European Journal of Surgical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Long-term nutrition in patients candidate to neoadjuvant and adjuvant treatments

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ARTICLE INFO

Article history:
Received 21 December 2022
Accepted 14 February 2023
Available online xxx

Keywords:
Cancer
Malnutrition
Sarcopenia
Neoadjuvant
Adjuvant
Chemotherapy
Radiotherapy
Targeted therapy
Immunotherapy
Endocrine therapy

ABSTRACT

To improve outcomes, to decrease the rate of local recurrence and development of distant metastases neoadjuvant and adjuvant therapies are employed in cancer patients in forms of radiation, chemo-, endocrine-, targeted-, and immunotherapy or their combination. Nutrition therapy plays important role in all phases of the cancer journey. From neoadjuvant therapy to prehabilitation, early postoperative nutrition, and long-term nutrition care during the adjuvant phase and survivorship determines the survival and quality of life of cancer patients.

During the neoadjuvant phase patients may be in poor nutritional condition which can be aggravated by the applied oncological treatment. Beside this apparent threat this period also gives an excellent opportunity to maintain or even improve the nutritional status of the patients by nutrition therapy. After surgery the burdening effects of the operation may jeopardize the execution of adjuvant therapy. After early postoperative feeding a long-term nutrition strategy should be developed for cancer patients in order to avoid nutritional deterioration during the usually lengthy postoperative therapy.

In this narrative review we discuss how preoperative nutritional status and medical nutrition therapy influence the results of surgery and after the operation what is the available evidence about nutritional status and outcome and the potentials to influence them by nutrition therapy.

1. Introduction

Surgery is the most curative treatment modality in oncology, reflecting that complete cure still can be achieved mostly in locally or loco regionally extended disease. Still both local recurrence and the formation of distant metastasis is a challenge in many cases. To improve outcomes in patients receiving surgery, neoadjuvant, or preoperative and adjuvant or postoperative treatments both in form of radio- and medical therapy or their combination is widely applied (Table 1). Poor nutritional status is known to have deteriorating effect on all aspects of outcomes of cancer patients including survival, recurrence, side effects and quality of life. Additionally, treating malnourished cancer patients worsen cost effectiveness, too. Beside preparing the patient to surgery the course of neoadjuvant therapy may have influence of the nutritional status of the patient. A burdensome therapy especially without appropriate nutritional intervention may induce malnutrition while with careful supportive care nutritional status could be maintained or even improved during preoperative therapy. Conversely, major surgery is known to cause considerable stress to the body including systemic inflammation and a period when optimal nutrition can hardly be maintained. Appropriate nutrition maybe hampered by the direct effect of surgical procedures or even by their complications. Several methods are used to avoid unnecessary burden from surgery such as enhanced recovery after surgery (ERAS) programs. Recently, the term „prehabilitation" appeared in the literature and practice in some pioneering clinical studies where nutritional support, physical exercise and mental preparation for surgery (even in neoadjuvant setting) are joined. Finally, nutritional status of patients after surgery has a profound effect on the outcomes of an active adjuvant oncology treatment. In this review we summarize the current knowledge about nutritional status of cancer patients during neoadjuvant and adjuvant

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https://doi.org/10.1016/j.ejso.2023.02.007

Please cite this article as: J. Lovey, A. Molnar and B. Banky, Long-term nutrition in patients candidate to neoadjuvant and adjuvant treatments, European Journal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2023.02.007

Table 1
Most important tumour types where neoadjuvant and adjuvant therapies are routinely performed.

Tumour type	Neoadjuvant	Adjuvant
Head and Neck cancer	X	X
Oesophageal cancer	X	X
Gastric cancer	X	X
Colorectal cancer	X	X
Hepatobiliary cancer		X
Pancreatic cancer	X	X
NSCLC	X	X
Breast cancer	X	X
Ovarian cancer	X	X
Uterine cancer		X
Cervical cancer		X
Prostate cancer		X
Bladder cancer	X	X
Soft tissue sarcoma		X
Skin cancer/Melanoma		X
Bone tumours	X	X
CNS tumours		X

treatment and discuss how to mitigate the deleterious effect of treatments on nutritional status of cancer patients.

2. Methods

Relevant databases such as MEDLINE, Web of Science and Cochrane Central have been searched on relevant keywords: cancer, nutrition, sarcopenia, cachexia, neoadjuvant, preoperative, adjuvant, postoperative, chemotherapy, radiation therapy, hormonal therapy, immunotherapy and their variations, respectively. Three independent scientists (surgeon, oncologist, dietician) reviewed the literature and selected the best available publications to include in this review. We focused only on the adjuvant and neoadjuvant phase of cancer treatment however, it is obvious that there is no strictly defined border between neoadjuvant and preoperative prehabilitation or adjuvant and survivorship phases (Picture I).

We aimed to focus on prospective randomized trials, however there are several clinical questions where only lower-level evidence is available. Abstracts and full-length articles of publications investigating the nutritional status, functional status, body composition, quality of life and treatment outcomes, as well as nutritional interventions in adult patients during neoadjuvant and adjuvant cancer treatment have been identified. Due to the low evidence level of publications, the heterogeneity of the reports, the low number of patients in most of the individual studies it was not possible to perform a systematic review or meta-analysis, therefore the results are interpreted in the form of a narrative review.

