Medical Nutrition International Industry

Better Care through Better Nutrition

VALUE OF MEDICAL NUTRITION IN ONCOLOGY

EVIDENCE DOSSIER 2020

Introduction

European health care systems overcome many challenges in the pursuit to provide cancer patients with the best of care, especially in the face of ever increasing economic and political pressures. Interventions that have been shown to improve patient outcomes whilst providing economic benefits should be integral to the planning and provision of safe and effective cancer care for all patients. Nutrition intervention with medical nutrition in the management of cancer-related malnutrition has been shown to have significant benefits both to patients and healthcare systems. Despite the guidelines and recommendations, many malnourished patients with cancer still do not receive nutritional support they need.

Policy-makers, payers and care providers need access to information that helps them to make informed, evidence-based decisions about the efficiencies in cancer care they recommend and provide. This dossier aims to synthesise all relevant information about the burden of malnutrition and high unmet needs in patients with cancer, relevant guidelines relating to medical nutrition in cancer care, and the rationale for and added value of medical nutrition as a key nutritional intervention strategy in the management of cancer-related malnutrition and involuntary weight loss.

This document (as an evidence repository) is intended to provide all stakeholders with an up-to-date and practical summary of all available evidence base on cancer-related malnutrition and the clinical, economic and humanistic value of medical nutrition interventions, including oral nutritional supplements (ONS), enteral tube feeding (ETF), and parenteral nutrition (PN).

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Medical Nutrition International Industry (MNI)

The Medical Nutrition International Industry (MNI) is the international trade association of companies providing products and services that support patient management and rehabilitation by the appropriate use of specialised nutritional support, including enteral and parenteral nutrition. The members of MNI are leading international companies in the development, manufacture and provision of Medical Nutrition and supporting services, namely Abbott, Baxter, B. Braun, Fresenius Kabi, FrieslandCampina Ingredients, Nestlé Health Science and Nutricia Advanced Medical Nutrition.

MNI's mission is to support the quality of nutritional interventions and services to best serve the interests of patients, healthcare professionals and healthcare providers, and to work to make specialised nutritional solutions available to more people around the world.

MNI nurtures and supports further research to fully explore the potential of Medical Nutrition in improving the health of patients suffering from acute or chronic disease. Working alongside key organisations in the nutritional care community such as the European Nutrition for Health Alliance (ENHA), an independent organisation that pursues a multi-stakeholder partnership in the European healthcare arena and the European Society for Clinical Nutrition and Metabolism (ESPEN), MNI promotes the transition of clinical nutrition research into standard practice through dissemination, support and implementation of best practices and guidelines related to malnutrition and Medical Nutrition. Through constructive engagement with policy makers, MNI aims to promote a balanced policy environment that enables the Medical Nutrition industry to meet the growing healthcare needs and expectations of its stakeholders. In collaboration with regulatory authorities and scientific bodies, MNI strives to shape a regulatory and reimbursement framework capable of meeting the needs of patients, healthcare professionals, payers and healthcare providers.

MNI is committed to achieving better care through better nutrition, across all ages and healthcare settings. Acutely aware of the pressures faced by healthcare organisations and that nutritional care is not always considered as an integral part of patient care, MNI aims to ensure that the evidence base for medical nutrition is available to decision makers and practitioners, thereby demonstrating the value of medical nutrition in improving patient outcomes and lowering the significant financial costs associated with malnutrition.

MNI also offers an annual grant to reward initiatives related to an optimal nutritional care approach. The grant selection is supported by ESPEN and the grant is awarded at the ESPEN Congress each year. Outlines of the annual submissions and winners as well as general information are available to view on the MNI website **http://medicalnutritionindustry.com/grant/mni-grant/**

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Medical Nutrition International Industry (MNI) members:

Contents

Abbreviations

AdHOC	Aged in home care project
AIOM	Italian Association of Medical Oncology
AML	Acute myeloid leukaemia
BIVA	Bioelectrical impedance vector analysis
BMI	Body mass index
CI	Confidence interval
CT	Computed tomography
DFS	Disease-free survival
ECOG	European Cooperative Oncology Group
EN	Enteral nutrition
EORTC	European Organisation for Research and Treatment of Cancer
ESPEN	European Society for Clinical Nutrition and Metabolism
ETF	Enteral tube feeding
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy - General
FFMA	Fat-free muscle area
GI	Gastrointestinal
GLIM	Global Leadership Initiative on Malnutrition
HADS-A	Hospital anxiety and depression scale – Anxiety
HADS-D	Hospital anxiety and depression scale – Depression
HAN	Home artificial nutrition
HPN	Home parenteral nutrition
HR	Hazard ratio
HRQoL	Health-related quality of life
ICDC	International consensus definition criteria
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
ITT	Intention-to-treat
kcal	Kilocalorie
kg	Kilograms
KPS	Karnofsky performance status
L3MMI	L3 muscle mass index
LC13	13-item Lung Cancer Questionnaire
LoS	Length of hospital stay
MD	Mean differences
MNA	Mini nutritional assessment

MST	Malnutrition screening tool
MUST	Malnutrition universal screening tool
NICE	National Institute for Health and Care Excellence
NR	Not reported
NRI	Nutritional risk index
NRS	Nutritional risk screening
NRS-2002	Nutritional risk screening (2002 method)
NS	Not significant
NSCLC	Non-small cell lung cancer
ONS	Oral nutritional supplement
OR	Odds ratio
OS	Overall survival
PA	Phase angle
PFS	Progression-free survival
PG-SGA	Patient-generated subjective global assessment
PN	Parenteral nutrition
PreMiO	Prevalence of Malnutrition in Oncology
PUFA	Polyunsaturated fatty acid
QALY	Quality-adjusted life year
QLQ-C30	Quality of life questionnaire-core 30
QoL	Quality of life
RCT	Randomised controlled trial
RFS	Relapse-free survival
RI	Remission induction
RR	Relative risk/risk ratio
SEOM	Spanish Society of Medical Oncology
SINPE	Society of Artificial Nutrition and Metabolism
SGA	Subjective global assessment
SMI	Skeletal muscle index
UK	United Kingdom
UTI	Urinary tract infection
VAS	Visual analogue scale
vs	versus
WLGS	Weight loss grading system

Glossary

BMI	Body mass index; weight (kg)/ height (m^2) <18.5 kg/m^2 – underweight 18.5 to 24.9 kg/m^2 – healthy weight 25 to 29.9 kg/m^2 – overweight 30 to 39.9 kg/m^2 – obese
Cachexia	Body weakness and wasting due to severe chronic illness
MNA	Mini nutritional assessment; 18-item scale assessing four different aspects: anthropometric assessment (BMI, weight loss, and arm and calf circumferences); general assessment (lifestyle, medication, mobility and presence of signs of depression or dementia); short dietary assessment (number of meals, food and fluid intake and autonomy of feeding); and subjective assessment (self-perception of health and nutrition) <17 – malnourished 17 to 23.5 – at risk of malnutrition ≥24 – normal nutritional status
MST	Malnutrition screening tool; 2-question screening tool assessing weight loss and appetite 0 to 1 – low risk of malnutrition 2 – moderate risk of malnutrition 3 to 5 – high risk of malnutrition
MUST	Malnutrition universal screening tool; assessment of BMI, unintentional weight loss in the preceding 3–6 months, and the presence of an acute disease resulting in absence of dietary intake for >5 days 0 – low risk of malnutrition 1 – moderate risk of malnutrition ≥2 – high risk of malnutrition
NRI	Nutritional risk index <83.5 – severe malnutrition 83.5 to 97.5 – moderate malnutrition 97.5 to 100 – mild malnutrition >100 – no malnutrition
NRS	Nutritional risk screening; based on weight loss, BMI, general condition, and amount of food intake in the preceding week, and patient's age and the severity of the underlying disease <3 – well nourished ≥3 – at risk of malnutrition/malnourished
Sarcopenia	Loss of skeletal muscle mass
SGA	Subjective global assessment A – well nourished B – at risk/moderately malnourished C – severely malnourished
SMI	Skeletal muscle index; calculated from image-based body composition analysis to provide an objective assessment of skeletal muscle quantity

Dossier purpose and audience

The Medical Nutrition International Industry association (MNI) conducted an evidence review based on a comprehensive systematic literature review (SLR) of the recently available scientific evidence for the management of cancer-related malnutrition in the European Union (EU). Best practice international guidelines were adhered to when conducting the SLR. Data sources included electronic databases, and handsearching covering conference proceedings, clinical trial registries and other grey literature sources.

According to the pre-approved search protocol and approved population, intervention, comparator(s), outcomes and study design (PICOS) elements for the review, all included evidence sources were screened and categorised to capture the type of evidence reported in each identified study (cancer-related malnutrition [epidemiology, clinical burden, humanistic burden and economic burden] and medical nutrition in oncology [clinical value, humanistic value, or economic value]) and the data reported for each category.

The evidence was reviewed, and a meaningful value story was developed with the aim of encouraging key stakeholders and decision-makers to make medical nutritional interventions an integral part of cancer care. A clear set of evidence-based claims and key value messages enable communication and engagement with health policy and decision makers, payers, healthcare providers and cancer patient organisations.

The dossier serves as a base and a primary source of information and all available evidence to support both internal alignment and external communications.

The geographic scope of the dossier is Europe, with a focus on the EU5.

The dossier is organised into the following sections:

- Executive summary
- Section 1: Background, including epidemiology of cancer-related malnutrition
- Section 2: Burden (clinical, quality of life, economic) of cancer-related malnutrition
- Section 3: Guidelines and clinical value of medical nutrition in oncology (including oral nutritional supplements [ONS], enteral tube feeding [ETF], and parenteral nutrition [PN])
- Section 4: Value (clinical, quality of life, economic) of cancer-related malnutrition
- References

Executive summary

Malnutrition in oncology

Malnutrition is common in adult patients with cancer, as both malignancy and therapeutic treatment may impact nutritional status. Studies in Europe show that in adult patients with cancer, the prevalence of malnutrition can be up to 30.9% (1), and up to 83% when looking at an older population (2). The prevalence of malnutrition increases with cancer progression (3), and can worsen during anti-cancer treatment (4, 5). Malnutrition in patients with cancer is known to occur across healthcare settings including in patients admitted to hospital (6), those living at home (7), and those in care homes (6), however it is still likely that malnutrition is under-recognised (8). Patients who are overweight or obese can also suffer from malnutrition and muscle loss; indeed 12.8% of patients with metastatic cancer who are overweight or obese in Europe were malnourished, and almost 50% were at risk of malnutrition (9).

Burden of disease

Cancer-related malnutrition, and an associated inflammatory response, can lead to break down of tissue and subsequent change in body composition, including skeletal muscle mass loss (10). This can have serious consequences for the patient, including increased mortality (11, 12), detrimental effects on anti-cancer treatments (e.g. dose-limiting toxicities, early termination of treatment, poor response) (13-15) and increased risk of post-operative (particularly serious) complications (16, 17). Malnutrition in patients with cancer is also associated with reduced functional capacity (18), psychosocial symptoms (18), and reduced health-related quality of life (19).

Direct medical costs are incurred when patients utilise healthcare resources such as healthcare professional consultations and hospitalisation. These are higher in patients with cancer and malnutrition or skeletal muscle loss (20-22). Studies have shown that patients with cancer who are malnourished or at risk of malnutrition have increased length of hospital stay (1, 20), and higher rates of readmission (23, 24) leading to increased healthcare resource utilisation (25, 26), and increased direct medical costs (20, 21).

Current guidelines and medical nutrition

European guidelines recommend early screening for nutritional risk and loss of skeletal muscle mass in patients with cancer (10, 27), and nutritional intervention in malnourished patients (10, 27). Nutritional support may be comprised of nutritional counselling, with or without artificial nutrition; either oral nutritional supplementation (ONS), enteral tube feeding (ETF) or parenteral nutrition (PN). However, despite the high prevalence of malnutrition amongst patients with cancer and clear guidelines, many malnourished patients with cancer still do not receive nutritional support (8).

Value of medical nutrition

Medical nutrition (ONS, ETF, or PN) is associated with improved clinical outcomes in patients with malnutrition (8, 28-31). These include lower weight loss (32), or even weight gain (28), improved survival (33), improved adherence and response to anti-cancer treatments (34, 35), and reduced risk of chemotherapy toxicity (32, 36). Furthermore, medical nutrition is associated with improved HRQoL in patients with malnutrition and cancer (37-40).

Medical nutrition is associated with lower direct medical costs (41), shorter hospital length of stay (41-43), and lower rates of complications (44, 45). Furthermore, medical nutrition is likely to be cost-effective (46).

Conclusions

The detrimental effects of malnutrition in patients with cancer are well acknowledged, however, despite the evidence, and the existence of clear guidelines, many malnourished patients with cancer still do not receive adequate nutritional support. There is a clear opportunity to improve recognition of this significant problem, leading to better patient outcomes and improved quality of life, and, consequently to reduction in use of healthcare resources and medical expenditure.

1. Background

Malnutrition is common amongst patients with cancer, regardless of healthcare setting and type of cancer

- Malnutrition is likely under-recognised (8) (Section 1.2.1)
- Malnutrition is common amongst patients with cancer, regardless of age (1-3, 16, 47-49) (Section 1.2.1)
- Advanced cancer is associated with higher prevalence of malnutrition than less-advanced cancer (3) (Section 1.2.1)
- Malnutrition is prevalent amongst patients with cancer, regardless of healthcare setting (6, 7, 50-52) (Section 1.2.2)
- Malnutrition and skeletal muscle mass loss are common regardless of cancer type (1, 53-57) (Section 1.2.3)
- Prevalence of malnutrition and skeletal muscle mass loss can worsen during anti-cancer treatment (4, 5, 58) (Section 1.2.4)
- Malnutrition and skeletal muscle mass loss are also prevalent in cancer patients who are overweight or obese (9) (Section 1.2.5)

1.1. Malnutrition in oncology

Patients with cancer are likely to develop malnutrition, as both malignancy and therapeutic treatment may impact nutritional status. Worldwide studies suggest the prevalence of malnutrition in patients with cancer can be up to 83%, with variations relating to cancer type, stage or patient age (2, 10).

Cancer-related malnutrition causes anorexia and tissue degradation, which leads to significant weight loss, changes in body composition and decreased functional capacity (10, 27, 59). Additional clinical complications of malnutrition, namely cachexia and sarcopenia, impact severely on patient functionality. Cancer cachexia is characterised by involuntary wasting of body mass, leading to body weakness. Patients with cachexia suffer from sustained weight loss and loss of skeletal muscle mass, which may be accompanied by loss of fat mass (59). Notably, cachexia is not always present in all malnourished patients, whereas all cachectic patients suffer from malnutrition (60). Sarcopenia, however, is exclusively characterised by loss of skeletal muscle mass, affecting strength and functional capacity of patients. Malnourished patients with cachexia and/or sarcopenia present with a higher risk of treatment-related toxicity, treatment discontinuation, poor response to treatment, including surgery, lower activity level, impaired quality of life (QoL) and poorer prognosis (61).

1.2. Prevalence of malnutrition in oncology

1.2.1. Malnutrition is prevalent amongst adult patients with cancer

Malnutrition is common in adult patients with cancer. Studies in Europe show that in adult patients with cancer, the prevalence of malnutrition can be as high as 83% when looking at an older population (Table 1).

