
	Rural	20 (44.4%)	0	1 (33.3%)	1 (50%)

SG = subtotal gastrectomy; TG = total gastrectomy. Score < 3—no nutritional risk; >3—nutritional risk.

3.2.4. PG-SGA

The PG-SGA score values were consistent, allowing for statistical tests: ranging from 4 to 27, with a group mean of 10.84 ± 5.16 and a median of 10. The skewness test result was −1.035. The average PG-SGA score in the TG group was slightly higher than in the SG group (10.86 vs. 10.83; $p = 0.981$), emphasizing the need for dietitian intervention in both groups (Table 3).

The PG-SGA score of B, requiring dietitian intervention, was recorded in 54.5% of patients in the TG group and 62.1% in the SG group, while PG-SGA of C, a critical indicator for changing nutritional management, was recorded in 13.6% of patients in the TG group and 10.3% in the SG group ($p = 0.856$). Patients classified as severely malnourished were more prevalent in the TG group.

Patients with a PG-SGA score of B were 3/4 male ($p = 0.026$), 83.3% were over 65 years old ($p = 0.001$), and 60% came from urban areas ($p = 0.609$). Meanwhile, patients with a PG-SGA score of C were 83.3% female ($p = 0.026$), all over 65 years old ($p = 0.001$), and 2/3 came from urban areas ($p = 0.609$) (Table 6).

Table 6. Distribution of cases based on PG-SGA scores and demographic characteristics.

PG-SGA Score		**A** **N = 1 (29.4%)**	**B** **N = 30 (58.8%)**	**C** **N = 6 (11.8%)**
Surgical treatment	SG (N = 29)	8 (27.6%)	18 (62.1%)	3 (10.3%)
	TG (N = 22)	7 (31.8%)	12 (54.5%)	3 (13.6%
Sex	Male	11 (73.3%)	22 (73.3%)	1 (16.7%)
	Female	4 (26.7%)	8 (26.7%)	5 (83.3%)
Age	<65 years	15 (100%)	5 (16.7%)	0
	≥65 years	0	25 (83.3%)	6 (100%)
Environment	Urban	7 (46.7%)	18 (60%)	4 (66.6%)
	Rural	8 (53.3%)	12 (40%)	2 (33.3%)

SG = subtotal gastrectomy; TG = total gastrectomy; A = well nourished; B = suspected or moderate malnutrition; C = severe malnutrition.

3.2.5. Score SNAQ-Indicator of Appetite and Eating Behavior

The SNAQ score values were consistent, allowing for statistical tests: ranging from 8 to 19, with a group mean of 14.22 ± 3.29 and a median of 14. The skewness test result was −0.072 (Table 3). No patient obtained the maximum score of 20.

The average SNAQ score in the TG group was slightly higher compared to the SG group (14.41 vs. 14.07; $p = 0.718$). A high SNAQ score was recorded in 95.5% of patients in the GT group and 93.1% in the GS group ($p = 0.139$). Surprisingly, a more satisfying appetite was found in the TG group.

Patients with a high SNAQ score were 68.8% male ($p = 0.071$), 58.3% were over 65 years old ($p = 0.211$), and 56.3% came from urban areas ($p = 0.556$). Meanwhile, patients with a low SNAQ score were all male ($p = 0.071$), over 65 years old ($p = 0.211$), and from urban areas ($p = 0.556$) (Table 7).

By plotting the ROC curve, it is confirmed that, in the studied cases, among the nutritional status parameters, there were no good predictors of radical gastrectomy (AUC < 0.600) (Figure 1, Table 8). A low AUC value near 0.5 and an irregular ROC curve suggest limited support for total gastrectomy from questionnaire results, warranting further investigation. Additionally, examining the questionnaire items and their relevance to the outcome of interest (support for total gastrectomy) may help identify any limitations or biases in the questionnaires.

Table 7. Distribution of cases based on SNAQ scores and demographic characteristics.

SNAQ Score		Low N = 1 (2%)	Moderate N = 2 (3.9%)	High N = 48 (94.1%)
Surgical treatment	SG (N = 29)	0	2 (6.9%)	27 (93.1%)
	TG (N = 22)	1 (31.8%)	0	21 (95.5%)
Sex	Male	1 (100%)	0	33 (68.8%)
	Female	0	2 (100%)	15 (31.3%)
Age	<65 years	0	0	20 (41.7%)
	≥65 years	1 (100%)	2 (100%)	28 (58.3%)
Environment	Urban	1 (100%)	1 (50%)	27 (56.3%)
	Rural	0	1 (50%)	21 (43.7%)

SG = subtotal gastrectomy; TG = total gastrectomy. Low = low risk of malnutrition; Moderate = moderate risk of malnutrition; High = high risk of malnutrition.

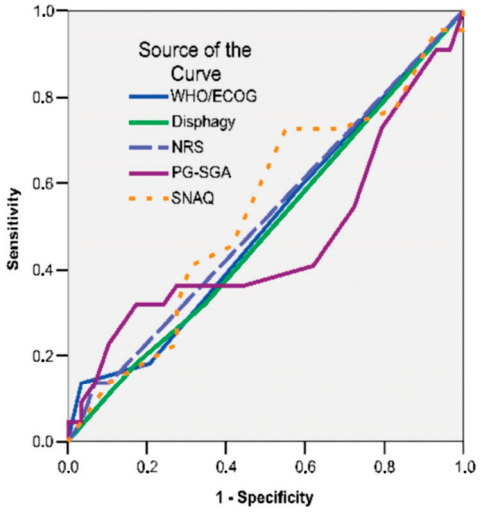

Figure 1. ROC Curve: Nutritional Status. Predictors of Radical Gastrectomy.

Table 8. ROC curve and AUC for the studied tests.

Test Result Variable (s)	Area	Std. Error (a)	Asymptotic Sig. (b)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
WHO/ECOG	0.505	0.083	0.947	0.343	0.668
Dysphagia	0.491	0.082	0.909	0.329	0.652
NRS-2002	0.518	0.083	0.827	0.356	0.680
PG-SGA	0.464	0.087	0.662	0.294	0.634
SNAQ	0.536	0.083	0.662	0.373	0.699

The test result variable(s), WHO/ECOG, dysphagia, NRS-2002, PG-SGA, SNAQ, has at least one tie between the positive and negative actual state groups. Statistics may be biased. a: under the nonparametric assumption. b: null hypothesis; true area = 0.5.

4. Discussion

In clinical practice, a combination of these tools may be used to comprehensively assess the nutritional status of GC patients and guide personalized nutritional interventions. Early identification of nutritional issues and proactive nutritional support are essential components of the multidisciplinary care approach for GC patients, aiming to improve treatment outcomes and quality of life.

In this study, the ORD, NRS-2002, and PG-SGA scores indicated a significantly higher risk of malnutrition when TG was performed. This could be attributed to the tumor's invasiveness that led to the TG and its local impact on nutritional assimilation. Additionally,

the systemic effects of cancer cachexia may contribute to the malnourished state. There was a greater proportion of patients with a high WHO/ECOG score of 3 in the TG group. An essential feature of this study is its exclusive focus on patients who underwent gastrectomy for potentially curable gastric cancer, with the exclusion of individuals with stage IV disease. This selection criterion was applied even though cancer cachexia prevalence ranges from 50% to 80% among patients with advanced cancer [11].

The NRS-2002 demonstrated limited concordance with the PG-SGA regarding the diagnosis of malnutrition. NRS-2002 discovered malnutrition in only 3.9% of patients, but the PG-SGA showed different degrees of malnutrition in 70.6% (58.8% moderate and 11.8% severe). The latter method is known to be more efficient for identifying this condition. The NRS-2002 can serve as a preliminary screening tool for identifying malnutrition and the risk of malnutrition in cancer patients, preceding the utilization of the PG-SGA [12]. Risk factors associated with severe malnutrition were female sex and age over 65 years.

In alignment with our research, Jendretzki et al. similarly affirmed that women and patients aged over 65 exhibit a significantly higher prevalence of nutritional issues [13].

Malnutrition frequently occurs in critically ill cancer patients and is linked to unfavorable outcomes. This condition can be effectively addressed through nutritional interventions. Numerous investigations indicate that individuals with gastrointestinal malignancies often experience significant weight loss before surgery, with an additional approximately 10% decrease in weight observed during the initial months following the procedure [9]. Malnutrition can potentially be addressed and reversed through straightforward methods like refeeding and nutritional supplementation via oral intake, enteral tube feeding, or parenteral nutrition. However, cancer cachexia presents as a complex syndrome, representing a specific type of chronic disease-related malnutrition accompanied by inflammation. Due to the intricate interconnection of its various components, there is no singularly effective treatment available for cancer cachexia [14,15]. According to the literature, Aydin et al. reported that malnutrition may exist despite a normal BMI, and the SGA can identify malnutrition even before the BMI falls below 20 kg/m^2. BMI serves as a straightforward tool, readily applicable in clinical settings; however, it cannot distinguish between fat and muscle mass, necessitating repeated measurements for clinical relevance. As individuals age, adiposity tends to increase while muscle mass declines, often without notable BMI alteration, therefore the concept of sarcopenic obesity warrants consideration. Hence, employing a combination of assessment methods is crucial for evaluating a patient's nutritional status effectively [16,17].

Several studies have shown a correlation between low serum albumin levels and extended hospital stays, medical complications, and higher mortality rates. However, conflicting findings indicate that low serum protein levels do not consistently signify malnutrition, nor does malnutrition always coincide with low serum protein levels. Inflammatory responses, liver disease, cancer, or idiopathic factors can influence various serum proteins and albumin levels [9,14,18].

Nutritional status, food intake, and disease severity should be evaluated regularly and at short intervals, ideally at least every 1–2 months, from the initial contact to promptly identify any decline in nutritional status [19]. Elevated scores on the NRS-2002 tool have been linked to higher rates of postoperative complications and prolonged hospital stays. Additionally, in a recent investigation assessing the effectiveness of the SNAQ in predicting postoperative mortality risk following GC surgery, an SNAQ score $\geq$1 was associated with an increased mortality rate compared to an SNAQ score below this threshold [20,21]. The SNAQ lacks adequacy as a predictive tool for identifying nutritional risk in ambulatory cancer patients, primarily due to its failure to consider specific factors like tumor stage and adverse treatment effects [22].