3. Results

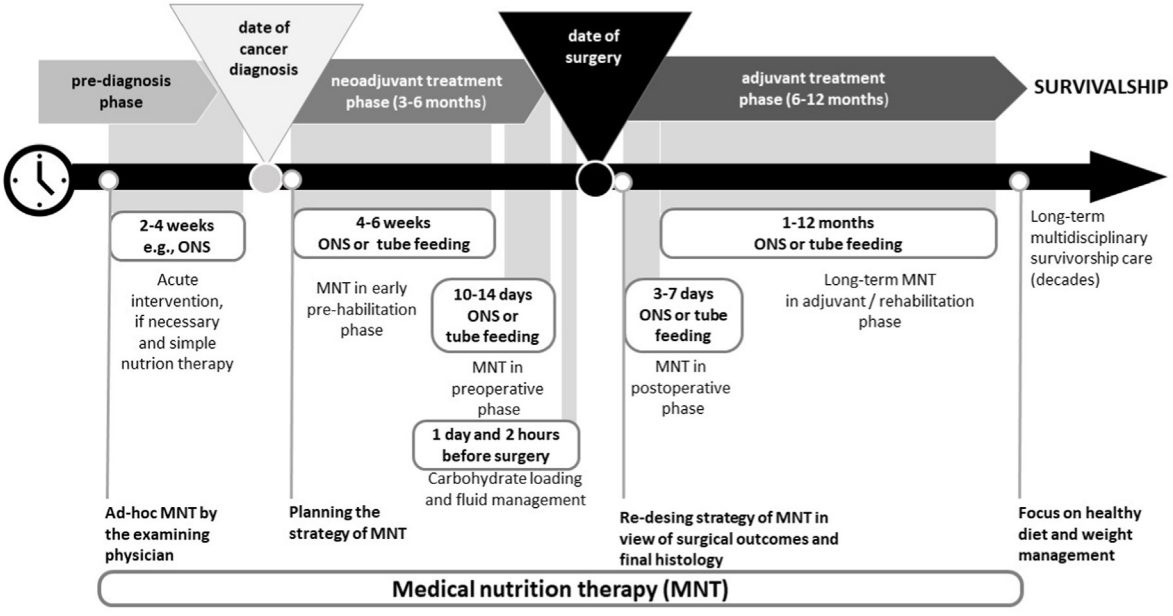
3.1. Process of nutritional interventions during neoadjuvant and adjuvant cancer therapy

Principles of medical nutrition therapy over the course of oncotherapy do not differ from the general rules of nutrition therapy. It consists of a repeated evaluation of malnutrition risk, body composition assessment, dietary counselling and oral, enteral, and rarely parenteral nutrition. Multidisciplinary management of nutritional impact syndromes is just as important as usual [1].

Impact of nutritional status of cancer patients in neoadjuvant treatment on clinical outcome.

It has long been realized that cancer patients may decline in nutritional status over the time. In terms of neoadjuvant treatment most of the literature of the last two decades still has not stepped any forth of these observational studies. Several retrospective and prospectively collected case series are available at various cancer types to underline the phenomenon of malnutrition/weight loss/sarcopenia over the course of neoadjuvant treatment, as well as their correlation with adverse outcome.

Oesophageal cancer is the most published clinical entity in this regard. Rietfeld et al. [2] found nutritional status (defined as weight loss of >5% and/or decline in fat free mass of $\geq$1.4 kg) to be deteriorating during neoadjuvant chemo-radiotherapy in as high as 49% of all patients. Interestingly, higher fat free muscle index (FFMI) was the only independent predictor of deterioration, at least in the



Picture I. Nutrition therapy and cancer patient journey.
ONS: oral nutritional supplement, MNT: medical nutrition therapy.

prospectively collected cohort of 101 patients. Guinan et al. [3] went into details of the role of skeletal muscle mass. Sarcopenia, covering both the loss of skeletal mass and loss of muscle function at the same time was assessed in a prospectively collected database of oesophageal cancer patients. On 28 cases assessed pre and post neoadjuvant treatment they found lean body mass reduced by 4.9 (95% confidence interval 3.2 to 6.7) kg and mean grip strength reduced by 4.3 (2.5–6.1) kg. This all has happened in spite of a maintained body weight. Their conclusion is that exercise and nutritional support are warranted to maintain muscle function. Yoon et al. [4] explored the loss of muscle mass in a similar condition by a machine learning model. Assessing a huge number of biological parameters, they found relative change in body mass index, albumin, prognostic nutritional index, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio over 50 days to be the best predicting factors of loss of muscle mass. The long-term effect of sarcopenia in patients receiving neoadjuvant treatment for oesophageal cancer was finally assessed in a meta-analysis by Jin et al. [5]. Preoperative sarcopenia was negatively associated with overall survival (OS). (HR = 1.290; 95% CI [1.078–1.543]; p = 0.005) and disease-free survival (DFS) (HR = 1.554; 95% CI [1.177–2.052]; p = 0.002). Huang et al. [6] in their single-centre retrospective cohort study of oesophageal cancer revealed an association between chemo-radiotherapy (CRT) related severe adverse events with mucositis, fever, and neutropenic fever and sarcopenia. Overall survival and disease-free survival were significantly better in the non-sarcopenia group. Noteworthily, sarcopenic patients who received nutritional support with enteral access had less severe mucositis. There was no difference in mortality of sarcopenia patients with nutritional support via enteral access or without. Moreover, sarcopenia and advanced tumour stage were independent factors for mortality outcome. Similarly, Jain et al. [7] found in a retrospective analysis of 125 oesophageal cancer patients, that weight loss and hypoalbuminemia occurred frequently during nCRT and were associated with multiple adverse toxicity outcomes including hematologic toxicity, non-hematologic toxicity, grade $\geq$3 toxicity. A special condition within sarcopenic patients is sarcopenic obesity. Anandavadivelan et al. [8] found sarcopenia present in 31 out of 72 prospectively followed oesophageal cancer patients (43%), while 10 (14%) were sarcopenic obese prior to chemotherapy. Sarcopenic patients (OR = 2.47; 95% CI: 0.88–6.93) showed a trend towards increased dose limiting toxicity (DLT) risk (p < 0.10), while in sarcopenic obese patients' risk of DLT increased significantly (OR = 5.54; 95% CI 1.12–27.44).