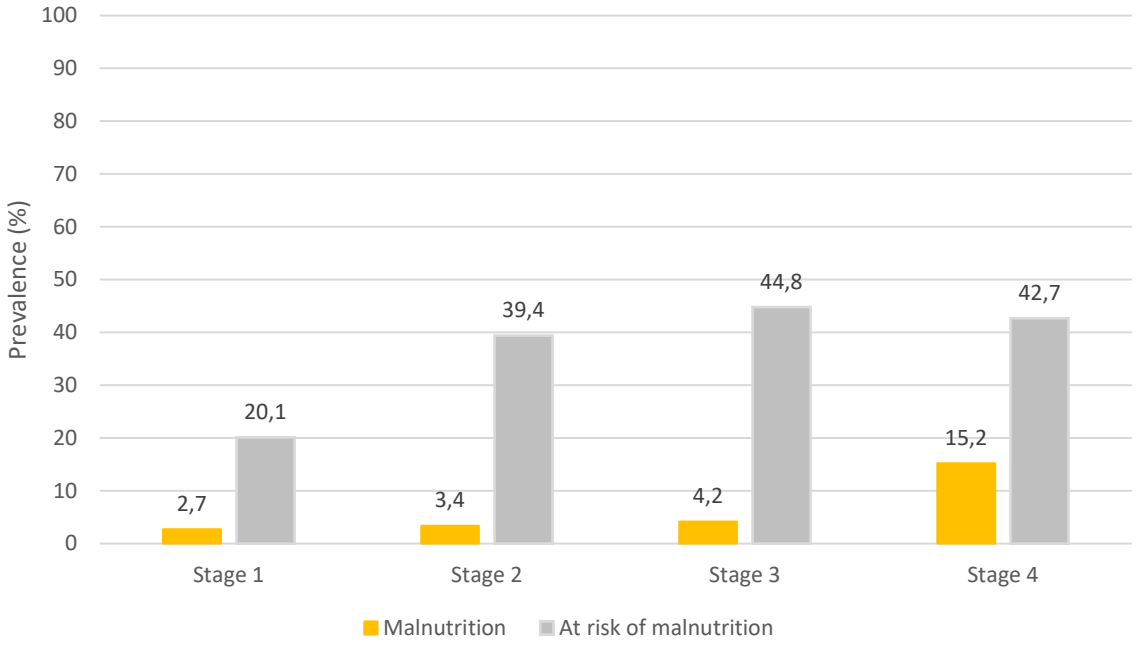
Table 1: Prevalence of malnutrition in adult patients with cancer

Country (reference)	Patient population	Measure used	Prevalence
Global (2)	Patients (>65 years) with solid malignancies scheduled to receive chemotherapy N=7,499	Various	• Malnutrition: up to 83% • At risk of malnutrition: 15–69.3%
Austria (62)	Patients (>70 years) with newly diagnosed haematological malignancies N=147	MNA	• Malnourished: 15% • At risk of malnutrition: 43%
France (1)	Patients (>18 years) hospitalised with cancer N=1,545	Nutricode BMI Weight loss	• Malnutrition: 30.9% ○ Moderate: 18.6% ○ Severe: 12.2%
France (48)	Younger (<70 years) vs older (≥70 years) patients Younger N=1,517; older N=578	Weight loss BMI Albuminemia	• Malnourished ○ <70 years: 36.7% ○ ≥70 years: 44.9%
France (49)	Patients (>70 years) receiving first-line chemotherapy N=364	MNA	• Malnourished: 12.9% • At risk of malnutrition: 52.3%
France (63)	>65 years with a diagnosis of solid cancer or hematologic malignancy N=266	MNA	• Malnourished: 17% • At risk of malnutrition: 47%
Germany (16)	Patients (>18 years) admitted to the Department of Radiation Oncology in a German hospital N=666	NRS	• Malnourished or at risk of malnutrition: 40.95%
Netherlands (64)	Patients (≥70 years) with head and neck cancer N=102	MNA	• Malnourished or at risk of malnutrition: 39.2%
Italy (3)	PreMiO study; treatment-naïve oncology patients (>18 years) N=1,952	MNA	• Malnourished: 8.7% • Risk of malnutrition: 42.4%
Netherlands (65)	Patients (>70 years) with non-Hodgkin lymphoma N=44	MNA	• Malnourished or at risk of malnutrition: 34%
UK (47)	Adult outpatients (age=NR) at a hospital trust N=207	NST	• Risk of malnutrition: 45–83%, depending on tumour site ○ Urological: 45% ○ Colorectal: 50% ○ Breast: 60% ○ Gynaecological 73% ○ Lung/mesothelioma: 76% ○ Upper GI: 83%

Abbreviations: BMI, body mass index; MNA, mini nutritional assessment; NR, not reported; NRS, nutritional risk screening; NST, nutritional screening tool.

Data from the Italian PreMiO study of treatment-naïve oncology patients showed that the prevalence of malnutrition increased with advancing cancer stage from 2.7% in those with Stage 1 cancer to 15.2% in those with Stage 4 (Figure 1) (3).

Figure 1: Prevalence of malnutrition in patients with cancer, by cancer stage



Source: Muscaritoli, 2017 (56).

A systematic review of cancer cachexia (identified using the search terms cachexia, weight loss, or malnutrition) in the European Union (EU) estimated that in 2013, the prevalence of cancer cachexia was 30% of patients at risk (56).

It is likely that malnutrition is under-recognised. In an analysis of French data, 10% of cancer patients were diagnosed with malnutrition at first hospitalisation and 13% were subsequently diagnosed (77% had no malnutrition diagnosis) (8). This was lower than the expected prevalence of malnutrition in these patients suggesting that, in clinical practice, cancer-related malnutrition is under-recognised, and under-treated (8).

1.2.2. Malnutrition is prevalent in patients with cancer across healthcare settings

Malnutrition in patients with cancer is known to occur across healthcare settings including in patients admitted to hospital, those living at home, and those in care homes (Table 2).

A UK survey of malnutrition reported that the prevalence of malnutrition was significantly higher amongst patients in hospital with cancer (34%) than those without cancer (23%) ($p<0.001$), and also amongst patients in care homes with cancer (55%) than those without cancer (40%) ($p=0.164$) (6). Similarly, a German study of cancer patients showed that the prevalence of malnutrition was 38.2% in patients with malignant disease compared with 13.0% in patients with non-malignant disease (51).

Table 2: Prevalence of malnutrition in adult patients with cancer, across care settings

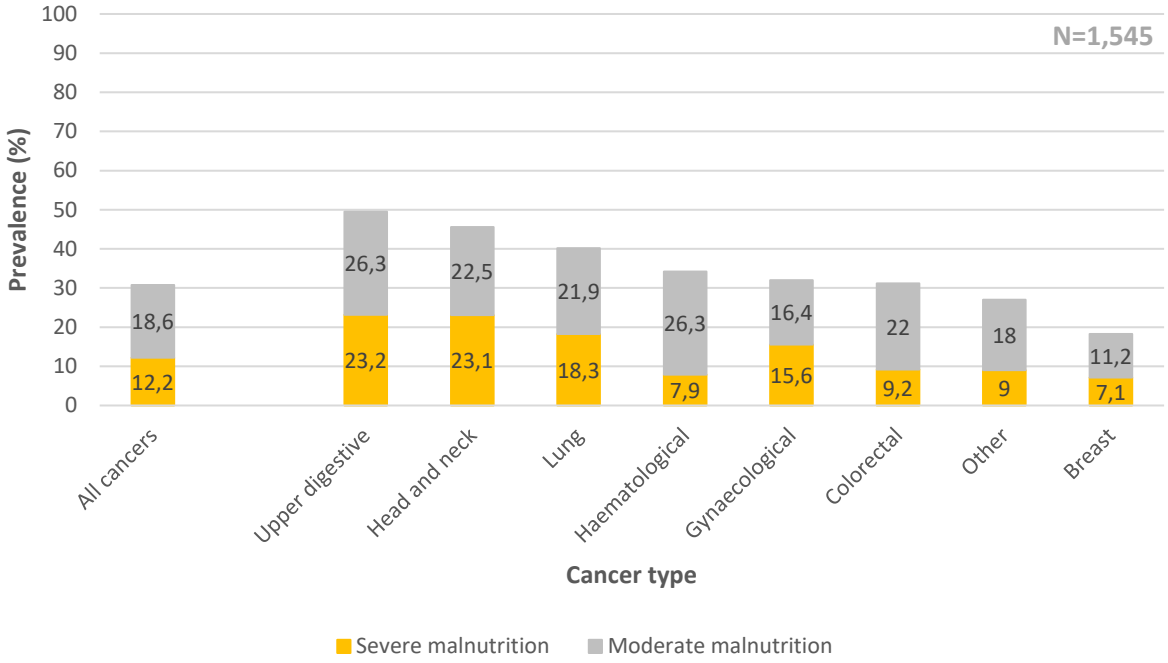
Country (reference)	Patient population	Measure used	Prevalence
In hospital			
UK (6)	Patients being admitted to hospital N=7,541, 15% of whom had cancer	MUST	• Malnourished: 34%
Ireland (6)	Patients being admitted to hospital N=1,102, 13% of whom had cancer	MUST	• Malnourished: 34%
Germany (51)	Cancer patients in hospital N=455	NRS-2002	• Malnourished: 38.2%
France (50)	Patients (≥18 years) hospitalised with cancer N=2,068	BMI	• Malnutrition: 39% ○ Pancreas: 66.7% ○ Oesophagus and/or stomach: 60.2% ○ Head and neck: 48.9% ○ Lung: 45.3% ○ Ovaries/uterus: 44.8% ○ Colon/rectum: 39.3% ○ Leukaemia/lymphoma: 34.0% ○ Breast: 20.5% ○ Prostate: 13.9%
In care homes			
UK (6)	Patients recently admitted to care homes N=523, 6% of whom had cancer	MUST	• Malnourished: 55%
At home			
Europe (7)	Older patients (≥65 years) with cancer in the Aged in Home Care (AdHOC) project N=321	Weight loss	• Severe malnutrition: 5.3% • Unintended weight loss: 22.1%
Community-dwelling			
Belgium & Denmark (52)	Older patients (≥70 years) N=274	MNA-SF	• Malnutrition: 66.1%

Abbreviations: BMI, body mass index; MNA-SF, mini nutritional assessment – short form; MST, malnutritional screening tool; MUST, malnutrition universal screening tool

1.2.3. Prevalence of malnutrition and muscle loss varies by cancer type

Malnutrition is prevalent in patients with cancer, regardless of the cancer site. In a French study of adults with cancer, the prevalence of malnutrition ranged from 18.3% in breast cancer to 49.5% in upper digestive cancer (Figure 2) (1). Further information on prevalence of malnutrition according to tumour site is available in Appendix A.

Figure 2: Estimated prevalence of malnutrition in France, by cancer type

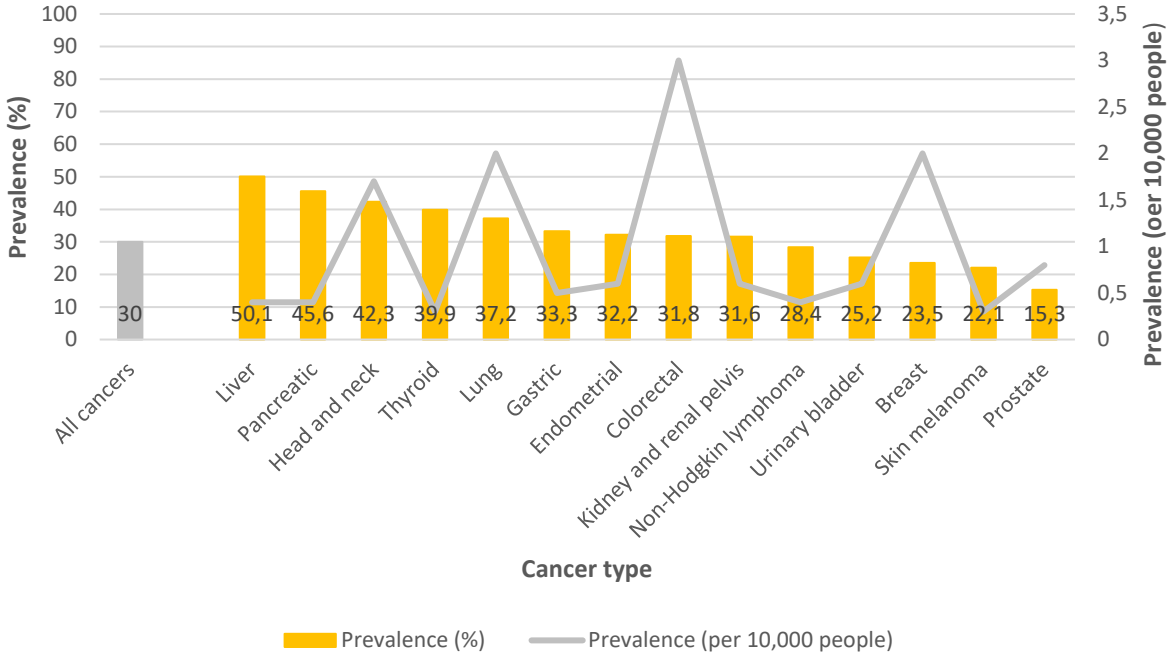


Source: Pressior, 2010 (1).
Malnutrition was defined following the recommendation of the French health authority (Haute Autorite´ de Sante´) and by the Nutricode labelled by the French society of parenteral and enteral nutrition 2006 using age (in years), BMI (in kg/m^2) and weight loss (in percentage over the previous 6 months). In patients ≤70 years, moderate malnutrition was defined as ≥10% weight loss over past 6 months or BMI <18.5 kg/m^2 and severe malnutrition as ≥15% weight loss over past 6 months or BMI <16 kg/m^2. In patients >70 years, moderate malnutrition was defined as ≥10% weight loss over past 6 months or BMI <21 kg/m^2 and severe malnutrition as ≥15% weight loss over past 6 months or BMI <18 kg/m^2.

A study of Italian patients with symptomatic oesophageal cancer showed that longer time to diagnosis was an independent predictor of severe malnutrition at diagnosis (increasing by 0.3% for each additional week, by 0.7% for every additional 2 weeks, or by 1.3% for every additional month) (66).

Cancer cachexia is prevalent across the EU. A systematic review of cancer cachexia in the EU estimated that in 2013, the prevalence of cancer cachexia was 30% of patients at risk of cachexia (i.e. patients with a diagnosis of cancer, but excluding those considered cured after 5 years of follow-up), equating to 15.8 per 10,000 people (Figure 3) (56). Cancer cachexia was most prevalent amongst patients with liver cancer, at 50.1%.

Figure 3: Estimated prevalence of cancer cachexia in the EU



Source: Anker, 2009 (56).

1.2.4. Prevalence of malnutrition and skeletal muscle mass loss can worsen during anti-cancer treatment

Data shows that the prevalence of malnutrition can increase during anti-cancer treatment. In a French study of patients undergoing allogeneic hematopoietic stem cell transplantation (N=84), 26% of patients were malnourished at hospital admission, rising to 57% at hospital discharge (4). Further data from a Slovenian study of patients with head and neck cancer (N=55) showed that before treatment, 16.4% of patients were malnourished, rising to 45.4% post-treatment (5).

Skeletal muscle mass loss can also become more prevalent during anti-cancer treatment. In a sample of 123 patients undergoing surgery for oesophageal cancer in the Netherlands, sarcopenia was present in 56% and 67% of patients before and after chemoradiotherapy, respectively (67). A systematic review of patients with pancreatic cancer (10 studies, including EU studies; N=1,685) showed that the prevalence of sarcopenia ranged from 29.7% to 65% in patients of normal weight (BMI 18.5–24.9 kg/m^2), and from 16.2% to 67% in patients who were overweight or obese (BMI >25 kg/m^2) (58). In Slovenian patients with head and neck cancer (N=55), 14.5% of patients were cachectic before treatment, rising to 38.2% post-treatment (5).

1.2.5. Malnutrition and skeletal muscle mass loss are also prevalent in cancer patients who are overweight or obese

Patients who are overweight or obese can also suffer from malnutrition and skeletal muscle mass loss. In a study of metastatic cancer patients who were overweight or obese in Europe (N=594), 12.8% of patients were malnourished (Mini Nutrition Assessment [MNA] <17), and almost 50% were at risk of malnutrition (MNA 17 to 23.5) (9). In a French study of adults with cancer (N=1,545), patients with obesity (BMI ≥30 kg/m^2 at 6 months before study start) were more prone to malnutrition vs those with normal body weight (38.8% vs 28.5%, p<0.01) (1).

In a systematic review of patients with pancreatic cancer (10 global and EU studies; N=1,685), the prevalence of sarcopenia ranged from 16.2% to 67% in patients who were overweight or obese (BMI >25 kg/m^2) (58).

2. Burden of disease

Malnutrition is associated with a significant clinical burden including increased mortality and a detrimental impact on anti-cancer treatments

- Malnutrition is associated with loss of skeletal muscle mass (68) (Section 2.1.1)
- Malnutrition and skeletal muscle mass loss are associated with increased mortality (69, 70) (Section 2.1.2)
- Malnutrition and loss of skeletal muscle mass are associated with increased mortality in cancer patients who are overweight or obese (71) (Section 2.1.3)
- Loss of skeletal muscle mass has a detrimental effect on patients' response to anti-cancer treatment (13, 65, 72-74) (Section 2.1.4)
- Patients with malnutrition or sarcopenia are at increased risk of post-operative complications (17, 75) (Section 2.1.5)

Malnutrition in cancer patients is associated with a humanistic burden including poorer HRQoL and reduced functional capacity

- Malnutrition and muscle loss in cancer patients are associated with reduced HRQoL (19, 76) (Section 2.2.1)
- Malnutrition and skeletal muscle mass loss in cancer patients are associated with reduced functional capacity (76) (Section 2.2.2)
- Malnutrition and skeletal muscle mass loss in cancer patients are associated with psychosocial symptoms (76, 77) (Section 2.2.3)

Malnutrition and loss of skeletal muscle mass in cancer patients are associated with a significant economic burden

- Length of hospital stay is increased in malnourished cancer patients (1, 20) (Section 2.3.1)
- Readmission rates are increased in malnourished cancer patients, or those with skeletal muscle mass loss (23) (Section 2.3.2)
- Healthcare resource use is increased in cancer patients with malnutrition or skeletal muscle mass loss (25, 26) (Section 2.3.3)
- Direct medical costs are increased in cancer patients with malnutrition or skeletal muscle mass loss (20, 22) (Section 2.3.4)

2.1. Clinical burden of malnutrition in patients with cancer

2.1.1. Malnutrition is associated with loss of skeletal muscle mass

Cancer-related malnutrition, and an associated inflammatory response, can lead to break down of tissue and subsequent change in body composition, including skeletal muscle mass loss (10). Both inactivity, resulting from disease burden, and cancer treatment can have serious adverse effects on

skeletal muscle mass (78, 79). Loss of lean body mass can lead to sarcopenia, which can impact significantly on patient functionality, physical strength, and QoL (80).