A recent study conducted by Chen et al. evaluated four NA tools, including SNAQ, NRS-2002, Universal Screening Tool (MUST), and the Malnutrition Screening Tool (MST). The results indicated that the former three exhibited favorable sensitivity and specificity. However, among patients with gastric cancer, MST exhibited superior performance in

identifying cachexia, as evidenced by its high sensitivity (84.3%), specificity (98.6%), and AUC (0.914, $p < 0.001$). On the other hand, the SNAQ tool displayed high specificity but relatively low sensitivity, thereby restricting its diagnostic effectiveness [15].

Hauner et al. (2020) conducted an assessment of MUST and NRS-2002 in outpatient cancer populations, finding both tools to be suitable, although their efficacy varied depending on the tumor type. They noted that patients with digestive tumors exhibited a higher prevalence of malnutrition according to MUST, with rates reaching 46.6%, whereas NRS-2002 identified a higher percentage of malnutrition, at 63.3%, among patients with hematopoietic tumors. Hence, it appears crucial to take into account that the tumor type also influences the selection of the most appropriate nutritional screening tool based on its specific characteristics [23].

Postoperative nutritional support plays a crucial role in preserving nutritional status during the catabolic phase following surgery. Shim et al. examined the perioperative nutritional status of 435 GC patients, showing a notable rise in the prevalence of severe malnutrition post-surgery (from 2.3% before surgery to 26.3% after surgery) [24]. Following surgical intervention, both appetite and dietary intake tend to decrease during the recovery period, with nutritional status requiring up to a year to fully recuperate [9]. Early nutrition can be safely initiated 6 h after surgery through a percutaneous jejunostomy tube. This early postoperative nutrition strategy helps mitigate the heightened metabolism associated with surgical trauma, preserves the integrity of the intestinal mucosal barrier, reduces the risk of intestinal-borne infections, and promotes the overall recovery of patients [25].

Study Limitations

The study's limitations include its small sample size of only 51 patients and its cross-sectional design allowing only for associations to be determined, without establishing causality between variables. For instance, the cross-sectional approach prevented the assessment of nutritional status changes over time and their impact on recovery. Furthermore, lacking data on nutritional status at cancer diagnosis hindered its consideration as a covariate in regression models. It is important to note that this study recruited a convenience sample from a single medical center, limiting the generalizability of the results to all GC patients. Confounding factors may lead to inaccurate estimates of the true association between variables. Despite these limitations, the study offers valuable insights into factors affecting the nutritional status of GC patients.

5. Conclusions

Patients afflicted with malignant gastrointestinal conditions frequently experience a heightened prevalence of malnutrition. In the context of cancer, diminished food intake and an increased energy deficit contribute to the decline in nutritional well-being. It holds significant importance to identify malnourished individuals both before surgery and throughout the postoperative monitoring phase. While objective nutritional parameters offer valuable insights, subjective assessments also play a role despite their inherent limitations in accurately gauging nutritional status. NRS-2002 is a viable option for initial screening before administering PG-SGA. Our study revealed that NRS-2002 showed only partial agreement with the PG-SGA in diagnosing malnutrition, while the ORD, NRS-2002, and PG-SGA scores collectively pointed to a notably increased risk of malnutrition following TG. This may be linked to the tumor's invasiveness necessitating TG. As such, evaluating the nutritional status of patients following gastrectomy necessitates a blend of objective metrics such as anthropometric measurements and laboratory tests, alongside subjective scoring systems during the postoperative observation period. Further investigation is warranted regarding nutritional screening tools tailored for cancer patients. This emphasizes the pressing requirement for additional studies to assess and compare existing tools, alongside the development of novel ones more suited to this condition, incorporating the factors outlined in this study.

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nutrients

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Article

Calorie Restriction and Time-Restricted Feeding: Effective Interventions in Overweight or Obese Patients Undergoing Radiotherapy Treatment with Curative Intent for Cancer

Carmen Vega [1], Esteban Barnafi [2], César Sánchez [3], Francisco Acevedo [3], Benjamin Walbaum [3], Alejandra Parada [4], Nicolás Rivas [2] and Tomás Merino [1,*]

[1] Cancer Center UC, Red de Salud Christus-UC, Santiago 8330032, Chile; cnvega1@uc.cl
[2] Faculty of Medicine, School of Medicine, Pontificia Universidad Católica de Chile, Santiago 8331150, Chile; estebanandres@barnafi.com (E.B.); nicolas.rivass@uc.cl (N.R.)
[3] Department of Hematology-Oncology, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago 8330077, Chile; csanchez@med.puc.cl (C.S.); fnaceved@uc.cl (F.A.); bvwalbau@uc.cl (B.W.)
[4] Department of Health Sciences, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago 7820436, Chile; acparada@uc.cl
* Correspondence: tmerino@med.puc.cl

Abstract: This study assesses the feasibility of calorie restriction (CR) and time-restricted feeding (TRF) in overweight and obese cancer patients who realized little to no physical activity undergoing curative radiotherapy, structured as a prospective, interventional, non-randomized open-label clinical trial. Of the 27 participants initially enrolled, 21 patients with breast cancer were selected for analysis. The participants self-selected into two dietary interventions: TRF, comprising a sugar and saturated fat-free diet calibrated to individual energy needs consumed within an 8 h eating window followed by a 16 h fast, or CR, involving a 25% reduction in total caloric intake from energy expenditure distributed across 4 meals and 1 snack with 55% carbohydrates, 15% protein, and 30% fats, excluding sugars and saturated fats. The primary goal was to evaluate the feasibility of these diets in the specific patient group. The results indicate that both interventions are effective and statistically significant for weight loss and reducing one's waist circumference, with TRF showing a potentially stronger impact and better adherence. Changes in the LDL, HDL, total cholesterol, triglycerides, glucose and insulin were not statistically significant.

Keywords: intermittent fasting; cancer; curative; radiotherapy; calorie restriction; time-restricted feeding; diet; nutrition; overweight; obesity

1. Introduction

In the last decade, cancer and cardiovascular diseases have established themselves as the first cause of morbidity and mortality collectively, with over 18 million new cases of cancer being registered only in 2020 [1]. These pathologies share common risk factors such as a sedentary lifestyle, poor diet, obesity and tobacco and alcohol consumption [2]. Notably, being overweight and obesity are modifiable risk factors present in 74.2% of the Chilean population [3].

Historically, calorie restriction (CR) has been used as a nutritional intervention due to its benefits in weight loss and metabolic health [4]. It is frequently applied in overweight people and, despite showing great results when applied in short-term durations (<6 months), it tends to have many difficulties with adherence when following it for extended periods of time [5].

Alternatives to CR exist, such as the Mediterranean diet or Paleolithic diet [6], and new research has shown more effective interventions for weight loss such as low-carbohydrate diets [7]. Nonetheless, the evidence remains inconclusive due to study limitations such as

the duration of trials, sample sizes, or definitions of the different diets [6]. In this context, new nutritional interventions have been explored, such as the ketogenic diet (KD) [8] and intermittent fasting (IF) (defined in Table 1), to measure their impact on weight loss and metabolic health.

Table 1. Nutritional intervention definitions and different approaches to IF [5]. In this study, we analyzed CR and IF, specifically the time-restricted feeding (TRF) approach. We also define other approaches so the reader understands the crucial differences between nutritional interventions and the key aspects of the various approaches to IF.

Intervention	Approach	Definition
Intermittent Fasting		Periods of voluntary abstinence from food and drink [5]. There are various ways to approach IF. Most of them have no caloric restriction associated or have caloric restriction for short periods of time.
	TRF	Fasting that requires limiting the consumption of calories to a window of time, typically between 4 and 12 h daily.
	5:2	Two days per week, for 24 h each day, an extremely low-calorie diet is applied.
	B2	Two large meals are eaten per day: breakfast between 6:00 a.m. and 10:00 a.m. and lunch between 12:00 p.m. and 4:00 p.m. No dinner.
Calorie Restriction		Nutritional intervention where the focus is on reducing energy intake but keeping adequate nutrition [9]. In general, 10–30% restriction is accepted as having beneficial effects and being tolerable [10,11].
Ketogenic Diet		Diet primarily consisting of high fat intake, moderate protein consumption and low carbohydrate intake. The macronutrient distribution typically ranges from approximately 55% to 60% fat, from 30% to 35% protein and from 5% to 10% carbohydrates [12].

IF is one of the most frequently cited diet patterns in 2023 among Americans aged 18–80 years [13]. Despite its popularity, the different approaches to IF (such as TRF, alternate day fasting or a 5:2 pattern) complicate the process of establishing robust scientific evidence.

IF has been shown to be more effective than normal dietary intake for weight loss but equally as effective as CR [14]. A randomized clinical trial (RCT) comparing the KD and IF revealed that while the KD was more effective than IF for short-term weight loss, these patients regained the lost weight in the following 6 months, while those in the IF group had lower weight loss during the intervention but maintained their weights after the followup period [15].

Templeman et al. [16] compared CR, 24 h fasting with 150% energy intake on alternate days and 24 h fasting with 200% energy intake on alternate days. He found alternate day fasting to be less effective than CR for fat mass reduction, with no cardiometabolic improvements.

There are studies which suggest that TRF is better than CR at improving glycemic control [17] and decreasing the time above the range [18], but it also causes a reduction in muscle mass [17], which could be attributed to the amount of protein consumed.

A 2023 review of TRF and specific health conditions found that TRF improved cardiometabolic risk factors and markers of liver fibrosis, improved lean muscle mass when paired with resistance training in patients with sarcopenia and improved insulin resistance independent of weight loss in people with diabetes mellitus type 2 [19], which if paired with weight reduction could be even more beneficial by achieving disease remission [20].

In an attempt to clarify the differences between CR and IF, there is an ongoing clinical trial in patients with polycystic ovary syndrome, but the results are still not available [21].