Sun et al. [9] found that pre-chemotherapy prognostic nutritional index (PNI) was significantly associated to overall survival (PNI high compared to PNI low group with a cut-off level at PNI = 45; HR = 2.237, 95% CI: 1.271–3.393, p = 0.005), while this association disappeared after chemotherapy in **advanced gastric cancer** (117 cases retrospectively assessed).

Pancreatic cancer with a high risk of deterioration in nutritional status requires neoadjuvant treatment, as well. Tashiro et al. [10] examined 161 patients undergoing pancreato-duodenectomy for pancreatic head cancer 67 of which had neoadjuvant treatment, the other 94 went on primary surgery. Prognostic nutritional index significantly worsened in the neoadjuvant group after neoadjuvant treatment, but no significant difference was found in the incidence of postoperative complications, length of hospital stays and time to postoperative adjuvant therapy between the neoadjuvant and the control group. Deterioration did not translate into adverse clinical outcome in this study. Similarly, Neumann et al. [11] in a prospectively collected data cohort of 100 cases found that locally advanced pancreatic cancer after receiving neoadjuvant chemo-radiation suffer a significant weight loss. Although patients who showed less weight reduction tended to survive longer, no statistical significance could be reached in this term.

For **locally advanced rectal cancer** neoadjuvant chemo-irradiation is the standard of care resulting in the best respectability and long-term local control. Yamano et al. [12] examined in a phase II. observational, multicentre study, whether nutritional status becomes affected over the neoadjuvant treatment. In the 41 patients involved in the study, 12 (29,3%) patients experienced body weight loss over 5% (p < 0.001) after CRT and before surgery. Significant changes were seen in serum albumin levels and body mass index (BMI) during and after CRT (p < 0.001), and in Malnutrition Universal Screening Tool (MUST) scores after CRT (p = 0.003) and before surgery (p = 0.035). These factors showed a strong association with outcome measures. Treatment completion was significantly associated with body weight low (BWL) (p = 0.028), MUST score (p = 0.013), and decreased serum albumin level (p = 0.001) after CRT. Regarding adverse events, MUST score before surgery (p = 0.009) and serum albumin level after CRT (p = 0.002) were significantly associated with diarrhoea severity. These statistical results raised the suspicion that clinical outcomes may be associated with the deterioration of nutritional status.

Finally, Okuno et al. [13] observed that loss of muscle mass during preoperative chemotherapy for **colorectal liver metastases** is a significant prognostic factor for poor survival. Their retrospective cohort of 169 cases proved that skeletal muscle index and body weight changed significantly during chemotherapy (skeletal muscle index: −0.52 cm^2/m^2, p = 0.03; body weight: +1.1 kg, p = 0.002). Patients with major muscle loss ($\geq$7%) had significantly shorter median relapse-free survival (RFS) and was an independent risk factor (HR 1.76; p = 0.045).

The lack of feeding obviously hinders the completion of any neoadjuvant therapies.

The first and probably main step of nutritional intervention is screening. In an Australian observational study, Deftereos et al. [14] found that almost every **upper GI cancer patient**, who underwent preoperative nutritional screening and counselling (60% of 200 patients) required nutritional support (100 cases out of 120, 92% of which were prescribed oral nutritional support (ONS)). Neoadjuvant treatment and malnutrition were the main independent predicting factors for requiring nutritional supplementation.

Recently, even a health coaching mobile app was developed and tested to help **oesophageal cancer** patients to keep a close control over malnutrition during neoadjuvant treatment. Yang et al. [15] presented their comparative pilot study of 38 patients aided with this app and proved that lower decrease in PNI can be achieved, however remote assistance was not efficient in preventing excessive muscle loss.

Most studies regarding the importance of nutrition over neoadjuvant treatment has been performed in oesophageal and pharyngeal cancer patients with *dysphagia*. In other words, the need for *maintaining* oral/enteral *nutrition* for the time frame of neoadjuvant therapy seems to be the most obvious indication that requires nutritional intervention. However, it is a question how oral/enteral access should be secured and how these interventions influence the effectivity of neoadjuvant treatment, prevent side effects, and help completion of treatment without dose-reduction. Table 2 shows the result of the literature about securing enteral access for nutrition therapy.

Effect of oral/enteral nutrition on the side-effects and clinical response on neoadjuvant therapy.

Regarding the clinical effect of enteral nutrition support during neoadjuvant chemotherapy of **oesophageal** cancer, Miyata et al. [16] found in a well-designed randomized, controlled trial that chemotherapy-related toxicity (leukopenia and neutropenia grade 3 or 4) was less frequent in the enteral nourished group than by

Table 2
How to secure oral/enteral nutritional access over the neoadjuvant treatment of upper GI malignancies.

