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ESMO HANDBOOK OF
NUTRITION AND CANCER

Edited by Aminah Jatoi, Stein Kaasa and Michiel Strijbos

2ND EDITION

ESMO Handbook Series

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Edited by

Aminah Jatoi
Department of Oncology, Mayo Clinic, Rochester, MN, USA

Stein Kaasa
Oncology and Palliative Medicine, University of Oslo, Oslo; Department of Oncology, Oslo University Hospital, Oslo; European Palliative Care Research Centre (PRC), Oslo University Hospital and Oslo University, Oslo, Norway

Michiel Strijbos
Department of Medical Oncology, GZA Hospitals Sint-Augustinus, Wilrijk, Belgium

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ESMO Head Office
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Via Ginevra 4
6900 Lugano
Switzerland
Tel: +41 (0)91 973 19 00
Email: publication_support@esmo.org
www.esmo.org

Contents

Editors

Aminah Jatoi

Department of Oncology, Mayo Clinic, Rochester, MN, USA

Aminah Jatoi, MD is the Betty J. Foust, MD and Parents' Professor of Oncology at the Mayo Clinic in Rochester, Minnesota, USA. A practising oncologist, she cares for patients with gastrointestinal and gynaecological malignancies. Her research interests focus largely on palliative and supportive care strategies for patients with cancer with a special interest in geriatric oncology.

She has authored or co-authored over 400 publications, and her research has been funded by the United States' National Institutes of Health as well as by various foundations. With dual training in both medical oncology and human nutrition, understanding nutritional issues in patients with cancer has remained a particularly salient aspect of Dr Jatoi's career interests.

Declaration of Interest:

Dr Jatoi reports institutional funding for advisory board membership from Novartis and Meter Health and an institutional research grant from AstraZeneca for an investigator-initiated research study.

Stein Kaasa

Oncology and Palliative Medicine, University of Oslo, Oslo; Department of Oncology, Oslo University Hospital, Oslo; European Palliative Care Research Centre (PRC), Oslo University Hospital and Oslo University, Oslo, Norway

Stein Kaasa is an MD with specialisation in medical oncology, radiotherapy and palliative medicine. In 1993 he was appointed the first Professor in Palliative Medicine in Scandinavia and was one of the founders of the Palliative Care Unit in Trondheim, Norway and is currently leader of the PRC.

He has been the National Cancer Director in Norway, President of the European Association for Palliative Care (EAPC) and leader of the EAPC Research Network, where he is currently the coordinator of the MyPath Project. He worked extensively to get palliative care and patient-centred care research on the agenda, both nationally and internationally. Currently he is Head of the Department of Oncology at Oslo University Hospital, Norway and Professor of Oncology and Palliative Medicine at the University of Oslo, Norway.

Professor Kaasa has published 546 articles and book chapters with an H index of 100. He is a member of the European Society for Medical Oncology (ESMO) Designated Centres Working Group.

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Professor Kaasa reports institutional funding for advisory board membership from Helsinn Healthcare, webinar lectures from Pfizer Norway and Nutricia Norway, a writing engagement from Nutricia Norway, invited speaker fees from MEDIDEO and Fresenius Kabi Deutschland, research grants from The Norwegian Cancer Society and the South-Eastern Norway Regional Health Authority for his work as coordinating principal investigator from Helseforsk, and from Nutricia Research for his work on the PROTES Project. He reports personal royalties from the *Oxford Textbook of Palliative Medicine*.

Michiel Strijbos

Department of Medical Oncology, GZA Hospitals Sint-Augustinus, Wilrijk, Belgium

Dr Michiel Strijbos is a Consultant Medical Oncologist at the Sint-Augustinus Hospital in Wilrijk, Belgium. He trained at Leuven University in Belgium and the Erasmus University in Rotterdam, Netherlands, where he graduated in 2004, and obtained his PhD in Tumour Immunology in 2009.

He is an investigator in clinical trials in genitourinary cancers and has a specific interest in health technology. Dr Strijbos has been a member of the ESMO Young Oncologists Committee and Chair of the ESMO Practising Oncologists Working Group. He is currently a member of the ESMO Educational Publications Working Group.

Dr Strijbos is the author of several papers published in indexed peer-reviewed international journals and has been an invited speaker at several national and international oncology meetings.

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Dr Strijbos reports personal speaker fees from Ipsen, Janssen, Bayer and MSD, personal advisory board fees from MSD, Bayer and Roche and a travel grant from Bayer. He holds stocks in Need Inc. and is employed part-time by Need Inc.

Contributors

Arends J. Universitätsklinikum Freiburg, Freiburg, Germany

Baracos V.E. Department of Oncology, University of Alberta, Edmonton, AB, Canada

Boeykens K. Nutrition Support Team, Vitaz Hospital, Sint-Niklaas, Belgium

Bozzetti F. Faculty of Medicine, University of Milan, Milan, Italy

Caccialanza R. Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Chasen M. Palliative and Supportive Care, William Osler Health System, Brampton, ON; McMaster University, Hamilton, ON, Canada

Dajani O. Oncology and Palliative Medicine, University of Oslo, Oslo; Department of Oncology, Oslo University Hospital, Oslo; European Palliative Care Research Centre (PRC), Oslo University Hospital and Oslo University, Oslo, Norway

Fallon M.T. Institute of Genetics and Cancer, University of Edinburgh, Edinburgh; Edinburgh Cancer Centre, NHS Lothian, Edinburgh, UK

Hjermstad M.J. Oncology and Palliative Medicine, University of Oslo, Oslo; Department of Oncology, Oslo University Hospital, Oslo; European Palliative Care Research Centre (PRC), Oslo University Hospital and Oslo University, Oslo, Norway

Hopkinson J.B. School of Healthcare Sciences, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK

Jatoi A. Department of Oncology, Mayo Clinic, Rochester, MN, USA

Kaasa S. Oncology and Palliative Medicine, University of Oslo, Oslo; Department of Oncology, Oslo University Hospital, Oslo; European Palliative Care Research Centre (PRC), Oslo University Hospital and Oslo University, Oslo, Norway

Laird B.J.A. Institute of Genetics and Cancer, University of Edinburgh, Edinburgh; Edinburgh Cancer Centre, NHS Lothian, Edinburgh; St Columba's Hospice Care, Edinburgh, UK

Laviano A. Department of Translational and Precision Medicine, Sapienza University, Rome, Italy

Lee M. Division of Clinical Trials and Biostatistics, Mayo Clinic, Rochester, MN, USA

Le-Rademacher J.G. Division of Clinical Trials and Biostatistics, Mayo Clinic, Rochester, MN; Department of Oncology, Mayo Clinic, Rochester, MN, USA

Ligibel J.A. Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Mislang A.R.A. Department of Medical Oncology, Flinders Centre for Innovation in Cancer, Flinders Medical Centre, Bedford Park, Adelaide, SA; College of Medicine and Public Health, Flinders University, Bedford Park, Adelaide, SA, Australia

Morgan G. Skåne University Hospital, Department of Medical and Radiation Oncology, Lund, Sweden

Mukherjee M.S. Caring Futures Institute, College of Nursing and Health Sciences, Flinders University, Bedford Park, Adelaide, SA, Australia

Ravasco P. Universidade Católica Portuguesa, Faculty of Medicine and Centre for Interdisciplinary Research in Health (CCIS-UCP), Lisbon; Egas Moniz School of Health and Science, Centre for Interdisciplinary Research Egas Moniz, Almada, Portugal

Schuetz P. Medical University Department, Division of General Internal and Emergency Medicine, Medical Faculty of the University of Basel, Kantonsspital Aarau, Aarau, Switzerland

Stanga Z. Division of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, University of Bern and Bern University Hospital, Bern, Switzerland

Strasser F. Cantonal Hospital St. Gallen and Cancer Fatigue Clinic, Onkologie Schaffhausen, Schaffhausen; Cantonal Hospital Münsterlingen, Münsterlingen; Center Radiotherapy Rüti, Rüti, Switzerland

To T.H.M. Research Centre for Palliative Care, Death and Dying, College of Nursing and Health Sciences, Flinders University, Bedford Park, Adelaide, SA; Southern Adelaide Palliative Service, Flinders Medical Centre, Bedford Park, Adelaide, SA; College of Medicine and Public Health, Flinders University, Bedford Park, Adelaide, SA, Australia

Yi D. Cicely Saunders Institute of Palliative Care, Policy & Rehabilitation, King's College London, London, UK

Reviewers

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Sara A. Arscott, Osher Center for Integrative Health, Department of Family Medicine and Community Health, University of Wisconsin - Madison, WI, USA

Vickie E. Baracos, Department of Oncology, University of Alberta, Edmonton, AB, Canada

Martin Chasen, Palliative and Supportive Care, William Osler Health System, Brampton, ON; McMaster University, Hamilton, ON, Canada

Karin Jordan, Department of Hematology, Oncology and Palliative Care, Klinikum Ernst von Bergmann Potsdam, Potsdam; Department of Medicine V, Hematology, Oncology and Rheumatology, University of Heidelberg, Heidelberg, Germany

Alessandro Laviano, Department of Translational and Precision Medicine, Sapienza University, Rome, Italy

Charles Loprinzi, Mayo Clinic, Rochester, MN, USA

Lisa Moloney, Academy of Nutrition and Dietetics, Chicago, IL, USA

Manpreet Mundi, Division of Endocrinology, Diabetes, Metabolism and Nutrition, Mayo Clinic, Rochester, MN, USA

Maurizio Muscaritoli, Sapienza University of Rome, Department of Translational and Precision Medicine, Rome, Italy

Elena Paillaud, Department of Geriatrics, European Georges Pompidou Hospital, Paris Cancer Institute CARPEM, Assistance-Publique Hôpitaux de Paris, Paris; Paris Est Créteil University, Inserm U995, IMRB Créteil, France

Philippe Paillet, Paris Est Créteil University, Inserm U995, IMRB Créteil; APHP, Department of Geriatrics, European Georges Pompidou Hospital, Unité de coordination en Onco-gériatrie Paris-Ouest, Paris, France

Olav Erich Yri, European Palliative Care Research Centre (PRC), Department of Oncology, Oslo University Hospital; Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Abbreviations

AEE	Activity-induced energy expenditure
AN	Artificial nutrition
ASCO	American Society of Clinical Oncology
ATP	Adenosine triphosphate
BCAA	Branched-chain amino acid
BIA	Bioimpedance analysis
BMI	Body mass index
BW	Body weight
CBA	Cost-benefit analysis
CC	Calf circumference
CEA	Cost-effectiveness analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
CT	Computed tomography
CUA	Cost-utility analysis
DASH	Dietary Approaches to Stopping Hypertension
DEE	Diet-induced energy expenditure
DEXA	Dual-energy X-ray absorptiometry
DHA	Docosahexaenoic acid
DRM	Disease-related malnutrition
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMR	Electronic medical record
EN	Enteral nutrition
EORTC QLQ-30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-30
EPA	Eicosapentaenoic acid
EQ-5D	EuroQol 5 Dimension
ERAS	Enhanced recovery after surgery
ESMO	European Society for Medical Oncology

ESPEN	European Society for Clinical Nutrition and Metabolism
EVOO	Extra virgin olive oil
FDA	Food and Drug Administration
GA	Geriatric assessment
GDF-15	Growth/differentiation factor-15
GI	Gastrointestinal
GLIM	Global Leadership Initiative on Malnutrition
HMB	Beta-hydroxy-beta-methylbutyrate
HR	Hazard ratio
i.v.	Intravenous
IARC	International Agency for Research on Cancer
IGF-1	Insulin-like growth factor 1
i-PARIHS	Integrated Promoting Action on Research Implementation in Health Services
IPOS	Integrated Palliative care Outcome Scale
Look AHEAD	Action for Health in Diabetes trial
MASCC	Multinational Association of Supportive Care in Cancer
MNA	Mini Nutritional Assessment
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NRS-2002	Nutritional Risk Screening 2002
NSAID	Non-steroidal anti-inflammatory drug
ONS	Oral nutritional supplement
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
PG-SGA	Patient-Generated Subjective Global Assessment
PhA	Phase angle
PICC	Peripherally inserted central catheter
PN	Parenteral nutrition
POS-E	Palliative care Outcome Scale for Economic evaluations
PRO	Problem, resources, outcome
PROM	Patient-reported outcome measure
PUFA	Polyunsaturated fatty acid
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
REE	Resting energy expenditure

RR	Risk ratio
SCM	Supportive Care Measure
SF-36	36-Item Short Form Health Survey
TEE	Total energy expenditure
WCRF	World Cancer Research Fund
WHO	World Health Organization

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Dr Michiel Strijbos, on behalf of all the Editors

Preface

Patients diagnosed with cancer are often overwhelmed. The diagnosis itself, the risk factors (or their absence) that might have led to the cancer diagnosis, the essential further testing and establishment of a cancer stage, the prognosis, the logistics of cancer therapy and the management of therapy-induced side effects and cancer-induced symptoms – all contribute to the overwhelming nature of cancer.

Throughout this complex journey and perhaps with the goal of acquiring some degree of control in their daily lives, patients frequently pose the following question to their healthcare providers: "What should I be eating?" The *ESMO Handbook of Nutrition and Cancer (Second edition)* is intended to help healthcare providers respond to this misleadingly simple – but ever so complex – question with accurate and pragmatic information from experts in the field. Providing succinct peer-reviewed chapters on a variety of pertinent topics, this handbook serves as a resource designed to help oncologists help patients, as these patients contend with what may be some of the most challenging circumstances of their lives.

Dr Aminah Jatoi, on behalf of all the Editors

Introduction

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A. Jatoi[1]

S. Kaasa[2]

[1]*Department of Oncology, Mayo Clinic, Rochester, MN, USA*
[2]*Oncology and Palliative Medicine, University of Oslo, Oslo; Department of Oncology, Oslo University Hospital, Oslo; European Palliative Care Research Centre (PRC), Oslo University Hospital and Oslo University, Oslo, Norway*

An old English proverb reads, *"Don't dig your grave with your own knife and fork."* If only it were that simple and if only clinicians were able to resort to one simple imperative when rendering nutritional advice to patients with cancer, to those with a history of cancer, and to individuals at risk for this disease! Had it been that simple, the editors of the *European Society for Medical Oncology (ESMO) Handbook of Nutrition and Cancer* and the staff at ESMO would have finished their task of finalising this second edition way ahead of schedule!

Instead, for this second edition of the *ESMO Handbook of Nutrition and Cancer*, dozens of experts well-versed in the interface between nutrition and cancer came together from around the globe to write, critique, edit, deliberate and update a variety of chapter-based topics that span all the way from the basic concepts of nutrition to the health economics of nutrition, all within the context of cancer. The topics covered in this handbook are grounded in basic, translational and clinical science. One topic focuses on cancer prevention. Others describe how to clinically assess patients with cancer for nutritional decline; how to review the prognostic significance of biomarkers (such as cross-sectional muscle area as measured on computed tomography scans), which serve to flag nutritional compromise; and how to manage patients who might benefit from nutritional counselling, caloric repletion, pharmacological interventions and supportive and palliative care. Recognising that cancer therapy itself can wreak havoc on nutritional parameters, we have

included a specific chapter dedicated to nutrition during cancer treatment. And in keeping with shifting worldwide demographics that point to a growing number of older patients with cancer in some countries and to an increasing number of patients who are surviving after a cancer diagnosis, these two populations are covered in their own respective chapters. Two new chapters – one on implementation science and the other on managing divergent recommendations from different information sources – now serve to address these important areas that are gaining further attention in medicine.

A product of tremendous effort on the part of many, the second edition of the *ESMO Handbook of Nutrition and Cancer* brings invaluable state-of-the-art management approaches, which go far beyond the accoutrements referenced in the old English proverb above and provide concrete, evidence-based recommendations. We sincerely hope that this handbook will help clinicians as they, in turn, work to help patients with cancer and their families.

Basic Concepts of Nutrition

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A. Laviano[1]

R. Caccialanza[2]

[1]*Department of Translational and Precision Medicine, Sapienza University, Rome, Italy*

[2]*Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*

Energy and Protein Balance

Living organisms require energy to grow, differentiate and procreate. Animals oxidise diet-derived macronutrients, i.e. carbohydrates, lipids and proteins, to produce energy and thus support their metabolic and anabolic needs. The universal energy 'currency' is adenosine triphosphate (ATP), which is synthesised in the presence of an excess of energy and degraded when energy is promptly needed. The turnover of ATP is very high, reaching 1.3 mmol/kg/sec, which leads to the complete exhaustion of the total body pool of ATP within one minute. Consequently, a constant supply of energy is needed, even during sleep and rest. As food intake is not a continuous process, between meals the organism has to utilise energy substrates from its reserves. Under normal (non-stress) situations, ingested carbohydrates, fat and protein are partly stored as glycogen and lipid. Accumulation of protein can occur only in a quantitatively limited manner, as may happen during the growth of an individual, the building of muscle, or recovery after illness associated with loss of proteins – especially muscle. During energy production, carbohydrates, protein, fat or alcohol are combusted, consuming oxygen, while carbon dioxide, water and heat are produced. Therefore, measurement of energy expenditure can be calculated from heat production – referred to as 'direct calorimetry'. However, more often, energy expenditure is calculated from oxygen consumption and/or carbon dioxide production – referred to as 'indirect calorimetry'.

Appetite and Its Control

Patients with cancer often report changes in their appetite and a reduced food intake. The analysis of the pathophysiology of food intake control explains the possible role of pharmacological agents to improve energy and protein intake. Food intake is governed by the coordinated recurrence of hunger, appetite, satiation and satiety. The hypothalamus integrates neural, metabolic and hormonal signals originating from peripheral tissues, and transduces these inputs into neuronal responses and, via second-order neuronal signalling pathways, into behavioural and metabolic responses. The hypothalamic melanocortin neurons mediate anorectic responses, whereas neurons expressing neuropeptide Y trigger the onset of appetite. Influencing the activity of these neuronal networks, a number of factors, including pro-inflammatory cytokines, neurotransmitters and peptides (i.e. GDF-15 [growth/differentiation factor-15], leptin), activate the anorexigenic pathway and mediate wasting.

Metabolism of Macro- and Micronutrients

Carbohydrates

Carbohydrates represent the largest part (40%–70%) of the total energy intake (recommendation: 45%–65%). Dietary carbohydrates are digested to hexoses (mainly glucose), which are absorbed in the portal circulation. Glucose is the universal source of energy for all cells, either via full oxidisation in the Krebs cycle or by glycolysis. Glucose metabolism is regulated by insulin. On the other hand, catabolic hormones (e.g. glucagon, adrenaline and cortisol) decrease glucose uptake in muscle and adipose tissue, and stimulate hepatic glucose production from lactate, glycerol and amino acids via gluconeogenesis.

Lipids

Lipids represent the most energy-dense component of energy intake. They constitute approximately 25%–50% of ingested energy (recommendation: 20%–35%). The majority is ingested as triglycerides (90%), while the remainder are phospholipids and cholesterol. After ingestion, lipids are emulsified to small droplets (primary micelles) that are hydrolysed

to free fatty acids, monoacylglycerol, cholesterol and phospholipids, which form secondary micelles, which are in turn hydrolysed and absorbed by enterocytes. Inside enterocytes, long-chain fatty acids are synthesised into chylomicrons which are released in the lymphatic system to the systemic blood circulation. The major proportion of chylomicron triglycerides is hydrolysed, and fatty acids are either stored in adipose tissue or oxidised as energy substrate. Lipids are not mere energy sources, since they may play a significant role in influencing human metabolism. The potential modulating effects of omega-3 polyunsaturated fatty acids (PUFAs) on inflammatory response suggest that they may contribute to shaping a favourable metabolic environment in patients with cancer. Large epidemiological studies and limited interventional trials appear to demonstrate that omega-3 PUFA intake, as either a dietary component or supplement, may preserve nutritional status, improve quality of life and possibly influence mortality. However, more robust clinical trials are needed before omega-3 PUFA supplementation can be routinely recommended.

Proteins and Amino Acids

Proteins represent 15%–20% of energy intake in a typical diet. The usual need for an adult is 0.8–1.2 g/kg of body weight (BW) /day. Ingested proteins are hydrolysed in the intestine to amino acids and oligopeptides, which are then further hydrolysed in enterocytes. Amino acids are the building blocks of body proteins. Their oxidisation to produce energy during fasting is associated with loss of muscle mass. During severe stress, the primary currency is glucose and hence, via the process of gluconeogenesis, body proteins are utilised in severe stress or inflammatory situations or during severe malnutrition.

Unlike carbohydrates and fat, proteins are not stored unless in association with the nitrogen accretion of body building or during repair and growth. This is apparent in the case of muscle mass, which is fully dependent on protein intake and physical activity. Bed rest usually leads to negative nitrogen balance in spite of sufficient protein and energy intakes. This is important especially in patients who lost weight due to malignant disease and its treatment. Since muscle contraction is a potent inducer of anabolism,

regaining of muscle in these patients, which is a relatively slow process, can be enhanced by preventing immobility and favouring mild to moderate physical activity when possible.

Nine essential amino acids cannot be synthesised in humans and are mandatory in the diet or during artificial nutrition. These are histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine.

As already discussed for lipids, a number of amino acids influence human metabolism in a way that could be exploited for patients with cancer. Leucine and its derivative HMB (beta-hydroxy-beta-methylbutyrate) have been shown to enhance muscle anabolism, even during catabolic conditions. Arginine is required for immune response and its provision within the tumour microenvironment increases antitumour activity of lymphocytes. Translation of this evidence into clinical practice is still limited due to the lack of robust clinical trials.

Fibres

Given the increased interest on the role of intestinal microbiota in enhancing the efficacy of anticancer therapies, the intake of fibre has gained considerable attention. As an example, daily intake of at least 20 g of fibre appears to enhance the efficacy of immunotherapy in melanoma patients.

Water and Electrolytes

Recommended intake of water ranges between 20 and 40 mL/kg BW/day (not counting for losses). Acute stress and inflammation are associated with water and sodium retention and loss of potassium, magnesium and phosphate. More importantly, dehydration is associated with sarcopenia and increased risk of all-cause mortality. Recovery is accompanied by water and sodium mobilisation and diuresis (loss of oedema) and by increased need of potassium, magnesium and phosphate to replenish intracellular loss. A similar situation is apparent during refeeding after long-term starvation. Decreased levels of plasma phosphate, potassium and magnesium lead to muscle paralysis, cardiac arrhythmias, water retention and even sudden death, the so-called ‘refeeding syndrome’.