These ongoing efforts to conclude which interventions are best for weight loss are particularly impactful in patients with cancer, due to the implication of being overweight and obesity in the origin and prognosis [22–24] of various types of cancer [25]. Breast cancer is of significant interest as it leads new cancer incidence rates among Chilean women [1].

The pathophysiological reasoning behind the effectiveness of these nutritional interventions has long been researched and explained [26–28]. There are preclinical studies that establish the impact from IF and CR on glucose regulation, resistance to stress and inflammation suppression [29]. Despite showing promising results in the regression of tumor volume and radiosensitivity of tumors in mice preclinical models [30–33], clinical trials are a must to determine the effect of these interventions on patients with cancer [34]. Unfortunately, available evidence on this matter is lacking, and even international guidelines (ACS, NCCN, ESPEN or ASCO) do not have a conclusive stance on their application [22,35–37].

The recommendations from these guidelines on breast cancer were reviewed, and they are summarized in Table 2.

Table 2. Summary of recommendations from international guidelines: the American Cancer Society (ACS)), National Comprehensive Cancer Network (NCCN), European Society for Clinical Nutrition and Metabolism (ESPEN) and American Society of Clinical Oncology (ASCO).

ACS	Published in 2022. Focuses mostly on body mass index (BMI), dietary patterns, specific food avoidance and physical activity.
NCCN	Published in 2022. Similar to the ACS, it focuses mostly on BMI, dietary patterns, specific food avoidance and physical activity. No mention of intermittent fasting or caloric restriction at all in their guidelines.
ESPEN	Published in 2021. Does not recommend fasting unless there is evidence of a benefit.
ASCO	Published in 2022. Mentions intermittent fasting as an intervention but refrains from recommending it as there is insufficient evidence, and points to 5 systematic reviews. These reviews revised 177 articles, where only 7 talked about any kind of weight loss intervention, and of these, 5 of them investigated short-term fasting, finding it to be well tolerated and have beneficial effects.

A 2020 literature review [38] found 9 clinical trials which focused on radiotherapy and the KD. These studies suggested that the KD may have a beneficial effect, but the small numbers of patients in these cohorts, absence of control groups and KD not being the only variable associated with a response to RT in three studies prevented them from drawing definitive conclusions.

A recent paper from June 2023 by Kalam et al. [39] synthesized results from 23 studies dating from 2020 onward where various approaches to IF were used. Studies involving IF found that the rates of severe toxicity decreased. Those combining fasting and the KD found it was well tolerated and decreased toxicity. Others investigating fasting-mimicking diets (FMDs), a low-calorie diet that is low in protein and carbohydrates but high in unsaturated fat, found it increased ketone bodies and improved plasma glucose but had variable compliance and conflicts of interest. Lastly, TRF showed the highest degree of adherence and helped decrease fatigue and improve visceral adipose tissue, whole-body fat mass, cardiometabolic outcomes, anxiety and depression.

A systematic review on the impact of IF on breast cancer from January 2023 by Anemoulis et al. [40], which included studies from 2009 to 2021, failed to conclude if there were beneficial effects from IF on quality of life (QoL), response after chemotherapy or an improvement in symptoms. They did, however, find that there could be a beneficial effect on chemotherapy-related adverse effects based on markers of DNA and leukocyte damage but required further validation.

A large RCT with 187 patients from 2022 [41] compared intermittent and continous energy restriction during chemotherapy for early breast cancer cases. This study concluded that an intermittent restriction approach had a bigger weight reduction than a continuous restriction when adjusted for total body water. In this cohort, 49.2% of patients with intermittent restriction and 32.7% of patients with continuous restriction underwent a statistically significant weight reduction (defined in the article as >3% weight loss).

The lack of evidence in this area of research and variety of nutritional interventions make it such that it is often overseen and difficult to gauge their real impact. Important international guidelines, such as those the ACS and NCCN published in 2021 and 2022, have no dedicated space for CR or IF with their various approaches in the entirety of their guidelines, whereas the ESPEN or ASCO group them together with other recommendations that, while they may have in common the modification of food intake, have different objectives and methods of implementation.

In practice, many patients show interest in a dietary modification that could increase their chances of success in treatment. A recent study evaluating CR and radiotherapy in breast cancer patients found that up to 75% would be part of a CR study [42]. However, adherence to dietary interventions is variable and can be explained by several reasons, such as depression, stress, previous weight loss attempts or negative perceptions of diet and exercise [43,44]. On the other hand, regular and frequent attendance of nutritional controls, physical exercise and educational materials and feeling in control over what they eat are factors that favor adherence [45,46].

In the growing field of nutritional interventions and cancer, there is still much to be elucidated. The studies we previously mentioned usually opted for one intervention and measured weights and metabolic outcomes. Thus, in this study, we compare two interventions in a similar cohort.

A prospective, interventional, non-randomized open-label clinical trial was built. It assessed the feasibility and effectiveness of CR and TRF in patients with breast cancer who were overweight or obese and were undergoing curative radiotherapy. CR and TRF were chosen due to their history, ease of application and, as previously exposed, evidence supporting them.

The main objective of this clinical trial was to evaluate the feasibility of either CR or TRF in breast cancer patients who are under curative radiotherapy treatment. The secondary outcomes are its effectiveness, as measured by weight loss at the end of the intervention, and changes in several metabolic (HLD, LDL, total cholesterol, triglycerides, glucose and insulin) and anthropometrical parameters (weight and waist circumference).

In this novelty clinical trial, we seek to establish guidelines for future works in this area which can be easily reproducible and improved upon and thus build the foundations for effective and efficient interventions such as TRF or CR.

To our knowledge, this is the first published work of this kind in developing countries, and it shows consistent results in favor of intervention.

2. Materials and Methods

We defined a prospective, interventional, non-randomized open-label clinical trial that assessed the feasibility and effectiveness of CR and TRF in patients with breast cancer and a body mass index (BMI) greater than 25 who were treated with curative radiotherapy. The main clinical characteristics of the analyzed cohort can be found in Table 3, and a summary of them is included in Table 4.

The inclusion criteria were as follows:

- $\geq$18 years old;
- Breast cancer diagnosed by biopsy;
- Overweight or obese, defined as a BMI $\geq$25 kg/m^2 or 30 kg/m^2, respectively;
- Indication of radiotherapy with a curative intent.

The exclusion criteria were as follows:

- A BMI <25 kg/m^2;

- Patients undergoing nutritional treatment or malnutrition;
- Patients with diabetes mellitus using insulin;
- Diagnosis of vascular ischemia, uncontrolled thyroid disease, mental illness without medical supervision, liver disease or malabsorption syndromes (inflammatory bowel disease or celiac disease);
- Patients with a gastric bypass or gastric sleeve;
- Use of corticosteroids or anti-depressants;
- A moderate or high level of physical activity.

Table 3. Clinical characteristics of patients.

Age	Cancer Type	cTNM	pTNM	Stage	EEE	Intervention
30	IDC—Luminal	cT2N1M0	ypT1N1M0	IB	2096	CR
34	IDC—TN	cT3N1M0	ypT1bN0M0	IIA	1922	CR
67	IDC—Luminal	cT1N0M0	pT2N3M0	IIIB	1977	CR
43	ILC—Luminal	cT1cN1M0	pT2mfN1M0	IB	2418	CR
53	Poorly Diff.—Luminal	cT2N1M0	ypT0?N0M0	ND	2085	CR
48	IDC—Luminal	cT2N1M0	ypT1N0M0	IB	1956	CR
70	IDC—Luminal	cT1N0M0	pT1cN0M0	IA	1818	CR
58	IDC—TN	cT2N2M0	ypT0N0M0	ND	2017	CR
36	IDC—Luminal	cT2N0M0	pT2N0M0	IB	2014	CR
49	IDC—Luminal	RB cT1N1; LB T1N0	RBypT0N0M0; LBypTisN1	IIA	2142	CR
65	ILC—Luminal	cT2N0M0	pT3N0M0	IIIA	1681	CR
43	IDC—Luminal	cT2N0M0	pT2N1M0	IB	2112	CR
60	IDC—Luminal	ND	pT2N1M0	IB	1800	CR
47	IDC—Luminal	cT1N0M0	pT1N0M0	IA	1621	CR
60	IDC—Luminal	cT1N0M0	pT1N1M0	IB	1944	CR
52	IDC—Luminal	cT1N0M0	pT1N1M0	IB	ND	CR
49	DCIS—Luminal	cTisN0M0	pTisN0M0	0	2000	TRF
62	IDC—Luminal	cT1N1M0	ypT2N1M0	IB	1736	TRF
55	IDC—TN	cT4bN0M0	pT0N0M0	ND	1922	TRF
48	IDC—Luminal	cT1N0M0	pT2N1M0	IB	2092	TRF
65	ILC—Luminal	cT1N0M0	pT2N1micM0	IB	1871	TRF

IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; DCIS = ductal carcinoma in situ; TN = triple-negative breast cancer; EEE = estimated energy expenditure; ND = no data; RB = right breast; LB = left breast.

Table 4. Summary of clinical characteristics of patients.

Number of Patients		***n* = 21**
Mean Age (years)		52
Cancer Type	IDC	16
	ILC	3
	DCIS	1
	Poorly Diff.	1
	Luminal	18
	TN	3
Stage	0	1
	1	13
	2	2
	3	2
Intervention	CR	16
	TRF	5

IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; DCIS = ductal carcinoma in situ; TN = triple-negative breast cancer; CR = calorie restriction; TRF = time-restricted feeding.

The recruitment process was carried out at the "Centro de Cáncer UC CHRISTUS" in Santiago, Chile, where patients with breast cancer are referred for radiotherapy. For their first consultation, if they met our selection process based on the inclusion and exclusion criteria and thus were suitable candidates, then the details of the study along with its risks

and benefits were explained. Patients who accepted being part of the study signed informed consent forms and were distributed between CR and IF according to their preferences.

The following steps were taken with each patient to ensure a thorough procedure.