Author	Tumour type	Study type	Patient number	Marker(s)	Main outcome
Brown et al., 2011 [71])	oesophageal	pilot, single-arm, Phase 2.	32	endoluminal stenting	safe and feasible
Bower et al., 2009 [72]	oesophageal	prospective database	25 + 19+14 cases	silicon-stent vs. naso-jejunal tube vs oral diet	least operative complication with stents
Siddiqui et al., 2009 [73]	oesophageal	pilot comparative study	12 + 24 cases	plastic stent vs laparoscopic jejunostomy	stents improve dysphagia score
Voisinet et al., 2021 [74]	oesophago-gastric	retrospective	31	feeding jejunostomy (FJ) vs no jejunal feeding	reduction in the development of sarcopenia
Mohamed et al., 2009 [75]	oesophageal	prospective cohort	15	FJ vs no jejunostomy	FJ prevent weight loss but not the development of sarcopenia
Huerter et al., 2019 [76]	oesophageal	retrospective	127	FJ vs no enteral access	FJ has no effect on outcomes of surgery. Low rate of FJ usage even if access placed.
Dalton et al., 2017 [77]	oesophageal	retrospective	94	FJ vs no enteral access	perioperative pneumonia rate lower than in control
Sunde et al., 2016 [78]	oesophageal and gastro-oesophageal	prospective cohort		risk of dysphagia and appetite after 4 cycles chemotherapy	improved appetite after neoadjuvant chemotherapy

parenteral nutrition (leukopenia: 17% vs 41%, p = 0.011, neutropenia: 36% vs 66%, p = 0.005), however there was no difference in tumour response rate (EN: 51%, PN: 55%, p = 0.886).

Jain et al. [7] similarly proved (on a retrospective analysis of 125 oesophageal cancer patients) that weight loss and hypalbuminaemia occur more frequently during neoadjuvant chemo-radiotherapy of oesophageal cancer and they are statistically associated to multiple adverse toxicity outcomes including hematologic toxicity, nonhematologic toxicity, grade ≥3 toxicity. Unfortunately, feeding jejunostomy although effectively prevented weight loss during nCRT ($p = 0.003$) but was not associated with reduced toxicity or improved survival. Noble et al. [17] in their study from 2013 also suggested that nutritional and laboratory markers may predict response of oesophago-gastric cancer to neoadjuvant therapy. Their retrospective analysis on 246 cases showed that only pre-chemotherapy serum albumin levels were suitable to predict pathological response. More importantly, pre-operative (post-neoadjuvant) immunonutritional markers, neutrophil-lymphocyte ratio (NLR) and albumin, were independent prognostic markers for overall survival and disease-free survival, respectively, after oesophageal cancer resection. These results underline the need to influence nutritional status over neoadjuvant therapy. Unfortunately, no prospective trials followed these promising retrospective results, therefore the causality of nutritional support on clinical outcome is still only a hypothesis.

To control the high rate of local and distant recurrence in **gastric cancer**, the use of neoadjuvant chemotherapy is now ususal. When thoroughly examining the clinico-pathological factors affecting the efficacy of neoadjuvant chemotherapy in a retrospective analysis of 203 gastric cancer patients Jiang et al. [18] found weight loss during neoadjuvant chemotherapy (OR = 2.110 [1.161–3.834], P = 0.014) was an independent risk factor of unfavourable therapy effect (beside poor differentiation or signet-ring cell histological type). *Oral nutritional supplementation* significantly diminished weight loss (p = 0.039), suggesting the indirect effect on clinical response. Similarly, *enteral nutrition* was found to markedly relieve the perioperative inflammatory responses, improve the body immunity (the levels of nutritional indexes, T cell subsets and immunoglobulins in the observation group were significantly higher than those in the control group (p < 0.05)) in gastric cancer patients [19] in a randomized prospective trial of 96 patients. In a recent study, Elaziz et al. [20] examined the role of ω-3 fatty acids as an adjunct to neoadjuvant FLOT regimen. In this small (42 cases) randomized trial the experimental group of ω-3 supplementation carried lower chemotherapy-related toxicity rate (diarrhoea, nausea and vomiting, as well as weight loss), less need for treatment gap, and improved clinical response on neoadjuvant therapy and less decline in nutritional state.

In **breast cancer** a number of studies dealt with the relation of neoadjuvant chemotherapy of advanced breast cancer and nutrition. Gourgue et al. [21] worked up a large number of cases (62) in a retrospective manner. They found that obesity (and high tumour apelin expression) was associated with reduced response to neoadjuvant chemotherapy (OR = 0.86, CI 0.74–0.99). This result is an important adjunct to the observations that obesity is a risk factor of developing breast cancer and reducing disease-free survival. Nutritional intervention (by providing *individualized diet plan*) in breast cancer patients undergoing neoadjuvant treatment in another randomized controlled trial (deSouza et al.) [22] found to be effective in preventing reduction in handgrip strength (no change in interventional group, while significant reduction (from 21.6 ± 5.9 kg to 18.8 ± 4.0 kg, p = 0.009) in control group). Additionally, tailored nutrition offered a better QoL during treatment, including better results for nausea/vomiting and loss of appetite compared to the control group. In gastrointestinal and haematological toxicities, the interventional group had lower frequencies of leukopenia and abdominal pain, as well.

