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Early Satiety in Cancer: An Investigation into a Highly Impactful Orphan Symptom

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A thesis submitted to Trinity College Dublin, the University of Dublin in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

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DECLARATION

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university, and it is entirely my own work.

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Informed consent was obtained from all participants in the studies described in this thesis.

Signed

_____

Aidan O'Donoghue

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LIST OF ABBREVIATIONS

abPG-SGA: Abridged Patient-Generated Subjective Global Assessment

AD: Autonomic Dysfunction

ADPM: Academic Department of Palliative Medicine

AgRP: Agouti Related Protein

AKPS: Australia-modified Karnofsky Performance Scale

ARC: Arcuate Nucleus

BIA: Bioelectrical Impedance Analysis

BMI: Body Mass Index

CAM: Complementary and Alternative Medicine

CART: Cocaine and Amphetamine Related Transcript

CC: Cancer Cachexia

CCK: Cholecystokinin

CNS: Central Nervous System

COVID-19: Coronavirus Disease 2019

EBM: Evidence Based Medicine

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire

ESPEN: European Society for Clinical Nutrition and Metabolism

EWGSOP: European Working Group on Sarcopenia in Older People

FFMI: Fat Free Mass Index

GA: Gastric Accommodation

GI: Gastrointestinal

GIP: Gastric Inhibitory Polypeptide

GLIM: Global Leadership Initiative on Malnutrition

GLP-1: Glucagon Like Peptide 1

HGS: Handgrip Strength

HSCP: Health and Social Care Professional

NIS: Nutrition Impact Symptom

NPY: Neuropeptide Y

ODW: Oncology Day Ward

OLH&CS: Our Lady's Hospice & Cares Services

OSQ: Open Symptom Questionnaire

OXM: Oxyntomodulin

PCU: Palliative Care Unit

PIL: Participant Information Leaflet

PPI: Patient Public Involvement

PYY: Peptide YY

POMC: Proopiomelanocortin

QoL: Quality of Life

RS: Raw Score

SEES: Symptom Experience of Early Satiety

SSS: Sensory Specific Satiety

STS: Sit to Stand

TUG: Timed Up and Go

VAS: Visual Analogue Scale

ABSTRACT

Patients with cancer experience multiple symptoms throughout the different stages of cancer care. One common symptom related to nutritional intake is known as early satiety. This symptom has no agreed definition but has been described as ‘feeling full quickly’. This thesis explored this symptom in cancer with a focus on two patient populations: those undergoing active anticancer treatment and those with advanced cancer receiving specialist palliative care.

A scoping review of the literature found early satiety is a chronically under-researched symptom in cancer. Where studies outlined how early satiety was identified, there were several different descriptions used and less than half used validated tools to identify it. This review also found it to be present in many different cancers and was unanimously the most common symptom post oesophagectomy in cancer. Early satiety was also associated with cachexia, poorer physical health, and shorter prognosis. Despite this impact, there was no clear pathophysiology identified and no studies investigated any potential treatment.

Patients with cancer had a high symptom burden, regardless of disease stage. Early satiety was almost never self-reported by patients unless assessed using a closed question symptom checklist. Despite rarely self-reporting it, early satiety was one of the most common symptoms, more common than other well-known symptoms in cancer of anorexia or nausea. It was also one of the only symptoms to be associated with both screened risk of malnutrition and diagnosed malnutrition.

To determine how patients with early satiety described it, a new questionnaire was developed and piloted on patients with advanced cancer. Once adjusted, it was then used on both cohorts. Most experiences regarding early satiety appeared to be individualised. There were mixed reports regarding when early satiety was first experienced and its severity. One commonality was that it reduced nutritional intake. Another was that none had ever been screened for early satiety prior to inclusion in this thesis.

Patients with cancer had a lower quality of life compared to normative values for the general population. Early satiety significantly impaired this quality of life alongside several other symptoms. It appeared to have a specific reduction in the role functioning component of quality of life. There appeared to be no impact of early satiety on physical functioning in cancer.

This thesis confirmed that early satiety is a highly impactful orphan symptom in cancer that impacts both physical and psychological health. It is under reported in both research and clinical care. This thesis also demonstrated the need for further research into this symptom to ensure improved patient care.

LAY ABSTRACT

People with cancer experience lots of different side effects from the cancer itself and the treatment. Almost everyone will experience some sort of issue that lowers their ability to eat, such as a loss in appetite, feeling nauseous, vomiting and changes in how foods taste and smell.

One issue that people experience in many different health conditions, including cancer is known as early satiety. This is also known as feeling full quickly. This thesis used four studies to answer the questions below:

1. What information has been published about early satiety in cancer?
2. Do people with cancer report their early satiety and does it make people more likely to be malnourished?
3. How do patients with early satiety describe their experience with the symptom?
4. Does early satiety influence people's ability to do normal daily activities and does it have an impact on quality of life?

The first study in this thesis looked at what scientific information has been published about early satiety to help better understand the symptom. All of the published studies in this area were read, and their results were put together. There were very few studies that researched early satiety. The results showed that it does not have a definition and there were lots of different ways it has been described. It is also common in lots of cancers, even after the cancer treatment has finished. There was no information on how it develops in cancer, or any treatment found. This was also the first time this type of study was done for this symptom.

In the second study of this thesis, people with cancer were asked about their symptoms and were tested for whether they were at risk of malnutrition, a condition where the body does not have enough nutrients to fuel it. Early satiety was almost never reported unless people were specifically asked about it. Despite not reporting it, early satiety increased the risk of malnutrition and was one of the only symptoms to be linked with diagnosed malnutrition.