2.1. Step 1: Initial Evaluation

- Nutritional evaluation. Before intervention began, baseline measurements of the weight, BMI, waist circumference, and serum levels of glucose, basal insulin and lipids were performed:
  - Weight: was measured with a calibrated scale on a hard surface, with participants removing shoes and heavy clothing and their arms at their sides.
  - Waist circumference was measured with the participant upright with his or her feet close together, arms to his or her sides and abdomen relaxed. The midpoint between the lower margin of the last palpable rib and the top of the iliac crest was located, and measuring tape was wrapped around the waist at this midpoint, ensuring it was horizontal all the way around and not compressing the skin. The participant was asked to breathe out normally before the measurement was taken.
  - The total energy expenditure was estimated through indirect calorimetry.
- Quality of life (QoL) was assessed through the EORTC-c30 and EORTC QLQ-BR23 questionnaires.
- Physical activity was evaluated through the international physical activity questionnaire (IPAQ) from the World Health Organization (WHO) to ensure the participants did not fit the exclusion criteria.
- Regarding eating habits, a 24 h food survey and consumption trend was used to determine the patients' eating habits (Supplementary Material, "Spreadsheet S1: 24-h Reminder Survey").

2.2. Step 2: Intervention

Each intervention was defined to start 2 weeks before the patient's oncologic treatment and last for 12 weeks. Once nutritional evaluation was completed, the participants were then assigned to TRF or CR according to their preferences. The patient distribution can be seen in Figure 1.

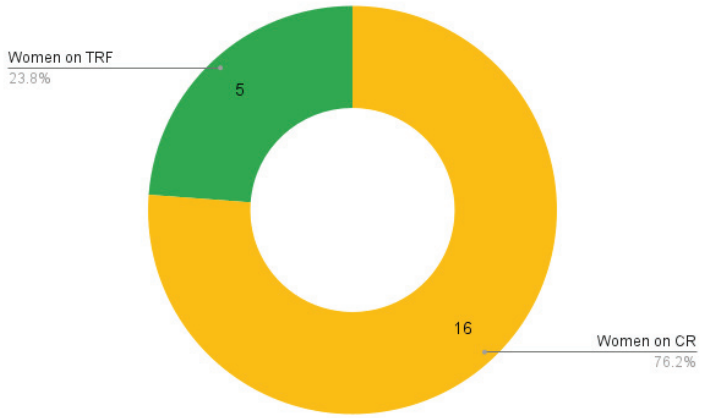

Figure 1. Patient distribution according to their chosen nutritional intervention (TRF or CR).

Nutritional guidelines were made and personalized for each patient according to their group, following certain rules:

- The TRF group followed a diet free of sugar and saturated fats, with caloric intake tailored to the patients' total energy expenditure. This was distributed over 8 h of food intake and a 16 h daily fast, adjusted to best fit their daily schedules.
- The CR group was based on The Obesity Society guidelines, with a total caloric intake 25% less than the total energy expenditure. This was distributed across four meals and

one snack according to the following proportions: 55% carbohydrates, 15% protein and 30% fat, without sugar or saturated fat.

An example of a meal plan can be seen in the Supplementary Materials ("Document S1: Meal Plan").

2.3. Step 3: Monitoring

Throughout the investigation, the following parameters were closely monitored:

- Treatment adherence: Patients were called once a week, and important concepts related to their intervention were reinforced. A dairy registry was considered initially but ultimately decided against due to the anxiety it generated in the patients.
- Toxicity: Once a week during their consultation with radiation oncology, the acute toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

2.4. Step 4: Final Evaluation

Twelve weeks after having started the intervention, and at least 4 weeks after finishing oncologic treatment, the following were measured:

- Acute toxicity;
- Weight and waist circumference;
- Fasting glucose, basal insulin and lipid profile;
- QoL with EORTC-c30 and EORTC QLQ-BR23.

3. Hypothesis

CR or TRF are feasible and effective interventions for overweight and obese patients with breast cancer undergoing curative radiotherapy.

4. Primary Objectives

We evaluate the feasibility and effectiveness of CR and TRF in overweight and obese patients with cancer under curative radiotherapy.

5. Secondary Objectives

- Assess the true adherence, defined as a reduction in body weight of at least 5% compared with the baseline and in at least 50% of the recruited patients;
- Establish which intervention (CR or TRF) has better adherence;
- Assess the impact on quality of life in patients under CR and TRF;
- Assess differences in weight and waist circumference in patients under CR and TRF;
- Assess differences in the serum levels of the fasting glucose, basal insulin and lipid profile for patients under CR and TRF;
- Assess acute toxicity grades $\geq$2 in patients under nutritional intervention.

6. Results

Descriptive statistics with a t test were used to characterize clinical and anthropometric data on the entire cohort. Variables with p values < 0.05 were considered statistically significant. Statistical analyses were conducted with STATA/IC (version 16.1, StataCorp, College Station, TX, USA).

Twenty-seven patients were recruited from April 2021 to May 2023. Two patients withdrew from the trial before treatment, and one patient did not receive radiotherapy (as seen in Figure 2). At the end of May 2023, 23 patients had completed 12 weeks of follow-ups, of which 21 were women and 2 were men.

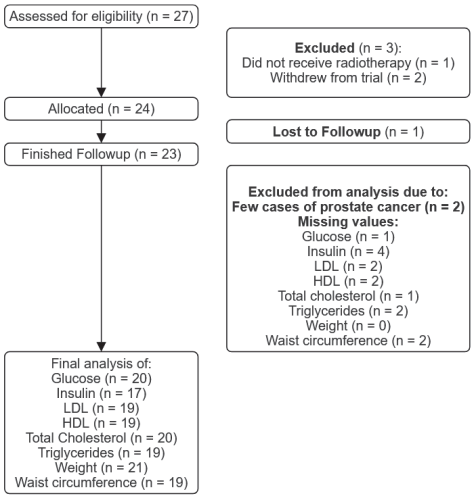

Figure 2. General outline of the study. Diagram depicting steps and results yielded by the study.

Of the 23 patients available for analysis, 21 were women with breast cancer, with luminal ductal carcinoma being the most common histologic subtype. From the 21 women with breast cancer, 14 received some kind of chemotherapy (neoadjuvant, adjuvant or both), and 19 received endocrine therapy. All 21 patients underwent whole breast radiotherapy (±regional nodal irradiation), and 11 received simultaneous integrated boosts to the tumor bed up to 45.75 Gy.

The remaining two patients were men with prostate cancer. However, they were left out of the analysis due to insufficient scientific significance and difficulty interpreting their results.

The following results were acquired from the data available in Tables 5 and 6. The findings are described in the following paragraphs.

In this study, we evaluated the effects of CR and TRF on various health parameters within each group. An overview can be seen in Figure 3, and the percent change per intervention for each of the measured parameters can be seen seen in Figure 4.

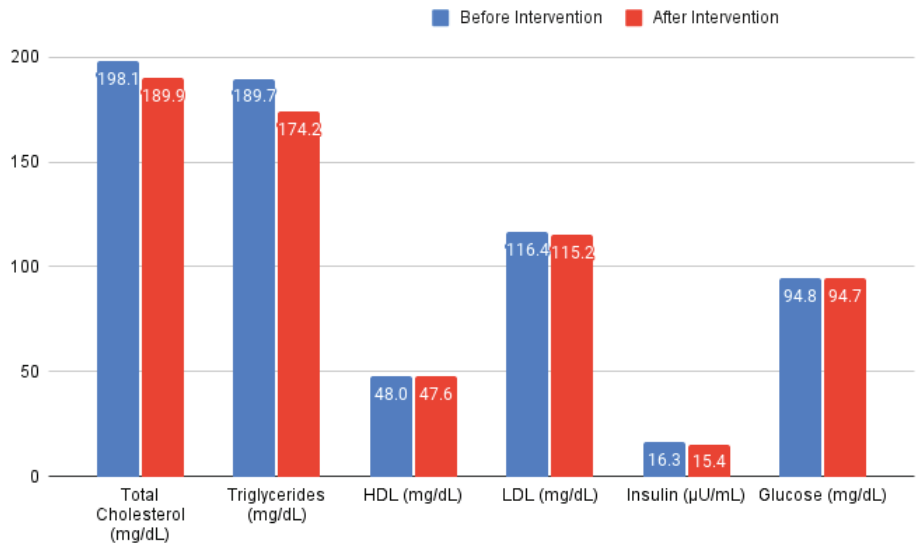

Figure 3. Differences in biochemical measurements before and after intervention. Changes shown in all of the cohorts independent of their chosen interventions.

Table 5. Table with metabolic parameters and their values before and after intervention for each patient.

		Total Cholesterol (mg/dL)		Triglycerides (mg/dL)		HDL (mg/dL)		LDL (mg/dL)		Insuline (µU/mL)		Glucose (mg/dL)	
Age	**Group**	**Baseline**	**Final**	**Baseline**	**Final**	**Baseline**	**Final**	**Baseline**	**Final**	**Baseline**	**Final**	**Baseline**	**Final**
30	CR	176	191.0	143	296.0	43	44.0	105.0	87.0	15.3	21.9	91	84.0
34	CR	244	214.0	236	157.0	51	56.0	146.0	126.6	9.9	11.8	87	95.0
67	CR	204	203.0	174	137.0	38	43.0	132.0	132.0	10.0	11.6	106	96.0
43	CR	169	207.0	133	112.0	49	64.0	93.0	121.0	13.0	8.8	85	78.0
53	CR	158	110.0	428	317.0	37	37.0	121.0	99.0	43.2	47.8	108	112.0
48	CR	160	137.0	212	334.0	35	30.0	82.0	41.0	15.4	18.7	102	103.0
70	CR	149	128.0	77	84.0	44	29.0	89.0	83.0	22.1	12.5	103	101.0
58	CR	182	184.0	241	228.0	38	34.0	96.0	104.0	10.0	11.9	106	113.0
36	CR	188	202.0	82	68.0	67	82.0	105.0	106.0	5.4	4.7	87	92.0
49	CR	163	171.0	81	90.0	60	58.0	86.0	95.0	15.3	18.1	96	91.0
65	CR	222	188.0	166	181.0	56	52.0	133.0	99.0	6.5	11.1	88	91.0
43	CR	204	168.0	356	179.0	22	26.0	111.0	107.0	67.8	17.3	102	85.0
60	CR	241	ND	180	ND	60	ND	145.0	ND	11.6	ND	81	ND
47	CR	244	280.0	76	127.0	56	65.0	172.8	189.0	7.8	ND	81	89.8
60	CR	230	188.0	360	404.0	43	33.0	115.0	155.0	13.6	15.4	91	75.0
52	CR	243	211.0	187	ND	67	ND	139.0	ND	9.3	ND	96	96.0
49	TRF	214	167.0	230	138.0	40	46.0	128.0	93.0	14.0	7.6	89	98.0
62	TRF	211	241.0	150	114.0	46	48.0	135.0	170.0	10.8	14.1	99	106.0
55	TRF	175	183.0	104	87.0	54	60.0	100.0	105.0	10.1	9.2	92	89.0
48	TRF	192	253.0	132	135.0	48	40.0	117.6	185.0	15.3	22	106	104.0
65	TRF	192	172.0	235	122.0	53	57.0	92.0	91.0	ND	13.4	94	91.0

CR = calorie restriction; TRF = time-restricted feeding; ND = no data.