Similarly, to breast cancer, an *individualized dietary* intervention was found to be beneficial in **colorectal cancer**, too. Ravasco et al. [23] demonstrated in a randomized comparative trial that individualized nutritional support significantly help reduction of nutritional deterioration over the neoadjuvant radiotherapy compared to routine supplementation or normal diet. This was mainly due to the amount of calorie intake to be superior in the interventional group. Additionally, worse radiotherapy toxicity and QoL were associated with deteriorated nutritional status and intake (p < 0.001). The maintenance in nutritional status translated to median better OS, as well. OS in „normal diet" group was 4.9 years (30% died), in „routine supplementation" group was 6.5 years (22% died), and in „individually nourished" group was 7.3 years (only 8% died): group 3 > group 2 > group 1 (p < 0.01).

3.2. Effect of nutritional therapy during neoadjuvant treatment on operability and surgical outcome

Worsening of nutritional status over the course of neoadjuvant therapy may negatively affect operability, operation outcomes, hence overall oncologic outcome, as well. In some cancer types of

nutritional status was correlated with operation outcomes; other studies also investigated the potential effect of nutritional therapy to modify surgical outcome.

In a retrospective cohort of 107 **oesophageal cancer** patients Zemanova et al. [24] showed that ONS helped with a *higher probability to attain full dosage of neoadjuvant chemo-radiotherapy and radical resection* than did those obtaining dietary advice alone. In the multivariate analysis, serum albumin level, nasogastric (NG) tube insertion and pre-treatment body weight loss were independent prognostic factors for OS, while serum albumin level *after* CRT and NG tube insertion were prognosticators for time to progression.

3.3. Multimodal prehabilitation

As loss of muscle mass and function (*sarcopenia*) was found to correlate well with fitness to surgery, as well as surgical outcome, recent studies tend to examine the *joint effect of nutritional therapy and physical exercise* (prehabilitation). In these studies, it is impossible to discriminate the effect of nutrition and exercise, therefore we have to assess their common consequences together.

In terms of prehabilitation during neoadjuvant treatment, there is a very small number of well-designed trials. Additionally, the available studies follow fairly different experimental methods, therefore their results can hardly be pooled or compared.

Xu et al. [25] demonstrated that a so called *„Walk-and-Eat Intervention"* (encompassing a nurse-led walking three times a week and weekly nutritional advice over 4–5 weeks of chemo-radiotherapy) can maintain physical fitness compared to the control group of standard care. Hundred meters less decline in 6-min walking distance ($p = 0.012$), 3 kg less decrease in hand-grip strength ($p = 0.002$) and 2.7 kg less reduction in body weight ($p < 0.001$) was found in their comparative trial of 60 cases of **oesophageal cancer** patients.

Recently the team of Miralpeix et al. [26] tested a group of women with **ovarian cancer** undergoing neoadjuvant chemotherapy and interval cytoreductive surgery if *trimodal prehabilitation (exercise, nutritional and psychological* support) can influence the outcome of surgical intervention. In a retrospective work-up comparing 14 patients of prehabilitation and 15 controls they found minimal advantages of the experimental arm: patients in the prehabilitation program showed higher mean total protein levels in both preoperative (7.4 vs. 6.8, $p = 0.004$) and postoperative (4.9 vs. 4.3, $p = 0.005$) assessments. Up to 40% of controls showed intraoperative complications vs. 14.3% of patients in the prehabilitation group, and the requirement of intraoperative blood transfusion was significantly lower in the prehabilitation group (14.3% vs. 53.3%, $p = 0.027$), however the correlation of these outcome measures with prehabilitation have not been proven.

Frail patients are considered to benefit more out of prehabilitation. **Hepato-pancreatico-biliary** surgery represents one of the highest-risk group of procedures. Baimas-George et al. [27] reported their analysis on a pilot of 19 cases undergoing neoadjuvant chemotherapy prior to HPB surgery. Only 10 out of them completed prehabilitation including nutritional therapy. Trimodal prehabilitation improved frailty score, however symptoms and laboratory markers did not show any change.

Trimodal prehabilitation including physical and nutritional (as well as psychic) support may have favourable effects on the whole metabolism, as well as the *tumour response on neoadjuvant treatment*. West et al. [28] in their unique study evaluated the effect of an exercised prehabilitation programme on tumour response in **rectal cancer** patients following neoadjuvant chemo-radiotherapy. 26 patients took part in the 6-week tailored exercise training with unmatched 9 controls. Tumour related outcome variables: MRI tumour regression grading (ymrTRG) at week 9 and 14; histopathological T-stage (ypT); and tumour regression grading (ypTRG) were compared. Beside a significantly improved fitness (oxygen uptake ($p < 0.001$) and anaerobic threshold ($p = 0.007$), prehabilitation resulted in an augmented pathological response (ypTRG, $p = 0.02$).

Functional outcomes (e.g., 6-min walking test (6MWT), hand grip strength) may be easily improved over a few weeks of prehabilitation, however just a certain proportion of cancer patients do benefit on hard outcome measures, like morbidity and mortality. The main question still arises, if biologic/metabolic effect of multimodal prehabilitation within a neoadjuvant setting may make this method useful for a broader spectrum of patients, as well.

Further, well designed prospective, randomized trials and large-number cohort studies focusing on nutritional treatment effects are needed to answer the large number of rising questions (Maurer et al.) [29].

