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Special Issue Reprint

Diet, Nutrition, Supplements and Integrative Oncology in Cancer Care

Edited by
Moshe Frenkel

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Diet, Nutrition, Supplements and Integrative Oncology in Cancer Care

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Editorial

Editorial: Diet, Nutrition, Supplements, and Integrative Oncology in Cancer Care

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Abstract: The Special Issue *"Diet, Nutrition, Supplements and Integrative Oncology in Cancer Care"* brings together emerging evidence and international perspectives on the pivotal role of nutrition and integrative approaches in oncology. Eight peer-reviewed articles explore the interface between dietary interventions, supplement use, and integrative care models. Collectively, these studies underscore that nutritional and complementary strategies are not peripheral but fundamental to improving patient outcomes, treatment tolerance, and quality of life. The collection has achieved wide dissemination—over 35,000 views and 33 citations—reflecting the growing global engagement with evidence-based integrative oncology. This Editorial summarizes the contributions of each paper, highlights cross-cutting insights, and situates their importance within a broader scientific and clinical context. Nutrition and dietary supplements are essential components of modern integrative oncology, supporting a transition toward patient-centered, holistic cancer care.

Editorial

The integration of diet, nutrition, and evidence-based complementary modalities into cancer care has become one of the most dynamic and transformative trends in contemporary oncology. Historically, oncology has focused primarily on tumor-directed treatments—surgery, chemotherapy, radiotherapy, and targeted therapies—while other determinants of patient outcomes have received less systematic attention. However, as cancer survivorship grows and the biological complexity of the disease becomes more well understood, it is increasingly evident that optimal care extends far beyond cytotoxic or molecular interventions.

Malnutrition, sarcopenia, and metabolic dysregulation remain highly prevalent among patients with cancer, affecting 30–80% of individuals depending on disease site and stage. These factors are not merely secondary complications but powerful determinants of treatment response, toxicity, and survival. Evidence demonstrates that nutritional deficiencies correlate with higher rates of infection, prolonged hospitalization, decreased treatment adherence, and impaired recovery. Conversely, adequate nutritional support has been shown to improve functional status, mitigate side effects, and enhance resilience throughout the cancer continuum.

Diet and supplements thus serve dual functions: they sustain physiological integrity during therapy and contribute to a biological milieu less favorable to tumor progression. Beyond macronutrients, bioactive compounds—such as polyphenols, omega-3 fatty acids, vitamins, and plant polysaccharides—can modulate inflammation, oxidative stress, immune response, and metabolic signaling. These molecular pathways bridge nutrition science with oncologic outcomes and highlight the mechanistic foundation for integrative interventions.

Within this context, integrative oncology provides a conceptual and clinical framework for incorporating nutrition and supplementation into patient-centered care. Defined as the evidence-informed use of complementary therapies alongside conventional treatment, integrative oncology emphasizes the whole person rather than the tumor alone. Nutrition, physical activity, stress reduction, and psychosocial support together form a comprehensive therapeutic ecosystem that optimizes healing capacity and quality of life [1–3].

The Special Issue *"Diet, Nutrition, Supplements and Integrative Oncology in Cancer Care"* was established to advance scholarly discussion, showcase emerging evidence, and facilitate collaboration among clinicians and scientists working at this interface. To date, eight papers have been published, collectively representing a diverse and high-impact contribution to the field.

Akad et al. [4] compared total versus subtotal gastrectomy in gastric cancer patients and assessed postoperative nutritional and biochemical parameters. Their study demonstrated how surgical choice directly influences nutritional recovery and metabolic stability, emphasizing the centrality of nutritional follow-up and individualized diet planning in oncologic surgery.

Berretta et al. [5] presented data from a multicenter retrospective study evaluating an integrative medicine model for cancer care. Their findings reveal that combining evidence-based complementary therapies—including nutritional counseling and dietary supplements—with standard oncologic treatment can significantly improve patient-reported outcomes and quality of life. This real-world analysis exemplifies how integrative frameworks can enhance multidisciplinary coordination.

Keizman et al. [6] reported prospective phase II data on the use of modified citrus pectin in men with non-metastatic biochemically relapsed prostate cancer. The study demonstrated durable disease stabilization with minimal toxicity, suggesting that certain natural compounds may have biologically meaningful roles when studied systematically in well-defined patient populations.

Andreazzoli et al. [7] explored an integrative approach to multiple myeloma care, emphasizing nutrition, supplements, and complementary modalities as core elements of supportive management. The authors propose a conceptual model for multidisciplinary collaboration, aligning nutritional strategies with pharmacologic regimens to reduce toxicity and strengthen patient resilience.

Garutti et al. [8] offered a comprehensive review of nutritional management for oncological symptoms such as anorexia, cachexia, mucositis, and dysgeusia. They highlight early nutritional assessment and intervention as essential to mitigating side effects and improving functional outcomes. Their synthesis positions the dietitian as an integral member of the oncology team.

Frenkel et al. [9] proposed a structured, ethical framework for clinicians when patients request to add dietary supplements during treatment. The suggested model emphasizes open communication, shared decision-making, and critical evaluation of available evidence. This article directly addresses one of the most common and complex encounters in integrative oncology—how to balance patient autonomy with clinical responsibility.

Afonso et al. [10] conducted a systematic review of vitamin D supplementation in oncology, concluding that while mechanistic rationale and observational associations are strong, clinical evidence remains heterogeneous. They call for rigorously designed randomized trials to determine optimal dosing and target populations, illustrating the need for precision in supplement research.

Finally, Cevolani Pires et al. [11] examined omega-3 supplementation in patients with pancreatic neoplasms, showing favorable effects on nutritional status and inflamma-

tory profiles. Their findings support the broader concept that nutritional modulation of inflammation can complement pharmacologic therapy in advanced malignancies.

Together, these eight papers illustrate the breadth of scientific inquiry at the intersection of diet, supplements, and cancer care. From mechanistic insights to clinical implementation, they collectively affirm that nutritional strategies are vital components of integrative oncology. Several overarching messages emerge.

First, nutrition and supplementation should be integrated early—beginning at diagnosis and extending through treatment, survivorship, and palliative care. Early intervention prevents deterioration of nutritional status and supports physical and psychological resilience. Second, evidence-based supplements, when appropriately selected and monitored, can complement conventional treatments without compromising safety or efficacy. Third, methodological rigor is paramount. As the demand for integrative approaches grows, only well-designed studies can provide the clarity needed for clinical guidelines and policy development.

The clinical relevance of these findings is underscored by converging international recommendations. The American Cancer Society emphasizes diet, physical activity, and weight management as central to both prevention and survivorship [1]. The joint SIO–ASCO clinical guidelines endorse integrative therapies—including nutritional counseling—as effective for symptom management during and after cancer treatment [2]. The World Cancer Research Fund and American Institute for Cancer Research likewise advocate for dietary patterns rich in plant-based foods and limited in processed meats, sugars, and alcohol as part of global cancer control strategies [3].

In integrative oncology, nutrition and supplementation are not adjunctive luxuries but evidence-supported necessities. They shape immune competence, metabolism, treatment tolerance, and emotional well-being. Moreover, nutrition provides patients with a sense of agency—a tangible way to participate actively in their own recovery. This empowerment is particularly significant in the face of chronic disease and uncertainty, aligning the biological and psychological dimensions of healing.

The impressive readership and citation data for this Special Issue—over 35,000 views and 33 citations—reflect a growing appetite for credible information in this space. Clinicians, dietitians, and researchers across disciplines are increasingly seeking practical frameworks to navigate the complex landscape of dietary claims and supplement use. By curating scientifically grounded content, this Special Issue contributes to elevating the discourse from anecdote to evidence.

Equally important is the diversity of its authorship. Contributors from Europe, the Middle East, and the Americas underscore the universal relevance of nutrition in oncology and the shared recognition that cultural and dietary diversity must inform care models. This international engagement fosters cross-pollination of ideas, supports regional adaptation of integrative practices, and promotes collaboration among institutions with complementary expertise.

As integrative oncology matures, several research priorities emerge. Future studies should explore the synergy between dietary interventions and conventional treatments, including immunotherapy and targeted agents. Advances in nutrigenomics and metabolomics hold promise for personalizing nutrition-based therapies, while longitudinal research is needed to clarify long-term survival and quality-of-life benefits. Health-policy analyses should assess the cost-effectiveness and accessibility of integrative nutritional services to ensure equitable implementation across healthcare systems.

Clinicians are encouraged to apply the lessons from these eight contributions in daily practice. Early referral to oncology nutrition specialists, systematic screening for supplement use, and open dialogue about evidence-based integrative options can trans-

form the patient experience. Integrating diet and supplement discussions into multidisciplinary tumor boards and survivorship programs can also normalize their role within mainstream oncology.

The achievements of this Special Issue attest to the maturity and momentum of integrative oncology as a scientific discipline. They also reflect the dedication of authors, reviewers, and readers committed to advancing a holistic, evidence-driven approach to cancer care. By uniting research on diet, nutrition, and supplementation, this collection not only informs clinical practice but also inspires continued inquiry into how we nourish the body, mind, and spirit through the cancer journey.

In conclusion, diet and nutrition are not ancillary considerations but essential foundations of integrative oncology. Evidence-based supplementation, when applied judiciously, can further enhance the therapeutic landscape. Together, these interventions embody a vision of cancer care that is scientifically rigorous, humanistic, and patient-centered—a vision that this Special Issue both exemplifies and advances.

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

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Article

Modified Citrus Pectin Treatment in Non-Metastatic Biochemically Relapsed Prostate Cancer: Long-Term Results of a Prospective Phase II Study

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Abstract: The optimal therapy for patients with non-metastatic biochemically relapsed prostate cancer (BRPC-M0) after local therapy is elusive. Thus, the evaluation of new non-toxic compounds in BRPC-M0 patients is warranted. PectaSol®-Modified citrus pectin (P-MCP) is a food supplement categorized as GRAS (Generally Recognized As Safe) by the FDA. It is a competitive inhibitor of the galectin-3 protein, which is involved in cancer pathogenesis. In an early report of the present phase 2 study, P-MCP treatment for 6 months led to prostate-specific antigen doubling time (PSADT) improvement in 75% of patients with BRPC-M0. Herein, we report the second long-term treatment phase of an additional 12 months of P-MCP therapy (4.8 g × 3/day orally) in patients without disease progression after the initial 6 months of therapy. Of the 46 patients that entered the second treatment phase, 7 patients withdrew consent and decided to continue therapy out of pocket, and 39 initiated the second treatment phase. After a total of 18 months of P-MCP treatment, 85% (n = 33) had a durable long-term response, with 62% (n = 24) showing decreased/stable PSA, 90% (n = 35) PSADT improvement, and all with negative scans. No patient had grade 3/4 toxicity. In conclusion, P-MCP may have long-term durable efficacy and is safe in BRPC-M0.

Keywords: modified citrus pectin; non-metastatic biochemically relapsed prostate cancer

1. Introduction

Globally, prostate cancer is the second most common solid tumor [1] and cause of cancer-related death in men from Westernized countries [2]. Although its etiology needs further elucidation, risk factors for prostate cancer development include age, family history, lifestyle, and hereditary syndromes [3]. With an age-standardized incidence rate of 31 per 100,000 [1] and approximately 1.5 million new cases reported in 2020 [1,4], prostate cancer

incidence is increasing worldwide [4,5] and presents a significant economic burden [6]. However, with the rapid evolution of treatment options [7], and changes in screening protocols [8], prostate cancer-related mortality patterns have stabilized [5]. Primary treatment options for localized prostate cancer include radical prostatectomy, radiation therapy, and androgen deprivation therapy (ADT) for advanced cases [9]. Within 10 years of treatment, 20–50% of patients will experience a biochemical relapse, with rising PSA and negative scans (BRPC-M0) [9–13]. In BRPC-M0 state, patients may remain asymptomatic and free of clinical evidence of disease for many years [14], and the PSA doubling time (PSADT) is a significant prognostic factor for development of future metastases and mortality [10,13,15–17]. The optimal therapy of patients with BRPC-MO is elusive [10,11,17–22] Androgen Deprivation Therapy (ADT) in this setting is associated with an uncertain survival benefit, may negatively impact quality of life, and increase comorbidities such as cardiovascular [10,14,23–25].

Thus, there is a need to evaluate new non-toxic therapies for BRPC-M0 [2,10,11,26–40]. Pectins comprise carbohydrate-soluble fiber found in plant cell walls and are indigestible to humans in their unmodified form [39]. Modified citrus pectin (MCP), with shorter polysaccharide units, are water soluble [39] and have demonstrated significant anticancer activity [38,39,41,42], potentially by disrupting tumor-promoting signaling by binding galactose-containing side chains to the carbohydrate recognition domains of galectins [38,43,44]. Galectins comprise an evolutionarily conserved family of endogenous glycan-binding proteins and they play multifunctional roles in tumor progression [38] through modulating and recalibrating inter- and intra-cellular signaling [45]. Galectins affect cellular responses, including cell aggregation, growth, differentiation, apoptosis, and proliferation [38,45,46], and may promote immune evasion of cancer cells [47]. Galectins, including Galectin1 (GAL1) and GAL3, have therefore been explored as potentially effective therapeutic targets for cancer patients [38,48,49].

PectaSol®-Modified Citrus Pectin (P-MCP; EcoNugenics Inc., Santa Rosa, CA, USA) is a commercially available polysaccharide and is a Galectin-3 (Gal-3) inhibitor, binding to the Galectin-3 carbohydrate recognition domain [38,43]. Derived from the pith of citrus fruit peels, and classified by the US-FDA as generally regarded as safe (GRAS), data suggest that P-MCP is associated with cytotoxicity and inhibition of cancer cells [39,50], including prostate cancer cells [30,38,41,42].

In clinical trials evaluating new compounds in BRPC-MO, common endpoints include PSA dynamics as reflected by the PSADT [17,21,51,52] and are used as surrogate endpoints, both as predictive and as stratification factors for clinical disease progression [17,53]. Prolongation of PSADT may be an early signal of efficacy of active compounds in clinical trials [24,26,54].

In previous clinical trials in BRPC-MO, P-MCP therapy was associated with a positive effect on prostate-specific antigen (PSA) dynamics, including a decrease in PSA level and lengthening of PSADT in a significant proportion of patients, [30,41]. A prolongation of PSADT was shown with P-MCP therapy for 6 [30] and 12 [41] months. Herein, we report the efficacy with an extended total treatment period of 18 months, using the cohort reported previously by Keizman et al. (Nutrients 2021) [30], for which an early benefit was reported after 6 months of P-MCP therapy.

2. Methods and Materials

Study design: The eligibility criteria are described in our previous publication [30]. Briefly, patients with BRPC-M0, rising PSA post-primary therapy (surgery and/or radiation), and negative scans were included. All patients had a normal level of serum testosterone > 150 ng/mL and Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 at study entry. All participating patients signed an Institutional Review Board (IRB)-approved consent form. Study participants were recruited between 2013 and 2019 from 5 medical centers in Israel (Meir, Rabin, Rambam, Soroka, and Tel-Aviv Sourasky). Patients were given 4.8 g of P-MCP to take orally 3 times per day for the duration of the

study. The P-MCP was provided by PectaSol-C®, EcoNugenics, Santa Rosa, CA, USA, in packs of 270 capsules. Patients without evidence of disease progression or dose-limiting toxicity after 6 months of therapy (n = 46) entered the second long-term phase of the study and were given an additional 12 months of treatment. A total of 39 patients completed the full 18 months of treatment. The study design is described in Figure 1.

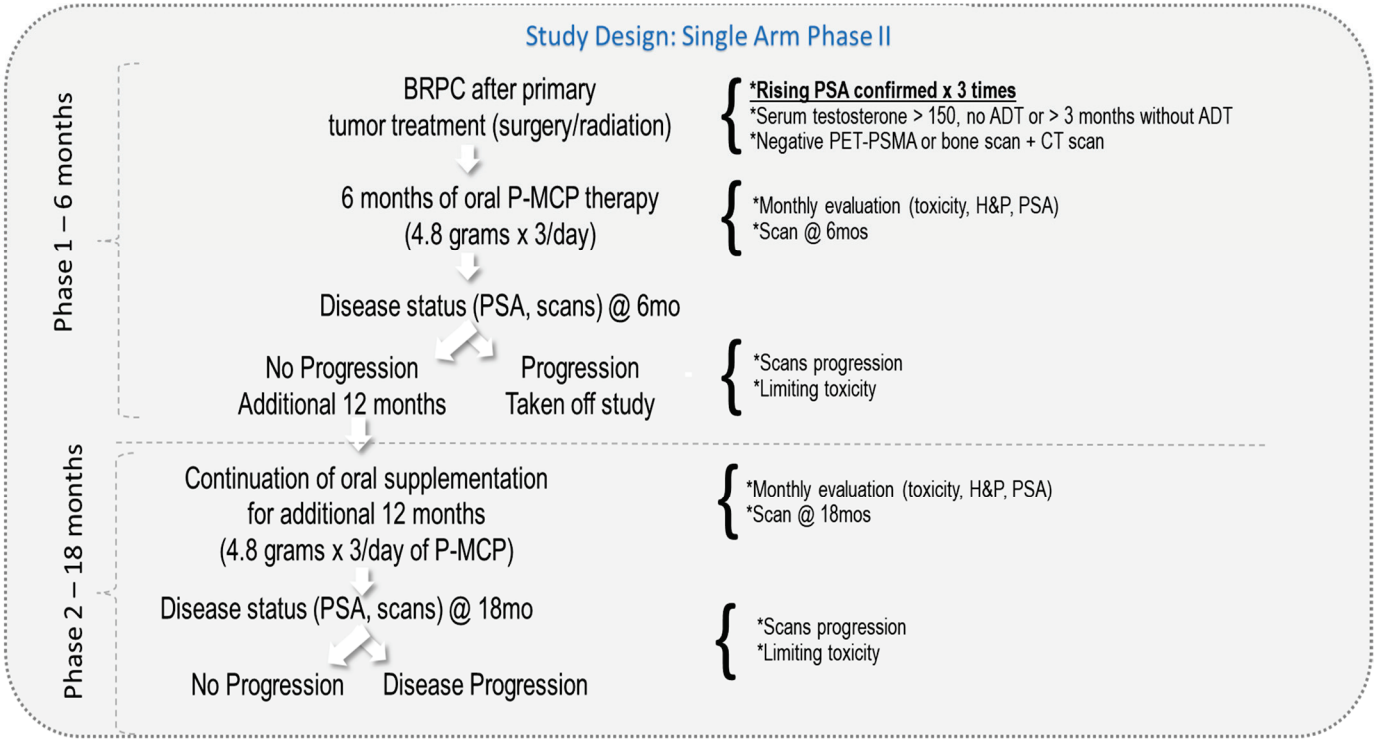

Figure 1. Study design.

Evaluation of disease status: Patients underwent monthly visits for toxicities, physical examinations, and serum PSA, with baseline measurements taken prior to starting the P-MCP treatment protocol. A positron emission tomography (PET)—prostate-specific membrane antigen (PSMA) scan was conducted after 6 and 18 months in patients without clinical or PSA progression, or earlier upon clinical or PSA progression. The primary efficacy endpoint was the rate of patients without PSA progression (defined as an increase of $\geq$ 25% from baseline) and/or patients with improvement (lengthening) of PSADT versus baseline. The post-baseline PSADT was calculated using baseline PSA measurements obtained at the start of the study and every month during treatment. Secondary endpoints included the rate of patients without radiologic progression and toxicity, and with treatment benefits according to the PSADT risk grouping (e.g., poor < 3 months, intermediate 3–8.99 months, and good $\geq$9 months) [30].

Duration of treatment: Treatment as per the protocol continued for 12 additional months or until biochemical or clinical disease progression or dose-limiting toxicity.

Disease progression was defined as biochemical progression without PSADT prolongation and/or new radiological evidence of metastases.

Safety evaluation of toxicity: Toxicity was defined according to the National Cancer Institute (NCI) Common Toxicity Criteria, with treatments terminated at grades 3/4 and patients monitored weekly until $\leq$grade 1 before restarting therapy. Treatment would be discontinued upon the recurrence of a same grade 3/4 event and for any toxicity requiring longer than 4 weeks to recover to $\leq$grade 1.

Statistical analysis: Comparisons between pre- and post-treatment endpoint parameters, and within groups were analyzed using the Wilcoxon Signed Rank test for abnormally distributed data, or the two-tailed Student t-test for normally distributed data, with re-

sults reported as number, percentage, mean or median, and standard deviation (SD). A p-value ≤ 0.05 was considered statistically significant.

Regulatory Considerations: The research was conducted in accordance with the approval by the IRB committee of our institution. The study was registered at ClinicalTrials.gov (accessed on 10 September 2012) (NCT01681823).

3. Results

Patients: Of the 46 patients that displayed a benefit from the initial 6 months of therapy (in terms of stabilization/decrease of PSA, and/or improvement of PSADT, and with negative scans) and that were eligible for the second phase of an additional 12 months of therapy (to create a total of 18 months of treatment), 7 patients withdrew consent during the first month of the additional year of therapy and chose to continue the effective therapy independently, out of pocket, due to the travel distance to monthly medical visits. Thus, 39 patients were treated as per the protocol for a total of 18 months of treatment. Patient pre-treatment characteristics are summarized in Table 1.

Table 1. Pre-treatment (baseline) patient characteristics.

Parameter	***n* = 39**
Age (years): Median (range)	75 (52–88)
Gleason: % (*n*)	
6	41% (*n* = 16)
7	38% (*n* = 15)
8–10	21% (*n* = 8)
Local therapy: % (*n*)	
Radical prostatectomy	18% (*n* = 7)
Radiation therapy	54% (*n* = 21)
Surgery+RT	28% (*n* = 11)
Prior ADT	38% (*n* = 15)
PSA (ng/mL): Median (range)	4.1 (0.28–30)
PSADT (months) risk grouping: % (*n*)	
Poor < 3	8% (*n* = 3)
Intermediate 3–8.99	33% (*n* = 13)
Good ≥ 9	59% (*n* = 23)
PSADT (months): Median (range)	
Whole cohort	10.3 (1.4–55)
Poor PSADT risk	1.6 (1.4–1.8)
Intermediate risk	5.12 (3.5–8.2)
Good risk	14.74 (9.10–54.6)

Long-term outcome as determined by PSA level, PSADT, and disease progression: Out of the 39 patients that entered the second phase of the study (the additional 12 months of therapy, creating a total of 18 months), 85% (*n* = 33) demonstrated a decreased or stable PSA (Figure 2) and/or improvement of PSADT (54%, *n* = 21), with negative scans (90%, *n* = 35). Median PSADT improved significantly versus baseline ($p = 0.003$), from a median pre-treatment PSADT of 10.3 (median range = 1.4–54.6) months to a median post-treatment PSADT of 43.5 (median range = 3.5–981.0) months (Tables 1 and 2).

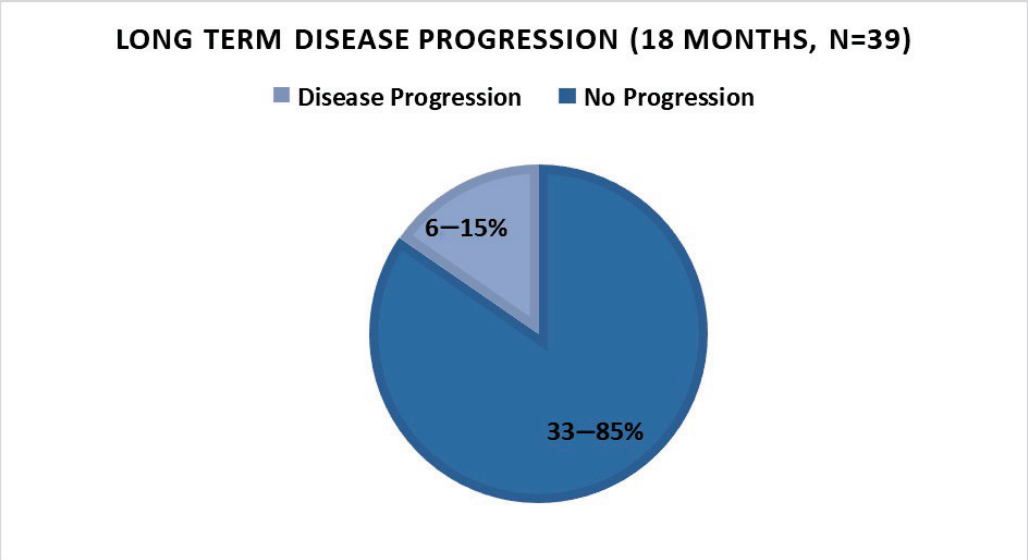

Figure 2. Disease progression status after 18 months of PectaSol®-Modified Citrus Pectin (P-MCP) therapy.

Table 2. Treatment characteristics and responses after 18 months of PectaSol®-Modified Citrus Pectin (P-MCP) therapy.

Parameter	Whole Cohort (n = 39)	According to Pre-Study PSADT (Months) Risk Grouping		
		Poor <3.00 (n = 3)	Intermediate 3.00–8.99 (n = 13)	Good ≥9.00 (n = 23)
Overall response to therapy (decrease or stabilization of PSA, and/or lengthening of PSADT, with negative scans)	85% (n = 33)	66% (n = 2)	77% (n = 10)	91% (n = 21)
PSA response Stable/decreased Progression	 54% (n = 21) 46% (n = 18)	 67% (n = 2) 33% (n = 1)	 23% (n = 3) 77% (n = 10)	 70% (n = 16) 30% (n = 7)
PSADT (months): Median (range)	43.5 (3.5–981)	9.8 (6–200)	18.3 (6.7–500)	47.7 (3.5–981)
PSADT (months) risk grouping: % (n)		0% (n = 0)	13% (n = 5)	87% (n = 34
PSADT lengthening	90% (n = 35)	100% (n = 3)	92% (n = 12)	87% (n = 20)
Change to a better PSADT risk grouping	36% (n = 14)	100% (n = 3)	85% (n = 11)	not applicable
Radiologic response Negative scans	 90% (n = 35)	 67% (n = 2)	 75% (n = 11)	 96% (n = 22)
Disease progression	10% (n = 4)	33% (n = 1)	15% (n = 2)	4% (n = 1)

The benefits of 18 months of therapy in terms of PSA stabilization or decrease and/or PSADT lengthening were seen in all PSADT risk groups (Table 2). There was also an improvement in PSADT risk grouping after 18 months of treatment (Table 2 and Figure 3). After 18 months of P-MCP therapy, all patients with a pre-treatment PSADT risk grouping of poor (<3 months) improved their PSADT to an intermediate–good risk, and most patients (77%) with a pre-treatment risk PSADT of intermediate improved their PSADT risk to good (Table 2 and Figure 3). In patients with a good risk pre-treatment PSADT, 91% retained their risk grouping, 87% of whom had an improved PSADT. After 18 months of therapy, no patients remained in the poor risk PSADT group, and the proportion of patients with a PSADT risk of good (≥9.00) increased from 59% (n = 23) at baseline to 87% (n = 34) after

18 months of therapy (Figure 3). The pre-treatment (baseline) distribution of PSADT risk groupings improved after 18 months of P-MCP therapy, with the proportion of patients in the poor risk PSADT group decreasing from 8% to 0%. Similarly, the proportion of patients in the intermediate PSADT risk group decreased from 33% to 13%, and the proportion of patients in the good risk group increased from 59% to 87% (Tables 1 and 2). There was a significant change in the median PSADT after 18 months of P-MCP therapy (Table 2) as compared to baseline (Table 2) for patients with a pre-treatment PSADT good risk (45.9 versus 14.7 months, $p = 0.027$) and intermediate risk (22.75 versus 5.1 months, $p = 0.0015$). Disease progression during the 18 months of therapy was observed in 18% ($n = 7$) of patients, 8% ($n = 3$) of which had PSA progression only (without radiological progression) and 10% ($n = 4$) had both PSA and radiologic progression.

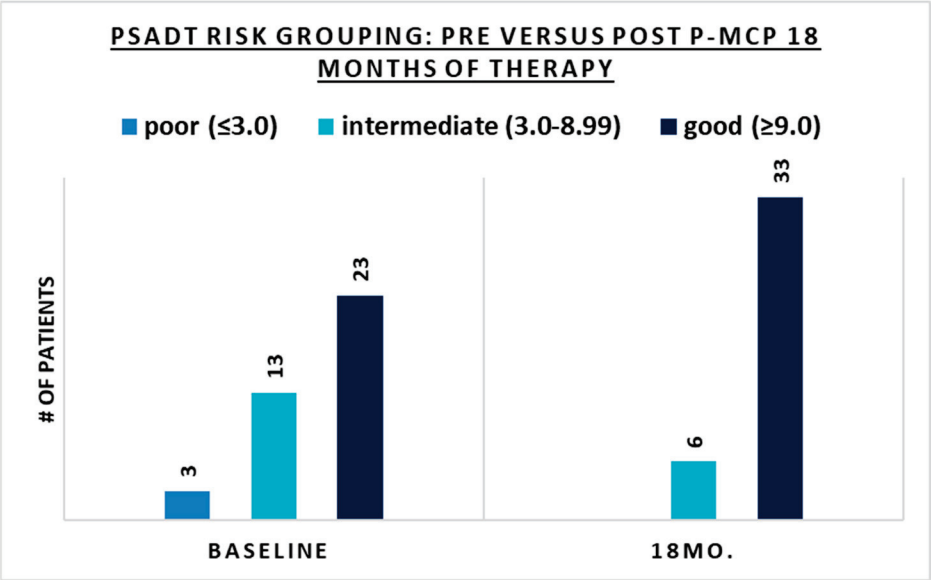

Figure 3. The number of patients in each PSADT risk group at baseline and after 18 months of PectaSol®-Modified Citrus Pectin (P-MCP) therapy.

Toxicity and compliance: None of the patients had grade 3/4 toxicity during the 18 months of therapy. Grade 1 toxicity was observed in 30% ($n = 12$) of patients during the first 6 months of therapy, and in 23% ($n = 9$) during the subsequent 12 months of therapy. This was transient and reversible bloating that did not require treatment discontinuation.

4. Discussion

Prostate cancer is a leading cause of death in men worldwide [1], with non-metastatic biochemical disease progression after primary treatment presenting as a therapeutic challenge [10,20]. In the setting of BRPC-M0. there is no proven standard therapy [2,10,11,14,20]. While ADT is effective in lowering PSA level, its long-term survival benefit is not proven, and it is toxic. Thus, there is a need to investigate less toxic compounds in this setting [26,28,30,31,41].

In an earlier report of the present trial, 6-month therapy with PectaSol®-Modified Citrus Pectin (P-MCP; EcoNugenics Inc., Santa Rosa, CA, USA) [30] led to a benefit in a significant proportion (78%) of patients with BRPC-M0. Herein, we reported continuation of a durable benefit after 12 more months of therapy in this cohort, with 85% of patients having a durable long-term response, 62% a decreased/stable PSA (versus baseline pre-treatment PSA), 90% a PSADT improvement (versus pre-treatment PSADT), and all with negative scans.

PSADT is the most important clinical prognostic factor in patients with BRCP-M0 and is associated with the development of future metastases [10,13,15–17,25]. Lengthening of

PSADT may be indicative of an effective therapeutic intervention [52]. Thus, the findings of the present study may suggest that therapy with P-MCP is active in managing BRPC-M0 patients over a durable period. Furthermore, most (95%) of the patients in the present study improved or kept to their PSADT risk grouping. Especially, all patients with a baseline pre-treatment poor PSADT risk, improved their risk grouping. Finally, the benefit of long-term P-MCP therapy was shown without significant toxicity, suggesting that P-MCP can be safely administered [16,20]. A major limitation of the present study is the lack of a placebo (control) arm. Additionally, the present study cohort is relatively small. Furthermore, although retrospective studies have shown that PSADT is a strong predictor of metastasis-free survival, overall survival [11,13], or both [26,53], further validation is required to establish whether change in PSADT is an acceptable endpoint for clinical trials in this patient population. Finally, due to the relatively small cohort of the present study, we were unable to correlate our results with the type of local therapy and to analyze predictive factors for the efficacy of P-MCP therapy (e.g., medications, smoking status, level of androgens, and genetic alterations). Moreover, genetic data were not collected during the present study. These should be tested in future studies. Nonetheless, numerically, P-MCP therapy in the present study was associated with a significant improvement of the expected progression rate in these patients, since, as per the historical data on the natural history of BRPC-M0, without active therapy, 80% of patients are expected to progress within 6 months [30]. In conclusion, in the present study we demonstrated that P-MCP therapy may be associated with a sustained benefit and is safe in patients with BRPC-M0. Future randomized larger clinical trials are needed to validate the present study results and to reveal the underlying mechanism of P-MCP therapy as a galectin inhibitor [38].

Author Contributions: D.K., M.F., A.P., I.K., E.R., D.S., I.L., R.M., O.Y., D.M., K.R., A.S., H.D. and I.E. contributed equally to this work. D.K. and I.E. devised the concept and designed the study. D.K., M.F., A.P., I.K., E.R., D.S., I.L., R.M., O.Y., D.M., K.R., I.W., R.G. and H.D. conducted the most experiments. D.K. and I.E. contributed to the manuscript writing. All authors have read and agreed to the published version of the manuscript.

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

Data Availability Statement: The data presented in the study are available with the investigator Daniel Keizman.

Conflicts of Interest: I.E. discloses being the developer of the sponsoring dietary supplement company but holds no ownership in the company. The other authors declare no potential conflict of interest.

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Review

Addressing Patient Requests to Add Dietary Supplements to Their Cancer Care—A Suggested Approach

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Abstract: Dietary supplements are widely utilized by cancer patients as part of a complementary and integrative approach to their healthcare. However, a significant portion of patients refrain from discussing their supplement use with their physicians, often due to the perceived indifference or negativity of their healthcare providers. This communication gap exposes patients to unreliable information sources and potential risks associated with uninformed supplementation. As the healthcare landscape evolves, there is an increasing recognition of the pivotal role that physicians play in guiding patients' healthcare decisions. A patient-centered perspective prioritizes the provision of evidence-based information tailored to the individual's needs. It advocates for open discussions about potential risks and fosters shared decision making, respecting patient autonomy. Additionally, this approach involves offering alternative options, documenting patient preferences, and ensuring ongoing support while coordinating with the healthcare team. To address these evolving needs, healthcare providers must adopt a transformative perspective, becoming expert guides who engage with their patients as informed and empowered participants. This revised approach emphasizes an open dialogue that balances presenting facts and acknowledging uncertainties surrounding dietary supplement use. Our narrative review of the literature underscores the importance of a practical approach, centered on transparent discussions and respect for patient autonomy. By following this approach, healthcare providers can empower patients to navigate the complexities of dietary supplement use within the context of cancer care, thereby safeguarding patient safety and overall well-being. Notably, our proposed tool highlights the utilization of reliable sources, the risk stratification of supplements, specific recommendations, and subsequent monitoring, providing a structured framework for informed decision making.

Keywords: complementary medicine; alternative medicine; integrative medicine; cancer care; oncology; nutritional supplements; natural products; dietary supplements; unmet needs; patient-centered care; patient–doctor communication; compassion; empathy

1. Introduction

A recent consumer survey conducted by the Council for Responsible Nutrition (CRN) unveiled an interesting trend in American healthcare habits: approximately three-quarters of Americans incorporate dietary supplements into their daily routines, with many users attributing the use of these supplements to their overall well-being [1].

Dietary supplements (DSs) represent a category of products designed to augment one's diet by providing dietary elements, such as vitamins, minerals, herbs or botanicals, amino acids, and other such constituents. These supplements come in various forms, such as pills, capsules, tablets, and liquids [2].

Among the diverse array of complementary and integrative therapies adopted by cancer patients, DSs rank among the most accessible and widely embraced. Previous studies have suggested that anywhere from 20% to 90% of individuals affected by cancer turn to these products as part of their healthcare regimen [3,4].

Despite their common use, patients tend to shy away from discussing their DS usage with their healthcare providers [5,6].

Moreover, healthcare professionals have voiced concerns about unsupervised supplement use potentially leading to adverse effects and unfavorable interactions, particularly in the context of cancer patients undergoing active treatment. For instance, according to animal studies in the Physician Data Query [7], vitamin C has been found to reduce the bioavailability of imatinib. Additionally, animal studies have indicated that vitamin C might hinder apoptosis when used alongside medications like doxorubicin, cisplatin, vincristine, methotrexate, and imatinib [8]. Pre-clinical research has also shown that EGCG, or green tea extract, can potentially counteract the anti-cancer effects of bortezomib. It is essential to note that most of these adverse interactions have only been observed in animal studies [7].

Regrettably, our current understanding of the effectiveness of DSs in cancer care remains limited, with only a handful of benefits substantiated through clinical trials. A systematic review from 2012 suggested that there were insufficient data to endorse the use of DSs in westernized populations, although vitamin D and omega-3 fatty acids were notable exceptions [9]. In a more recent development, the 2018 World Cancer Research Fund/American Institute for Cancer Research Report cast doubt on the potential of DSs to enhance the prognosis or overall survival after a cancer diagnosis, drawing on evidence from observational studies and clinical trials [10]. According to this report, the primary course of action should be to obtain essential nutrients from dietary sources, with supplements to be considered only when a deficiency is demonstrated either biochemically (e.g., low plasma vitamin D levels, B12 deficiency) or clinically (e.g., low bone density). The authors added that DSs should also be contemplated when nutrient intake persistently falls below two-thirds of the recommended levels. The report unequivocally discouraged the use of supplements for cancer prevention.

Given this consensus among experts about the lack of evidence supporting the use of DSs for cancer patients, and the potential risks associated with their use alongside cancer treatments, the question arises as to why DSs remain popular among patients.

In one study, nearly 40% of patients attending an integrative oncology clinic in a major comprehensive cancer center said they arrived with the intention of discussing their supplement usage [11]. Of these patients, 75% were already using vitamins, and nearly 30% were using herbs before their consultation, all with the expectation of addressing these matters with their physicians.

In a more recent study at another comprehensive cancer center, approximately 50% of adult patients with breast, colorectal, lung, or prostate cancers undergoing active treatment reported using various DSs [12].

Furthermore, numerous studies have indicated that even cancer survivors are more inclined to use DSs [13,14]. In one study, the prevalence of DS use was notably higher among American cancer survivors (70.4%) compared to cancer-free individuals (51.2%) [13].

Recent research has offered the intriguing possibility that these DSs might confer some beneficial effects to cancer patients [15,16]. These findings have suggested that modifying certain nutrients in one's diet could influence the effectiveness of cancer therapies and alleviate cancer-related symptoms [15]. At times, DSs may even enhance the efficacy of cancer treatments [16].

Nutrients can influence epigenetic states through mechanisms that include DNA methylation, histone modifications, and miRNA-dependent gene silencing [17]. These alterations have been associated with either an increased or a decreased risk of cancer development. There is compelling evidence that certain foods play a protective role in

cancer prevention by directly inhibiting tumor progression, or by altering the tumor's microenvironment to create unfavorable conditions for tumor initiation or growth [16,17].

This body of evidence indicates that patients may have valid reasons for exploring DS usage. Consequently, there is a growing need to provide well-informed guidance on this issue in an oncology setting.

To unlock the potential benefits of DSs, additional clinical studies are required to determine the optimal dosages, most effective administration methods, and the bioavailability of various supplements. This ongoing research could validate and maximize the beneficial effects that have already been observed.

In this paper, we shall explore patients' motivations for using DSs and how their use might affect patient–doctor communication, and we will describe a possible approach for addressing the need for guidance on this issue, which has been expressed by patients and families affected by cancer.

2. Motivations for Supplement Use

Understanding the motivations that drive patients to adopt dietary supplements (DSs) is pivotal, especially in the context of cancer care. These motivations provide valuable insights into why patients choose to integrate DSs into their journey with cancer.

One of the primary motivations for using DSs among cancer patients is the management of treatment side effects [5,6,18–24]. These side effects encompass issues like nausea, fatigue, and digestive challenges often associated with treatments such as chemotherapy, radiation, and immunotherapy. Additionally, patients dealing with anxiety tend to rely more on DSs, seeking psychological support and a sense of empowerment to take charge of their healthcare decisions [20]. For many, the objective of DS use is to enhance their quality of life rather than aiming solely for a cure [5,6,18–20].