Table 6. Analysis of the impact of TRF and CR on metabolic and anthropometrical parameters. Std Dev = standard deviation; CI = confidence interval.

Parameter	Group	Mean Change	Std Dev	95% CI	*p* Value
Total Cholesterol	CR TRF	10.27 −6.4	28.11 42.09	[−5.30, 25.83] [−58.67, 45.87]	0.179 0.751
Triglycerides	CR TRF	3.64 51	85.51 49.553	[−45.73, 53.02] [−10.53, 112.53]	0.876 0.083
HDL	CR TRF	1.00 −2	8.64 5.83	[−5.99, 3.99] [−9.24, 5.24]	0.672 0.486
LDL	CR TRF	−3.01 −14.28	22.77 38.73	[−10.13, 16.16] [−62.37, 33.81]	0.629 0.457
Weight	CR TRF	3.02 6.84	3.99 3.85	[0.89, 5.15] [2.05, 11.62]	0.009 0.017
Waist Circumference	CR TRF	4.14 7.5	5.67 1.66	[0.87, 7.41] [5.44, 9.55]	0.017 0.004
Insulin	CR TRF	2.76 −0.675	14.94 5.649	[−6.26, 11.79] [−9.66, 8.31]	0.518 0.826
Glucose	CR TRF	1.81 −1.6	8.30 5.90	[−2.78, 6.41] [−8.92, 5.72]	0.412 0.577

For the total cholesterol, the CR group exhibited a nonsignificant mean increase, while the TRF group showed a nonsignificant mean decrease, indicating considerable variability in the responses within both groups. The triglyceride levels in the CR group slightly increased, whereas the TRF group showed a more substantial increase, yet neither were statistically significant.

The HDL changes were minimal and not significant in either group. The LDL levels also did not show significant changes.

Weight changes were significant in both groups, with the CR group losing an average of 3.02 kg (CI = [0.89, 5.15], *p* value = 0.009) and the TRF group losing an average of 6.84 kg (CI = [2.05, 11.62], *p* value = 0.017), suggesting the effectiveness of both interventions in weight reduction. The waist circumference also significantly decreased (CR: mean change = 4.14, CI = [0.87, 7.41], *p* value = 0.017; TRF: mean change = 7.5, CI = [5.44, 9.55], *p* value = 0.004).

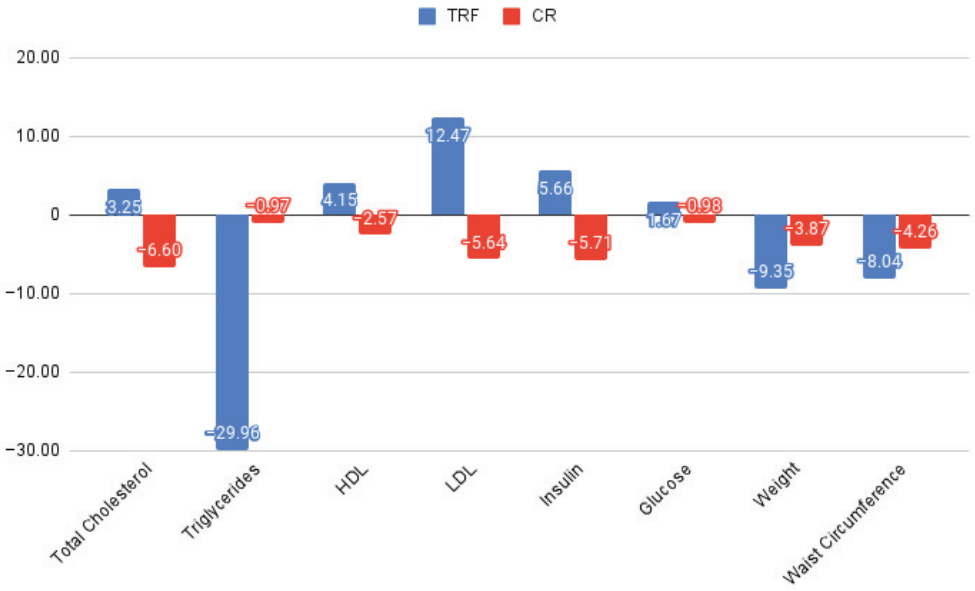

Figure 4. Differences in anthropometric and biochemical measurements between interventions (percentages).

For insulin, the changes were not significant in either group. Similarly, the glucose levels did not exhibit significant changes.

In conclusion, while both the CR and TRF interventions were effective at reducing weights and waist circumferences, their impact on the lipid profile and glucose and insulin levels were not significant. The variability within each parameter suggests a differential response to the dietary interventions.

A percentage analysis of the data from Tables 5 and 7 was performed, and it yielded the following results:

- There was a reported loss of 5% or more of the initial weight (adherence) in 57.1% of patients (12/21). Thus, both interventions as a whole attained true adherence.
- When evaluating each intervention by itself, only TRF showed true adherence, with 100% of those who chose it adhering to it (5 out of 5), whereas only 43.75% (7 out of 16) of those in the CR group adhered to the intervention.

Table 7. Anthropometry values before and after intervention. Also included is the percent change in weight, which was used to measure adherence.

		Weight (kg)			Waist Circumference (cm)	
Age	**Group**	**Baseline**	**Final**	**% Change**	**Baseline**	**Final**
30	CR	82.8	78.1	−5.68	91	86.0
34	CR	70.0	63.0	−10.00	84	79.0
67	CR	83.5	89.0	6.59	107	116.0
43	CR	103.0	100.0	−2.91	ND	ND
53	CR	82.5	83.5	1.21	104	101.0
48	CR	72.5	71.6	−1.24	93	93.5
70	CR	72.3	63.5	−12.17	97.5	88.0
58	CR	77.0	75.0	−2.60	108	101.0
36	CR	76.8	72.0	−6.25	85.5	81.0
49	CR	86.2	86.0	−0.23	96.5	95.0
65	CR	62.6	60.5	−3.35	88	85.0
43	CR	84.0	73.3	−12.74	98	90.5
60	CR	71.0	66.0	−7.04	96	ND
47	CR	67.0	68.0	1.49	89	90.0
60	CR	81.2	77.0	−5.17	102	95.0
52	CR	77.0	74.6	−3.12	107.5	92.0
49	TRF	75.8	62.3	−17.81	92	83.0
62	TRF	66.5	61.0	−8.27	102	96.0
55	TRF	70.0	66.0	−5.71	85	79.0
48	TRF	77.4	72.8	−5.94	93	86.0
65	TRF	76.1	69.5	−8.67	94.5	85.0

7. Discussion

Our findings show that 57.1% of the patients lost 5% or more of their initial weight, and statistically significant changes were seen in terms of weight and waist circumference. This shows that a nutrition intervention of these characteristics is feasible, attains true adherence and is effective at reducing anthropometric parameters in participants. Changes in the metabolic parameters were not statistically significant.

Our results are consistent with the available literature. TRF showed similar results to the work of Kalam et al. [39], with a high degree of adherence and decrease in weight, and Harvie et al. [41], where IF had a bigger drop in weight compared with CR. However, differences in the mean changes may be explained by the fact that they used another approach of IF which focuses on the amount of calories consumed. The participants in their cohort underwent 2 days of 650–1000 kcal/day before chemotherapy infusion compared with our approach, where we focused on the window of time calories were consumed within.

Of interest are the differences between the findings and the systematic review from Anemoulis et al. [40], where no beneficial effects from IF could be concluded. This could be explained by the type of IF approach utilized in the studies considered in their reviews, where only one of them specified the use of TRF and the others were variations of calorie-restricting approaches of IF. One included Ramadan-fasting patients, and one used an FMD,

while the others employed varied hours of fasting before and after chemotherapy. This reinforces the need for clear and established definitions of IF and its different approaches, as well as an urgent necessity for evidence in this field.

Compared with the 2020 literature review from Icard [38], which focused on the KD, our study can draw definite conclusions on the impact on participants' weights and waist circumferences from TRF and CR.

We found that both TRF and CR managed to impact the weight and waist circumference. We also found that TRF was the superior intervention for weight loss (6.84 kg versus 3.02 kg) and waist circumference reduction (7.5 cm versus 4.14 cm). No statistically significant conclusions could be drawn from changes to the metabolic parameters. The closest parameter to statistical significance was the effect of the use of TRF on triglycerides (with a p value of 0.083), but more research is required to further cement these findings in the international literature.

Not only did these interventions as a group achieve true adherence with 57.1% of the participants achieving 5% weight loss, but 100% of the patients within the TRF group showed true adherence, in comparison with only 43.75% adhering in the CR group, despite the previous literature indicating that breast cancer patients favored a CR approach [42]. These findings could be due to how TRF does not restrict the amount of calories in a certain day but rather restricts the timing of meals to 4–12 h a day (8 h in this study), and thus it may be easier to carry on in cancer patients busy with other aspects of the treatment process. Further research is needed on this aspect.