Body Composition Assessment

Human metabolism aims to preserve body cell mass and body composition. Body composition can be assessed using various techniques, the sensitivity and specificity of which differ significantly. Measurement or estimation of adipose and muscle tissues play a relevant role in predicting the outcome of patients with cancer. Robust clinical evidence demonstrates that early quantitative and qualitative changes in muscle and adipose tissues predict chemotherapy-associated toxicity, the risk of low relative dose intensity of chemotherapy, the degradation rate of immune checkpoint inhibitors and, ultimately, progression-free and overall survival. Consequently, the early assessment of nutritional status, including body composition when feasible, is now recommended by international guidelines (European Society for Clinical Nutrition and Metabolism [ESPEN] and European Society for Medical Oncology [ESMO]) on the management of patients with cancer.

Considering the contributory, yet relevant, role of body composition changes in informing the clinical decisions on the long-term management of patients with cancer, it is self-evident that muscle mass and adipose tissue should be measured rather than estimated. The gold standard for the measurement of body composition changes in patients with cancer, as well as in other diseases, is the analysis of tissue density using a computed tomography (CT) scan at the level of the third lumbar vertebra. This technique allows a precise measurement not only of quantitative changes, i.e. sarcopenia, but of qualitative changes as well, including fat infiltration within muscle mass, i.e. myosteatosis.

CT scan analysis is facilitated by using software which automatically calculates the tissue attenuation as expressed by Hounsfield units and derives the quantity of muscle and adipose tissues. Nevertheless, CT-based body composition assessment remains poorly implemented in clinical practice. To overcome at least some of the barriers, more levels along the spine have been proposed, without major success. Also, the use of other imaging techniques, including dual-energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI) and ultrasound of quadriceps muscle, have been proposed but their feasibility and reliability remain questionable at the time of publication.

So far, no biochemical biomarker of nutritional status and body composition has been proposed and robustly validated. Therefore, in daily clinical practice, body composition is estimated rather than measured. Anthropometry (measurement of circumferences and skinfolds) has been shown to be affected by large inter- and intra-observer variability and is not routinely implemented. In contrast, a very easily performed yet robust predictor of muscle mass in patients with cancer is calf circumference (CC), which has been demonstrated to predict mortality. Bioimpedance analysis (BIA), which derives fat mass and fat-free mass from hydration status using validated formulae, is used routinely. This gives reasonable data for patients who are in a stable condition; however, caution is necessary for subjects who are acutely ill and have hydration problems (ascites, hydrothorax, etc.). In recent years, phase angle (PhA), a raw BIA variable, has received much attention because studies have suggested its potential as an index of body cell mass and cellular integrity. In particular, a low PhA is associated with malnutrition and poor outcome in patients with cancer.

Measuring/estimating nutritional status and body composition allows to estimate energy stores, which are presented in Table 1.

Table 1 Normal Body Energy Stores in Well-nourished, Non-obese Individuals.
Adapted from: Garrow JS. Energy stores in man, their composition and measurement. Proc Nutr Soc 1982; 41:175–181.

Fuel type	kg	kcal
Fat (1 kg fat = 1.1 kg adipose tissue)	15	141 000
Protein (1 kg protein = 4 kg muscle tissue)	12	40 000
Glycogen (liver)	0.2	400
Glycogen (muscle)	0.5	800
Glucose (blood)	0.02	80

Given that exact measurement of body compartments is difficult, the key is to regularly measure changes in body compartments, either to prompt nutritional therapy or to monitor its efficacy. When this is not feasible, regular measurement of BW and calculation of changes in BW and body mass index (BMI) are also clinically relevant and useful. In summary, healthcare professionals should take advantage of imaging prescribed for

any clinical indications to also check and monitor the body composition changes of their patients. Nutritional status can also be estimated by using BIA, CC, etc. When body composition cannot be measured nor estimated, non-volitional weight loss is a good proxy of deteriorating nutritional status. Interestingly, combining BMI with non-volitional weight loss (%) in the previous months predicts survival in patients with cancer.

Diagnosis of Malnutrition

Nutritional Screening

Nutritional screening needs to be simple, rapid and easily performed on hospital admission or at each oncological visit. This procedure serves as a baseline and dictates appropriate nutritional intervention. Several screening tools exist, based on actual BW, recent weight loss and recent food intake. Nutritional screening should be a mandatory and regular part of the medical care of cancer patients, given the increased risk of disease- and therapy-related undernutrition. The ESPEN guidelines recommend the use of specific screening tools according to the clinical setting. However, the key is using any tool which has been validated in the specific clinical setting. It is important to differentiate nutritional screening from nutritional assessment beyond the competencies needed to perform them. In fact, nutritional assessment is key to select the group of patients within a larger population which may suffer from malnutrition. By performing nutritional assessment, not only is the perception of a risk translated into a definite diagnosis of malnutrition, more importantly it highlights the body compartment mostly affected as well as the factors determining malnutrition.

Nutritional Assessment

Nutritional assessment is a more detailed evaluation of nutritional status, aimed at diagnosing the presence of malnutrition and at informing the provision of nutritional support. Nutritional assessment is clinically indicated in cancer patients because of their higher risk for malnutrition.

Given the complexity of nutritional assessment, which may prevent its implementation in daily clinical routine, an easily applicable protocol

for the diagnosis of malnutrition, involving widely available criteria, has been recently proposed by an international panel of experts from European, North American, Latin American and Asian clinical nutrition societies. The so-called Global Leadership Initiative on Malnutrition (GLIM) criteria recommend that patients at nutritional risk, based on a validated screening tool, are assessed for the presence of aetiological and phenotypic criteria (Table 2).

Table 2 GLIM Criteria.
Adapted from: Cederholm T, Jensen GL, Correia MITD, et al; GLIM Core Leadership Committee; GLIM Working Group. GLIM criteria for the diagnosis of malnutrition – a consensus report from the global clinical nutrition community. Clin Nutr 2019; 38:1–9.

Phenotypic criteria	Non-volitional weight loss[1]
	Low BMI[2]
	Reduced muscle mass[3]
Aetiological criteria	Reduced food intake or assimilation[4]
	Disease burden/inflammatory condition[5]

[1] >5% within the past 6 months, or >10% beyond 6 months.
[2] <20 if <70 years, or <22 if >70 years; Asia: <18.5 if <70 years, or <20 if >70 years.
[3] Reduced by validated body composition measuring techniques (i.e. DEXA, BIA, CT, MRI; when not available, physical examination or standard anthropometric measures such as mid-arm muscle or calf circumferences may be used).
[4] ≤50% of ERs >1 week, or any reduction for >2 weeks, or any chronic GI condition that adversely impacts food assimilation or absorption.
[5] Acute disease/injury or chronic disease-related (C-reactive protein may be used as a supportive laboratory measure).
Abbreviations: BIA, bioimpedance analysis; BMI, body mass index; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; ER, energy requirement; GI, gastrointestinal; GLIM, Global Leadership Initiative on Malnutrition; MRI, magnetic resonance imaging.

Patients with at least one aetiological and one phenotypic criterion can be diagnosed with malnutrition. It is acknowledged that the proposed framework may minimise the metabolic and functional complexity of nutritional status. However, it is important to remember that the assessment of the nutritional domains involved in preserving nutritional status, and thus health, remains necessary after having posed a diagnosis of malnutrition. This analysis guides the provision of a qualitatively and quantitatively appropriate nutritional intervention and allows for monitoring and fine tuning of its efficacy.

The domains of nutritional assessment can be divided into:

- Measurement of nutrient balance (nutrition balance, intake and output)

- Measurement of body composition (BMI, anthropometry, BIA, imaging)
- Measurement of inflammatory activity (C-reactive protein, neutrophil-to-lymphocyte ratio, leukocyte count)
- Measurement of function (muscle function [dynamometry], respiratory function, immune function)

For all methods of nutritional assessment, measurements must be repeated at various time intervals according to clinical status and needs, because it is the directional change that guides therapy. Each test has its unique advantages and limitations. However, their interpretation must take into consideration the underlying disease, the ongoing therapy and the overall clinical picture. In summary, patients should be empowered and responsible for monitoring their BW every 2-3 weeks, and immediately report non-volitional weight loss >5% of their usual BW. It is also advisable that changes in their functional ability be reported even in the absence of significant weight loss.

Influence of Undernutrition on Physiological Functioning

Undernutrition and negative energy balance have substantial effects on energy stores and organ function. The rapidity of energy store loss and change in organ function depend on the degree of energy and protein deficiency as well as on clinical conditions during starvation. These are dependent on food intake as well as on the presence of stress factors including trauma, blood loss, inflammation or other conditions.

Simple Starvation

In simple starvation, the substrate–hormone profile is not disturbed by acute stress or inflammation. It is characterised by hormonal adaptation, decreased resting energy expenditure (REE) and also by reduction of physical activity. Energy need is furnished mainly by fat tissue and ketone bodies, whereas the protein compartment is relatively preserved. This enables long-term survival during famine periods (60–70 days in normal-weight subjects).

Stress Starvation

Acute and chronic diseases, including cancer, lead to systemic inflammation. This is associated with a greater need for glucose as a substrate to mount the immune response and sustain the recovery phase. On the other hand, systemic inflammation is associated with insulin resistance, leading to hyperglycaemia and the development of anorexia and reduced food intake. From a mechanistic point of view, systemic inflammation appears to promote self-recovery based on endogenous stores and metabolic switch. In particular, muscles are degraded to amino acids, which in turn are converted via gluconeogenesis to glucose for use by inflammatory tissue and cells of the immune system. An increase in fatty acid turnover occurs, with decreased production of ketone bodies, insulin resistance and fat accumulation in various organs. Phenotypically, stress starvation is characterised by rapid loss of muscle, reduction of adipose tissue and decrease of muscle function. This constellation of symptoms and clinical signs is defined as 'disease-related malnutrition with inflammation' (i.e. cachexia), to differentiate it from simple starvation. As survival is dependent mainly on the degree of the protein loss, and the amount of lean body mass is determined by genetics and physical stature, the period of starvation in these conditions is significantly lower (usually 14-21 days, depending on inflammatory activity).

It is therefore apparent that nutritional therapy in cancer patients with malnutrition should always consider its two major causative factors: reduced food intake or impaired digestion and absorption by the gut mucosa, and metabolic changes induced by inflammation. Of great importance is the evidence that the nutritional and metabolic status of a patient with cancer may well change over their long clinical journey, requiring mostly replenishment of calorie and protein gaps at some time points, while in contrast modulation of inflammation and metabolic changes may represent the key intervention at other time points.

Physiological Function and Deficiency States of Trace Elements and Vitamins

Although a limited daily intake of micronutrients is required, trace

elements (essential inorganic micronutrients) and vitamins (essential organic micronutrients) play a critical role in health and disease. Their role can be classified as follows: cofactors in metabolism, coenzymes in metabolism, control functions, structural components, antioxidants.

Recommendations for the daily intake of micronutrients have been developed. These are based on the intakes associated with health. Therefore, they are adequate for planning food strategy for a population, but are less useful for the individual. During disease, the concentrations of many trace elements decrease, and this has been associated with reduced oxidative defence, impaired immune response and deranged metabolism. However, clinical trials testing the effects of trace element supplementation during acute and chronic illness have not yielded consistently positive results, and their use in patients with cancer should be cautiously considered, particularly during anticancer treatments.

Obesity in Cancer Patients

Malnutrition is a broad term, which defines pathological deviations from optimal nutritional status. Consequently, overnutrition, i.e. obesity, is included under the umbrella of malnutrition syndromes. There is still debate on whether obesity, beyond predisposing to certain types of cancer, may also protect from rapid wasting and therefore extend survival of patients with cancer. Much of the debate is based on the variable body composition of obese patients.

The majority of patients with cancer in Europe and North America are either overweight or obese, based on their BMI. However, body composition studies consistently show that obese patients may well present sarcopenia (i.e. sarcopaenic obesity). In patients with cancer, sarcopaenic obesity has been shown to be associated with poor clinical outcomes. Body composition analysis is therefore recommended in obese patients with cancer, to reveal hidden nutritional deficits and inform a tailored nutritional intervention promoting supervised weight loss/stability, consisting of mostly adipose tissue loss and preservation of muscle mass.

Goals of Nutritional Therapy

Nutritional therapy is based on a stepwise approach to the unmet substrate needs of patients. Based on the patient's potential to meet at least part of their requirements via the oral route, on the existence of a functioning gut, and on the feasibility to have access to the gastrointestinal tract or to the circulatory system, nutritional therapy includes counselling, supplementation with food or oral nutritional supplements, enteral nutrition and finally parenteral nutrition, either peripherally or centrally infused. Given the current technology, it can be said that all patients can be fed, and therefore not feeding a patient remains a clinical decision.

The goal of nutritional therapy in cancer patients is to prevent and treat undernutrition, which in turn impacts on physiological functioning, i.e. muscle function, cardiovascular function, respiratory function, gastrointestinal function, immune function, cognitive function and thermoregulation.

Qualitatively and quantitatively appropriate nutritional intake is key to better toleration of the catabolic effects of the growing tumour and anticancer therapies. Evidence shows that nutritional therapy during any catabolic crisis (surgery, chemotherapy, radiotherapy, etc.) not only improves short-term outcomes, but better prepares the patient for the next catabolic crisis. Therefore, omitting to adequately feed a patient with cancer not only reduces their chances of tolerating aggressive therapies, but limits the benefit from the following therapeutic steps during the long clinical journey.

Nutritional Requirements of Adults

A critical factor in maintaining health or alternatively in recovering quickly from disease is ensuring that adequate energy and protein requirements are met. In a healthy adult with stable weight, physical and cognitive performance depend on the tight balance between energy expenditure and energy intake.

Different components define total energy expenditure (TEE), and in particular: REE, the energy needed to preserve basic vital functions,

diet-induced energy expenditure (DEE), the energy spent to digest and absorb nutrients, and activity-induced energy expenditure (AEE), the energy spent on physical activity. The determinants of TEE may vary widely according to each individual's lifestyle, age, sex and body composition. In clinical practice, the contribution of acute and chronic diseases to increase REE (i.e. hypermetabolism) should always be considered.

To calculate daily energy requirements, daily energy expenditure should be assessed. REE can be measured by indirect calorimetry. However, in clinical practice, REE is more frequently estimated by equations. An easy and practical approach to estimate REE consists of multiplying the BW and the daily energy requirements of BW. This ranges from 20 to 35 kcal/kg BW/day. These formulae do not consider body composition, and may under- or overestimate disease-induced hypermetabolism in the presence of severe malnutrition and obesity. In this regard, international guidelines suggest measuring REE rather than estimating it. Given the variability of REE along the clinical journey of a patient with cancer, regular measurement of REE may prevent the complications associated with over- and under-feeding.

Diet and Dietary Patterns

The journey of cancer patients is characterised by a progressive nutritional and functional decline, accelerated by catabolic crisis (i.e. surgery, chemotherapy, radiotherapy, etc.). Effective nutritional therapy should inform patients on the recommended long-term lifestyle changes associated with longer survival and better quality of life, and implement specific and tailored interventions during the catabolic crisis.

Given the role of diet in influencing the risk for cancer, it has been postulated that diet may also have a specific role in reducing the progression of cancer. A number of 'anticancer' diets have been proposed (e.g. vegetarian, vegan, ketogenic, basic, etc.), none of which has been validated by robust clinical or epidemiological data. In contrast, a Mediterranean-style diet, which includes fruit, vegetables and whole cereals, and favours plant protein over animal protein, appears to extend survival when implemented in conjunction with other lifestyle habits.

Caloric restriction is associated with reduced risk of cancer. Whether short-term and supervised caloric restriction also benefits cancer patients receiving anticancer therapies remains to be tested in clinical trials. Preliminary reports addressing the link between circadian rhythms and food intake have drawn considerable interest. If efficacy is demonstrated by clinical trials, limiting the feeding time to less than 12 hours synchronous with the light/dark cycle may represent an additional opportunity to enhance the efficacy of anticancer therapies.

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Role of Nutrition in Cancer Prevention

3

G. Morgan

Skåne University Hospital, Department of Medical and Radiation Oncology, Lund, Sweden

Nutrition is important for survival. Food affects not only human development, but also the development of diseases, and cancer is not an exception. This chapter will cover a variety of topics related to nutrition that affect the ability to reduce the risk of developing certain types of cancers.

Basic Concepts of Nutrition

Nutrients are essential for life and keep the body in balance by maintaining and replenishing cells. A balanced diet is made up of the five food groups: fruits, vegetables, cereals, proteins and dairy products. These contain six major classes of nutrients: carbohydrates, fats, minerals, proteins, vitamins and water. These nutrients are the key building blocks and their daily intake is required for human development. In cancer care, nutrients play a critical role, helping to fight disease more effectively, in healing, in recuperation and even in prevention.

Body Fatness

Obesity or excess body fat is a major risk factor for cancer. According to research from the American Cancer Society, in the United States excess body weight is thought to be responsible for ~11% of cancers in women, ~5% of cancers in men and ~7% of all cancer deaths (Rock et al, 2020). Evidence suggests that increased cancer risk may be associated with increased body weight and a body mass index (BMI) outside the healthy range. Some studies have shown that being obese or overweight during childhood and in young adulthood could be a stronger risk factor than

weight gain in later life. Research is ongoing to try to better understand this link and how it affects and increases cancer risk (Stone et al, 2018). Although the mechanisms are not yet known, the role of inflammation has been suggested, since it may influence the cells' ability to live longer, or encourage blood-vessel growth, which may even aid cancer cells to metastasise. Maintaining a stable, healthy weight may reduce the levels of hormones such as insulin, androgens and oestrogens, which are also related to cancer risk. Significant benefits are associated with weight loss in overweight/obese persons: decreasing their risk of heart disease and diabetes, increasing mobility and, in some cases, reducing pain. Hence, obesity and excess body fat negatively affect general health and can also increase the risk of developing cancer.

Physical Activity

There are possible links between cancer risk and a person's level of physical activity. These activities can vary from walking, running, swimming or cycling to doing household chores.

Observational studies, where subjects report their physical activity and are followed for cancer diagnosis, have yet to prove the relationship, but point out the possible link (McTiernan et al, 2019). It has been proposed that physical activity may be protective against the occurrence of some cancers by lowering the level of sex hormones, preventing high levels of insulin, reducing inflammation, altering metabolism or improving the function of the immune system. However, it is not just an active lifestyle that has the potential to reduce cancer risk, but conversely, a sedentary lifestyle has been shown to be a risk factor for developing chronic health conditions and an early death.

To achieve substantial health benefits, 150-300 minutes of moderate intensity aerobic activity or 75-100 minutes of vigorous aerobic activity per week are recommended (Yang, 2019). For a more complete workout, this can be coupled with strength and balance training.

For cancer survivors, not only is it safe to engage in exercise, but it is recommended. There is evidence that moderate-intensity aerobic exercise or resistance training after cancer treatment has the potential to reduce stress,

depression, anxiety and fatigue, which patients may experience as a result of their cancer diagnosis. Some studies in breast cancer survivors have shown that those who were physically active had a 42% lower risk of death from any cause and a 40% lower risk of dying of breast cancer than those who were inactive; studies in colorectal cancer and prostate cancer have shown similar effects (Spei et al, 2019). Although research is still ongoing, physicians can strongly promote exercising and avoiding a sedentary lifestyle.

Plant Food

There is increasing evidence that a vegetarian diet is associated with a decreased risk of cancer. Certain studies have demonstrated that people who consume little or no red meat have a lower risk of developing colorectal cancer. Some of these studies have also shown that there is a lower risk of postmenopausal breast cancer in women who follow a vegetarian diet. It is unclear whether it is the plant-based diet or the absence of meat that reduces the risk of cancer. However, it cannot be denied that a diet rich in fruits, cereals, vegetables and legumes is part of a healthy lifestyle and has been linked with potential lower cancer rates.

One possible correlation between plant-based diets and lower cancer rates is the exposure to phytochemicals, which have an anti-inflammatory effect and protect cells from damage, and may thereby have a role in cancer prevention. It has been observed that cruciferous vegetables have a positive influence on cancer prevention. Higher levels of fibre consumption may also be beneficial. Studies have found that young women who had a diet rich in fibre were 25% less likely to be diagnosed with cancer later in life (Farvid et al, 2016). Another study showed that a daily intake of 10 g of fibre could decrease the risk of colon cancer by 10% (Aune et al, 2011). A possible explanation is the lower caloric intake, as people who eat a plant-based diet often consume fewer calories, in turn helping to maintain a stable weight.

It is important to note that people who do not eat meat should make sure they are getting their daily allowances of vitamin B12, zinc, calcium and omega-3 fatty acids, which are normally found in meat and other animal foods.

Red Meat

The link between red meat and cancer is well established. A study found that a daily intake of 100 g of red meat increases the risk of colorectal polyps by 2% (Aykan, 2015). Another study showed that a weekly intake of 700 g of red meat increases the risk of bowel cancer. Although red meat has long been a staple of many Western diets, increased red meat consumption has been proportionally linked to higher mortality risk, possibly due to the promotion of cardiometabolic disturbances. When cooked at high temperatures, red meat produces compounds, some of which may be carcinogenic when consumed. For this reason, the World Health Organization (WHO) has classified red meat as a Group 2A carcinogen. This does not mean that red meat must be avoided completely, but rather consumed in moderation. The recommended quantity is 1 serving (90-100 g raw or 65 g cooked) of lean red meat per day or 2 servings 3-4 times per week, with a total of 350-500 g of cooked red meat a week.

Processed Meat

There is strong evidence that processed meat causes cancer; so strong that ham, bacon, salami and Frankfurt sausages are classified as Group 1 carcinogens by the WHO. Studies are very clear about the association, with some findings showing that consuming processed meat increases the risk of colorectal polyps by 29%, increasing the risk for stomach and bowel cancer (Santarelli et al, 2008). The risk of developing bowel cancer increases 1.18 times for every 50 g of processed meat consumed per day.

The nitrates present in processed meats generate N-nitroso compounds in the gut, and these compounds are known to damage the bowel lining, potentially leading to cancer. The chemicals in processed meat contribute to their carcinogenic potential. Exposure to these chemicals increases inflammation in the tissues and leads to an increased risk of developing cancers. For these reasons, there is no recommended serving for processed meat, but rather these should all be excluded from the diet to reduce the risk of cancer.

Alcohol

Alcohol has been directly linked to at least seven types of cancer: mouth and upper throat, larynx, oesophagus, breast, liver and bowel cancer. There is a correlation between the amount of alcohol consumed and the increased risk of developing cancer, and there is no threshold. In the European Union, ~80 000 people died from alcohol-attributable cancer in 2016, equivalent to 1.9 million years of life lost due to disability or premature mortality. Looking at worldwide incidence, it is estimated that alcohol is the cause of ~3 million deaths each year, of which >400 000 are from cancer (Rehm et al, 2021).