Furthermore, cancer patients frequently turn to DSs with the aim of boosting their immune systems [5,6,18–20]. A robust immune response is crucial, helping patients fend off infections, recover from treatments, and maintain their overall health. Many view DSs, particularly those rich in vitamins, minerals, and antioxidants, as allies in fortifying their immune defenses.

Moreover, the fear of cancer recurrence is a prevalent concern among survivors [5,6,19,20]. To allay this anxiety, some individuals resort to DSs, believing in their anti-cancer properties, which they perceive as a protective shield against disease recurrence, and which offer a sense of security and control.

The pursuit of control and empowerment stands as a significant driver of DS usage [5,6,19,20]. A cancer diagnosis can often leave patients feeling adrift in a sea of uncertainty. DSs serve as a means of active participation in healthcare decisions, providing patients with a sense of control and autonomy over their health.

Improving the overall quality of life remains a central objective in using supplements [5,6,19,20]. Patients seek enhancements not only of their physical well-being, but also of their emotional and mental health. The holistic approach offered by supplement use, addressing the body, mind, and spirit, presents an attractive option for enhancing overall well-being.

Cultural factors and deeply ingrained beliefs significantly influence DS use [22–24]. Cultural practices and traditions often encourage specific supplement usage for health and healing, which patients tend to respect and follow.

Additionally, the allure of a natural and holistic approach to health often steers patients toward DSs. Faced with a life-altering diagnosis, patients view supplement use as an act of self-care, a form of self-advocacy that allows them to take charge of their health and play an active role in their treatment journey.

Patients source their information from various channels, including friends, family, the internet, and popular media, which influences their decisions [5,6,19,20]. The credibility and accuracy of these sources vary widely, contributing complexity to the decision-making process.

Recognizing and comprehending these motivations is essential for healthcare providers. It enables them to approach DS discussions with empathy, to engage in productive conversations, address patient concerns, and guide patients toward safe and informed choices. Effective communication should take into account the multifaceted motivations behind supplement use, and aim to support the holistic well-being of patients [19].

3. Challenges in Physician–Patient Communication

Effective communication between physicians and patients with cancer regarding the use of DSs is a multifaceted process fraught with several challenges. These challenges can significantly affect the patient–provider relationship, the quality of care, and patient outcomes [19].

One fundamental challenge is the limited knowledge many physicians have about DSs. Medical education primarily focuses on conventional treatments and pharmaceuticals, leaving healthcare providers ill-equipped to discuss DSs with their patients. This knowledge gap results in a lack of guidance on this topic. A survey of US oncologists revealed that not even half discussed DS use with their patients [23].

On the patient side, there is often a reluctance to disclose supplement use to their physicians [21]. This reluctance can stem from a variety of factors, including a fear of judgment or disapproval, concerns about the physician's lack of knowledge about supplements, a perception that conventional medicine providers do not want them to use alternative therapies, or sometimes even a fear that their physician will discontinue the conventional cancer therapies [18–20]. This lack of openness leads to a breakdown in the exchange of information, with physicians often unaware of their patients' supplement usage [18].

The absence of robust scientific evidence about DS use poses a substantial challenge. Supplements often lack the same level of rigorous research and safety data required of pharmaceutical drugs. The lack of clinical trials and comprehensive evidence make it difficult for physicians to provide evidence-based recommendations or to make informed decisions about supplement use. Both patients and physicians may feel uncertain about the effectiveness and safety of specific supplements [5,6,18–20].

Moreover, clinicians and patients alike may have concerns about the out-of-pocket financial investment that DSs demand, potentially further straining patients' resources and distracting patients from an evidence-based focus on a well-rounded, whole food, plant-based diet. Adult cancer survivors spend approximately USD 6.8 billion annually on DSs [24]. Further research on the safety and efficacy of DS use in patients with cancer is imperative to ensure a balanced cost/benefit ratio.

Time constraints in clinical settings can be a practical challenge. Physicians often have limited time during patient appointments. Discussing DSs can be time consuming, involving a detailed review of the patient's supplement regimen, potential interactions with prescribed medications, and patient education. These time constraints may hinder comprehensive discussions, leaving patients feeling unheard and misunderstood.

In some healthcare systems, physicians may not receive reimbursement for discussing DSs or providing integrative care. This financial disincentive can lead to a lack of motivation to engage in in-depth conversations about supplements with patients, creating a disconnect between patient needs and healthcare provider priorities [19].

Differences in beliefs between patients and physicians can be a significant obstacle to effective communication. While patients may see supplements as a way to complement their conventional treatments and improve their well-being, physicians who do not share this perspective may struggle to effectively communicate or support these choices. These differing beliefs can result in misunderstandings and a lack of trust [19].

Patients often encounter information about DSs that is conflicting, confusing, or misleading. Physicians must help patients with the complex task of sifting through this information by clarifying misconceptions, and providing evidence-based guidance [5,6].

Physicians must also manage patient expectations. Patients may have high hopes for DSs, anticipating significant benefits. Balancing these expectations with realistic, evidence-

based information about the potential benefits and limitations of supplements can be a delicate task [5,6,19].

Trust is built on the belief that physicians have their patients' best interests at heart, and when patients feel their choices are not acknowledged or respected, trust begins to wane [19].

Patients may feel misunderstood by their healthcare providers. DS use is often deeply rooted in patients' beliefs, experiences, and personal wellness philosophies. When physicians fail to appreciate these perspectives and the reasons behind supplement use, patients can feel alienated. This can lead patients to the belief that their healthcare providers lack the understanding needed to offer personalized care, further eroding trust.

A lack of open dialogue can create an atmosphere of secrecy and opacity within the physician–patient relationship. Patients might feel that their physicians are withholding information or are not providing a complete picture of their care. Such feelings of secrecy can breed mistrust, leading to doubts about the transparency and honesty of the healthcare provider.

A breakdown in trust can influence treatment decisions. Patients who perceive their physicians as disregarding their preferences or choices regarding DSs may become more hesitant to follow their treatment plans or make informed decisions about their care. This can have consequences for treatment adherence and outcomes and patients' overall well-being [19,20].

Moreover, a breakdown in trust may drive some patients to seek alternative healthcare providers who are more receptive to discussing and supporting DS use. While this can provide patients with a sense of understanding and alignment with their values, it may not always lead to the best healthcare outcomes, especially if the alternative providers lack conventional medical training or fail to communicate with the patients' physicians [5,6,19].

Balancing their patients' need for autonomy with the need to make well-informed choices is a challenge for healthcare providers. Encouraging open discussions, providing evidence-based information, and engaging in shared decision making are vital steps for supporting patient autonomy. This balance ensures that patients may make autonomous, well-informed choices about DSs while prioritizing their safety and overall well-being [19].

4. Developing an Approach to Address Cancer Patients' Requests to Incorporate Dietary Supplements

To respond effectively to the requests of cancer patients seeking to integrate DSs into their treatment, healthcare providers must embrace a patient-centered perspective that acknowledges the patient's need for autonomy and empowerment. In today's healthcare landscape, patients increasingly value physicians who recognize patients' role as empowered participants in shaping their own healthcare choices. Physicians should be seen as informed intermediaries, expert guides, and consultants, with the patient at the center of decision making. The optimal approach involves discussing both the facts and uncertainties surrounding DS use with the patient, facilitating a mutually informed decision-making process [19].

In 2009, the Society of Integrative Oncology (SIO) issued guidelines for the inclusion of complementary medicine in cancer care, and these guidelines included recommendations concerning the use of nutritional supplements. The SIO advised that patients interested in using DSs should consult with trained professionals who could provide support, set realistic expectations, and weigh the potential risks and benefits [25].

Recognizing the importance of addressing patients' requests to incorporate DSs into their care, the Clinical Practice Committee of the SIO, in 2012, identified the necessity of a comprehensive approach suitable for integrative oncology settings. This approach places the patient at the center, aiming to provide evidence-based information tailored to the individual patient's needs, the discussion of potential risks, and to promote shared decision making. To make progress in this effort to effectively advise patients on the integration of DSs, the committee members compiled a list of 10 DSs that, at the time, were considered

safe and had enough supporting evidence for their use to be discussed with patients. These DSs were deemed appropriate for integration in specific situations, and this list was relevant at the time of publication in 2012–2013 [5].

A prominent comprehensive cancer center in the United States recently introduced another innovative care model that involves the use of a dedicated pharmacist to offer guidance to patients on the use of DSs [26]. In this program, integrative medicine providers who are engaged in counseling patients to address unmet symptom needs prescribe DSs when deemed appropriate, considering the clinical context, patient preferences, and available research evidence, using the clinical pharmacist as an additional professional who helps with providing this advice [26]. To assess the feasibility and outcomes of this approach, researchers conducted a retrospective analysis using medical records. The results demonstrated the viability of integrating DSs into an academic oncology setting, showing high patient satisfaction levels and minimal adverse events [26].

Recognizing the evolving landscape of DS use in cancer care, we emphasize the need for a general approach to be provided by integrative oncologists. This approach should be adaptable for integration into oncology settings where additional professionals may not be available, and which rely primarily on the expertise of the integrative practitioner. Such an approach should be patient-centered, and encompass the provision of evidence-based information, tailored assessments of individual patient needs, discussions about potential risks, encouragement of shared decision making, respect for patient autonomy, the presentation of alternative options, the documentation of physician and patient preferences, and the provision of ongoing support, all while ensuring coordination with other members of the healthcare team. Staying informed and supporting informed and empowered choices are the key components of this comprehensive approach, which ultimately enables patients to make well-informed decisions that prioritize their safety and well-being in the context of cancer care.

When a patient requests the addition of DSs to their cancer care, healthcare providers must dedicate sufficient time to address the patient's needs thoroughly. To provide an informed response, providers should use reliable sources, such as About Herbs from Memorial Sloan Kettering Cancer Center [27] or the Natural Medicine Database [28], to evaluate the safety and efficacy of the supplement in question, the potential side effects, drug–herb–nutrient interactions, and product quality. The findings from such searches can be divided into three categories based on the risk and benefit value (Figure 1):

1. High risk and low or unknown benefit;
2. Questionable risk and low or unknown benefit;
3. Minimal risk and clinical clues regarding its benefit.

4.1. High Risk and Low or Unknown Benefit

If the research findings indicate that the use of a particular DS raises significant safety concerns, such as the potential for side effects and interactions, while the benefits remain unclear and are primarily based on speculation rather than clinical research, it is advisable to discourage such use. In such cases, healthcare providers should engage in a discussion that acknowledges the risks involved and also documents these concerns.

4.2. Questionable Risk and Low or Unknown Benefit

When the research findings reveal no known safety or interaction concerns based on clinical research, yet there is no concrete evidence of clinical benefits, patients should not be dissuaded from using a supplement. It is important to respect their choice, even if their motivations for using a supplement are not based on scientific evidence. In such situations, an open and honest discussion with patients about their motivations, as well as a detailed discussion of the advantages and disadvantages of supplement use, should take place. Given the absence of major safety concerns, the approach should be to empower patients to make their own informed decisions regarding the use of a supplement.

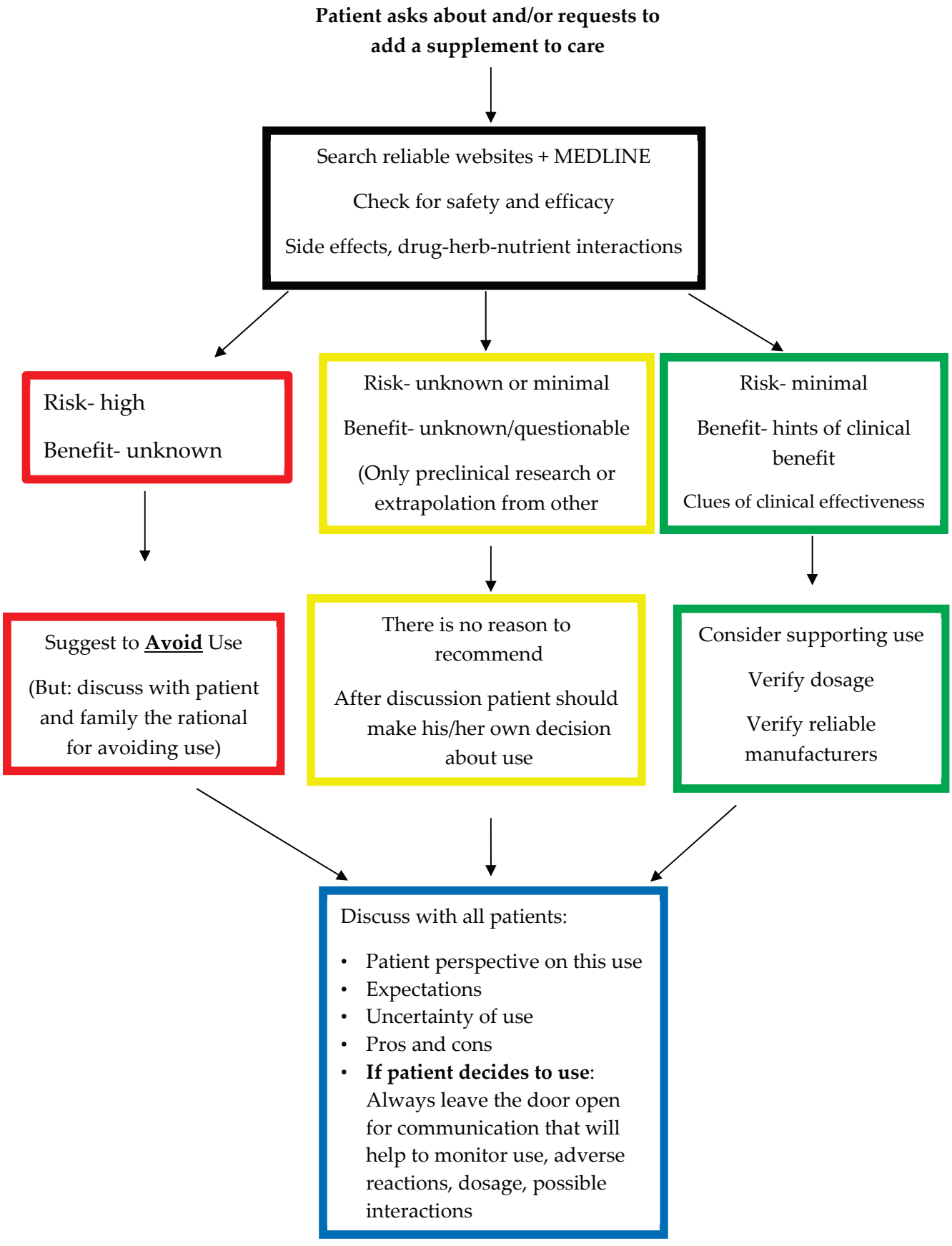

Figure 1. A suggested approach for addressing patients' requests to add dietary supplements to their cancer care.

4.3. Minimal Risk with Clinical Clues Regarding the Benefit

When the research findings indicate that the risk associated with a supplement's use is minimal, and there are clinical clues suggesting potential benefits, patients can receive support for this specific use. Even in this favorable scenario, healthcare providers should engage in an open discussion with their patients about the advantages and disadvantages of the supplement. This discussion should also include recommendations of high-quality products, if available, as well as a conversation about the optimal dosage. Additionally, a plan for further follow-up to monitor the use of the supplement should be established.

A discussion about DS use should take place with all patients who seek advice about DSs during and after their cancer care. Patient perspectives and expectations should be explored, and the inherent uncertainty in DS use should be discussed, including the pros and cons, for all three categories.

It is crucial to emphasize that even if patients choose to go against their advice, healthcare providers should maintain an open channel of communication, coupled with empathy and compassion. This approach will help to maintain communication and the monitoring of DS use, adverse reactions, and potential interactions, which is essential for intervention or treatment adjustments. Another important aspect of approaching DS use among cancer patients is informing the oncologist regarding the recommendations and patients' decisions. This information will help the oncologist to understand the rationale behind supplement use and to help monitor for adverse effects or interactions, in case they need to add new medications to the treatment plan for the cancer.

The physician's role does not conclude with the initial discussion. Ongoing support and monitoring are vital as patients integrate DSs into their care plan. Collaboration with other healthcare team members, such as oncologists and nurses, is essential to promote patient safety and well-being, by ensuring that DSs do not interfere with the conventional treatments.

Remaining informed and updated is a commitment that physicians must uphold. The ever-evolving landscape of DSs and their role in cancer care demands a continuous dedication to learning. Ongoing education and staying informed about the emerging evidence are essential to providing patients with the most current and evidence-based information.

The ultimate goal is to empower patients to make well-informed and empowered choices. By encouraging and supporting patients in their quest to make informed decisions, physicians can ensure that patients are well equipped to navigate the intricate path of dietary supplement use in the context of cancer care. This comprehensive approach places patient safety and well-being at the forefront of healthcare decision making.

This suggested approach addresses cancer patients' requests to integrate DSs into their care with a clear patient–doctor communication process relating to safety and efficacy, in a patient-centered manner.

5. Recommending Dietary Supplements as Food

Discussing nutrition with patients affected by cancer is one of the main issues discussed in the integrative oncology setting [29]. Nutrition and DSs, in many situations, are commonly discussed in the same encounter. Many DSs are derived from food, and although some DSs are combinations of multiple ingredients, not all are. Therefore, advising the patient to eat the whole food that the supplement is derived from is another strategy that might help meet the patient's expectations. One example is the use of mushroom supplements for cancer. The data support an association between high dietary mushroom consumption and a lower risk of cancer [30]. Mushrooms are anti-inflammatory and immune-enhancing, and are often used in Asian countries during cancer treatment. However, due to the paucity of clinical data from many other countries, we suggest the dietary consumption of mushrooms that are accessible to the patients, instead of using them as supplements. Green tea is another example; its active ingredient, ECGC, has been found to be beneficial. However, ECGC consumption as a supplement has a risk of hepatotoxicity and, therefore, the dietary consumption of green tea is recommended. For

supplements comprising several ingredients, the clinician should review the ingredients and recommend the use of their dietary form when possible.

6. Conclusions

In summary, effective communication between physicians and cancer patients regarding dietary supplement (DS) use stands as a cornerstone for establishing trust and ensuring optimal care provision. Acknowledging and actively addressing the inherent challenges to this communication process are pivotal for fortifying the patient–provider relationship, elevating care standards and, ultimately, leading to improved patient outcomes.

To meet these challenges and to achieve enhanced patient-centered care, healthcare providers must adopt a paradigm shift, viewing patients as informed participants in their healthcare decisions. Physicians should evolve into expert guides and consultants, valuing and respecting patient autonomy and empowerment. Our proposed approach advocates for engaging in an open dialogue that comprehensively considers both the factual information and uncertainties related to DSs, fostering mutually informed decision making.

Central to this recommended approach is the emphasis on open discussion, transparency, and the utmost regard for patient autonomy. By adhering to such principles, healthcare providers can effectively navigate the intricacies of discussing dietary supplement use in the realm of cancer care, prioritizing the safety and overall well-being of the patient. Furthermore, in implementing this approach, it is imperative to integrate reliable sources of information, engage in risk stratification, and offer specific recommendations tailored to the individual patient's needs. Subsequent monitoring ensures continued support and guidance, further reinforcing patient safety and optimal health outcomes. This comprehensive approach not only addresses the challenges inherent in physician–patient communication regarding DSs, but also equips patients with the necessary knowledge and tools with which to make informed choices, thereby optimizing their cancer care journey.

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nutrients

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Review

Nutritional Management of Oncological Symptoms: A Comprehensive Review

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Abstract: Throughout their experience of illness and during the course of treatment, a substantial proportion of cancer patients are prone to develop nutritional and/or metabolic disturbances. Additionally, cancer patients often encounter long-term side effects from therapies, which may lead to impaired digestion, nutrient absorption or bowel motility. Therefore, the preservation and maintenance of an optimal and balanced nutritional status are pivotal to achieving a better prognosis, increasing the tolerance and adherence to cancer therapies and improving the overall quality of life. In this context, personalized nutritional programs are essential for addressing conditions predisposing to weight loss, feeding difficulties, digestion problems and intestinal irregularity, with the goal of promoting adequate nutrient absorption and minimizing the detrimental effects of treatment regimens. The focus of this research is to examine the most common clinical conditions and metabolic changes that cancer patients may experience, including stomatitis, xerostomia, diarrhea, nausea, vomiting, dysphagia, sub-occlusion, dysgeusia, dysosmia, anorexia, and cachexia. Furthermore, we present a pragmatic example of a multidisciplinary workflow that incorporates customized recipes tailored to individual clinical scenarios, all while maintaining the hedonic value of the meals.

Keywords: cancer; nutrition; stomatitis; xerostomia; diarrhea; nausea; vomiting; dysphagia; anorexia; cachexia

1. Introduction

In cancer patients, advances in oncological treatments have significantly improved survival rate [1,2].

However, anticancer therapies can lead to nutritional and/or metabolic alterations, and an insufficient consideration of nutritional status during treatment carries significant implications for patients' quality of life and their capacity to adhere to different available treatments, thereby adversely affecting prognosis [3].

Furthermore, even when a state of malnutrition is detected, corrective measures are often not adequately implemented [1].

In this context, preserving an optimal and well-balanced nutritional profile enhances the tolerance to cancer therapies, enabling the preservation of a good quality of life (QoL) [4,5].

Indeed, precise nutritional guidance is required depending on the specific disease, treatment, and the patient's clinical conditions.

Personalized nutritional programs are essential in all those conditions predisposing to weight loss and difficulties in feeding, digestion, and intestinal regularity, so as to promote adequate nutrient absorption and minimize the detrimental effects of treatment regimens.

From the initial assessment and throughout the later stages of the disease, it is imperative to evaluate the dietary intake of cancer patients to promptly detect any nutritional deficiencies. Neglecting these deficiencies can lead to a decline in their nutritional status and have a substantial impact on the effectiveness of cancer treatments, ultimately diminishing the patient's chances of survival [1,6]. In this context, through a literature review, we present an overview of the prevalent clinical conditions and metabolic changes observed in cancer patients. Our aim is to offer a concise reference guide encompassing primary nutritional strategies, including both pharmacological and non-pharmacological interventions, designed to mitigate and address the symptoms experienced by cancer patients, thereby optimizing their overall outcomes. In addition, we provide a practical illustration of a multidisciplinary workflow for incorporating customized recipes tailored to specific clinical scenarios.

2. Material and Methods

We first performed a literature screening to find relevant titles and abstracts about nutrition and clinical conditions in cancer patients (Figure 1). After that, a more extensive PubMed literature search was conducted to identify key clinical trial reports and review articles covering the most prevalent side effects of common anticancer treatments. The search strategy comprised the following keywords: "xerostomia" (OR "stomatitis" OR "mucositis" OR "oral mucositis" OR "diarrhea" OR "constipation" OR "nausea" OR "vomiting" OR "dysphagia" OR "sub-occlusion" OR "dysgeusia" OR "dysosmia" OR "anorexia" OR "cachexia") AND ("nutritional status" OR "nutrition") AND ("cancer patients" OR "cancer" OR "neoplasia" OR "tumor"). Relevant narrative and systematic reviews, as well as meta-analyses and reports of small retrospective and prospective clinical trials, were included in order to provide a comprehensive description of a specific clinical problem. Such descriptions would cover a general definition of the issue, epidemiological data, the most common presenting symptoms, and pharmacological and non-pharmacological treatment options. Initially, neither formal inclusion and exclusion criteria nor time filters were applied. Later, the resulting first draft of the literature search was refined using the CrossRef system, excluding possible duplicated, corrected or retracted articles, and the timeframe was limited to research papers published between January 2000 and September 2023. Relevant nutritional recommendations, as well as guidelines published by the Multinational Association of Supportive Care in Cancer (MASCC) and by major oncology societies, were also included in the final selection, which was made by a panel of four experienced medical oncologists; only full-text English articles were considered.

After presenting an update on the above-mentioned side effects of anticancer therapies in the form of a narrative review, we developed a draft of a conceptualized multidisciplinary platform, consisting of a 5-step workflow, to test specific food recipes for three selected clinical scenarios. The involved team was composed of six medical oncologists, two nutritionists and a three-Michelin-star chef. Further details on such nutritional workflows are provided below in a specific section of the present work.

2.1. Xerostomia

Xerostomia refers to a subjective feeling of oral dryness often associated with a decreased salivary secretion [7]. This condition may affect up to 40% of the global population, with a higher prevalence among older adults and postmenopausal women [8–10].

The primary predisposing and contributing factors encompass autoimmune diseases (such as Sjögren syndrome and rheumatoid arthritis), endocrine disorders (uncontrolled diabetes mellitus, and thyroid diseases) and viral infections (HIV, HTLV-1, and HCV) [7,11].

In addition, in cancer patients undergoing radiation therapy, xerostomia stands out as the most frequently reported oral symptom [12,13], particularly in patients with head and neck (H&N) cancer. For these patients, salivary gland hypofunction depends on the cumulative radiation dose administered and the volume subjected to irradiation, leading to a potentially dramatic impact on QoL [14–16].

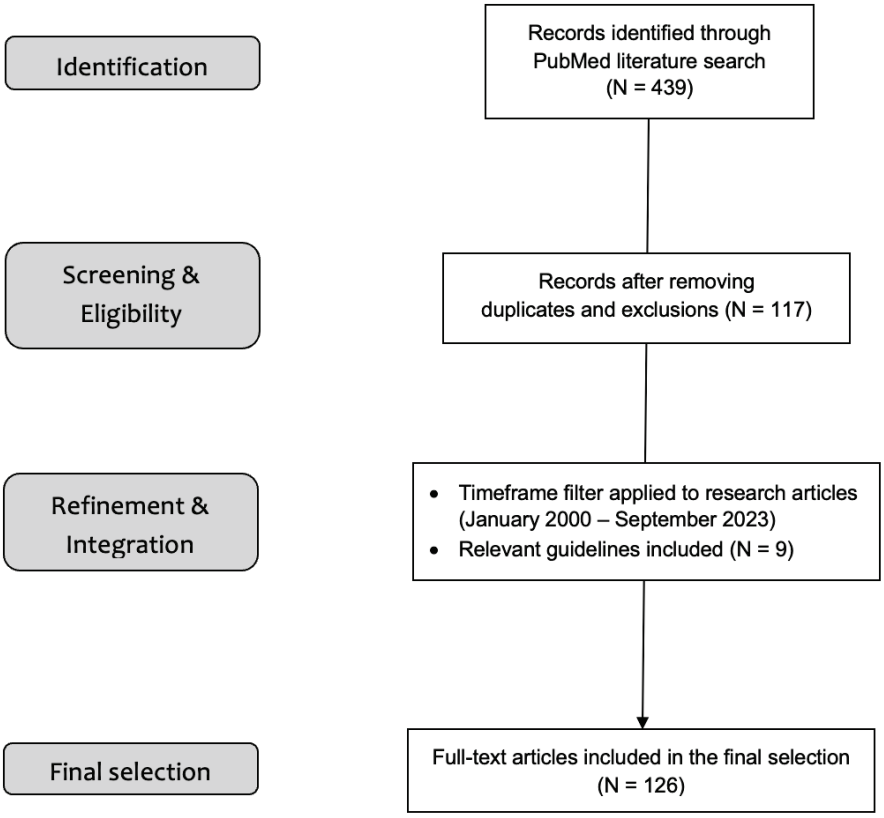

Figure 1. Flow diagram of the literature search process.

Similarly, some chemotherapy agents like anthracyclines, cyclophosphamide, 5-fluorouracil (5-FU) and methotrexate are also able to reduce salivary gland function that is typically less severe and reversible after completion of treatment [17]. Other drugs associated with xerostomia are antidepressants, beta-2-adrenergic agonists, inhaled steroids, and benzodiazepine derivatives (diazepam, lorazepam) [7,8].

Clinical manifestations of xerostomia mainly affect the oral cavity and the upper part of the digestive tube and include difficulties in food ingestion, swallowing and even speaking in severe cases, burning mouth and/or tongue, fissures in lips and mouth mucosa, and susceptibility to caries [7,8].

Therefore, symptomatic treatment to mitigate the abovementioned adverse effects of salivary gland hypofunction and xerostomia is important.

Pharmacological agents stimulating muscarinic receptors, like pilocarpine, bethanecol, and cevimeline are reported to be effective and may be offered after radiotherapy, even though the improvement is only transitory [18–20]. Saliva stimulants (e.g., sugar-free, non-acidic chewing gums), topical lubricants and saliva substitutes are especially recommended when it is still possible to increase saliva flow rate to relieve symptoms associated to xerostomia, although the long-term benefits are still uncertain [18,19,21]. Acupuncture has also been tested both during and after radiation therapy in H&N cancer patients, and while there is little evidence that this intervention is able to increase saliva flow rate, some patients have experienced an improvement in xerostomia-associated symptoms [18,19,22].

While there is no standard, highly effective treatment for the prevention and management of xerostomia, it is strongly advisable to maintain proper oral hygiene through regular teeth cleaning. This practice serves to mitigate the risk of potential infections, such as oral candidiasis, and to uphold the highest possible QoL [19]. Nutritional counselling is another important resource to provide to these patients. Based on everyday life and insights from previously published works [23], some fundamental suggestions can be offered to patients, focusing on introducing different flavors such as marinating meat, poultry or fish or cooking them in naturally sweet juices; increasing the use of spice, herbs and seasonings;

preferring fresh vegetables (also in combination with tasty dressings) or fruit smoothies without neglecting the importance of regular and small sips of fluids. Moreover, it is preferable to flavor boiled or steamed foods by adding salt.

Because gastric acid production increases saliva secretion, it would not be incorrect to think that sour foods may be beneficial for those patients with partial xerostomia, as opposed to total xerostomia where acidic foods may be avoided [24].

Conversely, certain suggestions may be inappropriate. These include ice chips/cubes, which offer only brief and inadequate relief, glycerol solutions that can have a drying effect on the mouth, acidic products like lemon solutions and pineapple chunks, which may intensify oral discomfort and contribute to dental demineralization, sweet and candies known for their high cariogenic potential, and vitamin C and antioxidants, as they may have a potential adverse impacts on cancer-related outcomes [19].

As a result, while nutrition certainly plays a role in reducing the development and exacerbation of xerostomia, available data remain limited. Investigating the role of early nutritional counselling and refining possible nutritional recommendations might be interesting fields of research in the near future.

2.2. Stomatitis

Stomatitis is a very common toxicity of cancer treatments consisting of inflammatory damage that can arise from oral to anal mucosa. It involves around 30–40% of patients receiving chemotherapy, being more frequent among H&N cancer patients in which it occurs up to 90% of cases [25,26].

Risk factors include exposure to radiation, cytotoxic drugs, or newer oral-targeted agents [27–31]. Younger age may also be a contributing factor, possibly due to a higher mucosa turnover, rendering it more susceptible to cytotoxic drugs. Other factors include pre-existing oral defects and diseases, such as poor hygiene, caries, and periodontal disease, as well as an inadequate nutritional status and differences in the oral microbiome [32–34]. Pyrosis can also contribute to the development of stomatitis; in fact, it represents an inflammatory alteration to the mucosa of the upper gastrointestinal (GI) tract, most frequently occurring as a consequence of excessive acid reflux from the stomach to the esophagus or even the laryngopharynx [35]. Some preliminary studies have identified possible associations between chronic gastro-esophageal or laryngeal reflux disease and an increased onset of H&N cancers, particularly within the larynx [36]. Moreover, a higher severity of reflux disease has been described as a potential, significant risk factor for more serious radiation-induced mucositis in patients with stage I-II laryngeal and hypopharyngeal cancers [36].

The main clinical manifestations range from oral mucosa erythema to multiple ulcerations and canker sores causing painful swallowing that can lead to diet modifications or difficulty in food or liquid ingestion [37–39].

Therapeutic management of stomatitis relies on the multiple approaches available, a combination of which seems to be required, as no single intervention has so far proven real effectiveness per se [27,40].

Saline and sodium bicarbonate mouthwashes are well-consolidated bland remedies which may help symptom management by cleaning the oral cavity, while benzydamine-based mouthwashes with their anti-inflammatory properties have shown to be effective as a preventive measure in patients undergoing chemotherapy and/or radiant therapy [40,41].

On the other hand, topical morphine 0.2% mouthwashes are suggested to reduce stomatitis-associated pain [40]. Furthermore, oral cryotherapy represents another preventive and easy practice playing a beneficial role on the associated dysgeusia and xerostomia [40,42–44].

Many natural remedies have also been considered, but a general lack of high-quality evidence is noted for many of them, such as zinc, vitamin D and E, selenium, folinic acid, propolis, and liquorice [42,45,46]. Conversely, honey has shown consistent positive effects in a combined topical and oral administration and is therefore suggested in H&N patients

treated with combined treatment; however, due to its high cariogenic potential, patients should adhere to a strict oral hygiene program [46,47].

Vitamin D levels have been extensively associated with cell proliferation and cancer [48,49]. Currently, there are not enough literature data to sustain vitamin D supplementation for cancer prevention. Indeed, in a randomized clinical trial, 2303 postmenopausal women were randomly given vitamin D and calcium supplementation or placebo. In this trial, no significant reduction in the risk of all-type cancer was observed after 4 years amongst the two treatment groups [50]. Furthermore, in another randomized clinical trial, 25,871 patients were randomized to receive vitamin D and omega-3 supplementation versus placebo and, also in this case, vitamin D supplementation did not result in a reduced incidence of breast, colorectal or prostate cancer or cardiovascular diseases compared to placebo [51]. The role of vitamin D as a therapeutic agent has also been explored in cancer patients [52–55]. In the AMATERASU randomized clinical trial, patients with early stage esophageal, gastric and colorectal cancer in follow up were randomized to receive vitamin D supplementation versus placebo. No significant difference in terms of relapse-free survival was observed amongst the two treatments [56]. In a post hoc analysis of this trial, serum anti-p53 antibodies were detected in about 1/3 of the patients. Within this subgroup of p53-immunoreactive patients, a significant improvement in relapse-free survival and in overall survival was reported in the vitamin D group, in contrast to the non–p53 immunoreactive subgroup, in which vitamin D supplementation had no survival impact. Therefore, these findings could suggest that vitamin D supplementation may reduce the risk of disease recurrence and mortality within p53-immunoreactive patients [53]. Similarly, in the SUNSHINE phase II clinical trial, 139 patients with metastatic colorectal cancer were randomized to receive treatment with mFOLFOX-bevacizumab with either high-dose or low-dose vitamin D3 supplementation. In this trial, the addition of high-dose vitamin D3 to conventional chemotherapy resulted in a statistically insignificant improvement in median PFS, thus warranting further investigations [55].

Importantly, complicated stomatitis may lead to longer hospitalizations and premature treatment discontinuation [38,57]. Proactively predicting, screening, and detecting early signs of lesions is therefore paramount for cancer patients about to begin treatments [40,45,58].

Aiming at a multidisciplinary preventive management to mitigate such potentially detrimental effects, nutritional counselling might also be integrated, even though evidence on its real utility is still missing.

Dietary suggestions should prioritize the following [40]: preferring soft or semisolid, mild-textured foods like pudding, creamed soups, fresh cheese, and mashed potatoes over rough-textured options; softening food by blending, soaking or moistening it to make it easier to consume; opting for cool or room-temperature foods, as well as tart, acidic or salty flavors, such as tomatoes, kiwi, and lemons; limiting the consumption of raw vegetables and carbonated drinks; using straws or similar devices to bypass severe mouth sores when necessary; and providing high-calorie or high-protein supplements in case of insufficient oral intake or cancer cachexia [23,40].

In summary, many options for managing stomatitis are already available to use; nonetheless, more research focusing on prevention plans, the personalization of treatment and the impact of nutritional management will surely be needed soon, given the high frequency of this condition among cancer patients, its potential impact on QoL and the continuous evolution of cancer therapy.

2.3. Diarrhea

The term "diarrhea" refers to the output of abnormally liquid stools at least three times in a day and it is a commonly reported adverse events amongst patients receiving systemic antineoplastic therapy including chemotherapy, target therapy and immunotherapy [59,60].

Diarrhea represents a potentially life-threatening complication, as it can cause an important loss of body fluids, consequently leading to hypotension, renal damage, electrolytic

imbalances, and cardiovascular events [61]. Thus, it is a major adverse effect requiring prompt pharmacological and non-pharmacological interventions.

For patients experiencing treatment-related diarrhea, a conservative approach, consisting of dietary modifications (also including an appropriate oral hydration) and anti-diarrheal agents (e.g., loperamide or additionally octreotide for more severe loperamide-refractory cases) can be proposed at first [62].

To restore the electrolyte balance and to avoid the risk of dehydration, abundant oral liquids with solutions rich in electrolytes and glucose (e.g., non-coffee drinks, juices and soups) should be proposed, considering that glucose is a major driver of sodium and water reabsorption [63,64].

Moreover, in general, patients with diarrhea can benefit from a diet structured around small and fractioned meals rich in soluble fibers (e.g., white rice, barley, oats, sweet potatoes and some fruits like apples and pears without skin), as they can increase stool consistency and delay bowel movements [65]. Soluble fibers dissolve in water, forming a kind of gel that can help absorb water in the stool, making it less liquid. However, it is important for patients with diarrhea to always consult a healthcare professional for personalized guidance, as dietary needs can vary from person to person and depend on the underlying cause of the diarrhea. In some cases, it may be necessary to avoid some of these sources of soluble fibers if they are not well tolerated.

It is important to note that not all fibers are the same. Insoluble fibers (such as whole grains, corn, and fruits with skin) can have the opposite effect, increasing the frequency of bowel movements, and should be avoided as they can accelerate the GI transit and stool frequency [65,66]. Also, foods and beverages with high osmolarity (i.e., salty foods and carbonated beverages), caffeine and theine should be excluded from the diets of patients experiencing diarrhea. This is because they may increase water excretion in the bowel and consequently increase the stool frequency [67].

Probiotics supplementation may offer a viable approach to mitigate treatment-related diarrhea by potentially aiding in the restoration of the integrity of gut microbiota. It is important to note that scientific evidence in this regard remains quite limited [68,69]. However, patients with a central venous catheter should exercise caution and refrain from probiotic supplementations that contain *Saccharomyces boulardii* due to the associated risk of fungaemia [70,71].

Moreover, different chemotherapeutic agents can damage the bowel mucosa, consequently leading to malabsorption. Lactose malabsorption and intolerance, which can cause diarrhea, are commonly observed in patients receiving chemotherapy containing fluoropyrimidines; such complications are generally reversed as soon as the treatment is interrupted [72]. However, these patients should be advised to follow a lactose-free diet (i.e., reducing the intake of milk and dairy products) throughout the treatment and, especially, if they develop diarrhea.

Finally, for more severe cases, hospitalization can instead be required for appropriate intravenous hydration, electrolyte correction and monitoring of the renal and cardiovascular functions [62].

2.4. Constipation

Constipation stands out as the prevalent syndrome affecting the intestines in cancer patients undergoing anti-cancer treatment. This condition, with multiple contributing factors, is marked by painful, uneasy, and incomplete bowel movements, along with sluggish and irregular peristalsis. These symptoms can adversely impact the quality of life [73]. As a result, addressing and mitigating constipation is an integral aspect of cancer care.

Depending on its etiology, constipation can be linked to abnormalities on colonic functions (primary) or to medication-adverse events, bowel obstruction/compression or metabolic diseases such as diabetes mellitus, hypothyroidism, hypercalcemia (secondary) [74,75].

In cancer patients receiving opioid therapy, constipation affects a substantial proportion, ranging from 15% to 90%, primarily as a result of opioids binding to gut receptors that decrease sensitivity to defecation reflexes [76]. On the other hand, antiemetic agents and certain chemotherapy drugs, such as like vinca alkaloids, platinum-based compounds, and taxanes, can also increase the likelihood of constipation due to their neuropathic effects, which results in enteric neuronal loss and subsequently reduces GI transit time [61]. Therefore, it is imperative to approach constipation management on an individual basis, with a crucial emphasis on pinpointing its precise underlying cause to facilitate the selection of the most appropriate treatment strategy.

Osmotic and stimulant laxatives are the basis of medical treatment constipation. Lactulose, magnesium hydroxide and polyethylene glycol are examples of osmotic laxatives drawing water into the gut and increasing the stool softness. On the other side, senna and cascara (stimulant laxatives) alter electrolyte transport resulting in intraluminal fluids secretion. If there is noclinical benefit, it can be helpful to employ prokinetic and prosecretory agents (i.e., linaclotide, lubiprostone, and prucalopride) [73,77–80].