In a French and Belgian study of patients with non-small cell lung cancer (NSCLC) (N=531), skeletal muscle mass loss was observed in 66.7% of patients with cachexia, and skeletal muscle mass loss with no clinically significant weight loss was observed in 66.3% of patients with pre-cachexia (68).

2.1.2. Malnutrition and skeletal muscle mass loss are associated with increased mortality

Malnutrition results in reduced survival in patients with cancer. In a study of Spanish oncology patients admitted to hospital (N=168), poor nutritional status (MNA <17.5) was associated with increased mortality, with a 3-fold increased risk of mortality (odds ratio [OR] 3.74 [95% confidence interval [CI]: 1.37 to 10.21], p=0.01), regardless of disease stage and age of patient (11). Analysis of a cohort of Irish cancer patients in palliative care (N=1,027), showed that weight loss of >10% in the preceding 3 months was associated with reduced survival (hazard ratio [HR] 2.501 [95% CI: 1.425 to 4.389], p=0.001) (12).

Further studies of skeletal muscle mass and mortality also show that the risk of mortality increases with skeletal muscle mass loss. A systematic review, including EU studies, examining the relationship between imaging-based body composition and systemic inflammation in patients with cancer showed that in 10 studies (N=5,202), low skeletal muscle index (SMI) was associated with shorter overall survival (OS) (69). A further systematic review and meta-analysis of patients with solid tumours (37 studies including EU studies; N=7,779) also showed that low SMI was associated with poor OS (81). Low SMI (vs high SMI) was associated with significantly poorer OS (HR 1.44 [95% CI: 1.32 to 1.56], p<0.001) (81). A systematic review assessing the impact of computed tomography (CT)-assessed sarcopenia on outcomes (13 studies, including EU studies N=2,884), found that sarcopenia was a significant independent predictor for reduced OS in the majority of studies that reported it (82). In a study of Italian and German patients with cancer (N=1,084), low creatinine height index (a body composition parameter) was independently associated with increased mortality (83). In Italian patients, there was an 84% increased risk of mortality (HR 1.84 [95% CI: 1.18 to 2.86], p=0.007), and in German patients there was a 52% increased risk (HR 1.52 [95% CI: 1.17 to 2.07], p=0.008).

Studies of patients with specific cancer types have shown that mortality is increased in patients with malnutrition or muscle loss – further details on these studies are provided in Appendix B.

In older patients (≥65 years) with cancer, a systematic review and meta-analysis (10 studies, including EU studies; N=4,692), found that malnutrition was significantly positively associated with increased risk of all-cause mortality (relative risk [RR] 1.73 [95% CI: 1.23 to 2.41]) compared with those with good nutritional status (70). Analyses in older French patients (>70 years of age) receiving first-line chemotherapy (N=364), showed that 1-year mortality was 70.5% in malnourished patients (MNA <17), 48.9% in those at risk for malnutrition (MNA 17 to 24), and 26.5% in those considered as well nourished (MNA ≥24) (49). Further analyses showed that in older (60–95 years) German patients with cancer (N=439), sarcopenia was independently associated, and nearly as predictive as an advanced disease stage for 1-year mortality, highlighting the importance of preservation of skeletal muscle mass and function (84).

2.1.3. Malnutrition and loss of skeletal muscle mass are associated with increased mortality in patients who are overweight or obese

The risk of mortality is also increased in patients who are overweight or obese. In metastatic cancer patients who were overweight or obese in the EU, median OS decreased with worsening nutritional status assessed with MNA (9). OS in well-nourished patients (MNA ≥24) was 17.8 months vs 8.2 months in patients at risk of malnutrition (MNA 17 to 23.5) vs 6.4 months in malnourished patients (MNA <17) (p<0.001).

A systematic review of patients with pancreatic cancer (11 studies, including 5 EU studies; N=2,297), showed that sarcopenia was associated with a 49% increased risk of mortality (adjusted HR 1.49 [95% CI: 1.27 to 1.74]), with the risk increasing two-fold in patients with sarcopenic obesity (adjusted HR 2.01 [95% CI: 1.55 to 2.61]) (85). Further analysis in an Austrian study of patients with resectable pancreatic ductal adenocarcinoma and sarcopenia, showed that OS was reduced from 23 months in patients with normal body weight (BMI <25 kg/m^2) to 14 months in patients who were overweight or obese (BMI ≥25 kg/m^2) (p=0.007) (71).

2.1.4. Loss of skeletal muscle mass has a detrimental effect on patients' response to anti-cancer treatment

Patients with loss of skeletal muscle mass during anti-cancer treatment experience poorer survival (Section 2.1.4.1), increased dose-limiting toxicity (Section 2.1.4.2), and poorer adherence to treatment (Section 2.1.4.3).

In a study of patients with locally advanced gastric cancer (N=48), more patients with sarcopenia than without sarcopenia experienced dose-limiting toxicity (64% vs 39%, p=0.181) (13). A similar trend was observed in patients with sarcopenic obesity compared with those without sarcopenia (80% vs 42%, p=0.165). Furthermore, more patients with sarcopenia (64% vs 28%, p=0.069) and sarcopenic obesity (100% vs 28%, p=0.004) terminated chemotherapy early compared with those without sarcopenia (13).

2.1.4.1. Loss of skeletal muscle mass during anti-cancer treatment is associated with increased mortality

Studies in patients with gastrointestinal (GI) cancer show that survival is lower in patients with lower skeletal muscle mass (72, 73). In Finnish patients with oesophageal cancer (N=115), a 2.98% decrease in skeletal muscle index during neoadjuvant treatment was associated with a poorer 2-year survival (p=0.04) (72), and in German patients with hepatic malignancies (N=56), sarcopenic patients with a low psoas muscle index (<13.39 mm/m^2) had a significantly lower median OS of 491 days vs 1,291 days for patients with psoas muscle index >13.39 mm/m^2 (73). Another study in patients with liver-predominant metastatic colorectal cancer undergoing radioembolization (N=77) indicated a significantly increased OS for patients with high fat-free muscle area (FFMA) compared with patients with low FFMA (median OS 273 vs 128 days; p=0.017) using Kaplan-Meier analysis. On multivariate Cox regression analysis, OS was best predicted by FFMA (HR 2.652; p<0.001) (86). In patients with advanced hepatocellular cancer treated with a kinase inhibitor (N=96), patients with sarcopenia showed significantly shorter OS than in patients without sarcopenia (39 weeks vs 61 weeks, p=0.02) (87).

2.1.4.2. Malnutrition and loss of skeletal muscle mass is associated with anti-cancer treatment dose toxicity

Patients with cancer often require intensive or chronic therapy to prevent disease progression or recurrence, which can result in significant toxicity (88). Treatment-related toxicity limits the delivery of appropriate doses of chemo- or radiotherapy and targeted therapies, encouraging treatment discontinuation and potentially having a detrimental effect with regards to future disease recurrence (89). Treatment strategies should therefore consider approaches which reduce cancer therapy-related toxicity (90). In patients receiving chemotherapy for the treatment of GI cancer, malnutrition was an independent predictor of toxicity-related chemotherapy dose-reductions (91). Therefore, underlying malnutrition in patients with cancer may be associated with increased treatment dose toxicity and adverse effects.

In a French study of patients with metastatic colorectal cancer (N=168), malnutrition according to Patient-Generated Subjective Global Assessment (PG-SGA; PG-SGA ≥9) was significantly associated with chemotherapy-related grade ≥2 clinical toxicities (OR 3.7 [95% CI: 1.7 to 8.4], p=0.001) (74).

Sarcopenia is a significant predictor of dose-limiting toxicity (92), and patients with low skeletal muscle mass have been seen to experience dose-limiting toxicity more frequently than those with normal skeletal muscle mass (44.3% vs 13.7%, p<0.001) (93). In a systematic review of studies reporting on the quantitative evaluation of cancer cachexia (53 studies, including EU studies, N=9138), 12 of 14 studies reported that sarcopenia had a significant association with increased incidence of dose-limiting toxicity or severe toxicity, regardless of cancer site or type of systemic therapy, with the exception of the toxicity of localised hepatic arterial infusion (94). In Dutch patients with metastatic colorectal cancer (N=414), a decrease in skeletal muscle index of more than 2% during chemotherapy treatment was associated with a 29% increased risk of dose-limiting toxicities (RR 1.29 [95% CI: 1.01 to 1.66]) (95). In a French study of patients who had undergone cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (N=97), sarcopenic patients experienced significantly more chemotherapy toxicities (57 vs 26 %; p=0.004), especially neutropenia (36 vs 17 %; p=0.04). In the multivariate analysis, sarcopenia was the only parameter independently associated with the risk of chemotherapy toxicity (OR 3.97 [95% CI: 1.52 to 10.39], p=0.005) (96). In patients with locally advanced head and neck squamous cell carcinoma receiving chemoradiation (n=100), dose-limiting toxicity was significantly higher in cachectic patients compared with non-cachectic patients (57% vs 25%; p=0.004) (97).

2.1.4.3. Malnutrition and sarcopenia are associated with lower adherence to anti-cancer treatment

Early treatment withdrawal in patients with cancer may be attributed to a number of reasons, namely, dose-related toxicities, prevalence of adverse events, worsening of comorbidities (e.g. malnutrition, sarcopenia) and decline of general condition (65). In particular, cancer-associated malnutrition increases treatment-associated side-effects, which may encourage treatment withdrawal (98).

In older Dutch patients with non-Hodgkin lymphoma (N=44), malnutrition was significantly associated with early treatment withdrawal (OR 8.29 [95% CI: 1.24 to 55.6], p=0.03) (65). Half of the patients withdrawing early from treatment had haematological toxicity Grade 3–4.

Similar effects are seen in studies of sarcopenia and cachexia. In German patients with locally advanced, gastric or gastro-oesophageal junction cancer (N=60), significantly more patients with sarcopenia terminated their chemotherapy earlier (50% vs 22.6%, p=0.037) (99), and in a UK study of

patients with NSCLC (N=24), cachexia was associated with a reduced number of chemotherapy cycles completed (*r*=0.431, p=0.03) (100).

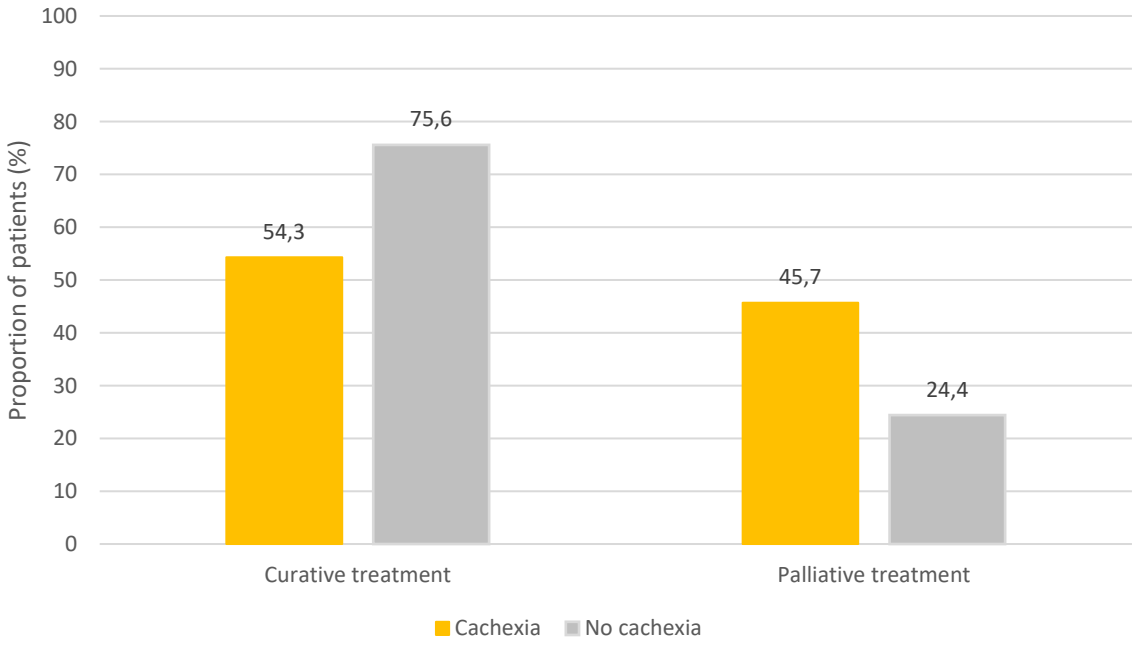
2.1.4.4. Loss of skeletal muscle mass are associated with a poor response to anti-cancer treatments

Loss of skeletal muscle mass is associated with a poor response to anti-cancer treatments. In a systematic review and meta-analysis of hepatocellular carcinoma patients (4 studies, including EU studies; N=586), sarcopenia was associated with increased risk of tumour recurrence (adjusted HR 1.76 [95% CI: 1.27 to 2.45]) (14), and in a systematic review and meta-analysis of head and neck cancer patients (11 studies, including EU studies; N=2,483), sarcopenia was associated with poorer OS (HR 1.97 [95% CI: 1.71 to 2.26]) and relapse-free survival (RFS; HR 1.74 [95% CI: 1.43 to 2.12]) (15).

In patients with advanced pancreatic cancer (N=165), early loss of skeletal muscle mass of ≥10% was associated with worse progression-free survival (PFS; HR 2.31 [95% CI: 1.30 to 4.09] p=0.004) vs <10% (101). A further study in patients with metastatic NSCLC treated with immune checkpoint inhibitors (N=55) showed that patients with cachexia had lower response rates (4% vs 37%, p=0.002), disease stabilisation rates (32% vs 81%, p=0.003), and shorter PFS (3.7 months vs 8.2 months, p=0.008) compared with patients without cachexia (102).

In a German study of patients with various types of cancer (N=503), 75.6% of patients without cachexia received curative treatment, dropping to 54.3% of patients with cachexia (Figure 4) (76).

Figure 4: Prevalence of malnutrition in patients with cancer, by cancer stage



Source: Schwarz, 2017 (76).

2.1.5. Patients with malnutrition or sarcopenia are at increased risk of post-operative complications

Post-operative complications can present as intra-abdominal infections, wound site infections, abscesses, thromboembolism and pneumonia, and pose significant morbidity on the patient (103). Moreover, post-operative complications may increase cancer recurrence rates (103), and also impact

negatively on DFS and OS (104). Certain cancer patients are of an increased risk of developing post-operative complications, particularly if they present with a comorbidity (e.g. diabetes, obesity).

Of adult patients (N=666) admitted to the Department of Radiation Oncology in a German hospital, more patients who were malnourished, or at risk of malnutrition (NRS score ≥3) experienced complications than those who were not at risk of malnutrition (68.60% vs 57.46%, p=0.0011) (16). In a study of Italian patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with a healthy BMI (18.50–24.99 kg/m^2), those who were malnourished were more prone to postoperative (53% vs 35%, p<0.05) and infectious complications (32.6% vs 9.8%, p<0.01) than well-nourished patients (17). There was also a trend for more serious post-operative complications (13.7% vs 23.4%, p=not significant [NS]) in malnourished patients.

In a meta-analysis of 53 studies, including EU studies (N=14,295), preoperative sarcopenia was associated with an increased risk of severe postoperative complications (75). Overall, 20% of patients experienced severe post-operative complications; including 24% of patients with sarcopenia and 18% or patients without sarcopenia, resulting in a 44% increased risk in patients with sarcopenia (pooled OR 1.44 [95% CI: 1.24 to 16.8], p<0.001).

Studies investigating the effects of malnutrition and muscle loss on post-operative complications also show similar results in GI cancer (105, 106), head and neck cancer (107), and lung cancer (108). Further details on studies of individual cancer types are provided in Appendix C.

