ESPEN Guideline

ESPEN guidelines on nutrition in cancer patients[☆]

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SUMMARY

Cancers are among the leading causes of morbidity and mortality worldwide, and the number of new cases is expected to rise significantly over the next decades. At the same time, all types of cancer treatment, such as surgery, radiation therapy, and pharmacological therapies are improving in sophistication, precision and in the power to target specific characteristics of individual cancers. Thus, while many cancers may still not be cured they may be converted to chronic diseases. All of these treatments, however, are impeded or precluded by the frequent development of malnutrition and metabolic derangements in cancer patients, induced by the tumor or by its treatment.

These evidence-based guidelines were developed to translate current best evidence and expert opinion into recommendations for multi-disciplinary teams responsible for identification, prevention, and treatment of reversible elements of malnutrition in adult cancer patients.

The guidelines were commissioned and financially supported by ESPEN and by the European Partnership for Action Against Cancer (EPAAC), an EU level initiative. Members of the guideline group were selected by ESPEN to include a range of professions and fields of expertise.

[☆] These guidelines have been officially endorsed by the European Society of Surgical Oncology (ESSO), the European Association for Palliative care (EAPC) and the Chinese Society of Clinical Oncology (CSCO).
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Hematopoietic stem cell transplantation
Palliative care
Nutrition assessment
Nutrition therapy
Exercise training

We searched for meta-analyses, systematic reviews and comparative studies based on clinical questions according to the PICO format. The evidence was evaluated and merged to develop clinical recommendations using the GRADE method. Due to the deficits in the available evidence, relevant still open questions were listed and should be addressed by future studies.

Malnutrition and a loss of muscle mass are frequent in cancer patients and have a negative effect on clinical outcome. They may be driven by inadequate food intake, decreased physical activity and catabolic metabolic derangements. To screen for, prevent, assess in detail, monitor and treat malnutrition standard operating procedures, responsibilities, and a quality control process should be established at each institution involved in treating cancer patients.

All cancer patients should be screened regularly for the risk or the presence of malnutrition. In all patients – with the exception of end of life care – energy and substrate requirements should be met by offering in a step-wise manner nutritional interventions from counseling to parenteral nutrition. However, benefits and risks of nutritional interventions have to be balanced with special consideration in patients with advanced disease. Nutritional care should always be accompanied by exercise training. To counter malnutrition in patients with advanced cancer there are few pharmacological agents and pharmaconutrients with only limited effects. Cancer survivors should engage in regular physical activity and adopt a prudent diet.

GL Nutrition in Cancer Patients – Outline

Abbreviations used

AML	acute myeloic leukemia
ASCO	American Society of Clinical Oncology
BCAA	branched-chain amino acids
BIA	bio impedance analysis
BMI	body mass index
BMT	bone marrow transplantation
BMR	basal metabolic rate
CHT	chemotherapy
CRP	C-reactive protein
d	day
DEXA	dual-energy x-ray absorptiometry
DHA	22:6 docosahexaenoic acid
ECOG	Eastern Cooperative Oncology Group
EAPC	European Association for Palliative Care
EFSA	European Food Safety Authority
EN	enteral nutrition
EPA	20:5 eicosapentaenoic acid
ERAS	enhanced recovery after surgery
ESMO	European Society for Medical Oncology
FDA	U.S. Food and Drug Agency
GI	gastrointestinal
GL	guideline
GPS	Glasgow Prognostic Score
GvHD	graft versus host disease
HCT	hematopoietic stem cell transplantation
HMB	ß-hydroxy methyl butyrate
HTA	16:4 hexadecatetraenoic acid
IGF-I	insulin-like growth factor I
ISOO	International Society of Oral Oncology
LOS	length of hospital stay (days)
MA	megestrol acetate
MASCC	Multinational Association of Supportive Care in Cancer
mGPS	modified Glasgow Prognostic Score
MNA	Mini Nutritional Assessment
MNI	Medical Nutrition International
MST	Malnutrition Screening Tool
MUST	Malnutrition Universal Screening Tool
NSAID	non-steroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
ONS	oral nutritional supplements
N-3 fatty acids	polyunsaturated fatty acids of the N-3 or omega-3 series
PAL	physical activity level
PEG	percutaneous endoscopic gastrostomy
PG-SGA	patient-generated Subjective Global Assessment
PICO	populations of interest, interventions, comparisons, outcomes
PN	parenteral nutrition
QoL	quality of life
RCT	randomized controlled trial
REE	resting energy expenditure
RT	radiotherapy
SARM	selective androgen receptor modulator
SGA	Subjective Global Assessment

Chapter O: Methods

O1. Basic information

1. Terms and abbreviations

A "***cancer patient***" is a patient with a cancer diagnosis who is either waiting for or on cancer directed treatment, on symptomatic treatment, and/or receiving palliative care.

Patients cured from their cancer are termed "***cancer survivors***".

"***Pharmaconutrients***" are nutrients supplied in pharmacological doses to modulate immune and metabolic functions and exert effects on clinical outcome.

(*continued*)

TEE	total energy expenditure
THC	tetrahydrocannabinol
TNF	tumor necrosis factor
TPN	total parenteral nutrition
WHO	World Health Organization

2. Goals of the guideline

Oncology is one of the areas of medicine where recent advances and progress can improve outcomes for patients. However, the frequent presence of malnutrition in cancer patients can limit their response to even the best therapies if nutritional issues are not appropriately managed. This highlights the need for a truly scientific appraisal of nutrition therapy in these patients [1].

We aimed with this document **to translate current evidence and expert opinion into recommendations for multi-disciplinary teams responsible for identification, prevention, and treatment of reversible elements of malnutrition in cancer patients**. Diagnosing and treating malnutrition and metabolic derangements are of major relevance for cancer patients and cancer survivors. Cancer patients are at risk of malnutrition, not only due to physical and metabolic effects of the cancer, but also due to the effects of anticancer therapies, and malnutrition is associated with poorer prognosis [2,3]. In addition, metabolic derangements like obesity and insulin resistance are associated with increased risks of cancer recurrence [4,5]. The **specific objectives** of this guideline, therefore, are **to improve early detection and treatment of malnutrition and metabolic derangements in cancer** patients and cancer survivors; to provide guidance to health care workers and patients on the most appropriate and effective management of nutritional and metabolic problems in cancer patients; and, by this, to lower the incidence and impact of malnutrition and metabolic derangements in cancer patients and survivors.

A number of clinical guidelines on nutrition in cancer patients have been published by ESPEN as well as by other national and international societies [6–9]. However, the impact of previous ESPEN and other guidelines has been limited due to the frequently only moderate interest of clinical oncologists in nutritional aspects of cancer care [10–14] and the fact that these GL mostly presented general recommendations and a small number of specific recommendations for common situations. In contrast to other recommendations dedicated to particular specialties, the present set of guidelines aims to help specialists in different medical disciplines involved in the care of cancer patients. The authors hope that these disease-specific guidelines will help to clarify previous statements and to facilitate their implementation.

Additional objectives of this guideline, therefore, were.

1) to develop a clear and simple GL structure to facilitate consensus building with other GL groups and societies
2) to choose and answer clinical questions with immediate relevance for day-to-day clinical care (based on expert consensus if evidence-based data were not available) to better connect to clinical practice, and
3) to highlight relevant questions that urgently require clinical research

This GL thus aims to inform clinical practice, establish clinical policy, promote European consensus, and improve patient outcomes.

3. Target population

This GL includes all **adult cancer patients** and all cancer survivors independent of severity of disease, stage of disease, or comorbidities.

4. Target users

This GL is intended to be used by clinical oncologists, health care providers involved in supportive care of cancer patients and cancer survivors, e.g. medical specialists involved in cancer treatment, family physicians, pharmacists, nurses, dieticians, nutritionists, and exercise physiologists, as well as by medical leaders and administrators of oncological institutes.

5. Professional groups involved

The following professionals were involved in preparing the guideline:

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Bachmann, Patrick (PB): IC; GL group
Baracos, Vickie (VB): Bio; GL group
Barthelemy, Nicole (NB): R; GL group
Bertz, Hartmut (HB): O, H, PM; GL group
de van der Schuren, Marian (MvS): Nut; GL group
Bozzetti, Federico (FB): S; GL group
Fearon, Ken (KF): S; GL group
Hütterer, Elisabeth (EH): Nut; GL group
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Kaasa, Stein (SK): R, PM; GL group
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Laird, Barry (BL): PM; GL group
Larsson, Maria (ML): Nur; GL group
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Solheim, Tora (TS): O; GL group
Strasser, Florian (FS): O, H, PM; GL group
Legend:
A — anesthesiology, Bio — biochemistry, G — gastroenterology, H — hematology, IC — intensive care, IM — internal medicine, Nur — nursing, Nut — nutrition, O — oncology, Pha — pharmacology, Phy —physiology, PM — palliative medicine, R — radiation oncology, S — surgery.

6. Patient views

There was an internal analysis on which topics might be most important from the patients' perspective and this included discussions based on the individual experiences of all group members involved in clinical care of cancer patients or survivors. The results were used to choose or adapt clinical questions to be answered by the guideline project. However, there was no formal involvement of patient groups in formulating the GL.

7. Conflict of interest and funding

The GL was commissioned by the European Society for Clinical Nutrition and Metabolism (ESPEN) and by the European Partnership for Action Against Cancer (EPAAC), an EU level initiative launched in 2009 and funded and coordinated by the European Commission and the EU Member States (www.epaac.eu). ESPEN and EPAAC provided financial support to perform the literature research and to cover travel costs incurred from two group meetings required for the consensus process. None of the funding bodies exerted an influence on the content of the guideline.

All group members were asked to return ICMJE Uniform Disclosure Forms for Potential Conflicts of Interest. The following competing interests were reported (A: Support for GL work; B: Support outside GL work; 1: Board membership, 2: Consultancy, 3: Employment, 4: Gifts, 5: Grants, 6: Honoraria, 7: Payment for

preparation of manuscripts, 8: Patents, 9: Royalties, 10: Stock, 11: Travel expenses, 12: Other):

AL: A: none, B: 2, 6, 7
BL: A: none, B: none
EH: A: none, B: none
EI: A: none, B: none
FB: A: none, B: 5, 6
FS: A: none, B: 2, 5, 6, 11
HB: A: none, B: 12
JA: A: none, B: 2, 6
JCP: A: none, B: none
KF: A: none, B: 2, 5, 6, 7, 11
LO: A: none, B: none
ML: A: none, B: none
MM: A: none, B: none
MS: A: none, B: 1
NB: A: none, B: none
PB: A: none, B: 2, 6, 11, 12
PR: A: none, B: none
SK: A: none, B: none
SM: A: none, B: none
TS: A: none, B: none
VB: A: none, B: none
ZK: A: none, B: 2, 6, 11

O2. Methods

1. Search strategy

Based on the ESPEN framework for disease-specific guidelines [1] we decided on topics to be covered through several rounds of discussion and modification. To initiate comprehensive de novo literature searches, we designed specific clinical questions which included concise definitions of the populations of interest, the interventions, the comparators, and the outcomes (PICO format). On a general note, the interventions of interest and outcomes depended on the populations. Definitions of the PICO parameters and the clinical PICO questions are given below.

We searched Pubmed and the Cochrane Library for recent, rigorous systematic reviews and meta-analyses that answered our clinical questions. In their absence, we looked for other systematic reviews and meta-analyses (i.e. those that were older and in need of an update, or those that only partially answered our question or those with methodological flaws), and, in the absence of these, we looked for comparative studies, whether randomized or not. Recent rigorous systematic reviews were summarized and the evidence evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method recommended for development of evidence-based guidelines [15–18].

The search phrase used was: ((Cancer OR carcinoma OR malignancy OR lymphoma OR leukemia OR myeloma OR melanoma OR metasta* OR bone marrow transplant) AND (nutrition* OR diet OR nourishment OR nutrient OR nutriment OR malnutrition OR malnourishment OR undernourishment OR cachexia OR anorexia OR calorie* OR lipid OR trace OR vitamin* OR protein OR taurine OR arginine OR glutamine OR fatty OR micronutrient* OR supplement* OR enteral OR parenteral OR EN OR TPN OR PN OR exercise OR physical activity OR muscle training)). The time period searched was January 1, 2006 to June 30, 2013. A total of 6600 records were retrieved and examined.

This structured procedure was supplemented by intensive hand-searching of journals and previous guidelines. We searched for the best evidence. The best evidence, in evidence-based medicine terms, is gained from methodologically sound randomized controlled trials (RCTs). However the decision to do an RCT does not always follow the burden of disease and trials may be missing important clinical questions for which no sponsor can be found.

We found good systematic reviews to answer some questions, although only for some populations of interest. The randomized controlled trials included in the systematic reviews were often of medium or low quality, with small sample size, often with no calculation of sample size, and with poor or unreported allocation concealment. Thus, for many cells in the matrix of the clinical questions, we found no evidence or only low quality evidence, and, in these cases, it was necessary to base our recommendations on our expert opinion. Due to these deficits in the available evidence base, we included an effort to outline future studies that are needed in order allow us to base our recommendations on more solid evidence in the years ahead.

Clinical questions in PICO format. Definition of parameters
Population: The populations of interest were defined by multiplication of the following matrices: cancer type; condition; treatment of cancer; nutritional status; age groups.

Cancer type: hematological, acute leukemia and bone marrow transplantation (BMT); hematological, all others; solid: lung, GI, head and neck cancer, other.

Condition: palliative, curative, survivor, terminal; functional capacity.

Treatment of cancer: chemotherapy or radiotherapy: by intensity (causes nausea/anorexia); radiotherapy to head and neck; radiotherapy to GI; surgery.

Nutritional status: malnourished/not malnourished; anorexia.
Age groups: 18 years or older.

Interventions: psychosocial support, screening, enteral nutrition, parenteral nutrition, increase calorie intake, increase protein intake, glutamine, immunonutrition, N3-fatty acids, ONS.

Outcomes: *Primary*: overall survival, disease-free survival, quality-of-life, performance status, completion of therapy, complications/LOS.

Secondary in order of importance: weight change, body weight, body mass index, other.

Parameter matrix for individual PICO questions

#	Group	Subgroup	Intervention	Outcome
1	cancer	curative RT	any nutrition therapy	all
2	cancer	GI failure	PN	all
3	cancer	vomiting	PN	all
4	cancer	GI failure	PN	all
5	cancer	intractable vomiting	PN	all
6	cancer	palliative CHT	any nutrition therapy	all
7	cancer	curative CHT	any nutrition therapy	all
8	cancer	terminal	ONS, EN, PN	all
9	cancer	palliative CHT	anti-cancer diet	all
10	cancer	curative CHT	anti-cancer diet	all
11	cancer	palliative CHT	anti-cancer diet	all
12	hematology	curative CHT	germ-reduced food	all
13	hematology	curative CHT	germ-reduced food	all

(continued)

#	Group	Subgroup	Intervention	Outcome
14	cancer	curative RT	tube feeding vs oral food	all
15	cancer	curative RT	PEG vs nasogastric tube	all
16	hematology	curative CHT	PN vs oral/enteral	all
17	hematology	curative CHT	PN vs oral/enteral	all
18	cancer	curative CHT	PN vs oral/enteral	all
19	cancer	curative CHT	PN vs oral/enteral	all
20	cancer	advanced, no antitumor therapy	PN vs oral/enteral	all
21	cancer	advanced, no antitumor therapy	lipid-rich vs normal nutritional support	all
22	cancer		screening	all
23	hematology		screening	all
24	cancer		screening	all
25	hematology		screening	all
26	cancer	curative RT	counselling	all
27	cancer	curative CHT	counselling	all
28	cancer	palliative CHT	counselling	all
29	hematology	allogeneic SCT	counselling on food risks	all
30	hematology	curative CHT	counselling on food risks	all
31	cancer	curative CHT	muscle training	all
32	cancer	curative RT	muscle training	all
33	hematology	curative CHT	muscle training	all
34	cancer	palliative CHT	muscle training	all
35	cancer	cured	muscle training	all
36	cancer	anti-cancer therapy	GI supportive care	all
37	cancer	treatment	psycho-social support	all
38	cancer	advanced	psycho-social support	all
39	cancer	anti-cancer therapy	psycho-social support	all
40	cancer	curative RT	ONS	all
41	cancer	anti-cancer therapy	pain treatment	all
42	cancer	curative CHT	ONS	all
43	cancer	curative CHT	ONS	all
44	cancer	palliative CHT	ONS	all
45	cancer	advanced, no antitumor therapy	ONS	all
46	cancer	advanced	NSAID	all
47	cancer	advanced	N-3 Fatty acids	all
48	hematology	curative CHT	N-3 Fatty acids	all
49	hematology	curative CHT	N-3 Fatty acids	all
50	cancer	advanced	corticosteroids	all
51	cancer	advanced	progestins	all
52	cancer	advanced	cannabinnoids	all
53	cancer	curative RT	glutamine	all
54	cancer	anti-cancer therapy	glutamine	all
55	hematology	curative CHT	glutamine	all
56	cancer	advanced	insulin	all
57	cancer	surgery	glutamine	all
58	cancer	curative CHT	EN/PN	all
59	cancer	curative CHT	EN/PN	all
60	cancer	curative CHT	EN/PN	all
61	cancer	advanced	additive EN/PN	all
62	cancer	advanced	additive EN/PN	all
63	cancer	surgery	perioperative EN	all
64	cancer	surgery	perioperative EN	All
65	cancer	surgery	perioperative ONS	All
66	cancer	surgery	perioperative ONS	All
67	cancer	surgery	perioperative ONS	All
68	cancer	surgery	perioperative PN	All
69	cancer	surgery	perioperative PN	All

2. Formulation of recommendations

Each guideline topic was assigned to several GL group members who evaluated the available evidence by applying the GRADE method and then formulated a recommendation that included a commentary linking the recommendation to the corresponding evidence and discussing its evaluation as well as the benefits, costs, and risks associated with the recommended action. The recommendations and commentaries were circulated within the GL group and changes suggested by the group were discussed with the primary authors of the topic. Disagreement was resolved at two consensus meetings. Final written voting on all 44 recommendations was obtained from the GL group members. Of the recommendations, 24 received 100% agreement (strong consensus), 20 received 75–95% agreement (consensus); no recommendation received less than 75% agreement.

All evidence from observational and randomized trials and from systematic reviews is presented in evidence tables. In general, each topic in the guideline sections B1-B5 and C1-C6 is associated with a separate evidence table (e.g. B2-3, C2-5, etc.). In some cases with little evidence available there is only one evidence table for the whole section (e.g. B4, C1, C6). Evidence tables contain information for all relevant studies mentioned in the respective topic or section. Only systematic reviews (SR), randomized controlled trials (RCT) and observational studies (OBS) are listed. Results generally are given without detailed statistical information; differences between groups are given only, if these were associated with statistical significance of at least $p < 0.05$ in the corresponding article.