Despite both interventions showing positive results, it seems that TRF as a nutritional intervention has both better adherence and improved anthropometric values. These results show that TRF should be considered as a nutritional intervention in breast cancer patients undergoing curative radiotherapy for the purpose of weight loss.

In this novel clinical trial, we proposed a straightforward and easy-to-replicate method with which to conscript patients and further study nutritional interventions aside from TRF or CR, which we believe can provide the basis for future nutritional intervention studies and open a window into other aspects of nutritional interventions, such as the impact on toxicity reduction which, although seen in animals [47,48], has yet to be reproduced and further explored in human participants.

To our knowledge, this is the first published work of this intervention in developing countries, and it showed consistent efficacy of the intervention.

8. Limitations and Future Directions of Work

The limitations of our work are the small sample size and small power for detecting differences in metabolic parameters, a relatively short period of surveillance, a lack of adherence by patients in the CR group to the guidelines given, limited generalization of the study due to only conscripting breast cancer patients, only evaluating the TRF approach of IF, the lack of long term followups, and the absence of a control group.

This work could be improved by an increase in the number of patients, including QoL and acute toxicity to create a more holistic view of the patient outcomes, including other cancer populations to further generalize our findings, increasing the time of surveillance, including a period of followups, employing other nutritional interventions such as the KD, alternate day fasting, or the FMD to better compare the results between interventions, measuring the blood levels of inflammatory response markers, measuring the blood levels of hormonal markers, measuring the fat mass and lean mass percentages, the inclusion of a control group, or the incorporation of feedback from the participants.

We believe these factors must be taken into account to ensure robust findings. Once international consensus is achieved between the different definitions and approaches of the various nutritional interventions, and a strong methodology is properly built and assured, future research should look to apply these conditions to different cohorts to better generalize these findings and eventually include them in international guidelines.

9. Conclusions

Cardiovascular diseases and cancer lead incidence and mortality rates worldwide, sharing common risk factors such as being overweight and obesity. These play an important role in the origin of breast cancer, and thus different interventions have been investigated to establish a faithful and reproducible way to achieve weight loss in cancer patients.

The theory behind the benefits of diet and weight loss in cancer has been largely studied and established in preclinical studies, but clinical studies that show these results in practice are few and far between and limited in their approach. This could be attributed to the numerous interventions in existence and a lack of agreement on definitions to establish which ones are best and also a lack of patients through which these interventions have been measured thoroughly.

Two of these interventions are TRF and CR. These nutritional interventions were chosen in this study due to their historical relevance and the evidence supporting them. Both CR and TRF achieved statistically significant weight loss and reductions in waist circumferences, but TRF showed a larger mean change in both weight loss and reductions in waist circumferences. Changes in the metabolic parameters were not statistically significant. Our findings are consistent with the literature. It can be concluded that TRF should be preferred over CR as a nutritional intervention for overweight or obese breast cancer patients undergoing radiotherapy treatment with curative intent.

Differences with the literature can be explained by the heterogeneity in the application of IF and its different approaches, lacking a formal definition. This leads to large differences in the fasting hours, number of fasting days, and the existence or nonexistence of a caloric restriction.

We propose a series of simple-to-apply and reproducible steps through which the metabolic parameters and anthropometry can be measured. We hope this helps establish concrete and well-established definitions of the various fasting regimes and motivates other researchers to further investigate and build the foundation of what we believe is a low-cost and effective way to lose weight and improve metabolic parameters.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/nu16040477/s1. The following supporting information has been uploaded together with the manuscript. Spreadsheet S1: 24 h reminder survey. Document S1: Meal plan.

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Institutional Review Board Statement: This study was conducted with the approval of the Comité Ético Científico de Ciencias de la Salud UC (CEC-Salud UC) on 06 January 2022 ID 201111010. This committee adheres to the ethical principles of Pontificia Universidad Católica de Chile, which considers respect for the dignity of the human person in any condition as a fundamental axis. This committee also complies with the Good Clinical Practice Guidelines defined by the International Conference on Harmonization (GCP-ICH) and with Chilean laws 19.628; 20.120, 20.584, and 20.850, which modify the health code.

Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study after the procedure and the steps involved were explained.

Data Availability Statement: All statements and conclusions made within this article have been made with the data and information contained within the provided supplements (tables and figures). No other data were used.

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Abbreviations

The following abbreviations are used in this manuscript:

CR	Calorie restriction
TRF	Time-restricted feeding
KD	Ketogenic diet
IF	Intermittent fasting
RCT	Randomized clinical trial
ACS	American Cancer Society
NCCN	National Comprehensive Cancer Network
ESPEN	The European Society for Clinical Nutrition and Metabolism
ASCO	American Society of Clinical Oncology
BMI	Body Mass Index
FMD	Fast-mimicking Diet
QoL	Quality of Life
IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma
DCIS	Ductal carcinoma in situ
TN	Triple-negative breast cancer
EEE	Estimated energy expenditure
ND	No data
RB	Right breast
LB	Left breast
IPAC	International Physical Activity Questionnaire
WHO	World Health Organization
CTCAE	Common Terminology Criteria for Adverse Events
Std Dev	Standard deviation
CI	Confidence interval

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Nutrition and Lifestyle-Related Factors as Predictors of Muscle Atrophy in Hematological Cancer Patients

Christiane S. Staxen [1,2,*], Sara E. Andersen [1,2], Lars M. Pedersen [1,3], Christian B. Poulsen [1,3] and Jens R. Andersen [2]

[1] Department of Hematology, Zealand University Hospital, 4000 Roskilde, Denmark
[2] Department of Nutrition, Exercise and Sports, University of Copenhagen, 1958 Frederiksberg, Denmark
[3] Department of Clinical Medicine, University of Copenhagen, 2200 Copenhagen, Denmark
* Correspondence: cstax@regionsjaelland.dk

Abstract: Background: Cancer and side effects from cytostatic treatment commonly affect nutritional status manifested as a decrease in muscle mass. We aimed to investigate the impact of nutrition and lifestyle-related factors on muscle mass in patients with hematological cancer. Methods: Dietary intake, food preferences, quality of life (QoL), and physical activity level (PAL) were monitored during 1–2 cytostatic treatment series. Body composition was estimated using bioelectrical impedance analysis (BIA). Results: 61 patients were included. Weight loss and loss of muscle mass were detected in 64% and 59% of the patients, respectively. Muscle mass was significantly positively correlated to increasing PAL (p = 0.003), while negatively correlated to increasing age (p = 0.03), physical QoL (p = 0.007), functional QoL (p = 0.05), self-perceived health (p = 0.004), and self-perceived QoL (p = 0.007). Weight was significantly positively correlated to increased intake of soft drinks (p = 0.02) as well as the favoring of bitter grain and cereal products (p = 0.03), while negatively correlated to increasing age (p = 0.03) and increasing meat intake (p = 0.009) Conclusions: Several nutritional and lifestyle-related factors affected change in body composition. The clinical significance of these changes should be investigated in controlled, interventional studies.

Keywords: cancer; hematology; cytostatic treatment; bioelectrical impedance analysis; muscle mass; nutrition; quality of life; physical activity

1. Introduction

Weight loss and especially the loss of muscle mass is frequently seen in cancer patients as a result of cachexia-associated metabolic changes which seem to be mediated by secretion of pro-inflammatory cytokines from cancer cells and from the immune system of the host, including tumor necrosis factor (TNF), interferon-gamma (IFN-γ), and several interleukins (IL-6, IL-1β) [1]. These metabolic changes involve increased proteolysis and lipolysis as the fuel for hepatic gluconeogenesis, mitochondrial dysfunction, and decreased insulin sensitivity [2,3]. Concurrently, loss of muscle mass in patients with hematological cancer is related to poor nutritional status, which is mainly described to be a result of the side effects of cytostatic treatment and/or the cancer disease itself [4,5]. Side effects with consequences for the patients' nutritional status include nausea, vomiting, changes in the sense of smell and taste, mucositis, decreased energy levels, and intestinal disorders, which can lead to malabsorption, diarrhea, and constipation [6–8].

Patients diagnosed with hematological malignancies often have a normal nutritional status at the time of diagnosis [5,9]; however, side effects from cytostatic treatment can adversely affect the nutritional status as treatment progresses [9,10]. Poor nutritional status and loss of muscle mass have been associated with increased chemo-induced toxicity [11–13], decreased cytostatic tolerance [14], and delay and/or reduction of cytostatic dosing [15,16], as well as inferior treatment outcome [17,18] and reduced survival rate [19–21].

The estimated prevalence of malnutrition and/or risk of malnutrition among different types of cancer patients have been reported to be between 30% and 80%, with the highest prevalence rates in patients with advanced stages of cancer [22–28].

Several studies assessing different cancer diagnoses have also associated the loss of muscle mass with a decrease in quality of life (QoL) [29–33], with decreased physical functionality [30,34], and with low physical activity level (PAL) [21]. These factors seem to further affect patients' nutritional status negatively [35–37].

A multimodal treatment approach has been shown to reduce the loss of muscle mass in patients with other types of cancer than the hematological [14,38]. The aim of this observational study was to investigate possible associations between energy and protein intake, food preferences, QoL, PAL, and eating and TV habits at main meals, with change of muscle mass as the primary endpoint and weight change as the secondary endpoint in hematologic cancer patients undergoing cytostatic treatment.

2. Materials and Methods

2.1. Patients

Patients receiving myelosuppressive cytostatic treatment for lymphoproliferative malignancies, acute leukemia, and multiple myeloma in the period 6 April–8 July 2021 at the Department of Hematology, Zealand University Hospital, Roskilde, Denmark, were consecutively enrolled in the study. The treatment took place either on an outpatient basis or at the ward. The inclusion criteria were ongoing myelosuppressive cytostatic treatment for hematological cancer with more than one treatment cycle remaining in their program, >18 years of age, signed informed consent, no need for an interpreter, no conditions which could interfere with their ability to understand the requirements of the study, not pregnant or breastfeeding. The Project was handled in accordance with the Principles of the Helsinki declaration and has been approved by The Research Ethics Committee for Faculties of SCIENCE and SUND (case: 504-0226/20-5000, 7 December 2020) as well as the Regional Scientific Ethics Committee of Zealand (project-ID-no: SJ881, 24 November 2020).