2.2. Quality of life burden of malnutrition in patients with cancer

2.2.1. Malnutrition and skeletal muscle mass loss in cancer patients are associated with reduced HRQoL

Malnutrition imparts a significant burden on patients with cancer, leading to prolonged hospital stays, increased treatment-related toxicity, impaired QoL and overall, a poorer prognosis (61). A number of studies have reported the significant effects of malnutrition on QoL, including physical functionality, emotions, cognitive functioning, and appetite (109). In Irish patients with terminal cancer (N=1,027) increasing levels of weight loss (graded using a BMI-adjusted weight loss grading system [WLGS]) were associated with poorer health-related QoL (HRQoL; measured using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item [EORTC QLQ-C30]), including a number of functional- (physical, role, emotional, cognitive, social, and global health) and symptom-related (fatigue, nausea and vomiting, pain, appetite loss, and dyspnoea) measurements (19).

In a prospective study of Spanish patients with resected cancer (N=747), the risk of malnutrition was found to be strongly associated with HRQoL in all three scales tested (functional, symptom and global; p<0.001 for each) (110). In a separate Polish study of patients with NSCLC (N=180), univariate analysis revealed that malnutrition was significantly correlated with decreased QoL using the EORTC QLQ-C30 and LC13 questionnaires (111). Further, in a prospective study of Irish adult oncology patients undergoing chemotherapy (N=1,015), percentage of weight loss was the biggest predictor of global QoL (112). In Spanish patients undergoing curative gastric cancer resection (N=76), patients with ≥10% body weight loss at two years post-surgery had lower scores in all items of the functional scales of EORTC QLQ-C30 than those without (113).

Cancer cachexia is also associated with reduced HRQoL. In a German study of patients with various types of cancer (N=503), patients with cachexia had significantly lower EORTC QLQ-C30 Global Health scores (median 50 vs 58 for non-cachectic patients; p<0.001) (76).

2.2.2. Malnutrition and skeletal muscle mass loss in cancer patients are associated with reduced functional capacity

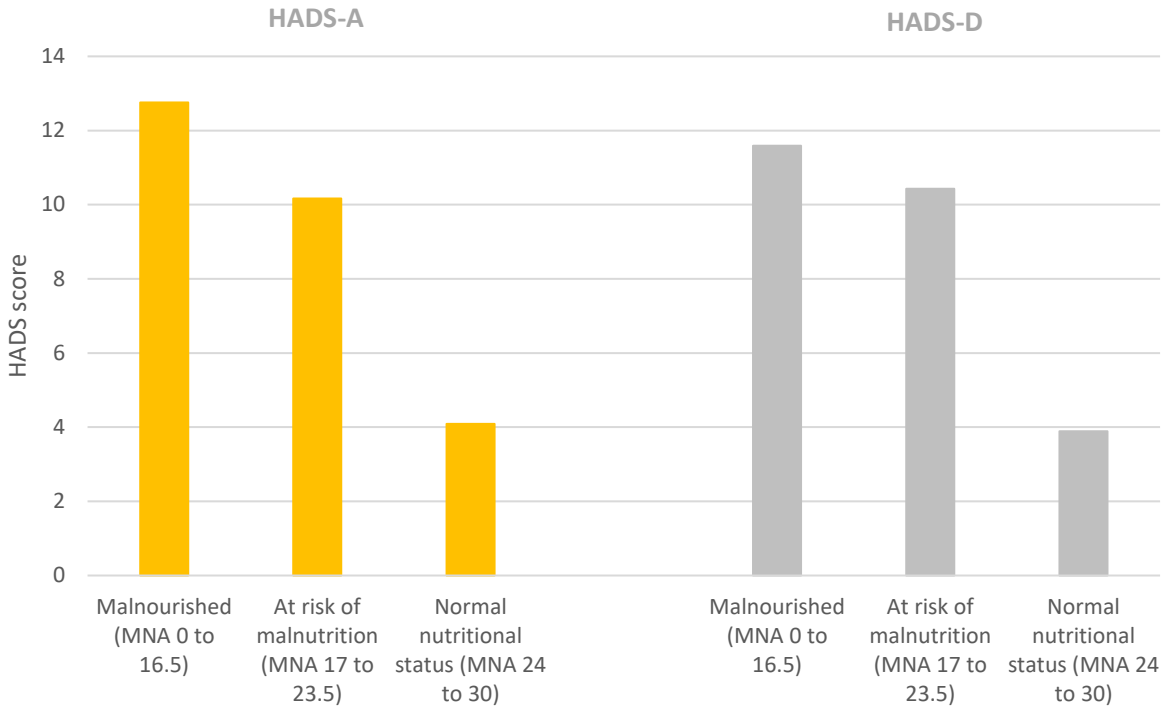
Malnutrition in cancer patients has a significant effect on physical state and functional capacity. Many patients present with increased pain, insomnia, loss of appetite, fatigue which in turn, leads to reduced cognitive functioning and physical wellbeing (109). In Polish patients with lung cancer (N=257), malnutrition was associated with increased perception of pain: malnourished patients (MNA 0 to 16.5), those at risk of malnutrition (MNA 17 to 23.5) and those with normal nutritional status (MNA 24 to 30) had diminishing VAS scores (5.69 vs 4.83 vs 2.69, p<0.001) (18). In a further Italian study of patients with locally advanced head and neck cancer (N=61), malnourished patients had significantly lower EORTC QLQ-C30 physical and role function scores (85±8 vs 92±8; p=0.043 and 72±19 vs 86±16; p=0.047, respectively) (114), and in a Polish study of patients with NSCLC (N=180), multivariate analysis revealed that malnutrition was an independent determinant of diminishing QoL within the physical functioning scale of the EORTC QLQ-C30 (β=–0.17, p=0.001) (111).

A Dutch study investigating the association between sarcopenia and physical independence during chemotherapy in older cancer patients (N=131) found that, compared with no sarcopenia, severe sarcopenia was associated with a decline in physical independence after chemotherapy (OR 5.95 [95% CI: 0.76 to 46.48]) (115). Furthermore, in a German study of patients with various types of cancer (N=503), patients with cachexia had significantly lower EORTC QLQ-C30 physical functioning scores (median 60 vs 80 for non-cachectic patients; p<0.001) (76).

2.2.3. Malnutrition and skeletal muscle mass loss in cancer patients are associated with psychosocial symptoms

As well as negatively impacting physical and cognitive functionality, malnutrition increases rates of depression and affects psychosocial performance and emotional wellbeing (109). In a Spanish study of hospitalised patients with cancer (N=282), malnourished patients were significantly more likely to present with anxiety and depression than those who were well-nourished (anxiety OR 2.4 [95% CI: 1.2 to 4.9], p=0.002; depression OR 3.5 [95% CI: 1.6 to 7.8], p=0.002) (77). A study of Polish patients with lung cancer (N=257) showed that malnutrition was associated with anxiety and depression (Figure 5) (18).

Figure 5: Effect of malnutrition on anxiety and depression scores in patients with cancer, measured using the Hospital Anxiety and Depression Scale



Source: Chabowski, 2018 (18).
Abbreviations: HADS-A, Hospital Anxiety and Depression Scale – Anxiety; HADS-D, Hospital Anxiety and Depression Scale – Depression.

Among Slovenian patients with head and neck cancer (N=40), poor nutritional status (i.e. those who were malnourished or cachectic) was associated with anxiety (measured using HADS-A, p=0.017 and p=0.020 at 2–3 weeks prior to chemoradiotherapy initiation, and at time of treatment completion, respectively) and depression (measured using HADS-D, p=0.045 and p=0.023 at time of treatment completion, and at 3 months follow-up, respectively) (116). In a further Italian study of patients with locally advanced head and neck cancer (N=61), malnourished patients had significantly lower EORTC QLQ-C30 social function scores (67±20 vs 86±20; p=0.024) (114).

Cachexia is also associated with psychosocial symptoms. In a UK-based study of exercise motivation in outpatients with lung and GI cancer with cachexia (N=196), patients typically reported very low levels of self-efficacy in terms of ability to undertake either aerobic or resistance type of structured exercises. The median score for perceived control over emotional and physical symptoms and relationships was 4.5 out of a maximum of 6 indicating reasonable control, although control over medical care and progression of the disease was lower (3.75 and 1.75, respectively) (117). In a further German study of patients with various types of cancer (N=503), patients with cachexia had significantly lower EORTC QLQ-C30 Social Functioning scores (median 50 vs 67 for non-cachectic patients; p<0.001) (76).

2.3. Economic burden of malnutrition in patients with cancer

Direct medical costs are incurred when patients utilise healthcare resources such as healthcare professional consultations and hospitals. These direct medical costs are further increased in patients with cancer and malnutrition or skeletal muscle mass loss.

2.3.1. Length of hospital stay is increased in malnourished cancer patients

Studies have shown that length of hospital stay (LoS) is increased in patients with cancer who are malnourished or at risk of malnutrition (Table 3). In a French study of adult inpatients with cancer (N=879), malnutrition was significantly associated with prolonged LoS (median 19.3±19.4 days for malnourished patients vs 13.3±19.4 days for others; p<0.0001) (1). Further data from an observational, cross-sectional, multicentre study in Spain (N=401) found that mean duration of hospitalisation was greater in patients at nutritional risk at discharge (12.1 days in malnourished vs 8.6 days in well-nourished patients) (20).

Table 3: Effect of malnutrition on LoS in patients with cancer

Country (reference)	Patient population	Effect on LoS
GI cancer		
France (118)	Patients with GI cancer N=644,720	Malnutrition diagnosis after first cancer hospitalisation vs diagnosis at first hospitalisation • Frequency of hospital stay 13.9 vs 6.8 stays • LoS 53 vs 38 days
UK (119)	Patients with CRC who received elective resection N=213	Malnutrition vs no malnutrition • LoS 16.4 vs 9.2 days, p=0.034
Head and neck cancer		
France (107)	Patients with head and neck cancer N=92	Malnutrition vs no malnutrition • LoS longer by 50% in patients with malnutrition, p=0.042
Neuroendocrine tumours		
Germany (57)	Patients with neuroendocrine neoplasms N=203	Risk of malnutrition/malnutrition (SGA B or C) vs normal nutritional status (SGA A) • LoS 8.8 days vs 4.0 days, p<0.001) High risk of malnutrition (NRS ≥3) vs normal nutritional status (NRS ≤2) • LoS A: 8.0 days vs 4.5 days, p<0.001
Multiple cancers		
Germany (16)	Patients with cancer N=666	Risk of malnutrition/malnutrition (NRS≥3) vs normal nutritional status • Difference in deviations of mean LoS 1.76 days, p=0.0047

Abbreviations: CRC, colorectal cancer; GI, gastrointestinal; LoS, length of hospital stay; NRS, nutritional risk screening; SGA, subjective global assessment.

LoS is also increased in patients with cancer with skeletal muscle mass loss (Table 4).

Table 4: Effect of skeletal muscle mass loss on LoS in patients with cancer

Country (reference)	Patient population	Effect on LoS
Oesophageal cancer		
Ireland (120)	Patients with oesophageal cancer undergoing multimodal therapy N=252	Preoperative sarcopenia vs no sarcopenia • Increased LoS, p=0.009
Head and neck cancer		
Finland (121)	Patients with head and neck cancer N=61	Low phase angle vs normal phase angle • LoS 19.1 days vs 8.8 days, p=0.002
The Netherlands (122)	Patients with head and neck cancer undergoing total laryngectomy N=235	Low skeletal muscle mass vs normal skeletal muscle mass • LoS 17 days vs 14 days, p<0.001
Gastric cancer		
Ireland (123)	Patients with gastric cancer who underwent surgical resection N=56	Sarcopenia vs no sarcopenia • ICU bed days 9.45 days vs 5.08 days, p=0.007

Abbreviations: CRC, colorectal cancer; ICU, intensive care unit; LoS, length of hospital stay.

2.3.2. Readmission rates are increased in malnourished cancer patients, or those with skeletal muscle mass loss

Patients with malnutrition or skeletal muscle mass loss experience higher rates of hospital readmission. In a study of Dutch patients with colorectal liver metastases (N=171), readmissions were more frequent in patients with sarcopenic obesity compared with patients without sarcopenic obesity (22.4% vs 9.8%, p=0.029) (23). Additionally, a retrospective study of patients with head and neck cancer undergoing surgery, radiotherapy or chemotherapy (N=152) found that patients who did not receive prophylactic gastronomy had significantly higher rates of hospital readmission than those who received prophylactic gastronomy (p=0.042) (24).

Furthermore, patients with cachexia require more unplanned hospitalisations, as noted in a study of patients with locally advanced head and neck squamous cell carcinoma receiving chemoradiation (N=100) (p=0.035) (97).

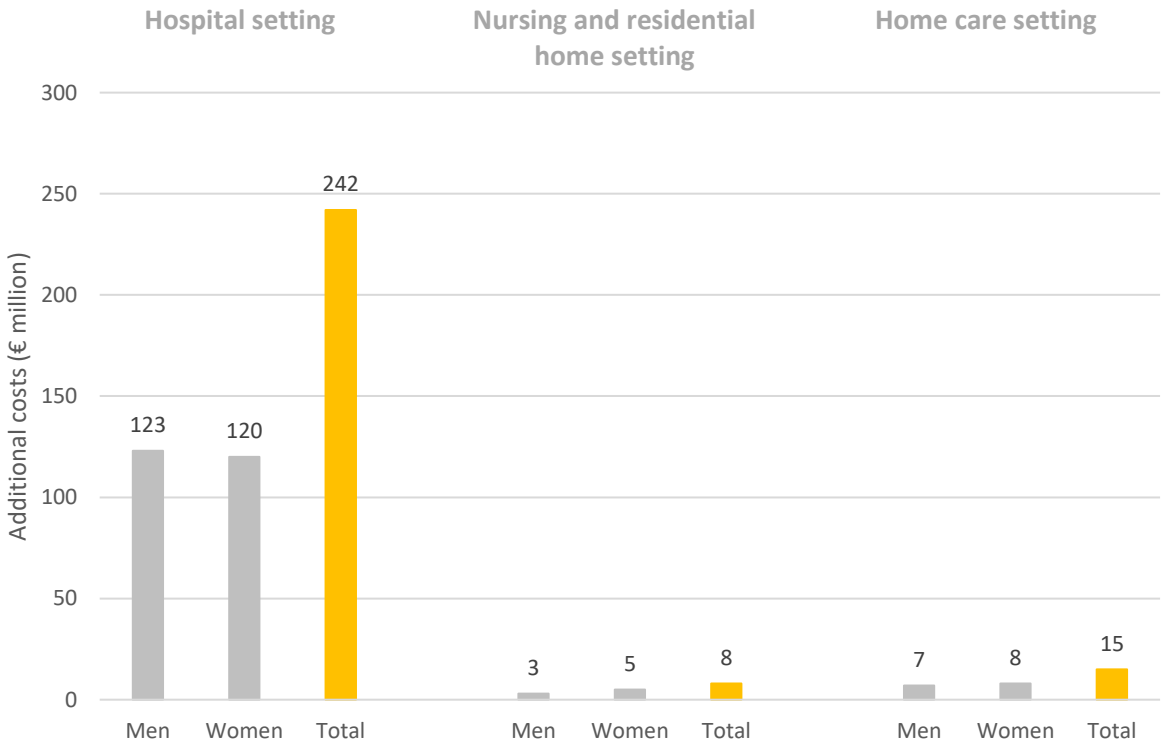
2.3.3. Healthcare resource use is increased in cancer patients with malnutrition or skeletal muscle mass loss

Malnutrition and skeletal muscle mass loss are associated with increased healthcare resource utilisation. In a study of elderly French cancer patients (median age 80 years; N=304), those who were malnourished (MNA <17) had significantly more nurse interventions, physiotherapist interventions, and social worker interventions (25). Further data from a Dutch study of patients who underwent cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal cancer (N=206), showed that sarcopenic patients underwent significantly more reoperations than nonsarcopenic patients (25.6 vs 12.1 %; p=0.012) (26).

2.3.4. Direct medical costs are increased in cancer patients with malnutrition or skeletal muscle mass loss

Malnutrition or skeletal muscle mass loss in patients with cancer are associated with increased direct medical costs. An observational, cross-sectional, multicentre study of cancer patients in Spain (N=401) found that healthcare costs were higher in patients at risk of malnutrition (NRS ≥3) vs those not at risk (NRS <3), both at admission (€7,855 vs €7,033, p=NR) and at discharge (€8,596 vs €6,652, p=0.001) (20). Further data from the Netherlands showed that the additional costs of cancer-related malnutrition were €265 million (Figure 6) (21).

Figure 6: Additional costs of cancer-related malnutrition in the Netherlands



Source: Freijer, 2013 (21).

In a Dutch study of patients who underwent curative-intent abdominal cancer surgery (N=452), median hospital costs were €2,183 higher in patients with low skeletal muscle mass compared with patients with high skeletal muscle mass (€17,144 vs €14,961; p<0.001) (22). In linear regression analysis, the low skeletal muscle mass was independently associated with higher total hospital costs, after adjusting for extent of surgery, sex, age, overweight, and American Society of Anesthesiologists (ASA) classification, and resulted in a cost increase of €4,061 (p=0.015). When skeletal muscle index was used as a continuous parameter, an incremental increase in skeletal muscle index (cm^2/m^2) was associated with €278 (p=0.027). The study suggests that increased costs may be directly related to the occurrence of (severe) complications requiring an increased use of resources such as prolonged and intensive care stay, laboratory tests, radiological examinations and radiological or surgical re-interventions.