A study published in *The Lancet Oncology* (Rumgay et al, 2021) found that in 2020, 4% of the world's newly diagnosed cases of oesophageal, mouth, larynx, colon, rectum, liver and breast cancers were attributed to alcohol intake: a total of 741 300 people. In this study, 75% of all alcohol-related cancers occurred in men. In women, there were 172 600 alcohol-related cancers, of which 98 300 were breast cancers. The study highlighted that the more people drank, the higher their risk of alcohol-related cancer was, with the greatest risk being for those consuming 2-6 drinks a day (28-84 g of pure alcohol). However, even those with a 'moderate' consumption (≤2 drinks per day) made up 14% (103 000) of alcohol-related cancer cases. Although there is no way to prevent cancer totally, risk reduction can be achieved by reducing alcohol intake. When combined with alcohol consumption, being overweight, poor oral hygiene and poor diet are additional factors which increase the risk of cancer, but perhaps the most damaging combination is that of drinking and smoking.

Binge drinking (>4 drinks in a short period, for men ≥5 drinks) may increase the risk for certain cancers compared with those who do not binge drink. Even if a person's alcohol consumption is light to moderate most of the time, any health benefits associated with that disappear with regular binge drinking. Examples of such potential benefits are reduced risk of developing or dying from heart disease and possibly decreased risk of ischaemic stroke. There is no exception to the alcohol rule, and this includes red wine which has been suggested as having an ability to prevent cancer, despite no clear evidence to prove this.

Arguably, the most important factor in increasing cancer risk seems to be the amount of alcohol consumed over time. Although the reality is that most people will sometimes enjoy a serving of alcohol, what can be recommended is doing so in moderation.

Dietary Supplements

Although the role of dietary supplements in cancer prevention is uncertain and at times confusing, there is no proven evidence that any available dietary supplement can help in preventing cancer. To ensure a healthy supply of vitamins and minerals, the best recommendation is a well-balanced diet.

Other Food Groups Associated With Cancer

Making the right choices regarding what you eat could have a great impact on your risk of developing cancer. The cancer most associated with a poor diet is colorectal cancer, and these poor diets have a common pattern: they are low in dairy, vegetables, fruits and whole cereals, and high in sugary beverages and processed meat.

Conclusion

Nutrition and exercise can play a central role in the risk of developing cancer. Although there is a big impact from one's own genetics, the choices we make in what we consume impact our body and it is up to us to determine if this will be a positive impact or a negative one.

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Psychosocial and Cultural Aspects of Nutrition

4

J.B. Hopkinson[1]

F. Strasser[2]

[1]*School of Healthcare Sciences, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK*

[2]*Cantonal Hospital St. Gallen and Cancer Fatigue Clinic, Onkologie Schaffhausen, Schaffhausen; Cantonal Hospital Münsterlingen, Münsterlingen; Center Radiotherapy Rüti, Rüti, Switzerland*

This chapter is about providing culturally sensitive psychosocial support for eating well when living with or at risk of cancer cachexia.

"In our family, we always laugh at the portions … because we've always eaten a lot. Always big healthy portions of meat, vegetables, you know, nice, homemade food. But Dad now hardly eats a saucerful … it's going to make you ill by not eating, if you're not getting the proper vitamins and nutrients that your body needs. And this is the problem. And it's trying to think, for my Mum and everyone else, what he can eat … Just seeing him losing weight … you feel helpless … it's very distressing."

(Jo, daughter of a patient with oesophageal cancer)

Anorexia, early satiety and other changes in eating are symptoms of cancer cachexia syndrome that can occur at any point across the cancer journey. These symptoms have a negative emotional and social impact on both patients and their family members, thus disrupting everyday life. They are associated with impaired physical function, reduced tolerance to anticancer treatment and reduced survival and have an adverse effect on quality of life. The psychosocial consequences of cancer cachexia include: conflict over food in families, accusations of healthcare professional neglect and distress, such as the helplessness expressed above by Jo.

Clinical Guidelines

The emotional and social effects of changing eating habits impact on nutrition in cancer patients. These effects are influenced by culture: the patient's values, beliefs and behavioural norms. The European Society for Medical Oncology (ESMO) guideline for the management of cancer cachexia in adult patients recommends multimodal intervention to include nutritional and psychosocial support. This management should include assessment of secondary causes of impaired nutritional intake, which can include cultural influence, and the management of related psychosocial distress. It should be integrated with oncology treatment, as multimodal intervention is likely of benefit across all stages of cachexia and before cancer is refractory. Supportive care is relevant throughout the continuum of the cancer experience, from diagnosis through treatment to post-treatment care, and should be available in all cancer treatment centres (as defined by the Multinational Association of Supportive Care in Cancer [MASCC]).

But what psychosocial issues should be managed and how? Our response to this question is based mainly on research with patients who have late-stage cancer. However, findings from our recent research with patients who have stage II-III colorectal cancer are consistent with this, suggesting that our recommendations translate to patients earlier in the disease trajectory.

What Psychosocial Issues Related to Nutrition Do Cancer Patients Face?

Factors Affecting the Patient's Oral Intake

Information about diet, food and nutrition is easily accessible, for example via the internet and social media. As a consequence, cancer patients can experience information overload or confusion and generic information can be difficult to apply in personal circumstances. Dominant discourse is about healthy eating to reduce the risk of all-cause disease. When overwhelmed by information or confused about what to do, this messaging can mislead patients, for example, patients who should take a high-energy, high-protein diet because they are malnourished.

Taking comfort through eating may also influence decisions about what to eat. Following a cancer diagnosis and during anticancer treatment, maintaining 'normal' eating habits can provide comfort. Eating what you have always eaten and following family mealtime routines can be reassuring for all involved. In contrast, poor appetite and involuntary weight loss are typically interpreted as indications of declining health and approaching death. Maintaining pre-illness dietary habits is reassuring but can distract from considering nutritional intake and risk of malnutrition following a cancer diagnosis and through treatment.

Factors Affecting the Role of the Family Carer

A growing number of cancer patients receive treatment and care in their own home. Family carers of people with cancer thus have an increasingly important role to play. Their role includes helping with the management of symptoms, treatment side effects and nutritional risk. Some carers describe their role as changing from a partner to a nurse.

The attitudes and beliefs of the family carer can influence the support provided for eating problems and nutritional risk in the patient. Like patients, they can find information about food, eating and cancer both conflicting and overwhelming. Like patients, they can be wrong to believe that healthy eating advocated to reduce the risk of disease is also a way to arrest cancer or even to cure it. Unlike patients, they often have no first-hand experience of cancer-induced eating difficulties and find them difficult to understand. Moreover, in some communities, the understanding of cancer and its progression is poor. Thus, cancer-induced sickness behaviours, such as food refusal, food aversions and poor appetite, can be wrongly attributed to a lack of will on the part of the patient – the family can believe the patient is not trying hard enough to eat.

Key Factors Affecting Eating-related Distress and Quality of Life

Differences between family members in understanding what causes eating problems in cancer patients can lead to disagreements in the home and even lead to force-feeding when the patient resists offers of food. Prior relationships between family members can also affect how disagreement is managed and whether it escalates to conflict. The known

association between mood and appetite suggests that addressing psychosocial issues may both improve the emotional health of the patient and help to optimise their nutritional intake.

Body image can be an eating-related source of distress identified using a distress thermometer, such as the National Comprehensive Cancer Network (NCCN) Distress Thermometer. Change in body image because of cancer and its treatments is associated with anxiety and depression. Psychosocial interventions can educate to aid understanding and emotional adjustment, mitigating body image concerns and benefitting relationships and nutritional status.

Despite the impact of eating-related problems on quality of life, many patients do not seek help for symptoms such as anorexia, nausea and sore mouth. Psychosocial obstacles to seeking help include:

i) belief that the clinician's role is around treatment rather than eating difficulties,

ii) belief that nothing can be done,

iii) reluctance to follow nutritional advice and

iv) perceived social benefits of weight loss, particularly for those who are overweight.

Healthcare professionals can also be reluctant to initiate discussion about involuntary weight and eating problems, lacking confidence that they know what to do or fearing they may cause distress. This may be particularly so when cultural difference leads to conflict between patient values and health-professional values and practices.

How Can Healthcare Professionals Help?

When psychosocial factors compromise nutrition in weight-losing cancer patients, the interventions described below have the potential to mitigate distress and improve nutritional intake. Amano et al (J Palliat Care 2020) validated an assessment tool to aid the identification of cachexia-related distress. The scale has three dimensions: coping with eating problems, coping with eating-related distress, and distress arising from family conflict.

Behavioural change techniques can be used within each of the three dimensions of cachexia-related distress. The techniques include normalising and encouraging appropriate goal setting. They can provide the framework for personalised education about cancer cachexia and nutrition that facilitates adherence to clinical advice. They can also support coping strategies to aid adaptation and alleviate distress in patients and their family members.

Culturally Sensitive Communication to Help the Patient Cope with Eating Problems

Using Indirect Methods of Communication

Offering advice on sensitive topics is difficult, as it involves communicating information in a context of competing values that can create barriers to trust and respect. Weight loss can be a sensitive topic. Weight loss may also not be apparent, particularly in patients who are obese. Thus opportunities to encourage patients to attend to their nutrition can be missed. Storytelling can be a constructive approach that is less confrontational than presenting factual information. Moreover, many people remember information in stories that they would otherwise forget. A story can be tailored to share information in a culturally sensitive way by using examples from the patient's own community. Although we all tell stories in our everyday lives, therapeutic storytelling is a skill learned through practice. The PRO approach is one approach to therapeutic storytelling. The PRO story presents a problem (P), offers alternative resources (R) to deal with it and ends with an outcome (O) desired by the characters in the story. For example, information about an appropriate diet for someone with a poor appetite and weight loss that challenges beliefs such as 'eating organic food cures cancer' can be communicated in a story. PRO stories can be developed from clinical experience, combining experiential learning from work with more than one patient. The story might begin: "I meet a lot of people who worry that they are not eating enough organic food. What you've just told me brings to mind another family I met …"

Information and Education to Dispel Myths and Misunderstandings

Discussing weight loss and eating concerns may reveal gaps in knowledge. The general public (and many healthcare professionals) have a poor understanding of cancer cachexia. People assume that, as in health, there is a balance between eating and weight: eating more leads to weight gain and eating less results in weight loss. The disturbance of this balance in primary cancer cachexia is not understood. The 'factory talk' can help patients with cancer cachexia understand their situation: "To build wooden furniture, both a wood supply (tree trunks) and a factory is needed." In cachexia, the factory (internal body processes) to transform nutrients into muscle is dysfunctional.

There is expert consensus that providing information about appropriate diet is an important part of managing the emotional aspects of cachexia. A belief in benefits, a 'feel-good' factor, influences whether patients engage with and adhere to nutritional advice. Understanding how nutrition can contribute to treatment outcomes and emotional wellbeing is likely to be important for this feel-good factor.

Cultural humility may be needed to learn about the patient's values, beliefs and behaviours relating to food and eating that should be taken into account when offering advice. Enquiring about concerns can be a way of opening up the possibility of providing information and education. Asking the person with cachexia: "What did you eat yesterday?", followed by: "Is this the same as before your cancer diagnosis?" can prompt talk that reveals misunderstandings or provides an opportunity to support self-management of nutritional risk. An example would be to identify preferred foods that are nutritionally dense, such as chocolate.

Coping with Eating-related Distress

Managing Disagreement

Teaching patients and their family members about the common causes and symptoms of cancer cachexia can help to address concerns and distress caused by misunderstandings. Presenting different perspectives on the same problem can also be helpful. This might be done using a PRO story that presents different ways patients can manage a problem such

as unwanted advice on what to eat. It can also be achieved by inviting different perspectives, such as by asking the patient and each family member to say what concerns them about eating problems. This can be surprising for all involved and can start a discussion leading to agreement on how to manage problems. Signposting to evidence-based patient resources about nutrition, eating and cancer can also be a way of presenting alternative perspectives and raising awareness of culturally appropriate solutions, such as when it is acceptable to break a religious fast.

Sometimes it is important to disrupt lack of concern, for example if it accompanies inappropriate self-management of undernutrition. For patients who are experiencing involuntary weight loss, it may be important to encourage adaptation of usual food and fluid intake to mitigate nutritional risk.

What About the Family?

Patient and family-member experiences of eating-related distress can be intertwined, which is why communication should be with carers as well as patients. Family traditions influence cooking methods, mealtimes, ingredients and beliefs about the relationship between food and health.

Family carers typically want to help the patient; they can feel responsible for nutritional care and may take charge of what the patient eats. Some try to coax, encourage or even force the patient to eat. While many patients recognise these behaviours as well-intentioned, their effects can be the opposite of that intended. Patients can find the pressure to eat inhibits their appetite: "If I'm forced to eat, I don't eat." Family pressure is usually motivated by anxiety and/or false beliefs, such as the belief that liquid food supplements provide less nutritional value than a proper meal. See Box 1 for a list of some of the other widely held 'common sense' beliefs that can inform family members' feeding behaviour and that may need to be challenged.

Talking with families about the patient's eating habits and weight loss can be a sensitive topic of conversation because of the feelings it evokes. For clinicians, an appropriate question to open a conversation is: "Are you concerned about what (patient's name) is eating?", followed by:

"Can you tell me about your concerns?" See Box 2 for other questions that can facilitate a conversation about weight loss and changing eating habits with a patient and their family. Providing information about cancer cachexia can mitigate eating and weight-related distress in family members. Furthermore, family members can help motivate patients to achieve nutritional goals. Where possible, nutritional care in cancer should have a family component.

Box 1 Mistaken 'common sense' beliefs that can inform the behaviour of family members.

- Solid foods have greater nutritional value than liquids
- Hot foods have greater nutritional value than cold foods
- People eat more when sharing a meal compared to when eating alone
- Eating between meals is always a bad habit
- Eating cakes and puddings is always harmful to health
- Not trying to eat is being awkward (or emotionally weak)
- The patient is starving to death, so should be force fed
- Food feeds the cancer, so it is best not to eat
- Fruit and vegetables can cure cancer
- It is always healthy to lose weight

Box 2 Questions that can facilitate discussion about weight loss and eating concerns.

Can you tell me about:
- any change in (patient's) weight?
- any change in the food (patient) eats?
- what (patient) ate yesterday (amount, timing, context)?

Why do you think:
- (patient) has lost weight?
- (patient) is having difficulty eating?
- (patient) is not interested in food?

How concerned do you feel about:
- the change in (patient's) weight?
- (patient) not eating certain foods?
- (patient) eating small portions?

Since involuntary weight loss and declining function almost always raise concerns about dying, these concerns merit acknowledgment. Support to prepare for end-of-life can be helpful for patients and family members.

Conclusion

Culturally sensitive psychosocial support for optimal oral nutritional intake when living with cachexia can:

- Enhance the quality of life of patients and family carers by helping them to cope with the emotional and social impact of disease-related malnutrition.
- Empower patients and family carers to be partners in cancer treatment through engagement in nutritional care.

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Nutritional Counselling and Intervention

5

P. Ravasco

Universidade Católica Portuguesa, Faculty of Medicine and Centre for Interdisciplinary Research in Health (CCIS-UCP), Lisbon; Egas Moniz School of Health and Science, Centre for Interdisciplinary Research Egas Moniz, Almada, Portugal

Individualised Nutritional Counselling

In clinical practice, oral nutrition is the priority in patients with cancer who can tolerate intensive nutritional counselling; this is not the case for patients at the end of life or with established cachexia. The aim of nutritional support is to ensure adequate intake of energy and nutrients by enabling the patient to eat normal food, enjoy eating and participate in meals with others as a component of their social life. Thus, oral nutrition is the preferred route since it is a significant part of the patient's daily routine and contributes to the patient's autonomy. On most occasions, eating is a source of pleasure and a privileged time to spend with family and friends. The acknowledgement that the prescribed diet is individualised and adequate for their needs empowers the patient with dimensions of control, contributing to their psychological wellbeing. All these factors may contribute to improving the patient's quality of life (QoL) and modulate acute and late treatment morbidities. Hence, dietary counselling must be based on a comprehensive assessment of the patient's situation and an evaluation of reasonable, available treatment options, resulting in a personalised approach.

An adequate food intake is recognised by the patient, as well as by their family and caregivers, as essential to maintaining daily activities, energy levels, functional capacity and the success of their cancer journey. Also, clinicians must acknowledge the patient's treatment objectives and plans,

and that the role of nutrition cannot drive treatment decisions. In patients undergoing anticancer therapy, ensuring an adequate energy and nutrient intake should be pursued vigorously.

Individualised dietary counselling must be based on a thorough assessment of various nutritional and clinical parameters evaluated during any nutritional consultation, using structured, specific and validated questionnaires. These include the 24-hour recall and/or the 72-hour registry (2 weekdays and 1 weekend day) of all meals and foods that have been consumed, as well as a food frequency questionnaire that provides data on food habits and patterns relative to the previous 12 months.

Also, the clinical nutritionist/dietician must evaluate the patient's dietary preferences, habits and/or intolerances or food aversions and record the daily meal distribution. The patient's psychological status, autonomy, cooperation and need for the help or support of others in the act of eating are fundamental dimensions that always precede any dietary counselling. A detailed symptom assessment is mandatory (Table 1).

After recording and interpreting these dimensions, the patient's nutritional requirements are calculated according to 25-30 kcal/kg body weight (BW)/day and 1.2-1.5 g protein/kg BW/day (considered to represent basic macronutrient requirements in patients with cancer), and a nutritionally adequate individualised diet is prescribed, containing the patient's preferred foods and respecting their habits. A full explanation to the patient/caregiver is the only way to ensure that the patient understands the prescription; therefore, effective communication skills are required to achieve maximum compliance. Informing the patient, their family and caregivers on the importance of the diet and its content (the types and amounts of food needed) is a fundamental step for the implementation of any dietary plan. A detailed dietary plan is constructed in accordance with the patient's opinions and must contain the number of meals, a timetable including the intervals between meals, and a list of the foods and their quantity, with alternative equivalent choices. A copy of this plan is then given to the patient as a nutritional guide for their daily dietary intake.

Table I Causes of Cancer-related Malnutrition.

■ Deterioration in taste, smell and appetite, as a consequence of the disease and/or therapy
■ Altered food preferences/avoidance/aversion
■ Anorexia
■ Dysphagia, odynophagia
■ Partial/total gastrointestinal obstruction or dysfunction
■ Early satiety, nausea and vomiting
■ Soreness, xerostomia, sticky saliva, painful throat, trismus
■ Oral lesions and oesophagitis
■ Radiotherapy-/chemotherapy-induced mucositis
■ Acute or chronic radiation enteritis during and after radiotherapy
■ Depression, anxiety
■ Pain

Goals of Individualised Nutrition in Cancer

The goals of individualised nutritional counselling differ between patients with early malignancy and curative treatment options and those in end-of-life situations. The content of this section refers to the first cohort of cancer patients. Major goals include: to arrange the patient's nutritional intake to ensure it meets their individual requirements in terms of energy and macro- and micronutrients, and to modulate symptoms by reducing the foods that may worsen them and/or increase foods that may reduce their severity. In many cases, concomitant pharmacological therapy for management of symptoms may be required. Dietary counselling involves the prescription of therapeutic diets using regular foods, which may be further modified to provide for individual requirements. If the patient is unable to meet their nutritional requirements via regular foods, oral nutritional supplements (ONSs) may be prescribed, the composition of which is based on the dietary deficits detected in the individual and from their detailed intake questionnaire. To achieve the highest level of compliance, the patient's usual dietary pattern should be maintained as much as possible. The type and quantity of food and the frequency of eating depend upon the patient, the disease and the therapeutic goal. The monitoring of patient compliance with recommendations and

weekly/bi-weekly consultations with a clinical nutritionist are considered essential to follow-up after nutritional counselling. Integration of dietary counselling with the regular treatment visit schedule is mandatory for timely adaptations.

Any nutritional intervention needs to take into account other factors, for example, digestive and absorptive capacity, the need to alleviate or arrest symptoms, psychological factors, and disease stage and progression. Therapeutic diets are regularly adjusted to the patient's reported diet, thereby recognising personal eating patterns and preferences, which form the basis for individualised dietary counselling. Prescribed diets include information on the type, amount and frequency of eating, and specify the caloric/protein level to attain, together with any restrictions and limited or increased individual dietary components.

The clinical nutritionist/dietician in charge of the individualised dietary counselling should always follow an evidence-based decision-making plan (Figure 1).

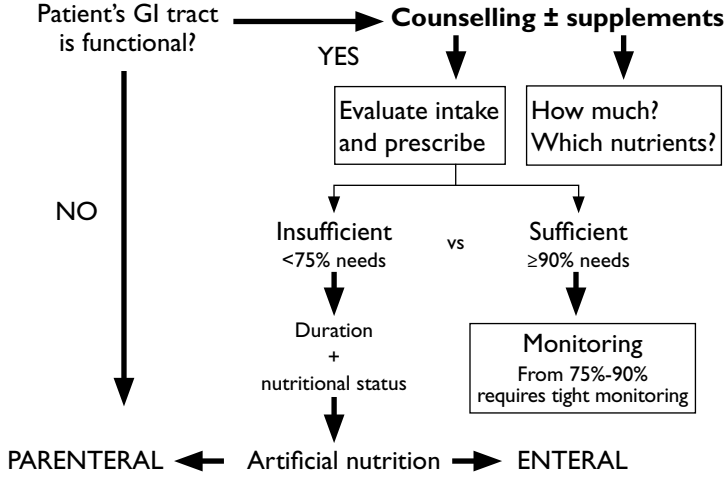

Figure 1 Nutritional support decision-making process for cancer patients with early-stage disease.
Abbreviation: GI, gastrointestinal.

Cancer patients who cannot eat adequate amounts of food should receive nutritional support as an essential component of best supportive care, to improve food intake, nutritional status, BW and QoL. Nutritional support in patients able to eat should be based on dietary counselling, guidance on choosing high-energy, high-protein foods, enriching foods (e.g. by adding fat/oils, protein powder) and use of ONSs. If this proves inadequate, tube feeding should be offered if the lower gastrointestinal (GI) tract is working; otherwise, parenteral nutrition is the method of choice. Separate routes of feeding may be combined for optimal effect.

What Does the Evidence Show About the Benefits of Individualised Nutritional Counselling?