Major GL topics are grouped in sections and recommendations are presented in boxes with information on the evidence level and

strength of the recommendation. In addition, important aspects are mentioned for future research.

3. GL review before publication

In August 2015 all GL recommendations were presented for external review on the ESPEN web site (www.espen.org) and votes on the statements as well as commentaries were collected online. 145 responses were received; of these, 119 contained votes on and/or comments to all 44 recommendations. These 119 responses originated from 17 employees of commercial companies and 102 non-industry ESPEN members. In a separate response the MNI (Medical Nutrition International) consortium collected and rephrased most commentaries which had been submitted online in a contiguous documented and presented this to ESPEN.

Considering all 145 responses, of the 44 recommendations 23 received strong consensus (>95% agreement), 20 received consensus (>75–90% agreement) and 1 received consent by a majority (72% agreement). The only topic collecting only majority agreement was the recommendation on fish oil (B5-7).

Further analysis of the 119 responders who voted and/or commented on all 44 recommendations yielded the following distribution of levels of agreement: among employees of commercial companies 14, 18, 3, 9 and among non-industry ESPEN members 26, 18, 0, 0 statements received strong consensus, consensus, majority consent or no consensus. The 9 recommendations without consensus (agreement ≤50%) among employees of commercial companies were referring to: supplementation with amino acids, fish oil and glutamine; enhanced recovery after surgery (ERAS) care, post-surgical care and immunonutrition in the context of traditional perioperative care; indications for artificial nutrition during chemotherapy.

All responses and comments received were considered by the GL group, written responses were prepared for each recommendation concerned and all agreed upon without dissent. During this process the guidelines were adapted as follows: the term "artificial nutrition" was substituted by "enteral" and/or "parenteral nutrition" as appropriate; for topics without sufficient consistent clinical data to support a recommendation a standard phrase was implemented throughout the guidelines and for these statements no "strength of recommendation" is given. With respect to the 9 recommendations receiving no consensus among employees of commercial companies, the following responses were implemented:

- Amino acids including glutamine: change of the title of section B5 to include pharmaconutrients; no change in the level of the recommendations.
- Fish oil: as suggested two sections on fish oil were merged into one.
- Surgery: The recommendation on ERAS was shortened by deleting a listing of types of artificial nutrition. The title and text of the recommendation on post-surgical care was revised to clarify the statement. The term "immunonutrition" was inserted into the title of recommendation C1-4.
- Chemotherapy: The text of recommendation C4-2 was amended to appropriately include additional indications for parenteral nutrition.

4. Updating guideline

The guideline will be updated regularly at 3-year intervals by ESPEN and the ESPEN special interest group (SIG) "Oncology". Regular updates will be done after updated review of the literature, a new Delphi process, and external review. In addition, the ESPEN-SIG will perform regular literature checks on a yearly basis to decide whether additional urgent updates are required based on new randomized controlled studies of low bias; urgent updates may be partial and concern only individual subtopics of the GL but will require a Delphi procedure and external review.

O3. Post-publication impact

1. Facilitators and barriers

Application of the guideline will be facilitated by implementing dedicated structures and processes and assigning responsibilities to dedicated professionals in each oncologic institution to organize and monitor nutritional and metabolic support. This process may be induced and promoted by incorporating relevant structural elements into accreditation procedures for oncologic centres of excellence.

The main barriers to application of the guideline are likely to be related to the relatively low esteem still associated with nutritional support in clinical oncology today as well as financial incentives to limit nutritional support [10–14,19,20]. These problems vary by region and may be traced to a number of causes, among them a lack of nutrition topics in medical and oncology specialist training, the low utilization of drugs in nutritional treatments, the ease of application and the relatively large therapeutic index of supplementary enteral or intravenous nutrients, the lack of specific malnutrition symptoms, the dearth of acute and generally rather unspecific effects of nutritional care, and finally, the sparsity of high quality evidence supporting diagnostic and therapeutic nutritional and metabolic interventions.

2. Tools for application

This guideline comes "as is" without any additional tools.

3. Costs associated with implementing the guideline

Nutritional management as proposed by the guideline will require screening for malnutrition in all and further assessment and treatment in a relevant fraction of cancer patients. Assuming requirements for hours of professional work for screening (0.1–0.2 h), assessment (0.2–0.5 h), nutrition management (0.5–1.5 h), and muscle training (0.5–1.5 h) per patient screened, assessed or treated, will result in a total of 0.3–2.0 h of nutritional/metabolic professional time for each patient seen by an oncologic institution.

4. Monitoring and auditing

Monitoring and auditing of the quality of nutritional and metabolic support is in its infancy. Application of the recommendations collected in the guideline may be monitored tentatively by the following criteria, where the degree of adherence cannot be defined at this time but needs to be fixed by the individual institution:

(1) The fraction of all cancer patients who are screened for malnutrition should exceed [e.g. 80] %.
(2) The fraction of cancer patients with a high-risk screening result who receive further nutritional assessment should exceed [e.g. 80] %.
(3) The fraction of cancer patients undergoing nutrition assessment in whom muscle mass is estimated should exceed [e.g. 80] %.
(4) The fraction of cancer patients with a high-risk screening result who receive nutritional therapy to improve energy and protein intake should exceed [e.g. 80] %.
(5) The fraction of cancer patients receiving nutritional therapy who are being reassessed after an interval of [e.g. 1–4] weeks should exceed [e.g. 80] %.
(6) The fraction of cancer patients receiving nutritional therapy who are simultaneously receiving interventions to improve skeletal muscle mass should exceed [e.g. 80] %.
(7) The fraction of cancer patients undergoing major surgery who are being treated under "Enhanced recovery after surgery (ERAS) should exceed [e.g. 80] %.

(8) The fraction of cancer patients undergoing radio(chemo-) therapy and are being tube fed who are being supported to maintain swallowing should exceed [e.g. 80] %.

(9) The fraction of cancer patients undergoing chemotherapy who have an average energy intake of less than 80% of the estimated requirement per month should not exceed [e.g. 20] %.

(10) The fraction of cancer patients who receive artificial nutrition during the terminal/dying phase should not exceed [e.g. 90] %.

Chapter A: Background

Definitions of "cancer patient" and "malnutrition"

What is a "cancer patient"? A cancer patient is a patient with a cancer diagnosis who is either waiting for or on cancer-directed treatment, on symptomatic treatment, and/or receiving palliative care. Patients cured from their cancer are termed "cancer survivors".

It is important to understand that the denomination "cancer patient" is quite general and will cover a patient during the whole trajectory of the disease, including neoadjuvant, curative, and adjuvant as well as different stages of treatment with palliative intent in the case of incurable disease. Patients at time of diagnosis may be in the cancer trajectory anywhere along its course, and move along it to cure or to palliation; therefore nutrition treatment concepts may need to be adapted accordingly (see Fig. 1).

There have been a number of different frameworks and specific definitions published during the last few years that deal with malnutrition and metabolic derangements in cancer patients [21–23].

The salient point is that, unlike simple malnutrition, the negative energy balance and skeletal muscle loss observed in cancer patients is driven by a combination of reduced food intake and metabolic derangements (e.g. elevated resting metabolic rate, insulin resistance, lipolysis, and proteolysis which aggravate weight loss and are provoked by systemic inflammation and catabolic
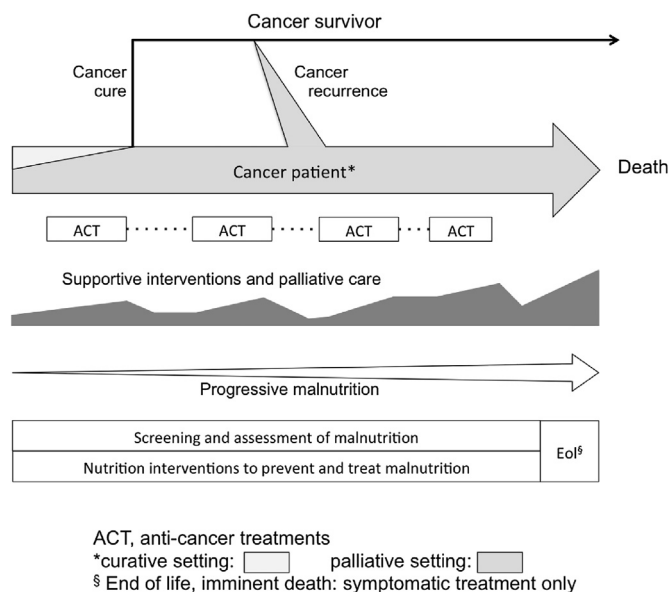

Fig. 1. Disease trajectories of cancer patients and survivors. Cancer recurrence in survivors usually results in incurable disease. During disease progression and repeated treatment cycles requirement for supportive and palliative care will vary. Malnutrition may develop at any time and will usually be progressive. Throughout the trajectory screening for and assessment of malnutrition are recommended in all cancer patients as are appropriate nutrition interventions. Nearing the end of life treatment needs to focus on symptomatic support including alleviating hunger and thirst while all additional nutritional support may do more harm than good.

factors) which may be host- or tumor-derived. Due to the presence of these metabolic changes, cancer-associated malnutrition can only be partially reversed by conventional nutritional support. Variation in terminology is found around the central concept of *cancer associated malnutrition* [22] or *cachexia* [21], *but regardless of these* different terms, the presence of reduced food intake and metabolic derangements is consistently acknowledged [24] Several new terms have appeared in the oncology literature including sarcopenia, precachexia, and refractory cachexia. However, these are still at the level of proposed terms and cannot at this time be presented as operational. Therefore, we tried to avoid using any of these unless stated explicitly and to rather speak separately about the pathophysiological and clinical components of malnutrition including systemic inflammation, anorexia, energy intake, depletion of muscle/fat mass, and reduced physical activity.

A1. Catabolic alterations in cancer patients

1: *Inadequate nutritional intake* is observed frequently in patients with cancer and is associated with weight loss, which may be severe.

For practical reasons, inadequacy of food intake has been considered to be present if a patient cannot eat for more than a week or if the estimated energy intake is <60% of requirement for more than 1–2 weeks [6,7].

The causes for impaired intake are complex and multifactorial. Reduced food intake is caused by primary anorexia (i.e. central nervous system level) and may be compounded by secondary impairments to oral intake, some of which are reversible with suitable medical management. Key secondary causes of reduced intake include oral ulceration, xerostomia, poor dentition, intestinal obstruction, malabsorption, constipation, diarrhoea, nausea, vomiting, reduced intestinal motility, chemosensory alteration, uncontrolled pain, and side effects of drugs. Total inability to eat due to factors such as bowel failure or complete obstruction cannot be tolerated and requires timely implementation of artificial nutrition (unless there are specific contraindications) to avoid starvation. Partial reduction in food intake also results in large caloric deficits over time and, in this instance, consideration should be given to the percent daily deficit (e.g. >25%, >50%, or >75% of energy requirements), the expected duration, as well as the degree of depletion of body reserves. A recent analysis of an international sample of over 11,000 patients with advanced stages of cancer provides a framework for evaluation of the depletion of body reserves [25]. Both a low BMI and the amount of weight loss independently predicted overall survival. When BMI and weight loss were entered into a multivariate analysis controlling for age, sex, cancer site, stage, and performance status a grading system based on combinations of BMI and weight loss could be developed differentiating groups with distinct median survival (grade 0 = longest, Grade 4 = shortest survival) (see Fig. 2).

2: *Muscle protein depletion* is a hallmark of cancer cachexia, severely impinging quality of life and negatively impacting physical function and treatment tolerance.

Studies of the body composition of patients with cancer reveal that it is specifically the loss of skeletal muscle—with or without loss of fat—which is the main aspect of cancer-associated malnutrition that predicts risk of physical impairment, post-operative complications, chemotherapy toxicity, and mortality [26,27]. A generally accepted value for severe depletion of muscle mass is an absolute muscularity below the 5th percentile. This can be assessed as follows: mid upper-arm muscle area by anthropometry (men <32 cm^2, women <18 cm^2); appendicular skeletal muscle index determined by dual energy x-ray absorptiometry (men <7.26 kg/

BMI (kg/m²)

Fig. 2. Grading scheme (grades 0–4) to predict overall survival in patients with advanced cancer. The grading scheme is based on groupings of BMI and weight loss showing distinct median survival (0: best, 4: worst prognosis). (p < 0.001; adjusted for age, sex, disease site, stage and performance status). (Adapted from 25).

m²; women <5.45 kg/m²); lumbar skeletal muscle index determined from oncological CT imaging (men <55 cm²/m²; women <39 cm²/m²); whole body fat-free mass index without bone determined by bioelectrical impedance (men <14.6 kg/m²; women <11.4 kg/m²). Muscle mass below these values is strongly associated with mortality in cancer patients, as well as complications of cancer surgery and dose-limiting toxicity during systemic anticancer therapy. The goals of nutritional and metabolic therapy, therefore, must place considerable emphasis on maintenance or gain of muscle mass. Since physical activity and performance status are impaired in many patients with cancer and this is often accompanied by a further loss of muscle mass, combined nutrition and physical therapy are recommended.

3: A _systemic inflammation syndrome_ **is frequently activated in patients with cancer. This can vary in degree but impacts all relevant metabolic pathways including:**

- Protein metabolism: systemic inflammation is associated with altered protein turnover, a loss of fat and muscle mass and an increase in the production of acute phase proteins.
- Carbohydrate metabolism: systemic inflammation is frequently associated with insulin resistance and impaired glucose tolerance.
- Lipid metabolism: The capacity for lipid oxidation is maintained or even increased in cancer patients and especially so in the presence of weight loss.

The collective derangements of dietary intake and metabolism described above are generally approached with nutrition therapy, medical management of pain and symptoms, pharmacological agents, and physical activity. It has been suggested that the efficacy of nutrition therapy may be optimized through synergy with physical activity and/or drugs (e.g. to promote muscle anabolism or to control inflammation or insulin resistance). Therefore, this GL considers nutritional therapy, as well as related drug and physical therapies.

A2. Effects on clinical outcome

4: Systemic inflammation is associated with the development of fatigue, impaired physical activity, anorexia, and weight loss. This inflammatory syndrome can also impair or prevent the recovery of skeletal muscle mass, even if energy intake is normalized by means of conventional nutritional support.

5: Weight loss [28], **impaired physical performance** [29], and systemic inflammation in patients with cancer are all independently associated with an unfavourable prognosis, increased toxicity of anticancer treatments resulting in reductions or interruptions of scheduled treatment, and reduced quality of life.

6: Weight loss, impaired physical performance, and systemic inflammation interact with each other and result in a **continuous deterioration** of the patient's overall state and well-being.

A3. Aims of nutrition therapy

7: Nutrition and metabolic interventions aim to maintain or improve food intake and mitigate metabolic derangements, maintain skeletal muscle mass and physical performance, reduce the risk of reductions or interruptions of scheduled anticancer treatments, and improve quality of life.

8: Given the high incidence of nutritional deficits and metabolic derangements among cancer patients, it appears reasonable to **monitor relevant parameters** regularly in all cancer patients and to initiate interventions early and against all relevant impairments to prevent excessive deficits.

9: Therapies for cancer-associated malnutrition include the following:

Nutrition counselling by a health care professional is regarded as the 1st line of nutrition therapy. Professional counselling, as distinct from brief and casual nutritional "advice", is a dedicated and repeated professional communication process that aims to provide patients with a thorough understanding of nutritional topics that can lead to lasting changes in eating habits. Clearly, the best way to maintain or increase energy and protein intake is with normal food. However, this is often difficult and, in addition to counselling, oral nutritional supplements are required. **Oral nutritional supplements** are commercially available homogeneous and usually nutritionally complete nutrient mixtures for oral consumption and are most often recommended to supplement volitional food intake.

If nutrient intake remains inadequate (see above), supplemental or complete nutrition by the oral, enteral or parenteral route may be indicated, depending on the level of function of the gastrointestinal tract. Parenteral nutrition may be indicated in instances of complete bowel obstruction or failure.

- **Artificial nutrition** is the non-volitional application of nutrients via enteral tubes (**enteral nutrition**) or parenteral infusions (**parenteral nutrition**).
- **Physical therapy** includes physical activities of daily life, resistance and aerobic exercise training, and techniques to increase muscle mass and/or muscle strength. In this context, physical therapy is intended to promote anabolism and therefore promote the retention and utilization of nutrients. Cancer patients are prone to physical deconditioning in addition to nutritional deficits. Inactivity causes muscle wasting, potentiates catabolic signals, and desensitizes muscle to anabolic factors.
- **Drug therapy.** In severely malnourished patients with advanced disease, pharmacologic agents are the main treatments used a) to stimulate appetite and/or gut motility, b) to decrease systemic inflammation and/or hypercatabolism, or c) to increase muscle mass and/or improve anabolism.

10: Nutrition, and especially artificial nutrition, are associated with **risks, burdens, and costs** that need to be weighed against the expected benefits, with the knowledge and consent of the patient. In advanced cancer, the expected benefits of nutrition therapy

(related to symptom relief, muscle mass and function, and cancer treatment tolerance) diminish during the weeks and days immediately preceding death. In this context, the burden and risks of artificial nutrition, such as physical attachment to a feeding device, gastrostomy or central venous catheter placement, and complications associated with the feeding device, must be cautiously considered.

11: Theoretical arguments that nutrients "feed the tumor" are not supported by evidence related to clinical outcome and should not be used to refuse, diminish, or stop feeding [7,30,31].

12: To organize and perform **screening for nutritional risk**, assessment of nutritional and metabolic parameters, nutrition therapy and monitoring of outcomes, we recommend that each institution involved in treating cancer patients define standard operating procedures, responsibilities, and a quality control process. Responsibilities may be divided by specifying level 1 (performed by oncologists, nurses, and other experts with non-nutrition centered training) and level 2 (professional) nutrition-related activities. Organizing a nutrition care process has been pioneered by some nutrition professionals [32–36] and should be an interdisciplinary mission.