3.4. Nutrition and adjuvant treatment

After radical surgery adjuvant therapy is given with the aim to eradicate remaining local or loco-regional tumour cells and to prevent the development of distant metastases. Accordingly, adjuvant therapy can be radiation therapy to improve local-loco regional control and medical therapy in the form of chemo-endocrine, targeted- and immunotherapy to reduce the occurrence of distant metastasis (Table 1). These modalities are often combined in order to increase efficacy. All of these modalities may cause nutritional impact symptoms. Radiation oncology causes local inflammation of the gastrointestinal tract, pain, swallowing dysfunction, dysgeusia, xerostomia, nausea and vomiting, bowel insufficiency etc. In long term, fibrosis caused by radiation may have significant impact on nutrition. In medical therapy chemotherapy has well-known effect on nutrition with nausea and vomiting, anorexia, taste alteration etc. Targeted and immunotherapy may cause nutritional impact symptoms, however, less frequently in the forms of anorexia and oral ulcers e.g., during targeted, and various immune-related side effects during immunotherapy such as autoimmune hepatitis. Endocrine therapy is regarded the least problematic in the view of nutrition. However, due to their effect on metabolism, hormonal therapy in breast and prostate cancer may lead to weight gain in fat beside loss of skeletal muscle, therefore these therapies may promote sarcopenic obesity [30]. While adjuvant radiotherapy may be maximum six or seven weeks long pharmaceutical therapies last longer. A simple adjuvant chemotherapy is 4–6 month long. With the use of less toxic agents such a targeted and immunotherapy a maintenance part of an adjuvant therapy is typically one-year long. Hormonal therapy is usually applied in breast cancer, and it takes at least 5 years. It means that nutritional management should be planned for a long period.

3.5. Timing of adjuvant therapy and effect of delays on outcome

There is no randomized trial providing high level evidence on the optimal timing of initiation of postsurgical adjuvant therapies in cancer. Based on lower-level evidence, guidelines suggest that adjuvant therapy should be initiated between 4 and 8 weeks after surgery and probably should not be delayed more than 12 weeks. Publications about the effect of delay on outcomes are contradictory. There are some data showing worse survival in colon, gastric, breast and ovarian cancer and glioblastoma and other that did not find any effect of delay in colon, gastric, lung and pancreatic cancer [31–34]. When analysing delays several publications mention nutritional problems as one of the causes of delays, however, there is no publication that specifically addresses the role of malnutrition, or sarcopenia in delaying adjuvant treatment.

3.6. Nutritional status and outcome of adjuvant cancer therapy in selected cancers

3.6.1. Breast cancer

In breast cancer adjuvant therapy may consist of radiation therapy as local or locoregional treatment. Depending on the biological features of the tumour, chemo, targeted and endocrine therapy can be administered. In certain cases, all of these modalities are used. It is long known that during adjuvant chemotherapy patients often experience weight gain, increase in fat mass, decrease in lean body mass (LBM), a way to sarcopenic obesity [35,36]. During adjuvant medical therapy eating preferences change in breast cancer patients. Palazzo et al. [37] found that during adjuvant chemotherapy sweet preference of BC patients changes that contributes to weight gain and increasing body fat mass. However, not only eating behaviour has negative impact, but it is also well known that chemotherapy causes metabolic changes including elevation of plasma lipid levels [38]. In an observational study van den Berg et al. found that higher absolute and relative fat mass, (HR 1.14 per 5 kg; 95% CI 1.04–1.25 and HR 1.21 per 5%; 95% CI 1.05–1.38) or lower relative lean body mass HR 0.83 per 5%; 95% CI 0.72–0.96 increase the risk of toxicity related treatment modifications [39]. Sheean et al. [30] performed a review on 15 publications about body composition change in breast cancer patient. While having limitations due to the heterogeneity of this studies and some confounding factors she found that 7 of the 15 papers showed decrease in lean body mass and 11 found increase in fat mass. Hormonal therapy especially tamoxifen has a clear negative impact on body composition. The negative change in body composition has clearly negative effect of outcomes, both in survival, local recurrence and quality of life [40]. Some randomized trials assess the feasibility of nutrition and lifestyle intervention it these patients. A multicentre randomized trial of a brief Adapted Physical Activity and Diet (APAD) program has been published by Jacot et al. [41]. They randomized 360 breast cancer patients for APAD versus usual supportive care. The primary endpoint was fatigue. There was no significant improvement in the examined endpoints, which supports the conclusion of the authors that short term intervention most probably has no major effect on outcomes. The APAD1 trial Carayol et al. randomized 143 patients for APAD versus usual care [42]. They found that APAD has a significant positive effect on fatigue, QoL, anxiety, depression at 18 and 26 weeks, which persisted on fatigue and QoL up to 12-month follow-up. Significant decrease in BMI, fat mass, and increased muscle endurance and cognitive flexibility also found up to 26 weeks after intervention. In a feasibility randomized trials “PASAPAS” Febvey-Combes et al. investigated the effect of a 6-month exercise-diet intervention on serum metabolic biomarkers [43]. They did not find significant differences, but the approach found to be feasible. Najafi et al. performed a randomized trial about the effect of dietary counselling on chemotherapy induced nausea and vomiting (CINV) and QoL of breast cancer patients receiving chemotherapy [44]. They found that counselling significantly decreased CINV and improved QoL.