Maintaining an adequate diet should be the first strategy to improve the QoL. Sufficient water intake and a high-fiber diet are recommended help to prevent issues like constipation: drinking at least 1.5–2 L of fluids per day and consuming fiber-rich foods can be helpful in avoiding chemical, mechanical and thermal irritation of the GI tract due to acid-forming fermentation and lower intestinal motility [81,82]. If the patient has difficulty with liquid intake, drinking small sips of liquids that are warm or at room temperature and are varied in flavor can make fluid intake more enjoyable and promote hydration [40,83]. Gradually increasing fiber intake can help the patient's digestive system adapt and can reduce the risk of digestive discomfort such as bloating, gas, and cramping. The daily recommended fiber intake is at least 25 g, with a 3/1 insoluble/soluble fiber ratio, replacing refined cereals with whole grains [40]. Consuming at least 5 servings of fresh fruits and vegetables per day can provide oncology patients with important nutrients and fiber, contributing to their overall health. Conversely, spicy, sour and salty foods should be reduced, as well as extremely hot or extremely cold ones, due to their irritant properties and lower water contents [40,81–83].

The use of dairy products containing bifidobacteria and lactobacilli can be helpful in normalizing intestinal microflora. Some dairy products containing these probiotics might help restore the balance of intestinal flora, which may be disrupted during oncology treatment.

It is important to note that the nutritional needs and wellbeing of an oncology patient can vary significantly depending on the type of cancer, the stage of the disease, and ongoing treatments. Therefore, it is essential for an oncology patient to receive personalized medical guidance from an oncologist and a dietitian to address their specific needs.

It is equally important to respond to the urge to eliminate and to maintain a regular schedule for bowel movements, preferably after breakfast. This can help prevent constipation. In addition, assuming a comfortable position, such as a squatting position, during evacuation can help facilitate the process [81].

As can be understood from these guidelines, constipation remains an important and complex issue in cancer patient that should be evaluated using a multidisciplinary approach involving medical oncologists, nutritionists, pharmacists and palliative care physicians.

2.5. Nausea and Vomiting

Nausea and vomiting (N/V) are two strictly connected biological phenomena that an organism uses to defend itself from pathological conditions and toxic substances. Nausea is defined as a subjective discomfort of the upper abdomen often followed by a forced and rapid emptying (emesis or vomiting) of the GI content [40,84,85].

Among cancer patients, N/V are frequently triggered by various treatments, including chemotherapy (referred to as CINV—chemotherapy-induced nausea and vomiting) or radiation therapy (known as RINV—radiation-induced nausea and vomiting). In addition to chemotherapy and radiation therapy, it is important to note that new therapies, such

as antibody–drug conjugates (ADC), can also induce emesis [86,87]. N/V can manifest in different time frames: acutely (within 24 h after treatment), in a delayed manner (more than 24 h later), or even before treatment is administered (anticipatory emesis) [88–90].

It is reported that over 60% of advanced cancer patients experience N/V at least once during oncological therapies, with a demonstrated detrimental impact on QoL and on the continuity of care [88,91].

The mainstay of acute and delayed emesis prophylaxis is pharmacological management based on the emetogenic potential of therapies as well as other patient factors and contributing causes. Actually, the major guidelines recommend a combination of two or three drugs in high and moderate emetogenic regimens (e.g., a serotonin receptor antagonist + dexamethasone ± a Neurokinin 1 (NK1) receptor antagonist) [90,92–94], while a single agent approach (e.g., metoclopramide) is preferred in low emetogenic agents [90,94,95].

As well as optimizing acute and delayed prophylaxis of CINV and RINV, benzodiazepines and various behavioral interventions (e.g., hypnosis, muscle relaxation, systemic desensitization) [88,89] are useful in minimizing anticipatory nausea. Among the other non-pharmacological interventions, acupressure showed slight improvements in nausea and retching experiences reducing the use of rescue antiemetics [96,97]. Similarly, ginger (*Zingiber officinale*) and cannabinoids have shown similar benefits for N/V management, probably owing to their anti-inflammatory, anti-spasmodic and prokinetic effects [98,99]. Also worthy of note for their ability to relieve the severity of nausea and vomiting are chamomile, peppermint, and cardamom [100–102].

Due to the increased risk of malnutrition in patients experiencing CINV/RINV, dietary interventions should be considered as an early measure to offer to cancer patients. However, it is important to note that no clinical trials have specifically investigated their role so far [103]. Based on the best practice standards and on expert opinions [23,40,103], several suggestions can be made during nutritional counselling for patients experiencing CINV/RINV. These recommendations can broadly be categorized into three different strategies.

The initial approach revolves around dietary habits, encompassing the consumption of small, frequent meals, the potential incorporation of light snacks between meals, minimizing extended fasting periods, administering antiemetics before meals, and refraining from eating or drinking until vomiting is managed.

The second strategy involves meal composition and focuses on reducing liquid intake during meals; avoiding the consumption of spicy, fatty, salty food and strong flavors; preferring bland foods, soft fruits or vegetables; choosing low-fat protein sources such as chicken, turkey and eggs; limiting foods that can cause gas or bloating such as pulses, cabbage and beans; and drinking clear liquids or teas, either warm or cold.

Finally, the third strategy includes eating in well-ventilated rooms with no food smells.

Interestingly, emerging from the preliminary data of small prospective trials [103,104] is the antiemetic effect of protein-rich meals, which seems to determine a significant trend towards reducing CINV, both alone and in combination with ginger. Although this mechanism is not fully elucidated yet, this may represent a novel nutritional approach to help overcome N/V in cancer patients.

In conclusion, despite the fact that much progress has been made in the treatment of CINV/RINV, these are still frequently reported by patients and affect tremendously their QoL. It is thus critical that research continues to further understand pathways underlying N/V, so as to develop multimodal approaches, comprising not only pharmacological, but also non-pharmacological and possibly nutritional interventions [40,105].

2.6. Dysphagia

The term "dysphagia" is used to indicate the difficulty in the transit of liquids and/or solid foods either from the oral cavity to the pharynx ("oropharyngeal dysphagia") or through the esophagus ("esophageal dysphagia") [59]. It is a common complication of different types of cancers (e.g., oral, esophageal, H&N and central nervous system (CNS)

cancers), but it can also arise as a consequence of chemoradiation therapy or surgical procedures in these regions [40]. Dysphagia could be caused by a neurological impairment of swallowing (neurologic dysphagia) or by a mechanical obstruction.

The material that is not swallowed can eventually enter the trachea and the lungs, leading to suffocation, aspiration pneumonia and other pulmonary disorders. Furthermore, dysphagia has been related to reduced caloric intake, weight loss and malnutrition, thus jeopardizing the health status and the survival outcomes of cancer patients [40,59]. Thereafter, it requires timely recognition and management, which can include both chemoradiation and surgery to shrink the tumor, thereby improving swallowing function, along with specific nutritional recommendations.

In patients presenting with dysphagia for which oral nutrition is contraindicated due to the disease itself or the ongoing treatment causing significant swallowing difficulties, or in cases where the patient has reached an end-stage disease with no chance of improving their dysphagia, enteral nutrition can be considered. Enteral nutrition can be administered through either a nasogastric tube or a percutaneous endoscopic gastrostomy (PEG) [72]. Among these options, PEG is considered a safer and more feasible choice.

Alternatively, when oral nutrition remains a viable option, it is advisable to recommend nutritional counseling to establish specific dietary guidelines to assist patients in maintaining an adequate daily calorie intake and preventing malnutrition and weight loss. Modifying the texture and viscosity of liquids, as well as semi-solid foods, can help to reduce the risk of aspiration [106]. Patients with dysphagia should be encouraged to consume small, fractionated semi-solid meals and prioritize foods with a firmer texture, such as cooked vegetables. These foods, when chewed, should not break apart in the upper digestive tract but instead form a compact bolus [40].

Similarly, to reduce the risk of choking and aspiration, sticky or bulky foods should be avoided. Moreover, liquids should be consumed with care, considering the risk of entrance into the pharynx. Therefore, thick liquids (e.g., yogurts) should be preferred, or fluids can be thickened [40]. Additionally, avoiding mixed textures and promoting the use of fats may facilitate the swallowing of food bolus. However, in cases of mechanical dysphagia, a more liquid form of foods and a reduction of fiber content could improve the swallowing process.

It is also important to provide patients with guidance on physical therapy and the correct posture to adopt during meals. For instance, exercises aimed at strengthening the jaw muscles and improving chewing and swallowing functions have been shown to be effective in managing dysphagia and increasing nutritional intake [106]. Furthermore, maintaining the proper body posture while eating is fundamental.

Patients experiencing dysphagia should, therefore, be instructed to always consume their meals when sitting; avoid lying down for a few hours (typically three hours) after eating; consider undergoing speech therapy (logopedic rehabilitation); and consider an appropriate examination of the oral cavity after meals to remove any food residue [40]. These measures can help improve the management of dysphagia and enhance the safety and effectiveness of eating for patients with swallowing difficulties.

2.7. Sub-Occlusion

Upper and lower GI sub-occlusion is a typical complication of different types of advanced cancers, such as GI and gynecological cancers. It is a condition that refers to the mechanical or functional obstruction of part of the bowel (the small and/or the large bowel), thus blocking the passage of the food. Impaired food transit related to an upper GI obstruction typically leads to regurgitation and vomit, whilst lower GI obstruction is mostly associated to abdominal distention and pain and the absence of stool and/or gas output [107].

The management of this condition can vary according to the extent of the obstruction and is mostly pharmacological and/or surgical.

Nausea and vomiting can be managed through the administration of medications that lower GI secretions (e.g., anticholinergics and somatostatin analogues) and/or antiemetic agents (i.e., metoclopramide for incomplete bowel obstruction). If medications are not enough to reduce the frequency of vomiting, the positioning of a nasogastric tube or the execution of a gastrostomy represent the most feasible options to decompress the obstruction [108]. Also, in the most severe cases of bowel obstruction, fasting is recommended. Therefore, intravenous hydration and total parenteral nutrition should be offered to these patients to avoid dehydration and electrolyte imbalances, provide adequate caloric intake and avoid the occurrence of malnutrition [108].

Opioids are generally sufficient in controlling abdominal pain in these patients [109] although they can worsen their intestinal motility.

Surgery is generally not performed to relieve a lower GI obstruction, and it is reserved to emergency situations (such as strangulation). Recently, however, metallic stent positioning has emerged as an option for treating gastric, small and large bowel obstructions [108].

For individuals experiencing sub-occlusion, the following nutritional strategies can be helpful: consuming smaller meal portions that are easier on the digestive system and may help reduce discomfort; opting for a diet lower in fiber (by selecting refined grains over whole grains and avoiding foods with high fiber content), as high-fiber foods can be more challenging to digest and may exacerbate discomfort; removing or avoiding the skins of fruits and vegetables to reduce the fiber content and make these foods easier to digest as well as cooking or peeling fruits and vegetables; staying hydrated with clear fluids to maintain regular bowel movements; and opting for foods with softer textures, such as minced or pureed dishes, which are easier on the digestive system, reduce the risk of intestinal discomfort, and alleviate pain or gas [110]. Dietary adjustments should be made in consultation with a healthcare professional to ensure that the individual receives the necessary nutrients while managing their sub-occlusion effectively.

2.8. Dysgeusia and Dysosmia

Around 50–60% of patients undergoing oncologic therapies are expected to have some form of taste and smell alteration [40].

Quantitative taste and smell disorders encompass conditions such as ageusia, hypogeusia, anosmia and hyposmia characterized by the complete absence or reduced perception of taste and smell, respectively [111]. On the other hand, dysgeusia and dysosmia are the most common quality alterations [112].

In cancer patients, these abnormalities depend on the tumor site (e.g., H&N cancer or trigeminal lesions) [113], nutritional deficiency (vitamin A, B6, B12, zinc and iron deficit) and the treatment used (chemotherapy, radiotherapy, or surgery) and their duration [40].

It is well known that platin- and taxane-based chemotherapy can alter taste and smell perception due to neurotoxic damage in cell receptors [40,114]. Additionally, oral and nasal disorders such as mucositis, xerostomia, rhinitis or infections (i.e., SARS-CoV-2) may contribute to the alteration of these pleasant senses.

Although there is no effective treatment, different trials have been conducted over the years [115,116].

Among these, it is worth noting those based on zinc and glutamine that failed to show the prevention of taste alteration. In fact, it has been shown that, if zinc is deficient, its replacement can mitigate and eventually improve gustatory function [19,115]. In severe forms, dysgeusia can be treated with benzydamine or lidocaine oral gel, relieving pain.

During cancer therapy, it is commonly observed that patients develop heightened sensitivity to bitter and salty tastes while experiencing a decreased perception of sweet tastes, with sour tastes being affected to a lesser extent [19,40]. Many cancer patients also report experiencing a continuous aftertaste that masks the true flavor of food. In response to these challenges, several measures can be taken to enhance the dining experience. To combat the aftertaste and keep the mouth fresh, cancer patients can use alcohol-free

mouthwash or menthol products [19]. Maintaining proper oral hygiene is also essential in this context.

To overcome food aversions and improve the intensity of flavor and smell, it is recommended to prepare toppings or dressings that make the food more appetizing [40].

Warm meals are generally not recommended for individuals with altered taste perceptions. Instead, opt for cold or lukewarm dishes [117]. Seasoning meat or fish with herbs and spices like rosemary, bay leaf, parsley, thyme, or Jamaica pepper can enhance flavor [40].

Olive oil, salt, and lemon dressings can be used for salads or roasted vegetables to improve taste and palatability. Marinating meat or fish before cooking, or grilling them with acidic products like lemon juice, wine, or beer, can be an excellent strategy to overcome food aversions and enhance flavor [19]. If there is an aversion to red meat, consider trying braised beef, or explore other protein sources like eggs, chicken, or ham. Using plastic cutlery can be beneficial in reducing the metallic taste that some cancer patients experience. Additionally, avoiding eating in overly warm environments can help improve the dining experience. These strategies can help cancer patients maintain their nutritional intake and enjoy their meals despite changes in taste perception and aftertaste. However, it is essential for patients to discuss dietary modifications and preferences with healthcare professionals to ensure they receive adequate nutrition during cancer therapy.

2.9. Anorexia

Among cancer patients, anorexia is the most prevalent eating disorder causing malnutrition, due to a decrease in the intake of nutritive elements, with a subsequent weight loss and ultimately cachexia development [40].

It typically occurs in about 50% of all cancer patients and is more common among GI cancers [40,118]. The resulting weight loss and metabolic alterations are considered poor prognostic factors and negative predictors of the response to antineoplastic agents.

Given the multifactorial pathogenesis, a combination of tumor-related and drugs-related causes have been reported [119]. Surgery, taste and smell alterations and anatomic or functional defects may contribute to a reduced daily caloric intake [40,120]. On the other hand, the side effects of oncology treatments such as mucositis, xerostomia or mouth sores may also induce GI discomfort, reducing appetite and promoting an early satiety [40].

Under normal conditions, the appetite regulatory center is the hypothalamus that controls homeostatic functions through the interaction of multiple signals [40,121].

Leptin and ghrelin are hormones that respectively regulate feelings of satiety and hunger. The former functions as a suppressor, while the latter acts as a stimulator of appetite. However, individuals with oncological diseases often experience impaired peripheral signaling, leading to an insufficient response to their energy requirements [40].

To tackle implications in terms of hospitalization and mortality, different therapies have been successful in improving appetite, playfulness, and general conditions. The important role of megestrol acetate, which is capable of reducing cytokines production leading to weight gain, has also been pointed out [122,123].

Other orexigenic agents are corticoids, progestogens and 5-hydroxytrypamine antagonist (olanzapine) which have proved their effectiveness in increasing fat mass and psychological aspects of cancer patients [124,125].

While drug therapy can be a component of treating symptoms of anorexia, it alone is not sufficient. Physical activity should be introduced promptly to help delay weight loss as much as possible [40].

However, it is crucial to calculate the patient's nutritional requirements and address any nutrient deficits that may be present [126,127]. Making food more appealing and tastier can help encourage eating. This can be achieved using toppings, contrasting colors, and serving small portions frequently [40]. Additionally, paying attention to the texture and smell of the food can stimulate oral feeding. Here are some dietary recommendations to address symptoms of anorexia: opt for small, frequent meals, especially well-cooked and energy-rich foods, particularly in the morning; include high-calorie and high-protein foods

in the diet (nuts, eggs, cheese, whole milk, oil, butter, and legumes); making homemade smoothies can be an effective way to increase calorie and nutrient intake; juices and cream soups can be easier to consume and provide valuable nutrients; and if red or processed meats are not well tolerated, they should be avoided [40].

But, if despite all this, patients continue losing weight, it is necessary to resort to nutritional supplements or even to artificial nutrition. For all these reasons, family support is becoming increasingly important.

2.10. Cachexia

Cancer cachexia (CC) is a complex medical condition often occurring in 50–80% of patients with end-stage disease as a result of metabolic alterations of the tumor and oncological treatment side effects [40]. CC is known for a progressive loss of muscle mass as part of a chronic inflammatory response causing emaciation, metabolic disorders, and physical deterioration [40,128].

It is a set of symptoms (anorexia, fatigue), signs (the loss of both muscle and fat mass) and biological alterations (hypoalbuminemia, hyperlacticaemia) that lead to a poor QoL and an increased morbidity and mortality [40].

Therefore, initial approaches should include increasing caloric intake and protein consumption. It could be an option to alleviate malnutrition with oral or intravenous nutritional supplements (enteral or parenteral nutrition) preventing dietary deficiency and stimulating protein anabolism [129,130]. At the same time, it can be useful to resort to appetite-stimulating medications (i.e., corticoids, megestrol acetate, and antidepressants), prokinetics (metoclopramide) and eicosapentaenoic acid (EPA) that might reduce lipolysis and proteolysis [40,131,132].

Given the substantial influence of nutritional status, it is advisable to endorse the consumption of high-energy and high-protein foods, particularly in the morning, aiming for a daily intake of 1.5 g of protein per kilogram of body weight, coupled with a caloric intake of 25 to 30 kcal per kg of BW. These foods may include avocados, pudding, cooked cereals, and oats as well as olive oil or butter. Meals should have delicate aromas and flavors, a homogeneous and creamy texture, and a soft consistency. Boiled, cooked, or grilled foods should be opted for as well. Other important suggestions include adding fruit jams and honey to yogurt or salads and pairing aged cheese with soup. Incorporating beef, chicken, or eggs into rice or sandwiches is also advisable [40].

Hence, optimal treatment decisions necessitate the involvement of a multidisciplinary team for the early diagnosis and management of this debilitating condition. This collaborative effort should engage family members, physicians, and psychologists to ensure a seamless continuum of care and alleviate the suffering of the patients.

2.11. Tailored Recipes

In the field of oncology, dietary modifications should be tailored to specific clinical scenarios. However, preserving the sensory enjoyment of meals and the pleasure of eating poses a notable challenge for cancer patients, whether they are in a hospital setting or at home.

Firstly, patients and their caregivers often lack knowledge about how to process and combine ingredients, since there is a shortage of recipes designed for the oncology context.

Secondly, many "medical recipes" often prioritize balance but neglect the hedonic component, resulting in nutritious but unappetizing meals.

In essence, it is essential for patients to receive guidance not only about "what to eat", but also about "how to prepare it". The field of gastronomy can provide strategies to enhance not just the quantity but also the quality of food intake. By improving the presentation of meals, food consumption can increase [133]. This way, each meal may transform into a moment of pleasure, contributing to both overall wellbeing and an improved nutritional status.

In order to address this clinical need, we created a workflow consisting of 5 steps (Figure 2).

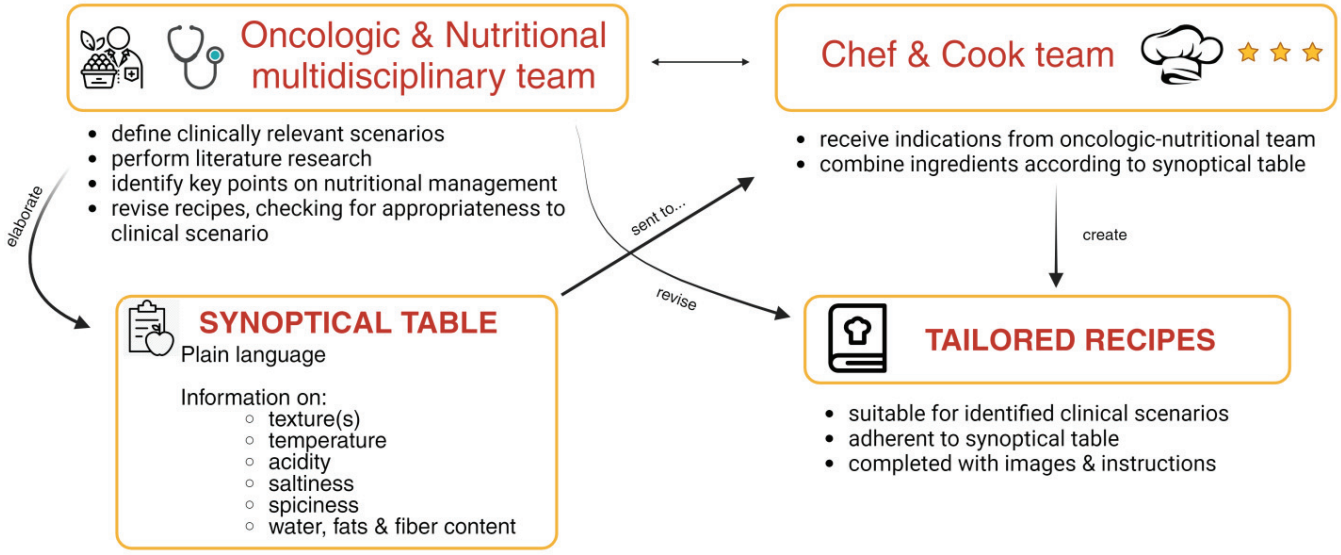

Figure 2. The workflow for the conceptualized multidisciplinary platform to create and clinically validate recipes for clinical scenarios. Made with Biorender.

- First, the oncologic and nutritional teams defined clinically relevant scenarios often encountered in the oncology setting;
- Second, the oncologic and nutritional teams performed a literature research for publications about nutritional management in that clinical scenario;
- Third, a synoptical table (Table 1) to translate in plain language the crucial features of the nutritional approach for that clinical scenario was created;
- Fourth, a chef and his team used that table to create a tailored recipe;
- Fifth, these recipes were analyzed and revised by nutritional team in order to check their appropriateness for clinical scenarios;
- Sixth, the recipes were modified accordingly to the revisions;
- Seventh, accepted recipes were implemented with a figure and detailed how-to instructions (Figure 3, Table 2, Supplementary File S1 for two additional recipes).

This workflow represents a useful and replicable system to create valuable and pragmatic recipes and/or lifestyle interventions for patients with cancer and their caregiver.

Table 1. The synoptical table to translate in plain language the crucial features of nutritional approach for each clinical scenario.

	Xerostomia	Stomatitis	Diarrhea	Nausea/Vomiting	Dysphagia (Mechanical)	Dysphagia (Neurological)	Sub-Occlusion	Dysgeusia and Dysosmia	Anorexia	Cachexia
Texture (IDDSI scale)	0–5	0–4	Any	Any	0–4	3–5	0–4	Any	Any	Any
Multiple textures	Any	Any	Any	Any	Avoid	Any	Any	Any	Any	Any
Temperature	Any	Low	Normal	Low	Any	Any	Any	Any to warm/hot	Any	Any
Sourness	Mild to high	Very low	Normal to low	Low	Any	Any	Any	Any	Any	Any
Sapidity	Any	Low to very low	Normal to low	Normal to low	Any	Any	Normal	Normal to very low	Any	Any
Spiciness	Any	Avoid	Low	Low	Any	Any	Normal to low	Normal to very high	Normal to very high	Normal to very high
Hydration	High	High	Low	Normal	High	High	High	Any	Any	Any
Fattiness	Normal	Normal	Low	Low to very low	High to very high	Normal	Any	High	High to very high	High to very high
Amount of fiber	Any	Any	Low to very low	Low	Avoid	Normal to avoid	Avoid	Any	Normal to low	Normal to low
Leading nutritional points	Proper oral hygiene Introducing different flavors Avoiding sour foods Acupuncture during and after radiation for H&N	Saline and sodium bicarbonate mouthwashes Oral cryotherapy Preferring soft or semisolid, mild-textured foods Opting for cool or room-temperature foods	Abundant oral liquids with solutions rich in electrolytes and glucose Probiotics supplementation Small and fractioned meals rich in soluble fibers Avoiding foods and beverages with high osmolarity, caffeine and theine	Eating small and frequent meals Having light snacks between meals Introducing ginger, chamomile, peppermint and cardamom Reducing liquid intake during meals Avoiding spicy, fatty, salty food and strong flavors Preferring bland foods, soft fruits or vegetables	Preferring more liquid forms of foods Reducing fiber content	Consuming small, fractionated semi-solid meals and thick liquids Prioritizing hard texture and fatty food Avoiding sticky or bulky foods, mixed textures	Consuming smaller meal portions Opting for a diet lower in fiber and softer-textured foods Selecting refined grains Avoiding foods with high fiber content, skins of fruits and vegetables	Preparing toppings or dressings Marinating meat or fish before cooking, or grilling them with acid products Opting for cold or lukewarm dishes Seasoning meat or fish with herbs and spices like rosemary, bay leaf, parsley, thyme, or Jamaica pepper Avoiding warm meals	Using toppings, contrasting colors, and serving small portions Opting for small, frequent meals, especially well-cooked and energy-rich foods, particularly in the morning Including high-calorie and high-protein foods in the diet (homemade smoothies, juices and cream soups)	Endorsing high-energy and high-protein foods with delicate aromas and flavors Preferring a homogeneous and creamy texture and a soft consistency Protein 1.5 g/day per kilogram of BW Opting for boiled, cooked, or grilled Adding fruit jams and honey to yogurt or salads and pairing aged cheese with soup

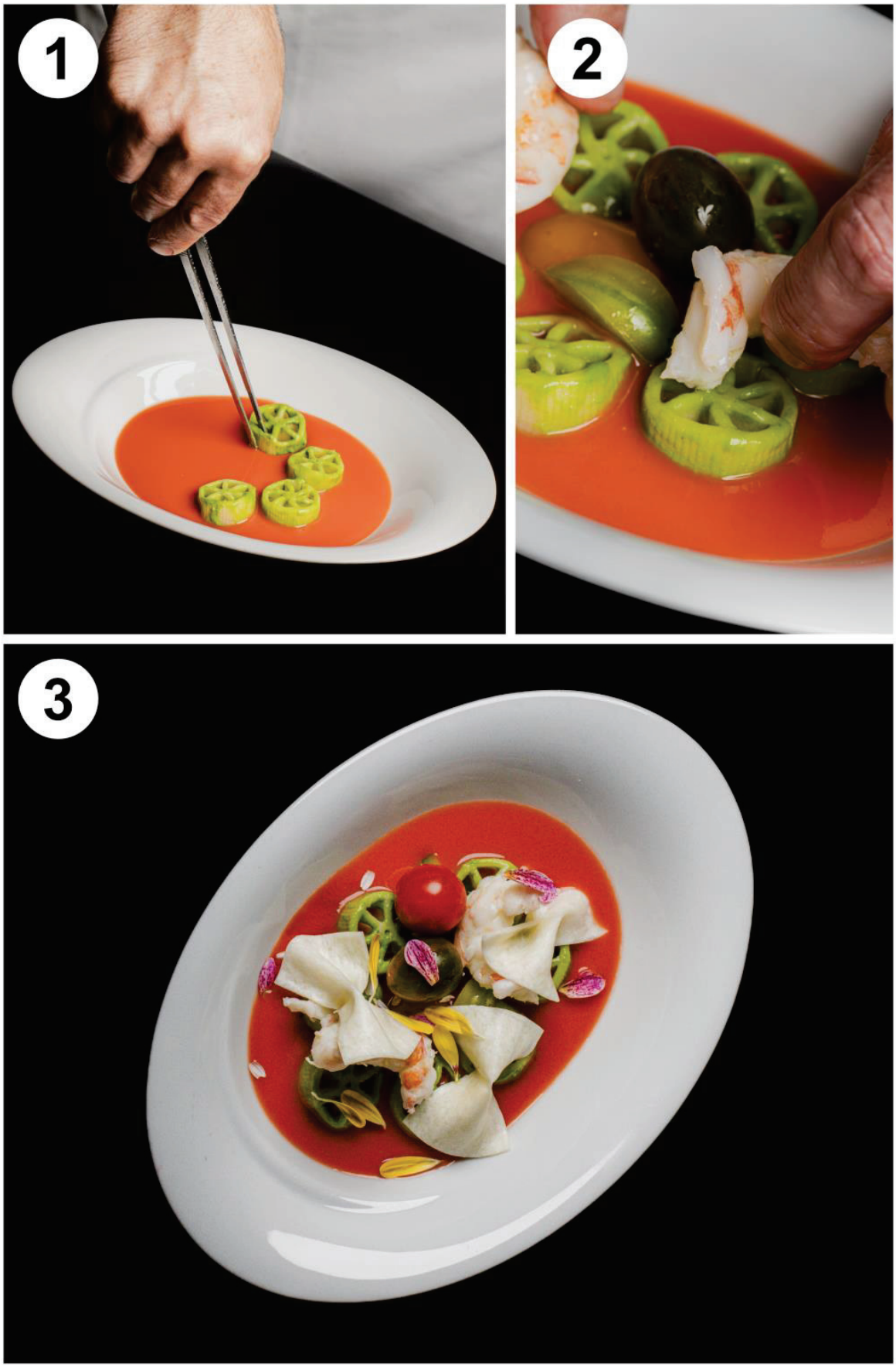

Figure 3. Iconographic material of the recipe for patients and their caregivers.

Table 2. Example of a recipe for cachexia/anorexia with its nutritional profile.

Fiori sulle farfalle (Flowers on butterflies)
Preparation and servings for two people

For the tomato soup:
Ingredients:

- Red grape tomatoes 150 g
- Red cherry tomatoes 150 g
- Extra virgin olive oil 15 g
- Salt 3 g
- Dulcita brown sugar 0.5 g

Procedure:

- Blend together date and cherry tomatoes, then stir in the remaining ingredients.
- Strain through a sieve.

For the cold pesto pasta:
Ingredients:

- *Benedetto Cavalieri* pasta wheels 60 g
- Basil pesto 30 g
- Water 10 g

Procedure:

- Cook the pasta wheels in boiling salted water (cooking time: 12–13 min), then cool them quickly in cold water and dry them using a paper towel.
- Toss them with a drizzle of extra virgin olive oil and basil pesto diluted with a spoonful of warm water.

For the mozzarella butterflies:
Ingredients:

- Cow's milk mozzarella cheese 60 g

Procedure:

- Cut the mozzarella into chunks and heat it in a microwave oven, with a little of its preserving water, until it becomes stringy and malleable.
- Drain off the excess liquid, place it between two sheets of baking paper and stretch it using a rolling pin (reaching a 2 mm thickness).
- Cut some 3 × 6 cm rectangles; pinch them in the center by means of the tip of a pair of tongs (previously heated in boiling water) to make butterflies

For the steamed langoustines:
Ingredients:

- Langoustines 6 pieces

Procedure:

- Peel and clean the langoustines.
- Steam for about 1 min.
- Cut them into medallions and season them with salt and a drizzle of extra virgin olive oil.

Plating

- Pour the cold tomato soup at the base of a soup bowl.
- Form a circle with the basil pesto pasta wheels, put various colored cherry tomatoes in the middle and season them with extra virgin olive oil and salt.
- Lay the mozzarella butterflies on top of the pasta, arrange the langoustines medallions and finish the dish with edible flowers' petals.

Caloric and nutrients labels (for one serving)

Calories, Kcal	484
Proteins, g	21
Fats, g	31
Saturated fatty acids, g	8
Monounsaturated fatty acids, g	18
Polyunsaturated fatty acids, g	3
Carbohydrates, g	31
Sugars, g	7
Fiber, g	3

2.12. Implications and Future Perspectives

Over the centuries, there has been a shift from perceiving nutrition as a means of sustenance and a tool for socialization and hedonism to a pivotal resource for individual and public health. The significant challenge in the field of oncological nutrition in the

coming years will be to achieve a higher level of personalization that considers the cultural, social, clinical, biological, genetic, and comorbidity context of the subject [134,135]. This goal is also based on the assumption that tumors exhibit strong heterogeneity, and each of them may be influenced by certain risk factors, such as overweight, exposure to toxins, genetic background, or even parameters once considered clinically neutral, such as the ABO blood group [136–139].

Although potentially applicable to the field of prevention, our work has focused on the management of cancer patients who have already developed symptoms related to the disease or its treatments. We aimed to establish a pragmatic workflow based on three steps: a literature review for the nutritional management of a specific symptom, the development of recipes adhering to literature recommendations, and a multidisciplinary review of the same.

The advantage of such an approach lies in its flexibility and easy applicability to almost all nutritional scenarios, not limited to oncology. However, the major limitation of this work is the need to validate, through a clinical study, whether this operational model is indeed effective in improving the quality of life of cancer patients. In addition, although we have not performed a systematic review on each oncologic symptom, it is already evident that there is a paucity of literature on these topics.

3. Conclusions

Customized nutrition in oncology continues to be a challenge due to the limited scientific data and the availability of suitable recipes. In this context, we have introduced a highly practical multidisciplinary framework for tailoring food preparation to address various common clinical scenarios encountered in oncology patients. Enhancing the quality of life holds a central position in contemporary medicine, especially in the field of oncology, and personalized recipes have the potential to be a strategic resource for improving nutritional wellbeing and bringing happiness to the numerous patients who must cope with cancer.

Preserving the hedonic value of meals and the enjoyment of eating is a significant challenge when it comes to cancer patients. However, gastronomy offers strategies to enhance not just the quantity, but also the quality of food consumption. Elevating the presentation of meals can lead to increased food intake. Consequently, each meal transforms into a moment of pleasure, contributing to both overall wellbeing and an enhanced nutritional status.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/nu15245068/s1, File S1: supplementary recipes.

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Abbreviations

5-fluorouracil, 5-FU; cancer cachexia, CC; chemotherapy, CINV; radiation therapy, RINV; eicosapentaenoic acid, EPA; gastrointestinal, GI; head and neck, H&N; percutaneous endoscopic gastrostomy, PEG; nausea and vomiting, N/V; neurokinin 1, NK1; quality of life, QoL.

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Review

Conceptualizing an Integrative Multiple Myeloma Care: The Role of Nutrition, Supplements, and Complementary Modalities

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Abstract: Multiple Myeloma (MM) is the second most prevalent hematologic malignancy, and its incidence has been increasing enormously in recent years. The prognosis of MM has changed radically with the introduction of new drugs that have improved life expectancy; recurrences are a common occurrence during the course of the disease and are characterized by an increase in refractory to treatment. Moreover, MM patients are challenged by quality of life-related concerns while limited conventional therapy may be offered. This includes bone pain and dialysis due to the complications of acute renal failure. We, therefore, believe that it is very important to add new treatment modalities, including supplements, nutritional modifications, acupuncture, and mind–body therapies, with the goal of improving treatment tolerance, effectiveness, and patients' quality of life. Moreover, many patients use some of these supplements on their own, in the hope of reducing the side effects, so it is even more important to know their action and potential. The purpose of this review is to illustrate all these strategies potentially available to enrich our approach to this, to date, incurable disease.

Keywords: Multiple Myeloma; nutrition; acupuncture; vitamin D; supplementation; integrative medicine

1. Introduction

Multiple Myeloma (MM) represents 10–15% of all hematological malignancies [1–3].

The last few years were characterized by a significant improvement in available therapies for this disease, including new-generation immune modulators and proteasome inhibitors (PIs), monoclonal antibodies, or immunotherapy (bispecific T-cell engagers or Chimeric Antigen Receptor T cell therapies, so-called CAR-T) [2].

Following this progress, the median overall survival has more than tripled [2]. However, MM is still an incurable disease and has become a chronic condition with patients experiencing many symptoms related to the disease itself or its treatment, which impacts health-related quality of life (QoL) [4–7]. These include pain, fatigue, sexual dysfunction, sleep disorders, immune deficiency, anxiety, depression, and/or loss of control [5–8], making patients with MM the most symptomatic in the haemato-oncologic field [9]. In the last few years, Integrative Oncology (IO) has been developed, and subsequently, Integrative Hematology (IH) was defined as a separate entity [10]. IO is a "patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments, and aims to optimize health, QoL, and clinical outcomes across the cancer care continuum" [11].

Specifically, in the case of MM, patients have been shown to use complementary and alternative medicine widely but, generally, without informing their hematologist [12], potentially leading to safety issues [13]. The integrative approach to the treatment of myeloma therefore has many objectives: firstly, a reduction in disease-related symptoms such as bone pain, which is very detrimental to the patient's life [9,14,15]; and a reduction in treatment side effects, allowing greater compliance to them as well as greater effectiveness. Another goal is to reduce the toxicity of drugs and improve the performance of the immune system. A patient with MM has many unmet needs, and a patient-centered approach, which includes mind–body techniques, can help to better manage the disease and therapies.

Finally, some techniques have also shown efficacy in improving the course of the disease [16]. In the present work, we aimed to review the different kinds of complementary and integrative techniques that may be effective and safe for the management of MM patients. The goal is also to propose preliminary consensus guidelines based on the existing literature for the safe and effective use of IH in MM.

2. Nutrition, Lifestyle Changes and Microbiota

2.1. Nutrition, Lifestyle Changes, and the Link with Pathogenesis and Progression of MM

Recently, a link between nutrition, lifestyle, and MM has emerged [17]. In addition, with the lengthening of the life of MM patients due to an improvement in the available treatments, it may be useful to design a nutritional-based consultation on how to improve the QoL of patients coping with MM. In particular, Monoclonal Gammopathy of Unknown Significance (MGUS) and Smoldering MM are situations in which preventive interventions may be considered.

In a study conducted with patients with MM, following diagnosis, 82% reported nutrition-related questions addressed to non-medical sources rather than the hematologist. Furthermore, 94% of those who received advice from a hematologist followed their instructions, which indicates that the hematologist's expertise can address this need [18].

Firstly, nutrition could play a role in MM prevention strategy. This could be important to take into account: the protective role in the pathogenesis of the MM of some foods may also be associated in some cases with an antitumor role in the stage of overt disease.

Several studies suggest an association between diet and MM incidence. For example, the Epic study shows cancer risk reduction in vegetarians, vegans, and fish eaters, especially regarding MM [19].

Some case-control studies confirm the trend toward the protective action of fish use [20,21]. A meta-analysis [22] focusing precisely on the relationship between fish intake and myeloma showed an inverse but not a linear relationship, suggesting that an intermediate weekly consumption, not too frequent, may be the right compromise between an intake of omega 3, presumably responsible for the beneficial effect, and that of ocean pollutants, unfortunately, present especially in large fish.

Omega 3, in addition to the known anti-inflammatory effect, has demonstrated a specific action on mouse models of MM in vitro in which they can reduce cell growth. The reduction in interleukin 6 (IL6) production could also be involved in specific anti-MM action [23].

Although some case-control studies have not shown a significant association between fruit consumption and MM risk, there is evidence showing a linear beneficial trend for such an association [24,25].

A recent Icelandic prospective study of cohorts showed that fruit consumption (equal to or greater than 3 times a week in adolescence) is associated with a reduced risk of MGUS and, when consumed in adulthood, with reduced progression of MGUS to MM [25].

Also, adequate consumption of cruciferous, tomatoes, and whole grains may reduce the risk of MGUS and MM, and an excess of refined sugars and sugar-sweetened beverages can increase it [25,26].

The beneficial effect of plant-based foods could be attributed to the action of dietary fibers on the production of butyrate-producing bacteria such as Faecalibacterium Praus-

nitzii. Also, the presence of molecules with antitumor activity such as isothiocyanates, indoles, and flavonoids (for example, lycopene from tomatoes) can be protective. Fibers and micronutrients in whole grains may be associated with the metabolic effects of glycemic index modulation, reduced insulin stimulation, and reduced production of insulin-like growth factor (IGF1). IGF1 is a molecule well known for its stimulating action on proliferative molecular pathways; also, in MM, its activity has been documented to involve the processes of homing, cell proliferation, apoptosis, angiogenesis, and bone metabolism [27]. The Epic study and other cohort studies show a higher incidence of MM in meat eaters and dairy consumers [19,28]. The high levels of IGF1 resulting from the consumption of dairy products could partly explain this correlation. *N*-nitroso compounds, heterocyclic amines, and heme present in meat could exert an oxidizing and pro-carcinogenic action as well.