3. Current guidelines and medical nutrition

Guidelines recommend early screening for nutritional risk, assessment of malnutrition, and nutritional intervention in patients with cancer

- European guidelines recommend early screening for nutritional risk and loss of skeletal muscle mass in patients with cancer (10, 27) (Section 3.1)
- Different measures exist for the assessment of nutritional risk in patients with cancer (124) (Section 3.2)
- European guidelines recommend nutritional intervention in malnourished patients (10, 27) (Section 3.4)
- Despite high prevalence of malnutrition amongst patients with cancer and clear guidelines, current practice regarding nutritional support for malnourished patients with cancer is inconsistent (8) (Section 3.4)

3.1. Current nutritional risk screening guidelines

European guidelines recommend early screening for nutritional risk and loss of skeletal muscle mass in patients with cancer (Table 5) (10, 27).

Table 5: Guidelines on nutritional risk screening in patients with cancer

Country/ Region	Name of guideline	Recommendations on diagnosis of malnutrition in cancer	Reference
EU	ESPEN guidelines on nutrition in cancer patients	Screen early in course of patients' treatment: Evaluate nutritional intake, weight change and BMI. Identify symptoms of anorexia, cachexia, and sarcopenia. Quantitative assessment of nutritional intake, symptoms, energy expenditure, muscle mass, physical performance, and degree of systemic inflammation.	Arends 2017 (27)
EU	ESPEN expert group recommendations for action against cancer-related malnutrition	Screening of all cancer patients for nutritional risk early in their course of care. Nutritional assessment should identify presence of anorexia, measure body composition, inflammatory biomarkers (eg: acute phase proteins, proinflammatory cytokines and alterations in white blood cell counts), resting energy expenditure and physical function.	Arends 2017 (10)
Italy	AIOM-SINPE practical recommendations for nutritional support in cancer patients	Nutritional screening utilising validated tools (NRS-2000, MUST, MST or MNA). Should be conducted upon diagnosis of malignancy and systematically repeated regularly. Consider inclusion of BIVA to calculate body composition.	Caccialanza 2016 (61)

Country/ Region	Name of guideline	Recommendations on diagnosis of malnutrition in cancer	Reference
Spain	SEOM clinical guidelines on nutrition in cancer patients (2018)	All oncology patients should be screened upon initial diagnosis and throughout treatment utilising a validated MST. Consider the evaluation of nutritional intake, weight loss and BMI, loss of muscle mass, physical performance and systemic inflammation.	de las Penas 2019 (59)

Abbreviations: AIOM, Italian Society of Medical Oncology; BIVA, bioelectrical impedance vector analysis; BMI, body mass index; ESPEN, European Society for Clinical Nutrition and Metabolism; MNA, mini nutritional assessment; MST, malnutrition screening tool; MUST, malnutrition universal screening tool; NRS, nutritional risk screening; SEOM, Spanish Society of Medical Oncology; SINPE, Italian Society of Artificial Nutrition and Metabolism.

3.2. Nutritional screening

Nutritional screening aims to identify malnutrition, or risk of malnutrition, as early as possible, allowing for early implementation of nutritional support in patients with cancer. In some countries, mandatory screening has been established (125-127) in attempt to combat the medical and economic burden or malnutrition. Dietary intake, body composition, physical activity and metabolic patterns are considered as key domains in the assessment of malnutrition in patients with cancer (27). However, there is no general consensus on individual methodologies to assess these domains, and measures. It is recommended for clinicians to consider using a validated nutritional assessment tool (NRS 2002, Malnutrition Universal Screening Tool [MUST], Malnutrition Screening Tool [MST] or MNA) for appropriate assessment of malnutrition (61, 128).

Different measures exist for the assessment of nutritional risk in patients with cancer; a systematic review of measures of malnutrition used in oncology patients between 1998 and 2013 (based on 160 identified studies) identified 37 different measures of malnutrition (124). Further studies have highlighted differences between the available measures:

- Use of PG-SGA detects more patients at nutritional risk, whereas NRS-2002 is a quicker and easier assessment (129)
- In patients with head and neck cancer, the Nutritional Risk Index (NRI) and L3 muscle mass index (L3MMI) have been identified as being better than BMI and Janssen's muscle mass index at diagnosing patients as being malnourished, and functional muscle assessment can be used to determine the degree of malnutrition (130)
- In patients with hepatocellular carcinoma (N=51), 37.3% of patients were identified as being at risk of malnutrition using the MNA (MNA 17–23.5), and 33.4% were identified using the NRS (NRS >2) (131)
- In outpatients with cancer (N=394), risk of malnutrition was detected in 22.6% of patients using the NUTRISCORE measure, in 28.2% using MST, and 19% using PG-SGA (132).

The definitions of cachexia and sarcopenia allow for the identification of specific signs or symptoms associated with malnutrition, or its risk, including loss of skeletal muscle mass and function (133). Traditionally, BMI estimation was used to identify patients with cancer who were at risk for malnutrition, a method now considered ineffective due to the global prevalence of obesity (10). Imaging techniques, such as CT, or body composition analysis (e.g. bioelectrical impedance vector

analysis [BIVA]), are recommended to evaluate loss of skeletal muscle mass (27, 61). As with measures of malnutrition, tools for identifying skeletal muscle mass loss also vary in sensitivity and specificity:

- Preliminary results of an Italian study suggest that CT is a more sensitive method for identifying sarcopenia, but BIVA is more specific (134)
- A systematic review of patients with abdominal malignancy (10 studies, N=2,584) noted that more patients were identified as sarcopenic when using CT scans rather than identified as malnourished when using BMI (135)
- Subjective global assessment and Global Leadership Initiative on Malnutrition (GLIM) criteria produce similar predictive values regarding 6-month mortality in cancer inpatients (136)
- Expert clinical assessment based on the 2011 cancer cachexia consensus domains can be used to classify patients according to cachexia status (137)
- GLIM criteria for malnutrition shows acceptable ability (vs international consensus definition criteria [ICDC]) for detecting cancer cachexia and pre-cachexia in patients with locally-advanced head and neck cancer (138)
- CT scans, conducted for preoperative staging, provide an opportunity to quantify lean muscle mass without additional cost or exposure to radiation and eliminate the inconvenience of further investigations (139).

3.3. Current nutritional support

As discussed in Section 2.1.1, malnutrition is associated with loss of skeletal muscle mass and cachexia. Nutritional supplementation is indicated in cases of malnutrition or risk of malnutrition; when patients are not expected to be able to eat food for 1 week or more, or if food intake is less than 60% of their needs for more than 1–2 weeks (27). A number of guidelines recommend the use of multimodal nutritional interventions with targeted, individualised plans (Section 3.4) (10, 61).

Nutritional support may be comprised of nutritional and dietary counselling, with or without artificial nutrition; either oral nutritional supplementation (ONS), enteral tube feeding (ETF) or parenteral nutrition (PN). The aims of nutritional support are to increase nutritional intake, decrease inflammation and hypermetabolic stress, and increase physical activity (10).

3.3.1. Nutritional counselling

Nutritional counselling and dietary advice are first offered to patients who are malnourished or at risk of malnourishment in order to manage symptoms and improve nutritional status. Patients who are capable of consuming food orally should be referred to an experienced dietician for dietary advice, which has proven efficacious in increasing protein intake, increasing body weight, improving body composition and improving certain aspects of QoL (59, 61). Nutritional counselling considers a patient's nutritional history, diagnosis and nutrition therapy, if required, and encourages patients to consume energy- and protein-rich foods (including fortified foods) and fluids according to individual patient needs (10, 27). If an enriched diet is not effective in improving nutritional status, oral nutritional supplements are recommended to achieve nutritional targets (27).

3.3.2. Oral nutritional supplementation (ONS)

Implementation of oral nutritional supplements (ONS) is considered in cases where nutritional counselling and recommended dietary measures fail to achieve patient protein-caloric requirements. ONS are energy-dense preparations which have demonstrated efficacy in improving nutritional outcomes when administered alongside nutritional counselling (10). Moreover, ONS with anti-catabolic and anti-inflammatory ingredients, in the form of essential amino acids or omega-3 fatty acids, may improve muscle protein synthesis (essential amino acids), and appetite, oral food intake, lean body mass and body weight (omega-3 fatty acids) in cancer patients (10). The European Society for Clinical Nutrition and Metabolism (ESPEN) expert group recommend the consideration of ONS with anti-inflammatory ingredients.

3.3.3. Artificial nutrition – Enteral tube feeding (ETF)

Enteral nutrition (EN), or enteral tube feeding (ETF), is indicated if oral nutrition remains inadequate (less than <60% of nutritional requirements) (59) despite nutritional intervention (nutritional counselling, ONS) (27, 61) and intact lower GI functionality. Such inadequate intake may occur in patients with tumours that impair oral intake or food transport via the upper GI tract (27). ETF may be delivered through trans-nasal (nasogastric or nasojejunal tube) or percutaneous (endoscopic or radiologically inserted, surgical gastrostomy or jejunostomy) route (61). ETF may be given preoperatively, with both European and American guidelines recommending immune-enhancing formulas in cancer patients undergoing major head-neck or abdominal surgery (140-142). Postoperatively, ETF is recommended for patients who are malnourished at the time of resection, in those who cannot reinitiate oral nutrition early, or in those who have inadequate food intake for more than 10 days (61).

3.3.4. Artificial nutrition – Parenteral nutrition (PN)

Parenteral nutrition (PN) is indicated in patients receiving cancer therapy who are facing a period of over 7 days of inadequate energy intake when nutritional counselling, ONS or EFT are not feasible, contraindicated or are ineffective due to impaired GI functionality (59, 61, 141, 143). PN is administered intravenously, requiring a catheter in order to administer nutritional preparations. The National Institute for Health and Care Excellence (NICE) recommend that PN should be introduced progressively, closely monitored and should cease as soon as a patient has received their nutritional recommendation (144).

PN may be administered at home (HPN), however only in suitable patients, considering their cognitive and physical wellbeing, life expectancy (over 2–3 months) and home environment (27, 59). HPN has a positive impact on health care costs, mainly by reducing the number and length of hospitalisations (145).

While PN may improve patient QoL and functionality, its administration should be considered with caution. Routine use is strongly not recommended (61), as PN may increase the risk of infections (and associated health care costs), and dysregulation of GI functionality (27).

3.4. Nutritional risk intervention guidelines

European guidelines recommend nutritional intervention in malnourished patients (Table 6) (10, 27).

Table 6: Guidelines on nutritional intervention in patients with cancer

Country/ Region	Name of Guideline	Recommendations on treatment of malnutrition in cancer	Reference
EU	European ESPEN guidelines on nutrition in cancer patients	Nutritional intervention: Increase oral intake in malnourished patients who are capable of eating. Includes dietary advice/nutritional counselling and ONS. Implementation of energy- and protein-rich foods and fluids. Avoidance of restrictive 'fad diets' which increase risk or aggravate malnutrition. Artificial nutrition (EN or PN) if oral nutrition remains inadequate.	Arends 2017 (27)
EU	ESPEN guidelines on nutrition in cancer patients	Application of nutritional care is dependent on medical history, appetite, cancer type, stage, and response to treatment. Introduction of nutritional counselling and support, eg: consumption of ~25–30 kcal/kg and 1.2–1.5g protein/kg per day (if total energy expenditure cannot be measured). Oral nutrition support (regular calorie-dense or fortified foods and ONS) in cases of pre-cachexia. ONS or enteral feeds with potential inclusion of anti-inflammatory ingredients (e.g.: omega-3 fatty acids) in cases with cachexia. Inclusion of physical activity.	Arends 2017 (10)
Italy	AIOM-SINPE practical recommendations for nutritional support in cancer patients	Dietary counselling should be initially considered, alongside administration of ONS. In cases of inadequate food intake, artificial nutrition (EN, PN) should deliver nutritional support. HAN is encouraged where possible. Avoidance of "alternative hypocaloric anti-cancer diets" (e.g. macrobiotic or vegan diets) to minimise persistent malnutrition.	Caccialanza 2016 (61)
Spain	SEOM clinical guidelines on nutrition in cancer patients (2018)	Nutritional counselling (including administration or ONS) is recommended for malnourished patients or those at risk of malnutrition capable of food consumption. Artificial nutrition (EN and PN) should be considered depending on patient's needs e.g. EN if oral intake is <60% of requirement in cases of GI preservation. PN: if oral feeding or use of GI tract are not possible. Incorporation of aerobic and resistance exercise.	de las Penas 2019 (59)

Abbreviations: AIOM, Italian Society of Medical Oncology; EN, enteral nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; GI, gastrointestinal; HAN, home artificial nutrition; ONS, oral nutritional supplementation; PN, parenteral nutrition; SEOM, Spanish Society of Medical Oncology; SINPE, Italian Society of Artificial Nutrition and Metabolism.

European guidelines for patients with cancer undergoing surgery also recommend nutritional intervention if patients are malnourished or at risk of malnutrition (Table 7) (146-148).

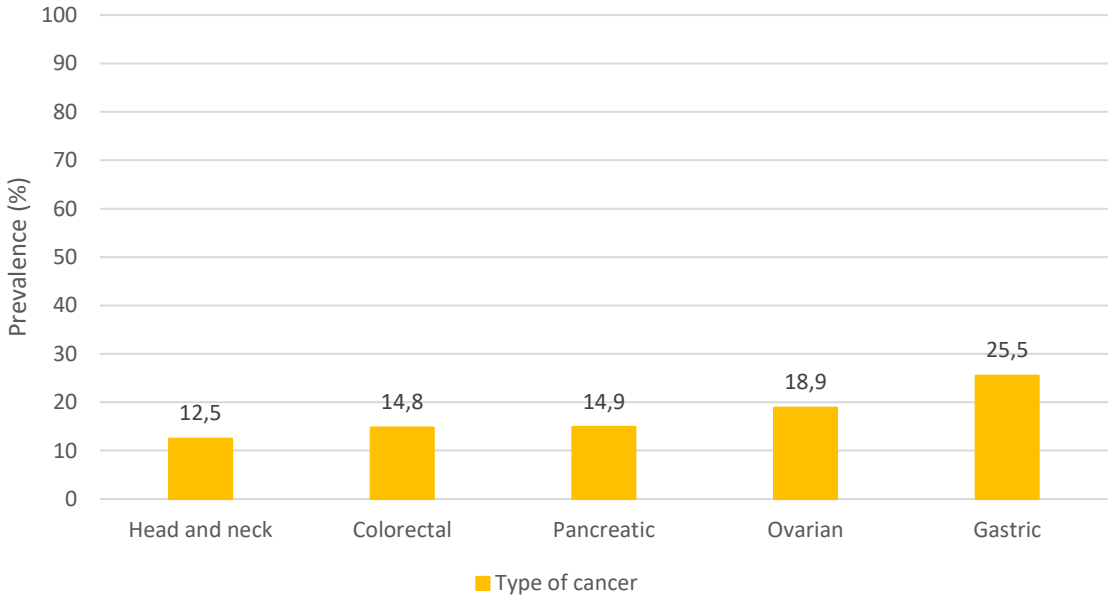
Table 7: Guidelines on nutritional intervention in patients with cancer undergoing surgery

Country/ Region	Name of Guideline	Recommendations on treatment of malnutrition in cancer	Reference
EU	ERAS: Guidelines for perioperative care for pancreaticoduodenectomy (2012)	Significantly malnourished patients should be optimised with oral supplements or enteral nutrition preoperatively	Lassen 2012 (146)
EU	ERAS: Guidelines for perioperative care in esophagectomy (2019)	Nutritional assessment should be undertaken in all patients with a view to detecting and optimising nutritional status before surgery In high-risk cases, enteral support is indicated, preferably using the GI tract with selective use of feeding tubes	Low 2019 (147)
EU	ERAS: Guidelines for perioperative care after radical cystectomy for bladder cancer (2013)	Preoperative nutritional support should be considered, especially for malnourished patient	Cerantola 2013 (148)

Abbreviations: ERAS, Enhanced Recovery After Surgery Society; GI, gastrointestinal.