Nutrition is a major issue in oncology, and nutritional decline may ensue from both the disease course and its treatment(s). This carries a negative prognosis. Symptomatic manifestations of antineoplastic treatments and their nutritional consequences have long been recognised, and the role of adjuvant oral nutritional counselling on patient outcomes has been demonstrated. Research focusing on outcomes, for example, hard evidence on the effectiveness of adjuvant nutrition, is essential to prove the value of any nutritional intervention. Research should be action-orientated, so that interventions leading to positive outcomes can be determined, and ineffective practices phased out or discarded.

In cancer patients under active treatment, despite the expected and experienced acute detrimental effects of treatments, individualised nutritional intervention, education and monitoring, as well as timely management of symptoms, improve nutritional and non-nutritional outcomes. Early individualised nutritional counselling contributes to reduced treatment toxicity and improved nutritional intake and status, as well as QoL. Such benefits in nutritional outcomes concur with what has been proposed as the causal pathway, i.e. optimising nutritional intake may be the most effective method for treating disease-related malnutrition. There is evidence in a range of health conditions to support the hypothesis that providing appropriate nutritional therapy leads to improved BW and fat free-mass, and that this generally reflects an improvement in protein-energy status.

Intensive individualised nutritional counselling has become the standard recommendation in the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, later also recommended in the European Society for Medical Oncology (ESMO) guidelines.

Studies have also shown that the nutritional content of the patient's diet with appropriate manipulation, and not just protein and calorie supplementation, is important to improve GI function and other symptomatic manifestations during treatment and in the medium term. Treatment toxicity and incidence/severity of symptoms are lower in patients who receive dietary counselling and education, and their recovery in the medium term tends to be faster. Dietary modifications may alter bowel functions, such as motility, enzyme secretion and nutrient absorption; likewise, nutrition modulates the GI flora, whose ecology is central to the pathogenesis of radiotherapy injury severity.

Nutrition is also a key determinant of QoL in cancer patients. Individualised dietary counselling, in association with an adequate dietary intake and nutritional status, contributes to improved QoL function scores in patients able to eat and in patients fit enough to comply with an individualised nutritional plan. It is unlikely that nutritional interventions will achieve the same level of improvement in the QoL of patients with advanced cancer and established anorexia-cachexia syndrome.

Conclusion

Nutrition is an effective complement to antineoplastic treatments. Early nutritional intervention is paramount to prevent nutritional and physiological deficits. It can modulate weight loss and morbidity, and maintain an adequate nutritional status, performance status and QoL. It has the potential to stabilise or improve the patient's clinical status and augment the potential for favourable response to therapy, recovery and prognosis. With the advent of more effective cancer therapies leading to an increased number of long-term survivors, greater emphasis is urgently required to provide the best care during treatment to improve the clinical course of patients. Early intervention and sensible partnerships with patients are the keys to success.

Key Messages

- Early identification of patients on antineoplastic therapy who are at risk of becoming or are already malnourished is critical for optimising treatment success and defining the urgency of nutritional intervention.
- Malnourished patients are at increased risk of being unable to tolerate the most effective 'level' and 'duration' of treatment, with significant implications for both short- (during treatment) and long-term outcomes.
- In cancer patients, food intake may be compromised by several factors including nutrition impact symptoms (e.g. nausea, vomiting, anorexia, dysphagia). If, after alleviating these symptoms, food intake is still inadequate, nutrition-based interventions should be initiated.
- In patients with inadequate food intake and/or who are receiving anticancer therapy, nutritional interventions should be escalated, as required. In other situations, low-risk interventions (e.g. counselling and ONSs) are preferred.
- To maintain nutritional status, patients should ingest at least 25-30 kcal/kg BW/day and 1.2-1.5 g protein/kg BW/day.
- Dietary counselling should be the first choice of nutritional support offered to improve oral intake and possibly weight gain in cachectic or at-risk patients who are able to eat. Dietary counselling should emphasise protein intake, an increased number of meals per day, include recommendations to modulate symptoms that impact nutritional intake and offer ONSs when necessary. An appropriately trained professional should guide this advice.
- ONSs can be supplied as part of dietary counselling to improve energy and protein intake.

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Cancer and the Nutritional Status

6

V.E. Baracos

Department of Oncology, University of Alberta, Edmonton, AB, Canada

Evaluation of the Nutritional Status of a Patient with Cancer

The wasting syndrome that accompanies malignant disease can be termed 'cancer-associated malnutrition'. This condition is primarily defined on a pathophysiological basis to consist of nutritional deficit in the presence of disease-related metabolic alterations. The cardinal diagnostic criterion for cancer-associated malnutrition is weight loss. Weight loss has already occurred at time of malignant diagnosis for many patients, continues over the course of cancer evolution and is particularly prominent in advanced/metastatic disease. Cumulative losses can be considerable, culminating in emaciation. In light of the progressive nature of weight loss, it is essential to record height and weight at presentation, and take a weight history from the patient or medical records (e.g. What was their weight 6 months ago? Their usual body weight prior to illness?). The severity of weight loss should be graded (Figure 1).

Grading allows the clinician to assess the degree to which the patient is already depleted and the presence of active weight loss. The topmost cancers associated with weight loss and malnutrition are pancreatic, hepatic, gastric, oesophageal and lung cancer; in the case of incurable cancers, all patients are at elevated risk of malnutrition. Future risks of weight loss should be considered; these may vary according to the anticipated treatment plan. Aggressive treatment, for example, radiotherapy with concurrent chemotherapy, is often associated with acute weight loss of >10%. For radiotherapy, the site of treatment may have important nutritional consequences, for example radiation to the oral cavity,

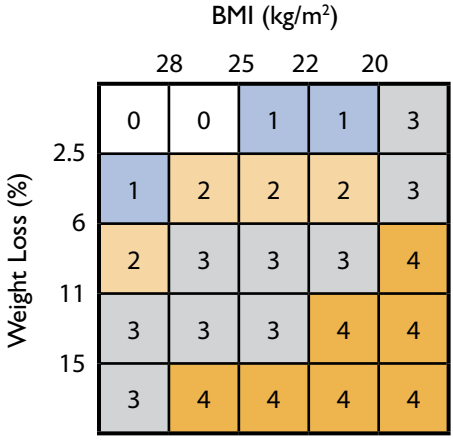

Figure 1 Classification of cancer-associated weight loss. This tool captures the intensity of weight loss, as well as the overall depletion of the body mass index (BMI), as defined by their association with mortality. Severity of weight loss is classified from Grade 0 (high BMI, no weight loss) through Grade 4 (large weight loss, low BMI).
From: Martin L, Senesse P, Gioulbasanis I, et al. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol 2015; 33:90–99.

laryngeal, pharyngeal and oesophageal regions: the resulting pain and mucositis impair dietary intake. Early assessment of weight-loss grade provides a benchmark against which future weights are compared, as well as a tool to prioritise patients for further investigation. At a time of endemic obesity and obesity-associated cancer, weight loss is nonetheless associated with poor clinical outcomes in obese patients with cancers of advanced stage.

A deficit of skeletal muscle mass is a diagnostic criterion for cancer-associated malnutrition. Loss of muscle may appear early and before the occurrence of a clinically apparent weight loss. Patients may have deficits in muscle mass at presentation and further losses of muscle over time, during treatment and disease progression. Muscle depletion is strongly associated with mortality, complications of cancer surgery and toxicity of systemic therapies. Computed tomography images used to follow cancer progression may be used to derive very precise radiological measures of

muscle mass/loss; however, these are not yet routine and are just emerging into clinical workflows. For many patients, muscle deficit goes undetected. It should be noted that malnutrition screening tools (e.g. Malnutrition Screening Tool, Malnutrition Universal Screening Tool, Mini Nutritional Assessment [MNA]) cannot be relied upon to detect reduced muscle mass. Muscle depletion is estimated to occur in one out of four obese patients with advanced-stage disease; however, clinical management protocols for sarcopaenic obese patients require development.

Reduced food intake and abnormal metabolism are the primary drivers of weight loss. The proportional contribution of these factors is variable among individuals. The severity of food intake impairment may be assessed with validated clinical tools: MNA, the Patient-Generated Subjective Global Assessment (PG-SGA) or the Ingesta 10-point numerical scale. These tools are validated for patient reporting and are anchored to the patient's knowledge of food intake that is normal for them, versus moderately or severely reduced food intake. Patients with reduced food intake should be referred for in-depth nutritional assessment and nutrition care. It is well established that symptoms experienced by patients constrain food intake; these are the 'nutrition impact symptoms' (e.g. lack of appetite, nausea, vomiting, constipation, diarrhoea, pain, fatigue, dry mouth, dysphagia, mouth sores, shortness of breath, chewing difficulty). A validated 17-item nutrition impact tool for evaluation of food intake impairment is available: the Head and Neck Patient Symptom Checklist.

The abnormal metabolism underlying wasting remains the most challenging aspect of cancer-associated malnutrition, and is particularly prominent in patients with advanced/unresectable cancers. Tumour mass and intrinsic metabolic activity may comprise a quantitatively important drain of nutrients, mainly in the case of widely disseminated metastatic disease. A variety of molecules derived from the tumour or resulting from tumour interactions with the host immune system can mediate wasting at the tissue level in both skeletal muscle and adipose tissue, as well as act on the central nervous system to accelerate wasting by generating sensory changes, anorexia, adrenal activation and fatigue. Inflammatory activity is strongly associated with weight loss, and inflammation reduces the benefit of nutritional therapy in hospitalised cancer patients.

Inflammation in this context may be assessed by the blood levels of the acute phase reactants C-reactive protein and albumin, or by raised neutrophil-lymphocyte ratios. For most inflammatory and catabolic effector molecules, there is currently no means of modifying their production or action, but these are considered potential therapeutic targets for the treatment of cancer-associated weight loss. Last, cytotoxic and targeted cancer therapies have been implicated as direct drivers of muscle and fat catabolism at the tissue level; however, protocols for prevention or treatment of these off-target effects are not yet available.

Cancer Anorexia and Cachexia: Causes and Treatment Options

Evidence-based guidelines are a primary resource for the management of cancer-associated malnutrition/wasting. These include guidelines for clinical nutrition in oncology (e.g. European Society for Clinical Nutrition and Metabolism [ESPEN] guidelines) and management of cancer cachexia (e.g. the European Society for Medical Oncology [ESMO], American Society of Clinical Oncology [ASCO]). Evidence remains insufficient to strongly endorse any pharmacological agent to improve clinical outcomes. There are currently no approved medications for cancer cachexia by either the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA). However, anamorelin, an appetite-stimulating agent targeting ghrelin receptors, received regulatory approval in Japan in 2021 for the treatment of patients with advanced/unresectable lung and gastrointestinal cancers. If concordant with the goals of care, clinicians may offer a short-term trial of a progesterone analogue or a corticosteroid to patients with advanced cancer experiencing loss of appetite.

Pain and Symptom Management at the Forefront

Medical management of pain and other symptoms may be important for the management of cancer-associated malnutrition. Potentially reversible causes of weight loss and reduced food intake need to be identified. Symptoms such as pain, nausea, vomiting, dry mouth (after anticancer treatments), dental problems, dysphagia, intestinal motility disorders, oesophageal obstruction, malabsorption, infection, psychological distress,

endocrine and metabolic disorders may be amenable to medical management. For example, common side effects of cytotoxic chemotherapy include anorexia, nausea and vomiting, and radiotherapy to the head and neck may give life-long oral problems. These effects can be substantial. Successful management of nausea may result in immediate restoration of appetite in proportion to the antiemetic effect. Evidence-based guidelines are available for nausea/vomiting (e.g. the Multinational Association of Supportive Care in Cancer [MASCC], ESMO, ASCO guidelines). Psychosocial factors can also act as barriers to food intake, for example mood disorders, food insecurity, lack of social support for assistance with meal preparation and poor dietary habits. These issues should be treated accordingly.

Specialist Consultation and Support

Specialist consultation is an important recourse for specific aspects of management. Inadequate dietary intake is endemic in patients with advanced cancer. Referral to specialist pain and symptom/supportive care teams, if available, may help reduce barriers to oral intake. When nutritional deficit is identified, referral to a nutrition expert (i.e. registered dietician) is advised for assessment and counselling, with the goal of providing patients and caregivers with practical and safe advice for feeding; education regarding high-protein, high-calorie, nutrient-dense food; and advice against fad diets and other unproven or extreme diets. Dietary counselling, with or without oral nutritional supplements, may increase body weight, and individualised nutritional support during hospital stay may reduce mortality in patients with different types of cancers. Gastroenterologist input may be required for specific issues such as stent, malignant bowel obstruction and artificial nutrition (gastrostomy, parenteral feeding). Enteral tube feeding and parenteral nutrition are not recommended for routine use in patients with advanced/unresectable cancers; however, parenteral nutrition may be offered to patients with early-stage disease as well as selected patients with conditions such as a reversible bowel obstruction, short bowel syndrome or other issues contributing to malabsorption. Further information on enteral and parenteral nutrition can be found in Chapter 8.

Conclusion

Cancer-associated malnutrition is a highly complex and, as of yet, not fully understood condition. A framework for a therapeutic platform begins with thorough assessment of the patient, including a history of and ongoing monitoring of the cumulative severity of weight loss and assessment of dietary intake and nutrition impact symptoms. Treatment decisions rely on identification of potential elements of wasting that are present, including tumour- and treatment-related effects, symptoms and psychosocial factors. While evidence is limited, clinicians do have avenues to mitigate malnutrition through evidence-based clinical practice guidelines, optimising pain and symptom management, and have recourse to refer their patients for specialist nutritional support and multidisciplinary supportive care/symptom management.

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Cancer Treatment and Nutrition

7

Z. Stanga[1]

P. Schuetz[2]

[1]*Division of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, University of Bern and Bern University Hospital, Bern, Switzerland*

[2]*Medical University Department, Division of General Internal and Emergency Medicine, Medical Faculty of the University of Basel, Kantonsspital Aarau, Aarau, Switzerland*

Numerous factors contribute to high malnutrition risk in patients with cancer including tumour-derived effectors release, causing loss of appetite and anorexia, and side effects of cancer treatment, again interfering with appetite and normal food intake. Disease-related malnutrition (DRM) or therapy-related malnutrition is a frequent problem in these patients and negatively influences clinical outcome. To prevent adverse consequences related to DRM, the ESPEN (European Society for Clinical Nutrition and Metabolism) recommends identifying malnourished patients with cancer through early screening followed by nutritional assessment, nutritional care planning and nutritional support. Different screening tools are recommended, including the Nutritional Risk Screening 2002 (NRS-2002) and the Patient-Generated Subjective Global Assessment (PG-SGA). The majority of patients with cancer suffer from systemic inflammation, which influences and stimulates the production of acute phase proteins – altering protein turnover and reducing muscle mass. This condition leads to impaired glucose tolerance and often to insulin resistance. Resulting symptoms are anorexia, weight loss, fatigue, weakness and reduced wellbeing.

Under these metabolic circumstances, adequate nutritional treatment plays an important role within multimodal cancer care. As DRM is linked

to worse prognosis and is difficult to reverse, nutritional therapy should ideally be initiated at an early stage beginning with cancer diagnosis, when the purpose of care is maintaining or improving nutritional status. The principal goals of nutritional therapy include preventing and treating DRM, reversing weight loss, and maintaining/improving strength and quality of life. Moreover, an adequate individual nutritional intervention may minimise nutritional complaints related to cancer treatment toxicity and thus, enhance energy and protein intake.

Nutritional Support During Cancer Treatment

Weight loss and muscle wasting are core factors that define DRM in patients with cancer and have been demonstrated to be a major cause of morbidity as well as robustly predicting complications and mortality. An impaired nutritional state during cancer treatment has been associated with a number of clinical consequences and a range of poor outcomes, including impaired functional status, more emergency hospital visits, increased in-hospital morbidity, increased length of hospital stay, more cancer treatment interruptions, compromised treatment efficacy, reduced quality of life and reduced survival. Currently, as shown in a USA population study from Tu et al (2022), a relevant proportion of patients with cancer is overweight (body mass index [BMI] 25-29.9 kg/m^2: 35.8%) or even obese (BMI ≥30 kg/m^2: 30.7%) at diagnosis. In this population, there is a lot of evidence supporting the safety of exercise and dietary interventions in the adjuvant and post-treatment settings; however, the optimal practice to reduce weight gain during cancer treatment and to achieve weight loss after treatment, across various early-stage cancers, has yet to be explored. In our opinion, these patients should be prescribed a high-protein intake with a slightly reduced energy intake.

Weight loss and muscle protein depletion are typical features of DRM. If this condition is compounded by chronic inflammation, then we talk about the cancer cachexia syndrome, which may range from mild metabolic disorders to devastating effects on nutritional status. Its clinical manifestations are stratified in three stages:

- Pre-cachexia:
  - Weight loss ≤5%, anorexia, increased inflammatory response and metabolic disturbances
- Cachexia:
  - Weight loss >5%, OR
  - BMI <20 kg/m^2 and weight loss >2%, OR
  - Sarcopenia and weight loss >2%
  - Often reduced food intake and systemic inflammation
- Refractory cachexia:
  - Severe weight loss and wasting, characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism
  - Cancer disease both pro-catabolic and not responsive to anticancer treatment
  - Low performance score
  - Expected survival <3 months

Direct and inexpensive measurement of muscle mass is still not available, but muscle function assessment provides important insights into muscle wasting in cancer.

Various authors have focused on nutritional risk as a cause of delay and even failure in the scheduled administration of anticancer treatment. DRM may be responsible for increased toxicity of anticancer drugs and for several complications following the treatment. It may cause changes in drug absorption, metabolism and ultimately elimination, as already reported for some drugs in the literature. Therefore, maintaining adequate energy intake during therapy is mandatory, and requires considerable commitment and motivation in most patients.

An important part of the nutritional care programme is individualised nutritional support to reach protein and energy goals, based on nutritional state, general conditions, patient tolerance, tumour site, stage of disease, treatment and related side effects. Management by dieticians is available in most cancer centres and hospitals. Tailored approaches are important to set realistic and achievable goals (Figure 1). Macronutrient requirements depend on the pathological condition of the patient, with energy intake

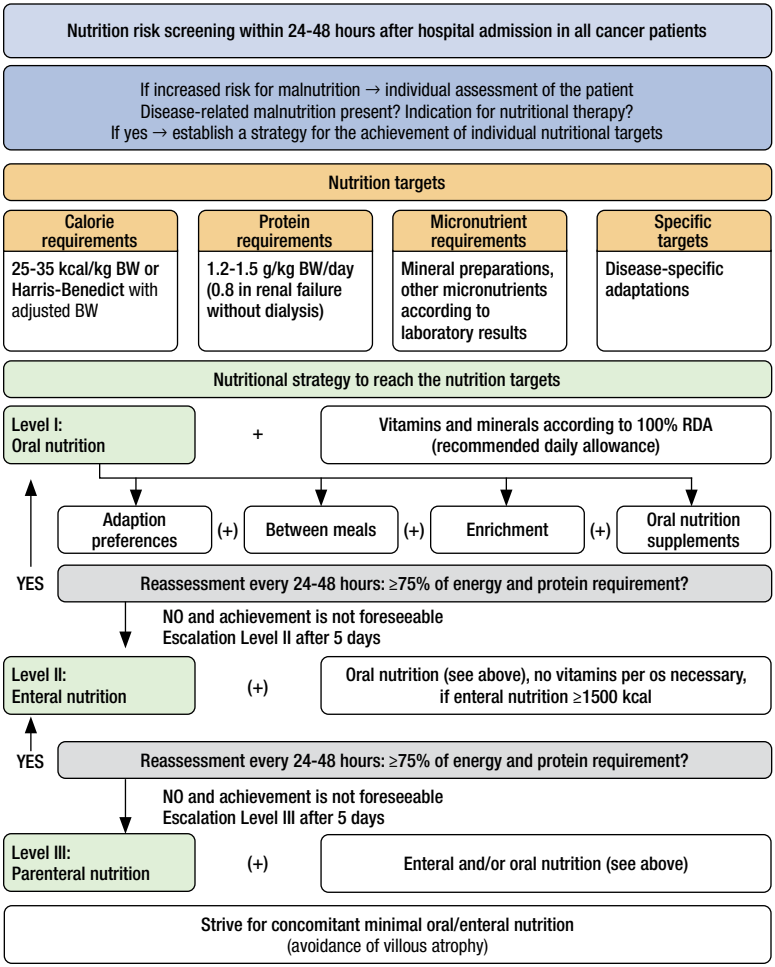

Figure 1 Nutritional support algorithm.

Adapted from: Bounoure L, Gomes F, Stanga Z, et al. Detection and treatment of medical inpatients with or at-risk of malnutrition: suggested procedures based on validated guidelines. Nutrition 2016; 32:790–798.

Abbreviation: BW, body weight.

varying between 25 and 35 kcal/kg body weight (BW)/day, depending on the patient's performance status and physical activity. The optimal daily protein intake should be between 1.2 and 1.5 g/kg BW to adjust for higher protein breakdown during acute disease and systemic inflammation, with lower targets for patients with acute renal failure (0.8 g/kg BW/day). To reach these goals and minimise weight loss as well as facilitate repair and regeneration of damaged tissues, dieticians should formulate an individualised nutrition plan for consideration by treating physicians, such as high-energy and high-protein diets providing adequate macro- and micronutrients. A therapeutic plan should be centred on oral nutrition in malnourished patients with cancer who are able to eat. This includes dietary advice, nutritional counselling and psycho-oncological support that may be needed to help and encourage patients to comply with their nutritional support requirements. If oral intake drops below 75% of daily energy requirements, the measures should include a patient-adapted intervention plan, starting with easy but essential measures such as the creation of a daily meal schedule (quantity, quality and presentation of menu), food adjustment according to patient preferences, food fortification (e.g. by adding protein or maltodextrin powder), introduction of small and frequent snacks between meals, and providing patients with oral sip drinks and oral nutritional supplements (ONSs). Favourite foods should be offered to tempt the appetite. The modification of food texture may be required to facilitate chewing and swallowing. Dry mouth and changes in taste perception may increase the effort required for optimal intake. The goal of oral intake is to achieve more than 75% of the daily energy requirements. As demonstrated in the EFFORT study published in 2019, further increase in nutritional support by enteral (EN) or parenteral nutrition (PN) in suitable patients was recommended if at least 75% of energy and protein targets could not be reached due to chronic insufficient dietary intake and/or uncontrollable malabsorption. If food intake has been decreased severely for a prolonged period, it is recommended to increase (oral, enteral or parenteral) nutrition slowly over several days and to take additional precautions to prevent refeeding syndrome. Adequate nutritional support should be supplemented by maintenance or an increased level of physical activity to support muscle mass, physical function and metabolic pattern.