Chapter B: General concepts of treatment relevant to all cancer patients

Section B1: Screening and assessment

B1 − 1	Screening
Strength of recommendation STRONG	*To detect nutritional disturbances at an early stage, we recommend to regularly evaluate nutritional intake, weight change and BMI, beginning with cancer diagnosis and repeated depending on the stability of the clinical situation.*
Level of evidence	Very low
Questions for research	relationship of screening to assessment Interventions and clinical outcomes

<u>Strong consensus</u>

Comments

Nutritional and metabolic derangements are frequent in cancer patients, carry prognostic significance [25,37], and are often amenable to treatment [38]. Nutrition risk screening aims to increase awareness and allow early recognition and treatment. To be efficient, screening should be brief, inexpensive, and highly sensitive and have good specificity. For this purpose BMI (body mass index = body weight/length^2), weight loss, and an index of food intake may be obtained directly, or via validated nutrition screening tools, e.g. Nutrition Risk Screening 2002 (NRS-2002), Malnutrition Universal Screening Tool (MUST), Malnutrition Screening Tool (MST), Mini Nutritional Assessment Short Form Revised [39].

Due to the fact that the medical and financial impact of malnutrition has been estimated to be high, mandatory screening has been established in some countries [36,40,41]. There also is sensitivity in public opinion with regard to perceived and real malnutrition of patients in institutional care. Clearly, the outcome of mandatory screening depends on a) action being taken as a result of an abnormal screen (further assessment) and b) initiated treatment strategies being effective. There is no consensus on how to evaluate screening and which cut-offs should initiate further assessment. It should also be noted that abnormal screening results by themselves do not provide enough information to design individualized nutrition pathways.

Although prospective cohort studies suggest some benefit [38], there is no randomised clinical trial evidence that general screening in heterogeneous cancer patient populations results in improved clinical outcomes or reduced morbidity or mortality [42,43]. These findings, however, are insufficient to dismiss screening entirely, and only serve to bring into question the content of current strategies for screening/assessment/treatment.

Nutritional intervention is, at least partially, effective and can improve clinical outcomes in certain cancer types (e.g. head and neck cancer) or treatments (e.g. chemoradiotherapy) where reduced food intake is prevalent and is not accompanied by severe metabolic derangements [44,45]. In such patients, conventional screening, assessment and appropriate nutrition intervention would be predicted to work well. In other patients with severe anorexia and metabolic derangements, these changes may be mitigated but not fully reversed by personalised multimodal supportive care [46,47]. Patients with abnormal screening, therefore, need to be followed up by a more specific assessment of the origin and severity of nutritional and metabolic derangements to detect which patients might benefit from appropriately designed interventions.

Further research is required to improve early identification of patients (e.g. use of body composition analysis to detect underlying loss of muscle mass or biomarkers of inflammation), to change the timing of intervention or to enhance the efficacy of the intervention.

B1 − 2	Assessment
Strength of recommendation STRONG	*In patients with abnormal screening, we recommend objective and quantitative assessment of nutritional intake, nutrition impact symptoms, muscle mass, physical performance and the degree of systemic inflammation.*
Level of evidence	Very low
Questions for research	Linking outcomes from current and future intervention trials with appropriate screening and assessment tools

<u>Consensus</u>

Comments

Assessment should justify, inform, and guide intervention. Assessment should be repeated at adequate intervals to judge the requirement for nutritional intervention and to monitor its effects (e.g. fortnightly, monthly, 6 monthly as appropriate). Performing the assessment may be more difficult in outpatients compared with inpatients and this needs to be addressed in the organization of the local nutrition care process.

Dietary intake, body composition, physical activity and the predominant metabolic pattern are thought to be key variables that influence cancer patients' overall body resource and function [21]. In patients identified as at-risk, assessment of these domains should be undertaken and used to guide nutritional intervention. There is no consensus on the individual methods to assess these domains. Frequently used nutrition assessment tools like Subjective Global Assessment (SGA) [48], Patient-Generated Subjective Global Assessment (PG-SGA) [49,50] and Minimal Nutrition Assessment (MNA) combine qualitative and semi-quantitative data to yield a comprehensive "malnutrition score" [51] but lack specific grading of deficits in the subdomains.

Reductions in food intake should be recognized and addressed early. Oral energy intake should be assessed at least qualitatively and, if possible, quantitatively, by using food and fluid records, diet history, food recalls or visual or verbal analogue scales [52—54]. Reduced food intake may result from a variety of causes. Nutritional treatment should, therefore, be preceded by an examination for treatable issues likely to impact intake (e.g. xerostomia, changes in smell and taste, nausea, vomiting, denture irritation, mucositis or thrush, constipation, diarrhoea, malabsorption, drug side-effects, infections, acute and chronic pain, and psychological distress).

Body weight should be corrected for excessive fluid loads (pleural effusion, ascites and/or edema). Assessment of muscle and fat reserves should preferably be based on specific measurements. This may be performed with variable degrees of sophistication and reliability (e.g. dual X-ray absorptiometry (DEXA), anthropometry, computed tomography scans at lumbar level 3 or bioimpedance analysis (BIA)) [21].

Physical performance may be graded using the WHO/ECOG scale (0 = normal performance, 4 = bed-bound) [55] or Karnofsky Performance Scale 0—100 [56]. More differentiated tools may be used to monitor daily activities or to quantitate physical performance (e.g. walking tests) or muscle function (e.g. dynamometers).

Systemic inflammation is characterized by an orchestrated pathophysiological network promoting catabolic processes and catabolism of muscle protein. The extent of systemic inflammation may be estimated by measuring serum C-reactive protein (CRP) and albumin. Grading the inflammatory response according to the modified Glasgow Prognostic Score (mGPS) is highly predictive of morbidity and mortality in cancer patients [37]. In many cancer patients, further catabolic factors are activated by the presence of pain, fatigue, constipation, nausea, vomiting and other relevant somatic symptoms as well as psychological distress [21].

Section B2 Energy and substrate requirements

B2 − 1	Energy requirements
Strength of recommendation STRONG	*We recommend, that total energy expenditure of cancer patients, if not measured individually, be assumed to be similar to healthy subjects and generally ranging between 25 and 30 kcal/kg/day.*
Level of evidence	Low
Questions for research	improve prediction of energy requirements in the individual patient

Consensus

Comments

The level of evidence is "low" because only a few studies including only a small number of patients have assessed total energy expenditure in cancer patients. However the strength of this recommendation relies on its biologic plausibility, which is the well-known benefits of energetically adequate nutrition and on the adverse metabolic and clinical effects of chronic malnutrition and starvation. An insufficient diet leads to chronic malnutrition. To maintain a stable nutritional state, the diet has to meet the patient's energy requirements which are the sum of the resting energy expenditure (REE), physical activity, and, in a small percentage, of diet-induced thermogenesis. Using hypercaloric artificial feeding in cancer patients with metabolic derangements who are losing weight, however, may fail to increase body weight (see section A, statement 4.) but rather lead to overfeeding with undesired metabolic effects. On this basis we recommend planning of a correct nutritional regimen in all patients with benign and malignant diseases.

There is no evidence that adequate nutritional support increases tumour growth in humans ([57]; see section A, statement 11).

To estimate total energy expenditure (TEE) in cancer patients it is necessary to consider resting energy expenditure (REE) and energy expenditure associated with physical activity.

Resting energy expenditure

There is evidence that REE is elevated in some cancer patients. In cancer patients, REE determined by indirect calorimetry, the gold standard, has been reported to be unchanged, increased, or decreased in relation to non-tumour bearing controls. In about 25% of patients with active cancer, REE measured by indirect calorimetry, was more than 10% higher, while in another 25% it was more than 10% lower than predicted energy expenditure. The extent or direction of the error, however, could not be predicted for individual cases [58,59]. In a large study from the group at Lundholm [60], approximately 50% of all cancer patients who were losing weight were hypermetabolic when compared to appropriate controls allowing for similarity in physical activity, body composition, age, and weight loss. Similarly, in newly diagnosed cancer patients, some 48% were hypermetabolic and displayed a higher ratio of measured versus predicted REE per kg of fat-free mass [61].

Comparing REE in patients with different types of cancers, some authors reported normal REE in patients with gastric or colorectal cancers [61—63]) and higher than expected REE in subjects with pancreatic or lung cancers [63—65]. While it remains unclear whether the origin of the primary cancer affects REE, the increase in REE in lung cancer patients has been related to the presence of a systemic inflammatory response [66].

There are few and inconsistent data regarding effects of cancer treatments on REE. Hansell et al. [62] studied 15 patients with colorectal cancer and did not observe any effects of curative surgery or of hepatic metastases on REE. Fredrix et al. [63] compared REE in healthy controls and 104 patients with gastric or colorectal cancer and 40 patients with non-small cell lung cancer before and 1 year after cancer surgery. Subjects with gastrointestinal cancers had normal REE, which rose slightly after surgery, while lung cancer patients had elevated REE which decreased after curative resection, but not if there was recurrence of the tumour. Chemotherapy treatment in twelve patients with newly diagnosed small cell lung cancer resulted in reduction of both circulating inflammatory mediators and REE [66,67].

Total energy expenditure

While REE is increased in a many cancer patients, when TEE is considered, this value appears to be lower in patients with advanced cancer when compared to predicted values for healthy individuals [64,65]; the main cause appears to be a reduction in daily physical activity. However, it needs to be considered that small differences between energy intake and energy expenditure will result in further weight loss. Sparse data obtained by using a wearable device to monitor daily activity (Sense-Wear armband; Sensormedics Italia Srl) indicate that TEE of weight-stable leukemic patients and of weight-losing bedridden patients with gastrointestinal tumours is about 24 and 28 kcal/kg/day, respectively [68,69]).

In conclusion, it appears sensible to initiate nutrition therapy assuming TEE to be similar to healthy controls. TEE may be estimated from standard formulas for REE and standard values for physical activity level (PAL) [64]. Alternatively, TEE may be predicted roughly by using rules of thumb and assuming TEE to be some 25—30 kcal/kg depending on the patient's performance status [6,7]. By these rough estimates TEE will be overestimated in obese and underestimated in severly malnourished patients. More

accurately, REE may be determined by indirect calorimetry and physical activity by wearable devices. It is essential, however, in the course of treatment to subsequently adapt provision of energy according to clinical effects on body weight and muscle mass [70,71].

B2 − 2	Protein requirement
Strength of recommendation STRONG	*We recommend that protein intake should be above 1 g/kg/day and, if possible up to 1.5 g/kg/day*
Level of evidence	Moderate
Questions for research	effect on clinical outcome of increased supply (1−2 g/kg/day) and composition of protein/amino acids

Strong consensus

Comments

The evidence to support this statement is moderate because the existing studies focused on metabolic endpoints and benefits and did not address clinical end-points. However metabolic investigations showed that an elevated protein intake promoted muscle protein anabolism in patients with cancer [72]. This potential benefit, in our opinion, may justify using a high protein diet.

Quantity of amino acid

The optimal nitrogen supply for cancer patients has not been determined and the recommendations of experts range between a minimum protein supply of 1 g/kg/day and a target supply of 1.2−2 g/kg/day [73−75], especially if inactivity and systemic inflammation are present [76]. Old age, inactivity and systemic inflammation are known to induce "anabolic resistance", i.e. decreased responsiveness of protein synthesis to anabolic stimuli [77]). Evidence-based recommendations for chronically ill older subjects call for a protein supply of 1.2−1.5 g/kg/d [78,79].

The mean ratio of REE to nutritional nitrogen requirement in the post-absorptive state has been estimated to be 130 kcal/g nitrogen [80−83]. Due to the fact that the net utilization of amino acids is less than 100%, the REE/nitrogen ratio of any nutritional admixture should be smaller and possibly closer to 100 kcal/g nitrogen.

Muscle protein synthesis is evidently not shut off completely in patients with cancer, because several studies suggest that this process is not impaired and remains responsive to the dietary supply of amino acids, albeit a somewhat higher quantity than in younger, healthy individuals [84].

According to a recent literature review [85] the dose of amino acids capable of supporting a positive protein balance in cancer patients might be close to 2 g/kg/day (Electronic supplementary material). This is in agreement with the recent investigation by Winter et al. [86] who showed that moderately cachectic lung cancer patients had considerable insulin resistance including impaired glucose utilization and whole-body protein anabolism but that a normal anabolic protein response could be re-established by hyperaminoacidemia.

In subjects with normal kidney function, intake of protein in doses up to and above 2 g/kg/d are safe [87]; in patients with acute or chronic renal failure protein supply should not exceed 1.0 or 1.2 g/kg/d, respectively [88].

Composition of amino acid mixtures

There is a general consensus that the vast majority of cancer patients requiring nutritional support for only a short period of time do not need any specifically formulated amino acid mixture (as opposed to good quality protein from animal, fish, dairy, and plant sources) [7]. However, in future studies, special attention should be paid to patients with overt malnutrition requiring nutritional support for several weeks because of the well-known abnormalities in energy and substrate metabolism in these conditions.

Data regarding the nutritional quality of proteins in cancer patients are very scarce. From a prospective, randomized, crossover trial involving patients with advanced intra-abdominal adenocarcinomas, Tayek et al. [89] and Hunter et al. [90] concluded that total parenteral nutrition enriched with branched chain amino acids resulted in an improved protein accretion and albumin synthesis when compared to standard amino acid solutions. Recently, Deutz et al. [91] reported the findings of a randomized clinical trial, showing that the administration of 40 g of amino acids (0.48 g/kg) when given as an oral nutritional supplement enriched in leucine- and N-3 fatty acids to non-malnourished patients with advanced cancer, led to a significant increase in the fractional synthetic rate of muscle protein when compared to feeding a conventional supplement containing 24 g of protein.

The role of supplementation with glutamine is still controversial despite some biologic rationale based on glutamine being semi-essential in catabolic conditions. A recent narrative review on the effects of glutamine supplementation on chemotherapy toxicity reported that only 8 of 24 studies using oral, and only 6 of 12 studies using parenteral glutamine reported a clinical benefit [92].

B2 − 3	Choice of energy substrates
Strength of recommendation STRONG	*In weight-losing cancer patients with insulin resistance we recommend to increase the ratio of energy from fat to energy from carbohydrates. This is intended to increase the energy density of the diet and to reduce the glycemic load.*
Level of evidence	Low
Questions for research	effect of a high fat diet on clinical outcome in patients with systemic inflammation/insulin resistance effect of varying the fat composition

Consensus

Comments

The optimal ratio of carbohydrates and fat in feeding cancer patients has not been determined but may be derived from pathophysiologic arguments. In patients with insulin resistance, uptake and oxidation of glucose by muscle cells is impaired; however, utilisation of fat is normal or increased [93] thus suggesting a benefit for a higher fat to carbohydrate ratio. For enteral feeding the energy density of the diet is important. This is achieved by increasing the proportion of fat. Most dietetic recommendations in anorectic cancer patients are focused on increasing the energy density of the diet and most commercially available products are touted and chosen because of their high energy density. It is well-known that low appetite, early satiety, and reduced bowel motility all conspire to limit the intake of low energy density foods.

The majority of intervention studies concerning the metabolic utilization of substrates have been performed during or after an intravenous administration to avoid any interference from unpredictable variations in intestinal absorption following enteral administration. In 1971, Waterhouse and Kemperman showed that fat was efficiently mobilized and utilized as a fuel source in cancer patients [94]. Similarly, several authors later demonstrated a very efficient mobilization and oxidation of endogenous fat in the post-absorptive state ranging from 0.7 to 1.9 g/kg/day (i.e. up to 60%−

80% of REE) both in weight-stable and weight-losing cancer patients [81,95–100]. Compared to healthy subjects the metabolic clearance of different lipid emulsions was increased in weight-stable and even more so in weight-losing cancer patients [100].

Fat emulsions supply essential fatty acids. The use of large amounts of standard soybean-based lipid emulsion, however, has been questioned because of the high content of N-6 PUFA, which has been associated with an increase in the production of proinflammatory eicosanoids [101]. Olive oil-based emulsions contain some 20% N-6 PUFA (i.e. enough to supply the essential fatty acids requirement) and 65% oleic acid. More recently, emulsions enriched in N-3 fatty acids have become commercially available. By competitive antagonism with N-6 fatty acids, N-3 fatty acids down-regulate PGE$_2$ production, activate peroxisomal proliferator-activated receptors [102], suppress the activation of genes involved in the inflammatory process [103], and, by this, may act to decrease inflammatory activity. Based on substantial biochemical and clinical evidence alternatives to N-6-based fatty emulsions may result in less proinflammatory effects, less immune suppression, and more antioxidant effects and, thus, may potentially be a more physiological energy source [101]. However, because there have been no clinical studies comparing the effects of different fat emulsions on outcomes in cancer patients, the role of these alternative emulsions is still not clearly defined.

There are additional advantages to replacing glucose with lipids in parenteral nutrition regimens. It appears prudent to try to limit the infectious risks associated with hyperglycaemia, which, albeit mainly reported in the non-oncologic setting, may be similarly expected in cancer patients with insulin resistance. Furthermore, glucose administration tends to cause a deleterious positive water balance. Gamble [104] first demonstrated that glucose reduces renal sodium excretion and, for the same reasons, the loss of extracellular fluid and Bloom [105] suggested that this effect was mediated by insulin, a potent anti-natriuretic and antidiuretic hormone [106] through increased sympathetic activity. The effects of glucose-based PN on water and sodium retention have been demonstrated by Rudman et al. [107] and were subsequently described in cancer patients by Fan et al. [108], Bozzetti et al. [109], and Gray and Meguid [110]. In cancer patients there may be excessive production of antidiuretic hormone (ADH) due to the tumour [111], to the presence of nausea, or to the administration of morphine. Furthermore, severe malnutrition is associated with loss of intracellular water and solutes which, via hypothalamic ADH release, result in serum osmolality and sodium at subnormal levels [112]. As a consequence, the clearance of free water is decreased, whereas the synthesis of endogenous water is maintained by the oxidation of carbohydrates and fat [113] and insensible water loss drops due to reduced physical activity [114].

B2 − 4	Vitamins and trace elements
Strength of recommendation STRONG	*We recommend that vitamins and minerals be supplied in amounts approximately equal to the RDA and discourage the use of high-dose micronutrients in the absence of specific deficiencies.*
Level of evidence	Low
Questions for research	Assessment of micronutrient status in cancer patients and effect of supplementation

Strong consensus

Comments

An overall premise of nutrition practice is to provide all patients with a nutritionally adequate diet, which includes all classes of micronutrients, especially those that are essential in the human diet [115]. In all forms of malnutrition there is a risk of micronutrient deficiency, especially, but not limited to, water soluble vitamins [116,117]. As regards the requirements of cancer patients for vitamins and trace elements, we rely on the review by Ströhle et al. [118] and statements recently reported by the American Cancer Society [119]: "1) In view of the restricted dietary pattern of tumor patients, the use of a multivitamin-multimineral supplement in physiological doses, i.e. nutrient amounts that approximately equal the recommended daily allowance, is a useful [120,121] and safe [122] measure. This also applies to cancer patients during chemo- and radiation therapy [122]."