Among other lifestyle factors, alcohol has a controversial impact on the incidence of MM, with a significant reduction in the incidence in moderate drinkers (2–2.9 drinks/day) [29].

It is not clear why this beneficial action of alcohol is different from what happens in other cancers. Still, it could be linked to a direct modulation of the immune system in light and moderate drinkers [30].

2.2. Obesity, Sarcopenia, and MM

The relationship between obesity, MGUS, and myeloma is well known. Not only does obesity affect the incidence of MM but also the progression from MGUS to MM and MM mortality rate. Many mechanisms are involved: the production of IL6 and leptin by fat cells leads to increased inflammation and cell proliferation; the reduction in adiponectin is associated with increased IL6, activation of NFkB, and osteoclastic maturation. Finally, the presence of a more significant adipose tissue in the bone marrow stimulates the proliferation of MM cells and their migration outside the bone marrow [31].

Another important risk factor to consider at diagnosis is the nutritional status of the patient, especially the presence of sarcopenia, which is a negative prognostic factor.

Sarcopenia is frequent in patients with MM at diagnosis; the presence of reduced subcutaneous adipose tissue is associated with a worse prognosis [32].

The Controlling Nutritional Status (CONUT) score is a simpler tool to use but equally effective in predicting the outcome of MM patients, especially those undergoing autologous stem cell transplantation (ASCT) [33].

Finally, the risk of muscle mass deficiency must never be neglected, and an adequate protein intake must be guaranteed to the patient at diagnosis and throughout the treatment, which can itself contribute to sarcopenia: nausea, mucositis, and lack of physical activity due to bone pain can, in fact, reduce the patient's food intake.

A daily protein intake of at least 1.4 g/kg appears to be necessary to obtain or maintain adequate muscle mass according to a recent systematic review [34].

2.3. The Role of Microbiota in the Pathogenesis and Treatment of MM

The microbiota of patients with MM shows less alpha diversity at diagnosis than controls [35]. Although there are conflicting data on the association of the disease with the presence of butyrate-producing bacteria, a dysbiotic feature seems to be present in patients with MM [35,36], and a correlation between levels of Interleukin 17 (IL17) in the bone marrow of patients with MM and the composition of the microbiota is currently being explored (NCT05712967) [37]. This increase could be induced by foods rich in salt and the subsequent increase in nitrogen-recycling bacteria (e.g., Klebsiella and Streptococcus) [38].

The microbiota is also inevitably involved in the link between nutrition and MM mentioned above, being the first mediator of the effect of food on the body.

This could affect not only the pathogenesis of the disease but also its course and response to therapy. A clinical study of 34 MM patients in maintenance therapy with lenalidomide showed interesting results in this regard. Patients following a plant-based diet had a higher fecal concentration of butyrate, the consequence of an increase in butyrate-producers E. Hallii and F. Prausnitzii [39]. The increased fecal butyrate concentration was

associated with a more sustained minimal residual disease negativity, which is known to be predictive of longer Progression-Free Survival [40].

Although this is a small study, these results suggest and confirm an essential association between nutrition, microbiota, and the effect of conventional therapy in MM patients. Recently, the detection of a specific microbiota in the bone marrow of patients with MM, mainly localized intracellularly, widens this scenario. The researchers hypothesize that the presence of intratumor MB is a consequence of an impairment of the gut MB and intestinal permeability, confirming a direct relationship between gut MB and the pathogenesis of MM [41]. Further well-designed clinical studies are necessary to clarify the therapeutic potential of an integrated approach that includes a "pro-microbiota" diet. At present, the Nutrivention3 study (NCT05640843) is a randomized, multi-center pilot study comparing 150 patients to evaluate the effects of a plant-based diet versus an omega 3 or placebo supplementation in patients with MGUS or SMM and high Body Mass Index on the concentration of fecal butyrate [42].

3. Natural Compounds and Vitamins: Their Potential Role in the Treatment of MM

3.1. Curcumin

Curcumin (diferuloylmethane), the main bioactive component of Turmeric (curcuma longa), has demonstrated anti-inflammatory, antibacterial, and anticancer in vitro effects against many cancer cell lines [43].

In MM, its action is expressed both by affecting specific signaling pathways and with an epigenetic modulatory effect.

Among the various effects, Nuclear factor kappa B (NFκB) inhibition appears to be particularly important in this disease: one of the backbones of MM therapy is, in fact, constituted by PIs, which cause NFκB inhibition. This would suggest a possible hypothetical interaction between curcumin and PIs.

In vitro, curcumin has been shown to enhance the cytotoxic effect of bortezomib (the first PI) [44]; it also synergizes with carfilzomib through a major downregulation of NFkB [45].

Curcumin was also reported to downregulate the expression of cyclin D1, inhibit STAT3 phosphorylation, and reduce IL6, even in patients with unfavorable cytogenetics and regardless of Tumor Protein 53 (TP53) status: this sensitivity to curcumin is also present both in the cells of patients at diagnosis and at recurrence, demonstrating that resistance phenomena do not occur [46,47].

Finally, it inhibits osteoclastogenesis by inhibiting RANKL [48].

The main reason for the incurability of MM could be related to the presence of cancer stem cells (CSCs): they confer treatment resistance and are associated with recurrence and poor prognosis. Recently, curcumin has been demonstrated to be efficient against these cells, increasing apoptosis [49].

As an epigenetic modulator, curcumin also appears to act in MM by inducing DNA methyltransferase (DNMT)-mediated mTOR methylation: hypermethylation of the mTOR promoter region would inhibit the antiapoptotic action of this molecular pathway [50]; unlike the hypomethylating drugs used in hematology, such as azacitidine, curcumin would not cause an overall change in DNA methylation but only the specific one caused by DNMT3a and DNMT3b, and this could give it more peculiar anti-myeloma activity.

Finally, in some mouse models, it increases chemosensitivity to dexamethasone, doxorubicin, and melphalan and synergizes not only with the action of bortezomib and carfilzomib but also with immunomodulatory imide drugs (IMiDs) such as lenalidomide and thalidomide [51]; synergy with lenalidomide is expressed through the suppression of the cereblon gene, which is exactly the target of the IMiDs.

However, the literature on the association of these promising in vitro effects with effective clinical action is presently limited.

The first study, published in 2009, involved 26 patients with MGUS treated with 4 g daily of curcumin; in this study, the monoclonal component decreased in 50% of

patients, in keeping with a reduction in markers of bone resorption [52]. Following, the authors published a randomized double-blind placebo-controlled trial in both MGUS and smoldering myeloma: they used curcumin in doses of 4 and 8 g daily, and this led to a reduction in the chain k/λ ratio by 35 and 36%, respectively, as well as the markers of bone resorption [53]. As not all cases of MGUS and smoldering myeloma evolve into frank disease, the use of conventional chemotherapy is not justified in these cases; precisely for this reason, supplements such as curcumin express all their chemopreventive potential in this phase of the pathogenesis of the disease.

In this regard, Zaidi et al. [54] published a case study in which curcumin (8 g daily) was associated with hyperbaric sessions that led to disease control in a case of refractory relapsed MM for 60 months, with an excellent safety profile.

A more recently published case study reported the efficacy of curcumin in replacing dexamethasone in patients who were intolerant to the latter. The authors treated 15 patients who were under treatment with regimens containing either IMiDs or PI combined with dexamethasone, substituting the latter with C3 complex curcumin at a dosage of 3–4 g daily. The researchers concluded that curcumin may act as a steroid-sparing agent in patients with MM who are intolerant of dexamethasone, with an excellent tolerability profile [55]. These data are exciting considering that in MM, we often use therapeutic regimens, if effective, up to progression; if these medications, as often happens, contain cortisone, the patient is frequently subjected to massive and prolonged doses of steroids and their heavy long-term side effects. Even with the aim of reducing steroid load and toxicity, curcumin is, therefore, an engaging weapon to take into consideration.

Finally, a pilot randomized trial was conducted [56] in which 33 newly diagnosed patients, ineligible for transplant, were randomized to receive melphalan 4 mg/m^2 plus prednisone 40 mg/m^2 for 7 days and curcumin 8 g/daily for 28 days or placebo for 4 cycles. Curcumin-treated patients showed a higher treatment response rate (75% vs. 33.3%) with a contextual reduction in NF-κB, IL-6, VEGF, and TNF-α levels. These few but promising results emphasize the need for more well-designed clinical studies to explore the potential additive healing effect of curcumin, as well as to identify the type of biochemical form most available (e.g., extract, liposomal, and water-soluble form).

3.2. Epigallocatechin Gallate (EGCG)

EGCG has shown an antiapoptotic effect on MM cells in vitro through the stimulation of ROS and a reduction in the levels of peroxiredoxin (an antioxidant molecule); moreover, a crucial role is played by the selective interaction with the laminin 1 receptor, which is much higher in patients with MM than in controls and whose absence prevents the apoptotic effect of EGCG [57]. Other mechanisms involve the inactivation of the enhancer of zeste homolog2 (EZH2) and the mitochondrial apoptosis pathway [58].

Although the in vitro antitumor efficacy of EGCG in MM is undisputed, its in vivo role and, in particular, its interaction with bortezomib, a backbone of the induction therapy, is controversial. In 2009, two contradictory studies were published in this regard. Golden et al., demonstrated that EGCG and other polyphenols derived from green tea prevented tumor cell apoptosis induced by bortezomib in vitro and in vivo at concentrations also easily achievable in humans: the antagonistic action of EGCG was evident only with boronic acid-based PIs, so the binding with the boronic acid of the molecule appears to be the mechanism underlying this inhibitory mechanism [59]. In the second work, however, a synergistic effect between the two substances was demonstrated, and this would be due, in the opinion of the authors, to the higher dosage of EGCG and bortezomib used [60]. The discrepancy of these data, the lack of clinical studies, and the possible difference between what happens in vitro and what occurs in vivo due to certain variables such as absorption and bioavailability impose a prudent attitude, especially until well-designed clinical trials are available.

Some more recent studies affirmed again the antagonism between the two substances [61,62]; in particular, Qiu et al. [62] have shown that EGCG may neutralize

bortezomib-induced apoptosis, activate Wnt/β-catenin signaling, and result in the accumulation of beta catenin, which subsequently activated c-myc and cyclin D1. The authors conclude by discouraging green tea intake during bortezomib therapy.

Finally, EGCG is very interesting for its action on glutaminolysis: MM cells have a glutamine addiction, which is responsible for their dependence on glutamine uptake. In a recent study [63], Li et al., showed that the combination of EGCG and telaglenastat, a glutaminase inhibitor, synergistically inhibits proliferation and induces apoptosis in MM cells in vitro. Targeting glutamine metabolism, therefore, should be a winning strategy.

3.3. Vitamin D

Vitamin D deficiency is found in most patients with MM at diagnosis, as in many other types of cancer. This deficit is described as "alarming" in patients with bone involvement [64]. Even some peculiar polymorphisms of the vitamin D receptor (VDR) gene may be a molecular marker of the risk of development of the disease [65].

Low levels of vitamin D correlate with an increased C-reactive protein (CRP) and the ISS stage at the time of diagnosis: they may, therefore, be predictive of more advanced disease [66]. It is very interesting to observe how the action of some drugs used in MM also passes through the modulation of the molecular pathway of vitamin D: bortezomib, for example, upregulates the production of VDR, and this effect is amplified in the presence of vitamin D.

Thalidomide- or bortezomib-induced neuropathy is more severe in the case of concomitant vitamin D deficiency, which, however, does not appear to influence the incidence [67].

Vitamin D and its active metabolite, calcitriol, act as modulators of the immune system: absolute lymphocyte count recovery and relapse-free survival after ASCT are improved after daily administration of calcitriol of 0.25 μg, as shown in a randomized-controlled trial (RCT) vs. placebo [68].

Interestingly, vitamin D can increase CD38 expression in plasma cells, thereby amplifying the binding of CD38-targeting antibodies; however, the cytotoxicity of the latter could be compromised in case of vitamin D deficiency, which would cause a worse performance of the macrophages associated with myeloma (MAMs). Lenalidomide and pomalidomide can restore the vitamin D pathway in the MAMs, improving their cytotoxicity. In doing so, vitamin D becomes a crucial link to improve the synergy between immune modulators and monoclonal antibodies [69].

The above data may support the rationale to test vitamin D levels at diagnosis and supplement them before starting therapy and during treatment with anti-CD38 and immunomodulatory drugs.

Noteworthily, vitamin D levels do not appear to be significantly associated with the coexistence of bone disease [70].

In Figure 1, the main mechanisms of action of the supplements most studied in the MM are presented.

3.4. Others

Ascorbic acid can reduce Bortezomib-induced neurotoxicity by leading to the recovery of damaged Schwann cells; unfortunately, it has been shown to inhibit Bortezomib cytotoxicity in vitro and in vivo, so its supplementation in patients who are on treatment with this PI is not recommended [71,72].

Despite its importance for the immune cells, it is ineffective in improving bone marrow recovery after ASCT both in MM and lymphoma patients, so its use is not advised in this setting [73].

Sulforaphane is an isothiocyanate derived from cruciferous vegetables, which has been shown to have similar action to bortezomib in inhibiting the degradation of inhibitory kappa B kinases (IkB), which, in turn, inhibits the proteasome complex.

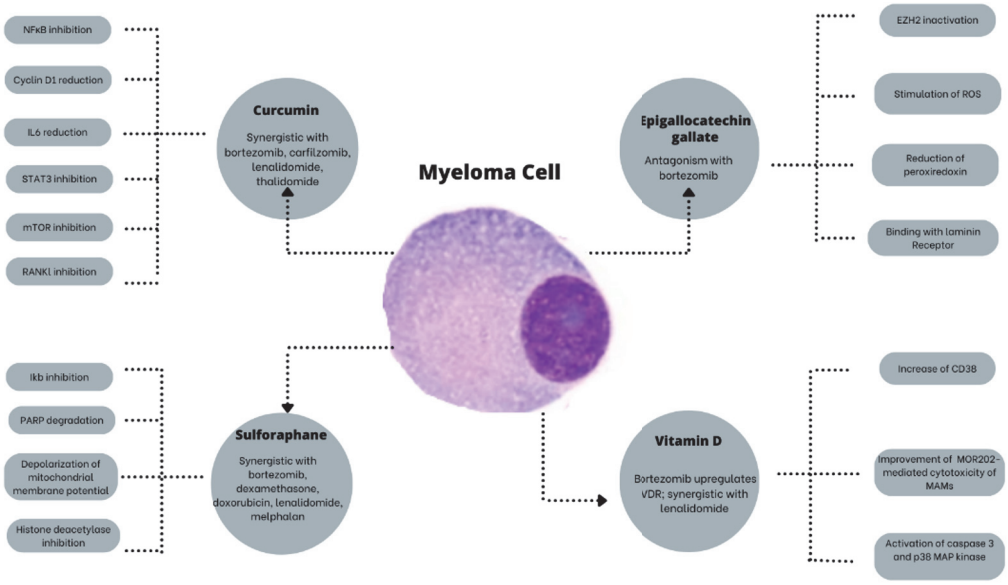

Figure 1. The main mechanisms of action of the most studied supplements in MM. EZH2: Enhancer of zeste homolog2; IkB: NkB inhibitor; IL6: interleukin 6; MAMs: Macrophages associated with myeloma; mTOR: Mammalian target of rapamycin; NfkB: Nuclear factor kappa B; PARP: poly ADP ribose polymerase; RANKL: Receptor activator of nuclear factor kappa-B ligand; ROS: Reactive oxygen species; STAT3: Signal transducer and activator of transcription 3; VDR: Vitamin D receptor.

Moreover, it shows synergy with dexamethasone, doxorubicin, bortezomib, and melphalan. In in vivo models, it leads to a reduction in the burden of disease and an increase in survival [74].

Resveratrol has shown strong antiangiogenic activity by regulating factors such as VEGF, matrix metalloproteinase-2 (MMP2), and matrix metalloproteinase-9 (MMP9).

By constitutively activating STAT3 and NFκB, it overcomes an essential mechanism of chemoresistance and it has a synergistic interaction with Bortezomib and Thalidomide [75]. There is insufficient clinical evidence to understand the clinical efficacy of resveratrol. In a single phase II study, it was administered in association with bortezomib: in this clinical experience, the toxicity profile was unacceptable, with 50% of patients developing severe renal failure. To date, resveratrol in combination with bortezomib is strongly discouraged. Further studies are needed to clarify the safety of this natural compound in this setting of patients [76].

Cannabinoids are compounds found in plants from the genus Cannabis, of which the most widely used is Cannabis Sativa. In recent years, their role in managing the patient's symptoms has emerged and they are used primarily to reduce chronic pain and chemotherapy-induced nausea and vomiting and stimulate appetite [77]. Since many different cell lines express CB1/CB2 receptors for cannabinoids, their anti-cancer potential has been extensively investigated recently, in in vitro and in vivo models: among the various plant components most studied for their antiapoptotic activity are delta-trans-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), with the latter being free of psychoactive effects. In contrast to the in vivo and in vitro settings, clinical research is limited, though suggests good patient tolerability even at high doses, particularly in glioblastoma and MM [78]. In MM, in vitro studies have demonstrated reduced viability of myeloma cells and proapoptotic activity in cannabinoid-treated MM cells, including dexamethasone-resistant cells. Cannabinoids can reduce the expression of the β5i subunit of the immunoproteasome, therefore increasing the efficacy of carfilzomib, a second-generation PI. In addition, they allow resistance mechanisms effectively linked to the expression levels of β5i to overcome [79]. These compounds are, therefore, promising not only for improving the symptoms and QoL of patients, but also for their anticancer and synergistic activities with currently used drugs. Further studies are needed to confirm this promising action.

Table 1 shows the potential use of the substances described above.

Table 1. Potential use of supplements or natural compounds in Multiple Myeloma.

Substance	Dose	Potential Chemotherapy Interaction	References
Vitamin D	To reach blood levels >30 ng/ml	Synergism with lenalidomide, pomalidomide, anti-CD38	[67–69]
Curcumin	6–8 g daily or liposomal formulation	Synergism with bortezomib, carfilzomib, thalidomide, melphalan	[44,45,51–56]
Epigallocatechin 3 gallate	1 g daily	Antagonism with bortezomib	[61,62]
Vitamin C	6–8 g daily	Antagonism with bortezomib	[71,72]
Cannabinoids	?	Synergism with carfilzomib	[79]
Sulforaphane	To be found	Synergism with dexamethasone, doxorubicin, bortezomib, and melphalan	[74]
Resveratrol	To be found	Antagonism with bortezomib; possible side effects, not recommended	[75,76]

4. Acupuncture

Pain is a common QoL-related concern experienced by MM-diagnosed patients, with various etiologies, such as mechanical due to bone lesions, neuropathic due to the side effects of prescribed drugs (mainly PIs or immune modulators), infections (post-herpetic neuralgia), or direct infiltration of light chains or amyloid into peripheral nerves [80]. The management of these symptoms with conventional drugs is generally unsatisfactory and subject to side effects, while acupuncture has been shown to relieve cancer-related pain safely [81]. In a bibliometric analysis summarizing research conducted between 2012 and 2022, acupuncture was suggested as a leading modality in the treatment of MM-related pain [82,83]. This is particularly in regard to treatment of chemotherapy-induced peripheral neuropathy (CIPN), which is an unmet need in Western medicine [80]. Acupuncture has been widely studied for this condition with positive results [84,85]. Specifically, the widely used proteasome inhibitor (PI) bortezomib can cause CIPN in up to 40% of patients [86]. A number of studies have demonstrated the effectiveness of acupuncture for bortezomib-induced peripheral neuropathy (BIPN). Following case reports [87], a retrospective case series on 5 patients demonstrated the immediate and long-lasting pain reduction associated with acupuncture in BIPN [88]. Acupoints included bilateral ear points and body points (Large Intestine 4 (LI4), Triple Energizer 5 (TE5), Large Intestine 11 (LI11), Stomach 40 (ST40), and BaFeng) on a weekly basis. The effect of the same protocol has been confirmed in 27 patients with BIPN, in which a reduction in specific symptoms has been observed (numbness/tingling in hands and feet, cold sensitivity, and unpleasant feelings), although nerve conduction velocities (NCV) were unchanged [89,90]. Electroacupuncture has also been shown to reduce pain severity and improve QoL, as well as specific motor functions in 19 patients with grade 2 or higher thalidomide- or bortezomib-induced neuropathy [91]. In a 54-patient Chinese RCT, the combination of acupuncture + moxibustion was shown to improve QoL compared to conventional drugs, although no difference was shown in the improvement of NCV [92]. Finally, an additional RCT assigned 104 myeloma patients with CIPN to a methylcobalamin-alone group or one associated with three 28-day cycles of acupuncture in acupoints different than previously described (LR3, ST43, GB41, SP6, ST36, SP10, ST25, GV14, GV12, GV11, GV9, BL13, BL17, and BL58). Each treatment cycle included three daily acupuncture treatments followed by 10 days of treatment once every other day.

This study showed that adding acupuncture led to a significant pain reduction while improving both daily activity and nerve conduction velocities compared to methylcobalamin alone [93]. These studies suggest that acupuncture may be an effective treatment

to improve QoL in patients suffering from Myeloma-related CIPN, although its effect on nerve conduction is controversial.

Another important challenge in patients with MM is ASCT, which is still a common practice guideline in fit patients following first-line induction and a reduction in disease burden. Deng et al., published an RCT with 60 patients who were assigned to true or sham acupuncture once daily for 5 days after receiving high-dose chemotherapy for ASCT [94]. Acupoints included GV20, Yintang (Ex-HN3), Heart 7 (HT7), Pericardium 6 (PC6), Stomach 36 (ST36), Spleen 6 (SP6), Kidney 3 (KI3), Liver 3 (LR3), and Ear Shen Men. Although the overall MD Anderson Symptom Inventory (MDASI) improved non-significantly during transplantation, at 15 days and at 30 days [94], true acupuncture was more effective than sham in alleviating nausea, poor appetite, and drowsiness [94,95]. This specifically improved sleep efficiency [96] and reduced the use of analgesics during ASCT and the number of opioid users post-ASCT among opioid-naïve patients [95,97].

Acupuncture's mechanism of action for such symptom relief in MM patients has been studied as well. A Chinese RCT showed that the improvement of QoL in MM patients following heat-sensitive moxibustion was associated with decreased inflammatory markers, strengthened T-cell immunity, and a rise in the expression of some micro-RNAs (miR-125a, miR-140-5p, and miR-302′) [98]. These chemo-biological changes seem to be involved in the pathophysiology of acupuncture treating MM-associated symptoms. Finally, a murine model mice study demonstrated the synergism between acupuncture and bortezomib in improving survival in mice with MM. The pathophysiology seems to function by decreasing ornithine [99].

Last but not least, acupuncture-related safety concerns should be recognized in patients with MM and decreased immune system activity. This includes neutropenia and hypo-gammaglobulinemia exposing patients to severe infections, as well as thrombocytopenia during ASCT with its high risk of bleeding. The risk of infection following acupuncture therapy is very low. Still, we should note a recent case report on the exacerbation of pyoderma gangrenosum in a patient with MM treated with acupuncture [100]. Therefore, acupuncture should always be practiced with extreme precaution in MM and other immune-compromised patients with active infection, and for skin infection, one should avoid puncturing affected areas. As for severe thrombocytopenia, a recent retrospective chart review analyzing 815 acupuncture sessions on thrombocytopenic patients with hematological malignancies demonstrated the safety of acupuncture even with platelet counts below 20×10^9/L [101]. Table 2 shows the possible indications of acupuncture in MM.

Table 2. Proposed guidelines on the indications of acupuncture in Multiple Myeloma.

Indication	Description	Outcomes	Safety	References
CIPN	Ear and/or body points at least 1/week Electro Moxibustion	Improves sensory and motor symptoms. Improves QoL. Effect on NCV?	Avoid puncturing infected areas [37]. Safe for thrombo-cytopenia [38]	[87–93]
HSCT after conditioning regimen	1/day for 5 days in ear and body points	Alleviates nausea. Improves appetite. Improves sleep quality. Decreases pain. Reduces opioid use.		[94–97]

Legend: CIPN: chemotherapy-induced peripheral neuropathy; Electro: electroacupuncture; HSCT: hematopoietic stem cell transplantation; NCV: nerve conduction velocity; QoL: quality-of-life.

5. Mind–Body Medicine

Mind–body medicine is one of the main IO modalities encompassing a wide spectrum of interventions from traditional medicine systems like Tibetan, Ayurvedic (e.g., Yoga), and Chinese (e.g., Qi Gong) medicine to more contemporary Western approaches of relaxation, guided imagery, hypnosis, and mindfulness-based interventions (MBI). The hallmarks of

many mind–body interventions are mindfulness and intention to berating, gentle touch, movement, and spirituality. Recent IO-related clinical guidelines on pain, depression, and anxiety co-published by the Society for Integrative Oncology (SIO) and the American Society of Clinical Oncology (ASCO) recommend mind–body medicine for the following indications: hypnosis in patients who experience procedural pain; MBIs, yoga, relaxation, and music therapy for treating symptoms of anxiety during active treatment; MBIs, yoga, tai chi, and/or qigong for treating anxiety symptoms after cancer treatment; MBIs, yoga, music therapy, and relaxation for depression symptoms during oncology treatment; and MBIs, yoga, and tai chi and/or qigong post-treatment depression [102,103]. In the field of Multiple Myeloma, Lamers et al., reported that as many as 52% of patients desired psychosocial interventions near diagnosis, where relaxation techniques were the most common preferred modality reported by 21% of patients [104]. This inclination toward mind–body intervention is perceived in the context of a coping strategy, which may also correlate with the immunological response after ASCT [105]. In the U.S., LeBlanc et al., reported a pilot RCT with a group of patients diagnosed with MM or Chronic Lymphocytic Leukemia, intending to examine the impact of a Mobile App to support self-management, which also included mindfulness activities [106]. The authors reported that distress tracking and guided meditations were among the most used functions within the app. In another study recruiting patients with a variety of hematological oncology diagnoses (13.8% with MM), patients were randomized to a single session of 30 min mindful breathing versus standard care and reported significantly less fatigue in the intervention group [107]. Bates and colleagues explored the impact of music therapy considered by some scholars in the context of mind–body medicine, while others categorize it independently among the art therapies discipline. The RCT explored symptom management following ASCT in patients with lymphoma or MM and found that the patients receiving music therapy used significantly less narcotic pain medication [108]. In the United Kingdom, semi-structured qualitative interviews in a purposive sample of MM patients suggested that spirituality is one of the main themes that patients perceive as important to consider regarding their QoL [7]. In a stimulating article, Saha and Mallik challenged rehabilitation with patients undergoing MM treatment, emphasizing patients' unmet spiritual needs in India [109]. In this regard, it is of utmost importance to consider the cross-cultural context of spirituality, which may be regarded in different cultures in close proximity to religion and/or mind–body medicine. In this regard, Sherman and colleagues in the United States studied prospectively religious coping and orientation among 94 myeloma patients undergoing ASCT [110]. The results suggested that religious struggle may contribute to adverse changes in health outcomes in this clinical setting.

6. Discussion

This narrative review aimed to identify the tools that can integrate conventional MM treatment to enhance its effectiveness and tolerability, as well as the quality of life and overall survival of patients with MM.

We have identified four fundamental pillars to build this approach: nutrition, acupuncture, mind–body techniques, and the use of supplements.

Nutrition, also through the remodeling of the microbiota, is, in our opinion and based on the available scientific literature, not only a useful tool in the preventive stage or in cases of MGUS but also an essential therapeutic tool to meet patients' unmet needs.

Many mechanisms are involved in food's effects, such as the modulation of IGF1, the reduction in inflammation, and butyrate's influence on the bone marrow microenvironment. This justifies the need for nutritional counseling and further clinical studies to lay the foundations for the definition of shared nutritional guidelines.

Acupuncture and mind–body techniques, which have a good safety profile, can provide valuable help in improving tolerance and compliance with treatment.

Among supplements and vitamins, we have identified those that have been most studied in MM both for their in vitro action and for their efficacy demonstrated in clinical

studies. Most of the data we have available unfortunately come from preclinical studies that, although promising, are not yet confirmed by clinical trials. For this reason, well-designed clinical trials are absolutely necessary: they will allow us to propose guidelines that include the recommended supplements but also provide warnings for those with bad safety profiles. It is also very important to take into account the potential interactions with conventional drugs used in MM. As we have seen, some substances such as vitamin C may limit the effectiveness of drugs such as bortezomib. These are substances often used by the patients without communicating to their hematologist, thinking that they are harmless. In-depth knowledge of the mechanisms of action and possible drug interactions is therefore mandatory. These interactions could also be synergistic, opening up new horizons for integrative therapy, which could be a way of making the best use of the drugs currently at our disposal.

7. Conclusions

Integrative oncology modalities may offer significant improvement of QoL-related concerns in patients coping with Multiple Myeloma diagnosis and treatment. This is particularly relevant in the present era where effective hematology treatment is associated with increased life expectancy.

In this narrative review, we examine the data regarding acupuncture, dietary interventions, and supplements, while also considering mind–body interventions as part of the entire hematologic approach (Figure 2).

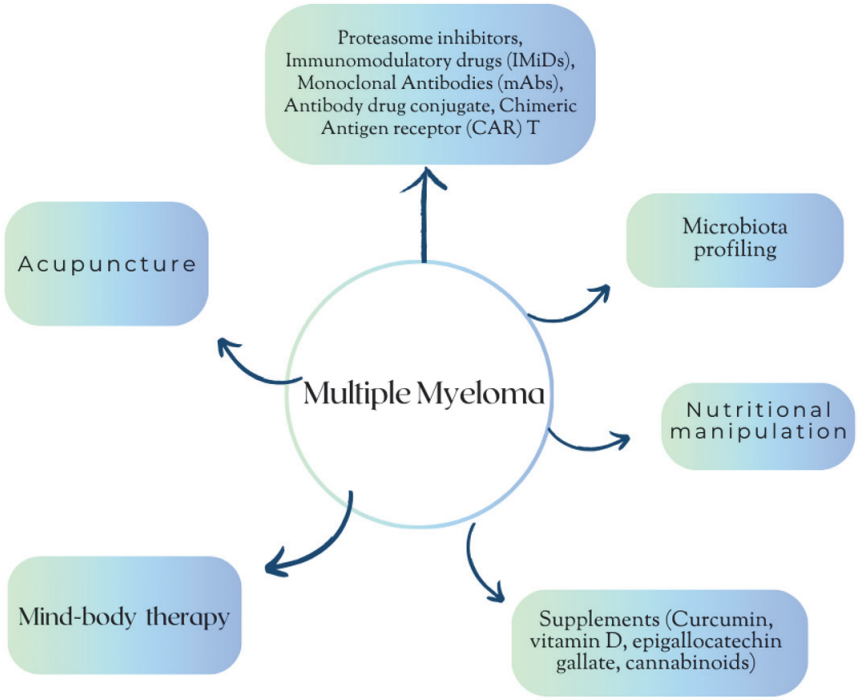

Figure 2. Multiple Myeloma: an integrative approach.

More studies, primarily randomized controlled, are needed to explore if the effect of these IH modalities is limited to enhanced supportive and palliative care or may also contribute to better therapy efficacy. Not least important is exploring IH modalities' effects regarding the safety and risk of drug interactions.

Further well-designed clinical trials will allow the construction of evidence-based guidelines.

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Abbreviations

ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplantation
BIPN	Bortezomib-induced peripheral neuropathy
CAR-T	Chimeric Antigen Receptor T cell
CB1	Cannabinoid type 1 receptors
CB2	Cannabinoid type 2 receptors
CBD	Cannabidiol
CIPN	Chemotherapy-induced peripheral neuropathy
CRP	C-reactive Protein
CSCs	Cancer stem cells
DNMT	DNA methyltransferase
EGCG	Epigallocatechin 3 gallate
EZH2	Enhancer of zeste homolog2
IH	Integrative Hematology
IGF1	Insulin-like growth factor 1
IkB	NkB inhibitor
IL6	Interleukin 6
IL17	Interleukin 17
IMiDs	Immunomodulatory imide drugs
IO	Integrative Oncology
MAMs	Macrophages associated with myeloma
MBI	Mindfulness-based interventions
MDASI	MD Anderson Symptom Inventory
MGUS	Monoclonal gammopathy of unknown significance
MM	Multiple Myeloma
MMP2	Matrix metalloproteinase-2
MMP9	Matrix metalloproteinase-9
mTOR	Mammalian target of rapamycin
NCV	Nerve conduction velocity
NfkB	Nuclear factor kappa B
PI	Proteasome inhibitor
PIs	Proteasome inhibitors
QoL	Quality of life
RANKL	Receptor activator of nuclear factor kappa-B ligand
RCT	Randomized-controlled trial
ROS	Reactive oxygen species
SIO	Society for Integrative Oncology
STAT3	Signal transducer and activator of transcription 3
THC	Delta-trans-9-tetrahydrocannabinol
TNFα	Tumor necrosis factor-α
TP53	Tumor protein p53
VEGF	Vascular endothelium growth factor
VDR	Vitamin D receptor

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Systematic Review

Omega-3 Supplementation and Nutritional Status in Patients with Pancreatic Neoplasms: A Systematic Review

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Abstract: Objectives: The purpose of this study was to synthesize and evaluate the evidence regarding the effects of omega-3 supplementation on the nutritional status of pancreatic cancer patients. Methods: A systematic review of clinical trials was conducted, adhering to the PRISMA Statement. MEDLINE/PubMed, EMBASE, CENTRAL Cochrane, Scopus, and Web of Science databases were searched up to 31 December 2022 without restrictions on the publication date or language. Independent reviewers extracted data and assessed the risk of bias. The internal validity and risk of bias in randomized controlled trials (RCT) were assessed using the revised Cochrane risk of bias tool for randomized trials-RoB2, while the risk of bias in non-randomized intervention studies was evaluated using the ROBINS-I tool. Results: Eight studies met all the inclusion criteria and were analyzed. Five of them were RCT, with the majority (n = 4) classified as low risk of bias, and the three quasi-experiments were deemed to have a moderate risk of bias. Among the studies investigating the outcome of weight gain/maintenance, six reported statistically significant positive results ($p < 0.05$). Conclusions: In conclusion, the presented evidence indicates that omega-3 supplementation in pancreatic cancer patients is safe, well-tolerated, and beneficial, as it contributes to the stabilization or increase in body weight, as well as a reduction in inflammatory biomarkers.

Keywords: omega-3 fatty acids; pancreatic neoplasms; nutritional status; systematic review

1. Introduction

Pancreatic cancer accounts for nearly 2.6% of all new cancer cases among both men and women [1,2]. Nonetheless, it is the seventh leading cause of cancer-related deaths in both sexes, representing 4.7% of all cancer deaths, which amounts to more than 466,003 deaths worldwide [1].

Among the risk factors for pancreatic cancer, notable ones include diabetes [3], high body mass index (BMI) [4], excessive alcohol consumption [5], and tobacco use [6]. Other risk factors correlating with pancreatic cancer incidence include a family history of cancer [7], pancreatitis [8], and genetic mutations, particularly in the BRCA1 and BRCA2 genes [9–12].

Patients with pancreatic cancer typically experience weight loss of over 10% of their body weight within six months [13]. As a result, the majority of these patients develop malnutrition [14], which can progress to cachexia [15]. The severity of these consequences is a significant risk factor for disease progression and overall low survival [16–18].

The weight loss associated with cancer cachexia is primarily due to a decrease in muscle mass, which may or may not be accompanied by loss of fat mass, affecting over half of oncology patients [16,18,19]. However, it cannot be fully reversed by conventional nutritional therapy, leading to progressive deterioration of the body composition [20,21].

According to the guidelines established by the European Society for Clinical Nutrition and Metabolism (ESPEN), with the publication of clinical nutrition guidelines in cancer, a

comprehensive assessment of nutritional status should be conducted soon after a patient undergoes oncological care [22]. Continuous monitoring is recommended, followed by the implementation of nutritional interventions regardless of the stage of the oncological disease [22,23].

For this assessment of nutritional status, the following methods are suggested by the European Society for Medical Oncology (ESMO): body composition, BMI, dietary intake, C-reactive protein, albumin, systemic inflammation, subjective global assessment (SGA), and patient-generated subjective global assessment (PG-SGA) [24].

In cancer, tumor cells synthesize pro-inflammatory cytokines and acute-phase proteins that modulate cancer cachexia by triggering proteolysis, leading to skeletal muscle depletion, and lipolysis, resulting in loss of adipose tissue mass [25]. Omega-3 fatty acids supplementation, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has been utilized as a preventive and therapeutic strategy for cachexia by reducing the production of inflammatory eicosanoids, cytokines such as IL-6 and IL-8, and NFκB activation [26]. This supplementation has been shown to increase food intake, promote weight gain, and improve body composition in patients [19,23,27].

Omega-3 fatty acids are polyunsaturated fatty acids (PUFAs) characterized by the presence of a double bond three atoms away from the terminal methyl group in their chemical structure [26]. They are widely found in natural oils of edible seeds and marine products and play an important role in lipid metabolism in humans. Omega-3 fatty acids are shown to suppress systemic inflammatory and oxidative responses, improve the appetite of patients, and enhance weight gain in cachectic patients with cancer [26,27].

Although systematic reviews have investigated the supplementation of omega-3 fatty acids and the improvement of nutritional status in various types of cancer, including head and neck cancer [28], gastrointestinal malignancy surgery [29], prostate cancer [30], and lung cancer undergoing radiotherapy and chemotherapy [31], there is still a lack of summarized evidence regarding the role of omega-3 in the nutritional status of pancreatic cancer patients.

It is noteworthy that because the pancreas is an organ of the gastrointestinal tract that produces digestive enzymes [32]; therefore, as a result, patients with pancreatic cancer will have a compromised nutrient metabolism, which leads to considerable weight loss with significant influence on nutritional status [33]. In addition, the treatment of these patients may place metabolic demands that will exacerbate any existing nutritional imbalances [34]. Therefore, here, we aimed to synthesize and evaluate the scientific evidence with regard to the effects of omega-3 supplementation on the nutritional status of pancreatic cancer patients.

2. Methods

2.1. Study Design

This is a systematic review of intervention studies [35] that adheres closely to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement 2020. The review was conducted to investigate the effect of omega-3 supplementation on the nutritional status of patients with pancreatic cancer. To ensure transparency in the conduct of this systematic review, and following the recommendation of the Cochrane Collaboration [35], the protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO/UK) (Registration ID: CRD42022332619), and subsequently, the study protocol was published elsewhere [36].

2.2. Search Strategy

The search was conducted in five electronic databases MEDLINE/PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane, EMBASE, Web of Science, and SCOPUS as described in detail on study protocol [36]. The searches were updated on 31 December 2022. The search strategy for identifying studies consisted of a combination of controlled descriptors (such as MeSH terms, Emtree terms), synonyms, and keywords,

as indicated in each database [37]. Boolean operators "AND", "OR", and "NOT" were used to combine the descriptors [38,39]. No language or time restrictions were applied. In addition to the aforementioned electronic databases, we searched clinical trial registries such as ClinicalTrials.gov, the WHO ICTRP, as well as conducted additional searches on organization websites and websites such as The British Library, Google Scholar, and preprints from medRxiv. Furthermore, we examined the reference lists of previously selected studies to identify additional relevant papers [40].

During the search strategy phase, the EndNoteweb was utilized to store, organize, and manage all the retrieved studies. The complete search strategy for each database and additional sources are detailed in Supplementary Material S1.

2.3. Eligibility

The selected studies followed the inclusion criteria based on the PICOS framework [41] as follows: primary studies derived from RCT and/or NRCT (quasi-experiments), assessing the effect of omega-3 supplementation in adult patients (>18 years) of both sexes and any ethnicity diagnosed with pancreatic cancer with the primary outcome being the nutritional status of the patient. Experimental studies conducted on animal models, in vivo and ex vivo studies on the topic were excluded, as well as observational studies, qualitative studies, reviews, and gray literature.

The studies were independently and blindly selected by 2 reviewers (LBCP and LCLJ). A third reviewer analyzed and made decisions regarding the inclusion or exclusion of articles with conflicting decisions [42]. During this stage of article inclusion and exclusion, the Rayyan™app (https://www.rayyan.ai/about-us/, accessed on 30 October 2024) [43] was used as a tool to assist in the eligibility phase.