3.6.2. Gastrointestinal cancers

In oesophageal cancer adjuvant therapy is rarely applied, the current protocols favour neoadjuvant chemo-radiation and surgery, therefor no significant literature about adjuvant treatment and nutrition is available.

In locally advanced gastric cancer perioperative chemotherapy is the standard treatment of choice, however until recently adjuvant chemo-radiation was also used especially in the United States. Nutritional status of gastric cancer patients who receive adjuvant chemotherapy or chemo-radiation strongly determines the outcome. Liu et al. [45] analysed the data of 688 patients retrospectively. They created a systemic prognostic score from inflammatory markers, PNI and Ca-19.9. They found that this score better predicted the cancer-specific survival than TNM stage alone. Similarly, Xia et al. [46] analysed the data of 1288 patients and found that low PNI is an independent risk factor of decreased cancer specific survival (CSS) (cut off PNI: 43,9, HR 1,287, CI95% 1.058–1.565). Li et al. [47] examined 223 patients who received adjuvant chemo-radiation and found that inflammatory markers (neutrophil-platelet score) and poor body composition, namely low NPI and sarcopenic obesity are independent prognostic factors of overall survival. Sun et al. found that weight loss after surgery predicts grade II-IV non haematological side effects of adjuvant chemo-radiation [48] while Aoyama et al. [49] found that body weight loss was also an independent risk factor of discontinuation of adjuvant S-1 chemotherapy. Therefore, nutritional support has a major role in the curative treatment of gastric cancer, however, high level evidence about the benefit of nutrition therapy is lacking and it has to be noted that nutrition therapy of gastric cancer patients is a great challenge. Before surgery the persisting tumour and the oncological therapy, after surgery the decrease is the stomach function is what makes it difficult. It is also known that the compliance of gastric cancer patients to nutrition therapy e.g., oral nutrition support is far from optimal. Jian et al. [50] found it as low as 24,7%.

Pancreatic cancer is a mostly an incurable disease. Twenty percent of the patients receive curative surgery and as the recurrence rate and the chance of developing distant metastasis is very high adjuvant chemotherapy is compulsory even after pathologically proven complete resection. Because of the bad prognosis there is a trend to use more and more intensive chemotherapy regimens even in the adjuvant setting. Dose density is very important, and these treatments are tolerated only by patients who are in good general condition, and it obviously contains good nutritional status. Poor nutritional status is a predictor of discontinuation or the decrease in the dose density of chemotherapy. Postoperative weight has been shown to decrease dose density and associated with the discontinuation of chemotherapy [51–53]. Again, though everybody is aware of the importance on nutritional interventions in pancreatic cancer there is no high-level evidence about the optimal use of nutritional therapy in the adjuvant setting. What seems important is that enteral feeding should be started as early as possible and long course use of parenteral nutrition should be avoided [54]. There is one randomized trial investigating the role of extended elemental diet. Mori et al. found that extended elemental diet did not have any effect on survival, but the side effects and unplanned readmissions were fewer in the intervention group [55].

In colorectal cancer poor nutritional status may lead to the omission of adjuvant chemotherapy as shown by Lee et al. [56]. A nutrition risk score (NRS) $\geq$4 resulted in higher risk of omission of adjuvant chemotherapy (26.3% vs. 13.6%, $p = 0.006$), which remained significant after adjusting for covariates (OR = 1.862, $p = 0.047$). In the C-SCAN study Cespedes Feliciano et al. found in 533 patients that low muscle mass was associated with early discontinuation increased toxicity and dose reduction of chemotherapy [57]. Influence of diet on outcomes in colon cancer patients receiving adjuvant chemotherapy has been extensively analysed on the data of the CALGB89803/Alliance randomized controlled trial. They found that artificially sweetened beverages have a negative, nut consumption, predicted good vitamin-D status, adherence to the American Cancer Society survivorship guidelines on diet and exercise have a positive effect on outcomes [58–61]. Fat intake of any kind had no effect [62], while dietary insulin load found in one analysis to have negative and in another analysis a non-significant positive impact on outcomes [63,64]. Finally in the most recent

Table 3
Most important prognostic and predictive biomarkers of nutrition and outcomes of neoadjuvant or adjuvant treatment.

Author	Tumour type	Study type	Patient number	Marker(s)	Main outcome
LI et al., 2022 [47]	Gastric cancer adjuvant	Retrospective	223	RBC distribution width, NPS, PNI NLR, NLP, LMR, SII	Inflammatory repose with nutritional condition is a strong prognostic factor
Liu et al., 2019 [45]	Gastric cancer adjuvant	Retrospective	688	CRP/Alb, PNI, weight loss	All independent negative prognostic factors
Hsueh et al., 2022 [79]	Oesophageal neoadjuvant	Prospective	123	pre-treatment ANS	Predictive for OS, side effects and resection rate
Abe et al., 2022 [80]	Oesophageal neoadjuvant	Retrospective	172	Alb-dNLR change	Independent prognostic factor for OS
Ding et al., 2022 [81]	Gastric neoadjuvant	Prospective	30	SII−PNI score	Predictive for response
Du et al., 2022 [82]	GEJ neoadjuvant	Retrospective	79	NLR, PNI, EOS	Predictive for survival
Sakai et al., 2020 [83]	Oesophageal	Retrospective	105	mGPS, CONUT, PNI, CAR, NLR, PLR	CAR is prognostic of OS
Li et al., 2020 [84]	Gastric neoadjuvant	Prospective	225	NLR, dLMR	Prognostic for survival
Kim et al., 2020 [85]	Pancreatic neoadjuvant	Retrospective	107	PNI	PNI is prognostic for OS
Nakatani et al., 2017 [86]	Oesophageal neoadjuvant	Retrospective	66	preop PNI	Prognostic for OS/RFS
Kvaener et al., 2018 [87]	Colorectal adjuvant	Prospective	66	Malnutrition and DNA	Malnutrition is prognostic for DNA damage