For oral and enteral feeding, daily requirements for micronutrients may be taken from recommendations of WHO/FAO as well as national and international nutrition societies [123–127]. Similarly, vitamins and trace elements should be generally substituted in parenteral nutrition unless there are contraindications. The supplementation of vitamins and trace elements is obligatory after a parenteral nutrition of more than 1 week. A standard dosage of vitamins and trace elements based on current dietary reference intakes for oral feeding is generally recommended unless certain clinical situations require other intakes [128]. In total, parenteral nutrition supplementing trace elements may avoid a decrease in plasma levels of those elements [129].

Quite frequently, deficiency of vitamin D is observed in cancer patients [118]; this has been associated with cancer incidence and prognosis [130–134]. Using a trial sequential meta-analysis of 40 RCTs including 7 documenting cancer incidences, Bolland et al. reported that vitamin D supplementation with or without calcium did not reduce skeletal or non-skeletal outcomes in unselected community-dwelling individuals by more than 15%; they concluded that future trials with similar designs were unlikely to alter these conclusions [135]. Another recent systematic review arrived at a similar conclusion [136]. However, it is not known whether using vitamin D supplements to normalize vitamin D levels in states of deficiency will improve prognosis in cancer patients.

In general, the use of single high-dose micronutrients should be avoided [119]. An estimated 50% of all cancer patients consume complementary or alternative medical products [137]); a large fraction of this is accounted for by multivitamin supplements [138]. A large meta-analysis of 68 randomized prevention trials including more than 230,000 participants found no protective effects of antioxidants but a slightly raised mortality in subjects consuming β-carotene, vitamin A, or vitamin E [139]. In a prospective observation in more than 290,000 men, consuming multivitamin supplements was associated with a significant increase in mortality from prostate carcinoma [140]. In patients with early colon cancer, use of multivitamin supplements was not associated with improved rates of cancer recurrence or overall survival [141]. Ristow et al., in a randomized design, supplied healthy subjects with vitamin C (1000 mg/day) and vitamin E (400 IU/day) or placebo during a 4-week physical exercise training program and observed an abrogation by the vitamins of the exercise-induced improvement in insulin resistance [142]. Five to eight years of dietary supplementation with β-carotene (25 mg) or tocopherol (50 mg) in smokers did not diminish and possibly increased the risk of lung cancer [143]. Neither long-term supplementation with vitamin E (400 IU/day) nor selenium (200 μg from selenomethionine) had a beneficial effect on incidence of prostate cancer [144]. A prospective observational trial in 4459 men with early prostate cancer reported mortality to be significantly increased by a factor of 2.6 in men supplementing selenium in doses of more than 140 μg/day [145]. In a RCT in 14,641 US

physicians combined supplementation with vitamin E (400 IU/day) and vitamin C (500 mg/day) for an average of 10 years was without any effect on cancer incidence [146].

Section B3 Nutrition interventions

B3 − 1	Efficacy of nutritional intervention
Strength of recommendation STRONG	*We recommend nutritional intervention to increase oral intake in cancer patients who are able to eat but are malnourished or at risk of malnutrition. This includes dietary advice, the treatment of symptoms and derangements impairing food intake (nutrition impact symptoms), and offering oral nutritional supplements.*
Level of evidence	Moderate
Questions for research	effect of dietary advice and ONS on clinical outcome

<u>Consensus</u>

Comments

General comments

Unfortunately, data are still lacking that define the optimal time for initiating nutritional support. However, malnutrition is associated with poorer prognosis and it is difficult to revert overt malnutrition in cancer patients with metabolic derangements [147,148]. Therefore, nutritional therapy should preferably be initiated when patients are not yet severely malnourished and when the goals of care include maintaining or improving nutritional status [21,23]. Nutritional support should be offered to patients who are likely to develop anorexia or gastrointestinal defects due to the side effects of treatment. Severely malnourished patients who are undergoing active treatment should be offered nutritional therapy immediately.

Next to supporting health, food and eating have important roles in psychological stabilization and social integration and by this impacting quality of life. Nutritional counselling should consider and aim for maintaining or improving all of these aspects. This will require ascertaining individual habits and preferences; in addition, effective counselling requires adequate communication skills to ensure high compliance with the individualized nutritional advice given [149].

Forms of nutritional support

Generally, the first form of nutritional support should be nutrition counselling to help manage symptoms and encourage the intake of energy-enriched foods and fluids that are better tolerated; a diet enriched in energy and protein is the preferred way to maintain or improve nutritional status. The additional use of ONS is advised when an enriched diet is not effective in reaching nutritional goals. Nutritional counselling includes nutritional history, diagnosis, and nutrition therapy. This should be performed by trained nutrition professionals (registered/accredited dieticians or nutritionists) on the basis of the nutrition care process [150]. This incorporates calculation or measurement of energy and nutrient requirements, food preparation and/or modifying of texture or nutrient content, increasing meal frequency by distribution of foods to several small meals, enriching dishes with energy- and protein-dense additives, offering oral nutritional supplements, a meal set-up plan that emphasizes supportive interventions to improve oral food intake (e.g.

treating mucositis and other symptoms), digestion (e.g. pancreatic enzymes) or absorption (e.g. slowing of rapid gastrointestinal transit), antiemetics, and other relevant conditions. Applicability of guideline recommendations on these topics is improved by using standardized diagnostic tools and therapeutic procedures [150–153].

Artificial nutrition is indicated if patients are unable to eat adequately (e.g. no food for more than one week or less than 60% of requirement for more than 1–2 weeks; see A.1). If a decision has been made to feed a patient, we recommend enteral nutrition if oral nutrition remains inadequate despite nutritional interventions (counselling, oral nutritional supplements), and parenteral nutrition if enteral nutrition is not sufficient or feasible.

Evidence supporting nutritional interventions

Nutritional therapy in cancer patients who are malnourished or at risk of malnutrition has been shown to improve body weight and energy intake but not survival [153,154]. In patients undergoing (adjuvant) radiotherapy there is good evidence that nutritional support improves intake and weight, and some aspects of quality of life [44,45,155]. A reliable effect on quality of life, however, could not be found in a systematic review and meta-analysis [156], thus pointing to a need for further investigations. One study suggested long-term positive effects of nutritional support on late radiation toxicity and mortality [157]. In patients undergoing chemotherapy, results are less conclusive [42].

Two recent systematic reviews and meta-analyses have addressed the efficacy of nutritional therapy on outcomes [153,156]. The systematic review and meta-analysis by Halfdanarson et al. studied the effect of nutritional counselling on quality of life [156]. Five randomized clinical trials with a total of 488 patients were included. The standardized mean difference in QoL scores between those who received nutritional counselling versus no nutritional counselling was 0.56 (95% confidence interval 0.01–1.14, p = 0.06). This borderline statistical significance, in combination with a point estimate in favour of the intervention, suggests that nutritional counselling may be justified in select patients suffering from especially poor oral intake and weight loss.

The aim of the systematic review by Baldwin et al. was to examine the evidence for an effect of dietary intervention (nutritional counselling, oral supplements, or both) in cancer patients who were malnourished or were at risk of malnutrition [153]. The review included 13 (quasi-)randomized controlled trials with a total of 1414 patients. No difference in survival was found (relative risk = 1.06, 95% confidence interval 0.92–1.22, P = 0.43; no heterogeneity, I^2 = 0%). Quality of life was significantly improved (both when including all studies and when removing the studies that accounted for high heterogeneity) on the global QoL scale, and on the "emotional functioning", "dyspnea", and "loss of appetite" scales. However, positive results were observed only in those studies in which the patients received (adjuvant) radiotherapy (no more tumour in situ), whereas negative results were obtained in the studies that included patients undergoing systemic chemotherapy. The interventions were associated with statistically significant improvements in body weight (mean difference in weight = 1.86 kg, 95% confidence interval 0.25–3.47, p = 0.02), but there was statistically significant heterogeneity. Groups receiving nutritional therapy had a significantly greater energy intake than groups receiving routine care, again with high heterogeneity. A post-hoc analysis found that

studies that offered both dietary advice and oral nutritional supplements had the greatest effect.

B3 − 2	Potentially harmful diets
Strength of recommendation STRONG	*We recommend to not use dietary provisions that restrict energy intake in patients with or at risk of malnutrition.*
Level of evidence	Low
Questions for research	Effects of fasting or fasting mimicking diets on wanted and unwanted effects of anticancer agents

Strong consensus

Comments

We recommend against all forms of diets that are not based on clinical evidence, have no proven efficacy, and that potentially could be harmful. Specific harms may include secondary micronutrient deficiency, exacerbation of malnutrition, and high cost. There are no diets known to reproducibly cure cancer or prevent cancer recurrence. Depending on region and culture, different, often complex and contradictory, dietary suggestions are proclaimed to antagonize cancer growth and are proposed as anticancer diets [158,159]. In many cases, the supporting arguments are neither based on scientific reasoning nor on solid evidence and the supporting information is derived from anecdote and unverifiable sources in the popular literature and Internet rather than peer-reviewed literature. Some diets may be described as fad diets (defined as an intense enthusiasm, especially one that is short-lived and not based on the object's qualities; a craze). Compliance for following extreme dietary regimens (e.g. carbohydrate-rich or fat-rich) is low [160,161].

We discourage dietary advice or diets, which increase the risk of inducing or aggravating malnutrition. Fad diets are generally highly restrictive in the type and quantity of specific foods, and, as such, generally restrict food intake. These diets increase the risk of insufficient intake of energy, fat, and protein, as well as generate risk of micronutrient deficiency. Some such diets also have low energy density and/or low protein content. In cancer patients who are already malnourished, this may be harmful and should be avoided. However, patients often are anxious to discuss dietary options and are eager to commit themselves to fighting their cancer by choosing foods that are perceived as "protective". This patient need should be recognized and acknowledged and it should initiate an unbiased discussion and counselling on what nutrition can and cannot achieve and on the risks associated with an inadequate or restrictive diet [158,159].

Due to their low palatability, ketogenic diets may lead to insufficient energy intake and weight loss [162]. Ketogenic diets which limit the intake of carbohydrates to very small amounts have been proposed to deplete tumour tissue of the glucose required for tumour cell metabolism [163–165]. While many tumours express glucose transporters with a low kM of 1.5–2 mM (GLUT1, GLUT 3) [166–173], interesting results have been obtained in in-vitro and in animal experiments. Transfecting normal cells with Akt diminishes their resistance to survival in glucose-free media [174] and supplying mice with low carbohydrate feed slows growth of implanted tumours [175] and prolongs survival [176]. However, there are no clinical trials demonstrating a benefit of a ketogenic diet in cancer patients. Two pilot trials without control groups in patients with glioblastoma [177] or mixed advanced solid tumours [162] did not

observe tumour responses. While it may be difficult to induce tumour responses with a ketogenic diet [178], this does not argue against preferring fat to supply energy to patients with advanced cancer and inflammation-induced insulin resistance [179].

Short-term (24–72 h) fasting before, during and after the application of anticancer agents has been suggested to possibly increase the effectivity and tolerability of cytotoxic treatment [180–184]. A small observational series and a small randomized trial reported good tolerability of this approach in humans [185,186]. Further trials are ongoing (NCT00936364, NCT00175837, NCT01802346, NCT02126449). Because of the risks of malnutrition and because patients might be tempted to prolong fasting episodes, without firm evidence of a benefit fasting during chemotherapy cannot be recommended.

B3 − 3	Modes of nutrition: when to escalate
Strength of recommendation STRONG	*If a decision has been made to feed a patient, we recommend enteral nutrition if oral nutrition remains inadequate despite nutritional interventions (counselling, ONS), and parenteral nutrition if enteral nutrition is not sufficient or feasible.*
Level of evidence	Moderate
Questions for research	effect of EN or PN or combinations on clinical outcome in patients with inadequate food intake

Strong consensus

Comments

In cancer patients who are unable to eat, digest or absorb food, artificial feeding may stabilize nutritional status. In patients with tumours that impair oral intake or food transport in the upper gastrointestinal tract, nutritional status can be stabilized by artificial enteral nutrition [187,188]. When comparing different options to perform enteral tube feeding, patients appear to prefer PEG to nasogastric tubes [147]. On the other hand, more recently it has been reported that in head and neck cancer patients complication rates were lower with nasogastric tubes compared to feeding via PEG while success rates were high [189].

In cases of severe intestinal insufficiency due to radiation enteritis, chronic bowel obstruction, short bowel syndrome, peritoneal carcinosis, or chylothorax, nutritional status can be maintained by parenteral nutrition [190–192]. However, it has not been proven whether artificial nutrition may improve nutritional status or clinical outcome in anorectic patients with preserved gastrointestinal function. Thus, a systematic review of controlled trials testing unconditional artificial versus oral feeding in patients with advanced cancer observed no benefit but rather increased complication rates for enteral as well as parenteral feeding [193]. This review did not exclude a benefit of artificial feeding in patients with prolonged inability to consume oral food, but it recommended against using the cancer diagnosis per se as an indication for supplying artificial nutrition. Due to this uncertainty and also considerations concerning costs and the risk of complications of artificial nutrition, we recommend increasing the invasiveness of the nutritional approach only after carefully assessing the inadequacy (see A.1) of the more physiological oral route.

If intestinal functions are preserved, enteral feeding may be as efficient as parenteral feeding [147]. Advantages of the enteral versus the parenteral route are the maintenance of

the gut barrier, less infectious complications, and lower costs.

While there are open questions about the specific indications for starting artificial nutrition, clinical practice, contraindications, complications, and monitoring of enteral and parenteral nutrition do not differ between cancer patients and patients with benign diseases [194]. Clinical practice differs from country to county mainly because of economic reasons, tradition, and ethical approach [195,196]. Ethical considerations for artificial nutrition relate to its use during the last weeks and days of life in advanced malignancies. The risks and detriments as well as the possible futility of artificial nutrition must be weighed against possible physiologic and or psychological benefits, for a given patient and family. The bioethical aspects of feeding patients with advanced disease have been considered [474]. As a general rule, the risks of PN are regarded to outweigh its benefits for patients with a prognosis of less than 2 months. However, in some cultures, active feeding in any form is regarded as essential.

B3 − 4	Refeeding syndrome
Strength of recommendation STRONG	*If oral food intake has been decreased severely for a prolonged period of time, we recommend to increase (oral, enteral or parenteral) nutrition only slowly over several days and to take additional precautions to prevent a refeeding syndrome.*
Level of evidence	Low
Questions for research	Assessment of phosphate, potassium and magnesium levels in malnourished cancer patients and response to artificial feeding

Consensus

Comments

Refeeding syndrome is defined as the potentially fatal shifts in fluids and electrolytes that may occur in severely malnourished patients receiving artificial refeeding (whether enterally or parenterally) [197,198]. These shifts result from feeding-induced hormonal and metabolic derangements and may cause serious clinical complications, including cardiac and neurological derangements [198,199]. The classic biochemical feature of refeeding syndrome is hypophosphataemia, but it may also feature abnormal sodium and fluid balance, changes in glucose, protein, and fat metabolism, thiamine deficiency, hypokalaemia, and hypomagnesaemia.

Risk of developing refeeding syndrome increases with the degree of the patient's nutritional depletion [200,201]. In patients with minimal food intake for at least 5 days, it has been recommended that no more than half of the calculated energy requirements be supplied during the first 2 days of feeding [202]. If depletion is severe, initial energy supply should not exceed 5–10 kcal/kg/day and then a slow increase of energy intake over 4–7 days can be provided until full substitution of requirements is reached [203]. Volume of circulation, fluid balance, heart rate and rhythm, as well as clinical status should be monitored closely. Before and during nutritional repletion it is prudent to supply vitamin B1 in daily doses of 200–300 mg as well as a balanced micronutrient mixture. The following electrolytes should be monitored and substituted, if necessary, by the oral, enteral, or parenteral route: potassium (requirement approximately 2–4 mmol/kg/day), phosphate (requirement approximately 0.3–0.6 mmol/kg/day) and magnesium (requirement approximately 0.2 mmol/kg/day if supplied intravenousy or 0.4 mmol/kg/day if supplied orally).

B3 − 5	Home artificial nutrition
Strength of recommendation STRONG	*In patients with chronic insufficient dietary intake and/or uncontrollable malabsorption, we recommend home artificial nutrition (either enteral or parenteral) in suitable patients*
Level of evidence	Low
Questions for research	Effect of long-term EN and PN on clinical outcome

Strong consensus

Comments

The bioethical aspects of feeding patients with advanced disease who are expected to survive weeks or days should be considered [204,205]. This includes respect for the religious, cultural and ethnic background of patients as well as social, emotional and existential aspects [206]. However, withdrawal of artificial feeding or deciding not to initiate artificial feeding in a patient who is unable to consume food is usually considered only in an end-of-life setting. There are data showing benefits of home artificial nutrition in cancer patients with chronic defects of dietary intake or absorption even in advanced cancer as long as there is a survival of more than a few weeks [207,208]. Benefit may clearly be inferred by the fact that some cancer patients survive many months and even years exclusively on PN, i.e. time frames over which any person without food would have otherwise succumbed to starvation [190,209].

Home parenteral nutrition (HPN) is a complex therapy and selecting patients suitable for this treatment option is a demanding task. It is important to evaluate the patient's cognitive and physical abilities before starting a HPN training program. The home environment, medical suitability, rehabilitation potential, social and economic factors, and reimbursement sources should be assessed by the extended nutrition team (including, for example, social workers and other designated health care professionals) before starting training for HPN [210].