2.4. Data Extraction

Initially, the screening of studies was based on their titles and abstracts and was performed independently by 2 researchers (LBCP and LCLJ), using previously published data extraction forms [37,39,44–51], as described in detail on study protocol [36].

2.5. Methodological Assessment of the Studies

The evidence level was classified using the Oxford Centre for Evidence-Based Medicine [52]. The internal validity and risk of bias of RCT were assessed using the revised RoB 2 [53]. This tool evaluates the risk of bias across five domains: (1) randomization process; (2) deviations from intended interventions; (3) missing outcome data; (4) outcome measurement; and (5) selective outcome reporting [53]. For the assessment of quasi-experimental studies, the ROBINS-I tool was used [54]. ROBINS-I comprises seven domains of bias organized chronologically in pre-intervention, during intervention, and post-intervention [54].

2.6. Data Synthesis

Due to the heterogeneity in methods, dosages, and protocols of omega-3 supplementation, we employed a descriptive vote counting approach along with a narrative synthesis to summarize the results [55,56]. For the narrative synthesis, we summarized the articles within each primary outcome category according to two main areas, namely omega-3 supplementation and nutritional status.

3. Results

3.1. Study Selection

The literature search across the five selected databases, as well as the additional searches in other sources, identified a total of 164 studies. Among these, 83 studies were identified as duplicates in the EndNote™ reference manager and were subsequently removed. A total of 81 studies proceeded to the title and abstract screening phase. In this stage, conducted using the Rayyan™app, 55 articles were excluded as they did not meet the inclusion criteria. The exclusion based on the title and abstract resulted in the pre-selection

of 26 studies, which were then subjected to thorough full-text reading. Following this step, 21 studies were excluded as they did not fully meet the inclusion criteria and therefore did not address the research question directly [Supplementary Material S2]. Additional searches were also conducted, identifying 19 articles, of which 16 were excluded for not meeting the inclusion criteria. Hence, a total of 8 studies were included for qualitative synthesis and analysis, as depicted in Figure 1.

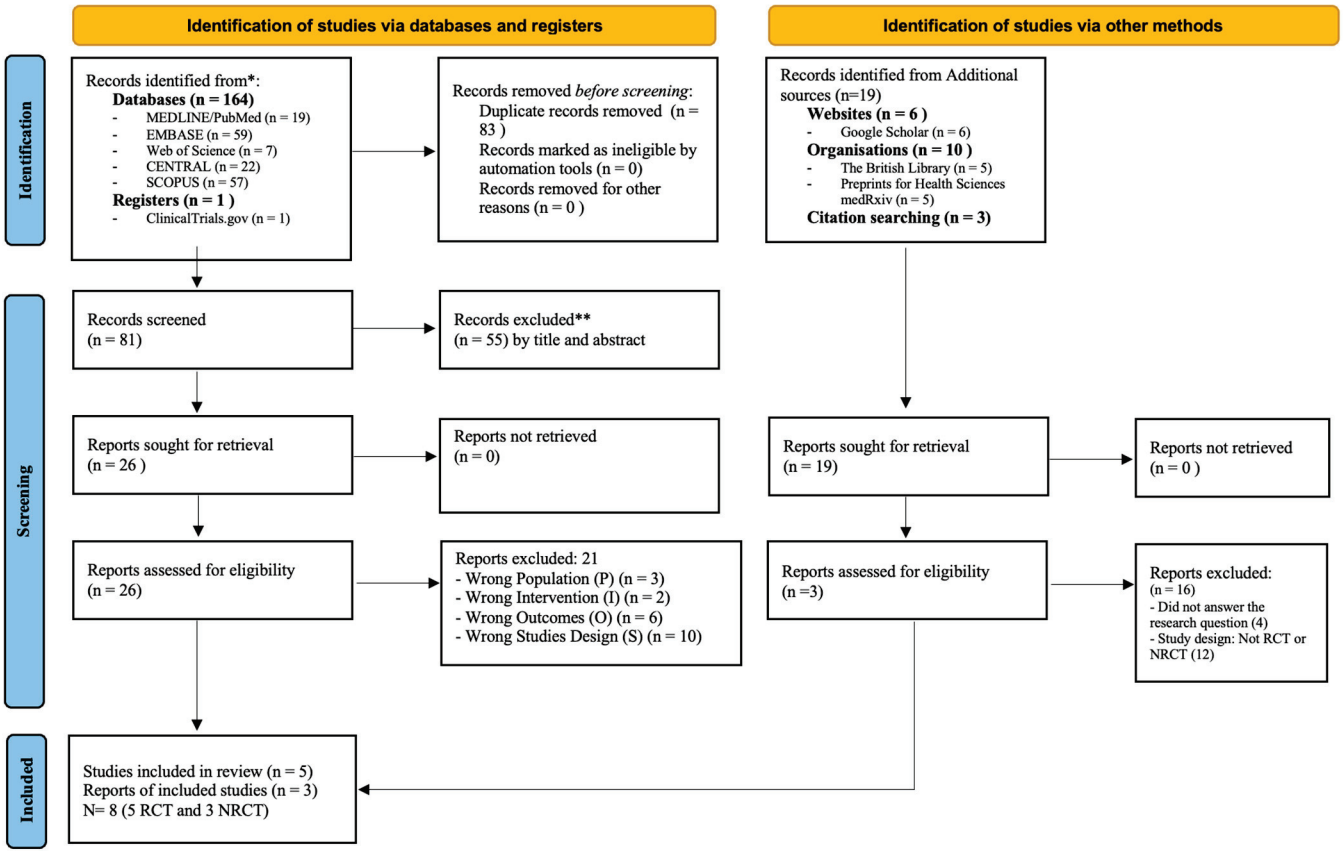

Figure 1. PRISMA Flowchart (* Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). ** If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.).

3.2. Characterization of the Studies

The eight selected articles provided data on a total of 588 patients, ranging in age from 50 to 78 years. Out of the eight studies, five were RCTs [57–61] and three were quasi-experimental studies [62–64]. The publication dates of the studies ranged from 1999 to 2019, and all were published in the English language. These studies were conducted in four different countries: Japan, Germany, Australia, and Scotland (Table 1).

Table 1. Characterization of the studies included in the systematic review.

Citation	Study Design	Aim	Sample	Type of Nutritional Supplement	Protocol	Follow-Up	Outcomes	Main Results	Conclusion
Ashida et al. [57] Japan	RCT	To investigate whether preoperative enteral diets enriched with EPA supplementation can reduce the incidence of hypercytokinemia	EG: (11), mean age = 64 (SD = 11) GC:(9), mean age = 69 (SD = 6)	Liquid	EG: supplementation (600 kcal/day) containing 2.0 g/d of EPA + 1200 kcal of regular food GC: standard isocaloric, isonitrogenous diet (600 kcal/d) without EPA + 1200 kcal of regular food	Supplementation for 7 days preoperatively	Primary: postoperative serum IL-6 concentration Secondary: postoperative nutritional status (serum albumin, prealbumin, transferrin, and EPA/AA ratio) and incidence of operative infectious complications	No statistically significant differences were identified in serious levels of IL-6 ($p = 0.68$), serum albumin ($p = 0.56$), prealbumin, transferrin ($p = 0.65$) and EPA/AA ratio after intervention	EPA supplementation had no marked impact on postoperative hypercytokinemia and nutritional status
Akita et al. [58] Japan	RCT	To clarify the usefulness of EPA-enriched supplementation during neoadjuvant chemoradiotherapy	EG: (31), mean age = 67.8 (SD = 10.7) GC: (31), mean age = 66.4 (SD = 9.8)	Liquid	EG: 2 vials (440 mL) (560 kcal) of EPA (Prosure®; Abbott Japan) per day + normal diet + 3 nutritional consultations (before, 3 weeks, and after radiotherapy). CG: Normal diet + 3 nutritional consultations (before, 3 weeks, and after radiotherapy).	During neoadjuvant chemoradiotherapy (about 5 weeks)	Primary: post/pre ratio of skeletal muscle mass and PMA cm^2 Secondary: nutritional parameters (serum prealbumin, serum albumin, BMI, and lymphocyte count	Only 45.2% of the EG patients consumed more than 50% of the supplement with EPA. No significant differences in nutritional parameters and skeletal muscle mass post-pre ratio were observed. However, patients who consumed 50% of the supplement had significantly better values than the CG. The PMA post/pre ratio was significantly higher in EG.	EPA supplementation can potentially improve the nutritional status of patients with pancreatic cancer under neoadjuvant chemoradiotherapy

Table 1. *Cont.*

Citation	Study Design	Aim	Sample	Type of Nutritional Supplement	Protocol	Follow-Up	Outcomes	Main Results	Conclusion
Werner et al. [59] Germany	RCT	To compare low-dose MPL and FO supplementation with the same amount of omega-3 in stabilizing weight.	EG FO: (18), mean age = 70.3 (SD = 8.24) EG MPL: (15), mean age = 71.3 (SD = 7.51)	Capsule	EG FO:500 mg capsule 3× daily: 60% FO, 40% MCT (6.9 g/100 g EPA and 13.6 g/100 g DHA) EG MPL: 500 mg capsule 3× daily: 35% omega-3 fatty acids phospholipids (mainly phosphatidylcholine) + 65% lipids neutral (8.5 g/100 g EPA and 12.3 g/100 g DHA); The final dose of omega-3 was 300 mg/day in both groups	During chemotherapy, radiotherapy, palliative care for 6 weeks	Primary: change in weight Secondary: nutritional status and quality of life	Weight stabilization EG FO ($p = 0.001$) and EG MPL ($p = 0.003$). Significant increase in EPA in plasma triglycerides of EG FO ($p = 0.001$) and EG MPL ($p = 0.01$)	The administration of omega-3 as FO or MPL is highly accepted, resulting in weight stabilization, and reflected in the increase in omega-3 in plasma lipids. However, MPL was better tolerated and accepted in the study group. In both groups, there were no significant changes in quality of life after 6 weeks.
Bauer et al. [60] (Australia)	RCT	To evaluate the effect of adherence to the nutritional prescription of an oral nutritional supplement with omega-3 and dense in protein and energy	EG: (87), mean age = 66.87 (SD = 1.0) GC MPL: (98), mean age = 68.37 (SD = 1.1)	Liquid	EG: 2 cans/day of a nutritional supplement rich in protein and energy + omega-3 fatty acids (1.1 g EPA). GC: isocaloric and nitrogenated control supplement without omega-3 fatty acids. Consume 1.5 cans/day (465 kcal and 24 g of protein) for both groups.	8 weeks	Primary: body composition and food intake Secondary: quality of life	There was a significant difference in energy and protein intake between patients in the EG compared to the CG ($p < 0.05$). The EG had an increase in weight of 0.5 kg compared to the CG, which decreased by 0.7 kg.	Adherence to the prescription of a protein- and energy-dense oral omega-3 supplement improved outcomes related to the nutritional status of patients with pancreatic cancer

Table 1. *Cont.*

Citation	Study Design	Aim	Sample	Type of Nutritional Supplement	Protocol	Follow-Up	Outcomes	Main Results	Conclusion
Fearon et al. [61] Multicentric (UK, Nether-lands, Canada, Italy, Belgium, and Australia)	RCT	To compare an omega-3-enriched protein and energy-dense supplement with an isocaloric, isonitrogenous supplement	EG: (95) mean age = 67 (SD = 1.0) CG: (105) mean age = 67 (SD = 1.0)	Liquid	EG:2 cans/day of omega-3-enriched protein and energy-dense supplement (480 mL, 620 kcal, 32 g protein, 2.2 g EPA) CG: 2 cans/day of the supplement (480 mL, 620 kcal, 32 g protein) without EPA	8 weeks	Primary: Weight, lean body mass, and food intake Secondary: quality of life	Compared with baseline loss rates, weight, and lean body mass loss were significantly attenuated in both study groups at four and eight weeks ($p < 0.001$ for all group comparisons).	At the average dose taken, enrichment with EPA did not provide a therapeutic advantage, and both supplements were equally effective in halting weight loss. The post hoc dose–response analysis suggests that, if taken in sufficient quantity, only the EPA-rich supplement results in weight gain and lean body mass. Weight gain was only associated with improved quality of life ($p < 0.01$) in EG.
Barber et al. [63] Glasgow, UK	NRCT	To examine the effect of a fish oil-enriched nutritional supplement on various mediators believed to play a role in cancer cachexia.	EG: (20) Median age = 62 (min/max: 51–75)	Liquid	EG: 2 cans/day supplement enriched with fish oil (2.2 g EPA and 0.96 g DHA)	3 weeks	Primary: weight Secondary: serum concentrations of interleukin IL-6, TNF-a, cortisol, insulin, and leptin	Significant drop in IL-6 production ($p = 0.015$), increase in the serum insulin concentration ($p = 0.0064$), decrease in the cortisol/insulin ratio ($p = 0.0084$), and these changes occurred in association with weight gain (median 1 kg, $p= 0.024$)	Several mediators of catabolism in cachexia were modulated by the administration of a nutritional supplement enriched with fish oil in patients with pancreatic cancer, which may explain the reversal of loss of weight in these patients

Table 1. *Cont.*

Citation	Study Design	Aim	Sample	Type of Nutritional Supplement	Protocol	Follow-Up	Outcomes	Main Results	Conclusion
Wigmore et al. [64] Scotland, UK	NRCT	To evaluate the acceptability and effects of oral supplementation with high-purity EPA in patients with advanced pancreatic cancer on weight loss	EG: (26), Median age = 56 (min/max: 39–75)	Capsule	EG: capsule containing 500 mg of EPA	EPA at 1 g/day in the 1st week, 2 g/day in the 2nd week, 4 g/day in the 3rd week, and 6 g/day after that	Weight and body composition	Supplementation was well tolerated. After supplementation, the weight remained stable. After 4 weeks of EPA supplementation, patients had a median weight gain of 0.5 kg ($p = 0.0009$ vs. baseline weight loss rate), and this weight stabilization persisted through the study period. 12-week study.	EPA is well tolerated, may stabilize weight in patients with cachectic pancreatic cancer, and should be tested as an anti-cachectic agent in RCT
Barber et al. [62] Scotland, UK	NRCT	To determine the effects of administering a nutritional supplement containing EPA-rich fish oil on acute-phase protein response levels	EG: (18) Median age = 64 (min/max: 56–66) CG: (18) Median age = 60 (min/max: 54–70) Healthy CG: (6) Median age = 54 (min/max: 50–56)	Liquid	EG: 2 cans/day supplement enriched with fish oil (2.18 g EPA and 0.92 g DHA) in a volume of 480 mL CG: full support without EPA and DHA supplementation	3 weeks	Primary: Positive and negative acute phase protein Minor: weight	Increased transferrin in EG ($p = 0.048$). In the CG, there was a reduction in albumin, transferrin, and prealbumin($p = 0.012$; $p = 0.0048$ and $p=$ 0.038, respectively) and increase in the positive concentration of CRP ($p = 00013$). The EG gained an average of 1 kg, and the CG lost an average of 2.8 kg of body weight	Acute-phase CRP can be stabilized by administering a nutritional supplement enriched with fish oil. This may have implications for reducing atrophy in these patients.

Abbreviations: RCT: randomized controlled trial; NRCT: nonrandomized controlled trial; EG: experimental group; CG: control group; SD: standard deviation; IL-6: interleukin-6; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; AA: arachidonic acid; BMI: body mass index; PMA: cm^2 area of the greater bilateral psoas muscle; MPL: marine phospholipids; FO: fish oil; MCT: medium-chain triglycerides; CRP: C-reactive protein; TNF-a: tumor necrosis factor-alpha.

3.3. Omega-3 Supplementation and Nutritional Status

With regard to the nutritional status of patients with pancreatic cancer supplemented with omega-3, the most commonly used outcomes for assessing the nutritional status shown in this systematic review includes: weight, body composition, serum albumin, prealbumin, transferrin, ratio EPA/AA, skeletal muscle mass, fat percentage, interleukin-6, BMI, psoas major muscle area (PMA), lymphocytes, total cholesterol, triglycerides, c-reactive protein, HbA1c (%), cortisol, insulin, skinfold arm, back, and iliac crest.

As for the form of omega-3 supplementation evaluated, out of the eight included studies, two [59,64] used capsules, while the other six [57,58,60–63] involved the consumption of liquid nutritional supplements. The amount of EPA varied between 300 mg [59] and 6 g [64] per day during the nutritional intervention.

It is worth noting that the study by Akita et al. [58] was the only one that, in addition to EPA supplementation, included three nutritional consultations. The study also reported that many patients (54.83%) were unable to consume the recommended amount of the EPA-enriched supplement due to its taste [58]. On the other hand, in the study by Ashida et al. [57], the supplement used contained 2 g of EPA and was the only one among the eight studies that, in addition to the supplement, provided 1200 kcal of regular food intake for seven days before the operation.

A prospective study with 200 patients undergoing treatment for gastrointestinal and hepatobiliary cancer, which investigated the underdiagnosis of malnutrition, endorses the need for referral to an oncology nutritionist—a pivotal health professional in the treatment of malnutrition and in choosing the nutritional intervention for the patient—after assessing the nutritional risk using screening tools [65].

3.4. Quality Assessment Findings

Regarding the level of evidence based on the Oxford Centre for Evidence-Based Medicine, it is observed that more than half of the article sample was classified as high-level evidence based solely on the study design, as the majority of the studies were RCTs (n = 5; 62.5%) [57–61] classified as evidence level 1B. These studies were followed by quasi-experimental designs (n = 3; 37.5%) [62–64], classified at level 2B. We have identified six studies with 1B and two studies with 2B level of reference according to Oxford Centre for Evidence-based Medicine levels of evidence.

The assessment of the risk of bias was presented according to the study design and is represented in Figure 2. The majority of RCTs (n = 4; 80%) [57,59–61] were classified as low overall risk of bias, meaning that all domains were classified as "low risk of bias". Only one RCT fell into the high overall risk of bias category [58] due to having "some concerns" in three domains (D1, D2, and D4). Figure 2A,B shows the assessment of bias risk for RCTs. It should be noted that bias due to missing outcome data or selective outcome reporting was not found in any of the RCTs (n = 5; 100%), so for both domains (D3 and D5), all RCTs were classified as low risk of bias according to RoB-2.

The analysis of risk of bias in nonrandomized intervention studies using the ROBINS-I tool (Table 2) indicated that all studies (n = 3; 100%) [62–64] presented a moderate risk of bias. The studies were classified as such mainly due to bias in participant selection as well as outcome measurement bias. In all quasi-experimental studies, the domains "bias in the classification of interventions", "bias due to deviations from intended interventions", and "bias in the selective reporting of outcomes" were well-reported and classified as low risk of bias.



Figure 2. Summary of risk of bias judgements of RCT included according to RoB 2. (**A**) Internal validity and risk of bias assessment based on the RoB 2 [57–61]. (**B**) Percentage of risk of bias among RCT by domains of the RoB 2. (+) = low risk of bias; (-) = some concerns; (×) = high risk of bias. * Domains: D1: Bias due to randomization; D2: bias due to deviation from intended interventions; D3: bias due to missing data; D4: bias due to outcome measurement; D5: bias due to selections of reported results.

Table 2. Evaluation by consensus of ROBINS-I between two reviewers per bias domain.

	* Domains ROBINS-I							Overall Judgment ROBINS-I
Study	**Confounding Bias**	**Participant Selection Bias**	**Classification of Intervention Bias**	**Bias Due to Intervention Deviations**	**Incomplete Data Bias**	**Outcome Measurement Bias**	**Selective Outcome Reporting Bias**	
Barber et al. [63]	Low	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Wigmore et al. [64]	Low	Moderate	Low	Low	Low	Moderate	Low	Moderate
Barber et al. [62]	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate

Acronyms: * ROBINS-I, risk of bias in non-randomized studies [54].

4. Discussion

4.1. Omega-3 Supplementation

A growing body of studies has addressed the protective impact of omega-3 polyunsaturated fatty acids on patients with cancer, positively modulating the nutritional status in different types of malignant neoplasms, such as gastrointestinal [29], head and neck [28], and lung cancers [31]. The beneficial effects of omega-3 polyunsaturated fatty acid consumption are likely related to several mechanisms of action, including the following: (1) production of lipid mediators with pro-resolution properties such as resolvins and protectins, which are important modulators of inflammation [66]; (2) activation of free fatty acid receptors, specifically Free Fatty Acid Receptor 1 (FFA1) and Free Fatty Acid Receptor 4 (FFA4), leading to a decrease in cachexia-related outcomes [67]; (3) inhibition of nuclear factor kappa B (NF-κB) and reduction in the production of cytokines such as IL-6 and IL-8 [26].

These findings are consistent with the recent publication of the clinical nutrition guidelines for cancer by the European Society for Clinical Nutrition (ESPEN) in 2021, which recommend the use of long-chain omega-3 polyunsaturated fatty acid supplements (EPA and DHA) or fish oil in patients with advanced cancer undergoing chemotherapy and at risk of weight loss or malnutrition [22]. The proposed recommendations by some authors range from 2 to 4 g per day of omega-3 fatty acids (in a 2:1 ratio of EPA and DHA) [19,68], with a suggestion of 2 g/day of EPA for individuals with advanced cancer receiving chemotherapy and at risk of weight loss [23].

We conducted this systematic review based on eight clinical trials, including five RCTs and three quasi-experiments. Upon evaluating the clinical trials included in this review, we observed different forms of omega-3 supplementation administration, regarding the dosage, form, as well as timing of the administered omega-3 interventions. The offered doses of omega-3 varied from 0.3 g to 6 g per day of EPA, with three studies also supplementing DHA at doses ranging from 0.92 g to 0.96 g per day. In terms of the form of omega-3 intervention, two studies used capsules, while six studies provided a liquid supplement. The duration of supplementation ranged from 1 to 12 weeks in patients with resectable or unresectable pancreatic cancer. Despite the heterogeneity observed, none of the studies reported a worsening outcome for the patient groups receiving the supplement.

A recent systematic review of randomized clinical trials [31] investigating the efficacy of omega-3 in patients with lung cancer undergoing radiotherapy and chemotherapy also reported heterogeneity in the results. This review identified seven articles in which the variation in omega-3 dosage ranged from 0.51 g to 2.2 g per day of EPA. Among these studies, four also supplemented with DHA at doses ranging from 0.2 g to 0.92 g per day. The duration of supplementation varied from 5 to 12 weeks and concluded that omega-3 can improve the nutritional status as well as regulating inflammation indicators in these patients.

Regarding nutritional supplementation, Werner et al. [59] utilized omega-3 capsules containing 300 mg of DHA and EPA, derived from marine phospholipids (MPL) or fish oil (FO), for a duration of 6 weeks in patients undergoing treatment for pancreatic cancer. On the other hand, Wigmore et al. [64] employed capsules containing 500 mg of EPA (95% pure). The administration period started at 1 g/day in the first week, with a weekly increment of 1 g of EPA until reaching a total of 6 g/day for 12 weeks. The patients in this study were also undergoing treatment for their condition. Both studies reported on adherence to the nutritional supplementation via capsules. The group that took MPL capsules demonstrated higher adherence compared to the FO group. However, patients who supplemented with 95% pure EPA reported that the capsules were unpleasant to consume due to occasional leakage of their contents, resulting in an unpleasant chemical taste.

Administering a high dose of EPA to cancer patients in the form of capsules does not appear to be highly effective [69]. These findings were demonstrated by Fearon et al. [69] in a study that aimed to examine the effects of two doses of 95% pure EPA (2 g per day and

4 g per day) compared to placebo over a period of 8 weeks in the process of cachexia, in a double-blind randomized clinical trial involving 518 patients with gastrointestinal and lung cancer. The trial provides an explanation for the apparent lack of efficacy of 4 g of EPA/day, attributing it to the possible unobserved adverse effects, resulting in patients taking fewer capsules compared to those on the 2 g dose [69]. It should be highlighted that the identification of effective nutritional counseling strategies helps the nutritionist choose the most effective option for dietary treatment [70].

The most commonly used oral liquid nutritional supplementation was a dietary supplement enriched with protein, energy, and omega-3 fatty acids [60–63]. The interventions aimed to provide approximately 610–698 kcal, 32–36 g of protein, and 1.6–2.2 g of EPA per day, with durations ranging from 3 to 8 weeks. In addition to EPA, the two studies by Barber et al. [62,63] also included an approximate addition of 0.96 g of DHA. Patients tolerated the supplement well in the studies conducted by Fearon et al. [61] and Barber et al. [63].

Another systematic review by De Van Der Schueren et al. [71] identified 11 RCTs, including five trials conducted with oral nutritional supplements high in protein, high in energy, and enriched with omega-3 fatty acids for cancer patients undergoing antineoplastic treatment. This study yielded similar results to ours, both in terms of the intervention and adherence. The interventions aimed to provide approximately 590–600 kcal, 32–33 g of protein, and 2–2.2 g of EPA per day, with durations ranging from 5 to 12 weeks. Good adherence was reported in 3 RCTs, with two trials reporting adherence rates between 70% and 80%, and one trial reporting that 80% of participants consumed the prescribed dose [71].

4.2. Nutritional Status

Cancer patients often experience a reduction in their usual food intake due to anorexia, which can occur either as a primary symptom or as a result of secondary causes [23]. Additionally, approximately 71% of patients with pancreatic cancer have cachexia at the time of diagnosis [72]. Cachexia is recognized as a multifactorial syndrome defined by pathological weight loss caused by ongoing loss of lean muscle mass, with or without loss of adipose tissue, as a result of reduced food intake, anorexia, abnormal metabolism, or a combination of them [20].

The decreased and/or insufficient intake of the necessary nutrients to meet metabolic and physiological demands can lead patients to a pathological state of malnutrition, characterized by the intense catabolism of muscle and adipose tissues and continuous involuntary weight loss [73–78].

Additionally, the side effects of treatments such as chemotherapy, radiation therapy, hormone therapy, and immunotherapy also contribute to malnutrition [27]. The identification of malnutrition or the risk of malnutrition is indicative for assessing the nutritional status of the patient, allowing for the detection of possible nutritional disorders and enabling early intervention [24].

Among the studies that investigated the outcome of weight gain/maintenance, six demonstrated positive results [59–64]. Of these, four studies used a dietary supplement with protein, energy, and enriched with omega-3 fatty acids, which may partially explain the weight gain [60–63]. In the RCT by Barber et al. [62], which included 0.92 g of DHA in addition to EPA, a significant difference in the pattern of weight loss was found between the two groups ($p = 0.0001$), with the exposure group gaining an average of 1 kg while the control group lost an average of 2.8 kg. The study by Barber et al. [63], which also used an EPA supplement with 0.96 g of DHA, showed a mean weight gain of 1.0 kg (interquartile range 0.1 to +2.0, $p = 0.024$) compared to baseline and significant drop in IL-6 production. Clinical evidence demonstrating the isolated effects of DHA on the nutritional status of cancer patients is still scarce [68].

It is important to highlight that, among the four studies that gave positive results for weight gain, only Barber et al. [63] investigated IL-6 and, after the intervention, partici-

pants had a significant drop in the concentration of this substance in their blood. These positive findings may reflect the ability of omega-3 to modulate circulating inflammatory biomarkers such as IL-1, IL-6 and TNF-α, emphasizing its inhibitory effect on inflammatory parameters related to muscle atrophy and lipolysis [79]. Additionally, omega-3 is associated with the production of pro-resolving mediators such as resolvins and protectins, which decrease leukocyte infiltration, leading to the cessation of the inflammatory process [80]. This generates a positive balance between muscle anabolism and catabolism, thereby favoring weight gain/maintenance [68].

Findings from the systematic review of RCTs whose patients received omega-3 in the adjuvant treatment for lung cancer, have pointed out similar results by demonstrating that six out of seven studies reported changes in body weight, and the heterogeneity test showed I^2 = 87.3%, $p < 0.001$ [31]. The assessment of the nutritional status in patients with pancreatic cancer can be performed using various, but low-cost and easy methods including body weight and lean body mass [24]. Low muscle mass has been associated with an increased incidence of toxicity, reduced effectiveness of chemotherapy in patients [24], worsened Karnofsky Performance Score [69], and negative impact on the quality of life of cancer patients [24]. However, the present systematic review identified only one study that reported a significant difference in patients who consumed 50% of the EPA-enriched supplement, showing significantly higher proportions of skeletal muscle mass compared to patients in the control group ($p = 0.042$) [58].

The transferrin investigation was conducted by both Barber et al. [62] and Ashida et al. [57]; however, only Barber et al. [62] showed positive results. The researchers concluded that acute phase proteins tend to progress in untreated patients but can be stabilized through the intake of a supplement enriched with fish oil, which will result in a reduction in atrophy in these patients [62]. The two studies that utilized capsules to supplement omega-3 showed similar results, with a significant stabilization of weight [59,64]. However, one study examined weight loss after 6 weeks of treatment in both groups compared to weight loss at baseline (GI: $p = 0.001$, GC: $p = 0.003$) [59]. The other study was a quasi-experiment lasting up to 12 weeks, and patients experienced a median weight gain of 0.5 kg compared to the rate of weight loss at the beginning of the study ($p = 0.0009$) [64].

These weight gain findings support the results of a randomized, triple-blind clinical trial that investigated the supplementation of omega-3 through capsules. The trial involved 40 women diagnosed with cervical cancer and showed a preservation of patients' nutritional status and skeletal muscle quality. These results suggest that omega-3 supplementation can normalize some metabolic changes associated with cancer, which normally prevent patients from maintaining their body weight during treatment. [80,81] When evaluating the outcomes, only the study by Ashida et al. [57] did not show an improvement in the nutritional status after 7 days of omega-3 intake, as it did not demonstrate a significant difference in postoperative hypercytokinemia rates ($p = 0.68$) between the groups. Furthermore, it was the sole study with a 7-day preoperative intervention period. Despite not observing a significant impact from the supplementation, Ashida et al. [57] reported mean IL-6 values of 174.0 pg/mL and 148.2 pg/mL in the treatment and control groups, respectively, on the first postoperative day. Previous studies have shown that these values varied from 162 to 431 pg/mL [82,83].

4.3. Study Strengths and Limitations

This study has notable strengths. Firstly, it employed a systematic approach with high adherence to the PRISMA 2020 checklist, ensuring methodological rigor. The study demonstrated high transparency, particularly in the advanced search strategy. Additionally, the study protocol was previously published in a leading peer-reviewed journal, further enhancing its methodological robustness. Risk of bias assessment was conducted using current and revised tools from the Cochrane Collaboration [35]. However, due to study heterogeneity, it was not possible to conduct a meta-analysis of the data. The moderate quality of quasi-experimental studies is also a limiting factor, although 80% of the included

RCTs exhibited low risk of bias and were well-reported. In addition, it is important to point out that, among the included studies, four used dietary supplements containing protein, energy, and enriched with omega-3 fatty acids; therefore, the data reported here require some caution. However, it is also important to highlight that all study participants received omega-3 supplementation, which is in accordance with the PICOS strategy of this systematic review. Nevertheless, this review provides valuable new insights to the literature by summarizing the available evidence specifically on this supplement for patients with pancreatic neoplasms.

5. Conclusions

In conclusion, the presented evidence indicates that omega-3 supplementation in patients with pancreatic cancer is safe, well-tolerated, and beneficial. It has been shown to stabilize or increase body weight, as well as reduce levels of inflammatory biomarkers. However, well-designed RCTs with low risk of bias are still needed to confirm these findings and establish an effective dosage of this supplementation for patients with pancreatic cancer. Furthermore, additional research is warranted to investigate the impact on lean mass gain and biomarkers of oxidative stress.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu16234036/s1.

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Systematic Review

A Systematic Review of Vitamin D Supplementation in Oncology: Chance of Science or Effectiveness?

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Abstract: Background: Vitamin D (VD) supplementation has increased considerably in the last decade, whether for the prevention or treatment of numerous diseases, including bone, cardiovascular, endocrine, neurologic, psychological, respiratory, infectious, or oncological. The primary objective of this scoping review was to examine and synthesize the scientific evidence on the role of VD in all-type cancer patients undergoing adjuvant and neoadjuvant therapy with chemotherapy (CT) or radiotherapy (RT), namely in improving side effects. Methods: This review was conducted by selecting papers from the CINAHL, Scopus and PubMed databases based on the descriptor terms mesh and title/abstract, taking into consideration the defined inclusion and exclusion criteria, following the PRISMA-ScR (PRISMA extension for scoping reviews) statement. Results: A total of 758 papers were identified in different databases during this review. However, using the inclusion and exclusion criteria, only five publications made up the final sample of the study. The studies included heterogeneous study methodologies, objectives, cancer diagnosis, as well as methods to assess body composition, which makes it difficult to compare them. Based on the analyzed studies, associations were found between bone density and VD in patients who underwent preoperative chemoradiotherapy (CRT). In patients with non-small-cell lung cancer receiving CT, some of the side effects associated with the treatment were attenuated and reduced. In addition, another of the studies analyzed found that VD deficiency (VDD) has been associated with increased peripheral neuropathy (PN) induced by CT in the treatment of breast cancer. VD supplementation was found to be safe and

effective. Conclusions: In this scoping review, VD is highlighted as a crucial factor in preventing the side effects of neoadjuvant RT or CT, as well as treating other treatment-related health conditions, such as osteoporosis, as well as ameliorating the side effects (nausea, vomiting, fatigue) associated with aggressive CT and RT.

Keywords: adverse effects; cancer; neoadjuvant therapy; neoplasm; vitamin D

1. Introduction

Vitamin D (VD) is a fat-soluble vitamin that acts as a precursor to 1,25-dihydroxyvitamin D in the body [1–10]. Its main functions include modulating calcium [9,11–13] and phosphorus homeostasis and osteosynthesis [11–13], bone structure [12,14–16], and physiological functions, as well as supporting nerve, immune, and muscle health [10,17,18]. The minimum level of 25-hydroxyvitamin D (25(OH)D) in serum is 30 ng/mL (75 nmol/L) [3,7,8,10]. Below this value, patients suffer from mild (29–20 ng/mL), moderate (19–10 ng/mL), or severe VD deficiency (VDD) [4,10]. Thus, the guidelines recommend daily supplementation with 1200 mg of calcium and 400 IU of VD [4,7]. However, this dose of VD is not sufficient to normalize the 25-dihydroxyvitamin D level in most patients undergoing adjuvant chemotherapy (CT) [7,8]. Over the past decade, VD supplements have been used to prevent or treat bone, cardiovascular, endocrine, neurological, psychiatric, respiratory, and infectious diseases or cancer [1,2].

Several studies have suggested that VDD increases the risk of infections, diabetes mellitus types 1 and 2, cardiovascular diseases, obesity, asthma, inflammatory bowel disease, colon, breast, prostate, and ovarian cancer, as well as some neurological conditions [1,6,19]. Apoptosis, invasion, stimulation of cell differentiation, inhibition of angiogenesis, anti-inflammatory and anti-proliferative effects, and metastasis are some ways VD influences the natural history of cancer [4,10,11]. Researchers have found that VDD is common among cancer patients [7,19]. In these patients, the prevalence of VDD varies from 14% to 92% [19]. CT and radiotherapy (RT) treatment may result in VDD as well as changes to bone metabolism, leading to osteoporosis and other skeletal problems, such as osteomalacia, increased fracture risk, decreased bone mineral density, avascular necrosis, and skeletal deformities [19–22]. Neoadjuvant therapy is the preoperative induction treatment of tumors with CT, RT, and endocrine therapy [22,23]. The correction of VDD is important [24] since low VD levels are associated with cancer prognosis in patients receiving adjuvant CT or neo-adjuvant RT [7,24]. It has been shown that VDD is strongly associated with cancer risk. Thus, VD supplementation may be crucial to cancer patients' lives. By preventing VDD, alleviating cancer-related adverse symptoms, such as fatigue, vomiting, and nausea, and improving cancer incidence, prognosis, and outcomes, VD supplementation can help prevent VDD from occurring [7,24].

Most VD supplements and fortified foods do not pose a risk of toxicity unless taken in very large doses. Physiological mechanisms limit the formation and metabolism of the vitamin [11,14,25–27]. Its original purpose was to reduce tumors and allow a mastectomy in place of a breast-conserving procedure. Cancer treatment is increasingly relying on it [22,23]. Originally defined as systemic therapy given before local treatment, the concept has been extended to include radiotherapy given before surgery [28]. Advantages may include better local and remote control, direct assessment, and organ preservation treatment [22]. On the other hand, potential disadvantages are the increased toxicity and cost, potential delay in effective treatment, and obscuring pathological staging [28–30].

By interfering with healthy cells in the body, CT can lead to the appearance of unwanted symptoms [22,29,31]. Adverse effects of CT can last a few days to a few weeks [28,32] and include hormonal and mood changes, anemia, absence or decrease in appetite, gastrointestinal adverse effects (gastrointestinal toxicity, vomiting, nausea, constipation, dysphagia, aversion to the smell or taste of food, anorexia), fatigue, mouth sores and opportunistic infections, neurotoxicity, and hematological toxicity [8,28,30,33]. Long-term CT can also cause changes in the heart, liver, lungs, and nervous system. It is pertinent to note that patients will experience different effects depending on the drug used. A treatment cycle's effects are not necessarily repeated in subsequent cycles [24,31]. A new strategy in neoadjuvant therapy, like other innovations in cancer treatment, must be evaluated closely against standard therapy for recurrence, survival, and impact on organ economy, as well as for quality of life and costs [24]. An adjuvant approach is usually recommended when a patient with early-stage cancer undergoes surgery or radiotherapy if this is considered to improve the prognosis and decrease the risk of recurrence. It is often determined based on the type and stage of the cancer whether the patient is a candidate for further treatment [24].

This study aimed to conduct a scoping review, which is a type of evidence synthesis that systematically identifies and maps the breadth of evidence available on a particular topic within or across particular contexts [34]. A scoping review can clarify key concepts in the literature and identify key related aspects, including those related to methodological research [34]. As with systematic reviews, this scoping review, of an exploratory nature, followed the PRISMA extension for scoping reviews [35,36] aiming to examine and synthesize the scientific evidence on the role of VD in cancer patients with any type of cancer undergoing adjuvant and neoadjuvant therapy with CT or RT, namely in improving side effects.

Thus, the guiding question for this paper was, "What is the role of Vitamin D in the side effects of adjuvant and neoadjuvant radiotherapy and chemotherapy in cancer patients?".

2. Materials and Methods

2.1. Search Strategy

The search was conducted through MEDLINE (via PubMed, National Library of Medicine, Bethesda, Maryland), CINAHL (via EBSCO, Ipswich, MA, USA), and Scopus (via Elsevier, Amsterdam, The Netherlands) databases, according to the descriptor terms mesh and title/summary described in the databases until 20 August 2022 (Appendix A).

As a starting point for this scoping review, the guiding question was formulated following the steps of the methodology defined by The Joanna Briggs Institute Reviewers' Manual 2015 formulation of the research question, according to the PCC model, which includes Population (P), Concept (C), and Context (C). In this review, the population focused on adult cancer patients, the concept addressed the adverse effects of vitamin D supplementation, and the context examined its effects on adjuvant and neoadjuvant radiotherapy and chemotherapy. The literature search was oriented to answer the following advanced question: what is the role of Vitamin D in the side effects of adjuvant and neoadjuvant RT and CT in cancer patients [35]?

The search in databases was conducted using Boolean operators (OR and AND), parentheses, quotation marks, and asterisks. Quotation marks were used to search for exact terms or expressions; parentheses were used to indicate a group of search terms or combine two or more groups of search terms, enabling all possible combinations of sentences; asterisks (*) were used to search all words derived from the precedent inflected part. Any filters to refine the search were not added. The searches were conducted in the

online database, and the results were exported to a Microsoft Office Excel® 2016 document (Microsoft Corporation, Redmond, WA, USA).

2.2. Selection Criteria

Titles and abstracts of all potentially relevant papers, and subsequently, full text, were reviewed to choose those that were eligible. Two investigators conducted both steps independently, and discordant results were resolved through consensus. The eligibility and exclusion criteria were defined to direct the search to answer the established question.