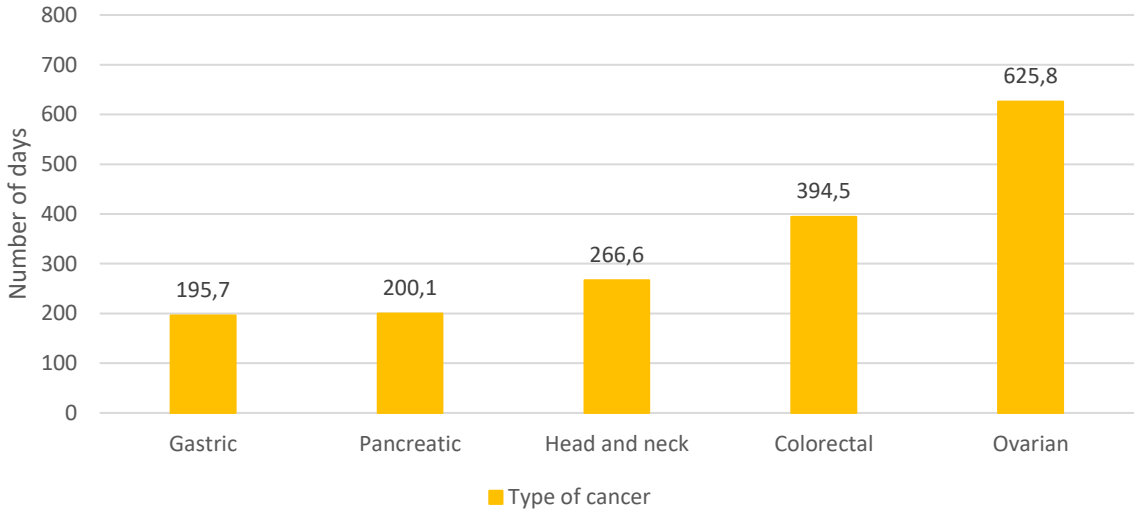
Despite the high prevalence of malnutrition amongst patients with cancer and clear guidelines, many malnourished patients with cancer still do not receive nutritional support (8). An analysis of German data (N=4,642) showed that only 16% of patients with Stage III/IV cancer receive HPN (ranging from 12.5% in head and neck cancer to 25.5% in gastric cancer) (Figure 7) (8). In these patients, HPN is initiated approximately 337 days after starting cancer treatment (ranging from 196 days in gastric cancer to 626 days in ovarian cancer) (Figure 8), and predominantly used as an end-of-life intervention, with a mean time-to-death of approximately 3 months (8). In Italy (N=58,468), 8.4% of metastatic cancer patients receive clinical nutrition (89% of these receive PN), and 3.1% of patients without metastases receive clinical nutrition (8).

Figure 7: Proportion of patients receiving home PN, by cancer type



Source: Caccialanza, 2020 (8).

Figure 8: Mean duration prior to home PN initiation, by cancer type



Source: Caccialanza, 2020 (8).

4. Value of medical nutrition

Medical nutrition is associated with improved clinical outcomes in patients with malnutrition

- Medical nutrition (oral nutritional supplements [ONS], enteral tube feeding [ETF], or parenteral nutrition [PN) is associated with improved clinical outcomes in patients with malnutrition (8, 28-31) (Section 4.1.1)
- Medical nutrition is associated with reduced weight loss in cancer patients (32) (Section 4.1.2)
- Medical nutrition is associated with improved survival in patients with cancer (33) (Section 4.1.3)
- Medical nutrition is associated with improved adherence and response to anti-cancer treatments (34, 35) (Section 4.1.4)
- Medical nutrition is associated with reduced risk of chemotherapy toxicity (149) (Section 4.1.5)

Medical nutrition is associated with improved HRQoL

- ONS is associated with improved HRQoL (37, 38) (Section 4.2.1.1)
- PN is associated with improved HRQoL (39, 40) (Section 4.2.1.2)

Medical nutrition is associated with reduced direct medical costs and resource use

- Medical nutrition is associated with decreased direct medical costs (41) (Section 4.3.1.1)
- Medical nutrition is associated with reduced length of hospital stay (42) (Section 4.3.1.2)
- Medical nutrition is associated with lower rates of complications (42, 44) (Section 4.3.1.3)
- Medical nutrition is likely to be cost-effective (46) (Section 4.3.2)

4.1. Clinical value of medical nutrition

4.1.1. Medical nutrition is associated with improved clinical outcomes in patients with cancer and malnutrition

A review of nutritional interventions to treat low skeletal muscle mass in patients with cancer concluded that understanding patients nutritional requirements could lead to targeted prescriptions to prevent or attenuate low skeletal muscle mass, thereby improving overall health, tolerance of anti-cancer treatment, and better survival (150).

4.1.1.1. Oral nutritional supplements are associated with improved clinical outcomes in cancer patients with malnutrition

Studies have shown that ONS in patients with cancer can increase body weight and improve malnutrition. In a systematic review and meta-analysis (9 studies; N=1,101) of ONS, supplements, particularly high protein oral supplementation, were associated with increased body weight ($p=0.0226$) (28). A further double-blind RCT of patients with newly diagnosed oesophageal cancer (N=64) comparing a nutritionally complete oral supplement with control interventions showed that after 4 weeks, a significantly higher weight gain was observed in the ONS group compared with the control group ($p<0.05$) (151). Additionally, a study of patients receiving ONS (fish oil or marine

phospholipids, N=60) showed that both groups experienced weight stabilisation in comparison with the weight loss observed prior to study start, with 47–50% of patients gaining weight (152).

Administration of ONS has also been associated with improved clinical outcomes such as increased OS and lower risk of post-operative complications. A systematic literature review and meta-analysis of patients undergoing surgery for GI cancer (16 studies, N=1,387) showed that preoperative immune-modulating nutrition (ONS or EN) reduced infectious complications (OR 0.52, 95% CI: 0.38 to 0.71, p<0.0001) when compared with control (isocaloric isonitrogeneous feed or normal diet) (153). In patients with oesophageal cancer at risk of malnutrition at baseline (NRI <100), initiation of oral supplementation at baseline was associated with improved OS (HR 0.13 [95% CI: 0.04 to 0.39], p<0.001 compared with no nutritional intervention (29). Furthermore, in patients with colorectal cancer (N=52), those receiving ONS experienced a reduction in the frequency of certain complications: wound dehiscence (2.2 times lower), infections (4.3 times lower), and anastomosis dehiscence (2.0 times lower) compared with those without ONS (41), and in a retrospective study of the use of ONS prior to abdominal surgery (N=55 control, and N=30 receiving ONS), 60% of patients in the control group compared with 26.7% of patients receiving ONS had complications following surgery (p=0.003) (154). Regarding survival, a retrospective analysis of patients with head and neck cancer (N=87), showed that 3-year OS was 59.0% in patients receiving nutritional support (dietary counselling and ONS) compared with 34.9% in patients who did not (p=0.007) (30). A double-blind randomised controlled trial (RCT) of patients with newly diagnosed oesophageal cancer (N=64) compared a nutritionally complete oral supplement with control interventions. After 4 weeks, a significantly higher weight gain was observed in the ONS group compared with the control group (p<0.05) (151)

4.1.1.2. ETF is associated with improved clinical outcomes in cancer patients with malnutrition

Administration of ETF in patients with cancer is associated with lower weight loss or weight stabilisation compared with nutritional counselling. In an open-label randomised controlled trial of patients with upper GI cancer (N=79), weight loss was significantly lower (–0.3±3.9 kg vs –3.6±4.8 kg, p<0.01) and total caloric intake significantly higher (40.6 kcal/kg vs 30.2 kcal/kg, p <0.001) in the home EN group compared with the nutritional counselling control group after 2 months (155). Furthermore, in a randomised trial comparing home EN with dietary counselling in patients with GI cancer (N=49), patients receiving dietary counselling suffered significant weight loss 2 months post-surgery (from 60.4±11.4 kg to 58.3±10.4 kg; p=0.014) whereas patients receiving home EN did not (31). A study examining the timing of weight loss in relation to administration of ETF in patients undergoing oesophagectomy (N=236) observed that weight loss primarily occurred after tube feeding was stopped, with a decrease in median BMI from 25.6 kg/m^2 (95% CI: 23.0 to 28.6) to 24.4 kg/m^2 (95% CI: 22.0 to 27.1) within 1 month (p<0.001), equating to a median 3.0 kg (95% CI: 1.0 to 5.3) weight loss (3.9%) (156).

ETF is also associated with reduced risk of post-operative complication. In patients undergoing total gastrectomy for gastric cancer (N=109), fewer patients receiving early postoperative enteral immunonutrition experienced post-operative complications (7.4% vs 20%, p<0.05) and anastomotic leaks (3.7% vs 7.3%, p<0.05) compared with isocaloric-isonitrogenous nutrition (43). A further prospective, randomised, double-blind trial of patients undergoing resection for pancreatic or gastric cancer (N=305), showed that patients receiving postoperative immunomodulating enteral diet experienced significantly lower rates of complications (28.3% vs 39.2%, p=0.04) than patients receiving standard oligopeptide diet (157). Significant reductions were also observed in overall

morbidity (47.1 vs 33.5%, p=0.01) and mortality (5.9 vs 1.3%, p=0.03). In a UK study of patients with upper GI cancer (N=121), complications were less common in patients receiving early EN vs patients kept nil by mouth (32.8% vs 50.9%, p=0.044), due to statistically significantly fewer wound infections (p=0.017) and chest infections (p=0.036) (158).

OS is also improved in patients with cancer receiving ETF; In a study of patients with oesophageal cancer at risk of malnutrition at baseline (NRI <100) initiation of ETF at baseline was associated with improved OS (HR 0.13 [95% CI: 0.03 to 0.50], p=0.003) compared with no nutritional intervention (29).

4.1.1.3. PN is associated with improved clinical outcomes in cancer patients with malnutrition

PN is associated with improvements in nutritional status and increased body weight in patients with cancer. In a study of patients with Stage III/IV cancer receiving chemotherapy and home PN (N=65) over 30% of patients showed improvement in PG-SGA assessment (p<0.01), with 5 patients reaching well-nourished status (159), and in patients with biliopancreatic mass lesions (N=100), early PN in a hospital setting increased body weight by 1.7 kg (95% CI:0.201 to 3.210, p=0.027), particularly in patients with malignant lesions where body weight was increased by 2.7 kg (95% CI:0.71 to 4.76, p<0.01) (160). A further prospective, observational, multicentre study of patients with GI cancer receiving home PN (N=370) found that patients' weight increased significantly by 2.7% (p<0.001), with 63% gaining weight after HPN administration, and 17.5% reaching their target weight (40). In a Dutch study of patients with acute myeloid leukaemia (AML, N=213), patients in a hospital where PN was used frequently (PN hospital) lost less weight than those in a hospital where PN was only used in exceptional cases (no PN hospital; between-group difference 7.7% [95% CI:4.1 to 11.2%]) (161). Among patients who received only one remission induction chemotherapy cycle (n=85), severe body weight loss of >10% occurred in 7% of PN hospital patients compared with 39% of no PN hospital patients (p=0.006). For patients receiving two remission induction cycles (n=128) this was 17% vs 70%, respectively (p<0.0001).

Furthermore, PN is associated with improvements in mortality; In patients with Stage III/IV cancer in Germany (N=4,642), initiation of HPN is associated with increased survival (81 days in head and neck cancer, 29 days in colorectal cancer, 84 days in pancreatic cancer, 41 days in ovarian cancer, 118 days in gastric cancer) vs no home PN (8). In a Dutch study of patients with AML (N=213), patients in a hospital where PN was used frequently (PN hospital) patients lost less weight than those in a hospital where PN was only used in exceptional cases (no PN hospital; between-group difference 7.7% [95% CI:4.1 to 11.2%]). Among patients who received only one remission induction (RI) chemotherapy cycle (n=85), severe body weight loss of >10% occurred in 7% of PN hospital patients compared with 39% of no PN hospital patients (p=0.006). For patients receiving two RI cycles (n=128) this was 17% vs 70%, respectively (p<0.0001) (161).

4.1.2. Medical nutrition is associated with reduced weight loss, or weight gain, in patients with cancer

In an Italian study of patients with head and neck cancer undergoing chemoradiotherapy (N=66), weight loss in patients who were referred for early nutritional intervention (ONS or ETF) was significantly lower 6 months after the end of treatment, compared with patients who did not receive a specifically designed early nutrition support programme (−2.4±8.2% vs −9.6±8.1% of pre-treatment weight, p<0.01) (32). In a further Italian study of patients with newly-diagnosed head and neck cancer undergoing radiotherapy (N=159), body weight loss was lower in patients receiving nutritional

counselling and ONS compared with counselling alone (mean difference 1.6 kg, 95% CI: 0.5 to 2.7, p=0.006) (162).

Further data from a systematic review and meta-analysis of RCTs in patients with cancer (11 studies, N=1,350) showed that ONS led to significant improvement in body weight compared with controls (+1.31 kg, 95% CI: 0.24 to 2.38, p=0.02) (28).

4.1.3. Medical nutrition is associated with improved survival in patients with cancer

Survival is improved in patients without malnutrition; A Dutch study in which patients scheduled for first-line chemotherapy (N=107) found that nutritional counselling (supported by ONS or EN if indicated) was associated with significant improvements in PFS (9.6 vs 7.6 months; p=0.039) and OS (21.7 vs 16.0 months; p=0.046) (33). A study of French patients undergoing lung cancer resection (N=304) concluded that body reserves impact the survival of patients, and that improving body fat and muscular mass prior to surgery should be considered (163).

4.1.4. Medical nutrition is associated with improved adherence and response to anti-cancer treatments

Adherence and response to anti-cancer treatments can be improved by medical nutrition; A study on the impact of a feeding jejunostomy on the preoperative management of patients with an oesogastric adenocarcinoma (N=114), found that 96% of patients in the feeding jejunostomy group successfully completed neoadjuvant treatment, compared with 81.6% of patients without feeding jejunostomy (p=0.004) (34). In a further Italian study of patients with newly-diagnosed head and neck cancer undergoing radiotherapy (N=159), use of ONS with nutritional counselling reduced the need for changes in scheduled anticancer treatments (i.e. dose reduction or termination) compared with counselling alone (HR 0.40, 95% CI: 0.18 to 0.91, p=0.029) (162). In a Spanish study (N=55, 85% with malnutrition), survival was improved (log rank 17.316, p<0.001) in patients who started chemotherapy during or after PN vs those who did not receive PN (35).

4.1.5. Medical nutrition is associated with reduced risk of chemotherapy toxicity

Chemotherapy toxicity can also be improved by medical nutrition. In patients with colorectal cancer undergoing chemotherapy (N=47), more patients receiving ONS were toxicity-event free (haematological toxicities 86% vs 29% of patients and GI toxicities 94% vs 29%) than patients without ONS (36). In an Italian study of patients with head and neck cancer undergoing chemoradiotherapy (N=66), toxicity-related breaks in radiotherapy >5 days and days of radiotherapy delayed for toxicity were both significantly less likely in patients who were referred for early nutritional intervention (ONS or ETF), compared with patients who did not receive a specifically designed early nutrition support programme (30.3% vs 63.6%, p<0.01, and 4.4±5.2 vs 7.6±6.5, p=0.038, respectively) (32).

4.2. Quality of life value of medical nutrition

4.2.1. Medical nutrition is associated with improved HRQoL

4.2.1.1. ONS is associated with improved HRQoL

Systematic literature reviews have concluded that ONS is associated with improvements in HRQoL. In one systematic review (13 studies; N=1,414), oral nutritional interventions were shown to have a beneficial effect on aspects of QoL including emotional functioning, dyspnoea (shortness of breath)

and loss of appetite (37). A further systematic review assessing evidence for nutritional support in patients with incurable cancer found that 8 of 11 studies reported improvements in QoL in patients receiving nutritional support, compared with control patients (38).

In a small randomised controlled trial of ONS in colorectal cancer (N=13), patients receiving ONS experienced an improvement in social function, while patients not receiving ONS experienced a decline (mean change 16.67 vs –13.89, p=0.038) (164). Patients in the control group experienced a >10 point increase in fatigue (considered clinically meaningful; the ONS group experienced reduced fatigue), and patients in the ONS group experienced a 10 point decrease in pain (also considered clinically meaningful; the control group experienced increased pain). In a further double-blind RCT of patients with newly diagnosed oesophageal cancer (N=64) a nutritionally complete oral supplement was compared with control interventions (151). After 4 weeks, Eastern Cooperative Oncology Group (ECOG) performance status was significantly different between the active and control groups (p<0.05). Performance status improved in 17.4% of the patients in the active group compared with 0% in the control group, was stable in 65.2% of the patients in the active group compared with 72.7% in the control group, and was worsened in 17.4% of the patients in the active group compared with 27.3% in the control group). In patients with colorectal cancer referred for radiotherapy (N=111), global QoL, physical function, and role function domains were statistically significantly improved at end of radiotherapy, and global QoL, and physical function were statistically significantly improved at 3 months after radiotherapy in patients receiving ONS compared with those receiving nutritional counselling alone (165).