Section B4: Exercise training

B4 − 1	Exercise in combination with nutrition
Strength of recommendation STRONG	*We recommend maintenance or an increased level of physical activity in cancer patients to support muscle mass, physical function and metabolic pattern.*
Level of evidence	High
Questions for research	effect of physical activity before, during and after anticancer treatment on clinical outcome, effect of combining an exercise program with nutritional support in curative and palliative settings

Consensus

Comments

Data from published randomised trials summarized in several meta-analyses provide relatively strong evidence that physical activity is well-tolerated and safe at different stages of cancer [211], and also that patients with advanced stages of disease are able and willing to engage in physical activity [212,213]. Physical exercise

intervention trials have closely followed exercise prescription guidelines for the general population. This consists of supervised or home-based moderate-intensity training (50—75% of baseline maximum heart rate or aerobic capacity), three sessions per week, for 10—60 min per exercise session. Physical activity in cancer patients is associated with maintenance or significant improvements in aerobic capacity, muscle strength, health-related quality of life, and self-esteem, and with reduction in fatigue and anxiety [214—216] (meta-analysis and RCT's, high grade evidence). However, most studies were conducted in patients with early stage breast cancer during and immediately after receiving therapy with a curative intent, while fewer studies were conducted that included patients with non-small lung cancer (NSCLC), hematologic malignancies, or advanced cancer. Cancer patients should be advised to reduce inactivity and to avoid living a sedentary lifestyle and advice should be individualized. For some patients, recommendations for physical activity should consist of motivating patients to take a daily walk in order to reduce risks of atrophy due to inactivity. Other patients would probably benefit from physical exercise programs conducted by appropriately trained experts.

relevance to food intake or absorption as well as in states typically associated with decreased appetite, like microbial infections, chronic pain, or psycho-social distress. This may include the following categories of agents, which are not a topic of this guideline, including suggested recommendations for their use:

- antiemetics to relieve nausea
- antimicrobials to eliminate fungal, bacterial, or viral causes of gastrointestinal or other infections
- analgesics to relieve chronic pain or pain associated with chewing, swallowing, or intestinal activity
- agents to induce saliva production in xerostomia
- anti-secretory agents to diminish excessive saliva production or vomiting in cases of impaired intestinal transport
- inhibitors of gastric acid secretion and other substances to treat or protect against symptomatic mucosal lesions or oesophageal reflux
- agents to maintain or normalize intestinal motility and to treat or avoid constipation or diarrhoea
- antidepressants, agents that relieve anxiety, mood modulators

B4 — 2	Type of exercise recommended
Strength of recommendation WEAK	*We suggest individualized resistance exercise in addition to aerobic exercise to maintain muscle strength and muscle mass.*
Level of evidence	Low
Questions for research	Differential and combined effects of resistance and endurance exercise on clinical outcome during anticancer therapy, in survivors and as a component of supportive and palliative care

Strong consensus

Comments

There is a strong theoretical basis for the implementation of physical activity in cancer treatment. Cancer patients, in general, report low levels of physical activity and both inactivity and cancer treatment [217,218] have serious adverse effects on muscle mass [219,220]. Additionally, physical activity will also decrease muscle catabolism and increase anabolism and also has the potential to reduce inflammation, all important pathophysiological factors in cancer cachexia. Physical activity should thus probably be integrated in multimodal treatment programs. A recent systematic review concluded that both aerobic and resistance exercise improves upper and lower body muscle strength more than usual care, and there is some indication that resistance exercise perhaps is more effective for improving muscle strength than aerobic exercise [215] (RCT's, high grade evidence). However, future studies confirming this hypothesis are needed.

Section B5. Pharmaconutrients and pharmacological agents

In malnourished or advanced cancer patients, pharmaconutrients and pharmacological agents may be used to target the main pathogenic mechanisms of cancer cachexia. "***Pharmaconutrients***" are nutrients supplied in pharmacological doses to modulate immune and metabolic functions and exert effects on clinical outcome. However, these agents cannot substitute for conventional or specialized nutritional support. The nutritional needs of cancer patients should be adequately met, independent of pharmaconutrient or pharmacologic treatment. Specific pharmacological agents may be required or helpful in gastrointestinal disorders with

B5 — 1	Corticosteroids to increase appetite
Strength of recommendation WEAK	*We suggest considering corticosteroids to increase the appetite of anorectic cancer patients with advanced disease for a restricted period of time (1—3 weeks) but to be aware of side effects (e.g. muscle wasting, insulin resistance, infections).*
Level of evidence	High
Questions for research	Better define settings for a beneficial effect of corticosteroids

Consensus

Comments

In a systematic review of pharmacological therapies for cancer-associated anorexia and weight loss in adult patients with non-haematological malignancies Yavuzsen et al. (2005) included 55 RCTs; they found only two classes of drugs (progestins and corticosteroids) to have sufficient evidence to support their use in cancer patients. Corticosteroids were the subject of 6 studies conducted in a total of 637 patients [221]. Three trials in 402 patients used methylprednisolone orally or intravenously at doses of 32—125 mg per day for 1—8 weeks. Versus placebo, significant improvements were seen in appetite and quality of life, but not in body weight. One trial in 61 patients involved prednisolone 10 mg per day for 6 weeks. Compared with placebo, appetite and well-being were significantly improved. Two trials in 184 patients used dexamethasone 3—8 mg per day for 4 days or until time of death. A transient improvement in appetite compared to placebo was seen. More recently, Paulsen et al. reported an improvement in loss of appetite and fatigue after 7 days of 32 mg of methylprednisolone per day [222]. There is insufficient evidence to recommend any particular corticosteroid drug over another [223].

The antianorectic effect of corticosteroids is transient and disappears after a few weeks [224] when myopathy and immunosuppression become manifest; insulin resistance is an early metabolic adverse effect, osteopenia is a long-term effect. Due to these adverse effects, particularly with longer duration of use, corticosteroids may be more suitable for patients with a short life expectancy, especially if they have other symptoms that may be alleviated by this class of drugs such as pain or nausea.

B5 − 2	Progestins to increase appetite
Strength of recommendation WEAK	*We suggest considering progestins to increase the appetite of anorectic cancer patients with advanced disease but to be aware of potential serious side effects (e.g. thromboembolism).*
Level of evidence	High
Questions for research	Prospective studies to evaluate the combined effects of appropriate nutritional support and progestins

Consensus

Comments

Progestins (megestrol acetate and medroxyprogesterone acetate) increase appetite and body weight but not fat-free mass; they may induce impotence, vaginal spotting, and thromboembolism. Progestins have been studied in more than 30 randomized clinical trials and the evidence has been reviewed in several systematic reviews and meta-analyses [221,225−227].

Yavuzsen et al. reviewed 29 trials using progestins in a total of 4139 cancer patients [221]. Twenty-three trials in 3436 patients involved megestrol acetate at doses of 160−1600 mg per day for 2 weeks to 2 years. Results for appetite and weight gain favoured megestrol acetate over placebo. Five trials comparing different doses suggested that the optimal dose is between 480 and 800 mg per day. The influence of megestrol acetate on quality of life was minimal. Six trials in 703 patients involved medroxyprogesterone acetate at doses of 300 mg−1200 mg per day for 6−12 weeks. Significant advantages were demonstrated for medroxyprogesterone acetate versus placebo in terms of appetite improvement, increased caloric intake, and weight gain or attenuation of weight loss. Effects on quality of life were inconsistent [221]. A more recent Cochrane review on megestrol acetate for treatment of the anorexia-cachexia syndrome analysed 35 trials comprising 3963 patients and concluded that this drug showed a benefit compared with placebo with regard to appetite and weight but resulted in higher rates of oedema, thromboembolic phenomena, and deaths [227].

B5 − 3	Cannabinoids to improve appetite
Strength of recommendation −	*There are insufficient consistent clinical data to recommend cannabinoids to improve taste disorders or anorexia in cancer patients*
Level of evidence	Low
Questions for research	Effects of cannabinoids on nutritional state in anorectic cancer patients with taste alterations

Consensus

Comments

Over the last few decades, intense basic research has provided insight in the effects and modes of action of the cannabinoids and their physiological receptors, especially in the brain. Cannabinoids act through G protein-coupled receptors, often as intercellular signals, similar to other neurotransmitters. Endo- and phyto-cannabinoids have been studied. „Endocannabinoids" refer to the endocannabinoid (neuromodular) system with the physiological ligands to the cannabinoid receptors involved in appetite regulation, pain-sensation, mood and memory functions. "Phytocannabinoids" are the representatives found in plants (marijhuana) also interacting with the physiological cannabinoid receptors, e.g. THC (tetrahydrocannabinol, dronabinol). They show primarily psychoactive properties [228].

Synthetic cannabinoids encompass a variety of distinct chemical classes. Investigation of these substances has led to the emergence of pharmacotherapy targets [229] which include, among others, those related to appetite, an issue in cancer patients. The main adverse events associated with cannabinoid use are euphoria, hallucinations, vertigo, psychosis, and cardiovascular disorders. Cannabis prescription must follow strict rules because it is listed as a narcotic and psychotropic drug.

Tetrahydrocannabinol (THC) is the principal psychoactive constituent of cannabis and commercially available as dronabinol. In a small phase II clinical trial testing dronabinol at 5 mg/day, a reduction in anorexia was found in 68% of patients with cancer cachexia, but there was a high drop-out rate due to adverse events [230]. In a prospective randomized placebo-controlled multi-center trial in 164 patients with advanced cancer and anorexia-cachexia syndrome cannabis extract or THC provided at a fixed dose of 5 mg per day for 6 weeks did not improve appetite or QoL [231]. In a RCT [232], 469 patients with cancer cachexia received the progestin megestrol acetate (800 mg/day) or dronabinol (2.5 mg bid) or both. A greater gain in appetite and weight was reported in the progestin and progestin-dronabinol treatment groups, compared with the dronabinol alone group. Patients treated with progestins showed a greater incidence of impotence, while there were no differences in neuropsychiatric adverse events. Finally, in a small pilot RCT in patients with advanced cancer, poor appetite, and chemosensory alterations, THC (2.5 mg bid) for 18 days resulted in improved chemosensory perception, better taste perception of foods, and improved pre-meal appetite compared to placebo [233].

Thus, although dronabinol may have the potential to improve chemosensory perception and appetite in patients with cancer anorexia, the limited and inconsistent evidence does not support a recommendation.

Other modulators of taste: The management of taste disorders is still unsatisfactory and the evidence on treatment options sparse [234]. An RCT in 18 patients undergoing radiotherapy compared oral zinc sulfate (3 × 45 mg/d) to placebo for 1 month and reported significant differences in some defined taste recognition tests [235]. However, a recent RCT in 58 cancer patients undergoing chemotherapy comparing zinc (2 × 50 mg elemental zinc equivalents orally) to placebo over 3 months could not detect differences in loss of smell and other parameters [236].

Other appetite stimulators: The gastric and pancreatic peptide ghrelin is a ligand for a receptor regulating pituitary growth hormone release; at the same time ghrelin increases appetite and food intake in healthy subjects and cancer patients [237]. Clinical use of natural ghrelin, however, is limited by the short half-life and the need for parenteral application [238,239]. The small molecular ghrelin analogue anamorelin has been studied in 2 phase III trials in cachectic patients with advanced non-small cell lung cancer. When given for 12 weeks, anamorelin resulted in improved appetite, body weight and lean body mass compared to placebo while hand grip strength did not improve [240]. Anamorelin is not approved for clinical use at this time.

B5 − 4	Androgens to increase muscle mass
Strength of recommendation −	*There are insufficient consistent clinical data to recommend currently approved androgenic steroids to increase muscle mass*
Level of evidence	Low
Questions for research	Mechanism and long term effects of SARMs in patients with cachexia.

Consensus

Comments

Endogenous and exogenous agents have been investigated and used to diminish muscle loss (proteolysis) or to stimulate protein synthesis. Among them, anabolic or anabolic-androgenic steroids were addressed because they mimic the male sex hormones (testosterone and dihydro-testosterone (DHT) and the less potent androstenedione) increasing protein synthesis, especially in skeletal muscle cells [241]. Their use as anabolics has androgenic and virilising effects. Natural androgens (anabolic steroids) are key in the differentiation and development of the male phenotype in vertebrates and bind to the androgen receptor; they are also the precursors of all oestrogens. Androgens also have important effects in the brain and influence human behaviour. In patients with advanced cancer, decreased free testosterone levels are frequently observed [242].

Typical representatives of androgens investigated in cancer patients include nandrolone decanoate (for i.m. use 200 mg per week) and oral oxandrolone or fluoxymesterone (20 mg per day).

In a randomised trial of 37 patients with NSCLC undergoing chemotherapy, nandrolone decanoate (200 mg per week) was compared to no additional therapy; the nandrolone-treated group showed a trend toward a smaller loss of body weight [243]. An RCT that included 475 cachectic cancer patients compared a steroid, a progestin, and fluoxymesterone. Fluoxymesterone (20 mg/day) resulted in less appetite stimulation compared to megestrol acetate (800 mg/day) and dexamethasone (3 mg/day), while the discontinuation rate due to toxicity was similar among the three treatment arms [244].

Non-steroidal androgens: Selective androgen receptor modulators (SARMs) are small non-steroid molecules designed to selectively activate the skeletal muscle androgen receptor and thus potentially avoid the adverse side effects of naturally occurring androgenic steroids. These substances are in early phase clinical trials and none of these agents has yet received approval for treatment in a cancer setting. In a phase 2 trial, the first-in-class agent, enobosarm, showed increased lean body mass as well as increased power and speed on a stair climbing test [245].

ß-Hydroxy-ß-methyl butyrate (HMB) is a metabolite of leucine and has been promoted as a dietary supplement to gain strength and lean body mass associated with resistance training [247]. HMB at the usual dose of 3 g/day has been claimed to be an anti-catabolic agent that minimises protein breakdown. There is some support for this in young previously untrained individuals, but this is less clear in older individuals. In an RCT, oral administration of a mixture of arginine, glutamine, and HMB for 24 weeks compared to an isonitrogenous mixture of non-essential amino acids improved fat free mass in advanced cancer patients [248]. More recently, in an RCT in 25 cancer patients with systemic inflammation undergoing anticancer treatment, oral supplementation with a leucine-enriched medical food was compared to a control medical food. Muscle fractional synthetic rate increased after ingestion of the leucine-enriched but not after the control food [91]. A larger RCT in 472 cachectic cancer patients tried to compare an oral mixture of HMB, glutamine, and argine with an isonitrogenous control mixture but failed because of the difficulties in compliance with such a regimen over 8 weeks; only 37% of the patients completed the protocol and no statistically significant differences were observed between the study groups [249]. While some results appear promising, data are inconsistent and in view of the reported compliance problems at this time these amino acid mixtures cannot be recommended for general use.

Glutamine levels drop in severe illness; however, it has not been proven that this is caused by glutamine depletion [250] On the other hand, tumour cells rapidly take up and metabolize glutamine [251] and it has been speculated that glutamine may contribute significantly to stabilizing the intracellular milieu against acidification [252]. Considering that glutamine is prominently involved in a multitude of metabolic pathways, it may be prudent to avoid long-term supplementation with glutamine in cancer cachexia without dedicated studies [253].

When amino acids are supplemented by PN in doses that meet the amino acid requirements, care should be given to the nitrogen concentration ratio of the PN bags, in order to avoid administration of excessively high volumes [85].

B5 − 5	Amino acids to increase fat free mass
Strength of recommendation −	*There are insufficient consistent clinical data to recommend the supplementation with branched-chain or other amino acids or metabolites to improve fat free mass.*
Level of evidence	Low
Questions for research	Effects of leucine or HMB (hydroxy methylbutyrate) in weight losing patients studied in large randomized trials

Strong consensus

Comments

Muscle protein depletion is a hallmark of cancer cachexia and, due to the frequent presence of anabolic resistance, dietary amino acid incorporation is impaired. Recent data suggest that in cancer cachexia-impaired protein balance and anabolic resistance in muscle may be overcome by simultaneously supplementing insulin and amino acids [86]. In a small metabolic trial of short duration in cachectic patients PN supplemented with branched-chain amino acids (BCAA) was shown to increases leucine flux and protein synthesis, while protein breakdown remained stable [89]. Long-term Insulin treatment at bed-time, however, was without effect on lean body mass. In a randomized study in 338 patients with cancer cachexia, daily insulin treatment (0.11 IU/kg/d) in addition to basic supportive care increased whole body fat but not lean body mass [246].

B5 − 6	Non steroidal antiinflammatory drugs (NSAID) to increase body weight
Strength of recommendation −	*There are insufficient consistent clinical data to recommend non-steroidal antiinflammatory drugs to improve body weight in weight losing cancer patients.*
Level of evidence	Low
Questions for research	Effect of NSAID on body composition and clinical outcome in cancer patients with systemic inflammation

Strong consensus

Comments

Based on the available data, group members concluded that more robust evidence based on well-performed large clinical trials is necessary to recommend routine use of NSAIDs in the prevention and treatment of cancer-related metabolic and nutritional derangements.

Non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the release of acute-phase proteins and cytokines by the tumour and host tissues. Several controlled clinical trials in cancer cachexia have shown that NSAIDs may improve or maintain body weight and/or muscle mass [254,255]. Combination therapy of the Cox-2 inhibitor celecoxib plus megestrol acetate plus L-carnitine was recently shown to increase lean body mass, improve total daily physical activity, functional status, and cancer cachexia symptoms [256].

Other anti-inflammatory drugs have been investigated for their effects on attenuating cachexia. Pentoxifylline is a drug derived from methylxanthine, with anti-inflammatory and TNF-alpha inhibition properties. Its efficacy in human cancer cachexia, however, has not been demonstrated [257]. Similarly, there is no reliable support for anticachectic acivity of other drugs with anti-inflammatory effects such as melatonin [258] or TNF-alpha antibodies [259]. Thalidomide has multiple immune-modulating, anti-inflammatory, and TNF-alpha and IL-6 inhibition properties. A Cochrane review concluded in 2012 [260] that there was a lack of well-conducted trials investigating the effect of thalidomide on cachexia, and that the available evidence [261–264] was inadequate to recommend its use in clinical practice. There are case reports [265–267] but no clinical trials investigating the effect of IL-6 antibodies on cancer cachexia.

In conclusion, the evidence is too limited to recommend NSAIDs or other anti-inflammatory drugs for the treatment of cachexia outside of clinical trials. NSAIDs may improve weight in cancer patients with cachexia, and there is some evidence of their effect on physical performance, self-reported quality of life, and inflammatory parameters. The effect of NSAIDs may be enhanced when administered in combination with other agents. The reason for not recommending NSAIDs with the intention of treating cachexia outside clinical trials is based on the inconsistency of the trials and the low quality of the trials (small number of included patients, large number of primary outcomes, and/or high attrition of patients during the trials), but it is also supported by the known potentially severe side effects of NSAIDs, even though the reviewed literature on use in cachexia reports only almost negligible toxicity [268].

B5 − 7	N-3 fatty acids to improve appetite and body weight
Strength of recommendation WEAK	*In patients with advanced cancer undergoing chemotherapy and at risk of weight loss or malnourished, we suggest to use supplementation with long-chain N-3 fatty acids or fish oil to stabilize or improve appetite, food intake, lean body mass and body weight.*
Level of evidence	Low
Questions for research	Effect of long chain N-3 fatty acids on body composition and clinical outcome in cancer patients undergoing antineoplastic treatment
	Effect of long chain N-3 fatty acids on quality of life and clinical outcome in patients with cancer cachexia

<u>Strong consensus</u>

Comments

Eicosapentaenoic acid (EPA [20:5(N-3)]) is a polyunsaturated long-chain N-3 fatty acid and a substrate for cyclooxygenase and lipoxygenase leading to eicosanoids of the 3- and 5-series, which display little or no inflammatory activity. EPA is a competitive antagonist of N-6 arachidonic acid, which is converted to strongly pro-inflammatory eicosanoids of the 2- and 4-series. N-3 long chain fatty acids are present in relatively high amounts in oily fish or are available as nutrition supplements. After oral intake, N-3 fatty acids are rapidly incorporated into cell membrane phospholipids [269].