As inclusion criteria, we included studies published in the last five years that included adults (≥18 years old) with a cancer diagnosis submitted to adjuvant and neoadjuvant RT or CT and that mentioned one of the side effects, such as hormonal and mood changes, anemia, absence or decrease in appetite, gastrointestinal adverse effects (gastrointestinal toxicity, vomiting, nausea, constipation, dysphagia, aversion to the smell or taste of food, anorexia), fatigue, mouth sores and opportunistic infections, neurotoxicity, and hematological toxicity.

Focusing on recent studies ensures that the data reflect the most up-to-date state of scientific knowledge. Including studies from longer periods could excessively broaden the scope of the review, making the analysis and synthesis of results more challenging. Restricting the inclusion to the last five years allows for a more targeted and manageable focus, which is particularly important in a systematic review.

This approach is especially relevant given the probable increase in interest in vitamin D supplementation during this period, likely driven by the COVID-19 pandemic. The pandemic highlighted the role of vitamin D in immune modulation and disease outcomes, leading to a surge in research into its applications, including oncology.

As exclusion criteria, we excluded articles with patients with hematologic tumors because they have significantly different biological and pathophysiological characteristics than solid tumors. This can result in very different responses to VD supplementation, introducing high variability in the results and making comparative analysis between studies difficult. In addition, we also excluded studies that did not focus on the relationship between VD (interventions in which VD is not used alone) and the treatment of patients with cancer because interventions that combine VD with other therapeutic factors make it difficult to determine the isolated impact of VD on clinical outcomes. This confounding of variables can compromise the validity of conclusions about the specific role of vitamin D.

The duplicates were excluded, and titles and abstracts of all potentially relevant papers, and subsequently, full text, were reviewed to choose those that were eligible.

These criteria help to ensure greater homogeneity, robustness, and relevance of the results for the target population studied.

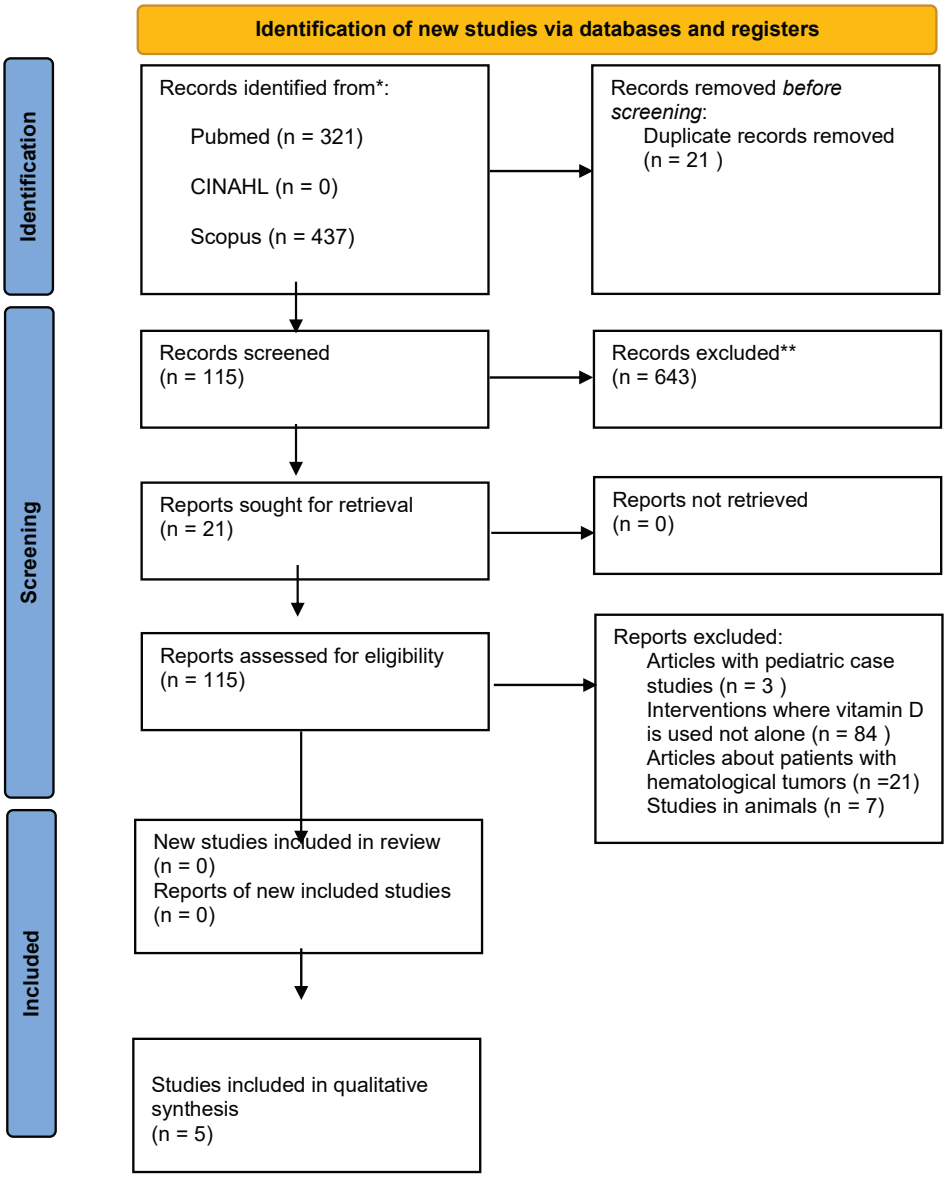
The scoping review followed the normative steps of the same enunciated in the PRISMA-ScR statement (Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for scoping reviews) [36].

2.3. Data Extraction

The data extraction of each study was based on the following information: the age of the population, the years examined, inclusion and exclusion criteria, cancer treatments, and VD supplementation.

3. Results

The flow diagram of included studies is represented in Figure 1. In the search of the MEDLINE, CINAHL, and Scopus databases, 758 records were identified. However, no papers were found in the CINAHL database after applying the search terms. After applying the inclusion and exclusion criteria, 643 papers were excluded. Thus, 115 papers were considered for eligibility, and 94 of these papers were excluded. The reading of the papers' titles and abstracts allowed for the selection of 21 publications of potential interest, which were fully analyzed. After this review, the final sample consisted of five studies (Appendix B).



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Figure 1. PRISMA-ScR 2020 study selection flow diagram.

Yamada et al. observed that after dividing patients into two groups based on changes in bone density, the group with low bone density exhibited a shorter metastasis-free survival time (DMFS) after surgery compared with the other group ($p < 0.05$) [37]. Univariate analysis identified decreased VD concentration (<20 pg/mL) as a risk factor for changes in bone density ($p = 0.04$) [37]. Furthermore, multivariate analysis revealed that preoperative CRT was the only factor significantly associated with altered bone density (±, OR: 5.8; $p = 0.04$) [37]. These findings highlight a potential link between VD levels and bone health in oncological patients, warranting further investigation.

Similarly, Laviano et al. examined the adverse event profiles of two groups, one receiving juice-based TMN (target medical nutrition) and the other an isocaloric comparator. The TMN group (mean age 65 years) experienced fewer adverse events, including diarrhea, nausea, vomiting, and neutropenia, compared with the comparison group (64 vs. 87 events, respectively) [38]. Although compliance was slightly lower in the TMN group (58.5%) compared with the comparator group (73.6%), safety parameters such as blood pressure and heart rate favored the TMN intervention. These findings suggest that TMN, which included VD, may have protective effects on vital signs and overall tolerance of treatment [38].

In a broader analysis, Alkan et al. investigated VDD prevalence in a cohort of 706 cancer patients, revealing that 72% (509 patients) were vitamin D deficient. Multivariate analysis identified several factors associated with VDD, including low sun exposure (OR: 1.4 [95% CI: 1.009–2.1], $p = 0.045$), palliative care status (OR: 1.5 [95% CI: 1.008–2.4], $p = 0.04$), and history of gastrointestinal surgery [6]. Notably, adjuvant treatment initially appeared as a risk factor (OR: 2.6 [95% CI: 1.3–5.1], $p = 0.006$); however, the small p-value indicated that the result might not be robust, leading to its rejection in this study. These data underscore the multifactorial nature of VDD in cancer patients and the need for targeted interventions.

Further emphasizing the implications of VD levels, Jennaro et al. reported that VD-deficient patients exhibited a higher mean increase in peripheral neuropathy (PN) than non-deficient patients, along with a non-significant trend toward increased risk of treatment discontinuation [19]. Multivariate models revealed an inverse association between baseline VD levels and PN, highlighting the potential protective role of adequate VD levels in mitigating this common treatment-related side effect.

Conversely, Chartron et al. focused on the effectiveness and safety of VD supplementation in breast cancer (BC) patients undergoing adjuvant CT. In the D1C6 phase of their study, 21 patients achieved normalization of VD levels, with high-dose VD supplementation increasing the normalization rate of serum 25-OH VD to 47%. VD and calcium supplementation were well tolerated, with no clinical toxicity events related to treatment. However, 29.5% of patients developed asymptomatic grade 1 hypercalciuria without renal function changes or clinical symptoms, prompting discontinuation of VD supplementation in 10 out of 13 patients receiving adjuvant CT [7]. These findings suggest that while VD supplementation can be beneficial, monitoring for potential side effects such as hypercalciuria is essential.

Together, these studies illustrate the multifaceted role of VD in cancer treatment, ranging from its influence on bone density and side effect mitigation to its safety and tolerability in various oncological contexts. Transitioning between these diverse findings highlights the complexity of VD's impact and the need for further research to optimize its use in oncology.

4. Discussion

To the best of our knowledge, this is the first scoping review aimed at evaluating the role of vitamin D (VD) supplementation in the side effects of adjuvant and neoadjuvant treatment of RT and CT in oncological patients.

While the studies included in this review present heterogeneity in methodologies, cancer diagnoses, and methods of assessing outcomes, they collectively underscore the potential role of VD in improving treatment tolerability and outcomes. This diversity highlights the need for standardized protocols to evaluate the effects of VD supplementation in cancer treatment, which could facilitate more robust comparisons in future research. In this paper, a review of the existing evidence is presented.

Yamada et al. concluded that patients undergoing preoperative CRT are at risk for impaired bone density, with VD supplementation potentially mitigating this risk and decreasing the incidence of distant metastases [37].

Similarly, Laviano et al. demonstrated that VD-containing TMN provided a favorable safety profile for non-small-cell lung cancer patients receiving CT, reducing adverse events like diarrhea, neutropenia, and nausea compared with isocaloric controls [38]. These findings align with the emerging understanding of VD as an adjuvant that may alleviate common side effects associated with cancer treatments.

Alkan et al.'s study concluded that the prevalence of VDD is high in cancer patients due to low exposure to sunlight, being in palliative or adjuvant settings, and a history of gastrointestinal surgery. These factors were classified as risk factors for VDD [6]. This underscores the multifactorial etiology of VDD in oncology, necessitating a tailored approach to prevention and management.

Jennaro et al. further established a connection between VDD and chemotherapy-induced peripheral neuropathy (PN) in breast cancer patients, suggesting that addressing VDD before treatment may reduce PN and improve therapeutic outcomes [19].

Chartron et al., in turn, concluded that VDD is very frequent in breast cancer patients and that this condition influences prognosis since taxanes, corticosteroids, behavioral changes (such as lack of sunlight exposure and poor dietary intake), and treatment-associated gastrointestinal side effects play a role in this initial decrease in VD levels [7].

They also concluded that VD supplementation increased the percentage of normalization of serum 25-OH VD concentration in breast cancer patients undergoing adjuvant CT and that this supplementation appears safe and effective [7].

A narrative review on patients undergoing hematopoietic stem cell transplantation (HSCT) further broadens the understanding of VD's effects on severe diseases. The review highlighted that low VD levels are common in HSCT patients, both pre- and post-transplant, and are associated with an increased risk of developing graft-versus-host disease (GVHD), particularly in its chronic form. However, the relationship with acute GVHD was inconsistent. Supplementation protocols varied significantly, but VD plays a relevant immunomodulatory role, influencing GVHD pathogenesis. These findings suggest that VD deficiency in HSCT patients may compromise transplantation outcomes, emphasizing the importance of standardizing supplementation in this context [39].

Beyond oncology, other studies have explored the role of VD in chronic diseases, providing valuable insights that reinforce the findings of this review. Research into COVID-19 suggests that VD plays a protective role, with studies reporting a correlation between adequate VD levels and reduced disease severity, mortality, and hospitalization times [40,41]. Although these findings stem from a different context, they highlight VD's potential in modulating immune responses and mitigating disease-related complications [41].

In other chronic conditions, VD's anticancer mechanisms have been linked to its interaction with the vitamin D receptor (VDR) and its modulation of gene expression. These

mechanisms, which include anti-inflammatory, antioxidant, and DNA repair activities, are also influenced by dysregulation in cancer [42]. Specifically, studies in prostate cancer reveal that VD analogs and combinations with other therapies may enhance anticancer effects, such as cell cycle arrest and apoptosis, although challenges like resistance to VD-based therapies remain [43].

Emerging therapeutic strategies also explore VD's role in enhancing photodynamic therapy (PDT) efficacy. In skin cancer, VD has been shown to increase protoporphyrin IX (PpIX) accumulation, boost immune responses, and improve treatment efficacy in combination with PDT [44,45]. Such findings suggest that VD's benefits extend beyond systemic supplementation to novel combinatory approaches [44].

The VITAL trial, a landmark study, showed no reduction in cancer incidence or mortality with VD supplementation in healthy adults [46]. However, the trial's focus on primary prevention rather than treatment or supplementation in deficient individuals highlights the need for further context-specific investigations [47].

Finally, evidence from Japanese breast cancer patients treated with neoadjuvant chemotherapy suggests that serum VD levels may influence prognosis, emphasizing the importance of monitoring and optimizing VD intake in oncological care [46].

In conclusion, this scoping review, supported by broader literature, underscores VD's potential role in mitigating cancer treatment side effects and improving patient outcomes. However, significant gaps remain, particularly regarding standardization in methodologies and the long-term impact of supplementation. Future research should prioritize these areas, exploring the broader applicability of VD-based interventions across cancer types and chronic diseases to fully realize their therapeutic potential.

4.1. Strengths and Limitations

This scoping review has several strengths and limitations. It involved an extensive research strategy and detailed screening to capture the breadth and depth of the literature in this field. To date, it is the first scoping review carried out on this topic, making it important for future clinical practice. An interdisciplinary team of nutritionists and researchers offering unique and complementary knowledge and perspectives completed it.

Some factors in the methodology of this review may have contributed to the limitations of its results, namely the definition of very strict inclusion and exclusion criteria, including the time limit of the last five years, which is why only five publications were selected. In addition, even though this review used three databases, searching other databases, such as the Web of Science, Mediclatina, and Embsase, may have yielded other published papers relevant to the purposes of this scoping review. However, it is important to note that access to Embase was not possible due to the lack of a subscription by the university. This review was also limited to papers in Portuguese, English, Spanish, and French. Other relevant papers on the subject may have been written in other languages and additional databases.

Moreover, the majority of the studies included a small sample without addressing whether the sample size was sufficient to detect an association, thus jeopardizing the generalizability of findings. Although the review is comprehensive, the limited sample sizes in the included studies restrict the generalization of results. Future research should prioritize larger cohort studies to address this limitation.

Thus, further studies can and should be conducted with the aim of better understanding the role of VD in the side effects of this treatment. Another limitation is that a critical analysis and bias assessment of the articles were not carried out, which may impact the interpretation and reliability of the included findings.

4.2. Future Directions

Future research should include longitudinal studies to evaluate the ongoing benefits or risks of VD supplementation in oncological patients. It is also essential to investigate the biological mechanisms by which VD modulates the side effects of chemotherapy and radiotherapy. Furthermore, multicenter randomized clinical trials should be designed to validate the efficacy and safety of VD supplementation in different cancer types and stages. In addition to clinical outcomes, these studies should incorporate holistic measures of impact, including assessments of quality of life and systemic health biomarkers, to better capture the full effects of VD supplementation.

Moreover, it is important to address existing research into VDD in the context of COVID-19.

5. Conclusions

In conclusion, the results of this scoping review suggest that VD supplementation may have a beneficial effect on the adverse effects associated with neoadjuvant treatment during RT or CT of oncological patients, both in the prevention and treatment of other health problems associated with treatment, such as osteoporosis, and in the mitigation of effects (nausea, vomiting, fatigue) resulting from aggressive CT and RT treatments.

However, few studies were found that directly link VD supplementation with the adverse effects of neoadjuvant treatment. Therefore, further studies are needed on this theme, particularly with more diversified samples regarding the age range and incidence of adverse effects associated with adjuvant and neoadjuvant RT and CT treatment of the oncological patient.

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

Abbreviations

The following abbreviations are used in this manuscript:

25(OH)D	25-hydroxyvitamin D
CT	Chemotherapy
PDAC	Pancreatic ductal adenocarcinoma
PN	Peripheral neuropathy
RT	Radiotherapy
VD	Vitamin D
VDD	Vitamin D deficiency
CRT	Chemoradiation
ELISA	Enzyme-linked immunosorbent assay
TMN	Targeted medical nutrition
NSCLC	Non-small cell lung cancer

Appendix A. Search Terms Used on PubMed, CINAHL, and Scopus Databases

Patients with Cancer	Vitamin D Supplementation	Adverse Effects	Effects of Neoadjuvant Treatment (Chemo and Radio)
Neoplasm Neoplasia Tumor Cancer Malignanc	Vitamin D Cholecalciferol Calciol (3 beta,5Z,7E)-9,10-Secocholesta-5,7,10(19)-trien-3-ol Hydroxyvitamin D Hydroxycholecalciferol Calcifediol 25-Hydroxycholecalciferol Monohydrate 25 Hydroxycholecalciferol Monohydrate 25-Hydroxyvitamin D 25 Hydroxyvitamin D Calcidiol 25-Hydroxycholecalciferol 25 Hydroxycholecalciferol Calcifediol, (3 beta,5E,7E)-Isomer Calcifediol Anhydrous Anhydrous, Calcifediol Dedrogyl Hidroferol Calcifediol, (3 alpha,5Z,7E)-Isomer Calderol Dihydroxycholecalciferols Dihydroxyvitamins D 24,25-Dihydroxyvitamin D 3 24,25-Dihydroxyvitamin D3 24,25-Dihydroxycholecalciferol 24,25 Dihydroxycholecalciferol 24,25 Dihydroxyvitamin D3 Dihydroxyvitamin D3, 24,25 24,25-Dihydroxyvitamin D 3, (3beta,5Z,7E,24R)-Isomer (24R)-24,25-Dihydroxyvitamin D3 24R,25-Dihydroxycholecalciferol 24R,25 Dihydroxycholecalciferol Calcitriol 1, 25-(OH)2D3 1,25-Dihydroxycholecalciferol 1,25 Dihydroxycholecalciferol 1,25-Dihydroxyvitamin D3 1,25 Dihydroxyvitamin D3 D3, 1,25-Dihydroxyvitamin 1 alpha,25-Dihydroxycholecalciferol 1 alpha,25-Dihydroxyvitamin D3 1 alpha,25 Dihydroxyvitamin D3 D3, 1 alpha,25-Dihydroxyvitamin Bocatriol Calcijex Calcitriol KyraMed KyraMed, Calcitriol Calcitriol-Nefro Calcitriol Nefro Decostriol MC1288 MC-1288 MC 1288 Osteotriol Renatriol Rocaltrol Silkis Sitriol Soltriol Tirocal 20-epi-1alpha,25-dihydroxycholecaliferol 1,25-dihydroxy-20-epi-Vitamin D3 1,25 dihydroxy 20 epi Vitamin D3 D3, 1,25-dihydroxy-20-epi-Vitamin 1,25(OH)2-20epi-D3 1 alpha, 25-dihydroxy-20-epi-Vitamin D3 Ergocalciferol 25-Hydroxyergocalciferol 25 Hydroxyergocalciferol 9,10-Secoergosta-5,7,10(19),22-tetraene-3 beta,25-diol Ercalcidiol 25-Hydroxycalciferol 25 Hydroxycalciferol Calciferols Dihydrotachysterol Tachystin Dihydrotachysterin Calcamine AT 10 AT-10 AT10	Adverse effects	Chemotherapy Adjuvant Drug Therapy Adjuvant Antineoplastic Agent Agents, Antineoplastic Antineoplastic Agent Agent, Antineoplastic Anticancer Agent Agent, Anticancer Anticancer Agents Agents, Anticancer Antineoplastic Drugs Drugs, Antineoplastic Antineoplastic Drug Drug, Antineoplastic Antineoplastic Antitumor Drug Drug, Antitumor Cancer Chemotherapy Agent Agent, Cancer Chemotherapy Chemotherapy Agent, Cancer Antineoplastics Antitumor Agents Agents, Antitumor Antitumor Drugs Drugs, Antitumor Cancer Chemotherapy Agents Agents, Cancer Chemotherapy Chemotherapy Agents, Cancer Cancer Chemotherapy Drugs Chemotherapy Drugs, Cancer Drugs, Cancer Chemotherapy Chemotherapeutic Anticancer Agents Agents, Chemotherapeutic Anticancer Chemotherapeutic Anticancer Drug Drug, Chemotherapeutic Anticancer Cancer Chemotherapy Drug Chemotherapy Drug, Cancer Drug, Cancer Chemotherapy Antitumor Agent Agent, Antitumor Hyperthermic Intraperitoneal Chemotherapy Intraperitoneal Chemotherapy, Hyperthermic HIPEC Hot Chemotherapy Chemotherapy, Hot Intraperitoneal Hyperthermic Chemotherapy Chemotherapy, Intraperitoneal Hyperthermic Hyperthermic Chemotherapy, Intraperitoneal Intraperitoneal Hyperthermic Chemotherapies Neoadjuvant Therapy Neoadjuvant Therapies Therapy, Neoadjuvant Neoadjuvant Treatment Neoadjuvant Treatments Treatment, Neoadjuvant Neoadjuvant Radiotherapy Neoadjuvant Radiotherapies Radiotherapy, Neoadjuvant Neoadjuvant Radiation Treatment Neoadjuvant Radiation Treatments Radiation Treatment, Neoadjuvant Treatment, Neoadjuvant Radiation Neoadjuvant Radiation Therapy Neoadjuvant Radiation Therapies Radiation Therapy, Neoadjuvant Therapy, Neoadjuvant Radiation Neoadjuvant Radiation Neoadjuvant Radiations Radiation, Neoadjuvant Neoadjuvant Systemic Therapy Neoadjuvant Systemic Therapies Systemic Therapy, Neoadjuvant Therapy, Neoadjuvant Systemic Neoadjuvant Systemic Treatment Neoadjuvant Systemic Treatments Systemic Treatment, Neoadjuvant Treatment, Neoadjuvant Systemic Neoadjuvant Chemotherapy Chemotherapy, Neoadjuvant Neoadjuvant Chemotherapies Neoadjuvant Chemotherapy Treatment Chemotherapy Treatment, Neoadjuvant Neoadjuvant Chemotherapy Treatments Treatment, Neoadjuvant Chemotherapy Neoadjuvant Chemoradiotherapy Chemoradiotherapy, Neoadjuvant Neoadjuvant Chemoradiotherapies Neoadjuvant Chemoradiation Therapy Chemoradiation Therapy, Neoadjuvant Neoadjuvant Chemoradiation Therapies Therapy, Neoadjuvant Chemoradiation Neoadjuvant Chemoradiation Treatment Chemoradiation Treatment, Neoadjuvant Neoadjuvant Chemoradiation Treatments Treatment, Neoadjuvant Chemoradiation Neoadjuvant Chemoradiation Chemoradiation, Neoadjuvant Neoadjuvant Chemoradiations

Terms used in the search syntax.

Appendix B. Summary of the Selected Studies

Reference	Country	Design	Cancer	n *	Aim	Intervention	Results
Yamada et al. (2017), [37]	Japan	Observational study	Pancreatic ductal adenocarcinoma (PDAC)	146	This study investigated distant metastases by analyzing VD levels and bone density in PDAC patients with or without preoperative CRT. The study focused particularly on vitamin D levels and bone density.	The study included 146 patients with PDAC who underwent surgery between 2007 and 2014. Some patients received preoperative CRT, while others did not. Bone density was assessed by computed tomography. Preoperative vitamin D levels were calculated using ELISA in 48 cases with available plasma. Patients were divided into two groups based on the change in bone density.	Patients treated with preoperative CRT tend to have compromised bone density, which is a predictor of distant metastasis. Vitamin D supplementation may decrease distant metastasis.
Laviano et al. (2019), [38]	The study was conducted at 16 centers in four countries: Croatia, Italy, Slovakia and Sweden	Randomized, double-blind, multicenter, controlled pilot trial	Non-small-cell lung cancer (NSCLC)	64	The primary objective of this study was to evaluate the safety and tolerability of TMN in NSCLC patients with cachexia who were receiving first-line chemotherapy. Secondary objectives included assessing the efficacy of TNM in improving clinically relevant measures such as changes in body weight, muscle function, lipid profiles, and TNM adherence.	Sixty-four patients receiving first-line CT for NSCLC with weight loss or low BMI were evaluated. Fifty-five of them were randomized to receive either juice-based TMN containing 25-hydroxy-vitamin D3 and other supplements or an isocaloric comparator twice daily for 12 weeks. Primary endpoints included the number/type of adverse events and changes in vital signs/laboratory parameters.	The TMN group had fewer adverse events (64 vs. 87) compared with the comparator group. The omega-3:omega-6 (O3:O6) ratio, the percentage of EPA and DHA, and vitamin D3 levels were significantly increased in the TMN group compared with the comparator group. Overall, it was concluded that TMN was well tolerated and had a favorable safety profile in patients with NSCLC receiving chemotherapy.
Alkan et al. (2019), [6]	The study was conducted at two oncology centers in Türkiye	Retrospective case-control study	Any type	706	This study aimed to define the prevalence of VDD in cancer patients and to establish the predictors of VDD to address a specific group of patients for screening.	A total of 706 outpatients treated with a diagnosis of cancer were evaluated. Clinical properties and 25(OH) D levels were assessed.	The study concluded that the prevalence of VDD is high in cancer patients and that female gender, low sunlight exposure, palliative or adjuvant treatment, and history of gastrointestinal surgery are associated with VDD.
Jennaro et al. (2020), [19]	United States, Ann Arbor, Michigan	Observational study	Breast cancer (BC)	60	The purpose of this study was to investigate associations between nutrient deficiencies (VD, vitamin B12, folate, or homocysteine) pre-treatment and the severity of PN during weekly paclitaxel treatment in breast cancer patients.	Patient-reported PN was collected at baseline and during treatment on the Quality of Life-Chemotherapy-Induced Questionnaire (CIPN20). The primary analysis tested associations between vitamin deficiency and the maximum increase from baseline on the CIPN20 sensory subscale (ΔCIPN8).	Pre-treatment VDD was associated with increased PN in women receiving weekly paclitaxel for breast cancer. VDD may be an easily detectable risk factor for PN that can be addressed before treatment to avoid interruptions and improve outcomes. Study suggests vitamin D as a possible modifiable biomarker for paclitaxel-induced PN.
Chartron et al. (2021), [7]	The study was conducted at two oncology centers in France	Bicentric phase II trial	Breast cancer (BC)	44	Analysis and report of the safety and efficacy of high-dose oral vitamin D supplementation to correct VDD d in 44 breast cancer patients treated early with adjuvant CT.	Patients received a dose of VD every 3 weeks from day 1 of cycle 1 to day 1 of cycle 5. The primary endpoint was the percentage of patients achieving normalization of serum 25-OH VD concentration on day 1 of cycle 6 (D1C6). Secondary endpoints assessed were VD, safety, and calcium parameters at baseline and during CT.	The high-dose VD regimen increased the percentage of normalization of serum 25-OH VD concentration in patients with early breast cancer receiving adjuvant chemotherapy. Asymptomatic hypercalciuria was common but without clinical consequences. Discontinuation of VD due to asymptomatic hypercalciuria was associated with a rapid decrease in serum VD concentration.

Vitamin D (VD), chemoradiotherapy (CRT), chemotherapy (CT), enzyme-linked immunosorbent assay (ELISA), targeted medical nutrition (TMN), vitamin D deficiency (VDD), peripheral neuropathy (PN). * n included in the analysis.

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Multidisciplinary Integrative Medicine Approach for Cancer Patients: A Multicenter Retrospective Study

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Abstract: Background: The use of complementary integrative medicine (CIM) by cancer patients is currently very common. The main reasons why patients turn to CIM are to improve quality of life (QoL) and support the immune system. Unfortunately, many patients rely on CIM self-prescription, neglecting the risk of interactions with anticancer treatments (ACTs). The primary objective is to demonstrate the feasibility of combining CIM and ACT in a multidisciplinary approach to improve the QoL of cancer patients and to reduce ACT's adverse events. Methods: Cancer patients were treated with CIM by expert physicians. CIM mainly consisted of vitamins C and D, the medicinal mushrooms blend U-CARE, and probiotics administered alone or in combination. The patients were followed-up by physicians and data were recorded in a detailed shared file. Results: A total of 54 cancer patients were treated with an integrative approach, especially during ACTs. The combination showed a good safety profile. No adverse events occurred in 92.6% of patients, whereas only 7.4% of patients experienced gastrointestinal or liver toxicity from the CIM approach. The main benefit of the CIM approach was improved fatigue and QoL, and this was mainly achieved by the concomitant use of polytherapy-based complementary medicine (PCM) and U-CARE. The toxicity improvement was mainly associated with the use of solely U-CARE. Conclusions: These results highlight the feasibility of the CIM approach in cancer patients addressed by a multidisciplinary team of experts in the

field. The patient-centered and evidence-based approach of CIM is an example of the comprehensive and coordinated strategy pursued by the EU in its programmatic document against cancer aiming to focus on the QoL of patients and to avoid potentially harmful CIM self-prescription.

Keywords: complementary integrative medicine; multidisciplinary approaches; cancer patients; quality of life; cancer-related fatigue; survival

1. Introduction

According to the National Center for Complementary and Integrative Health (NCCIH), the integrative medicine (IM) approach combines traditional medicine (TM) with complementary medicine (CM) approaches shown to be safe and effective [1]. Despite the concomitant use of complementary approaches with oncological treatments being controversial, a large proportion of cancer patients (20–50%) use them to manage the adverse events (AEs) of anticancer treatments (ACTs) or even to treat cancer [2–5]. Complementary and integrative medicine (CIM) approaches are highly heterogeneous, including a wide range of practices and biological products such as herbs/botanicals, vitamins, probiotics, and medicinal mushroom blends and non-biological products such as meditation and yoga (according to the five categories identified by the NCCIH) [1]. A major concern is patients' sources of information about CIM: the main source is the media (48%), followed by friends and relatives (19%), and only 6% by healthcare practitioners [3,6]. Nevertheless, the physician remains the leading figure that patients trust and want to be guided by in their oncological decision-making. In contrast, only 48% of physicians are in favor of using the CIM approach, which is mainly due to an individual interest in this topic [7]. The limited knowledge of CIM also depends on the lack of university courses on the topic in many countries, which could enable a new generation of doctors to meet patients' needs and avoid potentially harmful self-prescribing [7]. The self-prescription of CIM, indeed, may increase the risk of unexpected toxicities, and the failure of anticancer treatments (ACTs), due to pharmacokinetic or pharmacodynamic interactions between TM and CIM. The supervised use of evidence-based CIM approaches may improve quality of life (QoL), adherence to ACTs [5], and in some cases also overall survival (OS) in cancer patients, likely due to the reduction in ACT-related adverse events (AEs) causing therapy discontinuation or delay [2]. A European Union (EU) programmatic document updated in 2022 on cancer indicated that science-based CIM could be useful to improve QoL, but it was recommended that such approaches should be supervised by healthcare institutions and physicians [8]. Based on these considerations, we describe a multicenter retrospective study of multidisciplinary CIM approaches in 54 cancer patients based on good clinical practice and according to the guidelines for CIM approaches [9,10]. The main objective of our research was to demonstrate the feasibility of a CIM approach in cancer patients through a multidisciplinary work. To this end, the endpoints focused on improving patients' QoL, reducing the side effects of ACTs, and ensuring the absence of AEs of complementary and integrative medicine. Secondly, in this—albeit small—patient group, we investigated how the improvement in managing ACTs potentially reflected on survival. The selection of the CIM approach depended on the clinical characteristics of the patients and the personal clinical experience of the physicians involved in the decision to use the CIM approach. As with ACTs, the CIM approach does not provide the same treatment for all cancer patients. Personalized CIM treatments based on parameters such as age, Eastern Cooperative Oncology Group performance status (ECOG PS), comorbidities, cancer-related symptoms, treatment

failure, ACT cycles received, AEs, and terminal illness were the strategies adopted by the multidisciplinary team for the 54 patients. Each CIM approach was shared and discussed with the patients and their relatives. The therapeutic rationale for administering a CIM approach, that in our study mainly consisted of natural products, was to improve QoL, reduce toxicities, and support the immune system to counteract disease progression.

2. Materials and Methods

2.1. Patients and CIM Approach

This retrospective study included patients regardless of gender, age, cancer type, and stage who have required a multi-target supportive treatment (ST) from their physician since 2021. Three oncologists closely monitored the 54 patients, although the multidisciplinary team also included radiotherapists, pharmacists, and nutritional biologists who helped to tailor the CIM approach. Patients received standard ACTs before or during the CIM and were treated with a CIM approach after the failure of ACTs and/or the appearance of serious and/or persistent ACT-related AEs. The CIM mainly consisted of vitamin C (VitC) and D (VitD), probiotics, and a blend of medicinal mushrooms (MMs) (Micotherapy U-CARE, owned by ADV Reform srl, Noceto, Italy) administered alone or in combination. In a few isolated cases, glutathione was also given. VitC was orally administered with a maximum of 2 g daily, except for one patient for whom the i.v. administration was preferred (4 g i.v. daily). VitD was orally administered based on basal plasma vitamin D levels, and the doses ranged from 60,000 IU monthly to 100,000 IU monthly. Probiotics were prescribed according to specific patients' needs. The most used strains were as follows: *Lactobacillus rhamnosus* LRH11, *Lactobacillus rhamnosus* GG, *Bifidobacterium lactis* BB12, *Lactobacillus acidophilus* LA5, *Lactobacillus acidophilus* LA14, *Enterococcus faecium* EF41, and *Saccharomyces cervisae subspecies boulardii*. Medicinal mushroom Micotherapy U-CARE has been registered by the Italian Ministry of Health as a dietary supplement (registration number 627 I.5.i.h.2/2020/627). It is produced from a hot water extract which is precipitated with ethanol and then freeze-dried. Each capsule contains a mixture of *Ganoderma lucidum, Grifola frondosa, Agaricus Blazei Murril, Cordyceps synensis,* and *Lentinula edodes* in equal amounts (300 mg) and titrated to a total of >30% of polysaccharides and >15% of β-(1,3)-D-glucans and β-(1-6)-D-glucans. The planned oral dose was 2 capsules daily between meals. Glutathione was only administered in cases of severe liver and kidney toxicity due to ACT or in some cases where ACT was suspended. Patients were treated in accordance with the Helsinki Declaration of 1964 and its subsequent amendments or equivalent ethical standards and local ethical guidelines. Patients were fully informed of the proposed CIM approach and signed the informed consent form. This study followed the reporting guidelines for studies [11].

2.2. Rationale for the CIM Approach Selection

Each CIM approach was closely patient-tailored, as stated in the Introduction Section of this manuscript. The CIM approach consisted of VitC and VitD, a medicinal mushrooms blend, probiotics, and glutathione. VitC improves HR-QoL and attenuates cancer-related adverse events. Despite most clinical benefits being provided by iv administration, the oral intake of VitC also enhanced HR-QoL [12]. In addition, VitC's immunomodulatory activity may be a promising integrative therapy in combination with immunotherapy as at high doses, it enhances immune checkpoint agents and increases CD8 T cell infiltration and cytotoxicity in the tumor microenvironment [12]. The use of VitD is supported by observational studies which have demonstrated that it is associated with longer survival in cancer patients. Notably, VitD reduces the lipid peroxidation usually involved in cardiovascular

and neurodegenerative diseases, as well as in cancer [13]. Recently, the role of VitD as a regulator of immune function has been elucidated, which is important in patients with a deregulated immune system such as cancer patients. In particular, VitD has been shown to be an important modulator of the expression of genes that regulate both the innate and adaptive immune systems [14]. It is known that the VitD receptor is expressed in several tumor cells, tissues, and, particularly, in the stroma of the tumor microenvironment, and we can therefore assume that it exerts a direct antitumor effect [13]. Particularly, its antitumoral effects include the inhibition of cell cycle, cell differentiation and apoptosis, autophagy, and angiogenesis via the regulation of signaling pathways such as PI3K/Akt/ERK1/2/MAPK, WNT/β-catenin, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling [15]. Due to both antitumor and anti-inflammatory activities in the tumor microenvironment, VitD represents a proper CIM approach to control tumor progression and enhance ACTs. Two recent metanalysis highlighted the negative impact of low VitD levels on time to outcome both in stage III CRC and metastatic CRC patients [16,17]. In addition, a metanalysis focused on BC patients emphasized that adequate pretreatment levels of VitD had a positive impact on progression-free survival (PFS) and response to neo-adjuvant chemotherapy [18]. Probiotics are non-pathogenic live microorganisms that play an active role in improving the health of the host when taken at the right amount [19]. Research on probiotics and their role in oncology highlights several promising aspects of their use in cancer prevention and treatment. Probiotics have shown potential to enhance anticancer immunity by modulating the gut microbiota and immune system [20]. Some studies emphasize the role played by probiotics in different cancer types, including CRC, oral, oropharyngeal, and skin cancers [21–23]. Probiotics modulate cancer through various pathways, including the downregulation of oncogene expression, inhibition of kinases, induction of autophagy, and reactivation of tumor suppressors [23]. By promoting healthy or immune-potentiating microbiota, probiotics help the immune system to detect and eliminate cancerous cells. Probiotics can improve the efficacy of conventional cancer treatments such as chemotherapy and immunotherapy while potentially reducing their AEs. They also contribute to cancer therapy by enhancing immune barrier function, inhibiting carcinogenic enzymes, promoting apoptosis, and maintaining redox homeostasis. Additionally, probiotics produce metabolites with anticarcinogenic properties that can act directly on cancer cells and indirectly as immunomodulatory signals [20]. The role of medicinal mushroom (MM) blends is more intriguing. Medicinal mushrooms have been used in TM for centuries, particularly in Asian cultures, and they are gaining popularity in modern clinical applications due to their potential health benefits. According to the NCI and the NCCIH, they can improve the HR-QoL, microbiota diversity, and immunomodulation [24,25]. Moreover, they were approved in addition to standard ACTs in Japan and China more than 30 years ago and have an extensive history of safe clinical use alone or combined with radiotherapy or ACTs [26,27]. The MM blends contain numerous bioactive compounds, including beta-glucans, triterpenes, ergothioneine, and ergosterols that influence several cancer-related pathways, often synergistically, by modulating the cellular targets involved in cell proliferation, survival, and angiogenesis [28]. For example, Reishi (*Ganoderma Lucidum*) and *Trametes Versicolor* (Turkey tail) exert hepatoprotective properties that can protect the liver from chemotherapy- and immunotherapy-related damages [29,30]. Medicinal mushrooms exert immune-enhancing activities via the stimulation of growth and differentiation of lymphocytes [31]. Trametes Versicolor extract, indeed, can increase CD8+ T cells and CD19+ B cells in BC patients. Reishi significantly increases IFN-γ, IL-2, IL-6, and NK cell (CD56+ cells) levels in lung cancer patients, thereby potentially increasing immune therapies [28]. Some mushrooms like Reishi, Cordyceps sinensys, Agaricus Blazei Murril, and Maitake reduce TH-2 cytokines with anti-inflammatory and

immune-enhancing functions. Protein complexes, polysaccharides, and β-glucans of MM reduce NF-kB expression in antigen-presenting cells (APCs) and increase the synthesis and release of interferon-gamma (INF-γ) from natural killer (NK) cells and TH-1 pathways, which leads to the activation of macrophages and cytotoxic lymphocytes with antitumor properties [28]. Mushroom blend extracts, such as U-CARE, exert their immunomodulating activity via branched-β1,3-β1,6 β-glucans due to their tertiary triple-helix structure and high conformational heterogeneity [32]. The diversity of branched-β-glucans contained in the mushroom mixture is transferred to APCs such as macrophages, dendritic cells (DCs), and NK cells by enhancing their non-self-recognition capabilities through the stimulation of specific receptors located on the cell membrane [33]. β-glucans also have a high prebiotic effect, which is mediated by microbiota. Particularly, β-glucans are degraded by bifidobacteria via a complex of glucanases anchored to a transmembrane domain. The blend of β-glucans thus exerts bifidogenic activity, increasing the robustness and biodiversity of the microbiota and the production of short-chain fatty acids (SCFAs), improving mucosal integrity, nutrient absorption, and drug response [34,35]. The incorporation of MMs into clinical practice is increasing, reflecting the merging of traditional knowledge and modern scientific research. Glutathione, a tripeptide widely present in tissues and cells, is preferentially concentrated in the liver, where its biologically active reduced form (GSH) plays an antioxidant and detoxifying role for cell homeostasis [36]. Given the antioxidant effect of GSH, its role in cancer therapy is twofold: (a) as a detoxification agent by conjugating xenobiotics and (b) the activation of some prodrugs in active metabolites [37]. However, in some cases, its role is controversial, like for the association of doxorubicin (DOX) and glutathione. Whilst the administration of exogenous GSH during DOX-based chemotherapy protects from hepatotoxicity and cardiotoxicity, on the other hand, it significantly decreases the antineoplastic effectiveness of DOX in a dose-dependent manner, thus proving the disadvantageous effect of GSH use [38]. In general, the administration of glutathione or its precursor N-acetylcysteine (NAC) is widely used to reduce the AEs of chemotherapy. The use of glutathione in our study was evaluated for each individual patient based on the type of chemotherapy and potential pharmacokinetic and pharmacodynamic effects with the drugs.