2.2. Data Collection

Every patient was followed through 1–2 arbitrary but consecutive treatment cycles, which will be referred to as the follow-up period. Clinical data were collected from medical records. The bioelectrical impedance analysis (BIA) method was used to estimate body composition and was performed on 8-point Seca 515/514® [39]. The BIA was performed immediately before or after the patients' planned cytostatic treatments. Questionnaire interviews were performed throughout the follow-up period, after the patient's attendance at the hospital and/or by telephone. 24 h dietary recalls [40] and food preference questionnaire interviews were conducted with two to five days intervals and subsequently quantified using the Danish program for analyzing the content of foods (Vitakost®, Kolding, Denmark). In addition, at every second contact, questionnaire interviews about QoL and PAL were conducted. Patients were interviewed regarding their eating and TV habits at main meals at the first interview and at the end of the follow-up period.

2.3. Questionnaires

The questionnaires were designed by the investigators by a selection of relevant parts from existing validated questionnaires. Prior to application, all questionnaires were tested on 15 healthy independent individuals of different ages to ensure a high level of understanding. Also, the food preference questionnaire was developed by the investigators, as no relevant pre-designed questionnaires were available. The following categories were included: change in intake, decreased appetite, experience of change in taste, and preferences for meat, fruit and vegetables, dairy products, grain and cereal products and soft drinks. The possible answer options in the questionnaire were categorized on a scale from 1–5 from "not at all" to "very much".

The questions regarding preferences referred to intake amount before and after initiation of treatment. Preferences for frying and relevant basic flavors were a topic in each category.

The applied QoL questionnaire was designed as an adjustment of the already-existing, validated questionnaires QLQ-C30 (ver. 3) [41] and FACT-Lym (ver. 4) [42]. The scale was copied from FACT-Lym, where all questions in the first four categories were included. Additionally, selected questions regarding side effects were included from QLQ-C30.

The category of physical well-being consisted of thirteen questions, including the most commonly-experienced side effects from cytostatic treatment. The social well-being category consisted of nine questions, the category of emotional well-being consisted of nine questions, and the functional well-being category consisted of eight questions. In addition, the applied adjusted questionnaire finally contained two questions regarding self-assessment of overall health and QoL, identical to the final category in the QLQ-C30 questionnaire.

The PAL questionnaire was designed to estimate change in PAL during cytostatic treatment. The questionnaire contained two questions scaled from 1–5 ("not at all"—"a lot"). The included questions were based on WHO's GPAQ analysis guide [43].

The questionnaire regarding eating and TV habits at main meals was designed by the investigators in order to estimate how often the patients were eating alone or with others, as well as how often the TV was turned on during meals. The questionnaire contained four questions scaled from 1–7 to indicate how many times a week the given eating circumstance occurred.

2.4. Statistical Analysis

All statistical analysis is performed using R (ver. 4.1.1). Descriptive data are presented as number (%) or mean ± SD.

All changes in weight, muscle, and fat mass are defined as weighted values of daily percentage change, depending on individual follow-up period duration. Energy and protein ingestion is measured as the difference between intake and the estimated requirement in %. Variables of food preferences are defined as the average preference during the follow-up period. Intake of food categories were assigned binary values prior to analysis.

Continuous data is analyzed using Pearson correlation analysis, presented by correlation coefficient r and p-value. A significance level of $p \leq 0.05$ is used.

A multiple linear regression analysis is performed to examine the influence of the discrete nutritional variables on the primary and secondary endpoints. Furthermore, a least absolute shrinkage and selection operator (LASSO) regression analysis method is used, aiming at enhancing the prediction accuracy of the statistical model by shrinking the regression coefficients associated with the least important variables to zero. This includes both variable selection and an L1 regularization method. A significance level of $p \leq 0.05$ is used.

3. Results

3.1. Baseline Characteristics

The baseline characteristics of the patients included in the study are shown in Table 1. The patients participated a mean of 36 days ± 13 and received a mean of 1.6 treatment cycles ± 0.5. A total of 107 patients with lymphoma, acute leukemia, or multiple myeloma diagnoses were referred for myelosuppressive cytostatic treatment. 41 (38%) patients did not meet the study's inclusion criteria, while 66 (62%) patients were enrolled in the study. A further four patients were excluded at the patient's request, while one patient was excluded due to missing BIA data at the end of the follow-up. Therefore, 61 (57%) patients could be included in the final study group available for study analyses.

Table 1. Basic characteristics of the 61 included patients. Values are presented as number (%) or mean ± SD.

Characteristics	Patients, n (%)/Mean ± SD
Sex	
Men	40 (65.6%)
Women	21 (34.4%)
Age (years)	66 ± 13
Diagnose	
Lymphoma	56 (91.8%)
Acute leukemia	3 (4.9%)
Multiple myeloma	2 (3.2%)
Number of cytostatic treatments before inclusion	2.4 ± 1.4
Treatment regime	
(R)-CHOP (+like) [1]	34 (55.7%)
(R)-Benda (+like) [2]	17 (27.9%)
ABVD (+like) [3]	5 (8.2%)
G-PEBEN [4]	1 (1.6%)
CY-VEL-DEX [5]	2 (3.3%)
DA 3 + 10 [6]	2 (3.3%)
Complete remission after end of full course of treatment	51 (84%)
BMI at inclusion	
18.5–24.9	21 (34.4%)
25–29.9	28 (45.9%)
>30	12 (19.7%)

[1] (Rituximab), cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone; [2] (Rituximab), bendamustine; [3] Doxorubicin hydrochloride, bleomycin sulfate, vinblastine sulfate, dacarbazine; [4] Pixantrone, etoposide, bendamustine; [5] Cyclophosphamide, bortezomib, dexamethasone; [6] Daunorubicin, Ara-C/Cytarabin.

3.2. Body Composition

BIA was performed two (24 patients (39.3%)) or three (37 patients (60.7%)) times in connection with a consecutive series of cytostatic treatment, a mean of 2.6 times ± 0.5. Changes in weight, muscle, and fat mass presented in Table 2 are classified as any measurable changes between the first and last measurement.

Table 2. Overview of the number (%) of patients with change in muscle and fat mass and weight during the study period, as well as mean ± SD of daily percentage change during the follow-up period, compared to the first measurement.

	Muscle Mass	Fat Mass	Weight
Decrease	36 (59.0)	26 (42.6)	39 (63.9)
Increase	23 (37.7)	34 (55.7)	22 (36.1)
No change	2 (3.3)	1 (1.6)	0
Daily percentage change	−0.07 ± 0.25	0.05 ± 0.44	−0.03 ± 0.13

Pearson correlation analysis showed statistically significant negative correlations between both age and change in weight ($p = 0.03$) as well as age and change in muscle mass ($p = 0.03$).

3.3. Nutritional Intake

24 h dietary recall interviews were performed a mean of 10.8 times ± 3.6 during the follow-up period, 5 times being the lowest number of dietary recalls and 17 times being the highest. Two patients (3%) met 100% of their estimated energy requirement, while 28 patients (46%) met 75%. One patient (1.6%) met 100% of their estimated protein requirement, while 22 patients (36%) met 75%.

79% of the patients experienced a decrease in appetite at some point during the follow-up period. The mean reduction in appetite score compared with the appetite score before the initiation of cytostatic treatment was 1.8 on the 1–5 scale (“not at all”–“a lot”). 77% of the patients experienced changes in flavor perception during the follow-up period, distributed over a total of 193 times.

No statistically significant correlations were found between change in either muscle mass nor weight and energy intake, protein intake, decreased appetite, or experience of residual flavor (Table 3).

Table 3. Results from Pearson correlation analysis between change in weight and change in muscle mass, and energy intake, protein intake, decreased appetite and experience of residual flavor. Comparing before and end of the follow-up period.

Variables	Muscle Mass		Weight	
	Pearson's r	*p*-Value	Pearson's r	*p*-Value
Energy intake	0.09	0.48	0.12	0.34
Protein intake	0.16	0.21	0.1	0.15
Decreased appetite	−0.18	0.15	−0.14	0.27
Experience of residual flavor	−0.14	0.30	−0.08	0.56

Patients were asked about their intake of different food categories before and after the initiation of cytostatic treatment a mean of 10.8 times ± 3.6. The average intake of meat, fruit and vegetables, dairy, and grain and cereal products decreased after the initiation of cytostatic treatment, while the average intake of soft drinks increased (Table 4).

Table 4. Average percentage distribution in intake for the individual food categories after the start of cytostatic treatment compared to intake before the initiation of cytostatic treatment for respectively the patients who lost muscle mass and the patients who did not during the follow-up period.

Variables	Decrease in Muscle Mass			No Decrease in Muscle Mass		
Intake	Decreased (%)	Unchanged (%)	Increased (%)	Decreased (%)	Unchanged (%)	Increased (%)
Meat	70.3	21.6	8.1	60.9	13.0	26.1
Fruit and vegetables	57.9	10.5	31.6	60.9	21.7	17.4
Dairy	52.6	29.0	18.4	65.2	13.1	21.7
Grain and cereal	63.2	26.3	10.5	52.2	34.8	13.0
Soft drinks	44.7	21.1	34.2	34.8	13.0	52.2

No statistically significant correlations were found between change in muscle mass and any preferences, while a statistically significant negative correlation was found between change in weight and preference for bitter grain and cereal products ($p = 0.03$) (Table 5).

Table 5. Correlations from multiple linear regression analysis between change in muscle mass and weight and increase in intake of included food categories compared with the intake before initiation of cytostatic treatment, as well as preferences for different flavor nuances.