Abbreviations: RBC: red blood cell, NPS: nutrition prognostic score, PNI: prognostic nutritional index, NLR: neutrophil lymphocyte ratio, NLP: dNLP: change in NLP, LMR: lymphocyte monocyte ratio dLMR: change in LMR, PLR: platelet lymphocyte ratio. SII: systemic immune-inflammation index, CRP: C-reactive protein, Alb: albumin, ANS: albumin and neutrophil-to-lymphocyte (NLR) ratio score EOS: eosinophilic granulocyte, mGPS: modified Glasgow Prognostic Scale, CONUT: controlling nutritional status, CAR: CRP albumin ratio, DNA: Deoxyribonucleic acid.

publication trialists incorporated healthy diet in a prediction model of outcome and in this model healthy diet has a positive overall effect on the outcome [65]. Protein intake is in the focus of cancer nutrition guidelines and has an important role to prevent sarcopenia. Mazzuca et al. used purified whey protein in a placebo-controlled trial. Patients receiving whey protein has favourable anthropometric parameters and also experienced significantly less toxicity [66]. Not frequently reported in the literature but elderly cancer patients suffer the consequences of malnutrition more than younger ones. In the GERICO trails, it was found that elderly, frail colorectal cancer patients undergoing adjuvant or palliative chemotherapy who received geriatric intervention which included nutrition therapy more likely completed the planned treatment and also their quality of life was better [67].

In various other tumours there are some reports about nutrition and adjuvant therapy. Edbrook et al. conducted a pilot randomized trial on endometrial cancer patients (ENhAncing Lifestyle Behaviours in EndometriaL CancEr (ENABLE)) and found that lifestyle intervention including nutrition is feasible a possibly beneficial during adjuvant treatment [68]. Boisselier et al. investigated the effect of an immune-modulating nutritional formula in a double−blind randomized GORTEC trial, IMPATOX, 180 patients have been involved. The formula contained l-arginine, omega-3 fatty acids and ribonucleic acids. There was no benefit in the intent to treat population, however those patients who were more that 75% compliant with the formula had a better 3-year overall survival (81% vs. 61% p = 0,034) [69].

3.6.3. Biomarkers, prognostic and predictive factors

There are several markers, usually combination of immune and nutrition factors are proposed as prognostic and predictive factors in patients undergoing neoadjuvant or adjuvant therapy, such as modified Glasgow Prognostic Score mGPS, NLR, PNI etc. In Table 3 there is a summary of the most important findings in the literature.

4. Conclusions

It is unequivocal from the literature that poor nutritional status, sarcopenia, cachexia and systemic inflammation results in poor outcomes in survival, side effects and quality of life of cancer patients independently from the phase of their cancer journey, including neoadjuvant and adjuvant period. It is less clear or better to say less supported by high-level evidence how much medical nutritional therapy can ameliorate nutritional status of patients and whether these positive effects translate to clinical benefit or not. As it is clear that nutrition plays and important role randomized trials omitting nutritional therapy on an arm would not be ethical. Prospective cohort or observational studies and well-designed real-world studies are feasible and could be helpful. In contrary, as our tools of our nutrition therapy are improving by time randomized trials would be extremely helpful to define the optimal process of nutrition therapy. It is well-known that clinical trials require financial resources and are demanding in human efforts and nutrition therapy has no such strong industry support as e.g., innovative cancer pharmaceuticals. A very positive recent development is that the EU launched the Mission on Cancer [70]. Diet and nutrition are part of specific goal 1 (Understanding cancer, UNCAN. eu) and 4 (Support quality of life) which may enable researchers to launch research in nutrition science. We do hope that in the future this very important aspect of cancer therapy will gain more attention and funding and several questions now open will be answered by the results of high-quality research.

Declaration of competing interest

Lovey J, Banky B, have no competing interests to declare.

Molnar A works for Danone Hungary Ltd. and participated in the authorship of the article as a co-author at the request of the National Association of Hungarian Dietitians as a member of the scientific committee.

CRediT authorship contribution statement

Jozsef Lovey: Article concepts, Article design, Data acquisition, Quality control of data and algorithms, Formal analysis, and interpretation, Manuscript preparation, Manuscript editing, Manuscript

review. **Andrea Molnar:** Article concepts, Article design, Data acquisition, Quality control of data and algorithms, Formal analysis, and interpretation, Manuscript preparation, Manuscript editing, Manuscript review. **Balazs Banky:** Article concepts, Article design, Data acquisition, Quality control of data and algorithms, Formal analysis, and interpretation, Manuscript preparation, Manuscript editing, Manuscript review.

Acknowledgement

Lovey J was supported by the National Research, Development and Innovation Fund of the Ministry of Culture and Innovatation under the National Laboratories Program (National Tumour Biology Laboratory (2022-2.1.1-NL-2022-00010)) Grant Agreement with the National Research, Development and Innovation Office.

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