Pharmaconutrients and Pharmacological Agents

Various substances can be used to stimulate the appetite of anorectic cancer patients during oncological treatment, but they are often associated with side effects and the evidence for an overall benefit of these treatments is weak. For a restricted time, corticosteroids, androgenic steroids or progestins may be utilised. There is not sufficient clinical data to support use of cannabinoids to improve taste disorders and anorexia in patients with cancer. Efforts to improve weight and lean body mass in catabolic cancer patients with supplementation of branched amino acids or metabolites, as well as the use of non-steroidal anti-inflammatory drugs (NSAIDs), are still a matter of debate due to insufficient clinical data, and are not recommended as routine practice.

In the presence of inflammation, dietary supplementation with specific nutrients (i.e. omega-3 fatty acids, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) may provide beneficial effects by modulating several aspects of the inflammatory response. The evidence demonstrating that the intake of omega-3 fatty acids from fish oil or from purer preparations of EPA/DHA results in enhanced efficacy of anticancer treatment, chemotherapy in particular, and increased clinical benefit on nutrition-related endpoints, is still insufficient (contradictory data in several systematic reviews). For individual administration, >2 g EPA/DHA/day may be used on a trial basis for a prolonged period of time (>8 weeks) for patients with advanced cancer.

Over the last decades, progress has led to reduced morbidity and mortality after cancer surgery. Even with such efforts, perioperative complications are frequent in oncology patients. Thus, minimising the risk of potential complications in the preoperative phase is mandatory. There is substantial evidence that a deteriorated preoperative nutritional status adversely affects outcome in terms of increased complications and reduced quality of life, which in turn have cost implications for the healthcare system. Impaired nutritional status before major surgery is related to increased incidence of nosocomial infections, longer length of stay (i.e. intensive care unit) and, frequently, readmission to hospital and higher mortality. DRM may also influence multiple organ dysfunctions, functional recovery, wound healing and the incidence of postoperative surgical wound

infections. The stress of surgery or trauma additionally increases protein and energy requirements by creating a hypermetabolic, catabolic state. As a result, identifying and treating DRM with appropriate nutritional support in patients with cancer prior to the operation is critical to achieve favourable patient outcomes. For patients undergoing either curative or palliative surgery, the ESPEN guidelines recommend management within an enhanced recovery after surgery (ERAS) programme. With special regard to patients with cancer with an obvious severe nutritional risk, those undergoing major cancer surgery of the neck (laryngectomy, pharyngectomy) or abdomen (oesophagectomy, gastrectomy and pancreatoduodenectomy) benefit from the use of immune-modulating oral/enteral formulae, namely enriched with arginine, omega-3 fatty acids and nucleotides, with or without glutamine.

Impact of Food on Anticancer Drugs (e.g. Interactions Between Anticancer Drugs and Nutritional or Herbal Supplements)

There is a paucity of clinical data in the literature regarding this issue. Use of herbal supplements and vitamins in patients receiving chemotherapy is common: McCune et al reported in 2004 a frequency of 78%, with 27% of the study participants being at risk of a detrimental chemotherapy-herbal and/or -vitamin interaction. Food interactions with anticancer drugs are often difficult to assess, given the polypharmacy that exists in oncology patients and the frequent inability to distinguish which factor is responsible for a specific toxicity. Food can interact with anticancer medicines through reduction of the bioavailability and/or by induction or inhibition of the metabolism of the administered drug (Table 1), often due to their metabolism by the cytochrome P450 system. There are some publications reporting that the most used herbal supplements among patients with cancer are echinacea, *Ginkgo biloba*, garlic, green and black tea, shark cartilage, grape seed extract and milk thistle. The most popular micronutrients are calcium, multivitamins, antioxidants, vitamin C and vitamin E.

Table 1 Potential Drug-Food Interactions and/or Important Side Effects Which Can Interfere with Metabolism.

Drug name	Potential interactions and/or side effects
L-asparaginase	Can cause azotaemia accompanied by an increase in calcium and phosphorus excretion due to increased protein degradation This therapy is frequently associated with impairment of pancreatic function that may be a result of decreased insulin synthesis, causing hyperglycaemia
Bexarotene	Grapefruit may increase the drug's effect
Carboplatin	Decreased serum electrolytes, specifically magnesium and potassium
Docetaxel	Milk thistle: decreased AUC Garlic: no significant modification to increased AUC Cannabis, echinacea: no significant modification of AUC
Estramustine	The bioavailability and peak serum concentrations of the drug are decreased following concomitant milk or food ingestion
Etoposide, VP-16	Grapefruit: decreased drug absorption Garlic: decreased AUC
Everolimus	Curcumin + piperine: decreased AUC
Imatinib	St John's wort: decreased AUC
Irinotecan, CPT-11	St John's wort: inductive effect Cannabis: no significant modification of AUC Milk thistle: no significant modification to decreased AUC
Methotrexate	Alcohol may cause liver damage
Plicamycin	Supplements of calcium and vitamin D may decrease the drug's effect
Procarbazine	Alcohol may cause headache, trouble breathing, flushed skin, sickness, nausea and vomiting. Avoid tyramine-containing foods. Maintain tyramine-free diet for 14 days after treatment ceases
Sunitinib	Grapefruit: increased AUC
Tamoxifen	Curcumin: decreased AUC Soy: no significant modification of AUC
Temozolomide	Food may slow or reduce the drug's effect
Busulfan, fluorouracil, methotrexate, topotecan	Food intake delays the absorption of the drug (effect on rate)
Altretamine, capecitabine, chlorambucil, estramustine, gefitinib, melphalan, thioguanine	Food intake decreases the absorption of the drug (effect on extent)
Erlotinib, tretinoin	Food intake increases the absorption of the drug (effect on extent and/or rate)

Abbreviation: AUC, area under the concentration-time curve.

Sudden and unexplained changes in the clinical response of a patient to prescribed chemotherapy could be the result of a food-drug interaction. Physicians should be aware of this possibility and initiate discussions with their patients about the consequences of ingesting nutritional supplements. Further studies evaluating how herbs or vitamins may alter the pharmacokinetics and pharmacodynamics of anticancer and supportive care medications are needed.

Monitoring of Nutritional Support During Cancer Treatment

First-line monitoring strategies should include routine, accurate, practical and non-time-consuming nutritional screening, which should be performed at diagnosis and before and during anticancer treatment. In patients at nutritional risk, assessment of nutritional status and metabolic parameters as well as monitoring of nutrition therapy and outcomes are of central importance. Therefore, it is recommended to monitor the following parameters before and during treatment:

- Primary tumour site affected and presence of metastases
- Pre-existing medical conditions
- Type and frequency of treatments, potential side effects, influence of malignancy on the ingestion, digestion and absorption of nutrients as well as nutrition impact symptoms (Table 2)
- Quality of current food intake and appetite. To demonstrate a reduction in normal food intake, a simple 24-48-hour recall or completion of Box 2 (food intake) of the PG-SGA is usually sufficient to calculate actual protein and energy intake
- Physical performance may be graded using the World Health Organization/Eastern Cooperative Oncology Group (WHO/ECOG) scale (0 = normal performance, 4 = bed-bound) or the Karnofsky Performance Scale (0-100)
- Quality of life should be measured with a standardised questionnaire, i.e. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-C30)

Table 2 Nutritionally Relevant Adverse Effects of Oncological Treatment.

Drugs frequently associated with severe nausea and vomiting Chemotherapy-induced nausea and vomiting is a debilitating side effect of cancer treatment, affecting up to 40% of patients	Drugs frequently associated with mucositis Oral mucositis is a common complication of chemotherapy, which may begin 5-10 days after the initiation of chemotherapy and lasts 7-14 days
Carmustine, BCNU	Actinomycin D
Carboplatin	Bleomycin
Cisplatin	Dactinomycin
Cyclophosphamide	Doxorubicin
Dacarbazine, DTIC	Fluorouracil (FU), 5-FU
Docetaxel	Etoposide
Doxorubicin	Irinotecan plus FU/leucovorin (IFL)
Epirubicin	Melphalan
Etoposide	Methotrexate
Lomustine	Vinblastine
Mustine hydrochloride, mechlorethamine hydrochloride USP	
Streptozocin	
Nutritional complications associated with radiotherapy	
Head and neck	Odynophagia, xerostomia, mucositis, anorexia, dysosmia, hypogeusia
Thorax	Dysphagia
Abdomen and pelvis	Anorexia, nausea, vomiting, diarrhoea, enteritis, colitis

- Height, weight and weight changes over time
- Dehydration or excessive fluid loads (hydration status)
- Assessment of muscle and fat mass reserves can be performed by anthropometry, bio-impedance analysis (BIA) or with more sophisticated analysis such as cross-sectional imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) or dual-energy X-ray absorptiometry (DEXA)
- Quantitate physical performance such as walking tests or measurements of muscle strength with a handheld dynamometer are easy to perform

- Laboratory tests such as serum albumin and prealbumin can be used as a pretreatment prognostic factor in patients with cancer, with low levels being associated with poor outcome. The extent of systemic inflammation, recognised as a precursor of cachexia, may be estimated by measuring serum C-reactive protein and albumin. The laboratory results must be interpreted carefully, as cancer and/or its treatment often results in pathological values independent of nutritional status
- Calculate the daily energy, protein and micronutrient requirements, and draw up the nutritional support concept (action plan)

Use/Indications of Parenteral and Enteral Nutrition During Cancer Treatment

Before the decision is made to implement non-volitional feeding, the caregiver must be fully informed about the patient's overall circumstances (underlying disease, disease development, prognosis, general and performance status, social situation, ethical aspects, patient's wishes, etc.). The functioning and capacity of the gastrointestinal tract, the underlying disease and patient tolerance must be assessed to determine the appropriate method of administration.

Enteral Nutrition

EN is considered when oral intake is insufficient to meet the nutritional needs of the patient, but gut function is preserved. Feeding solutions should be introduced to the gastrointestinal tract where absorption is possible. Modified feeds (e.g. peptide-based formulae) may be used to overcome gastrointestinal incapacity. The insertion of an enteral access is an interdisciplinary decision. The treating medical team, the general practitioner, the patient and the patient's family must be involved in the evaluation. Patients with swallowing difficulties or mucositis can usually use nasogastric (duration <3 weeks) or gastrostomy (>3 weeks) tubes to overcome nutritional obstacles. Feeding tubes are beneficial in facilitating adequate nutrition and hydration during cancer treatment. Percutaneous endoscopic gastrostomy (PEG) has rapidly become a standard procedure for nutritional purposes – for example, in patients with severe

mucositis – to prevent weight loss and interruption of radiotherapy. Percutaneous tubes are preferred over nasogastric tubes in patients with head and neck cancer. Prophylactic PEG placement at treatment initiation, prior to development of mucositis and weight loss, is recommended more and more often. Although PEG insertion is considered relatively safe and has a low rate of significant associated complications, it is not a completely benign procedure. Frequent complications associated with PEG are local site infections, tube blockage and migration or dislodgement. Serious complications, such as peritonitis, fistula development or abscess, are relatively rare.

Major complications of enteral tube feeding are diarrhoea and abdominal cramps, secondary to the high osmotic load. Tube feeding may be contraindicated in situations of severe gastrointestinal dysfunction or bleeding, intractable vomiting or diarrhoea. Use of and indications for EN in patients with cancer are listed in Table 3.

Parenteral Nutrition

For selected patients, parenteral delivery of nutrition is the only practicable way to guarantee receipt of daily energy requirements (short-term PN: 2-3 weeks). Long-term (home) PN (duration >3 weeks) should be applied through a tunnelled central venous catheter (e.g. Hickman® device), implanted port systems (e.g. Port-a-Cath®) or a peripherally inserted central catheter (PICC), and may be recommended, for instance, in hypophagic/(sub)obstructed patients (e.g. peritoneal carcinomatosis) if their performance status is acceptable and they are expected to die from DRM prior to the tumour dissemination. A careful and in-depth risk-benefit analysis should be performed to justify use of PN in patients with cancer, because of the high potential for life-threatening complications, such as catheter-related and metabolic problems. Use of and indications for PN in patients with cancer are listed in Table 4.

The most frequent, and for all involved stressful, problem with eating and drinking is the decision whether and by what means progressive malnutrition with important weight loss and functional decline should be counteracted in end-of-life situations. As soon as nutrition is ensured by technical aids (non-volitional feeding), the question arises whether

Table 3 Use of/Indications for EN in Patients with Cancer According to the ESPEN Guidelines.

During curative or palliative anticancer drug treatment
■ It is advisable to ensure an adequate nutritional intake and to maintain physical activity
■ In general, start (supplemental) EN if malnutrition already exists or if it is anticipated that the patient will be unable to eat for >7 days
■ Start EN if inadequate food intake (<75% of estimated energy expenditure for >10 days) is anticipated
■ In patients losing weight due to insufficient oral food intake despite counselling and ONSs, EN should be provided to improve or maintain nutritional status
■ Use tube feeding if an obstructing head and neck or oesophageal cancer interferes with swallowing or if severe local mucositis is expected
■ In general, use standard formulae. In weight-losing cancer patients with insulin resistance, it is recommended to increase the ratio of energy from fat to energy from carbohydrates
■ There are insufficient consistent clinical data to recommend glutamine supplementation during conventional cytotoxic or targeted therapy
■ Routine EN during chemotherapy has no effect on tumour response to chemotherapy or on chemotherapy-associated undesirable effects, and therefore is not considered useful
■ EN should be preferred in patients with cancer because it is more cost-effective than PN and results in fewer complications
During radiotherapy
■ It is recommended that during radiotherapy – with special attention to radiotherapy of the head and neck, thorax and GI tract – an adequate nutritional intake should be ensured primarily by individualised nutritional counselling and/or with use of ONSs, in order to avoid nutritional deterioration, maintain intake and avoid radiotherapy interruptions
■ It is recommended to screen for and manage dysphagia and to encourage and educate patients on how to maintain their swallowing function during EN
■ EN using nasogastric or percutaneous tubes is recommended in radiation-induced severe mucositis or obstructive tumours of the head and neck or thorax
■ Because of radiation-induced oral and oesophageal mucositis, a PEG may be preferred
■ Routine EN is not indicated during radiotherapy
■ There are insufficient consistent clinical data to recommend glutamine to prevent radiation-induced enteritis/diarrhoea, stomatitis, oesophagitis or skin toxicity
■ There are insufficient consistent clinical data to recommend probiotics to reduce radiation-induced diarrhoea
During high-dose chemotherapy and haematopoietic stem cell transplantation
■ During intensive chemotherapy and after stem cell transplantation, it is recommended to maintain physical activity and to ensure an adequate nutritional intake. This may require EN and/or PN
■ If oral nutrition is inadequate, EN is preferable to PN unless there is severe mucositis, intractable vomiting, ileus, severe malabsorption, protracted diarrhoea or symptomatic GI graft-versus-host disease
■ The routine use of EN during stem cell transplantation is not recommended
■ If oral intake is decreased, PN may be preferred to EN in certain situations (i.e. increased risk of haemorrhage and infections associated with enteral tube placement in immunocompromised and thrombocytopaenic patients)
■ There are insufficient consistent clinical data to recommend a low-bacterial diet for patients more than 30 days after allogeneic transplantation
■ There are insufficient consistent clinical data to recommend glutamine to improve clinical outcome in patients undergoing high-dose chemotherapy and haematopoietic stem cell transplantation

Table 3 Use of/Indications for EN in Patients with Cancer According to the ESPEN Guidelines. (Continued)

Methods of administration
■ Continuous: administered at a constant steady rate based on 20-22 hours/day, allowing for interruptions in delivery. Patients may initially benefit from a continuous infusion to establish tolerance to EN and later transition to an intermittent or bolus infusion ■ Cyclic: administered at a constantly increased rate over 8-12 hours, often overnight. This feeding method should be considered for patients who are active during the day and desire free time 'off the pump' ■ Intermittent or bolus: the volume of desired feeding is divided over several feedings per day. Feedings are usually given over a 30-60-minute period. Intermittent or bolus feeding can be administered by gravity dip or syringe bolus for those patients with gastric feeding tubes (bolus feeding occurs 3-4 times per day)

Abbreviations: EN, enteral nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; GI, gastrointestinal; ONS, oral nutritional supplement; PEG, percutaneous endoscopic gastrostomy; PN, parenteral nutrition.

Table 4 Use of/Indications for PN in Patients with Cancer According to the ESPEN Guidelines.

During curative or palliative anticancer drug treatment
■ In a patient undergoing curative anticancer drug treatment, where oral and/or enteral food intake is inadequate (<75% of estimated daily energy requirements is anticipated for >10 days), it is recommended to evaluate supplemental PN ■ The majority of patients requiring PN for only a short period do not need a special formulation ■ A higher percentage of the lipid component (e.g. 50% of non-protein energy) may be beneficial for those patients with frank cachexia needing prolonged PN ■ PN is ineffective and probably harmful in non-aphagic patients in whom there is no gastrointestinal reason for intestinal failure
During chemo-/radiotherapy
■ PN is not generally recommended during radiotherapy, only if adequate oral and/or enteral nutrition is not possible, e.g. in severe radiation enteritis or severe malabsorption, because it is usually better tolerated and more efficient in preventing nutritional deterioration ■ Long-term PN is often indicated in patients with sub-acute/chronic radiation enteropathy ■ PN is recommended in patients with severe mucositis or severe radiation enteritis ■ The routine use of PN during chemotherapy, radiotherapy or combined therapy is not recommended
During high-dose chemotherapy and haematopoietic stem cell transplantation
■ In haematopoietic stem cell transplantation, PN should be reserved for those patients with severe mucositis, ileus or intractable vomiting ■ No clear recommendation can be made as to the time of introduction of PN in those patients. Its withdrawal should be considered when patients are able to tolerate approximately 75% of their requirements enterally
Methods of administration
■ In patients with transient and partial gastrointestinal failure, peripheral PN can be administered as a complement to enteral or oral nutrition ■ Analogous to EN, PN can be administered in a continuous (over 20-22 hours/day) or a cyclic mode (over 8-12 hours, often overnight). Cyclic administration is recommended in patients with home PN ■ Solutions not exceeding 850 mOsm/L (osmolarity) can be infused for a short period peripherally via peripheral cannula or midline ■ The use of infusion pumps is recommended, but is not practised in all countries

Abbreviations: EN, enteral nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; PN, parenteral nutrition.

nutrition remains a fundamental right or has rather become a negotiable therapeutic measure. This is where ethical and ideological attitudes towards life and the personal experiences of all involved come together. The extent of, and decisions for, nutritional support must be individualised and should change according to the course of disease. The nutritional interventions should be chosen with the aim of maintaining well-being/quality of life and controlling symptoms. Nutritional measures in the end-of-life phase should be kept to a minimum and evaluated on a case-by-case basis with the medical care team, patients and relatives.

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Nutritional Support for the Advanced Cancer Patient

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F. Bozzetti[1]

M. Chasen[2]

K. Boeykens[3]

[1]*Faculty of Medicine, University of Milan, Milan, Italy*
[2]*Palliative and Supportive Care, William Osler Health System, Brampton, ON; McMaster University, Hamilton, ON, Canada*
[3]*Nutrition Support Team, Vitaz Hospital, Sint-Niklaas, Belgium*

Nutritional Support During Best Supportive Care

The use of enteral (EN) or parenteral (PN) nutrition to feed patients with advanced cancer was introduced in clinical practice following the seminal paper from DeWys et al in 1980, which showed that weight loss was an independent negative prognostic factor on survival length. Subsequent large studies have also shown that the lower the body mass index (BMI), the lower the weight loss required to be associated with mortality. Both weight loss and poor food intake are independently associated with mortality. Weight loss has consistently been shown to be significantly associated with shorter failure-free and overall survival and decreased response, quality of life and performance status. More recently, several studies on body compartments have demonstrated that the depletion of muscle mass plays a major role in the outcome of these patients. The malnutrition–mortality association does not directly imply that there is a cause–effect relationship between these indications and malnutrition, because patients with more advanced cancer more often exhibit severe weight loss, anorexia and systemic inflammation. However, there are studies reporting that patients with incurable cancer survive longer than one would expect with complete macronutrient starvation if they are

supported through PN. The experience of patients with malignant bowel obstruction receiving or not receiving PN is consistent with this thinking.

Clinical Situations for Nutritional Support

Overall, nutritional support of the advanced cancer patient may be used in two broad clinical conditions:

I. To enable patients to receive life-prolonging anticancer therapies;

II. To improve the nutritional status of patients with incurable cancer who are expected to die from starvation and nutritional deterioration rather than from cancer progression.

In the real world, these two conditions can sometimes overlap because in some incurable cancers, further oncological treatments can be attempted, and some patients are supported during intensive oncological therapy even if clinicians are indeed quite sceptical about the possibility of achieving a significant result.

Regardless of the indication, the type of nutritional treatment depends on the functionality of the gastrointestinal (GI) tract and the need for either total nutritional support or only supplementation.

I. Patients Who Are Malnourished, Anorectic and Are Candidates for Anticancer Therapies Or

II. Patients Who Are Expected to Face Severe GI Toxicity

Usually, these patients have a functioning GI tract and may benefit from oral nutritional supplements (ONSs), sometimes combined with antianorectic agents (e.g. megestrol acetate, anamorelin). ONSs are not a substitute for a complete meal, but can be integrated with suboptimal oral feeding. Since these patients frequently experience symptoms of early satiety, ONSs should be taken in-between meals so as not to compromise the food intake at lunch or dinner. Liquid formulae with high caloric density (2 kcal/mL) may sometimes be preferable; it is recommended to use formulae with different tastes to maintain good compliance. The use of omega-3- or protein-enriched formulations has been successful in restoring the fat-free mass and improving the quality of life of patients in

comparative trials and in some subgroups of patients within randomised controlled trials (RCTs). However, as of today these cannot be considered standard treatment procedures. Recently, a few RCTs have demonstrated that ONSs administered for some weeks may improve tolerance to chemotherapy and radiotherapy and improve long-term outcome. In patients with head and neck cancer, the oral route is often not practicable; a nasogastric feeding tube or a gastrostomy are valid alternatives. The choice between the two modalities as either prophylactic or 'on demand' is still controversial.