Variables	Muscle Mass		Weight	
	Estimate	*p*-Value	Estimate	*p*-Value
Increase in intake				
Meat	−0.09	0.54	−0.18	0.009
Fruit and vegetables	−0.07	0.47	0.01	0.74
Dairy	0.01	0.90	0.03	0.49
Grain and cereal	0.17	0.20	0.08	0.15
Soft drinks	0.04	0.60	0.07	0.02
Meat preference				
Red meat	0.18	0.33	−0.002	0.98
Dark meat	0.20	0.07	0.02	0.69
Light meat	0.07	0.42	0.05	0.20
Fruit and vegetables preferences				
Sweet	−0.01	0.90	−0.07	0.15
Sour	−0.01	0.89	0.006	0.82
Bitter	0.05	0.31	0.01	0.68

Table 5. *Cont.*

Variables	Muscle Mass		Weight	
	Estimate	***p*-Value**	**Estimate**	***p*-Value**
Dairy preferences				
Sweet	−0.03	0.45	−0.02	0.63
Sour	0.03	0.49	0.001	0.95
Salty	−0.02	0.67	0.006	0.78
Umami	0.004	0.94	−0.008	0.70
Grain and cereal preferences				
Sweet	−0.01	0.81	0.02	0.44
Sour	−0.01	0.74	−0.001	0.95
Bitter	0.03	0.55	0.05	0.03
Soft drink preferences				
Sweet	−0.0009	0.99	−0.01	0.66
Sour	0.03	0.58	0.002	0.94
Bitter	−0.01	0.85	0.006	0.72

A statistically significant negative correlation was found between weight change and increase in meat intake ($p = 0.009$), while a statistically significant positive correlation was found between weight change and increased consumption of soft drinks ($p = 0.02$) (Table 5).

3.4. QoL, Physical Activity and Eating Situations

Patients were asked about their QoL and PAL a mean of 5.8 times ± 1.7, while they were asked about their eating habits a mean of 2 times ± 0.

The highest average decrease in QoL within the investigated parameters was found in the following order (mean ± SD): functional well-being (1.94 ± 0.59) > physical well-being (1.81 ± 0.42) > emotional well-being (1.44 ± 0.29) > social well-being (1.30 ± 0.39). Correlations are presented in Table 6.

Table 6. Results from Pearson correlation analysis between change in weight and change in muscle mass and the variables of QoL, PAL, and eating and TV habits at main meals.

Variables	Muscle Mass		Weight	
	Pearson's r	***p*-Value**	**Pearson's r**	***p*-Value**
QoL				
Physical	−0.34	0.007	−0.05	0.70
Social	−0.25	0.05	0.10	0.43
Emotional	−0.23	0.08	−0.15	0.26
Functional	−0.26	0.05	0.01	0.92
Self-perceived health [1]	0.37	0.004	0.21	0.10
Self-perceived QoL [1]	0.34	0.007	0.17	0.19
Physical activity				
PAL	0.37	0.003	0.17	0.18
Eating and TV-habits				
Eating with others	0.05	0.72	0.04	0.78
Eating alone	−0.02	0.90	−0.21	0.11
TV on with others	−0.06	0.66	0.008	0.95
TV on alone	0.08	0.54	−0.06	0.64

[1] The scale of self-perceived health and QoL were reversed compared to scales on QoL.

Due to the reversed scale of self-perceived health and QoL, this suggests that all parameters of decreased QoL and low self-perceived health and QoL seem to have affected the change in muscle mass negatively while no categories affected change in weight.

The average score of PAL was 3.48. A weak statistically significant positive correlation was found between PAL and change in muscle mass ($p = 0.003$). This suggests that increased levels of physical activity seem to have a positive effect on the change in muscle mass.

No statistically significant correlations were found between eating and TV habits at main meals and change in neither muscle mass nor weight.

3.5. LASSO Regression Analysis

LASSO regressions were generated with change in muscle mass and weight in percent as dependent variables, with the purpose of attaining the subset of predictors that reduces the prediction error for the measurable dependent variable and thereby increases model accuracy and model interpretability. For the training and test of the model, an 80/20 split of data was used. After selection in the LASSO model, no independent variables were found relevant for change in muscle mass or weight for further hypothesis testing.

4. Discussion

The main findings of this study are that PAL and QoL have a positive effect on change in muscle mass during cytostatic treatment. On the contrary, our data suggest that diet adjustments and food preferences have less impact on the change of muscle mass and weight, while eating and TV habits seem to have no impact at all.

A decrease in muscle mass and weight is widely seen in cancer patients undergoing chemotherapeutic treatment [33,44–47], which aligns with the distribution of body mass development in the present study, since the majority of the subjects had a decrease in both muscle mass (59.0%) and weight (62.9%) concurrently to an increase in fat mass (55.7%). The beneficial effect of physical activity on the maintenance of muscle mass in hematological cancer patients undergoing cytostatic treatment has been reported in previous studies [48,49]. Therefore, the results in the present study were expected. One study found that physical activity in combination with a high protein intake over 12 weeks in hematological cancer patients [50]. At the same time, they found that a low level of physical activity combined with a high intake of protein led to a decrease in muscle mass and increased fat mass, which supports the result seen in the present study, that physical activity might affect body composition more than nutritional intake. Physical activity is also documented to reduce fatigue [51,52] and improve both handgrip force and functional mobility in hematologic cancer patients [52]. In addition, a higher level of physical activity appears to have beneficial effects in terms of improving sleep, both quality and duration, which is seen to affect QoL [53]. An increased level of sleep-mediating cytokines, such as IL-6, TNF-α, and sTNF-R in cancer patients could cause impaired sleep quality [54].

A change in muscle mass was in the present study affected by the categories physical and functional well-being as well as self-perceived health and QoL or vice-versa. This correlation has also been reported in similar studies of a wide range of cancers [31–33,55], but not in all [56]. Concurrently, QoL is reported to be consistently higher for patients who have high PAL. The largest decrease of QoL, which was found in the categories of functional and physical well-being, is equivalent to the results found in a study where the EORTC QLQ-C30 questionnaire is used as well [57].

Increasing age seems to have a negative effect on change in both muscle mass and weight, which is to be expected. Concurrently, the results show that the five youngest patients all experienced an increase in weight, which had a marked impact on the result. If they were to be considered as outliers and removed from the analysis, the correlation with age would no longer be statistically significant. Conventionally, sarcopenia is caused by many factors, such as decrease in PAL, loss of neuromuscular junctions, changes in hormones, and chronic diseases with inflammation [58,59]. Muscle mass and muscle strength is expected to decrease with age [60], but the presence of severe disease seems to change that.

The dietary composition as well as the investigated food preferences do not seem to have as important an effect on maintenance of muscle mass and weight as expected. However, the results have been obtained from a narrow amount of data due to very small subgroups.

In the present study, the majority did not meet their energy or protein requirements. It is well documented that low energy and protein intake leads to loss of both muscle mass and weight, normally explained by an increase in demands in cancer patients [26,61–63]. Nevertheless, this cannot be confirmed in the present study. The results could possibly have aligned more with those of the former-mentioned studies if the follow-up period had been longer, since larger fluctuations in muscle mass and weight may not be expected short term. In one study, it is suggested that meeting the minimum energy recommendations (25 kcal/kg/day) may not be sufficient to attenuate loss of muscle mass in head and neck cancer patients [64]. On the contrary, it has been demonstrated that an intake of protein at 1.2 g/kg/day in hematological cancer patients had a positive impact on muscle mass changes [50]. The recommendation of 1.2–1.5 g/kg/day is based on such studies [65], but other studies in cancer patients did not disclose this effect, not even in patients in remission [66]. The present results could not confirm the recommendation either and explanations could be several. Besides the already-mentioned short follow-up period, the patients might have had a relatively good nutritional status when enrolled in our study, which could be explained by the national treatment guarantee giving patients a legal right to start treatment within 4 weeks after the diagnosis has been established in all malignant diseases.

A decreased appetite and taste alterations are well known side effects from cytostatic treatment [28,67] but the present results do not support these findings, neither concerning decreased appetite nor residual flavor, and no correlations between decreases in either muscle mass nor weight was found, in contradiction to other reported results in similar patient groups [68] and in patients with lung cancer [69]. There are some challenges in our method regarding the estimations of decreased appetite and the presence of residual flavor since the construction of the scales exclusively made it possible to measure respectively the absence of decreased appetite and the presence of residual flavor. On the opposite. It was not possible to measure increased appetite or improved taste because it was estimated from a "one-way" scale. Results might have aligned with the previous mentioned studies.

Considering the study's strengths, worth mentioning are the close monitoring and the insurance of data validity, as well as statistical analysis encompassing confounders. The repeated use of the 24 h dietary recall method, including intake at both weekdays and weekend days, decreases the risk of errors due to day-to-day variation [70]. A study comparing the 24 h dietary recall method with the doubly-labeled water method, found three 24 h dietary recalls to be sufficient when estimating energy intake [71]. They did not find additional recalls to improve the estimation further. In spite of that, is must be reasonable to assume that day-to-day variations have been eliminated to a satisfying extent in the present study.

The study design has some limitations as well, the short follow-up period being the most obvious, which also to some degree counteracts the close monitoring. This results in a fragmented understanding of the challenges that the patients may face, which mean that important confounders might be overlooked. Furthermore, the size of the study cohort limits the opportunity to achieve an adequate understanding of the relationship between nutritional intake, QoL, physical activity, and muscle atrophy. A combination of a larger study cohort and a prolonged follow-up period might have allowed the methodical strengths of this study to be more prominent.

There was a potential heterogeneity within the patient group in terms of both diagnosis, treatment regimens of different intensity, varying duration between initiation of chemotherapy and monitoring of the patient, and different degrees of response to the cytostatic treatment with a risk that these may constitute confounding variables. However, the size of the study cohort does not enable any analysis of the possible influence of the individual factors. Further larger, controlled studies with a homogeneous patient cohort and a longitudinal design with longer monitoring are therefore warranted.

5. Conclusions

We have shown that nutritional and lifestyle-related factors affected the change in weight and muscle mass in patients with hematological cancer. The effect on muscle mass and weight was most evident in relation to physical activity, while dietary components seem to have less importance. Our study needs further validation in larger studies, including associations with clinically relevant variables such as treatment response and long-term outcome of the malignancy. Intervention studies investigating the impact of programs for dietary measures and physical activity on treatment toxicity, response, survival and QoL are also justified.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author on reasonable request.

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