Fish oil (most frequently used doses: 4–6 g/day) as well as long-chain N-3 fatty acids (1–2 g/day) diminish inflammatory responses in cancer patients as evidenced by a decrease in inflammatory markers (interleukin 6 or C-reactive protein) and resting energy expenditure [270–274]. Fearon [275] presented dose relationships for N-3 fatty acids across patients in the treatment arm of a randomized clinical trial, these data suggest that at least 2 g/day are required for clinical benefit on nutrition-related endpoints.

Several small clinical trials, including between 13 and 92 patients and using fish oil supplements or oral nutritional supplements (containing 0.4–2.2 g/day of EPA) in patients with advanced cancer, reported improvements in appetite, energy intake, body weight, lean body mass, and/or in physical activity [64,272,276–279]. Four of these trials were RCT [64,272,276,279]. In two other trials, compared to a control group supplementation with fish oil improved response of the tumour to anticancer treatment (open controlled design; n = 40; 2.2 g/day EPA) [280] and even resulted in an increase in overall survival (RCT; n = 60; 18 g/day fish oil) [281]. In the largest of these trials, Sanchez Lara et al. studied 92 patients with advanced lung cancer undergoing chemotherapy in a randomized placebo-controlled design. Patients receiving an oral nutritional supplement containing fish oil (2.2 g/day EPA) compared to those receiving a control supplement maintained better body weight, lean body mass, and reported less symptoms of anorexia, fatigue, and neuropathic toxicity [279]. Beneficial effects of fish oil were observed especially in trials studying patients undergoing chemotherapy; this included improvements in physical activity and quality of life [276] (RCT; n = 40; 2 g/day EPA), appetite as well as intake of energy and protein [279], body weight [277] and lean body mass [279]. In contrast to these positive findings, there were several randomized trials, including from 60 to 518 patients, which did not demonstrate a benefit associated with supplemental intake of fish oil (n = 60; 1.8 g/day EPA [282], n = 200; 2.2 g/day EPA [275], n = 421; 2.2 g/day EPA [283] or purified EPA ethyl ester (n = 518; 0 vs 2 vs 4 g/day EPA [284].

Three systematic reviews conducted in 2007, 2009, and 2012 concluded that there was insufficient evidence to support a recommendation for long chain omega-3 fatty acids to treat cancer cachexia [285–287]. Studies published after June 2010, however, were not included in these reviews. Another systematic review published in 2007 included non-randomized clinical trials in addition to RCT and concluded that an intake of >1.5 g/day of long-chain fatty acids improved appetite, body weight, post-surgical morbidity, and quality of life in weight-losing cancer patients [288]. A recent systematic review assessed supplementation with long-chain N-3 fatty acids in cancer patients during chemo- and/or radiotherapy and reported beneficial effects when compared to a control arm, most prominently a conservation of body composition [289].

Safety issues

When supplemented in usual doses (see above) fish oil and long-chain N-3 fatty acids are mostly well-tolerated. Mild gastrointestinal effects were reported; the taste, a fishy aftertaste or fish belching, may impair compliance [282]. A single one-armed study in children and adolescents reported increased bleeding during supplementation with 1–5 g/day of fish oil [290]. A review of all available studies on this topic by the European Food Safety Authority (EFSA) concluded in 2012 that increased bleeding has not been reported by any other trial and that long-term supplemental intakes of EPA and DHA combined up to about 5 g/day do not appear to increase the risk of spontaneous bleeding episodes or bleeding complications [291]. Thus, supplemental intakes of EPA and DHA combined at doses up to 5 g/day, and supplemental intakes of EPA alone up to 1.8 g/day, do not raise safety concerns for adults [291]. Recently, ibrutinib has been introduced in the treatment of chronic lymphocytic lymphoma; ibrutinib has bees associated with epistaxis in patients taking fish oil supplements; therefore, patients receiving ibrutinib should be counselled to avoid fish oil supplements.

While there is no convincing clinical evidence to show interactions of fish oil and anticancer drug effectivity, this topic has been discussion based on clinical and preclinical data.

In preclinical models, long chain N-3 fatty acids may augment cytotoxicity of several agents by increasing oxidative stress [292,293]. Acting as competitive antagonists of N-6 arachidonic acid, N-3 fatty acids may modulate the balance of eicosanoids with different inflammatory potencies, including the production of prostaglandin E2, which has been shown to enhance tumor cell proliferation [294]. Recently, it has been shown in an in-vitro pancreatic cancer cell model that a lipid solution containing fish oil improved the antiproliferative and antiinvasive effects of gemcitabine [295]. Other preclinical data obtained from animal experiments and tissue cultures have been interpreted to demonstrate induction of chemotherapy resistance by a specific long-chain N-3 fatty acid (16:4 hexadecatetraenoic acid, HTA) [296] but not by eicosapentaenoic acid (EPA). HTA appears to be produced by mesenchymal stem cells after exposure to platinum compounds [296] and HTA has been reported to impair the efficacy of a number of different antineoplastic agents, possibly by protecting against induction of apoptosis [296]. HTA could be found in several fish oils as well as in human plasma after consumption of these fish oils; concentrations were very low, though in the range of those used in the in-vitro model [297].

There are no clinical data to indicate an attenuation of chemotherapy efficacy by N-3 fatty acids [298]. Rather, clinical data appear to show an enhancing effect of N-3 fatty acids from fish oil on the therapeutic effectivity of several cytotoxic agents [298]. Non-randomized clinical trials have shown improved responses to chemotherapy in patients with lung cancer during supplementation with fish oil [280] and in women with advanced breast cancer during supplementation with oral N-3 docosahexaenoic acid (DHA, 1.8 g/day) [299]. A randomized trial in patients with lung cancer comparing an oral nutritional supplement containing fish oil (2 g/day EPA) with a standard ONS, however, could not detect an effect on response to chemotherapy (paclitaxel and either cisplatin or carboplatin) [279].

Interestingly, there are several reports on protective effects of fish oil on chemotherapy-induced toxicities. After traumatic lesion of nervous tissues, N-3 fatty acids may exert neuroprotective effects [300,301]. This might be of interest for the prevention of clinically relevant neuropathy induced by several groups of chemotherapy agents (e.g. platinum, vinca alkaloids, taxoids). In a small randomized trial in 20 patients with breast cancer receiving paclitaxel therapy, oral supplementation with N-3 fatty acids (0.19 g/day EPA + 1.04 g/day DHA) reduced the incidence of neuropathy from 60 to 30% [302]. A larger randomized trial in 90 patients with lung cancer receiving combination chemotherapy with platinum and paclitaxel compared an oral nutritional supplement (ONS) containing fish oil with a standard ONS; while changes in neuropathy were not a primary aim in this trial, intake of the fish oil containing ONS was associated with a lower rate of neuropathy [279]. An RCT in 70 patients with acute lymphoblastic leukemia who were in the maintenance phase compared fish oil (0.18 g/day EPA + 0.12 g/day DHA) with placebo during 6 months of methotrexate treatment and observed no unwanted effects for fish oil compared to placebo but rather improved maintenance of liver function [303]. While these data on potential protective activities against chemotherapy-induced toxicities are interesting, a recommendation on these effects cannot be made without more information on long-term clinical outcomes.

Due to the inconsistencies in the reported effects but with several positive trials published during the last few years reporting nutritional benefits, a plausible biological rationale, only mild side effects and no convincingly serious safety issues a weak recommendation for the use of fish oil and long-chain N-3 fatty acids has been made.

B5 — 8	Prokinetic drugs to improve early satiety
Strength of recommendation WEAK	*In patients complaining about early satiety, after diagnosing and treating constipation, we suggest to consider prokinetic agents, but to be aware of potential adverse effects of metoclopramide on the central nervous system and of domperidone on cardiac rhythm*
Level of evidence	Moderate
Questions for research	Effect of prokinetics on oral nutritional intake in the context of optimal nutritional counselling

Consensus

Comments

Pro-kinetic agents such as metoclopramide or domperidone stimulate gastric emptying and they are frequently used to improve early satiety [46,304]. Two RCTs compared metoclopramide in doses of 40 or 80 mg/day with placebo in patients with advanced cancer and chronic nausea and observed an improvement in nausea but not in appetite or caloric intake [305,306]. Domperidone has been reported in case studies and small trials to improve satiety in anorexia nervosa [307—309]. Following the withdrawal of cisapride from the market, domperidone has been utilized with increasing frequency for the symptomatic treatment of upper gastrointestinal tract motility disorders and to control nausea and vomiting [310]. The phytopharmacon STW5 (Iberogast®) has been shown to be at least as effective as metoclopramide in improving symptoms of functional dyspepsia [311].

Tolerability of metoclopramide and domperidone is usually good. The safety profile of metoclopramide, however, includes somnolence, depression, hallucinations, and especially extrapyramidal symptoms and potentially irreversible late dyskinesias. While intravenous bolus doses of domperidone have been linked to the potential to cause QT prolongation and torsade de pointes tachycardia, the risk of development of QT prolongation and torsade des pointes with the administration of usual therapeutic doses of oral domperidone appears to be low [312].

Chapter C: Interventions relevant to specific patient categories

Section C1: Surgery

C1 — 1	Enhanced recovery after surgery (ERAS) care
Strength of recommendation STRONG	*For all cancer patients undergoing either curative or palliative surgery we recommend management within an enhanced recovery after surgery (ERAS) program; within this program every patient should be screened for malnutrition and if deemed at risk, given additional nutritional support.*
Level of evidence	High
Questions for research	optimal components including nutrition of ERAS protocol for oncology patients
	The role of immunonutrition (arginine, N-3 fatty acids, nucleotides) when upper GI cancer patients are managed within an ERAS pathway.
	The role of N-3 enriched oral supplements/enteral nutrition in upper GI cancer patients for preservation of lean body mass and optimisation of organ function.

Consensus

Comments

In the current surgical environment, cancer patients undergoing surgery should be managed within an enhanced recovery after surgery (ERAS) programme that seeks to minimise surgical stress, maintain nutritional status, reduce complications and optimise rate of recovery [313]. The key domains of such a programme include minimal opiate-based pain control, early mobilisation, early return of GI function and, where possible, minimal access (laparoscopic) surgery [314]. Nutritional components of ERAS include avoiding fasting, pre-operative fluid and carbohydrate loading, and recommencement of oral diet on the first post-operative day [315]. Data suggest that when all patients receive such optimised nutritional and metabolic care, the metabolic response to surgery can be minimised [316] and some indices of moderate nutritional risk are no longer associated with adverse outcome [317]. For patients identified to be at severe nutritional risk, alternative strategies to major surgery should be considered (e.g. endoscopic stenting).

C1 − 2	Surgery: Multimodal oncological pathway
Strength of recommendation STRONG	*For a patient undergoing repeated surgery as part of a multimodal oncological pathway, we recommend management of each surgical episode within an ERAS program.*
Level of evidence	Low
Questions for research	role of multimodal rehabilitation during prolonged oncological therapy

Consensus

Comments

Patients undergoing multimodal oncological care are at particular risk of progressive nutritional decline. Modern cancer care has evolved so that patients frequently undergo concurrent/sequential/repeated surgery, chemotherapy and/or radiotherapy for primary or metastatic disease. In order to minimise a stepwise decline in nutritional status during such arduous anti-cancer therapy, it is essential to minimise the nutritional/metabolic impact of repeated surgery and manage each surgical episode within the context of an ERAS pathway.

C1 − 3	Postsurgical care and care after hospital discharge
Strength of recommendation STRONG	*In surgical cancer patients at risk of malnutrition or who are already malnourished we recommend appropriate nutritional support both during hospital care and following discharge from hospital.*
Level of evidence	Moderate
Questions for research	The optimal post-operative regimen in terms of type, preparation and access to normal food ± oral nutritional supplements for patients managed within an ERAS pathway.

Consensus

Comments

Patients at moderate or severe nutritional risk (especially those undergoing upper GI cancer surgery) should be considered for routine post-operative nutritional support (where relevant by oral or enteral route) and consideration should be given to the extending such support when the patient is discharged into the community [318,319].

C1 − 4	Immunonutrition (arginine, N-3 fatty acids, nucleotides) in perioperative care
Strength of recommendation STRONG	*In upper GI cancer patients undergoing surgical resection in the context of traditional perioperative care we recommend oral/enteral immunonutrition.*
Level of evidence	High
Questions for research	Specifying the role of the individual constituents of immunonutrition regimens

Strong consensus

Comments

Classical studies in surgical nutrition identified weight loss (>10%) and low albumin (<30 g/l) as risk factors for adverse outcome [320]. In this context, upper GI cancer patients predicted to be at severe nutritional risk experienced reduced complications from pre-operative PN [321]. Subsequently, it was demonstrated that upper GI cancer patients managed within a traditional pattern of peri-operative care experienced a reduction in post-operative infective complications when given oral/enteral so-called "immune-modulating nutrition" in the peri-operative period [322]. The term "immune-modulating nutrition" or "immunonutrition" refers to liquid nutritional supplements enriched with specific nutrients. The role of the individual constituents of immunonutrition regimens remains to be resolved.

C2 − 1	Radiotherapy: Ensuring adequate nutritional intake
Strength of recommendation STRONG	*We recommend that during radiotherapy (RT) — with special attention to RT of the head and neck, thorax and gastrointestinal tract — an adequate nutritional intake should be ensured primarily by individualized nutritional counseling and/or with use of oral nutritional supplements (ONS), in order to avoid nutritional deterioration, maintain intake and avoid RT interruptions*
Level of evidence	Moderate
Questions for research	Effect of nutritional support on clinical outcome including survival

Section C2. Radiotherapy

Strong consensus

Comments

Radiotherapy to the head and neck or esophagus induces mucositis, decreased food intake, and weight loss in up to 80% of patients [323–334]. Similarly, radiotherapy of the pelvic region is associated with gastrointestinal symptoms in up to 80% of patients [335]. Nutritional support can diminish the negative effects of radiotherapy on nutritional status. Several RCTs have demonstrated that individualized nutritional counselling by a trained professional compared to conventional food without dietary education improves nutritional intake, body weight, and quality of life [44,45,326,334,336] and thus may benefit patients by allowing them to avoid treatment interruptions and complete planned radiotherapy. These findings agree with similar data reported from prospective controlled trials [324,331] and several retrospective analyses [323,327,329,330,332]. The aims of the nutritional counselling should be to supply energy and protein requirements, to minimize weight loss, and to maintain quality of life; there are no

recommendations for specific foods or supplements like antioxidants [152].

Evidence is inconclusive on whether oral nutritional supplements (ONS) or enteral feeding may improve clinical outcomes without individual nutritional counselling. A systematic review and meta-analysis concluded that ONS during radiotherapy increases energy intake [337], but this has been questioned recently [338]. Ravasco et al., in two 3-armed RCTs, treated patients with colorectal (111 patients) [44] as well as head and neck cancer [45](75 patients) undergoing radiotherapy with either individualized counselling including ONS (if required), a protein-rich ONS without counselling, or standard nutritional care. Compared to standard care, counselling or ONS alone improved energy intake, protein intake, and quality of life during treatment. However, only the counseled patients maintained this improved status for 3 months after radiotherapy. Most interestingly, follow-up for a mean of 6.5 years in the colorectal cancer patients demonstrated an improved survival in the patients who received nutrition counselling during radiotherapy [157]. A systematic review of 10 RCTs investigating nutritional care in head and neck cancer patients during radio(chemo)therapy found beneficial effects of nutrition counselling on nutritional status and quality of life, but no isolated effects of ONS or enteral nutrition [155].

In conclusion, all patients undergoing radiation of the gastrointestinal tract or the head and neck region should receive thorough nutrition assessment, adequate nutritional counselling and, if necessary, nutritional support according to symptoms and nutritional status [152,339]. The guideline of the Clinical Oncological Society of Australia recommends weekly contacts by dieticians during radiotherapy of head and neck cancers and follow-up every 2 weeks for at least 6 weeks [340]. If nutritional support is required, this should be initiated early and if energy intake is inadequate ONS are recommended [44,45,323,326,327,334,336] or enteral tube feeding [327,329—332,341] should be offered.

These recommendations are not invalidated by a secondary analysis of an RCT in 1073 patients with head and neck cancer that reported worse locoregional control and survival in patients who received nutritional support prior to starting radiotherapy compared to patients who started radiotherapy without nutrition support [342]. Most likely, early nutritional support was an indication of a depleted nutritional status and the statistical corrections applied by the authors did not compensate for clinically relevant differences in the retrospectively assigned groups.

Few patients receiving radiochemotherapy have been studied and evidence for the effects of nutritional interventions on clinical outcome including overall survival is inconclusive and should be improved.

In patients with obstructing head and neck or esophageal cancers and in settings with expected severe radiation-induced oral or esophageal mucositis, there is a high risk for weight loss, decreased physical performance, dehydration, decreased treatment tolerance, and increased treatment interruptions [147,323,326,327,343—345]. Enteral tube feeding is indicated in cases of severe dysphagia and inadequate energy intake [203]. For ethical reasons this has not been investigated in randomized trials. However, prospective and retrospective observational trials in patients with inadequate food intake have demonstrated that enteral compared to oral feeding reduces weight loss [323,327,329—331,341,345], and the frequency and duration of treatment interruptions and rehospitalizations [323,327,332].

In high-risk situations, e.g. hypopharyngeal primary site, T4 tumor, female sex, or combined radiochemotherapy [346], prophylactic tube feeding (as opposed to enteral feeding initiated after development of dysphagia) may maintain nutritional status and avoid interruption of treatment. Unfortunately, there is only one RCT of low methodological quality supporting this assumption [347]. In 40 patients with head and neck cancer undergoing radiotherapy or radiochemotherapy early initiation of nasogastric feeding decreased weight loss compared to normal food and tube feeding only as required [347]. Several, mostly retrospective observational, studies similarly observed improved body weight and lower incidences of rehospitalization and treatment interruptions for patients treated with early compared to later or no enteral nutrition [323,327,329—332,341,343].