2.3. Data Collection

Patients' data were collected in a shared file, continuously updated from the three oncologists who followed-up the patients. Only those prescribing CIM were allowed to access the shared file. The data collected included patients' biographical and clinical data, type of ACT, PS at diagnosis and at the start of the CIM treatment, type of CIM treatment, goals of the CIM treatment and benefits achieved, and any AEs. In particular, among AEs, we evaluated cancer-related fatigue (CRF) in patients integrating supplements, employing a validated assessment tool widely used in oncology research called the Brief Fatigue Inventory (BFI). In brief, the BFI was administered to assess the severity and impact of fatigue on daily activities. This self-reported questionnaire consists of nine items, including the worst fatigue in the last 24 h and its interference with mood, walking ability, normal work, and enjoyment of life. Fatigue assessments were conducted at the baseline (before supplement initiation) and at scheduled follow-up visits to monitor changes over time.

2.4. Statistical Analysis

All the data were reported into the prospective Excel database (Microsoft, Washington, DC, USA version 16.78, 2023). Based on the presence or absence of locoregional recurrence, clinicopathological variables were compared between the groups using the T test for

continuous variables. Fisher's exact test was applied in cases of dichotomous variables, and the Monte Carlo test was used in cases of non-dichotomous variables. Multivariate logistic regression analysis was performed to identify the risk predictors of DCIS recurrence. Only p-value < 0.05 was statistically significant. The Kaplan–Meier curve was adopted to evaluate recurrence, and the log-rank test was used to assess statistically significant differences between the groups. A logistic regression statistical model was used to estimate the effect of factors on LLR. Pearson's test was adopted to appraise the correlation between the variables. All the statistical analyses were performed in SPSS statistical package version 23.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Clinicopathological Profile and Treatment Landscape of Oncology Patients Receiving Complementary Medicine

The heterogeneity of the patient population in terms of clinical characteristics, disease stage, treatment modalities, and metastatic patterns, highlighting the complexity of managing oncological patients who explore CIM approaches, is detailed in Table 1. The analysis included 54 patients, with a median age of 62 years, ranging from 28 to 83 years. Most patients were younger than 70 years (75.9%). Females made up a slight majority, representing 57.4% of the cohort. The most common types of cancer were BC (25.9%), CNS tumors (20.4%), and CRC (16.6%). Other cancers included urogynecological malignancies (11.1%), non-colorectal gastrointestinal tumors (7.4%), hematologic malignancies (7.4%), and a small percentage of lung, multiple cancers, or less common cancers (3.7%). Advanced-stage disease was predominant, seen in 83.3% of cases, while early-stage cancers accounted for 16.7%. Histological grading revealed that 68.5% of tumors were high-grade (G2/3), while 31.5% were low-grade (G1). Metastatic disease was common, with 33.3% of patients presenting multiple metastatic sites. Uncommon metastatic locations, such as cutis, adrenal glands, spleen, and ocular tissues, were observed in 14.8% of cases. Notably, 20.3% of patients had no metastases at the time of analysis. The ECOG PS was favorable for most patients, with 77.7% having a score of 0–1, indicating good functional capacity. A diverse range of ACTs was administered, with chemotherapy being the most common (37.7%). Hormone therapy (14.8%), targeted therapies (9.2%), and anti-angiogenic drugs (7.4%) were also employed. Only one patient received immunotherapy (1.8%) or radiotherapy (1.8%). Combinational treatment regimens were administered to 24.1% of the cohort, while 3.7% did not receive any active treatment.

The distribution of lifestyle factors and comorbidities among the study population may highlight distinct patterns relevant to CIM in oncology (Table 2). Interestingly, nearly half of the patients (48.1%) adhered to a healthy lifestyle, which was the most prevalent category. Sedentary behavior was observed in 31.5% of the population, indicating a significant proportion with limited physical activity. A smaller segment, comprising 13.0%, reported an active lifestyle. Smoking was reported by only 7.4% of patients, reflecting the low prevalence of this risk behavior in the cohort. In terms of comorbidities, most participants (61.1%) had no concurrent medical conditions, suggesting a relatively healthy baseline in a significant portion of the population. Among those with comorbidities, cardiovascular conditions were the most frequently reported (14.8%), followed by metabolic disorders (9.3%). Liver conditions and anxiety–depression syndrome were equally represented at 5.6% each. A minority of participants (3.7%) presented with multiple comorbidities, reflecting a more complex health status.

Table 1. Clinicopathological characteristics of analyzed patients.

Variable	No. (%)
Age	
Median: 62 y; range (28–83 y)	
<70 y	41 (75.9)
≥70 y	13 (24.1)
Gender	
Female	31 (57.4)
Male	23 (42.6)
Type of cancer	
Breast	14 (25.9)
CNS	11 (20.4)
Colorectal	9 (16.6)
Urogynecological	6 (11.1)
GI non colorectal	4 (7.4)
Hematologic	4 (7.4)
Multiple cancers	2 (3.7)
Lung	2 (3.7)
Other	2 (3.7)
Stage	
Advanced	45 (83.3)
Early	9 (16.7)
Grading	
G1	17 (31.5)
G2/3	37 (68.5)
Metastatic sites	
Not applicable	11 (20.3)
Lymph nodes	6 (11.1)
Liver	4 (7.4)
Bone	3 (5.5)
Peritoneum/Pleura	3 (5.5)
Lung	1 (1.8)
Multiple sites	18 (33.3)
Other *	8 (14.8)
PS ECOG	
0–1	42 (77.7)
2–3	12 (22.2)
Type of oncological treatment	
Chemotherapy	20 (37.7)
Hormone therapy	8 (14.8)
Target therapy	5 (9.2)
Anti-angiogenic drugs	4 (7.4)
Immunotherapy	1 (1.8)
Radiotherapy	1 (1.8)
None	2 (3.7)
Combinations	13 (24.1)

* Other refers to uncommon metastatic sites, including cutis, adrenal glands, spleen, and ocular sites. CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

Table 2. Distribution of lifestyle factors and comorbidities in the study population.

Variable	No. (%)
Lifestyle	
Healthy	26 (48.1)
Sedentary	17 (31.5)
Active	7 (13.0)
Smoking	4 (7.4)
Comorbidities	
None	33 (61.1)
Cardiovascular	8 (14.8)
Metabolic	5 (9.3)
Liver	3 (5.6)
Anxiety–depression syndrome	3 (5.6)
Multiple morbidities	2 (3.7)

3.2. Oncological Treatment Duration, Toxicity, and Responses in Patients Receiving CIM

The results presented in Table 3 provide a comprehensive overview of the duration of ACTs, the spectrum of treatment-related AEs, and therapeutic responses in patients who received CIM alongside standard ACTs. These data underscore the potential for CIM to coexist with ACTs, providing insights into treatment duration, tolerability, and therapeutic efficacy. Regarding treatment duration, most patients (59.2%) underwent ACTs for over 12 months, suggesting sustained therapy for many patients. Conversely, approximately 20.4% of patients each reported treatment durations of less than 6 months or between 6 and 12 months, indicating variability in treatment continuity. Regarding ACTs toxicity, most patients experienced manageable AEs, with 64.8% reporting toxicity levels below grade 2 (G2). Severe toxicities (above grade 3) were rare, occurring in only 3.7% of patients. Interestingly, 31.5% of patients did not report any toxic events, highlighting the tolerability of the treatment regimens in a significant subset of the cohort. Notably, 20.4% of patients achieved a CR, and 38.7% showed a PR, collectively accounting for nearly 60% of patients who experienced meaningful tumor reduction. This positive result is obviously influenced by the presence of gastrointestinal, urogynecological, and hematological neoplasms. Stable disease was observed in 34.7% of patients, indicating disease control in these cases, while 6.1% of patients experienced disease progression.

Table 3. Duration, toxicities, and responses to oncological treatments.

Variable	No. (%)
Oncological treatment duration	
<6 months	11 (20.4)
≥6–<12 months	11 (20.4)
≥12 months	32 (59.2)
Toxicity *	
≤G2	35 (64.8)
Hematologic	15
Non-hematologic	41
Fatigue	20
Gastrointestinal	13
Neurologic	3
Cutis	1
Renal	1

Table 3. *Cont.*

Variable	No. (%)
≥G3	2 (3.7)
Renal	1
Gastrointestinal	1
No toxicity	17 (31.5)
Best response **	
Complete response	10 (20.4)
Partial response	19 (38.7)
Stable disease	17 (34.7)
Progressive disease	3 (6.1)

* The total number of patients experiencing toxic events does not equal 35 because a single patient may experience more than one type of toxicity. ** The total number of patients does not amount to 54 because 5 patients received integrative treatment as part of an adjuvant therapeutic program (systemic or local).

3.3. Implementation of CIM Approach in the Oncological Practice

Table 4 describes several qualitative and quantitative relationships between ACTs and CIM. At the initiation of CIM, most patients (72.2%) had an ECOG PS of 0–1, indicating relatively good functional status, while a smaller subset (25.9%) had more impaired performance with ECOG PS 2–3. The type of CIM varied, with nearly half of the patients (46.3%) utilizing a combination of U-CARE and polytherapy-based complementary medicine (PCM), followed by 40.7% opting solely for U-CARE and 12.9% relying exclusively on polytherapy-based CIM. CIM approaches were predominantly associated with systemic ACTs, with 37% of patients starting during the first line of cancer therapy, 31.4% in the second line, and 22.2% beyond the second line. Only a minority of patients (5.6%) used CIM in an adjuvant setting, and 3.8% were not undergoing systemic therapy. In terms of timing, CIM was most frequently initiated during ACTs (72.2%), while smaller proportions began at the time of diagnosis (7.4%), at the initiation of ACTs (11.1%), or following its completion (9.3%). Patients reported different motivations for starting CIM. General support was the most common reason (40.7%), followed by support for managing AEs (12.1%) and immunomodulation (1.8%). Notably, nearly half (44.4%) pursued CIM for a combination of these reasons. The duration of CIM administration was evenly distributed, with 37% receiving treatment for less than 3 months, 25.9% for 3–6 months, and another 37% for more than 6 months, reflecting a mix of short- and longer-term engagement with these therapies.

Table 4. Oncological treatments and integrative medicine.

Variable	No. (%)
PS ECOG at the start of CIM	
0–1	39 (72.2)
2–3	14 (25.9)
Type of complementary therapy	
U-CARE + Polytherapy-based complementary medicine	25 (46.3)
U-CARE	22 (40.7)
Polytherapy-based complementary medicine	7 (12.9)
Line of therapy associated with CIM	
First	20 (37.0)
Second	17 (31.4)
Beyond second line	12 (22.2)
Adjuvant	3 (5.6)
No systemic therapy	2 (3.8)

Table 4. *Cont.*

Variable	No. (%)
Relationship between the timing of CIM and ACTs	
Initiation at the time of cancer diagnosis	4 (7.4)
Initiation at the onset of ACT	6 (11.1)
Initiation during ACT	39 (72.2)
Initiation following the completion of ACT	5 (9.3)
Motivations for initiating CIM	
General support	22 (40.7)
Support for toxicity	7 (12.1)
Immunomodulation	1 (1.8)
More than one of the above reasons	24 (44.4)
Duration of CIM	
≤3 months	20 (37.0)
>3–≤6 months	14 (25.9)
>6 months	20 (37.0)

ECOG: Eastern Cooperative Oncology Group; PS: performance status; U-CARE: Micotherapy U-CARE.

3.4. Clinical Benefit, Toxicity, and Costs of Cim Approach

The analysis of clinical outcomes, toxicity, and costs associated with CIM administration is reported in Table 5. Regarding clinical benefits, most patients (44.4%) experienced an improvement in fatigue and overall QoL. Improvements in either QoL or ACT-related toxicity were reported in 11.1% of patients for each category, while 11.1% of patients reported no benefit from the CIM therapies. Smaller subsets of patients experienced combined benefits, including fatigue and toxicity relief (3.7%), tumor shrinkage alone (1.8%), or in combination with QoL improvement (1.8%). A subset of 12.1% reported multiple benefits spanning several categories, highlighting the potential multidimensional impact of these treatments in certain cases. Toxicity associated with CIM was minimal. Nearly ninety-three percent (92.6%) of patients reported no AEs. Among those who experienced toxicity, the most common AEs were gastrointestinal (5.5%) and liver-related toxicity (1.8%). Notably, pharmacological interaction testing, performed in 17 patients, did not include any of those who experienced toxicity, underscoring a potential area for further investigation. Cost analysis showed that CIM was generally affordable, with 74.1% of patients incurring monthly expenses of less than EUR 100. However, 35.9% of patients reported costs exceeding EUR 100 per month, indicating variability in financial burden depending on the type of IM prescribed.

Table 5. Clinical benefit, toxicity, and costs of complementary products.

Variable	No. (%)
Type of clinical benefit	
Fatigue and QoL improvement	24 (44.4)
Toxicity improvement	6 (11.1)
QoL improvement	6 (11.1)
No benefit	6 (11.1)
Fatigue and toxicity improvement	2 (3.7)
Improvement in tumor shrinkage	1 (1.8)
Toxicity and QoL improvement	1 (1.8)
Improvement in tumor shrinkage and QoL	1 (1.8)
Multiple benefits	7 (12.1)

Table 5. *Cont.*

Variable	No. (%)
Type of toxicity *	
No toxicity	50 (92.6)
Gastrointestinal	3 (5.5)
Liver	1 (1.8)
Costs	
<EUR 100 per month	40 (74.1)
>EUR 100 per month	14 (35.9)

* A pharmacological interaction test was conducted in 17 patients, but it was not performed for any of the patients who experienced toxicity from CIM.

3.5. Factors Influencing Response to Cim and Survival

The univariate analysis examined factors associated with clinical benefit from CIM and their potential impact on OS (Table 6). Among the variables analyzed (age, gender, lifestyle, type of cancer, type of CIM and its duration, ECOG PS at cancer diagnosis or at CIM initiation, cancer stage, timing of CIM initiation, setting of therapy, and best response to ACT), none were significantly associated with clinical benefit from CIM. The Kaplan–Meier survival curves stratified by these factors are reported in Figure 1. However, ECOG PS at cancer diagnosis and best response to oncological treatment were significantly associated with survival outcomes. Specifically, patients with an ECOG score of 2 had a markedly higher risk of death (HR: 16.8, 95% CI: 3.78–74.5, $p = 0.0002$) compared to those with a PS ECOG of 1. Additionally, patients with progressive disease had significantly worse survival outcomes compared to those achieving a complete response (HR: 11.91, 95% CI: 0.29–48.37, $p = 0.0076$).

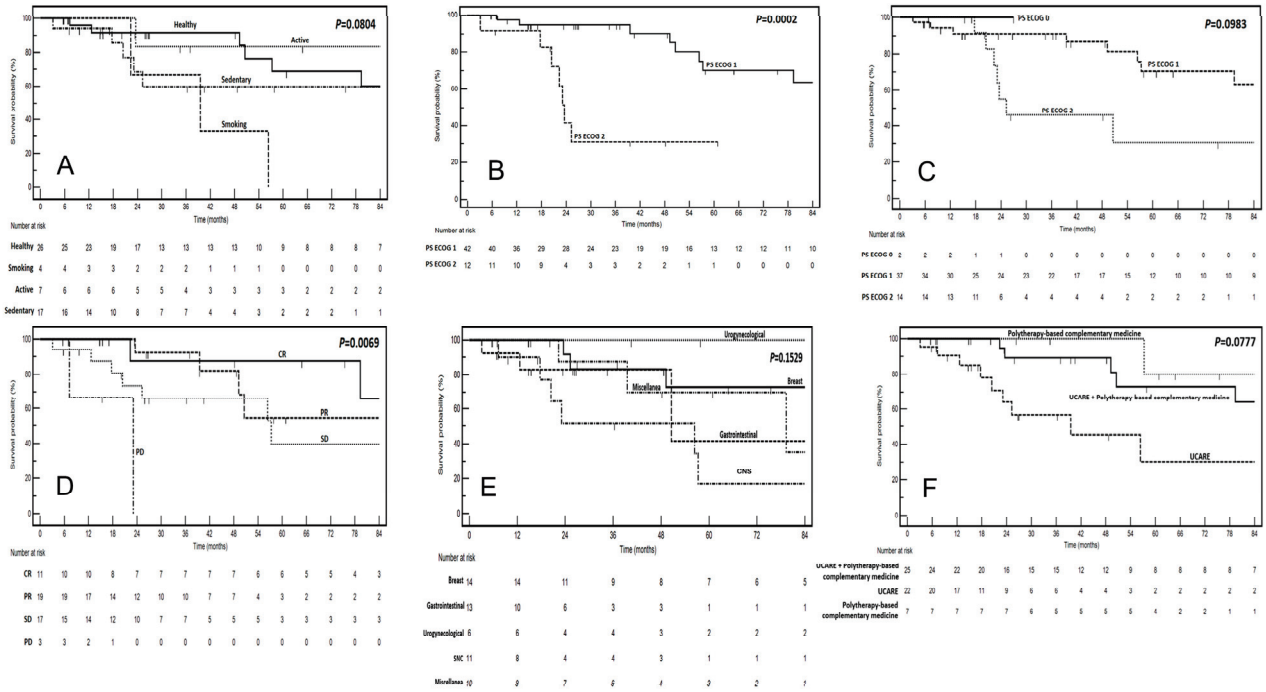

Figure 1. Kaplan–Meier curves illustrating survival stratified by the following factors are presented: (**A**) lifestyle, (**B**) PS ECOG at cancer diagnosis, (**C**) PS ECOG at the start of complementary therapy, (**D**) best response, (**E**) cancer type, and (**F**) type of complementary therapy. Log-rank test *p*-values are reported in the corresponding figures. The number of events is indicated at the bottom of each figure.

Table 6. Factors influencing response to CIM and survival (at univariate analysis).

Variable	Clinical Benefit from CIM		*p* (at Chi-Square test)	HR for OS	95% CIs	*p* (at Log-Rank Test)
	Yes	No				
Age						
<70 y	35	6		1		
≥70 y	13	0	0.1472	0.97	0.31–3.01	0.9663
Gender						
Male	20	3		1		
Female	28	3	0.6998	0.50	0.17–1.42	0.1960
Lifestyle						
Healthy	23	3		1		
Sedentary	16	1		1.72	0.57–5.14	
Active	6	1		0.91	0.24–3.33	
Smoking	3	1	0.7225	4.55	0.51–40.3	0.0804
Type of cancer						
Breast	13	1		1		
CNS	10	1		3.74	1.03–13.56	
Gastrointestinal	12	1		2.45	0.63–9.51	
Urogynecological	6	0		0.81	0.18–3.63	
Miscellanea	7	3	0.3101	1.73	0.46–6.49	0.1529
Type of complementary therapy						
U-CARE	23	2		1		
U-CARE + Polytherapy-based complementary medicine	18	4		0.49	0.18–1.36	
Polytherapy-based complementary medicine	7	0	0.3273	0.19	0.05–0.78	0.0777
Duration of CIM						
<3 months	17	3		1		
>3–≤6 months	13	1		0.75	0.24–2.34	
>6 months	18	2	0.7579	0.29	0.09–0.92	0.1551
PS ECOG at cancer diagnosis						
0	-	-				
1	37	5		1		
2	11	1	0.7309	16.8	3.78–74.5	0.0002
3	-	-				
PS ECOG at CIM start						
0	1	1				
1	32	5		1		
2	14	0	0.0844	2.46	0.83–7.28	0.0983
3	-	-				
Stage						
Early	8	1		1		
Advanced	40	5	1.0000	1.73	0.52–5.76	0.3684
Timing of CIM initiation						
At the time of cancer diagnosis	4	0		1		
At the onset of ACT	6	0		0.33	0.04–2.45	
During ACT	39	6		0.16	0.01–1.74	
Following the completion of ACT	5	0	0.4582	2.02	0.47–8.06	0.1831
Line of therapy associated with CIM						
First	18	2		1		
Second	14	3		1.23	0.37–4.12	
Beyond second line	11	1		1.37	0.39–4.76	
Adjuvant	2	0		1.19	0.29–4.81	
No systemic therapy	3	0	0.8303	1.26	0.14–11.0	0.9896
Best response to oncological treatment						
Complete response	9	1		1		
Partial response	17	2		1.43	0.44–4.57	
Stable disease	15	2		2.18	0.71–6.70	
Progressive disease	2	1	0.7186	11.91	0.29–48.37	0.0076

HR: hazard ratio; OS: overall survival; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; PS: performance status; ACT: anticancer treatment.

3.6. Associations Between Response to Act, Cancer Type, and Cim

The analyses included in Table 7 were conducted for descriptive purposes only. Regarding cancer types, patients with BC and gastrointestinal cancers showed more favorable responses to oncological treatments, with higher frequencies of complete response (CR) and partial response (PR) compared to other cancer types. In contrast, patients with CNS cancers predominantly exhibited stable disease (SD) or progressive disease (PD), with no CR or PR observed. Similarly, patients with urogynecological cancers had limited favorable responses, while the "miscellanea" group (including hematologic malignancies) demonstrated the most notable distribution of CR and PR outcomes, reflecting heterogeneity within this category ($p = 0.0019$). Regarding the CIM approach, the combination of U-CARE and PCM was associated with a higher proportion of favorable responses, including 6 cases of CR and 11 cases of PR, compared to either U-CARE or PCM alone. Specifically, U-CARE alone resulted in fewer CRs and PRs and a higher prevalence of SD, while PCM alone also produced fewer CRs and PRs but showed no cases of PD. The differences among these groups were statistically significant ($p = 0.041$).

Table 7. Associations between response to oncological treatments and type of cancer and CIM.

Variable	Best Response to Oncological Treatments				*p*
	CR	**PR**	**SD**	**PD**	
Type of cancer					
Breast	3	7	3	0	
CNS	0	0	8	2	
Gastrointestinal	2	7	2	0	
Urogynecological	0	1	3	1	
Miscellanea	5	4	1	0	0.0019
Type of complementary therapy					
U-CARE + Polytherapy-based complementary medicine	6	11	4	1	
U-CARE	1	6	12	2	
Polytherapy-based complementary medicine	3	2	1	0	0.041

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; CNS: central nervous system; U-CARE: Micotherapy U-CARE.

3.7. Factors Predicting OS in Cancer Patients Treated with CIM

A multivariate analysis was performed following a careful and consensus-based selection of specific variables (Table 8). Among the variables evaluated, PS, as assessed by ECOG at the time of cancer diagnosis, emerged as a statistically significant predictor of survival outcomes. Patients with a PS of 2 exhibited a hazard ratio (HR) of 4.86 (95% CI: 1.24–19.0, $p = 0.0232$), indicating a more than fourfold increased risk of mortality compared to those with a PS of 0–1. This finding highlights the critical role played by initial functional status in determining survival outcomes.

Table 8. Multivariate analysis of selected prognostic factors influencing overall survival (OS) in cancer patients receiving CIM approach.

Variable	HR for OS	95% CIs	*p*
Age			
<70 y	1		
≥70 y	1.16	0.33–4.12	0.7236

Table 8. *Cont.*

Variable	HR for OS	95% CIs	*p*
Gender			
Male	1		
Female	0.46	0.15–1.38	0.2151
PS ECOG *			
0–1	1		
2	4.86	1.24–19.0	0.0232
PS ECOG **			
0–1	1		
2	3.15	1.18–8.36	0.3001
Type of cancer			
Breast	1		
CNS	3.76	1.08–14.6	0.0816
Gastrointestinal	2.46	0.63–10.06	0.1222
Urogynecological	0.81	0.17–3.84	0.2948
Miscellanea	1.83	0.44–6.52	0.3308
Type of complementary therapy			
U-CARE	1		
U-CARE + polytherapy-based complementary medicine	0.48	0.17–1.35	0.9117
Polytherapy-based complementary medicine	0.18	0.04–0.77	0.9882

CI: confidence interval; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; OS: overall survival; PS: performance status; U-CARE: Micotherapy U-CARE. * at cancer diagnosis; ** at IM start.

3.8. Comparative Efficacy of CIM in Oncology: Cancer-Specific Applications and Multidimensional Clinical Benefits

The results summarized in Table 9 highlight significant differences in the distribution of cancer types and the clinical benefits associated with CIM, specifically PCM, U-CARE, and their combination (U-CARE + PCM). These therapies exhibit distinct patterns of utilization and effectiveness across cancer types and clinical outcomes. BC was the most frequently treated with U-CARE + PCM, with eight cases, compared to three cases for PCM and U-CARE individually, suggesting either a preference for or enhanced efficacy of the combined approach for this cancer type. In contrast, CNS cancers predominantly relied on U-CARE alone, with 10 cases, while PCM or U-CARE + PCM use was minimal or absent. Gastrointestinal cancers exhibited a more balanced distribution, with moderate use across all three therapy modalities. Notably, urogynecological cancers were exclusively treated with U-CARE + PCM, indicating a potential unique suitability of this combination for such malignancies. For miscellaneous cancers, the distribution was more varied, although the combined approach remained prominent. These variations in therapy applications across cancer types were statistically significant ($p = 0.004$). The distribution of clinical benefits further highlights the distinct contributions of each therapy. Improvements in fatigue and QoL were overwhelmingly associated with U-CARE + PCM, with 20 cases compared to 3 for PCM and 1 for U-CARE. Conversely, improvements in toxicity were most notable with U-CARE alone (four cases), whereas PCM showed no efficacy in this area. The combined U-CARE + PCM approach demonstrated the broadest efficacy, providing benefits across multiple clinical categories.

Table 9. Distribution of cancer types and clinical benefits across complementary therapies.

Variable	Type of Complementary Therapy			*p*
	PCM	U-CARE	U-CARE + PCM	
Type of cancer				
Breast	3	3	8	
CNS	1	10	0	
Gastrointestinal	2	6	5	
Urogynecological	0	0	6	
Miscellanea	1	3	6	0.0041
Type of clinical benefit				
Fatigue and QoL improvement	3	1	20	
Toxicity improvement	0	4	2	
QoL improvement	1	5	0	
No benefit	1	5	0	
Fatigue and toxicity improvement	0	0	2	
Improvement in tumor shrinkage	0	1	0	
Toxicity and QoL improvement	0	1	0	
Improvement in tumor shrinkage and QoL	1	0	0	
Multiple benefits	1	5	1	0.0003

PCM: polytherapy-based complementary medicine, including a combination of probiotics, vitamins, curcumin, and aloe vera; QoL: quality of life; U-CARE: Micotherapy U-CARE; CNS: central nervous system.

4. Discussion

Scientific advances in oncology have led to the development of innovative drugs that can improve survival. The result is ACTs that can last for years and, while keeping the disease under control, can sometimes affect the patient's QoL [39]. Patients themselves often turn to CIM to reduce ACT-related side effects and improve QoL, often relying on non-evidence-based sources with the risk of compromising cancer therapies and incurring unwanted toxicities [3,40]. Today, there is a strong need to improve QoL in cancer patients, especially cancer survivors. For this reason, it is necessary for healthcare professionals, especially oncologists, to increase their knowledge of CIM and begin to feel comfortable with these complementary therapies [7]. This effort is required not only by patients themselves, who see the oncologist as a key reference figure in their treatment decision-making, but also by the European Union, which in a policy document in 2022 emphasized the importance of shared recommendations on integrated supportive care, including evidence-based complementary therapies [8]. A relevant aspect is the need to develop a patient-centered and -informed CIM approach in which the use of complementary therapies is decided by an experienced multidisciplinary team and under the ongoing supervision of healthcare professionals. To this end, it is necessary for health professionals to be continuously updated in the field of integrated medicine, perhaps even by introducing specific courses at university level to train future professionals capable of meeting the needs of cancer patients.

From a biochemical point of view, mycotherapy and probiotics exert beneficial biochemical effects in cancer patients by modulating immune responses, reducing inflammation, enhancing gut microbiota composition, and influencing the metabolic pathways associated with tumor progression. Medicinal mushrooms contain bioactive compounds

such as beta-glucans, triterpenes, and polysaccharides that interact with pattern recognition receptors (PRRs) like Dectin-1 and Toll-like receptors (TLRs) on macrophages and dendritic cells [41]. This interaction stimulates NF-κB and MAPK signaling pathways, leading to the increased production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-12, which enhance cytotoxic T cell activity while reducing immunosuppressive factors like IL-10. Additionally, beta-glucans activate the complement system via the alternative pathway, enhancing phagocytosis and natural killer (NK) cell-mediated cytotoxicity against tumor cells [42]. Mycotherapy also modulates oxidative stress through the activation of the Nrf2-ARE pathway, which upregulates antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), counteracting reactive oxygen species (ROS)-induced DNA damage that contributes to cancer progression. Polysaccharides and triterpenes in medicinal mushrooms, such as ganoderic acids from *Ganoderma lucidum*, inhibit angiogenesis by downregulating VEGF and HIF-1α expression, thereby limiting tumor vascularization and nutrient supply [43]. Certain fungal-derived metabolites also exhibit direct apoptotic effects via mitochondrial cytochrome c release and caspase activation, modulating intrinsic apoptotic pathways in malignant cells [44]. Probiotics influence cancer progression through microbiota–host interactions that regulate immune function and metabolic homeostasis. *Lactobacillus* and *Bifidobacterium* species produce short-chain fatty acids (SCFAs), particularly butyrate, which serve as histone deacetylase (HDAC) inhibitors, promoting the epigenetic modulation of genes involved in apoptosis and cell cycle arrest [45]. Butyrate also enhances regulatory T cell (Treg) differentiation via the activation of G-protein-coupled receptors (GPR41/GPR43), contributing to immune homeostasis. Moreover, probiotics enhance intestinal barrier integrity by upregulating tight junction proteins such as occludin and claudin, preventing bacterial translocation and systemic inflammation. Moreover, probiotic-derived metabolites such as indole derivatives and polyamines modulate inflammatory signaling by inhibiting NF-κB and reducing the production of pro-inflammatory cytokines like IL-6 and IL-1β, which are often elevated in cancer-associated inflammation [46]. Some bacterial strains, such as *Lactobacillus rhamnosus*, could promote the expression of mucins (MUC2, MUC5AC), which create a protective mucus layer, reducing the risk of pathogen-induced oncogenic inflammation. The gut microbiota also influences tryptophan metabolism, shifting kynurenine pathway flux toward the production of immunosuppressive metabolites that affect T cell function in the tumor microenvironment [47]. Therefore, by integrating mycotherapy and probiotics, cancer patients could experience synergistic benefits that enhance immune surveillance, mitigate oxidative stress, and reduce chronic inflammation, ultimately contributing to improved treatment outcomes and QoL [48].

This retrospective multicenter study described the implementation of a CIM approach in the oncology field carried out by a multidisciplinary team. The ability to manage the prescription of CIM by a specialized team, working in close collaboration, brought benefits to the majority of 54 patients, in terms of improved QoL, cancer-related fatigue, and adherence to ACTs, while limiting harmful self-prescription [49]. Our study showed a safety profile for the combination of CIM approaches and ACTs. Only 5.6% of patients reported gastrointestinal toxicity and 1.8% hepatic toxicity, highlighting a reasonable safety profile. Additionally, in 17 out of 54 patients, regardless of the appearance of toxicity, drug–drug interaction tests were performed using online checker tools to ensure no interference with the ACTs [50,51]. As shown by the results, a considerable proportion of patients (44.4%) who received CIM reported a reduction in cancer-related fatigue and an improvement in QoL, which may have contributed to better adherence and continuity with ACTs. While the improved management of ACT side effects and fatigue is expected to support treatment adherence by reducing delays or discontinuation, any potential association with survival

outcomes should be interpreted with caution, given this study's sample size. The results of this retrospective study demonstrate that the combination of U-CARE and PCM was associated with a higher proportion of favorable responses, including 6 cases of CR and 11 cases of PR, compared to either U-CARE or PCM alone. Although the literature data regarding the benefits in terms of survival outcomes with the use of CIM in early stages of disease are conflicting [52], in our study, with the limitations of the small number of patients in this setting (5.6%), no statistically significant differences were observed. Our study included only some of the practices encompassed by CIM, which may therefore lead to a lower incidence of adverse events compared to the data available in the literature [53]. Furthermore, most patients included in this study had a healthy lifestyle at the baseline (48.1%) and did not have comorbidities (61.1%), which reduced the risk of interactions even with non-oncological concomitant medications. The collected data provide a range of useful information, even in clinical practice, for the management of oncological patients before, during, and after ACTs. Moreover, the increasing use of CIM further emphasizes the importance of conducting targeted prospective studies aimed at gaining a more detailed understanding of the potential synergism between CIM and ACTs, as well as their long-term effects. In addition to conventional medical treatments, many patients, particularly those in non-curative settings, incorporate CIM as part of their therapeutic approach, aiming to improve overall survival and QoL. This phenomenon is well documented in oncology, where patients frequently use complementary interventions such as herbal medicine, acupuncture, mind–body therapies, and dietary supplements alongside standard treatments. Emerging evidence also suggests that cim plays a role in improving general survival and health outcomes in non-cancer populations. For instance, cardiovascular patients benefit from lifestyle-based complementary approaches, including meditation, yoga, and plant-based diets, which have been associated with improved cardiovascular function and reduced mortality risk. Similarly, in chronic illnesses such as neurodegenerative disorders and autoimmune diseases, CIM, including dietary interventions, probiotics, and antioxidant supplementation, has shown potential in mitigating disease progression and enhancing survival. While these approaches are widely adopted, their efficacy and safety require rigorous scientific validation through high-quality clinical trials. Integrating CIM into evidence-based practice may provide a holistic approach to patient care, emphasizing both disease management and overall longevity. There are some limitations to this study, among which some are based on its retrospective nature. Moreover, the included patients presented heterogeneous cancer types and different disease stages, which can partly affect the results. Selected CIM approaches also vary between patients, although this may be due to the personalization of the integrative treatments delivered in a patient-centered way. In many cases, the CIM approach consisted of the combination of multiple complementary treatments, whereas some patients were administered a single complementary treatment. Another limitation includes QoL and cancer-related fatigue evaluation being affected by the retrospective nature of this study. This parameter was collected based on the clinical assessment during the patients' follow-up and the patients' self-perceived health status without using a dedicated questionnaire.

5. Conclusions

This retrospective study suggests that the CIM approach may be a feasible strategy to improve the QoL of cancer patients as well as reduce toxicities and fatigue during or after ACTs regardless of both the type of cancer and the disease stage. A key element that emerged from this study was the multidisciplinary assessment carried out for each patient to select the most appropriate CIM treatment, and the presence of health professionals trained in CIM. The feasibility of a CIM approach to cancer care and the QoL of chronic

and non-chronic cancer patients are the focuses of this study, but we also considered EU recommendations that emphasize the importance of developing an evidence-based, integrative, and patient-centered approach and, where appropriate, promoting the CIM under the supervision of health professionals [8]. Furthermore, to our knowledge, this is the first manuscript to describe a CIM strategy based primarily on a micotherapy approach by a multidisciplinary team of physicians who are experts in this field. Further well-designed and prospective studies are needed to confirm the benefits seen in this retrospective study and to better understand the mechanisms underlying the synergism between ACTs and CIM.

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Nutritional and Biochemical Outcomes After Total Versus Subtotal Gastrectomy: Insights into Early Postoperative Prognosis

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Abstract: Gastric cancer remains a significant global health burden, with curative treatment relying on surgical resection, typically total or subtotal gastrectomy. However, the procedure frequently triggers acute metabolic and nutritional disturbances that may impact recovery. **Objective**: This prospective study aimed to investigate whether the type of gastrectomy (total vs. subtotal) influences early postoperative biochemical and hematological alterations, with particular attention to nutritional impact. **Methods**: A cohort of 295 patients (123 female, 172 male) who underwent gastrectomy for gastric cancer at the Institute of Oncology Iași (2023–2024) was evaluated. Laboratory parameters, including hemoglobin, hematocrit, lymphocyte and platelet counts, serum albumin, total protein, sodium, potassium, creatinine, and urea, were analyzed preoperatively and on postoperative day 14 using standard clinical methods. **Results**: Anemia was observed in over 90% of patients, irrespective of sex or procedure type. Electrolyte imbalances (notably hyponatremia and hypokalemia) and indicators of nutritional deficit (hypoalbuminemia, low creatinine) were highly prevalent, with a greater frequency among female patients. Total gastrectomy was associated with more severe biochemical and nutritional alterations compared to subtotal procedures. **Conclusions**: Total gastrectomy significantly exacerbates early postoperative metabolic and nutritional derangements. These findings reinforce the need for proactive, personalized postoperative nutritional and electrolyte management strategies to support recovery and reduce complication risks.

Keywords: gastric cancer (GC); gastrectomy; carcinoembryonic antigen (CEA); carbohydrate antigen 19-9 (CA19-9); prognostic factors

1. Introduction

Gastric cancer (GC) is a biologically diverse and highly aggressive malignancy, currently ranking as the fourth most common cause of cancer-related mortality worldwide. GC represents a major global health burden, with over 1 million new cases and approximately 770,000 deaths reported annually, according to GLOBOCAN 2020 data [1]. It is the fifth most commonly diagnosed cancer and the fourth leading cause of cancer-related mortality worldwide. The incidence varies by region, with the highest rates observed in East Asia, Eastern Europe, and parts of South America. Despite advancements in surgical techniques, chemotherapy, and targeted therapies, the overall prognosis for GC remains poor, particularly in patients diagnosed at advanced stages. Risk factors include Helicobacter pylori infection, dietary habits, smoking, and genetic predisposition. Multimodal approaches are now standard in locally advanced disease, but outcomes are still largely dependent on the timing of diagnosis and the physiological status of the patient [1].

In this study, we aimed to compare early postoperative biochemical and nutritional changes between total and subtotal gastrectomy in patients with gastric cancer, focusing on the acute postoperative phase (up to 14 days). The goal was to determine whether the extent of gastric resection leads to distinct metabolic and hematological alterations relevant to nutritional status, thereby supporting the need for tailored postoperative monitoring and intervention strategies.

Due to its subtle clinical presentation and frequently asymptomatic early stages, GC is often diagnosed at an advanced stage, complicating curative interventions and contributing to elevated recurrence rates and unfavorable long-term prognosis [2].

Serum tumor markers, either produced directly by tumor cells or induced in response to the presence of neoplastic tissue, serve as valuable indicators of tumor burden and biological behavior [3]. These biomarkers have been widely employed in GC for early detection, monitoring for recurrence after curative resection, and assessing prognosis [4].

Among the most studied biomarkers, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) have been proposed as potential prognostic indicators in GC [5–7].

Tumor markers reflect underlying genetic, molecular, and cellular changes driven by malignancy, and they are widely used not only for diagnostic purposes but also for disease surveillance and evaluation of treatment efficacy [4,8,9].