4.2.1.2. PN is associated with improved HRQoL

Studies show that HRQoL is also improved following administration of PN in patients with cancer. In an observational, prospective study (N=767), HPN resulted in a significant improvement in QoL measured using Functional Assessment of Cancer Therapy- General (FACT-G; 3.2% increase in FACT-G score, p<0.0001) (39). In a prospective, observational, multicentre study of patients with GI cancer receiving HPN (N=370) found that QoL (measured by FACT-G) significantly improved 28 days after HPN administration (global scores improved from 48.9 to 50.3 [p=0.007] and physical scores improved from 49.1 to 54.8 [p<0.001]) (40). A study of QoL in advanced cancer patients receiving HPN and concurrent oncological therapy (N=111) showed that QoL was maintained or even showed an improvement (domains of global QoL, physical, role, emotional functioning, appetite loss and fatigue) in some scores according to the EORTC QLQ-C30 (166). In patients (N=65) with Stage III/IV cancer receiving chemotherapy and HPN, the mean Karnofsky Performance Status (KPS) increased from 67.4 at baseline to 72.5 at 90 days (p<0.01) and the proportion of patients with KPS ≥70 increased from 66.2% at baseline to 77% at 90 days (159). In an RCT of patients with terminal GI cancer (N=47), QoL (measured using EORTC QLQ-C15-PAL [Core 15-item, palliative care]) was significantly better at 12 weeks (p<0.05) in those receiving HPN, particularly for parameters around nausea, depression, and constipation (167).

4.3. Economic value of medical nutrition

4.3.1. Medical nutrition is associated with reduced direct medical costs and healthcare resource use

4.3.1.1. Medical nutrition is associated with decreased direct medical costs

Direct medical costs were lower in patients receiving medical nutrition. In patients with colorectal cancer (N=52), mean daily hospital costs were reduced by 11% (€479 vs €538, p=0.005) for those receiving ONS compared with those without ONS (41).

4.3.1.2. Medical nutrition is associated with reduced length of hospital stay

Several studies show that LoS is reduced in patients with cancer receiving medical nutrition. A systematic review on the effects of n-3 polyunsaturated fatty acid (PUFA) in patients with abdominal cancer found that in a pooled analysis of eight studies reporting LoS outcomes (N=883), PUFA intake was associated with significantly shorter LoS (mean differences [MD] –2.47 [95% CI: –3.25 to –1.69]) compared with conventional nutrition in a fixed-effects model (45).

These results are supported by output from individual studies in different cancer types. In surgical cancer patients receiving medical nutrition (standard or immune-modulating EN, or standard or immune-modulating PN; N=969), those who were well nourished generally had shorter LoS than those who were malnourished (12.4 to 12.9 days vs 13.1 to 17.1 days, p=NR) (42). In patients with colorectal cancer (N=52), those receiving ONS experienced shorter LoS (9.4 days vs 12 days, p=0.02) compared with those without ONS (41). In patients undergoing total gastrectomy for gastric cancer (N=109), LoS was shorter in patients receiving early postoperative enteral immunonutrition (12.7 days vs 15.9 days, p=0.029) compared with isocaloric-isonitrogenous nutrition (43). In a retrospective study of the use of ONS prior to abdominal surgery (N=55 no ONS, and N=30 receiving ONS), LoS was 8 days in patients without ONS compared with 6.5 days in patients receiving ONS (p=0.02) (154). In a UK study of patients with upper GI cancer (N=121), LoS was statistically significantly shorter in patients receiving early EN vs patients kept nil by mouth (16 days vs 19 days, p=0.023) (158). In a prospective, randomised, double-blind trial of patients undergoing resection for pancreatic or gastric cancer (N=305), patients receiving postoperative immunomodulating enteral diet experienced significantly shorter postoperative hospital stays (median 13.1 days compared with 17.1 days for patients receiving standard oligopeptide diet) (157). A systematic literature review and meta-analysis of patients undergoing surgery for GI cancer (16 studies, N=1,387) showed that preoperative immune-modulating nutrition (ONS or EN) reduced length of hospital stay (weighted mean difference –1.57 days, 95% CI: 2.48 to –0.66, p=0.0007) when compared with control (isocaloric isonitrogeneous feed or normal diet) (153). In a multicentre, prospective, randomised, double-blind study of patients with head and neck cancer (N=205 in intention-to-treat [ITT] analysis), 64 patients consumed ≥75% of theoretical nutritional intake. In this group of patients there was a significant reductions in median length of post-operative stay (18 vs 25 days; p=0.05) in patients who received perioperative immunonutrition compared with patients who received a reference diet (without immune nutrients) (168).

4.3.1.3. Medical nutrition is associated with lower rates of complications

Furthermore, studies show that medical nutrition is also associated with lower rates of complications. A systematic review and meta-analysis (61 studies; N=5,983) found that immunonutrition (delivered as ONS, EN or PN) was associated with lower rates of postoperative wound infections (pooled RR 0.72

[95% CI: 0.60 to 0.87], p=0.0008), respiratory tract infections (pooled RR 0.70 [95% CI: 0.59 to 0.84], p=0.0001), and urinary tract infections (UTIs; pooled RR 0.69 [95% CI: 0.51 to 0.94], p=0.02) (44). A further systematic review on the effects of n-3 polyunsaturated fatty acid (PUFA) in patients with abdominal cancer (15 studies; N=654) found that in a pooled analysis of six studies that reported rates of complications, ONS supplemented with PUFA was associated with a lower total complication rate (RR, 0.70 [95% CI: 0.58 to 0.84]) in a fixed-effects model (45).

In surgical cancer patients receiving medical nutrition (standard or immune-modulating EN, or standard or immune-modulating PN; N=969), those who were well nourished generally had lower rates of infectious complications, than those who were malnourished (23.1 to 25.2% vs 28.3 to 39.2%, p=NR) (42). In a randomised controlled trial (N=101) investigating the impact of preoperative ONS on postoperative complications, ONS was found to reduce the risk of surgical site infections or chest infections compared with no preoperative ONS (OR adjusted for random baseline differences 0.341 [95% CI: 0.128 to 0.909], p=0.031) (169). In a prospective analysis of patients with pancreatic cancer (N=92), severe complications were significantly less frequent in the ONS group compared with the control group (23.3% vs 42.5%, p=0.006) (170). In a multicentre, prospective, randomised, double-blind study of patients with head and neck cancer (N=205 in ITT analysis), 64 patients consumed ≥75% of theoretical nutritional intake. In this group of patients there were significant reductions in infectious complications (OR 0.24; p=0.05) and surgical site infections (OR 0.17; p=0.04) in patients who received perioperative immunonutrition compared with patients who received a reference diet (without immune nutrients) (168).

4.3.2. Medical nutrition is likely to be cost-effective

Home-based PN in addition to ETF in patients with Stage IV pancreatic cancer in the UK is estimated to be associated with an increase in 0.14 quality-adjusted life years (QALYs) at an increased cost of £5,832 to £12,905 vs ETF alone (dependent on whether nursing and home delivery for ETF and supplemental PN were provided separately); with an estimated ICER of £41,350 to £91,501 per QALY gained (46).

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Appendix A:
Prevalence of malnutrition and muscle loss, by cancer type

GI cancer

Patients with GI cancer frequently experience malnutrition (Table 8) and muscle loss (Table 9).

Table 8: Prevalence of malnutrition in adult patients with GI cancer

Country (reference)	Patient population	Measure used	Prevalence
GI cancer			
France (8)	Patients (age=NR) at first hospitalisation for GI cancer N=570,727	NR†	• Malnutrition: 10%
Colorectal cancer			
France (1)	Adult (>18 years) inpatients and outpatients with malignant diagnosis N=156	BMI Weight	• Malnutrition: 31.2% ○ Severe: 9.2% ○ Moderate: 22%
Germany (171)	Patients (age=NR) with rectal cancer N=9,789	NRS	• Risk of malnutrition: 53.9%
Italy (172)	Patients (≥44 years) undergoing surgery for colorectal cancer N=78	MNA	• Malnourished: 24.3% • Risk of malnutrition: 46.1%
UK (173)	Patients (mean age 66 years) undergoing surgery for colorectal cancer N=363	MUST	• Risk of malnutrition: 21% ○ High risk: 12% ○ Medium risk: 9%
Oesophageal cancer			
Spain (174)	Patients (mean age 64.5 years) admitted to hospital for oesophageal cancer N=44	MUST NRS	• Malnutrition: 75%
Gastric cancer			
Spain (175)	Patients (44–88 years) admitted to hospital for gastric cancer N=101	NRS GLIM criteria	• Risk of malnutrition: 64.9% • Malnutrition: 54.3% ○ Severe: 29.2% ○ Moderate: 20.8%
Upper digestive cancer			
France (1)	Adult (>18 years) inpatients and outpatients with malignant diagnosis N=103	BMI Weight	• Malnutrition: 49.5% ○ Severe: 23.2% ○ Moderate: 26.3%

†Malnutrition was identified in database via ICD-10 malnutrition diagnosis code and accompanying diagnosis code of at least moderate or severe malnutrition in the Program for the Medicalization of Information Systems database.
Abbreviations: BMI, body mass index; GI, gastrointestinal; GLIM, Global Leadership Initiative on Malnutrition; MNA, mini nutritional assessment; MUST, malnutrition universal screening tool; NR, not reported; NRS, nutritional risk screening.

Table 9: Prevalence of muscle loss in adult patients with GI cancer

Country (reference)	Patient population	Measure used	Prevalence
GI cancer			
Global† (53)	Patients (median age 64.6 years) undergoing surgery or adjuvant therapy for GI cancer N=21,875 from 70 studies	CT imaging BMI	• Sarcopenia: 34.7%
Colorectal cancer			
Global† (176)	Patients with preoperative/prechemotherapy-treated colorectal cancer N=190 from 3 studies	BIA	• Sarcopenia: 32%
EU† (56)	Patients with colorectal cancer experiencing weight-loss N=724 from 4 studies	Weight loss BMI	• Cachexia: 31.8%
France (177)	Patients (median age 59.5 years) undergoing surgery for colorectal cancer N=214	BMI CT imaging	• Sarcopenia: 42%
Oesophageal cancer			
Global† (176)	Patients with either preoperative or prechemotherapy-treated oesophageal cancer N=636 from 7 studies	BIA	• Sarcopenia: 44%
Netherlands (67)	Patients (mean age 63 years) undergoing surgery for oesophageal cancer N=123	CT imaging	Before chemoradiotherapy • Sarcopenia: 56% After chemoradiotherapy • Sarcopenia: 67%
Gastric cancer			
Global† (176)	Patients with preoperative gastric cancer N=687 from 5 studies	BIA	• Sarcopenia: 21%
EU† (56)	Patients with gastric cancer N=108 from 1 study	Weight loss BMI	• Cachexia: 33.3%
Liver cancer			
EU† (56)	Patients with liver cancer N=25 from 1 study	Weight loss BMI	• Cachexia: 50.1%
Netherlands (178)	Patients (>22 years) with hepatocellular carcinoma	CT imaging	• Sarcopenia: 57.8%
Pancreatic cancer			
Global† (179)	Patients with pancreatic cancer N=3,675 from 15 studies	CT imaging	• Sarcopenia: 32.7%

Country (reference)	Patient population	Measure used	Prevalence
Global† (85)	Patients (>60 years) with pancreatic cancer N=2,297 from 11 studies	CT imaging BMI	• Sarcopenia: 45.4% • Sarcopenia + obesity: 13%
Global† (58)	Patients with pancreatic cancer N=1,685 from 10 studies	CT imaging	Normal weight (BMI 18.5–24.9 kg/m^2) • Sarcopenia: 29.7% to 65% Overweight or obese (BMI >25 kg/m^2) • Sarcopenia: 16.2% to 67%
EU† (56)	Patients with pancreatic cancer N=423 from 4 studies	Weight loss BMI	• Cachexia: 45.6%

†Data generated from a systematic review.
Abbreviations: BIA, bioelectrical impedance analysis; BMI, body mass index; CT, computed tomography; GI, gastrointestinal.

Head and neck cancer

Patients with head and neck cancer are at risk of malnutrition (Table 10) and muscle loss (Table 11).

Table 10: Prevalence of malnutrition in adult patients with head and neck cancer

Country (reference)	Patient population	Measure used	Prevalence
Finland (180)	Patients (>33 years) with primary HNSCC N=65	PG-SGA	• Malnutrition: 34%

France (1)	Adult (>18 years) inpatients and outpatients with malignant diagnosis
	N=179
		BMI
		Weight
			• Malnutrition: 45.6%
			  ○ Severe: 23.1%
			  ○ Moderate: 22.5%

Poland (181)	Patients (>18 years) with newly diagnosed head and neck cancer N=75	SGA	• Malnutrition (moderate or severe): 40%
Slovenia (5)	Patients (>18 years) with HNSCC treated with chemo- or radiotherapy N=55	NRS	Before treatment • Malnutrition: 16.4% After treatment • Malnutrition: 45.4%

Abbreviations: BMI, body mass index; HNSCC, head and neck squamous cell carcinoma; NRS, nutritional risk screening PG-SGA, patient-generated subjective global assessment; SGA, subjective global assessment.

Table 11: Prevalence of muscle loss in adult patients with head and neck cancer

Country (reference)	Patient population	Measure used	Prevalence
EU† (56)	Patients with head and neck cancer N=607 from 3 studies	Weight loss BMI	• Cachexia: 42.3%
Finland (180)	Patients (>33 years) with primary HNSCC	PG-SGA	• Sarcopenia: 46%

Country (reference)	Patient population	Measure used	Prevalence
	N=65		• Cachexia: 31%
Slovenia (5)	Patients (>18 years) with HNSCC treated with chemo- or radiotherapy N=55	NRS	Before treatment • Cachexia: 14.5% After treatment • Cachexia: 38.2%

†Data generated from a systematic review.
Abbreviations: BMI, body mass index; NRS, nutritional risk screening PG-SGA, patient-generated subjective global assessment.

Lung cancer

Patients with lung cancer are at risk of malnutrition (Table 12) and muscle loss (Table 13).

Table 12: Prevalence of malnutrition in adult patients with lung cancer

Country (reference)	Patient population	Measure used	Prevalence
France (1)	Adult (>18 years) inpatients and outpatients with malignant diagnosis N=90	BMI Weight	• Malnutrition: 40.2% ○ Severe: 18.3% ○ Moderate: 21.9%
Poland (111)	Patients (>18 years) with NSCLC undergoing therapy N=180	MNA	• Undernourished: 51.1% • Risk of malnutrition: 23.9%

Abbreviations: BMI, body mass index; MNA, mini nutritional assessment; NSCLC, non-small cell lung cancer.

Table 13: Prevalence of muscle loss in adult patients with lung cancer

Country (reference)	Patient population	Measure used	Prevalence
Global (108)	Patients undergoing lung resection N=1,010	CT-assessed muscle mass	• Sarcopenia: 42.8%
EU† (56)	Patients with lung cancer N=707 from 4 studies	BMI Weight	• Cachexia: 37.2%
Belgium and France (68)	Patients (>18 years) with NSCLC N=531	CT imaging	• Cachexia: 38.7% • Pre-cachexia: 33.8%
UK† (176)	Patients with lung cancer, prechemotherapy N=62 from 1 study	BIA	• Sarcopenia: 19%

†Data generated from a systematic review.
Abbreviations: BIA, bioelectrical impedance analysis; BMI, body mass index; CT, computed tomography; NSCLC, non-small cell lung cancer.

Bone and soft tissue (osteosarcoma) cancer

Patients with bone and soft tissue (osteosarcoma) cancer are at risk of malnutrition (Table 14) and muscle loss (Table 15).

Table 14: Prevalence of malnutrition in adult patients with bone and soft tissue (osteosarcoma) cancer

Country (reference)	Patient population	Measure used	Prevalence
France (54)	Patients (>34 years) undergoing surgery for retroperitoneal liposarcoma N=40	PINI NRI	• Malnutrition: 52.5%
Holland (55)	Patients with spinal metastases undergoing surgical treatment N=39	PG-SGA	• Malnutrition: 92%

Abbreviations: NRI, nutritional risk index; PG-SGA, patient-generated subjective global assessment; PINI, prognostic inflammatory and nutritional index.

Table 15: Prevalence of muscle loss in adult patients with bone and soft tissue (osteosarcoma) cancer

Country (reference)	Patient population	Measure used	Prevalence
Germany (182)	Patients (age=NR) with advanced or metastatic soft tissue sarcoma N=89	CT imaging	• Sarcopenia:31%
Holland (183)	Patients (median age 67 years) with spinal metastases treated with palliative radiation therapy N=310	CT imaging	• Sarcopenia: 26%

†Data generated from a systematic review.
Abbreviations: CT, computed tomography; NR, not reported.

Gynaecological cancer

Patients with gynaecological cancer are at risk of malnutrition (Table 16) and muscle loss (Table 17).