Enteral nutrition may be supplied for short periods <30 days via nasogastric tubes or for longer periods via percutaneous gastrostomies [203,328,348]. Percutaneous endoscopic gastrostomies (PEG) compared to radiologically inserted gastrostomies (RIG) appear to be associated with a lower risk of peritonitis and mortality [349]. Comparisons between PEG and nasogastric tubes in head and neck cancer patients have been reported in 1 RCT [187] and 3 systematic reviews [328,350,351]; another systematic review comparing PEG to nasogastric tubes in dysphagic patients included 9 RCT [352]. Body weight may be maintained similarly by both PEG and nasogastric feeding [351]. Risk of tube dislodgement is lower [351,352] and quality of life is possibly better with PEG [187,353], while nasogastric tubes are associated with less dysphagia [351] and earlier weaning after completion of radiotherapy [328,351]. Risks of pneumonia and other infections are similar [328,351,352].

Only one RCT compared standard enteral nutrition to a specialized formula [354]. In 111 patients with head and neck or oesophageal cancer undergoing radiotherapy, prophylactic PEG was inserted and patients were fed with a standard enteral formula or with a formula enriched in N-3 fatty acids (Supportan®). At the end of treatment the intervention group displayed better screening scores but the observed difference in loss of body cell mass did not reach the level of significance [354].

C2 — 2	Radiotherapy: Use of tube feeding
Strength of recommendation STRONG	*We recommend enteral feeding using naso-gastric or percutaneous tubes (e.g. PEG) in radiation-induced severe mucositis or in obstructive tumors of the head-neck or thorax.*
Level of evidence	Low
Questions for research	Effect of prophylactic/early enteral feeding on clinical outcome
	Effect of specialized enteral formula on nutritional status and clinical outcome

Strong consensus

Comments

C2 — 3	Radiotherapy: Maintaining swallowing function
Strength of recommendation STRONG	*We recommend to screen for and manage dysphagia and to encourage and educate patients on how to maintain their swallowing function during enteral nutrition.*
Level of evidence	Low
Questions for research	Effect of swallowing exercise on dysphagia in patients receiving enteral feeding

Strong consensus

Comments

Dysphagia or swallowing dysfunction has been reported in 30—50% of head and neck cancer patients treated with intensive radio(chemo)therapy [355]. These patients are at risk of pneumonia and sepsis [355] and in more than 75% symptoms will not improve or even worsen over time [356]. Predicting which patients will develop swallowing dysfunction is complex and challenging, and risk is influenced by radiation dose, area of treatment, and combination with chemotherapy [355]. A consensus group recently recommended assessment of all patients at risk for swallowing difficulties before and during treatment and regularly during follow-up, and that all patients with dysphagia be prescribed professionally supervised swallowing exercises. If enteral nutrition is required, patients should be encouraged to continue to swallow and patients should be weaned from artificial nutrition as quickly and safely as possible [355]. Possibly because percutaneous endoscopic gastrostomies are tolerated longer than nasogastric feeding tubes, enteral nutrition via PEG compared to nasogastric tubes has been associated with a higher incidence of dysphagia [346,351,353] and a longer requirement of use [187,351]. Therefore, dysphagia assessment and prophylactic as well as therapeutic interventions should be used regularly.

C2 − 4	Radiation-induced diarrhea: glutamine
Strength of recommendation −	*There are insufficient consistent clinical data to recommend glutamine to prevent radiation-induced enteritis/diarrhea, stomatitis, esophagitis or skin toxicity.*
Level of evidence	Low
Questions for research	Effect of glutamine on oral/esophageal mucositis and skin toxicity

Strong consensus

Comment

Interest in glutamine relies on the high glutamine turnover of gastrointestinal mucosa [250] and on animal experiments where protective effects of glutamine against gut toxicity of different noxious interventions have been observed [357]. Oral glutamine has been compared to placebo in patients receiving pelvic radiation in 4 controlled trials [358—361]. In patients receiving glutamine, one trial (possibly not randomized; 23 of 36 patients received daily 3 × 15 g glutamine, 13 patients received glucose) observed a reduction in the severity of radiation-induced enteritis [361], one RCT reported an unexpected increase in the incidence of enteritis (69 patients, glutamine 30 g/day vs casein 30 g/day) [360], and two RCT did not find any effects (129 patients, glutamine 8 g vs placebo [358]; 33 patients, glutamine 30 g/day vs maltodextrin 30 g/day [359]). This does not support the use of glutamine to protect against radiation-induced enteritis.

There is some evidence for potential beneficial effects of glutamine against radiation-induced mucositis and skin toxicity. Two small randomized trials reported that either mouthwashes with glutamine (16 g/day; 17 patients) [362] or intravenous glutamine (0.3 g/kg/day; 29 patients) [363] when compared to placebo (sodium chloride) decreased the incidence, severity, and duration of radiation-induced mucositis. In two other small RCT patients undergoing radio- or radiochemotherapy received 3 × 10 g oral glutamine per day or placebo; one trial randomizing 40 patients reported a less severe mucositis in patients taking glutamine [364], while the other trial in 58 patients observed no benefit of glutamine [365]. In a non-randomized trial 104 patients with lung cancer undergoing radiotherapy were offered oral glutamine powder (30 g/day); severity of radiation-induced esophagitis was lower and there were fewer interruptions of treatment in 56 patients who chose to take glutamine when compared to those patients who declined glutamine [366].

Recently, two small randomized trials in women who received radiotherapy for early breast cancer compared oral glutamine (0.5 g/kg/day; 17 patients [367]; 15 g/day; 40 patients [368]) to oral dextrose. Both trials observed less skin toxicity in women receiving glutamine (mainly toxicity grade 1, scale 0—4) compared to the control groups (mainly grade 2). Glutamine has been associated with higher tumor relapse rates in hematopoietic stem cell transplantation patients [369]; thus, recommending glutamine will require solving this safety issue and more robust efficacy data [370].

C2 − 5	Radiation-induced diarrhea: probiotics
Strength of recommendation −	*There are insufficient consistent clinical data to recommend probiotics to reduce radiation-induced diarrhea.*
Level of evidence	Low
Questions for research	Effect of probiotics on radiation-induced diarrhea and treatment completion rate

Strong consensus

Comment

Radiotherapy of the pelvic region is associated with gastrointestinal symptoms in up to 80% of patients [335]. This includes altered bowel habits (94%), loose stools (80%), increased stool frequency (74%), urgency (39%), and fecal incontinence (37%) [335], which often continue after the end of the treatment [371]. In fact, symptoms after radiotherapy are manifestations of new onset gastrointestinal physiological deficits induced by the radiotherapy, including changes in gut flora [372]. Six RCT have reported on potential protective effects of oral probiotics, especially lactobacillus and bifidus species [373—378]. However, trials differed in the bacterial strains used and there were weaknesses in methodological quality.

Three RCT (with 206, 85, and 246 patients) observed no effects of probiotics on diarrhea [373,375,377], while 3 other RCT (with 24, 490, and 63 patients) reported a reduction in the incidence of diarrhea with the use of probiotics [374,376,378]. All 4 trials which investigated faeces consistency unanimously reported a significant benefit in patients receiving probiotics [375—378]. Five of these trials were included in 3 separate systematic reviews published in 2013. All reviews concluded cautiously that there was inconclusive evidence supporting a prophylactic effect of probiotics against radiation-induced diarrhea [379—381]. In conclusion, though there is some indication for protective effects of probiotics, due to the heterogeneity of the data and the limited study quality no recommendation can be made. In addition, the saftety of using probiotics has to be reliably addressed, before these products can be recommended in immunocompromised patients.

C2 − 6	Radiotherapy: Use of parenteral nutrition
Strength of recommendation STRONG	*We do not recommend parenteral nutrition (PN) as a general treatment in radiotherapy but only if adequate oral/enteral nutrition is not possible, e.g. in severe radiation enteritis or severe malabsorption*
Level of evidence	Moderate
Questions for research	Comparing feasibility and efficacy of enteral vs parenteral nutrition in patients requiring artificial nutrition

Consensus

Comment

Radiotherapy of the head and neck or pelvic region is associated with gastrointestinal symptoms and weight loss in up to 80% of patients [323–332,382]. However, general, i.e. unconditional, use of PN in all patients undergoing radiotherapy carries more risk of harm than benefit and, therefore, is not recommended [193]. We recommend oral over enteral and enteral over parenteral feeding. The use of PN is indicated if oral/enteral food tolerance is insufficient to supply the required amounts of energy and nutrients. This is the case with chronic severe enteral food intolerance (like untreatable nausea, vomiting, abdominal pain, malabsorption, or diarrhea) that cannot be overcome by tube feeding. Chronic radiation enteritis has been reported in up to 20% of patients receiving pelvic radiotherapy [383]; intestinal failure develops in approximately 5% [190] and in these patients home parenteral nutrition appears to be a reasonable treatment option [192] possibly superior to surgical intervention [384,385].

Section C3: Medical oncology: Curative or palliative anticancer drug treatment

C3 − 1	Medical oncology: Ensuring adequate nutrition
Strength of recommendation STRONG	_During anticancer drug treatment we recommend to ensure an adequate nutritional intake and to maintain physical activity._
Level of evidence	Very low
Questions for research	Effects of nutritional intervention during cytostatic and targeted therapies on treatment tolerance, response to treatment and overall survival

Strong consensus

Comments

Regular assessments of nutritional intake and physical activity are required during anticancer drug treatment to prevent weight loss and decreases in muscle mass and function. In cases of insufficient nutritional intake and/or physical activity, actions to reverse this are required. However, this does not require treating all patients with artificial nutrition.

Weight loss before chemotherapy is associated with an increased risk of dose-limiting toxicity as well as a worse performance status, impaired quality of life, and shorter survival. Poor responses to anticancer treatment may be due to the requirement for dose reductions in antineoplastic drugs as well as more frequent interruptions in therapy [2]. Not only weight loss but also a low muscle mass may be associated with increased toxicity of cytostatic agents [386]. Weight loss is a common side effect of targeted therapies [387] and multikinase inhibitors have been reported to result in skeletal muscle wasting [218]. In addition, low muscle mass has been shown to be a risk factor for toxicity in these patients [388].

Weight stabilisation for patients with gastro-intestinal and lung cancers is correlated with significant improvements in survival [2,389]. Due to the fact that anorexia and taste alterations are very common, personalised dietetic counselling, associated with ONS if necessary, has been recommended in cases of overt malnutrition, for patients with decreased oral intake, and when requested by patients or families (expert opinion) [390].

Dietetic counselling and/or ONS (oral nutritional supplement) may improve nutritional intake and quality of life and stabilise body weight [42,153,337]. In 28 patients with oesophageal cancers undergoing neo-adjuvant chemotherapy, intensified nutritional advice/care was associated with reduced post-operative complications and less weight loss compared to 35 historical controls [391]. Most trials could not detect effects of nutritional interventions on response to anticancer treatment or on overall survival [42,153,289,337]. Deviating from this pattern, a large combined case−control and cohort trial in 628 patients with colorectal cancer undergoing chemotherapy reported a longer survival (19.1 vs 12.4 months) in patients who accepted nutritional support consisting of counselling, ONS and megestrolacetate compared to a control group without nutritional support [392]. More recently, a small randomised pilot trial in 20 patients with malignancy-related cachexia compared standard nutritional treatment to an individualised nutrition intervention program which was escalated from counselling to ONS, to enteral tube feeding and parenteral nutrition as required to avoid a caloric deficit. The program was associated with improved body weight and survival [393].

C3 − 2	Medical oncology: Use of enteral and parenteral nutrition
Strength of recommendation STRONG	_In a patient undergoing curative anticancer drug treatment, if oral food intake is inadequate despite counselling and oral nutritional supplements (ONS), we recommend supplemental enteral or, if this is not sufficient or possible, parenteral nutrition._
Level of evidence	Very low
Questions for research	In patients with inadequate nutritional intake, who are undergoing curative anticancer drug treatment: -Effect of artificial nutrition on treatment tolerance, treatment completion, relapse rate and overall survival - Effect of enteral vs parenteral nutrition on complications, treatment completion, relapse rate and overall survival

Consensus

Comments

Due to the detrimental effects of decreases in weight and muscle mass on quality of life, treatment toxicity, and survival, malnourished or weight losing cancer patients receiving anticancer treatment who are anticipated to be unable to ingest and/or absorb adequate nutrients for more than 1−2 weeks (see A.1) are candidates for artificial nutrition, preferably by the enteral route [7,204]. However, there is no place for indiscriminate use of artificial nutrition in all cancer patients as a "routine" adjunct to cytotoxic therapy [6,7,9].

Several systematic reviews analysing "routine" (i.e. not triggered by severe malnutrition and/or a relevant caloric deficit) artificial nutrition in cancer patients during chemotherapy concluded that there was no beneficial effect of enteral or parenteral nutrition on survival [193,337,394]. Indeed PN was associated with increased complications (+40%; 95% confidence interval 14−66), infections (+16%; 8−23), and a decreased tumour response (−7%; −12 to −1). There are no data on EN or PN in weight losing patients receiving targeted therapy.

Data on artificial nutrition supplied according to caloric demand during standard cytostatic therapies are scarce. Studies comparing enteral to parenteral nutrition showed that EN is feasible and, compared to PN, may be associated with a lower rate of complications [395,396].

C3 − 3	Medical oncology: Use of glutamine
Strength of recommendation −	*There are insufficient consistent clinical data to recommend glutamine supplementation during conventional cytotoxic or targeted therapy.*
Level of evidence	Low
Questions for research	Effect of glutamine on drug-induced neuropathy

Strong consensus

Comments

Oral mucositis and diarrhea are frequent chemotherapy side effects. Interest in glutamine was triggered by the observation of a high turnover of glutamine by gastrointestinal mucosa, the liver, the central nervous system, and immune cells [92]. Glutamine levels decrease in critical illness, but it is not known whether this is the result of a deficiency [250]. Preclinical evidence has pointed to protective effects of glutamine against different gut injuries [357]. Beneficial effects of oral and parenteral supplementation of glutamine have been reported on chemotherapy-induced mucosal inflammation [363], vomiting and diarrhea [397,398] and cytopenia [399]. Of note, however, glutamine is metabolized at a high rate by cancer cells [251] and it has been speculated that glutamine is relevant in stabilizing cancer cells against intracellular acidification [252]. Considering the diverse effects of glutamine in metabolism, it may be wise not to promote supplementation without studies on clinical long-term effects.

Evidence to support the effect of glutamine on chemotherapy-associated unwanted effects is contradictory. A review on chemotherapy-induced oral mucositis found several very small studies that reported positive effects of glutamine while larger studies were negative [357]. A more recent systematic review analysing 15 prospective and retrospective trials in cancer patients undergoing chemo-, radio or radio-chemotherapy [400] found positive effects of oral glutamine on mucositis in 11 of these 15 trials. Among the 6 prospective and placebo-controlled trials, however, 2 trials reported a benefit of glutamine while in 4 trials no effect was observed [400].

A systematic review and meta-analysis of 8 RCTs (16—40 g/day glutamine; 3 trials oral, 5 intravenous route) on the prevention of chemotherapy-induced diarrhea reported a significant shortening of the duration of diarrhea from 3 to 2 days but no effect on diarrhea severity [398]. After analysing these trials a MASCC (Multinational Association of Supportive Care in Cancer)/ISOO (International Society of Oral Oncology) guideline group concluded that there was insufficient evidence to recommend on the therapeutic use of glutamine [380]. Based on animal experiments, glutamine has been studied to prevent chemotherapy-induced neuropathy [357]. In a randomized trial in 86 patients with colorectal cancer 30 g/day of oral glutamine significantly reduced oxaliplatin-induced neuropathy of grades 3—4 [401].

Considering the heterogeneity of these data and the lack of information on glutamine effects on tumor response, no recommendation on the therapeutic use of glutamine is possible.

Section C4: Medical oncology: High-dose chemotherapy and hematopoietic stem cell transplantation (HCT)

C4 − 1	High-dose chemotherapy and HCT: Ensuring adequate nutrition and physical activity
Strength of recommendation STRONG	*During intensive chemotherapy and after stem cell transplantation we recommend to maintain physical activity and to ensure an adequate nutritional intake. This may require enteral and/or parenteral nutrition.*
Level of evidence	Very low
Questions for research	Effects of physical activity on clinical outcome

Strong consensus

Comments

Many patients referred for autologous and especially those referred for allogeneic hematopoietic stem cell (HCT) transplantation are malnourished at admission. The high-dose radio-/chemotherapy associated with the treatment and its typical spectrum of side effects, including nausea, vomiting, mucositis, diarrhea, and infections, further impacts oral food tolerance and patients lose weight particularly in the first 40 days after admission [402]. This weight loss has a negative effect on clinical outcomes [403]. Therefore, patients should be screened and assessed for impending or overt malnutrition at admission and after that monitored weekly during their HCT for adequate nutrient intake, metabolism, and physical activity. If deficits are observed, nutrition support, including counselling, ONS, EN and/or PN, should be initiated early to avoid or minimize further loss of weight and body cell mass.

Parenteral nutrition may have specific benefits by providing the option to supply selected nutrient mixtures. In patients undergoing allogeneic bone marrow transplantation for hematologic malignancies, reduced rates of lethal acute graft-versus-host disease were observed with parenteral nutrition regimens containing a high content of long-chain fatty acids [404]. Parenteral nutrition should be supplied by an expert team and should be tailored to the individual patient's requirements. A randomised clinical trial in 59 HCT patients compared nutritional support, including an individualised PN program implemented by an experienced team of clinical pharmacists, with routine nutritional support on a bone marrow transplantation ward. Allocation to the special PN program resulted in better nutritional status and shorter hospital stay [405].

A number of factors are responsible for muscle weakness and muscle loss including the underlying malignant disease, pre-HCT therapy, immobilization during HCT, and side-effects of drugs like corticosteroids [406]. In a randomized trial in 70 patients after high-dose chemotherapy and autologous HCT, patients assigned to daily 30-minute ergometer training responded with higher maximal physical performance, but also less neutropenia, thrombopenia, diarrhea, and pain at discharge as well as a shorter length of hospital stay [407]. Aerobic exercise has also been demonstrated in a pilot trial [408] and in an RCT [409] to improve the physical performance of cancer patients recovering from high dose chemotherapy. Therefore, it is recommended that patients be encouraged and supported to perform muscle training and to increase their physical activity before, during, and after HCT [410,411]. An outpatient physical exercise program should be continued after hospital discharge [409]. Physical performance may be graded using the WHO/ECOG scale [54]. Muscle mass may be estimated by anthropometry or by bioimpedance analysis [402,412]. More differentiated tools may be used to monitor daily

activities or to quantitate physical performance (e.g. walking tests) or muscle function (e.g. dynamometers) on a regular basis [413].