III. Patients With Incurable Cancer

This issue is sometimes controversial also because the term 'advanced cancer patient' may apply to different types of patients. Regarding the indication for nutritional support, the term 'malignant (sub)obstruction' is used when referring to patients who have exhausted all available oncological therapies, are severely malnourished, and starving because of anorexia or a condition of chronic gut dysfunction. These patients are 'oncologically' but not 'biologically' terminal. They are not cachectic and could succumb to nutritional deterioration rather than tumour progression. It is noteworthy that in a recent multinational survey of experience and attitudes towards commencing home PN for patients with advanced cancer, the combination of malnutrition and cachexia accounted for the most common reason for the use of home PN in this patient cohort. There may be a rationale for feeding these patients intravenously if it can be reasonably estimated that their survival will be longer than 3 months, due to the tumour spread. Consolidated experience has shown that healthy people on a hunger strike die within 2 months, while patients with malignant small bowel obstruction survive 1 month without PN and 3 months or more with PN. There are several prognostic factors for predicting survival in such patients on home PN and, in 2015, a prognostic nomogram including performance status, type of primary, tumour spread and Glasgow Prognostic Score was built to identify patients who are likely to survive less than 1 month compared to those surviving more than 9 months (Figure 1).

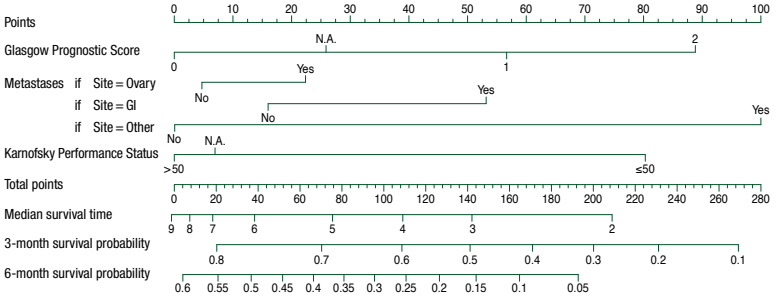

Figure 1 Cox modelling-based nomogram for predicting 3-, 6-month and median OS in cancer patients receiving home parenteral nutrition.
From: Bozzetti F, Cotogni P, Lo Vullo S, et al. Development and validation of a nomogram to predict survival in incurable cachectic cancer patients on home parenteral nutrition. Ann Oncol 2015;26: 2335-2340.

Abbreviations: GI, gastrointestinal; N.A. not available; OS, overall survival.

Reasons to Consider Initiation, Withholding and/or Withdrawing Artificial Nutrition and Hydration in Patients Who Are Imminently Dying

Artificial nutrition (AN) and hydration should be considered separately for two reasons: first, it is possible to hydrate a patient without nourishment, as AN provides both macronutrients and water and, second, the patient populations fit for AN and those fit for hydration are different.

AN in hospital and at home has no role in the imminently dying patient but can be considered when the patient has an expected survival of less than 2 months due to starvation but not due to cachexia. If this is the case and there is the possibility of home PN, the oncologist could propose this to the patient. The main goal of PN is to provide all the necessary care at home with the presumption that if palliation of symptoms is effective in hospital, receiving intravenous (i.v.) nutrition at home should further improve the quality of life of the patient. From the start of the programme, the clinician must explain to the patient and their family what achievable treatment goals can be expected and the myriad of factors besides the nutritional status that affect quality of life. Plans should

be made to decrease the energy content or stop the PN when disease progression and/or a deterioration in the quality of life of the patient is seen. Oncologists should not force the use of home PN on patients with a presumably favourable outcome because of the weakness of the available predictive outcomes; however, they should not deny this approach to highly motivated patients.

Regarding hydration of imminently dying patients, there is a paucity of investigations on this subject, and the few RCTs that have studied the effect of i.v. solutions were not specific for rehydration. Isotonic balanced solutions containing dextrose may prevent feelings of thirst and confusion, but it is important to avoid fluid overload in patients with respiratory failure. The infusion of iso-osmolar fluids can be administered subcutaneously (hypodermoclysis), sparing venous infusion which may be problematic in these situations.

General Principles of Nutritional Support

The oncologist should be aware that even the best nutritional support can only prevent or blunt further nutritional deterioration and cannot fully reverse a status of cachexia. Cachexia cannot be equated to simple starvation because it is caused not only by poor intake of nutrients, but also a deranged metabolism driven by systemic inflammation. This does not mean that malnourished patients with high inflammatory markers should not receive AN, because all the physiological functions of the body's organs still require appropriate substrates.

The traditional nutritional approach follows a rule that prefers use of the oral route as the initial step and the i.v. route as the final approach, hence following the old dictum 'if the gut works, use it'. Whereas this is true in most cases, several patients with advanced cancer have a working gut, but the presence of anorexia, nausea, dysgeusia and/or early satiation can preclude efficient use of the oral route.

Experience has shown that ONSs are particularly useful when symptoms of cachexia are minimal. They are prescribed preventatively to anticancer treatments associated with GI toxicity or for patients recovering after

treatment. They cannot fully meet the nutritional needs of patients who may require ≥30 kcal/kg body weight (BW)/day and 1.2-1.5 g amino acid/kg BW/day; however, even minor amounts can prove clinically beneficial. If patients are totally starving and their GI tract is not working or accessible, the only alternative is PN. Some pros and cons of EN and PN are reported in Table 1. Whatever the choice of feeding route, it is noteworthy that patients with advanced cancer metabolise fat better than healthy people, hence the regimen should be fat-enriched. Regarding amino acid content, it is important to give protein rich in essential amino acids, especially branched-chain amino acids (BCAAs) or leucine, which have a special anabolic function.

Table I Pros and Cons of Enteral and Parenteral Nutrition.

Enteral nutrition		Parenteral nutrition	
Pros	Cons	Pros	Cons
Simpler	Requires a functioning gut	Higher compliance with the desired quality/ quantity of nutrients	More demanding
Low cost	May require a gastric tube	Better modulation of the substrates	More expensive
Safer	A critical volume is obligatory to meet all requirements	Regimen may be adjusted without withdrawing the administration	Potentially more dangerous as regards metabolic/infective complications
Metabolically better in the long-term	Adverse effects may lead to discontinuation	Compliance is generally good	

The value of exercise in addition to the nutritional support should be emphasised and encouraged in order to promote muscle strength and improve the daily functionality of patients.

The Role of Ketones

It is known that about 50% of human tumours have a glycolytic phenotype and their growth could be impaired in conditions of caloric restriction. This is associated with high levels of ketones in the body, which cancer cells cannot metabolise because of a deficient mitochondrial function.

However, a safer way to realise hyperketonaemic glucose deprivation to the tumour is the use of a eucaloric ketogenic diet in which fats account for about 70%-75%, protein 20%-25% and carbohydrates 5%-10% of total energy intake. There are many scattered reports on the feasibility and metabolic efficacy of this approach, which should be reserved only to patients with high fluorodeoxyglucose uptake on a positron emission tomography (PET) scan. The major problem is the palatability of these diets, which decreases long-term patient compliance, while such a regimen by vein appears to be well accepted. In consideration of the good metabolic utilisation of fat by cancer patients and the introduction of ketone-enriched diets or supplements to the market, this approach will be developed in the near future.

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Nutrition in the Older Patient with Cancer

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M.S. Mukherjee[1]

T.H.M. To[2,3,5]

A.R.A. Mislang[4,5]

[1]*Caring Futures Institute, College of Nursing and Health Sciences, Flinders University, Bedford Park, Adelaide, SA, Australia*

[2]*Research Centre for Palliative Care, Death and Dying, College of Nursing and Health Sciences, Flinders University, Bedford Park, Adelaide, SA, Australia*

[3]*Southern Adelaide Palliative Service, Flinders Medical Centre, Bedford Park, Adelaide, SA, Australia*

[4]*Department of Medical Oncology, Flinders Centre for Innovation in Cancer, Flinders Medical Centre, Bedford Park, Adelaide, SA, Australia*

[5]*College of Medicine and Public Health, Flinders University, Bedford Park, Adelaide, SA, Australia*

More than 50% of the patients with cancer are aged 70 years or older. The management of older adults with cancer is complex due to the presence of competing comorbidities, polypharmacy, cognitive dysfunction, functional impairments and frailty – all contributing to and/or causing nutritional deficits. Older adults have additional nutritional needs compared with younger adults, due to age-related physiological changes. Pre-existing deficiencies may be compounded by the presence of comorbidities, including cancer and its treatment.

Malnutrition is defined as a suboptimal intake of nutrients and/or a state where an increased nutritional requirement is not met, resulting in poorer outcomes. Malnutrition can be diagnosed by the presence of at least one phenotypic criterion (non-volitional weight loss, low body mass index [BMI], reduced muscle mass) and at least one aetiologic criterion (reduced food intake and/or absorption, increased inflammation).

In older adults with cancer, the prevalence of malnutrition ranges from 3% to 83% depending on the nutrition screening tools used, and cancer site and stage. The risk of mortality from malnutrition is two-fold and is associated with lower quality of life, longer hospital stays and more frequent readmissions. While malnutrition in adults with cancer is frequently mentioned in the literature, 'cancer cachexia' is increasingly the preferred term. Cachexia is defined as a multifactorial syndrome involving complex, pathological metabolic changes, systemic inflammation, continuous loss of fat and muscle mass, fatigue and anorexia due to activation of catabolic pathways. This acknowledges the complexity of the factors involved in muscle wasting and the metabolic changes due to cancer-associated catabolic and inflammatory pathways, which may not simply be reversed by the provision of nutritional support, unlike malnutrition. Notably, weight loss or BMI alone are not sufficient to diagnose cachexia, as gain in adipose tissue can offset loss in skeletal muscle. Evans et al's (2008) criteria for diagnosing cancer cachexia include weight loss in the presence of any of three of the following: anorexia, fatigue, decreased muscle mass and strength, decline in free fat mass and inflammation/anaemia/low serum albumin. All patients with cachexia have malnutrition but not *vice versa*. Sarcopenia, on the other hand, can be a physiological process exacerbated by the increase in metabolic and inflammatory states from cancer, and is diagnosed primarily by loss of muscle strength or function. It has been associated with poor outcomes such as falls, fractures, physical disability and mortality. In this chapter, we will use cachexia to encompass the nutritional impairments seen in older adults with cancer.

The prevalence of cachexia in older adults with cancer is 52%-62%, and sarcopenia is present in up to 57%. Both cachexia and sarcopenia are progressive, debilitating disorders of muscle deficiency that negatively affect functional performance, leading to 'frailty', a state of reduced physiological reserve characterised by a marked vulnerability to adverse health events. In older adults with cancer, frailty is associated with lower treatment tolerance, greater risk of treatment-related toxicity, post-surgical complications and mortality. Often, this leads to premature cessation of treatment and shorter survival.

In this chapter, we highlight the increased risk of nutritional impairments in older adults with cancer, and provide a stepwise approach for screening, assessment and management of their nutritional needs, to improve outcomes. Table 1 summarises these steps and offers examples of interventions that can be adapted by clinicians caring for older adults with cancer, depending on available resources.

Step 1: Recognise the Risk Factors of Cachexia in Older Adults with Cancer

Several factors increase the risk of cachexia in older adults with cancer. Often, the symptoms commence prior to the diagnosis of cancer. Although the nutritional risk factors mentioned below are not specific to older adults with cancer, older adults are at an increased risk for nutritional impairment, due to higher pre-existing rates of malnutrition in the general population, the prevalence of multimorbidity and reduced physiological reserve associated with ageing and comorbidity. Recognising and understanding factors that make them susceptible to nutritional risk is crucial in order to undertake regular assessments and proactive measures to counteract cachexia.

Cancer-related Risk Factors

Different cancer sites and stages can have a different impact on the nutritional status. The risk of developing cachexia is very high (80%-90%) among patients with pancreatic, liver or lung cancer, high (50%-70%) among patients with colon, gastric or head and neck cancer, moderate (30%-40%) for patients with endometrial, bladder or renal cancer, and low (20%-30%) for those with breast cancer, melanoma or prostate cancer.

The tumour itself may induce anorexia purportedly via the neuropeptide Y signalling cascade, which may increase production of inflammatory cytokines and compete with host cells for substrates; this process persists in the presence of a progressive, metastatic disease.

Table 1 Steps to Screen, Assess and Manage Nutritional Impairments in Older Adults with Cancer.

Assessment	Suggested interventions
Step 1: Recognise the risk factors of cachexia in older adults with cancer	

Assess disease- and treatment-related aetiology
• Cancer type and cancer stage. Certain cancers such as pancreatic, liver, lung, colon, gastric or head and neck cancer increase risk of cachexia
• Metastatic disease
• Toxicities from anticancer treatment: i.e. surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy
	Early recognition of factors that increase risk of nutritional impairment and proactive referral for intervention
	Look for symptoms, side effects and other aggravating factors:
	• Malnutrition
	• Hydration status
	• Non-volitional weight loss
	• Micronutrient deficiencies
	• Presence of nutrition impact symptoms
	  ◦ Early satiety
	  ◦ Ageusia
	  ◦ Fatigue, frailty
	  ◦ Mouth ulcers/sores/poor dentition
	  ◦ Dry mouth
	  ◦ Dysphagia/odynophagia
	  ◦ Malabsorption
	  ◦ Gastrointestinal (GI) dysfunction, constipation, diarrhoea, vomiting, nausea, pancreatic exocrine insufficiency, steatorrhoea, dumping syndrome
	  ◦ Pain

Assess psychosocial-related aetiology	Assess/monitor for any of the following: • Anxiety/depression • Cognitive impairment • Financial constraints • Poor access to food/mobility • Functional impairment/falls • Social isolation
Step 2: Perform nutritional screening and assessment in older adults with cancer	

Use of validated screening tools:
• Mini Nutritional Assessment (MNA)
• Malnutrition Universal Screening Tool (MUST)
• Short Nutritional Assessment Questionnaire (SNAQ)
• Patient-Generated Subjective Global Assessment (PG-SGA)
• G-8 Questionnaire
Use of comprehensive assessments:
• Geriatric Assessment (GA)
Use of objective tools where available:
• Computed tomography (CT)
• Magnetic resonance imaging (MRI)
• Dual-energy X-ray absorptiometry (DEXA)
• Bioelectrical impedance analysis (BIA)
	Screen opportunistically, periodically and on clinical need
	Use tools that you are most familiar with and/or are widely accepted in your healthcare facility
	Key factors to assess include:
	• Weight loss
	  ◦ >5% in 6 months
	  ◦ >10% beyond 6 months
	• Low BMI (body mass index)
	  ◦ <22 if more than 70 years old
	• Reduced muscle mass (objective tests or physical examination, functional tests, mid-arm or calf circumference)
	• Reduced food intake
	  ◦ <50% of requirements for >1 week
	  ◦ Any reduction for >2 weeks
	  ◦ GI disorder affecting nutrient absorption
	• Frailty

Table 1 Steps to Screen, Assess and Manage Nutritional Impairments in Older Adults with Cancer. (Continued)

Assessment	Suggested interventions
Step 3: Managing nutritional impairments in older adults with cancer	

Undertake a multidisciplinary approach involving the:
• Patient
• General practitioner
• Dietician
• Physiotherapist
• Pharmacist
• Specialist physicians
• Carers
• Social workers
	• Meet energy and protein requirements:
	  ◦ Protein: 1-1.5 g/kg body weight (BW)/day
	  ◦ Energy: in malnourished patients, aim for 32-38 kcal/kg BW/day
	• Individualise dietary strategies, dietary education, provision of resources to include high protein and high energy foods:
	  ◦ Protein: eggs, chicken, fish, red meat, legumes, milk, yoghurt, nuts, tofu
	  ◦ Energy: cereals, starchy vegetables, fats, avocado, cheese, nuts, ice cream
	• Provide oral nutritional supplements (ONSs), if indicated
	• Suggest food fortification techniques, if indicated:
	  ◦ Addition of ONS/protein/skimmed milk powder to full-cream milk, porridge, scrambled eggs, breakfast cereal, soups
	  ◦ Increasing cheese/oil/margarine content in dishes such as pasta, curries, salads, mashed potato, vegetables, meat etc.
	• Suggest shopping and cooking aids, meal delivery programmes, shared and supervised meals, texture modification of diet
	• Consider enteral nutrition if inadequate intake persists (e.g. less than 50% of their requirements for 1 week)
	• Monitor and correct vitamin/mineral/micronutrient deficiencies, as required
	• Provision of pharmacological (e.g. antiemetics, corticosteroids, prokinetics) and non-pharmacological (e.g. dry, bland and cold foods, or avoiding fatty and very sweet foods) strategies to manage nutrition impact symptoms
	• Choose a less emetogenic regimen, if possible
	• Manage treatment-related toxicities proactively
	• Enable patients to self-manage their nutritional needs by adapting meal-planning skills, engaging in healthy dietary practices and improving access to support
	• Exercise regimen
	• Optimal management of comorbidities

Monitor and reassess: • Nutritional and hydration status • Disease state • Response to treatment • Patient preferences	• Regular weight and nutritional status monitoring. Repeat screening weekly for inpatients, especially in presence of clinical concern • Monitor all factors mentioned in Step 1 • Routinely check micronutrient status, albumin and electrolytes • Arrange for reviews with the multidisciplinary team, as indicated

Treatment-related Risk Factors

The provision of anticancer treatment can cause nutrition impact symptoms (Table 1). This can result in decreased dietary intake, sarcopenia and frailty, exacerbating the risk of cachexia.

Chemotherapy drugs can also induce micronutrient imbalances. For example, cisplatin can increase renal excretion of magnesium, potassium and L-carnitine; methotrexate and pemetrexed could lead to folic acid depletion; and certain anticancer drugs metabolised by CYP3A4, such as cyclophosphamide and paclitaxel, could potentially alter the synthesis or degradation of vitamin D. Immunotherapy can enhance proinflammatory status and alteration of gut flora, leading to colitis. Surgical resection can cause alterations in gut motility leading to nutrient malabsorption and subsequent deficiencies in macronutrients and fat- and water-soluble vitamins.

Age-related and Other Factors

Common geriatric symptoms such as frailty, functional impairment and cognitive and/or mood disorders are associated with a greater risk of malnutrition and poor prognosis. For example, according to Poisson et al (2021), in hospitalised older adults with cancer, poor physical function, dementia and depression increased the risk of cachexia, and were associated with an increased length of stay and mortality.

Several socioeconomical, psychological, religious and cultural factors, including poverty, poor education and self-imposed dietary restrictions, can also contribute to malnutrition. Nutritional status may decline further in the presence of social isolation.

Functional impairments may limit the ability to self-feed, or to access food. Even in supported environments such as nursing homes, supervised feeding may be necessary to meet the nutritional requirements.

Step 2: Perform Nutritional Screening and Assessment in Older Adults with Cancer

Table 1 shows widely available and validated subjective malnutrition screening tools to help identify patients at risk of malnutrition. These

tools measure parameters such as BMI, non-volitional weight loss over the previous 3 to 6 months, decrease in oral intake, muscle and fat loss, and functional status. They are free to use and easily replicated. Conversely, there are also objective tools that can be used, if available.

Another tool, the G-8, which has been validated in geriatric oncology, covers both nutritional and geriatric parameters to screen patients who would benefit from a geriatric assessment (GA). GA evaluates several domains such as demographic and social factors, comorbidities, function, geriatric syndromes, cognition, mood, nutrition and treatment-related toxicity, which can help personalise cancer treatment decision-making according to overall health status.

These tools may assist members of the multidisciplinary team in managing the nutritional needs of older adults with cancer.

Step 3: Manage Nutritional Impairments in Older Adults with Cancer

Currently, there is no effective treatment to completely reverse cachexia, highlighting the need for early diagnosis and intervention. As the causes of decline in nutritional status are often dynamic and multifactorial, interventions should be targeted to each contributing cause and personalised according to the patient's needs. Under some circumstances, palliative care alone may be appropriate.

For older adults with cancer, the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend a protein intake of 1.0-1.5 g/kg body weight (BW)/day. The recommended energy intake is 32-38 kcal/kg BW/day if malnourished and 27-30 kcal/kg BW/day if not. Malnutrition can be treated, and nutrition impact symptoms alleviated, through a dietician's prescription of an individualised diet including food fortification and/or oral nutritional supplements (ONSs) that meet the energy, protein and micronutrient requirements of the patient (Table 1).

In the absence of specific deficiencies, supply of micronutrients in accordance with the recommended daily allowance is suggested. Surgeries involving gastrectomy or intestinal resection can increase the risk of

micronutrient deficiencies such as vitamin B12, calcium, magnesium, folate and iron, which should be monitored every 3 months and corrected as required. Similarly, the Whipple procedure (pancreaticoduodenectomy) for pancreatic cancer increases the risk of micronutrient deficiencies, such as fat-soluble vitamins A, D, E and K, and minerals such as calcium, magnesium, folate, selenium and iron, and should be monitored and supplemented as required. These are particularly relevant in older adults with cancer, as iron deficiency (anaemia) increases the risk for chemotherapy-related toxicities, and deficiencies in vitamin D and minerals exacerbate bone loss, osteoporosis, falls and fractures.

Treatment-induced nutrition impact symptoms can be alleviated by modifying treatment regimens (i.e. reducing the drug dose or choosing less emetogenic or gut-toxic regimens, if possible), and/or using adjunct pharmacological and non-pharmacological strategies to manage symptoms and improve nutrition, as shown in Table 1.

Other interventions such as social support may help improve access to, and facilitate the intake of, food. In cases of patients with sarcopenia and frailty, the involvement of an exercise physiologist will aid the rehabilitation and optimisation of muscle and strength (Table 1).

Conclusion

Older adults with cancer are more vulnerable to cachexia and other nutritional impairments which can cause adverse outcomes. Early recognition of risk factors, routine and regular assessments of nutritional and overall health status, as well as proactive provision of personalised interventions are essential and must be incorporated in the routine oncological care.

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Energy Balance, Nutrition, Cancer Incidence and Survivorship

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J. Arends[1]

J.A. Ligibel[2]

[1]*Universitätsklinikum Freiburg, Freiburg, Germany*
[2]*Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA*

'Energy balance' refers to the balance between energy ingested through food, energy expended through physical activity and metabolism, and energy stored as adipose tissue. These three aspects of the energy balance equation – diet, physical activity and adiposity – have increasingly been linked to the risk of developing and dying from cancer. This chapter provides an overview of the data linking energy balance to cancer risk and outcomes, from observational and interventional trials, as well as a brief exploration of the biological mechanisms through which energy balance is believed to impact cancer.

Energy Balance and Cancer Risk

Observational Evidence

Obesity, inactivity and poor dietary quality are well-established risk factors for the development of cancer. The World Cancer Research Fund (WCRF) estimates that 30%-50% of cancer cases around the world occur due to preventable causes, with obesity, which impacts more than 640 million people worldwide, rapidly becoming one of the most common preventable causes of cancer in the developed world. Current analyses of more than 1000 reports linking obesity to cancer risk by the International Agency for Research on Cancer (IARC) and the WCRF suggest that obesity increases the risk of more than a dozen malignancies, including

common cancers such as those of the breast, colon, endometrium, kidney and oesophagus.