Table 16: Prevalence of malnutrition in adult patients with gynaecological cancer

Country (reference)	Patient population	Measure used	Prevalence
France (1)	Adult (>18 years) inpatients and outpatients with malignant diagnosis N=137	BMI Weight	• Malnutrition: 32% ○ Severe: 15.6% ○ Moderate: 16.4%

Abbreviations: BMI, body mass index.

Table 17: Prevalence of muscle loss in adult patients with gynaecological cancer

Country (reference)	Patient population	Measure used	Prevalence
EU† (56)	Patients (mean age 59 years) with endometrial cancer N=224 from 2 studies	BMI Weight	• Cachexia: 32.2%
Holland (184)	Patients (age=NR) with ovarian cancer N=123	CT imaging	• Low baseline skeletal muscle index: 62%

†Data generated from a systematic review.
Abbreviations: BMI, body mass index; CT, computed tomography; NR, not reported.

Renal cancer

Patients with renal cancer are at risk of muscle loss (Table 18).

Table 18: Prevalence of muscle loss in adult patients with renal cancer

Country (reference)	Patient population	Measure used	Prevalence
EU† (56)	Patients (age=NR) with urinary bladder cancer N=NR from NR studies	BMI Weight	• Cachexia: 25.2%
EU† (56)	Patients (age=NR) with kidney and renal pelvis cancer N=NR from NR studies	BMI Weight	• Cachexia: 31.6%

†Data generated from a systematic review.
Abbreviations: BMI, body mass index; NR, not reported.

Brain cancer

Patients with brain cancer are at risk of malnutrition (Table 19).

Table 19: Prevalence of malnutrition in adult patients with brain cancer

Country (reference)	Patient population	Measure used	Prevalence
Germany (57)	Patients (≥18 years) with neuroendocrine neoplasms N=203	SGA NRS	• Malnutrition or at risk of malnutrition: 25.1% • High risk of malnutrition: 21.7%
Germany (185)	Patients (age=NR) with neuroendocrine tumours N=26	SGA Body weight	• Severe or moderate malnutrition: 36%

Abbreviations: NR, not reported; NRS, nutritional risk screening; SGA, subjective global assessment.

Haematological malignancies

Patients with haematological malignancies are at risk of malnutrition (Table 20).

Table 20: Prevalence of malnutrition in adult patients with haematological malignancies

Country (reference)	Patient population	Measure used	Prevalence
Austria (62)	Patients (>70 years) with newly diagnosed haematological malignancies N=147	MNA BMI	• Malnutrition: 15% • At risk of malnutrition: 43%

France (1)	Adult (>18 years) inpatients and outpatients with malignant diagnosis
	N=156
		BMI
		Weight
			• Malnutrition: 34.2%
			  ○ Severe: 7.9%
			  ○ Moderate: 26.3%

France (4)	Patients (>18 years) undergoing allogeneic hematopoietic stem cell transplantation N=84	NRI	Hospital admission • Malnutrition: 26% Hospital discharge • Malnutrition: 57%
Netherlands (65)	Patients (>70 years) with non-Hodgkin lymphoma N=44	MNA	• Malnutrition or at risk of malnutrition: 34%

Abbreviations: BMI, body mass index; MNA, mini nutritional assessment; NRI, nutritional risk index.

Appendix B:
Effect of malnutrition and muscle loss on mortality, by cancer type

GI cancer

Mortality is increased in patients with GI cancer and malnutrition (Table 21) and muscle loss (Table 22).

Table 21: Effect of malnutrition on mortality in patients with GI cancer

Country (reference)	Patient population	Effect on mortality
GI cancer		
UK (186)	Patients with small bowel obstruction due to primary tumours of the intestine or intra-abdominal malignancy N=205	NRI (low risk, moderate risk, and high risk) • In-hospital mortality ○ Moderate risk-adjusted HR 3.99 [95% CI: 0.92 to 17.29], p=0.064 ○ High risk-adjusted HR 6.47 [95% CI: 1.44 to 29.09], p=0.015
Colorectal cancer		
Ireland (187)	Patients receiving palliative chemotherapy for colorectal cancer N=268	Loss of >6.4% subcutaneous fat over 100 days vs stabilisation/gain • HR 2.2 [95% CI: 1.07 to 4.62], p=0.033
Oesophageal cancer		
Britain (29)	Patients with oesophageal cancer N=258	NRI <100 vs NRI ≥100 • Median survival time 15.7 months vs 31.6 months, HR 12.5 [95% CI: 5.2 to 29.6], p<0.001

†Data generated from a systematic review.
Abbreviations: CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; NRI, nutritional risk index.

Table 22: Effect of muscle loss on mortality in adult patients with GI cancer

Country (reference)	Patient population	Effect on mortality
GI cancer		
Global† (53)	Patients with GI cancer N=21,875 from 70 studies	Sarcopenia vs no sarcopenia • Mortality HR 1.602 [95% CI: 1.369 to 1.873], p<0.001 • Disease-free mortality HR 1.461 [95% CI: 1.297 to 1.646], p<0.001
Colorectal cancer		
Austria (188)	Patients with CRC liver metastases who underwent liver resection N=355	Sarcopenia vs no sarcopenia • OS HR 1.47 [95% CI: 1.03 to 2.46], p=0.03 • Disease-free mortality HR 1.74 [95% CI: 1.09 to 3.4], p=0.05

Country (reference)	Patient population	Effect on mortality
The Netherlands (189)	Patients with CRC undergoing elective open colon resection N=91	Sarcopenia vs no sarcopenia • OS HR 8.54 [95 % CI 1.07 to 68.32] • Median OS: 37.4 vs 63.0 months, p=0.013
Oesophageal cancer		
Global† (190)	Patients with oesophageal cancer 13 studies	Sarcopenia vs no sarcopenia • OS HR 1.67 [95% CI: 1.18 to 2.38], p=0.004
Belgium (191)	Patients with oesophageal cancer N=155	Low muscle mass vs normal muscle mass and sarcopenia vs no sarcopenia • 5-year mortality (low muscle mass) HR 1.63 [95% CI: 1.04 to 2.56], p=0.03 • 5-year mortality (sarcopenia) HR 1.77 [95% CI: 1.12 to 2.79], p=0.01
Global† (192)	Patients with oesophageal cancer post-oesophagectomy N=1,520 from 11 studies	Sarcopenia vs no sarcopenia • 3-year mortality 51.6% vs 65.4%, p<0.001 • 5-year mortality 41.2 % vs 52.2%, p=0.018 • OS HR 1.58 [95% CI: 1.35 to 1.85], p<0.001 • DFS HR 1.46 [95% CI: 1.12 to 1.90], p=0.005
Gastric cancer		
Global† (105)	Patients with gastric cancer N=2,412 from 9 studies (mortality) N=1,702 from 9 studies (disease-specific mortality)	Pre-operative low muscle mass vs normal muscle mass • Mortality HR 1.81 [95% CI: 1.52 to 2.14] • Disease-specific mortality HR 1.58 [95% CI: 1.36 to 1.84]
Pancreatic cancer		
Italy (101)	Patients with advanced pancreatic cancer N=165	Early loss of skeletal muscle mass of ≥10% vs <10% loss of skeletal muscle mass • OS HR 2.16 [95% CI: 1.23 to 3.78], p=0.007
Liver cancer		
Global† (14)	Patients with hepatocellular carcinoma N=2,513 from 10 studies	Sarcopenia vs no sarcopenia • All-cause mortality adjusted HR 1.95 [95% CI: 1.60 to 2.37]
The Netherlands (178)	Patients with hepatocellular carcinoma N=90	Sarcopenia vs no sarcopenia • OS 33 months vs 105 months; HR 3.756, p=0.001
Germany (193)	Patients with hepatocellular carcinoma N=58	Low FFMA vs normal • OS 197 vs 294 days, p=0.024; HR 2.675, p=0.011 • PFS 109 vs 185 days, p=0.068

†Data generated from a systematic review.
Abbreviations: BIA, bioelectrical impedance analysis; BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; CT, computed tomography; DFS, disease-free survival; FFMA, fat-free muscle area; GI, gastrointestinal; HR, hazard ratio; OS, overall survival.

Head and neck cancer

Mortality is decreased in patients with head and neck cancer and malnutrition (Table 23) or muscle loss (Table 24).

Table 23: Effect of malnutrition on mortality in adult patients with head and neck cancer

Country (reference)	Patient population	Measure used Prevalence
Germany (194)	Patients with head and neck cancer N=42	BIA (PA <5.0 vs PA >5.0) • OS: 13.84 months vs 51.16 months, p=0.016
The Netherlands (64)	Patients with head and neck cancer (≥70 years) N=102	MNA (≤11 vs >11) • Mortality HR 3.40 [95% CI: 1.83 to 6.33

Abbreviations: BIA, bioimpedance analysis; CI, confidence interval; HR, hazard ratio; MNA, mini nutrition assessment; PA, phase angle.

Table 24: Effect of muscle loss in adult patients on mortality with head and neck cancer

Country (reference)	Patient population	Effect on mortality
The Netherlands (195)	Patients with head and neck cancer (≥70 years) N=85	Sarcopenia vs no sarcopenia • Median OS 12.07 months vs 13.60 months, p=0.02 • 3-year OS 39% vs 75%, p=0.03
The Netherlands (122)	Patients with head and neck cancer undergoing total laryngectomy N=235	Low skeletal muscle mass vs normal skeletal muscle mass • OS 18.5 months vs 30.1 months, p<0.001

Abbreviations: CI, confidence interval; OS, overall survival.

Lung cancer

Mortality is decreased in patients with lung cancer and muscle loss (Table 25).

Table 25: Effect of muscle loss on mortality in adult patients with lung cancer

Country (reference)	Patient population	Effect on mortality
Global† (196)	Patients with lung cancer N=1,117 from 10 studies	Sarcopenia vs no sarcopenia • Mortality HR 1.96 [95% CI: 1.49 to 2.59], p<0.001
Global† (108)	Patients undergoing lung resection N=636 from 3 studies	Sarcopenia vs no sarcopenia • Mortality HR 2.31 [95% CI: 1.26 to 4.24], p=0 .007

†Data generated from a systematic review.
Abbreviations: CI, confidence interval; HR, hazard ratio.

Gynaecological cancer

Mortality is decreased in patients with gynaecological cancer and muscle loss (Table 26)

Table 26: Effect of muscle loss on mortality in adult patients with gynaecological cancer

Country (reference)	Patient population	Effect on mortality
Italy (197)	Patients with ovarian cancer presenting with bowel obstruction N=40	Cachexia vs no cachexia • Mortality OR 3.2 [95% CI: 1.5 to 6.6], p=0.001

Abbreviations: CI, confidence interval; OR, odds ratio.

Haematological malignancies

Mortality is decreased in patients with haematological malignancies and muscle loss (Table 27).

Table 27: Prevalence of malnutrition on mortality in adult patients with haematological malignancies

Country (reference)	Patient population	Effect on mortality
Austria (62)	Patients (>70 years) with newly diagnosed haematological malignancies N=147	Low BMI vs normal BMI • OS at 2 years HR 3.3 [95% CI: 1.8 to 6.0], p<0.001

Abbreviations: BMI, body mass index; HR, hazard ratio; OS, overall survival.

Appendix C:
Effect of malnutrition and muscle loss on risk of post operative complications, by cancer type

GI cancer

Risk of post-operative complications is increased in patients with GI cancer and malnutrition (Table 28) and muscle loss (Table 29).

Table 28: Effect of malnutrition on post-operative complications in patients with GI cancer

Country (reference)	Patient population	Effect on post-operative complications
Colorectal cancer		
UK (119)	Patients with CRC who received elective CRC resection	PNI <40 vs PNI >40 • PNI score <40 was associated with severity of post-operative complications, p=0.001

Abbreviations: PNI, prognostic nutritional index.

Table 29: Effect of muscle loss on post-operative complications in patients with GI cancer

Country (reference)	Patient population	Effect on post-operative complications
GI cancer		
Global† (53)	Patients with GI cancer N=21,875 from 70 studies	Pre-operative sarcopenia vs no sarcopenia • Total complications RR 1.188 [95% CI: 1.083 to 1.303], p<0.001 • Major complications RR 1.228 [95% CI: 1.042 to 1.448], p=0.014
Global† (106)	Patients with GI cancer undergoing surgery N=7,176 from 29 studies	Pre-operative sarcopenia vs no sarcopenia • All complications RR 1.35 [95% CI: 1.12 to 1.61], p=0.001 • Major complications RR 1.40 [95% CI: 1.20 to 1.64], p<0.001
Colorectal cancer		
Britain (198)	Patients with CRC undergoing resection N=199	Sarcopenia vs no sarcopenia • Significant complications adjusted OR 6.33 [95% CI: 1.65 to 24.23], p=0.007 • Anastomotic leak in patients with anastomosis adjusted OR 14.37 [95% CI: 1.37 to 150.04], p=0.026
The Netherlands (189)	Patients with CRC undergoing elective open colon resection N=91	Sarcopenic obesity vs no sarcopenic obesity • Severe complications, p≤0.008
Oesophageal cancer		
Global† (199)	Patients with oesophageal neoplasia undergoing oesophagectomy	Sarcopenia vs no sarcopenia

	N=1,859 from 10 studies	• Respiratory complications RR 1.64 [95% CI: 1.21 to 2.22] • Anastomotic leaks RR 1.39 [95% CI: 1.10 to 1.76]
Global† (190)	Patients with oesophageal cancer N=NR from 7 studies	Sarcopenia vs no sarcopenia • Pulmonary complications after oesophagectomy OR 2.03 [95% CI: 1.32 to 3.11], p=0.001
Ireland (120)	Patients with locally advanced oesophageal cancer undergoing multimodal therapy N=252	Pre-operative sarcopenia vs no sarcopenia • Major postoperative complications OR 5.30 [95% CI: 1.94 to 14.45], p=0.001 • Pulmonary complications OR 2.17 [95% CI: 1.12 to 4.23], p=0.023 • Pneumonia OR 2.33 [95% CI: 1.18 to 4.61], p=0.015
Gastric cancer		
Germany (99)	Patients with gastric or gastro-oesophageal junction cancer N=60	Sarcopenia vs no sarcopenia • Perioperative complications: 43.3% vs 17.0%, p=0.009
Ireland (123)	Patients with gastric adenocarcinoma who underwent surgical resection N=56	Sarcopenia vs no sarcopenia • Serious in-hospital complications OR 3.508, p=0.042
Global† (105)	Patients with gastric cancer N=2,100 from 12 studies (post-operative complications) N=1,614 from 9 studies (severe post-operative complications)	Pre-operative low muscle mass vs normal muscle mass • Post-operative complications OR 2.09 [95% CI: 1.55 to 2.83] • Severe post-operative complications OR 1.73 [95% CI: 1.14 to 2.63]
Pancreatic cancer		
Italy (96)	Patients with pancreatic cancer who experienced a major complication following pancreaticoduodenectomy N=120	Sarcopenic obesity vs no sarcopenic obesity • Failure to rescue (defined as the probability of death after a complication) OR 5.71 [95% CI: 1.58 to 20.72], p=0.008
Liver cancer		
The Netherlands (178)	Patients with hepatocellular carcinoma N=90	Sarcopenia vs no sarcopenia • Major complications: 32.7% vs 13.2%, p=0.033

†Data generated from a systematic review.
Abbreviations: CI, confidence interval; CRC, colorectal cancer; GI, gastrointestinal; HR, hazard ratio; OR, odds ratio; RR, relative risk.

Head and neck cancer

Risk of post-operative complications is increased in patients with head and neck cancer and muscle loss (Table 30).

Table 30: Effect of muscle loss on post-operative complications in patients with head and neck cancer

Country (reference)	Patient population	Effect on post-operative complications
France (107)	Patients with head and neck cancer N=92	Malnutrition (NRI <97.5) vs no malnutrition (NRI >97.5) • Risk of post-operative complication: 62% vs 17%, p<0.001 Sarcopenia vs no sarcopenia • Risk of post-operative complication: 56% vs 22%, p<0.01)
The Netherlands (122)	Patients with head and neck cancer undergoing total laryngectomy N=235	Low skeletal muscle mass vs normal skeletal muscle mass • Pharyngocutaneous fistula 34.9% vs 20.6%, p=0.02

Abbreviations: NRI, nutritional risk index.

Lung cancer

Risk of post-operative complications is increased in patients with lung cancer and muscle loss (Table 13).

Table 31: Effect of muscle loss on post-operative complications in patients with lung cancer

Country (reference)	Patient population	Effect on post-operative complications
Global† (108)	Patients with lung cancer undergoing lung resection N=636 from 4 studies	Sarcopenia vs no sarcopenia • Early post-operative complications OR: 2.51 [95% CI: 1.55 to 4.08], p<0.001)

†Data generated from a systematic review.
Abbreviations: CI, confidence interval; OR, odds ratio.

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