C4 − 2	High-dose chemotherapy and HCT: Enteral and parenteral nutrition
Strength of recommendation WEAK	*If oral nutrition is inadequate we suggest preferring enteral tube feeding to parenteral nutrition, unless there is severe mucositis, intractable vomiting, ileus, severe malabsorption, protracted diarrhea or symptomatic gastrointestinal graft versus host disease (GvHD).*
Level of evidence	Low
Questions for research	Comparing efficacy of enteral vs parenteral nutrition on clinical outcome and complication rates

Strong consensus

Comments

Artificial nutrition is indicated if a patient cannot be fed adequately by volitional food intake. If the intestinal tract is not severely compromised, enteral nutrition generally should be preferred. Several recent studies support preferring EN over PN in allogeneic HCT [414,415]. Data show a trend toward fewer complications using enteral compared to parenteral nutrition during this procedure especially for infectious complications [415]. However, an increased risk of local bleeding and/or infection in these patients has to be considered. After autologous HCT, PN will be necessary only in a few cases. After allogeneic HCT PN will be necessary more frequently and for prolonged periods because of severe toxic mucositis, GI infections, and GI graft versus host disease (GvHD). PN should be performed by experienced experts to avoid PN side effects and to obtain best clinical results. A recent RCT [405] and a controlled trial [416] showed the advantage of pharmacist-controlled and individualized parenteral nutrition regimens when compared to standard parenteral care regarding weight gain and length of hospital stay.

C4 − 3	High-dose chemotherapy and HCT: Low bacterial diet
Strength of recommendation −	*There are insufficient consistent clinical data to recommend a low bacterial diet for patients more than 30 days after allogeneic transplantation*
Level of evidence	Low
Questions for research	Definition of factors predicting beneficial effects of a low bacterial diet Comparing benefits of food safety guidelines vs neutropenic diet

Strong consensus

Comments

Due to the severe, and sometimes protracted, immunesuppression induced by high dose chemotherapy conditioning regimens there is a risk of food borne infections associated with them. In the 1980s the use of neutropenic diets after HCT was instituted as a means of preventing infection from organisms colonizing the gastrointestinal tract [417]. However, evidence supporting this practice is lacking and there have been differing views on how long low bacterial diets should be required after undergoing HCT. The guidelines for infection prevention of the U.S. Centers for Disease Control (CDC) recommend no special food after the neutropenic phase of HCT [418]. A recent Cochrane database review identified 7 studies investigating low bacterial diets during chemotherapy-induced neutropenia but found only 3 RCTs among these studies, each with methodological limitations and none considered the post-neutropenia phase [419]. The authors concluded that there was no evidence to support the use of a low bacterial diet for the prevention of infection and related outcomes [419]. Trifilio published a retrospective review of 726 consecutive HCT patients. Infection rates were higher among the 363 patients who received a neutropenic diet compared to 363 patients who received a general hospital diet [417]. In an RCT, Gardner et al. provided diets containing either only fresh or only cooked fruits and vegetables to 78 patients receiving induction chemotherapy for newly diagnosed acute myeloid leukemia (AML); rates of major infection, fever of unknown origin and survival did not differ between the groups [420]. In a similar but smaller randomized study in pediatric oncology patients there was no difference in infection rates in children receiving a neutropenic or a standard diet prepared according to general FDA food safety guidelines [421].

There is no published evidence to support a low bacterial diet during the neutropenic phase, and it is, therefore, difficult to argue for a germ-free diet after leucocyte engraftment. No data are available for the special case of severe intestinal graft versus host disease after allogeneic HCT. However, as opposed to the use of neutropenic diets, the emerging practice to minimize the risk of food borne infections appears to be to emphasise strict adherence to food safety guidelines, which recommend hand washing and also safe steps in food shopping, storage, preparation, thawing, cooking, serving, refreezing, and cold storage [421].

C4 − 4	High-dose chemotherapy and HCT: Glutamine
Strength of recommendation −	*There are insufficient consistent clinical data to recommend glutamine to improve clinical outcome in patients undergoing high-dose chemotherapy and hematopoetic stem cell transplantation.*
Level of evidence	Low
Questions for research	Effect of glutamine on mucositis, diarrhea, clinical infections, graft versus host disease and malignancy relapse rate

Strong consensus

Comments

Some nutritional substrates, such as glutamine, may influence physiological mechanisms and have been proposed to protect the intestinal mucosa from the impact of aggressive chemotherapy and radiotherapy, support recovery of the hematopoietic and immune system after cytoreductive therapies, optimize nitrogen balance and muscle protein synthesis, and improve antioxidant systems [422,423]. Interest in supplying glutamine to patients undergoing hematopoietic cell transplantation (HCT) was initiated when Ziegler et al. reported an RCT in 45 patients with haematologic malignancies undergoing allogeneic bone marrow transplantation. Patients receiving parenteral nutrition (PN) supplemented with glutamine compared to control patients receiving PN without glutamine

had improved nitrogen balance, fewer infections, and shorter hospital stays [424]. During the following years, this triggered a number of similar small trials. Among them, one RCT comparing PN supplemented with glutamine with glutamine-free PN in autologous transplant patients reported more severe oral mucositis and more relapses in the glutamine group [369]. In 2009, Crowther et al. published a systematic review and meta-analysis of 17 RCTs concluding that supplementation of glutamine in HCT may decrease the severity and the duration of mucositis, the incidence of clinical infections (relative risk 0.75) and of graft versus host disease (relative risk 0.42); however, it may also increase the rate of relapse of the malignancy (relative risk 2.91); no effect on mortality could be detected [370]. Importantly, the authors remarked that "many of the studies were small and scored poorly on methodological quality" [370]. In recent years, only one further RCT has been published that compared glutamine supplementation of PN to standard PN in 120 children with haematological malignancies and HCT did not affect severity or duration of mucositis, engraftment, graft versus host disease, relapse rate, or mortality [425]. Based on this information, the use of glutamine in HCT cannot be recommended at this time.

Section C5: Cancer survivors

C5 – 1	Cancer survivors: Physical activity
Strength of recommendation STRONG	*We recommend that cancer survivors engage in regular physical activity.*
Level of evidence	Low
Questions for research	Effects of physical activity on physical function, recurrence and survival in cancer survivors

Consensus

Comments

There is a strong theoretical background for advising cancer survivors to engage in physical activity. Physical activity is an effective strategy to improve aerobic capacity, physical fitness, and function in cancer survivors [214,409,426] (RCT and meta-analysis; high grade evidence). A question of major interest is whether physical activity can alter the risk of cancer recurrence following curative cancer treatment. Several observational studies have shown that physical activity is associated with reduced recurrence and mortality among breast and colon cancer survivors, however, there is currently insufficient evidence regarding the association between physical activity and mortality for survivors of other cancers [427—429] (Overall survival: low grade evidence). Cancer survivors should be offered physical activity and dietary advice to prevent obesity, because obesity might be a risk factor for recurrence and reduced survival in patients after breast cancer or colorectalcancer [430,431] (overall survival: low grade evidence). Preliminary results from randomised trials of physical activity suggest beneficial changes in the circulating levels of insulin, insulin-related pathways, and inflammation parameters [429]. However, rigorous randomized controlled trials are warranted to confirm these results. As soon as possible after finishing treatment, cancer survivors should adopt a physically active lifestyle of at least 30 min (preferably 45—60 min) of moderate-to-vigorous physical activity on at least

5 days per week, including both endurance and strength exercise [124,432].

C5 – 2	Cancer survivors: Body weight and lifestyle
Strength of recommendation STRONG	*In cancer survivors we recommend to maintain a healthy weight (BMI 18.5—25 kg/m^2) and to maintain a healthy lifestyle, which includes being physically active and a diet based on vegetables, fruits and whole grains and low in saturated fat, red meat and alcohol.*
Level of evidence	Low
Questions for research	Effects of a healthy diet on metabolic syndrome, quality of life, cancer relapse rates and overall survival

Strong consensus

Comments

Cancer survivors are often highly motivated to seek information about food choices, physical activity, and dietary supplements to improve their treatment outcomes, quality of life, and overall survival. Several recently published reviews indicate that obesity and metabolic syndrome might be independent risk factors for recurrence and reduced survival in breast and gastric cancer patients [430,433] (overall survival, low grade evidence). Moreover, cancer survivors are at a significantly higher risk of developing second primary cancers and other chronic diseases such as coronary heart disease, diabetes, and osteoporosis [434]. Guidelines to prevent these diseases are even more important for cancer survivors than for people without a previous history of a cancer disease [124,435].

Cancer survivors should strive to maintain a healthy weight and avoid excessive weight gain throughout life by balancing calorie intake with physical activity. Survivors who are overweight or obese should strive to reduce weight and be as lean as possible. The best diet to advise is a plant-based diet high in vegetables, fruits and whole grains, and low in saturated fats, red meats, and alcohol [124,432,436].

However, it is unclear whether plant-based foods have an effect on cancer recurrence rates. High blood levels of vegetable-derived carotenoids have been associated with a decreased risk of breast cancer recurrence [437]. Two large RCTs counselling breast cancer survivors to reduce fat intake (WINS trial, 2437 women) or to simultaneously decrease the intake of fat and increase the intake of vegetables (WHEL trial, 3088 women) after 5—7 years of observation could not reliably detect an effect on recurrence rates or mortality [438,439]. In an observational study, Pierce et al. reported decreased rates of breast cancer recurrence only in women who had a high intake of plant-based foods in combination with regular moderate physical activity when compared to women with either less physical activity and/or lower intake of vegetables and fruits [440].

Current evidence does not support large effects of food choices on cancer incidence [436,441—443]. High consumption of red meat (beef, pork, mutton) is associated with an increase in the risk of colorectal cancer [436,442], breast cancer [444], and overall cancer mortality [445]. Consumption of vegetables and fruits exerts limited protective effects against cancers associated with smoking or drinking [446]. On the other hand, there is reliable evidence that a diet rich in vegetables and fruits is associated with a decreased risk of cardiovascular and overall mortality [441]. Therefore, a similar diet should be recommended to cancer survivors.

Section C6: Patients with advanced cancer receiving no anticancer treatment

In advanced cancer there is the challenge of a progressing and often disseminated tumour in combination with the debilitating syndrome of inadequate food intake, inactivity, and metabolic derangements further promoting anorexia, fatigue, and catabolism. Anticancer treatment needs to consider diminishing body resources, quality of life, and physical as well as emotional resistance. Optimal palliative cancer care has been outlined by the European Society for Medical Oncology ESMO [447], the European Association for Palliative Care EAPC [448,449], the American Society of Clinical Oncology ASCO [450], and the World Health Organization WHO [451]. The WHO calls for the early integration of palliative care interventions (diagnostic, therapeutic, coordinative) by oncologists, palliative care specialists, and other experts within multi-professional teams and anticancer treatment from early in the course of disease and then until death and beyond. Decisions on nutritional interventions have to consider social, cultural, emotional and existential aspects as well as the patients' spiritual and ethnic background and needs [206].

C6 − 1	Advanced cancer: Screening and assessment
Strength of recommendation STRONG	*We recommend to routinely screen all patients with advanced cancer for inadequate nutritional intake, weight loss and low body mass index, and if found at risk, to assess these patients further for both treatable nutrition impact symptoms and metabolic derangements.*
Level of evidence	Low
Questions for research	Effects of malnutrition screening programs combined with multidisciplinary interventions on quality of life in cancer patients with advanced disease

<u>Consensus</u>

Comments

Patients with an advanced cancer may have a life expectancy of several months to several years. In these patients, deficits in nutritional status may impair performance status, quality of life, tolerance to anticancer treatments, and survival. In patients with shorter expected survival, alleviating nutrition impact symptoms may relieve the burden of the disease [452]. Due to the fact that nutritional support adjusted to individual needs may be beneficial in all of these patients, screening for and assessment of nutritional deficits is justified and required.

It is recommended to proceed with screening and assessment in patients with advanced cancer as outlined in section B1.

Patients identified by screening as having decreased oral intake require assessment of nutritional status by quantifying the amount and quality of nutritional intake (calories, proteins, frequency of meals), nutrition-impact signs and symptoms (e.g., stomatitis, dysphagia, early satiety, abdominal pain, constipation) as well as eating- or weight loss-associated psychosocial distress. We recommend obtaining and documenting objective data for current body mass index (BMI), extent of weight loss (% of original weight) during the preceding two to six months, performance status, and inflammatory status (C-reactive protein, albumin).

C6 − 2	Nutrition support in patients with advanced cancer
Strength of recommendation STRONG	*We recommend offering and implementing nutritional interventions in patients with advanced cancer only after considering together with the patient the prognosis of the malignant disease and both the expected benefit on quality of life and potentially survival as well as the burden associated with nutritional care.*
Level of evidence	Low
Questions for research	Effects of nutritional care on quality of life in patients with advanced cancer

<u>Consensus</u>

Comments

The benefit of nutritional support in patients with advanced cancer should be carefully considered, taking into account all relevant aspects, including the cancer prognosis [453,454], potential benefits of available anticancer treatments, nutritional status, and the potential effect of nutrition therapy as well as expectations and wishes of the patient and close relatives or partners [206].

Expected survival is most important. If expected survival is several months or years nutrition therapy should be given with the aim to secure an adequate intake of energy and protein, to diminish metabolic disturbances, and to maintain an adequate performance status and subjective quality of life. If a patient in this prognostic group is unable to eat, artificial nutrition may improve survival [190,206,209]. If expected survival is in the range of few to several weeks, interventions should be non-invasive and primarily aimed at psychosocial and existential support.

Nutritional support may include interventions to diminish nutrition impact symptoms, nutritional counselling, nutritional supplements, physical activity training, anti-inflammatory or anticatabolic pharmacologic agents as well as artificial nutrition. However, general palliative care interventions such as understanding of the illness, preparation for end of life including patient's will, legacy, forgiveness, pre-mortal mourning, place of death discussions, and caring around the dying process as well as spiritual and existential aspects have to be considered in relation to nutrition therapy in palliative patients.

Ideally, these considerations should be discussed and the consequences should be supported by a multi-professional team providing all the competencies of nutrition, oncology and palliative care [452,455]. Nutrition support, including oral nutritional supplements, enteral or parenteral, or combined interventions, should be prescribed according to the patient's energy and protein needs, and consideriing tolerability. As part of routine practice, reasonable short- and medium-term outcomes should be defined together with the patient. These include changes in physical function and perceived quality-of-life; chosen outcomes should be monitored to estimate stabilisation or improvement and should serve to decide on further nutritional support.

Patients with a comparably good prognosis and an expected overall survival of at least several months [453,455] as well as patients with low tumor activity and no inflammatory reaction (CRP < 10 mg/dl) [454] should receive adequate nutritional counselling and support including oral, enteral or, if required, parenteral nutrition, or combinations. Performance status should not influence decision making for or against nutritional support in these patients. Patients, who, despite oncologic therapy, have rapidly progressive disease, activated systemic inflammation, and/or an

ECOG performance status of ≥ 3, are less likely to benefit from nutritional support. However, patients should be assessed on an individual basis and, if appropriate, a trial of oral nutritional support should be offered with the aim of providing primarily symptomatic benefit.

Nutritional support should receive special consideration if patients are receiving palliative anti-cancer treatment. There is agreement that unconditional artificial nutrition in all patients undergoing anticancer therapy is associated overall with more harm than benefit [193,394,456] and should be avoided [6,7,9]. However, treatment-induced and thus iatrogenic deterioration of nutritional status should initiate adequate prophylactic or symptomatic supportive care including "permissive" nutritional support [389,457].

Few studies have been performed with the aim of demonstrating an objective benefit of nutritional support in advanced cancer patients. Individualized nutritional support may improve energy intake and quality of life in patients undergoing radiotherapy [44,45] and, in very advanced disease, it may decrease bed sores [458]. An escalating nutritional approach including, if necessary, parenteral nutrition may improve survival in cachectic patients with inadequate food intake [459]. In patients with advanced disease and chronic intestinal failure, parenteral nutrition may prolong quality of life and survival [1,458–460], especially in patients with initially preserved performance index [461,462]. Several professional societies have recommended consideration of parenteral nutrition if patients cannot be fed with other techniques and expected survival is more than 1–3 months [6,7,9,394]. Predicting survival in individual patients may be approached by clinical judgement and/or scoring systems [463,475] but is intrinsically difficult [464].

C6 − 3	Very advanced terminal phase
Strength of recommendation STRONG	*In dying patients, we recommend that treatment be based on comfort. Artificial hydration and nutrition are unlikely to provide any benefit for most patients. However, in acute confusional states, we suggest to use a short and limited hydration to rule out dehydration as precipiting cause.*
Level of evidence	Low
Questions for research	Predicting reversibilty in acute confusional states

Strong consensus

Comments

There are no clear criteria to ascertain the beginning of the dying phase; therefore, a nutritional intervention in this phase of life should be followed in an individualized manner [206]. There is little or no benefit from nutritional support in the last weeks of life, since it will not result in any functional or comfort benefit for the patient. In fact, during terminal hypometabolism, normal amounts of energy and substrates may be excessive and induce metabolic distress. Still, not infrequently, relatives and caregivers may demand artificial nutrition or hydration for terminally ill patients [465]. Psychosocial distress of and among family members or other proxies should be addressed by communication and educational interventions provided by multi-professional teams [466]. Respect for the religious, ethnic and cultural background of patients and their families has to be granted [206]. This may regard decisions to withdraw or withhold artificial nutrition in cases where there is no indication or no benefit may be achieved and will require appropriate communication and agreement.

Food and artificial nutrition may have social, emotional, and existential significance for the individual patient and family members [205]. Also small amounts of food can have a significant meaning for the individual and contribute to a sense of wellbeing, autonomy, and dignity [467]. It is mandatory to explain that the goal is comfort and to explain and communicate pros and cons of continued nutritional treatment with patients, family members, and the care team [205,468]. Hunger is rare in imminently dying patients and minimal amounts of desired food may provide appropriate comfort [469]. A patient who has been classified as imminently dying but is awake and is hungry may have been misdiagnosed. In such cases, the patient should be reassessed and may require treatment. Routine hydration showed no improvement in [465] or only limited effects [468,470] on symptoms and quality of life in cancer patients who are imminently dying [468,470,471].

In the imminently dying patient, artificial hydration may be tried if a clear very short-term goal is sought, such as improvement or maintenance of cognition. Thus, a short trial (24 h) of artificial hydration in a patient who is collaptic or delirious might be appropriate to exclude reversible symptomatic dehydration, but this requires evaluation on a regular basis in order to avoid symptoms of fluid retention [472]. The optimal choice of hydration fluid in this setting has not been determined; physiologic saline, Ringer's, Ringer's Lactate and glucose 5% solutions are being used.

Artificial hydration should not be used for thirst palliation or mouth dryness (often caused by medications like opioids) [468]; oral care measures are effective to comfort these patients [205,469,473].

Appendix A. Supplementary data: Evidence tables

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2016.07.015.

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