Although not as well studied as the relationship between obesity and cancer, physical inactivity has also increasingly been linked to higher cancer risk. In 2018, the United States Physical Activity Guidelines Advisory Committee reviewed 45 systematic reviews and meta-analyses of observational data evaluating the relationship between physical activity patterns and cancer risk, and concluded that there was strong evidence that higher levels of physical activity were associated with lower risk of several cancers, including cancers of the breast, colon, endometrium, oesophagus, kidney and stomach.

The relationship between diet and cancer risk has been somewhat less consistent, likely due in part to the complexities of measuring diet and the vast number of potential dietary factors for consideration. A 2018 update of the relationship between diet and cancer risk conducted by the WCRF suggested that alcohol intake increased the risk of several different cancers, including cancers of the mouth, pharynx, larynx, oesophagus, liver, colorectum and breast. Processed and red meat intake were also associated with increased risk of colorectal cancer, and coffee consumption was associated with a decreased risk of endometrial and liver cancers. Current research focuses on the relationship between cancer risk and broader dietary patterns, such as the Healthy Eating Index and Mediterranean diet and Dietary Approaches to Stopping Hypertension (DASH), in an effort to better understand the totality of diet in relation to cancer risk.

Interventional Evidence

Despite the extensive observational data linking energy balance factors to cancer risk, there has been only one randomised controlled trial (RCT) that was designed to test the impact of dietary change on cancer risk, and no RCTs designed to test the impact of weight loss or increased physical activity. The US-based Women's Health Initiative Dietary Modification (WHIDM) trial randomised 48 835 postmenopausal women with no history of cancer to a dietary intervention designed to reduce fat intake and increase daily servings of fruits and vegetables, or to a usual diet control

group, with co-primary endpoints testing the impact of the dietary intervention on breast and colorectal cancers. The dietary intervention was successful in changing dietary patterns, with a significant reduction in the percentage of calories consumed as fat and an increase in fruits and vegetable servings in the intervention group, and induced modest weight loss of 2.2 kg at 1 year and 0.8 kg at 6 years. However, there was no significant reduction in breast (hazard ratio [HR] 0.91, 95% confidence interval [CI]: 0.83-1.0) or colorectal cancers (HR 1.08, 95% CI: 0.90-1.29) after a median follow-up of 8.1 years.

A few RCTs designed to evaluate the impact of energy balance interventions on other endpoints have included cancer incidence as a secondary endpoint, providing provocative preliminary evidence that weight loss, dietary change and/or increased physical activity could lower cancer risk. The Look AHEAD (Action for Health in Diabetes) trial randomised 4859 people with type 2 diabetes and a body mass index (BMI) ≥25 kg/m^2 to a diet- and exercise-based weight loss intervention or to a diabetes support and education control group; results showed a 16% reduction in obesity-related cancers in the weight loss group, though this comparison was not statistically significant (HR 0.84, 95% CI: 0.68-1.04). The Prevención con Dieta Mediterránea (PREDIMED) study evaluated the impact of a Mediterranean diet, supplemented with either nuts or extra virgin olive oil (EVOO), on the risk of heart disease in older individuals with cardiovascular risk factors such as hypertension and diabetes and found a 62% reduction in breast cancer incidence in women randomised to the Mediterranean diet plus EVOO versus controls (HR 0.38, 95% CI: 0.16-0.87).

Energy Balance in Cancer Survivorship

Observational Evidence

Growing evidence suggests that energy balance factors influence not only the risk of developing cancer, but also outcomes such as cancer-related mortality and cancer recurrence. Obesity in particular has been the focus of many reports. A recent systematic review and meta-analysis of 203 studies looking at the relationship between BMI and cancer outcomes, including both individuals with early-stage and advanced cancers, found that obesity was associated with a higher risk of overall

mortality (HR 1.14, 95% CI: 1.09-1.19), higher cancer-specific mortality (HR 1.17, 95% CI: 1.12-1.23) and, in individuals with early-stage disease, increased risk of cancer recurrence (HR 1.13, 95% CI: 1.07-1.19). Notably, poor outcomes associated with obesity were primarily seen in individuals with cancers of the breast, colorectum and prostate, whereas obesity was associated with better outcomes in individuals with melanoma, lung cancer and renal cell cancer, potentially due in part to better outcomes with immunotherapy in individuals with obesity in some cancers.

A number of reports have also looked at the relationship between physical activity patterns after cancer diagnosis and the risk of cancer-related and all-cause mortality in cancer survivors. The 2018 US Physical Activity Guidelines Advisory Committee summarised 18 systematic reviews and meta-analyses looking at the relationship between physical activity patterns and all-cause and cancer-specific mortality and concluded that there was moderate-level evidence that higher levels of physical activity were associated with a relative 38% reduction in the risk of cancer-specific mortality in individuals with cancers of the colorectum, breast and prostate. Higher levels of physical activity were also associated with a 40%-50% lower risk of all-cause mortality in breast and colorectal cancers, but evidence for prostate cancer was more limited.

Finally, observational evidence suggests that healthier dietary patterns after cancer diagnosis are associated with improved disease-free and overall survival in some cancers, although evidence suggesting that intake of specific foods impacts cancer outcomes is largely lacking. In particular, Western-pattern diets, those with a higher intake of red meats and processed foods, are associated with worse survival outcomes in colorectal cancer and prostate cancer. The one individual beverage that has been more consistently linked to outcomes after diagnosis of some cancers is alcohol, for which higher intakes (more than 2 drink equivalents/day, i.e. more than 30 g/day) have been associated with increased risk of all-cause mortality in individuals with hepatocellular cancer (risk ratio [RR] 1.21, 95% CI: 1.07-1.36), laryngeal and pharyngeal cancers (RR 1.48, 95% CI: 1.08-2.02) and head and neck cancers (RR 1.39, 95% CI: 1.10-1.76).

Interventional Evidence

A number of RCTs have been designed to evaluate the impact of weight loss, increased physical activity and dietary change after cancer diagnosis on the risk of cancer recurrence and mortality. Two trials, the Women's Healthy Eating and Living (WHEL) study and the Women's Intervention Nutrition Study (WINS), enrolled women with early-stage breast cancer and evaluated the impact of reducing dietary fat, with or without increasing the intake of vegetables, fruits and dietary fibre, on the risk of breast cancer recurrence. The trials had somewhat disparate results, with the WINS trial showing a 24% improvement in disease-free survival at a median follow-up of 60 months in individuals participating in the low-fat dietary programme relative to controls (HR 0.76, 95% CI: 0.60-0.98), whereas there was no reduction in recurrence in the low-fat diet group in WHEL (16.7% versus 16.9%, $p = 0.63$) at a mean follow-up of 7.3 years. Notably, participants in the WINS trial randomised to the low-fat diet intervention lost an average of ≈2.7 kg versus controls, whereas the WHEL intervention did not result in weight loss.

A number of ongoing trials will test the impact of weight loss, dietary change and physical activity on cancer recurrence and mortality in breast, colon, prostate and ovarian cancers (Table 1). The results of these trials will help define the role of energy balance interventions in cancer survivorship over the years to come.

Mechanisms

The energy imbalance resulting from an overabundance of foods (especially processed) for increasingly inactive populations may be seen as the main driver for the spreading of (the global pandemic of) obesity, metabolic syndrome and type 2 diabetes to sizeable fractions of populations across the globe. All are characterised by chronically activated low-grade systemic inflammation, insulin resistance and hyperglycaemia as well as complex endocrine derangements, including increased levels of sex-steroid hormones (oestrogen and testosterone) and insulin-like growth factor 1 (IGF-1), their respective binding proteins (sex hormone-binding globulin, IGF-binding protein-1 and -2) and, finally, increased oxidative stress at the cellular level.

Table 1 Ongoing Phase III Randomised Controlled Trials of Energy Balance Interventions in Cancer Survivors.

Study	Population	Location	Intervention	Status	Primary Outcome
Breast Cancer					
Breast Cancer WEight Loss (BWEL) (A011401) NCT02750826	Breast cancer - Stage II-III - HER2-negative - BMI ≥27 kg/m^2 (N=3181)	USA, Canada	Weight loss intervention (diet plus physical activity) plus health education versus health education attention control	Accrual completed	Invasive disease-free survival
SUCCESS C NCT00847444	Breast cancer - Stage II-III - HER2-negative - BMI 24-40 kg/m^2 (N=2292)	Germany	Weight loss intervention (diet and physical activity) versus general lifestyle education	Accrual completed; preliminary findings presented at 2018 San Antonio Breast Cancer Symposium	Disease-free survival
Diet and Androgens (DIANA-5) NCT05019989	Breast cancer - Stage I-III - ER-negative cancer and/or metabolic syndrome or elevated testosterone (N=1542)	Italy	Mediterranean, macrobiotic diet pattern plus physical activity versus general lifestyle intervention	Accrual completed	Disease-free survival
Ovarian Cancer					
Lifestyle Intervention for Ovarian Cancer Enhanced Survival (LIVES) (GOG-225) NCT00719303	Ovarian cancer - Stage II-IV - No evidence of disease by CT scan and CA125 (N=1205)	USA	Diet and physical activity intervention versus general health education attention control	Accrual completed	Progression-free survival
Colon Cancer					
Colon Health and Life-Long Exercise Change (CHALLENGE) (CO.21) NCT00819208	Colon cancer - High-risk stage II and stage III - Performing <150 minutes of moderate intensity or 75 minutes of vigorous physical activity/ week (N=962)	Canada, UK, Australia	Supervised, structured physical activity intervention versus attention control condition	Enrolling	Disease-free survival

Table 1 Ongoing Phase III Randomised Controlled Trials of Energy Balance Interventions in Cancer Survivors. (Continued)

Study	Population	Location	Intervention	Status	Primary Outcome
Prostate Cancer					
Intense Exercise for Survival among Men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL-GAP4) NCT04507698	Prostate cancer - Stage IV - Castrate-resistant - No prior chemotherapy (N=866)	Australia, USA, Canada, UK, Europe	Supervised exercise (high intensity) intervention versus self-directed exercise (provision of guidelines)	Enrolling	Overall survival

Abbreviations: BMI, body mass index; CA125, cancer antigen 125; CT, computed tomography; ER, oestrogen receptor; GOG, Gynecologic Oncology Group; HER2, human epidermal growth factor receptor 2.

Cellular regulation is altered by these metabolic changes, including the balance between cell differentiation and proliferation, deregulated epigenetic mechanisms (especially site-specific DNA hypermethylation in parallel with global hypomethylation) initiating genetic instability and leading to aberrant gene expression. Further, histone acetylation may be disturbed, again initiating aberrant gene expression with silencing of tumour suppressor genes and/or activation of oncogenes. While connections between diet and epigenetic alterations, on the one hand, and between epigenetic alterations and cancer, on the other, are supported by both observational studies in humans as well as animal models, it is still less certain whether diet is directly linked to epigenetic alterations and whether these epigenetic alterations directly increase or decrease the risk of human cancer.

To counteract and slow these developments, it has been proposed to aim for lowering cell proliferation and increasing differentiation by decreasing sex hormone and growth hormone levels and inflammation. To achieve this, energy imbalances, obesity and other metabolic derangements need to be avoided or minimised. This will require lifestyle changes in the direction of earlier periods of human evolution, including generally increasing physical activity, adapting food intake to actual energy requirements and preferring natural over processed foods. The arguments to avoid overfeeding are supported by observations showing that moderate caloric restriction may increase health and survival in a large number of animal models.

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Navigating Nutritional Decision-Making

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M. Lee[1]
A. Jatoi[2]
J.G. Le-Rademacher[1,2]
[1]*Division of Clinical Trials and Biostatistics, Mayo Clinic, Rochester, MN, USA*
[2]*Department of Oncology, Mayo Clinic, Rochester, MN, USA*

A *New York Times* article from a few years ago began with the statement:

> *There's a decent chance you'll be reading about diet soda studies until you die, [but] the odds are exceedingly good it won't be the soda that kills you.*

Indeed, nutritional research – much of which focuses on decreasing cancer risk and on improving outcomes after a cancer diagnosis – is seemingly ubiquitous and, at times, seemingly contradictory in its findings and recommendations. Understanding study designs and the data they generate can be daunting for patients as well as for clinicians. Here we outline three illustrative points that clinicians should consider when discussing scientific findings on nutrition and cancer with patients. We also allude to other points of importance and provide resources that may help clinicians help patients (Tables 1 and 2).

An Association Should Not Imply Causation: Understanding Studies with Different Designs

Statistically significant associations abound, but proof of causality relies on well-conducted, well-reported placebo-controlled trials. A relevant case in point focuses on beta (β)-carotene and its previously touted role in lung cancer prevention. Carotenoids, such as β-carotene, are abundant in plants,

Table 1 Partial List of Trial Issues to Consider.

Trial design issue
Potential disconnect between association and causality
Undue focus on secondary endpoints
Ignoring patient dropout and data absence
Single-site or multi-site study
Confirmation of outcome measures during trial conduct
Appropriate degree of monitoring and reporting of toxicity
High degree of intervention fidelity from patient to patient
Slow or swift patient recruitment

Table 2 Relevant Databases.

Center for Food Safety and Applied Nutrition (CFSAN)	https://www.fda.gov/about-fda/fda-organization/center-food-safety-and-applied-nutrition-cfsan
FDA Adverse Event Reporting System (FAERS): Latest Quarterly Data Files	https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files
Licensed Natural Health Products Database (LNHPD)	https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/applications-submissions/product-licensing/licensed-natural-health-products-database.html
Natural Medicines databases	https://naturalmedicines.therapeuticresearch.com/databases.aspx
Dietary Supplement Label Database (DSLD)	https://ods.od.nih.gov/Research/Dietary_Supplement_Label_Database.aspx
The Committee on Herbal Medicinal Products (HMPC)	https://www.ema.europa.eu/en/human-regulatory/herbal-medicinal-products
European Food Safety Authority	https://www.efsa.europa.eu/en/topics/topic/health-claims

(24 May 2023, date last accessed)
Abbreviation: FDA, Food and Drug Administration.

functioning as antioxidants, modulators of cell proliferation and regulators of immune function. Such preclinical data support the hypothesis that an inverse relationship exists between carotenoid consumption and lung cancer development. Epidemiological studies that examined such associations did in fact find such an inverse relationship. For example, Abar et al (2016) focused on 17 prospective studies with 3603 patients who developed

lung cancer within a cohort of 458 434 participants. Examining blood levels of alpha (α)-carotene, β-carotene, total carotenoids and retinol, these investigators observed an inverse relationship between lung cancer risk or mortality and carotenoid concentrations, with lower risk ratios indicative of lower cancer risk: 0.66 (95% confidence interval [CI]: 0.55–0.80) per 5 μg/100 mL of α-carotene (in five studies), 0.84 (95% CI: 0.76–0.94) per 20 μg/100 mL of β-carotene (in nine studies), 0.66 (95% CI: 0.54–0.81) per 100 μg/100 mL of total carotenoids (in four studies) and 0.81 (95% CI: 0.73–0.90) per 70 μg/100 mL of retinol (in eight studies). Clearly, such findings invite further study.

However, double-blind, randomised, placebo-controlled clinical trial data warn against advising patients at high risk for cancer to take carotenoid supplements. The Beta-Carotene and Retinol Efficacy Trial (CARET) randomly assigned 18 000 individuals at high risk for lung cancer to β-carotene 30 mg per day and 25 000 IU of retinol palmitate per day versus matching placebos, only to conclude that the carotenoid supplementation had an opposite effect of that hypothesised: after a mean follow-up of 4 years, individuals who received the β-carotene and retinol manifested a relative risk of lung cancer of 1.28 (95% CI: 1.04–1.57), compared with placebo-exposed patients. Furthermore, in an almost simultaneously conducted interventional trial – the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study – which tested β-carotene 20 mg per day (in conjunction with vitamin E) in individuals at high risk for lung cancer, these other investigators generated similar findings: "Unexpectedly, we observed a higher incidence of lung cancer among the men who received beta-carotene than among those who did not (change in incidence, 18%; 95% CI: 3%–36%)." Additionally, "Total mortality was 8% higher (95% CI: 1%–16%) among the participants who received beta-carotene than among those who did not…"

These two studies underscore the importance of double-blind, randomised, placebo-controlled trials for final nutritional recommendations. Observational studies may be subject to selection bias or confounding effects while randomised trials minimise these risks, hence making selection bias and unknown confounders less of an influence on trial outcomes. Admittedly, the above two trials raise other issues – such as concerns about ingesting

discrete supplements, such as pills as opposed to consuming whole foods that presumably contain just the necessary tincture and combination of multiple micronutrients; how investigators choose the 'right dose' of a supplement; alarms about taking 'high dose' supplements, as ostensibly prescribed in the two trials referenced above; and the rationale for administering a nutrient to an individual with no apparent deficiency of that nutrient. For the purposes of this chapter, the main illustrative point is that observational nutritional studies can be misleading and that placebo-controlled, randomised, controlled data carry guiding value.

Secondary Outcomes Should Not Guide Definitive Clinical Recommendations

On 25 December 1996, the *Journal of the American Medical Association (JAMA*) reported on a randomised, placebo-controlled trial (Clark et al) that sought to determine if oral selenium (200 μg per day) decreased the risk of basal or squamous cell carcinomas of the skin. The trial included 1312 patients, clearly stated its primary endpoint, reported 377 new cases of basal cell skin cancer with selenium versus 350 with placebo (risk ratio [RR] 1.10; 95% CI: 0.95–1.28) along with 218 new squamous cell skin cancers with selenium and 190 with placebo (RR 1.14; 95% CI: 0.93–1.39), and appropriately concluded: "Selenium treatment did not protect against development of basal or squamous cell carcinomas of the skin."

Twenty-five years later, if one searches the internet for information on that study, the following can be found:

> *Just last Christmas Eve was a memorable date for people who have been taking antioxidants to prevent disease. CNN and other networks reported on a study from the Dec. 25, 1996, issue of the Journal of the American Medical Association (JAMA) showing that selenium reduced cancer mortality in humans by 50 percent over a 10-year period of time. CNN carried a more extensive report and emphasized that Americans could buy in health food stores the selenium tablets used in the JAMA study.*

This directly quoted commentary makes two important points. First, the findings from secondary endpoints can become overinflated in their importance. Although the secondary endpoints from Clark et al did, in fact, suggest selenium-treated individuals manifested a statistically significant decrease in the incidence of prostate cancer, lung cancer and colorectal cancer, these findings were just that: secondary endpoints, which can generate spurious findings, as appears to have been the case here and as further explained below. Importantly, secondary outcomes need to be interpreted with caution, because among other issues, studies are not always specifically powered to assess them and there are risks of type I errors when there are multiple secondary endpoints. Second, the viability of digitised memory banks, which can keep obsolete data and erroneous conclusions alive on the internet, underscores the role of clinicians as educators in such matters as the de-emphasis of secondary endpoints.

Since the publication of the original trial from Clark et al, three other large, definitive studies have focused on selenium and its respective and purported roles in the prevention of prostate cancer, lung cancer and colon cancer. Each of these trials examined cancer incidence (or, as in the case of colon cancer, polyps) as the primary endpoint for each of the cancers of interest, but each showed selenium does not prevent cancer (or polyps). In effect, these statistically significant secondary endpoints in the study from Clark et al eventually proved to be of no consequence.

As a case in point, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) for prostate cancer recruited 35 533 healthy men, and randomly assigned these men in a double-blinded manner to selenium 200 µg per day + placebo versus daily vitamin E + placebo versus both versus neither (double-dummy design). It demonstrated that these interventions "did not prevent prostate cancer;" cost over $110 million; appeared to put to rest the hypothesis that selenium, as prescribed in the trial, serves as a cancer chemopreventive agent; and at times even suggested adverse effects from such supplementation. This evolution of information underscores the clinician's role in providing patients with up-to-date and accurate information.

Missing Data Can Mislead

Patients who have an advanced cancer are often too ill to continue with clinical trial participation, despite their best efforts; these patients sometimes choose to cease trial participation – a decision that results in missing data. Through no fault of their own, these patients who drop out can create challenges in the interpretation of trial results. For example, in 1999, Barber et al reported on a single-arm study that tested an omega-3 fatty acid product to treat cancer-associated weight loss. Twenty patients were enrolled, but by week 3, two patients had dropped out; and by week 7, seven patients had dropped out. Not surprisingly, comparisons between baseline and 7-week data showed improvements in weight ($p = 0.033$), in lean body mass with bioelectrical impedance ($p = 0.0047$) and in Karnofsky scores ($p = 0.046$). However, one might wonder whether these favourable findings could be artefactual and the result of only dropout bias. Presumably, the more robust patients remained in the trial, driving the 7-week results in a more favourable direction. Small pilot studies – such as this one – yield important data, but their findings should not be overstated. Although Barber et al reported their results with an appropriate degree of caution, it is perhaps too easy for others to ignore how patient dropout can incur a potential for bias. Following this trial, a few hundred patients with advanced cancer and weight loss were treated with a similar omega-3 fatty acid product within the context of large phase III trials; none reported product efficacy.

Managing an Absence of Data

Still other aspects of study design come into play when deciding whether a nutritional intervention should be recommended to a patient with cancer or at risk for cancer. These other aspects of study design also include but are not limited to the following: whether a trial was conducted as a single-site or multi-site study with the latter allowing for greater generalisability of results, whether a trial was undertaken with the appropriate degree of confirmation of outcome measures and an appropriate degree of monitoring and reporting of toxicity, whether the intervention was prescribed with a high degree of fidelity (or a well-monitored, reproducible administration of the intervention) from patient to patient, and

whether recruitment was slow or swift, with the latter more likely to allow for the generalisability of findings.

But perhaps the most vexing problem is an absence of relevant data. Often no definitive clinical trials are available to provide guidance, leaving patients and clinicians to make decisions with little or no data. Under such circumstances, we recommend that discussions with patients consider the goals of cancer therapy. A patient who is receiving cancer therapy with curative intent should perhaps be advised against taking an understudied nutritional intervention, such as a high-dose supplement. In contrast, patients who are no longer receiving curatively intended cancer therapy may find that a nutritional intervention helps them feel more empowered, more in control of their circumstances. Clinicians should partner with patients to discuss the cost of nutritional interventions and to review resources, such as those in Table 2, to provide guidance on side effects. Clinicians should also work to build trust so that patients are comfortable in reporting to their healthcare providers what they are taking. The recruitment of a dietician to the study team can also be most helpful. This absence of data can make the bond between patients and clinicians stronger at a time when patients need it the most.