Malnutrition is a common and clinically relevant concern among patients with gastric cancer, affecting up to 80% of cases at various disease stages. This condition arises from a combination of reduced oral intake due to tumor location and dysphagia, increased catabolism driven by systemic inflammation, and side effects of treatments such as chemotherapy or surgery. Malnourished patients are at greater risk for postoperative complications, including impaired wound healing, infectious morbidity, and prolonged hospitalization. Several studies have also demonstrated that nutritional deficits independently predict poor long-term oncologic outcomes and decreased survival. Therefore, early recognition and correction of metabolic and nutritional imbalances are essential components of perioperative care in gastric cancer management [10,11].

The type and extent of surgical resection play a central role in determining the degree of postoperative metabolic stress and nutritional compromise. Total gastrectomy, which entails the complete removal of the stomach, results in the loss of gastric reservoir function, intrinsic factor secretion, and critical hormones involved in appetite and digestion. These physiological losses contribute to significant postoperative challenges, including malabsorption, rapid weight loss, anemia, and hypoalbuminemia. In contrast, subtotal gastrectomy typically preserves more digestive capacity, leading to relatively less severe disturbances. The degree of postoperative nutritional impairment is thus closely linked

to surgical extent, making it essential to evaluate these changes in relation to the surgical approach [12,13].

Although the long-term nutritional and metabolic consequences of gastrectomy have been widely studied, limited data exist regarding the acute-phase biochemical alterations occurring in the first two postoperative weeks. Most existing studies focus on survival or complication rates but do not systematically analyze how early postoperative laboratory profiles evolve depending on the type of surgery. This gap in knowledge limits our ability to implement early, targeted nutritional interventions. By comparing total and subtotal gastrectomy outcomes in a prospective design, the current study aims to identify short-term hematological and biochemical patterns with potential prognostic significance and to support the development of more personalized postoperative care strategies [14].

2. Materials and Methods

In this study, we conducted a comprehensive analysis of the longitudinal evolution of key biochemical and hematological parameters in a cohort of patients who underwent total gastrectomy (TG) and subtotal gastrectomy (STG) (n = 295).

The patients were selected over the last two years (2023–2024) and were monitored at the Institute of Oncology Iași, where the surgical intervention was also performed. The diagnosis of gastric cancer was histologically confirmed by endoscopic biopsy. Tumor staging was performed using contrast-enhanced thoraco-abdominal computed tomography (CT), which enabled precise assessment of tumor location, depth of invasion, and regional lymph node involvement. All cases were reviewed in a multidisciplinary tumor board composed of surgeons, oncologists, radiologists, and nutritionists to determine the optimal therapeutic strategy. Only patients who were eligible for curative resection and did not receive neoadjuvant chemotherapy were included in order to avoid confounding the postoperative biochemical and nutritional data under analysis. Candidates for upfront surgery were selected based on clinical stage T1–T3N0–N1 without evidence of distant metastasis, good performance status (ECOG 0–1), and absence of major comorbidities that would contraindicate immediate surgical intervention. The type of gastrectomy was selected in accordance with established surgical guidelines, based primarily on preoperative tumor location, extent of local invasion, and oncologic safety margins. Tumor localization was determined preoperatively through upper gastrointestinal endoscopy and CT imaging. Accordingly, total gastrectomy (TG) was indicated for proximally located or diffusely infiltrative tumors, while subtotal gastrectomy (STG) was performed for tumors confined to the distal part of the stomach (Table 1) [15,16].

Postoperative follow-up included histopathological evaluation of the resected specimens, with full pTNM staging, assessment of tumor differentiation, and identification of lymphovascular or perineural invasion. Based on these findings and in accordance with international guidelines (ESMO, NCCN), patients presenting with stage II or III disease, nodal involvement, or other high-risk pathological features were recommended for adjuvant chemotherapy [15,17]. These decisions were made by a multidisciplinary tumor board, and eligible patients were referred to oncology for individualized treatment planning. Patients undergoing adjuvant therapy were further monitored by oncologists through a structured follow-up protocol that included periodic clinical evaluations, laboratory tests, nutritional status monitoring, imaging (such as contrast-enhanced CT every 6 months), and tumor marker assessments (CEA and CA 19-9) to ensure oncologic control.

Table 1. Demographic and clinical characteristics of the study population (mean and percentage distribution). STG, subtotal gastrectomy; TG, total gastrectomy.

		Sex	Living Environment	Type of Resection	Number of Positive Lymph Nodes	Local Invasion	Age
	Description	295	295	295	295	295	295
Mean		0.59	0.56	0.5	8.3	0.5	64.9
Standard Deviation		0.5	0.4	0.5	11.6	0.4	10.4
Description	Feminine Rural areas STG-Distal location No invasion	123 (41.7%)	131 (44.4%)	145 (49.2%)		133 (45.1%)	
	Masculine Urban areas TG- Proximal location invasion	172 (58.3%)	164 (55.6%)	150 (50.8%)		162 (54.9%)	
Classification	Tubular Adenocarcinoma				123 (41.7%)		
	Papillary Adenocarcinoma				34 (11.5%)		
	Mucinous Adenocarcinoma				28 (9.5%)		
	Signet-Ring Cell Adenocarcinoma				23 (7.8%)		
	Mixed-Type Adenocarcinoma				87 (29.5%)		

The primary focus of the study was to assess the impact of the surgical technique, TG versus STG, on postoperative biochemical and hematological parameters. Lymph node status and local tumor invasion were taken into account when determining the type of surgical intervention, in accordance with oncological practice. These factors were not directly analyzed in the scope of this study. This analysis aims to contribute to a better understanding of the physiological response following different extents of gastric resection, supporting more informed perioperative management.

Histopathological analysis was based on the World Health Organization (WHO) classification of gastric adenocarcinoma, which defines the following subtypes, each influencing surgical approach and prognosis:

Tubular Adenocarcinoma: Well-organized glandular structures, varying differentiation (G1–G3), influencing the extent of lymph node dissection and resection margins.

Papillary Adenocarcinoma: Papillary projections into the lumen are often associated with higher lymphatic invasion, necessitating more extensive lymphadenectomy.

Mucinous Adenocarcinoma: $\geq$50% extracellular mucus, correlated with poor prognosis and peritoneal dissemination, frequently requiring TG.

Signet-Ring Cell Adenocarcinoma: Characterized by poorly cohesive tumor cells, early peritoneal spread, and diffuse invasion, often necessitating TG with D2 lymphadenectomy.

Mixed-Type Adenocarcinoma: Combination of intestinal and diffuse components, influencing the choice between subtotal or TG based on the dominant histological pattern. Globally, tubular adenocarcinoma accounts for approximately 40–50% of gastric cancer cases, papillary adenocarcinoma for 5–10%, mucinous adenocarcinoma for 3–7%, signet-

ring cell carcinoma for 15–25%, and mixed-type adenocarcinoma for 10–15%, according to WHO classifications and large-scale histopathological studies [18–21].

By establishing these associations, this section aims to clarify how tumor burden, lymph node metastasis, and histopathological characteristics guide the selection of the most indicated surgical approach, ultimately influencing patient outcomes and recurrence risks.

The analysis of surgical type according to gender showed that among female patients (n = 122), 65 underwent STG (53.3%) and 57 TG (46.7%), whereas among male patients (n = 172), 80 underwent STG (46.5%) and 92 TG (53.5%). This indicates a slightly higher tendency towards TG among male patients compared to female patients.

2.1. Baseline and Postoperative Dynamics of Biochemical and Nutritional Markers in GC Surgery

Peripheral blood samples were taken before surgical intervention and two weeks postoperatively under rigorous and standardized conditions to ensure the uniformity and accuracy of the results. Sampling was performed preoperatively after a minimum fasting period of 8 h to minimize external influences on metabolic and nutritional parameters. The collection took place 24 h before the surgical intervention, a time point deemed optimal for capturing the patients' baseline biochemical and hematological status. All procedures adhered to good laboratory practice guidelines, utilizing sterile materials and standardized techniques to prevent contamination or sample degradation.

2.2. Evaluation of Biochemical Profiles

The analysis encompassed a comprehensive panel of biochemical and hematological parameters, selected to provide an in-depth evaluation of the patient's metabolic and nutritional status. Among the assessed markers were serum albumin, prealbumin, sodium, potassium, creatinine, urea, hemoglobin, hematocrit, lymphocytes, and platelets. These parameters were chosen for their relevance in assessing nutritional status, systemic inflammatory response, renal function, hematological balance, and tumor burden (Table 2).

Table 2. Baseline normative data for biochemical and hematological markers. ALB, serum albumin; Creat, creatinine; HB, hemoglobin; HT, hematocrit; K, potassium; Ly, lymphocytes; Na, sodium; PLT, platelets; PT, proteins; WBC, white blood count.

Test Name	Reference Range
PLT	150,000–400,000 cellule/μL
Ly	1000–4800 cellule/μL
HB	F: 12–16/M: 13–17 g/dL
PT	6.4–8.3 g/dL
WBC	4000–10,000 cellule/μL
Creat	F: 0.6–1.1/M: 0.7–1.3 mg/dL
HT	F: 36–46/M: 40–50%
K	3.5–5.1 mmol/L
Urea	10–50 mg/dL
Na	135–145 mmol/L
ALB	3.5–5.0 g/dL

Data distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. None of the biochemical parameters followed a normal distribution. To compare the two surgical groups (TG vs. STG), the Mann–Whitney U test was used for nonparametric variables, including biochemical markers, tumor markers, and nutritional parameters, both

preoperatively and at 14-day follow-up. Statistical analyses were performed using SPSS version 26.0, with a significance level set at $p < 0.05$. The results highlight the relevance of integrating oncological and biochemical evaluations in selecting the optimal surgical approach and improving perioperative patient care.

3. Results

3.1. Patient Characteristics

In this study, we analyzed a cohort of $n = 295$ patients who underwent TG or STG at the Institute of Oncology Iași during 2023–2024. The demographic characteristics of the study population provide valuable insights into the patient profile and potential influencing factors. The mean age of the patients was 64.96 years (±10.45 SD), with a median age of 66 years and an age range between 31 and 85 years, suggesting that GC predominantly affects elderly individuals, consistent with existing epidemiological data (Figure 1). Regarding sex distribution, 59% of the patients were male ($n = 174$) and 41% were female ($n = 121$), reaffirming the higher prevalence of GC in men. Concerning the living environment, 56% of the patients ($n = 164$) resided in urban areas, while 44% ($n = 131$) were from rural regions, indicating a relatively balanced distribution between urban and rural settings.

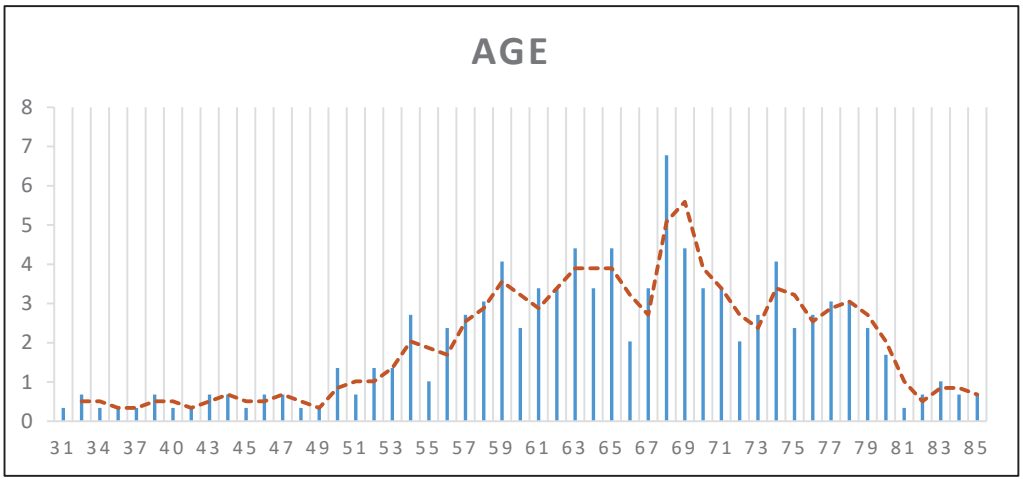

Figure 1. Age distribution of the study population.

In this study, we aimed to evaluate the clinicopathological and biochemical determinants influencing the extent of gastrectomy, comparing TG, $n = 150$ and STG, $n = 145$ in a cohort of $n = 295$ patients.

The primary objective of this study was to analyze the biochemical and hematological changes associated with two types of surgical intervention for GC, in accordance with current clinical guidelines. Surgical approach was selected based on established oncological criteria, including lymph node involvement, histopathological tumor grading according to WHO classification, and the presence of loco-regional invasion. Understanding how surgical extent influences physiological responses is essential for optimizing perioperative management and improving patient outcomes.

Regarding local invasion, the cohort was composed of two distinct subgroups: 133 patients (45.1%) showed no evidence of loco-regional tumor infiltration, while 162 patients (54.9%) presented with confirmed local invasion at diagnosis. This distribution suggests a slight predominance of invasive cases, supporting the advanced presentation commonly observed in GC.

For the number of positive lymph nodes, values ranged broadly from 0 to 67, indicating considerable variability in nodal involvement. A substantial portion of patients (25.8%) had

no lymph node metastases, while the remaining exhibited varying degrees of lymphatic dissemination. Although most patients clustered in the lower range (1–10 positive nodes), a smaller subgroup displayed extensive nodal spread, with values exceeding 30 in a few cases, highlighting the biological heterogeneity of GC and its diverse metastatic potential.

To assess differences between the two groups, a Mann-Whitney U test was performed for each variable. The analysis revealed that the number of positive lymph nodes ($p = 0.01$) and loco-regional invasion ($p = 0.001$) demonstrated statistically significant differences between patients undergoing TG versus STG. Patients with a higher burden of lymphatic metastases and extensive local invasion were significantly more likely to undergo TG, reinforcing the idea that tumor dissemination plays a pivotal role in the extent of surgical resection. The mean rank for positive lymph nodes was (M = 135.3) in the STG group and (M = 160.2) in the TG group, indicating a higher metastatic burden in patients requiring more extensive resection. Similarly, patients presenting with local tumor invasion were more frequently associated with TG. The mean rank in the TG group was 161.40, compared to 134.14 in the subtotal group, indicating a greater burden of loco-regional disease in those requiring a more extensive surgical approach. The statistical analysis yielded a Mann-Whitney U value of 8.86 and a *p*-value of 0.001, confirming a highly significant difference between the two groups. This reinforces the clinical observation that local invasion serves as a critical criterion in determining the extent of gastric resection, supporting TG as the preferred intervention.

Regarding histopathological tumor grading, based on the WHO classification, it revealed a varied distribution of adenocarcinoma subtypes. Tubular adenocarcinoma represented the largest group ($n = 123$, 41.7%), followed by papillary adenocarcinoma ($n = 34$, 11.5%), mucinous adenocarcinoma ($n = 28$, 9.5%), signet-ring cell adenocarcinoma ($n = 87$, 29.5%), and mixed-type adenocarcinoma ($n = 23$, 7.8%). The variability in these histopathological subtypes highlights the heterogeneity of GC within the studied cohort.

The results ($p = 0.09$) indicated a trend toward a greater prevalence of poorly differentiated tumors in the TG group, although the difference did not reach statistical significance. The grading system included subtypes such as tubular, papillary, mucinous, signet-ring cell adenocarcinomas, and mixed, each with varying degrees of differentiation and biological aggressiveness. While poorly differentiated tumors were more frequently observed in patients undergoing TG, the lack of statistical significance suggests that grading alone is not the primary determinant in surgical decision-making, but rather, it acts as a secondary factor in conjunction with lymph node metastasis and locoregional invasion.

Although both CEA and CA19-9 levels remained above the reference range, the continued decline observed indicates the absence of early recurrence and potential prognostic value in postoperative monitoring. These results reinforce the importance of serial measurements over time, rather than relying on single preoperative values, and support their role in postoperative surveillance as recommended by current oncologic guidelines.

3.2. Comparative Analysis of Biochemical Parameteres at Baseline and Follow-Up

Prior to surgical intervention, a baseline panel of biochemical, hematological, and nutritional parameters was obtained for all patients. These preoperative measurements revealed values largely within normal reference ranges across both STG and TG groups. No statistically or clinically significant differences were observed between the two groups at this stage, indicating a comparable physiological and nutritional status prior to surgery. This uniformity supports the premise that any subsequent metabolic or hematological alterations observed postoperatively can be attributed primarily to the type and extent of surgical intervention rather than pre-existing disparities. A summary of the preoperative values is provided in Tables 3 and 4.

Table 3. Descriptive statistics (mean) for biochemical parameters in patients undergoing STG preoperatively, $n = 145$, $p > 0.05$. ALB, serum albumin; Creat, creatinine; HB, hemoglobin; HT, hematocrit; K, potassium; Ly, lymphocytes; Na, sodium; PLT, platelets; PNI, prognostic nutritional index; PT, proteins; WBC, white blood count.

Subtotal Gastrectomy												
	PLT	**Ly**	**HB**	**PT**	**WBC**	**Creat**	**HT**	**K**	**Urea**	**Na**	**PNI**	**ALB**
Mean	325.4 ± 1.24	2.018 ± 0.98	13.6 ± 1.13	53.75 ± 0.89	7.2 ± 1.05	0.82 ± 1.31	43.02 ± 1.17	3.97 ± 0.94	27.38 ± 1.22	137.5 ± 1.08	49.75 ± 2.32	4.36 ± 1.15

Table 4. Descriptive statistics (mean) for biochemical parameters in patients undergoing TG preoperative baseline values $n = 150$, $p > 0.05$. ALB, serum albumin; Creat, creatinine; HB, hemoglobin; HT, hematocrit; K, potassium; Ly, lymphocytes; Na, sodium; PLT, platelets; PNI, prognostic nutritional index; PT, proteins; WBC, white blood count.

Total Gastrectomy												
	PLT	**Ly**	**HB**	**PT**	**WBC**	**Creat**	**HT**	**K**	**Urea**	**Na**	**PNI**	**ALB**
Mean	310.4 ± 0.87	1.814 ± 1.02	13.4 ± 0.95	55.5 ± 1.1	8.8 ± 0.93	0.8 ± 1.09	42.9 ± 2.4	3.8 ± 1.3	28.3 ± 1.7	138.4 ± 1.12	53.5 ± 0.78	4.4 ± 1.12

The postoperative dataset used in this study was collected on postoperative day 14, representing the most comprehensive and consistent time point for which laboratory data were available across the entire patient cohort. This early postoperative window was selected to capture acute physiological responses to STG and TG, including changes in hematologic profiles, electrolyte balance, protein metabolism, and nutritional indicators. Although longer-term follow-up measurements would offer greater insight into recovery patterns and sustained outcomes, such data were not uniformly available. Therefore, the analysis focused on this standardized early time point to allow for consistent intergroup comparison and to identify early postoperative trends associated with each surgical technique.

The presence of such hematological impairments highlights the increased risk of anemia following TG, likely due to more extensive blood loss, reduced iron absorption, and diminished intrinsic factor production affecting vitamin B12 metabolism. Significant differences were identified in electrolyte levels, with sodium ($p = 0.005$) and potassium ($p = 0.02$) being more affected in TG patients. These alterations may reflect postoperative fluid imbalances, altered renal excretion, and the physiological adaptations to total loss of gastric function, increasing the likelihood of electrolyte disturbances requiring close postoperative monitoring (Tables 5 and 6) (Figures 2 and 3).

Table 5. Descriptive statistics for biochemical parameters in patients undergoing STG, post-operative baseline values $n = 145$. ALB, serum albumin; Creat, creatinine; HB, hemoglobin; HT, hematocrit; K, potassium; Ly, lymphocytes; Na, sodium; PLT, platelets; PNI, prognostic nutritional index; PT, proteins; WBC, white blood count.

Subtotal Gastrectomy												
	PLT	**Ly**	**HB**	**PT**	**WBC**	**Creat**	**HT**	**K**	**Urea**	**Na**	**PNI**	**ALB**
Mean	333.3 ± 9.4	2.112 ± 134.3	10.4 ± 0.2	43.4 ± 2.4	8.72 ± 0.7	0.89 ± 0.02	32.7 ± 0.6	4.2 ± 0.03	40.3 ± 1.19	138.6 ± 0.34	48.2 ± 0.99	3.9 ± 0.05
p	0.05	0.3	0.01	0.2	0.2	0.1	0.02	0.02	0.3	0.005	0.1	0.1

Table 6. Descriptive statistics for biochemical parameters in patients undergoing TG, postoperative baseline values $n = 150$. ALB, serum albumin; Creat, creatinine; HB, hemoglobin; HT, hematocrit; K, potassium; Ly, lymphocytes; Na, sodium; PLT, platelets; PNI, prognostic nutritional index; PT, proteins; WBC, white blood count.

	Total Gastrectomy											
	PLT	**Ly**	**HB**	**PT**	**WBC**	**Creat**	**HT**	**K**	**Urea**	**Na**	**PNI**	**ALB**
Mean	308.01 ± 9.1	1.962 ± 86.4	11.2 ± 0.19	47.4 ± 2.4	10.1 ± 1.12	0.9 ± 0.05	34.4 ± 0.49	4.3 ± 0.03	38.6 ± 1.17	139.9 ± 0.28	50.01 ± 0.85	4.07 ± 0.049
p	0.05	0.3	0.01	0.2	0.2	0.1	0.02	0.02	0.3	0.005	0.1	0.1

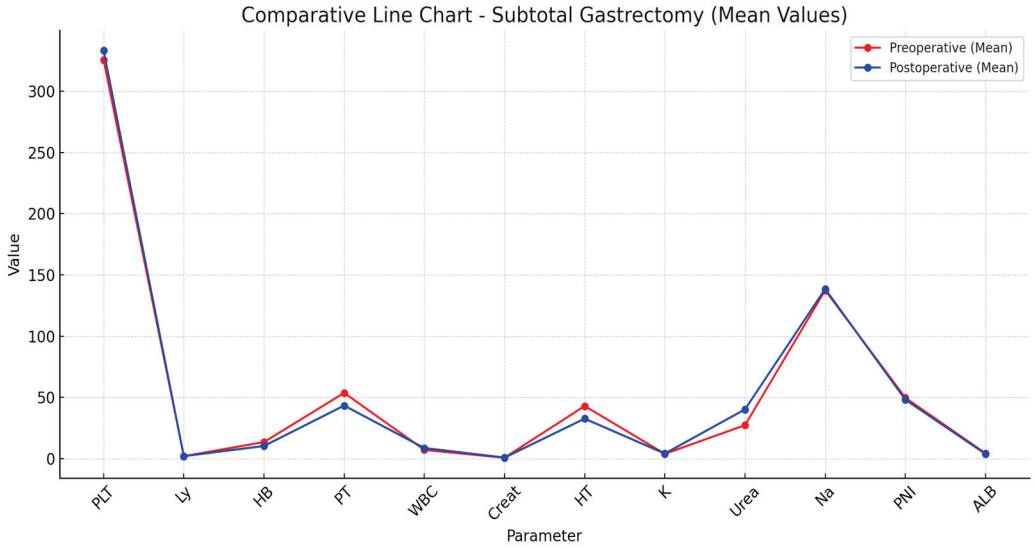

Figure 2. Comparative line chart. Subtotal Gastrectomy: ALB, serum albumin; Creat, creatinine; HB, hemoglobin; HT, hematocrit; K, potassium; Ly, lymphocytes; Na, sodium; PLT, platelets; PNI, prognostic nutritional index; PT, proteins; WBC, white blood count.

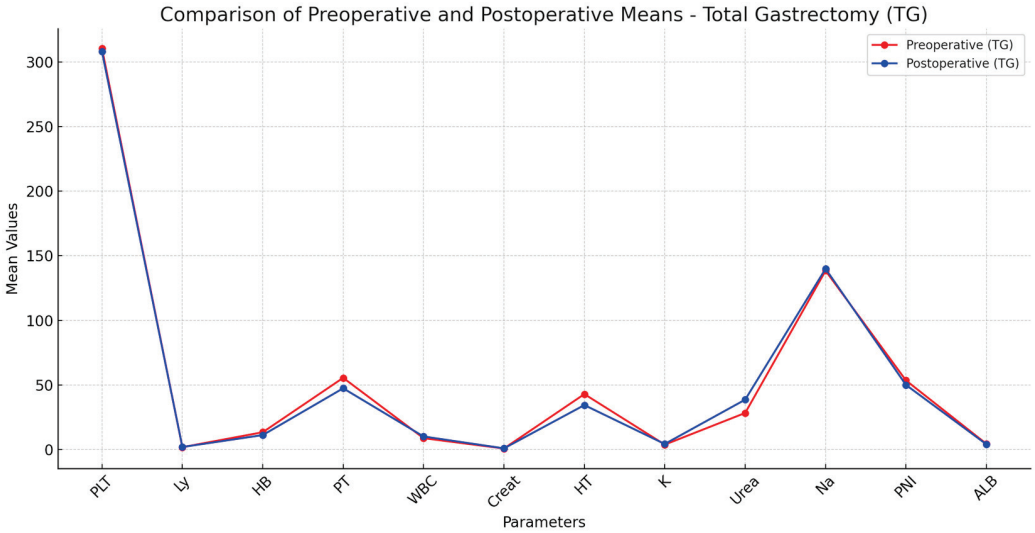

Figure 3. Comparative line chart. Total Gastrectomy: ALB, serum albumin; Creat, creatinine; HB, hemoglobin; HT, hematocrit; K, potassium; Ly, lymphocytes; Na, sodium; PLT, platelets; PNI, prognostic nutritional index; PT, proteins; TG, total gastrectomy; WBC, white blood count.

Beyond these statistically significant findings, trends were also noted in platelet count and protein metabolism. The mean platelet count was lower in TG patients ($p = 0.05$), suggesting a possible association with thrombocytopenia, though not reaching statistical significance. Additionally, albumin ($p = 0.1$) and total protein ($p = 0.2$) levels tended to show more depletion in TG patients, reinforcing the known risk of protein-energy malnutrition following total gastric resection.

The observed decrease in albumin may be attributed to impaired protein digestion and absorption, which are exacerbated by the complete removal of the stomach and subsequent malabsorption of essential nutrients. A similar trend was observed in the prognostic nutritional index (PNI), which showed lower values in TG ($p = 0.1$), suggesting a greater nutritional burden postoperatively. While these findings were not statistically significant, they highlight the clinical relevance of nutritional interventions in TG patients.

Conversely, renal function markers such as creatinine ($p = 0.1$) and urea ($p = 0.3$) showed no significant differences between groups, indicating that, despite altered protein metabolism, renal impairment was not a distinguishing factor between TG and STG.

The comparative analysis between total and STG groups revealed significant differences in key hematological and biochemical parameters, reflecting the physiological burden associated with more extensive surgical resection. Patients undergoing TG demonstrated significantly lower hemoglobin and hematocrit levels ($p = 0.01$), as well as reduced platelet counts ($p = 0.01$), indicating a more pronounced hematologic impact. Additionally, electrolyte imbalances were more evident in the TG group, with sodium ($p = 0.008$) and potassium ($p = 0.01$) levels significantly lower compared to those who underwent subtotal resection, suggesting a heightened risk of fluid and electrolyte disturbances in this study. Although renal function markers such as creatinine and urea showed no statistically significant differences ($p > 0.05$), their variability highlights the potential influence of individual metabolic responses. Nutritional indicators, including serum albumin and the PNI, were also lower in the TG group, though without statistical significance ($p > 0.05$). These findings collectively underscore the greater metabolic and hematologic vulnerability of patients undergoing TG and support the implementation of tailored postoperative monitoring and early nutritional intervention in this group (Table 7) (Figure 4).

Table 7. Comparative Descriptive Statistics of Biochemical Parameters in Patients Undergoing TG versus STG ($n = 295$). ALB, serum albumin; Creat, creatinine; HB, hemoglobin; HT, hematocrit; K, potassium; Ly, lymphocytes; Na, sodium; PLT, platelets; PNI, prognostic nutritional index; PT, proteins; STG, subtotal gastrectomy; TG, total gastrectomy; WBC, white blood count.

Subtotal Gastrectomy vs. Total Gastrectomy												
	PLT	**Ly**	**HB**	**PT**	**WBC**	**Creat**	**HT**	**K**	**Urea**	**Na**	**PNI**	**ALB**
Mean STG	160.2	153.17	140.57	144.42	164.61	146.75	142.97	135.28	150.92	134.97	143.76	142.81
Mean TG	135.72	142.8	155.48	151.61	131.28	139.25	153.06	160.8	145.06	161.12	152.27	153.23
Mann Whitney U	9.073	10.113	9.779	10.348	8.419	9.978	10.134	8.996	10.445	8.948	10.250	10.109
p	0.01	0.2	0.01	0.4	0.001	0.1	0.01	0.01	0.3	0.008	0.3	0.2

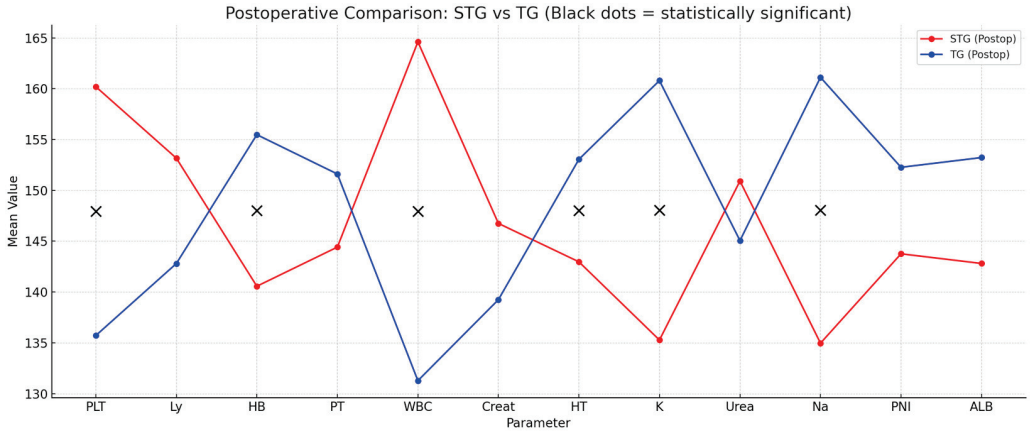

Figure 4. Postoperative comparison STG vs. TG: ALB, serum albumin; Creat, creatinine; HB, hemoglobin; HT, hematocrit; K, potassium; Ly, lymphocytes; Na, sodium; PLT, platelets; PNI, prognostic nutritional index; PT, proteins; STG, subtotal gastrectomy; TG, total gastrectomy; WBC, white blood count; X symbol indicates statistical significance.

4. Discussion

Gastrectomy, whether total or subtotal, is a fundamental surgical intervention for the management of GC, particularly in cases of locally advanced disease. This procedure induces significant physiological alterations in the digestive system, often resulting in severe malnutrition due to anatomical and functional changes that adversely affect dietary intake, digestion, and nutrient absorption.

GC remains a highly aggressive and biologically diverse malignancy, with considerable variability in prognosis even within the same clinical stage. This heterogeneity underscores the need for personalized surgical strategies and accurate risk stratification [22].

The ongoing debate between subtotal and TG, particularly in distal GC, highlights the importance of balancing oncological radicality with surgical safety. Although TG is often perceived as more extensive, it may be associated with higher perioperative risk without necessarily offering superior long-term survival. In cases where oncologic outcomes are comparable, the surgical approach associated with lower morbidity may be preferable [23].

Given the high prevalence and aggressive nature of GC, current research highlights the pivotal role of surgery, especially gastrectomy, as the primary curative strategy for patients with advanced localized disease. However, the profound metabolic and nutritional implications of this intervention necessitate comprehensive perioperative management. The present study evaluated the clinical and biochemical factors associated with the extent of surgical resection in patients diagnosed with GC. Our findings underscore the critical role of nodal metastasis and locoregional tumor invasion in surgical decision-making. Specifically, the number of positive lymph nodes and the presence of local invasion emerged as the most robust predictive indicators for selecting TG, aligning with the findings of previous studies that emphasized the oncological burden as a central determinant of surgical extent [24,25]. Tumor markers such as CEA and CA 19-9 were measured postoperatively; however, their inclusion in the primary analysis was avoided, as the timing of assessment, only 14 days after surgery, was considered too early to yield clinically meaningful insights. While a decrease in marker levels was noted in some patients, the variation lacked statistical significance and was not sufficient to support robust conclusions regarding short-term treatment response or recurrence risk. Similar variability in the prognostic utility of these markers across different patient subgroups and tumor stages was also reported by Zhou et al. (2015) [26]. Although serum levels of CA19-9 and CEA are frequently elevated in gastrointestinal malignancies and have been correlated with tumor burden, their role as standalone determinants in preoperative decision-making remains limited [27,28]. There-

fore, while included in our analysis for exploratory purposes, these markers should be interpreted with caution and integrated within a broader oncologic and clinical assessment.

The evaluation of biochemical and hematological parameters in patients undergoing GC surgery provided a valuable overview of their preoperative physiological status. This allowed for the early detection of nutritional deficiencies and inflammatory risk factors, which can be proactively addressed through tailored perioperative interventions. The preoperative data also served as a reliable baseline for assessing the physiological impact of surgical resection, supporting a more informed and individualized patient management strategy. Postoperative analysis revealed significant alterations in key metabolic indicators, particularly in patients undergoing TG. The loss of gastric secretory function was associated with notable disruptions in fluid and electrolyte homeostasis, including hyponatremia and hypokalemia, which may predispose patients to renal dysfunction and delayed recovery. These imbalances, along with hypoalbuminemia and hematological shifts, were found to adversely affect clinical trajectory. Understanding and addressing these metabolic consequences is essential for optimizing perioperative care, reducing morbidity, and improving long-term outcomes in GC patients.

Nutritional support during the 14-day postoperative period was delivered on an individual basis rather than through a formal protocol, but under the supervision of a clinical nutritionist. Electrolyte disturbances, most frequently hypokalemia, were corrected promptly with intravenous potassium replacement; mild to moderate hyponatremia received intravenous isotonic saline (0.9% sodium chloride solution) as part of fluid and electrolyte management, based on individual clinical and laboratory findings; and patients who exhibited clinically relevant hypoalbuminemia received targeted protein supplementation with human serum albumin solutions. These interventions were guided by daily laboratory monitoring and physician judgement, ensuring that overt ionic or protein deficits were addressed before discharge.

The analysis demonstrated distinct hematological and biochemical alterations associated with the extent of gastric resection, suggesting a more significant physiological burden in patients undergoing TG. Lower postoperative levels of hemoglobin, hematocrit, and platelet count in this group may reflect a more profound impact on hematopoietic balance and perioperative hemodynamics. Moreover, the observed disturbances in serum sodium and potassium levels indicate a disruption in electrolyte homeostasis, likely secondary to the loss of gastric regulatory functions and changes in fluid distribution following complete gastric removal. Although renal function markers remained within comparable ranges, interindividual variability suggests differences in metabolic adaptation and renal reserve. From a nutritional standpoint, the downward trends in serum albumin and prognostic nutritional index among patients with TG highlight an increased vulnerability to protein-energy depletion, even in the absence of overt clinical signs. These findings emphasize the need for proactive metabolic surveillance and early nutritional support strategies, particularly in patients undergoing more extensive resections, to mitigate the risk of postoperative complications and support optimal recovery.

Surgical trauma, particularly in oncologic procedures, induces significant immunological changes that can influence both short- and long-term outcomes. It is well-established that white blood cell (WBC) subsets undergo dynamic changes in peripheral blood following major surgery due to factors such as neutrophil survival and lymphocyte apoptosis. These changes, which reflect the patient's immunologic status, are modulated by surgical stress, psychological factors, and tumor burden and have been proposed as prognostic markers in cancer populations. Given that cancer patients may already present with an altered immune profile, the immunosuppressive effect of surgery may further increase the risk of tumor progression or metastasis if immune competence is not restored promptly.

Thus, understanding perioperative immune dynamics is essential, especially in the context of patient-specific variables such as sex [29–31].

While our study did not reveal statistically significant differences in biochemical or hematological markers between male and female patients, emerging evidence suggests that gender-related immunological responses to surgical stress do exist and may be clinically relevant. A study by Mi Sook Gwak et al. (2007) [32] found that female patients exhibited a more immunocompromised profile of WBC subsets in peripheral blood in the early postoperative period after gastrectomy for gastric cancer. The authors concluded that these transient immune differences may influence long-term outcomes, including tumor recurrence, and emphasized the need for further investigation. These findings, while not replicated in our dataset, highlight the possibility of subtle, sex-specific immune perturbations that may not be apparent in standard laboratory parameters but could manifest in functional immune shifts or clinical outcomes over time [32].

Sex-related differences in immune response may, in part, be mediated by hormonal influences. Testosterone and progesterone are generally associated with anti-inflammatory responses, whereas estrogen has a more complex role, exhibiting either pro- or anti-inflammatory effects depending on its concentration and the tissue microenvironment. Although these mechanisms were not directly assessed in our study, they offer a plausible biological explanation for the sex-related immune variability reported in the literature [33].

Our findings further highlight the increased biological burden associated with TG. Comparative analysis of biochemical parameters between patients undergoing total versus STG revealed significant postoperative differences in hemoglobin, hematocrit, sodium, and potassium levels, indicating a greater risk of anemia and electrolyte imbalance in the TG group. This observation is clinically relevant, as it underscores the necessity for intensified monitoring and proactive supportive care in patients subjected to more extensive resections. While the biochemical and hematological data analyzed in this study were collected during the early postoperative period, they were used to assess the immediate physiological impact of subtotal versus TG. This timeframe was selected to capture acute metabolic and nutritional alterations attributable to surgical stress, extent of resection, and early postoperative adaptation.

The previous literature supports the need for a nuanced approach to surgical planning in GC. Palaj et al. (2021) [24] emphasized that while STG may be the preferred approach for middle and distal-third tumors due to similar survival rates and lower complication risks, TG continues to be widely practiced, particularly in high-volume Western centers [24,34].

In parallel, there is a growing recognition of the prognostic value of hematological parameters in GC. Recent studies, such as the one by Feng et al. (2018), have demonstrated that low lymphocyte counts and high monocyte counts are associated with poorer outcomes in GC, with lymphocyte levels emerging as independent prognostic markers [35]. These findings resonate with our results, particularly in relation to lymphocyte and platelet-to-lymphocyte ratio (PLR), further supporting the utility of these inexpensive and accessible parameters in clinical risk stratification.

This study was designed to explore acute postoperative changes in biochemical and hematological parameters, with follow-up limited to the first 14 days after surgery. The rationale behind this approach was to isolate and examine the physiological impact of the type of gastrectomy performed, independent of each patient's preexisting metabolic or nutritional status. By comparing postoperative outcomes between STG and TG groups at a fixed time point, we aimed to highlight interventional differences in nutritional burden and systemic recovery. This strategy allows for a clearer evaluation of how surgical extent alone influences early postoperative nutritional status, hematologic parameters, and metabolic stability, without the confounding effect of variable baseline conditions. Emphasis was

placed particularly on the PNI, albumin levels, and electrolyte disturbances, as these are clinically relevant indicators of postoperative nutritional risk and are known to correlate with recovery trajectories and complication rates. While individual trajectories may provide valuable insight in longitudinal studies, our primary aim was to delineate the early impact of surgical strategy on systemic physiology, thus justifying the choice of a cross-sectional comparative model.

Although patients are, in theory, enrolled in outpatient surveillance following discharge, structured long-term follow-up beyond the hospital stay (e.g., at one or three months) was not included in the present study design, as a proportion of patients underwent adjuvant therapy after surgery, which could significantly alter hematological and biochemical profiles. To avoid such confounding factors, we chose to focus exclusively on the acute postoperative period in order to assess the direct impact of the surgical intervention on metabolic and nutritional parameters. We acknowledge this as a limitation, as the long-term trajectory of these early biochemical alterations remains unknown. Future prospective studies should incorporate extended follow-up periods in order to assess whether such disturbances persist, resolve, or worsen over time, and to enable a more robust correlation between early laboratory findings and long-term clinical outcomes.

5. Conclusions

The findings of this study demonstrate that the extent of gastric resection has a measurable impact on early postoperative biochemical and hematological profiles, with TG patients exhibiting more significant disturbances in hemoglobin, hematocrit, white blood cells, platelets, sodium, and potassium levels. These differences reflect a higher metabolic burden and increased risk of early postoperative complications in this group. The observed trends in albumin and protein levels, though not always statistically significant, further emphasize the need for vigilant nutritional and biochemical surveillance. These results support the implementation of specific postoperative care strategies, prioritizing early nutritional intervention and targeted correction of electrolyte and hematological imbalances, particularly in patients undergoing TG.

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