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Implementation Science to Advance Nutritional Care in Cancer

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M.J. Hjermstad

O. Dajani

S. Kaasa

Oncology and Palliative Medicine, University of Oslo, Oslo; Department of Oncology, Oslo University Hospital, Oslo; European Palliative Care Research Centre (PRC), Oslo University Hospital and Oslo University, Oslo, Norway

Evidence-based guidelines emphasise the importance of routine screening for nutritional deficits in patients with cancer, not only in those at risk of malnutrition. These guidelines target all adults at all stages of disease including survivors, irrespective of whether the treatment intention is curative, life-prolonging or palliative. However, given the high prevalence of malnutrition in cancer patients, varying between 20% and 70%, the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines documented that the nutrition guidelines regarding routine assessment, patient-centred advice and/or provision of nutritional support are not adhered to in daily clinical practice. More specifically, routine screening for nutritional deficits using objective measures and patient-reported outcomes is not performed.

The main objective of this chapter is to emphasise the need for a thorough, well-planned strategy to increase the chances for success in implementing better routines for nutritional screening into clinical practice. We strongly advocate using the basic principles of implementation science, which aims to close the gap between academia and practice by evaluating the most suitable strategies to implement evidence-based knowledge into the given setting.

This chapter focuses on how to implement the evidence-based recommendations for nutritional care into routine clinical practice at all institutions treating cancer patients. This goal is explicitly stated in the ESPEN guidelines on nutrition in cancer patients.

Nutritional deficits must be assessed and managed according to the nutritional care process of screening, assessment, intervention, monitoring and evaluation. For patients to benefit from the nutritional advice given, a patient-centred care approach is paramount: acknowledging the perceptions, needs and values of the individual patient, and ensuring patient participation in all clinical decisions. This is not only important from the patient's point of view, but also increases the chances for successful implementation in clinical cancer care. Practical nutrition guidelines encompass validated, stepwise and consensus-based recommendations about when, who and how to screen, and procedures for subsequent interventions. Examples are when and how to offer patients basic nutritional support and treatment, how to modify the anticancer and supportive treatments to improve nutritional status, when to refer to the dieticians, and guiding patients in how to optimise their diet and exercise regularly.

Why Do We See These Evidence-Practice Gaps in Nutritional Care in Cancer?

Given the positive clinical effects of routine malnutrition screening, it is surprising that this is not part of the clinical routine in cancer care. However, this complies with the generally dismal incorporation of evidence-based knowledge into clinical practice, with common time lags of 10 years or more.

We believe that several factors may explain the poor integration of nutritional care in cancer, albeit not being excuses thereof:

- Low awareness of the importance of nutritional status on the effectiveness of cancer treatment
- Inconsistent outcome data from studies on the benefits of nutritional support

- Limited knowledge of nutrition science among medical oncology, surgery, radiotherapy and nursing staff, reinforced by little emphasis in basic and specialist curricula
- A predominant disease-centred focus in cancer care, which to a small extent incorporates the patient's evaluation of nutritional problems and other symptoms in the treatment decisions
- Unsystematic use of patient-reported outcome measures (PROMs) that supplement the clinical data with valuable patient-centred information
- Poor compliance with routine malnutrition screening
- Disproportionately low engagement in clinical studies on nutrition in oncology, as opposed to other oncological trials
- The siloed organisation in medicine, with nutritional expertise and dieticians separated from the core clinical team
- Economic considerations, with marginal numbers of dieticians, even in university hospitals

The Rationale for Using an Implementation Science Strategy to Improve Adherence to Evidence-Based Nutrition Guidelines?

An explicit, consensus-based strategy for the delivery of patient-centred care including nutritional care is, to the best of our knowledge, not implemented in routine cancer care. Furthermore, it is time to admit that the poor adherence to nutrition guidelines represents a profound problem that necessitates a significant change. This applies to all organisational levels such as managerial, professional and individual, with robust top-down and bottom-up implementation plans.

A wide array of both passive and active strategies has been used to improve practice. However, when these actions are not performed systematically, chances for success are small. Our impression is that the two most neglected factors in any change plan are a thorough identification of barriers and facilitators and the anchoring of the change activities at all levels involved. A traditional assumption has been that presenting convincing

evidence-based results would suffice to see an uptake in practice. However, this is the exception rather than the rule, as the traditional research methods with control of context, followed by interventions and analyses, most often fall short in producing sustainable changes in practice.

The slow uptake of new evidence and technologies in clinical practice as well as the opposite, namely ending medications with little effects (e.g. extensive tube feeding at end-of-life), has led to the growing field of research on knowledge transfer. Implementation science has been defined as: *'The scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services'*; in other words, testing strategies to move evidence-based clinical innovations into practice, given the actual context.

In conventional clinical trials, the outcomes are either objectively measured clinical parameters, for example, lower blood pressure or the effect of chemotherapy on tumour size, or they may be patient-reported, such as less dysphagia after radiotherapy, reduced pain after opioid switch, etc. This contrasts with the outcome measures in implementation projects that focus on how the implementation process goes, and how healthcare providers adhere to the plan. Furthermore, the strategy is not to control the context as in randomised clinical trials, but to plan the process of change, repeatedly evaluate changes at all levels involved and adjust as necessary in iterative processes.

A prerequisite for success is to acknowledge that most changes in healthcare represent complex changes, given the complexity of organisational dynamics and the formal and informal social subsystems and rules. How these systems act and interact must be fully understood and all expected and potential barriers and facilitators must be identified upfront, with action plans at hand. Using a validated framework from implementation science can be beneficial when evaluating an implementation or designing an implementation study.

Important aspects in this context are:

- Performing a gap analysis that assesses the current situation, determines the goal state and shows the gap between the two

- The results of this analysis form the basis for the actions needed and the implementation plan
- Scoping the context in which the changes will take place
- Scoping available evidence-based guidelines
- Anchoring the project at all levels involved
- Identifying local barriers/facilitators
- Establishing an implementation team and identifying champions
- Developing the communication information and education plan
- Developing the evaluation plan

Some implementation science strategies are relatively similar and developed as an inherent part of the implementation process itself. One example is the Integrated Promoting Action on Research Implementation in Health Services (i-PARIHS) framework, which claims that successful implementation relies on essential factors of the context, the quality and type of evidence, and *the facilitation* of the evidence into practice. The phases of facilitation are related: *review and share, clarify and engage, assess and measure, act and implement,* in iterative cycles until uptake in practice. These principles are not very different from the Plan-Do-Study-Act model (the Deming or Shewhart Cycle), also emphasising the iterative process that creates more knowledge by each iteration. As most implementation projects are iterative by nature, changes underway provide important information about the best steps to succeed with the implementation.

An implementation plan that is specifically designed for the context in which the changes will take place, approved and supported in full by management at all levels, is instrumental. Implementing the use of checklists after hip surgery is fundamentally different from implementing mandatory nutritional screening in a cancer outpatient clinic. Failure to perform thorough and detailed planning bounces back with unexpected determinants that prevent the success of the implementation. Thus, it is essential to focus on, define and approach facilitators and barriers at all levels before start and during the process of change, and document the planned and the unexpected changes along the way to move forward.

Thus, any implementation, be it large or small, must focus on multiple organisational and individual levels, bottom-up and top-down, throughout the actual department, clinic or unit, and not only the patient–healthcare provider dyads. Common mistakes that prevent success are insufficient attention to the central role of the individual healthcare provider in determining the process and outcomes of implementation, and to the wider social and administrative consequences of the implementation.

How to Implement Nutritional Care as Part of Cancer Care, the Practical Perspective

First, it must be acknowledged by management at all levels that quality cancer care is not provided without nutritional care as an integrated part, followed by a decision to change prior to defining the project group. The intention and rationale must be understood by managers and stakeholders, and anchoring of the entire project, including the need for resources and the anticipated timeline, must be ensured at all relevant levels of the institution (Figure 1). These factors must also be shared and discussed with the multidisciplinary teams involved, on multiple occasions.

Barriers and facilitators must be identified, with plans for handling these. Notably, these may vary across the involved hospitals and units.

Following the implementation science way of thinking, the final outcome is the uptake of nutritional screening routines in the participating units: clinic, department and wards, by the individual healthcare providers. The latter is the unit of observation, whose performance and fidelity to the project serve as process indicators, coupled with descriptive data on the prevalence of screening to substantiate compliance. Thus, the selected multicomponent implementation strategy must be presented, discussed and revised as necessary prior to project start, supported by iterative educational and informational activities. These can focus on the evidence-based data from a scoping of current practice on nutritional assessment in the actual unit(s) and can consist of presentations about the experiences, change of professional roles, and how this improved patient outcomes by early adopters of nutritional screening programmes.

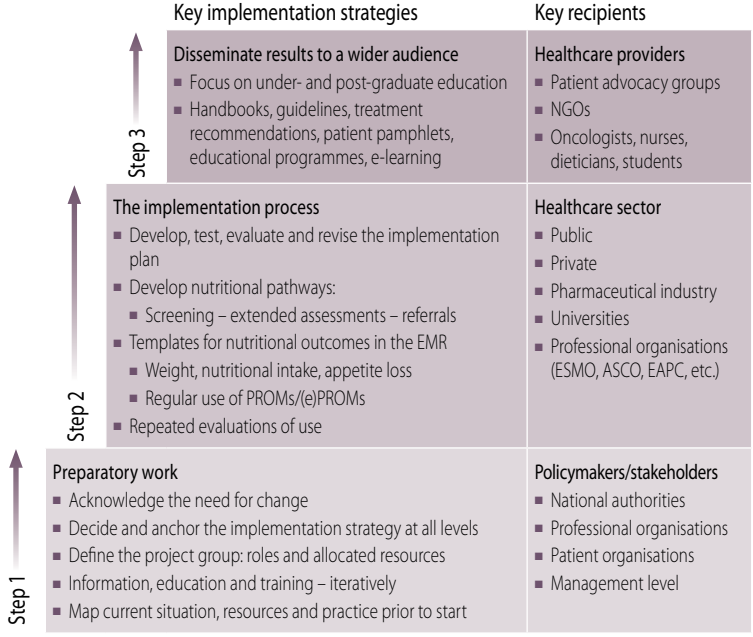

Figure 1 The nutritional care implementation ladder.

Abbreviations: ASCO, American Society of Clinical Oncology; (e)PROM, (electronic) PROM; EAPC, European Association of Palliative Care; EMR, electronic medical record; ESMO, European Society for Medical Oncology; NGO, non-governmental organisation; PROM, patient-reported outcome measure.

Provision of resources may facilitate uptake. This includes nomination and training of champions and super-users who can provide interactive assistance and clinical supervision, with allocated time to do this. Certain changes in the infrastructure are advantageous, for example, templates for mandatory registrations such as weight, nutritional intake and appetite loss in the electronic medical records (EMRs), alert functions connected to aberrant values in, for example, weight, body mass index (BMI) and metabolic risk factors, facilitated referral procedure to dieticians, etc. Developing standardised nutritional pathways in the EMRs for time- and/or needs-based nutritional screening, extended assessment and referrals is advantageous.

It is advisable to set a starting point early in the process, to ensure timely planning of the implementation strategy and assess for readiness at all levels before start. The overall implementation plan defines how the project or change will be executed, describes the reason behind the project and its defined goals, delineates all steps involved, presents the timeline and lists the resources, financial and human, that are necessary. In a clinical setting, the plan must be adapted to the different departments and units and be specified in detail.

In short, the implementation of nutritional care as an integrated part of cancer care is a stepwise and iterative process directed at multiple levels of healthcare, not only the healthcare provider–cancer patient dyads. Addressing the scientific importance of nutrition on treatment and patient-centred outcomes must go further than the individual clinical unit. Thus, recipients also include managers and policy makers, stakeholders, professional and lay healthcare organisations, and the pharmaceutical industry for initiation of substantially more clinical studies with nutrition-related primary outcomes.

Conclusion

Placing nutritional care higher on the agenda at all levels of healthcare in cancer gives momentum. The use of implementation science strategies increases the chances of successfully improving the quality of cancer care. This adheres to the explicit requirements of nutrition guidelines: that screening, prevention, detailed assessment, monitoring and treating of malnutrition should be done at all cancer clinics.

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Health Economics in Oncology Nutrition Research

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M.T. Fallon[1,2]

D.Yi[3]

B.J.A. Laird[1,2,4]

[1]*Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK*
[2]*Edinburgh Cancer Centre, NHS Lothian, Edinburgh, UK*
[3]*Cicely Saunders Institute of Palliative Care, Policy & Rehabilitation, King's College London, London, UK*
[4]*St Columba's Hospice Care, Edinburgh, UK*

Health economics can be a very emotive topic, particularly for patients and carers. Therefore, it is helpful to understand the general concepts, which are much broader than simply the financial cost of a particular medicine.

A key general concept is defining the value of healthcare, which can be considered as 'what is gained, relative to what is lost'. In this context, there are three value dimensions:

1. Societal: how well assets are distributed to different subgroups of the population (equity in resource distribution).
2. Technical: how well resources are used to improve outcomes for all (improving quality and safety of services).
3. Personal: how well the outcome relates to the values of each individual (understanding what matters most to the patient).

Contrary to popular misconception, value is not the same as quality of care or how much money is spent. High-quality care to the wrong patient or at the wrong time (or in the wrong place) is still low value. Similarly, better value is not necessarily achieved by higher expenditure. Nevertheless,

even to the right person at the right time, there will still be an inevitable cost. Clearly, maximising value in healthcare resources requires understanding both what we seek to achieve and the effectiveness of the means to achieve it; this is the purpose of health economics. People used to a universal healthcare system may struggle to see the value of healthcare, rather than perceive it as a basic right, and rarely question where these resources originate.

Defining Health Economics

So, what is health economics? 'Economics is a science which studies human behaviour as a relationship between ends and scarce means which have alternative use' (Robbins, 1932). Thus, economics is a science of choice. Health economics is therefore the science of choice within the healthcare context. The aim is to distribute a constrained health budget to maximise overall population health, as public and third sector healthcare providers have the objective of health maximisation using their fixed budget. The budget is insufficient to reimburse all desired care costs, therefore choices need to be made between interventions to prioritise those that provide the best patient outcomes per unit of expenditure. If investment is made in suboptimal treatments, then the benefits that may have been obtained from alternative treatments that fall outside the available budget are forgone. This 'lost health' is referred to as the opportunity cost, defined as 'the value of forgone benefit which could be obtained from a resource in its next-best alternative use'. Fundamentally, money that is spent on a certain intervention/treatment/drug cannot be spent on something else.

In reality, healthcare systems are so complex that the opportunity cost is typically not identifiable; that is, we do not know what other healthcare intervention we may have displaced. Defining a perspective of the health economic analysis is important as costs and benefits associated with interventions can be narrowed down. The economic evaluation framework quantifies the relevantly measured outcomes of specific health interventions and balances them against the cost, from a predetermined perspective of analysis (a societal or a national health system). With such a framework, we can therefore minimise 'waste' by identifying and

exchanging treatments that may be of minimal benefit for more effective ones. The complexities above can be applied to nutrition in cancer patients.

Measuring Economic Outcomes – Potential Approaches

In the field of oncology, the importance of optimising nutrition is becoming increasingly recognised. Many international guidelines advocate the importance of nutritional assessment and interventions alongside surgical and oncological treatments. However, there remains a paucity of evidence to support nutritional interventions. In a bid to redress this, the last decade has seen a rise in the number of oncology trials of nutritional interventions.

Specifically, these have often focused on cancer cachexia: disease-related malnutrition with systemic inflammation. Using lung cancer as an example (where there are 50 000 cases in the United Kingdom [UK] per year and, of these, approximately 20 000 have cachexia at diagnosis), the average patient incurs around £10 000 of secondary care costs in their first year after diagnosis. Therefore, if successful, identifying cachexia early in lung cancer has the potential to influence the care of 20 000 patients, and even a 25% reduction in costs associated with this would save the National Health Service (NHS) £50 million annually.

To date, late-phase trials have assessed the efficacy of interventions targeting appetite, muscle or combinations thereof, to prevent or treat cachexia. Such studies have had varying measures of success; however, with the potential for these therapies to enter routine oncology care, it is critical that they are deemed to be cost-effective. Yet, inbuilt economic evaluation of nutritional interventions in the field of oncology remains the exception rather than the rule.

Cost-Benefit Analysis

Cost-benefit analysis (CBA) compares the costs and effects of interventions, placing a monetary value on health benefits. It is difficult to

determine how much value to put on 'better appetite' from an oncology nutrition intervention, for example. However, results from CBA can be used for resource allocation decision-making in different healthcare settings. Cost-utility analysis (CUA) measures effects of interventions in combined quantity and quality. If weight gains from nutritional interventions enable cancer patients to better tolerate therapeutic interventions, leading to extended days of life, quality-adjusted life year (QALY) is a good outcome measurement in a trial. CUA studies are used routinely to inform resource allocations across different healthcare settings, but CUA does not include non-health effects (e.g. ability to work), which can be a major drawback. The focus of cost-effectiveness analysis (CEA) is the impact of interventions on the clinical outcome. Effects of interventions are measured in physical units (e.g. weight change, blood pressure). Results from several CEA studies can be compared as long as they employ the same outcome measurements (calorie intake or weight gain). In contrast, budget allocations among different healthcare settings cannot use the CEA results for decision-making.

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Task Force has developed a 24-item checklist of recommendations which researchers should consider when designing trials which have economic evaluation inbuilt. Specifically, model-based evaluation (including primary and secondary care) considering potential risks/benefits (e.g. survival advantage) may have relevance in oncology nutrition trials. A key consideration here is value for money and, in the cancer setting, where resources are finite in the face of increasingly expensive therapies; this is critical. These approaches are being incorporated in non-malignant trials but the principles are easily transferred to cancer. Brown et al (2020) propose that data collection for economic evaluation is prospectively planned alongside other assessments in randomised nutrition trials. They argue that this will help inform decision-makers about potential interventions to be implemented based on whether they provide value for money, or not. The primary outcome of trials may be of clinical interest and needs to be translated into health-related quality measures to be used in economic evaluations. Collecting health-related quality measures as a secondary outcome needs to be determined with a

consideration of characteristics of patients and interventions. Oncology nutrition interventions for life extension can use the EuroQol 5 Dimension (EQ-5D) or the 36-Item Short Form Health Survey (SF-36). However, these health-related quality measurements are not sensitive enough to record the possible changes made by interventions at the end of life. The Palliative care Outcome Scale for Economic evaluations (POS-E) based on the Integrated Palliative care Outcome Scale (IPOS) or ICECAP Supportive Care Measure (SCM) have been suggested as alternatives. It is also important to decide when to collect these outcome measures: is the trial endpoint the most appropriate endpoint for the economic evaluation?

This idea has been further conceptualised by O'Sullivan et al (2005). Termed 'piggyback' evaluation, it involves health-economic data being collected within the context of an otherwise typical clinical trial. The authors highlight key design and potential limitations in conducting such evaluations:

- Resource consumption in trials may differ from practice, and may not resemble real-world practice
- Casefinding can occur due to monitoring requirements in trials
- Participant compliance is reinforced in trials
- Data are collected for intermediate health outcomes versus longer term effects

These aspects present challenges for piggyback health-economic evaluation in clinical trials; however, they can be addressed. One option is to differentiate clearly between protocol costs and total costs. Casefinding can be addressed through randomised approaches if a comparator arm is present and even more so if blinding is included. However, one of the main ways to attenuate limitations of piggyback evaluations in clinical trials is to design studies that resemble clinical practice as much as possible. To illustrate, the control arm can be 'standard care' rather than any specific 'sham intervention', allowing a direct assessment of economic evaluation in as realistic a setting as possible.

Health Economics in Nutrition Research

In clinical nutrition, trial design is challenging for several reasons, including the adjunct nature of nutritional interventions, stratification, which is usually by disease rather than nutritional state, and the lack of consensus on a nutrition trial control group. It has also been argued that the key consideration is the choice of endpoints. Rather than using the classical endpoints of a biomedical model (e.g. survival) or patient-reported outcomes, a multi-component outcome model, where classical and patient-reported endpoints are combined, may be used but is dependent on study design and intervention.

Despite these observations, there remains a paucity of trials which address nutritional interventions in the oncology setting. Therefore, the practical application of nutritional evaluation in cancer nutrition trials needs further elucidation. However, such work is possible. A recent feasibility trial (Hall et al, 2021) examining an exercise and nutrition intervention for people with advanced cancer included health-economic analysis endpoints. This randomised trial with a standard-care control arm incorporated real-life economic data including health professional contact and hospital admissions. The analyses demonstrated that the experimental arm (nutrition/exercise intervention) was less expensive than the control arm. As such, should larger studies demonstrate efficacy and the intervention be considered for clinical practice, cost-saving tenets will support implementation in the clinic.

Another consideration is that the effect and objectives of a nutritional intervention are different at different stages of the clinical pathway. Prehabilitation and on-treatment support are now common concepts based on the theory that early identification and optimisation of nutritional status will synergise with the curative or palliative treatments. Here a cost per QALY endpoint is appropriate. Improved fitness for treatment will generally increase treatment costs but decrease toxicity/complications and related costs. At the other end of the spectrum is end-of-life care. Here the objectives are not to extend life, therefore QALYs may not be an appropriate outcome measure. Costs of care are borne by a mix of agencies including primary and secondary healthcare services, the third

sector (e.g. government, insurance companies), family, social services and the wider economy, for example where carers are taken out of the workplace.

More effort (collecting additional data even at extra time points) and resources (conducting economic analysis) can be challenging for clinicians or researchers working in oncology nutrition. However, health economics helps to cumulate evidence on the 'value for money' of nutritional interventions in oncology, which is key to serving patients in need and their families better. Developing guidelines or checklists for economic evaluations in oncology interventions may come next.

When considering analyses, different approaches are applicable and will be influenced by the stakeholder. Drug, device and food regulators will look at the safety, efficacy and quality of manufacture, whereas health technology assessors will evaluate efficacy and cost-effectiveness. This contrasts with patients and carers, where patient-centred outcomes are of most utility, while in routine clinical care, clinicians will value evidence-based medicine. Industry stakeholders are most interested in profitability and market access, whereas healthcare management will focus on budget impact and compatibility with service configuration.

When assessing health economics in oncology nutrition trials, a combination of clinical-efficacy assessment with real-world studies is needed to understand effectiveness. These should be embedded in the clinical pathway using appropriate implementation models, variation in care and outcomes. Such standards are achievable, but most importantly essential to assess truly the impact of oncology nutritional interventions.

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