The third study in this thesis wanted to see how people who had early satiety described what it is. They were asked questions about it such as when they first experienced it, does it limit how much they can eat, have they ever been asked about it before this study. Everyone seemed to have a different experience of early satiety. One part that everyone had in common was that it limits how much they can eat, and they had never been asked about the symptom before. Half of the people with early satiety found a way to help manage it, but there were lots of different ways found. Other studies can take these ways to help people with early satiety and scientifically test them to see if any of them are the most beneficial. There were also some interesting links between early satiety and quality of life.

The final study followed on from these hints. Quality of life was measured using a well-known questionnaire. Early satiety did result in a reduced quality of life. It was however not linked with the ability to do normal daily activities. This study also found that people with cancer have less strength than people without cancer and might be at risk of falling.

Overall, the work done in this thesis showed that early satiety is very common in people with cancer. Despite how common it is, as well as how much it impacts

people’s physical and mental health, there is very little information about it that has been published. This thesis also showed what studies should be done in the future to better understand early satiety and eventually find a way to treat it.

OUTPUTS

Related to this thesis

Papers

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Book Chapters

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Oral Presentations

Sources of Diet and Nutrition Advice After a Cancer Diagnosis

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The Symptom Experience of Early Satiety in Advanced Cancer

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Taste and Smell abnormalities in Advanced Cancer. IAPC Education and Research Seminar, February 2019

The Symptom Experience of Early Satiety – A Pilot Study. Multinational Association of Supportive Care in Cancer (MASCC) / International Society of Oral Oncology (ISOO) Annual Conference, virtual conference, June 2021. Support Care Cancer 2021 Jun 15;1-261 OTHER-26. doi: 10.1007/s00520-021-06285-8. Online ahead of print

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1 INTRODUCTION AND LITERATURE REVIEW

1.1 Cancer

Cancer is a group of over 100 diseases that are related to the uncontrolled proliferation of cells. A mass of these cells is known as a tumour. These tumours can develop in virtually any bodily tissue.[1] As the tumour continues to grow and develop, it begins to occupy more and more space in the body. It must invade neighbouring tissue and continue to grow, or tumour cells move to another area of the body. This thesis will focus on a heterogeneous cancer cohort rather than any specific cancer.

1.1.1 Incidence

In Ireland, there are approximately 40,000 new cases of cancer annually.[2] Cancer is the cause of the most deaths in Ireland accounting for approximately 30% of deaths per year.[2] This accounts for 24 cancer deaths daily. The incidence of cancer continues to rise with an expected 50% increase by 2040.[3] The number of cancer survivors however is increasing. The needs of these survivors are not met in Ireland[4] despite the predictions of continued growth.[5]

1.1.2 Staging

Cancers are classified using the TNM staging classification. This system is internationally recognised and maintained by the 'Union for International Cancer Control'. It is a beneficial system as it allows standard communication across all areas of oncology from oncologists to researchers. It also allows for comparison between different cancers and treatments. The aspects of TNM are as follows:

- T – Primary site of the tumour
- N – Whether there is local lymph node involvement
- M – The presence or absence of tumour metastasis

Although this staging system appears basic on the surface, it is indeed much more than above and allows for a detailed staging of disease. The anatomical stage classification of the disease is given in Roman numerals (I, II, III, IV). There may also be further clarification as to how the TNM was determined. When stating TNM or cTNM, it is implied that the staging was determined based on clinical examination. When there has been surgical investigation of the tumour, pTNM is written. This allows for two distinct systems of clinical and pathological TNM. Finally, there are additional descriptors as follows:

- X – Sometimes there may not be accurate staging of the disease before therapy starts. This may be due to time constraints or difficulty determining stage based only on clinical examination. In this instance, X is used to highlight that this aspect of the staging is unclear. For example, TX indicates that the primary site of the tumour could not be determined.
- y – If neoadjuvant treatment is recommended, the stage of the disease before surgery or radiotherapy may be different if no neoadjuvant treatment was done. In this instance, y precedes the TNM to indicate that it was a pre-neoadjuvant staging.
- R – This classification is used to indicate the remaining disease after treatment.
- r – This descriptor is used to describe the extent of the disease at the time of recurrence.

1.1.3 Advanced Disease

As part of this thesis, research was conducted on cancer patients with advanced disease receiving specialist palliative care. Palliative care is defined by the World Health Organisation as follows[6]:

> 'Palliative care is an approach that improves the quality of life of patients (adults and children) and their families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual.'

The goals of palliative care are centred around quality of life and symptom management. Despite preconceived notions, palliative care is not limited to end of life care. Early integration of palliative care has been shown to improve quality of life and potentially survival in those with advanced cancer.[7-9] There is likely to be a continued increase in the number of presentations with advanced disease in the coming years due to the delays in diagnosis and treatment caused by the Coronavirus disease 2019 (COVID-19).[10]

1.1.4 Nutritional Side Effects Of Cancer

Three common side effects of cancer and its treatment are sarcopenia, malnutrition, and cachexia. Although these are present in a variety of illnesses, all three are highly prevalent in cancer.

1.1.4.1 Sarcopenia

Sarcopenia refers to the progressive loss of muscle mass that is often associated with several adverse outcomes.[11] It is a formally recognised muscle disease by the International Classification of Disease.[12] The gold standard for the diagnosis of sarcopenia is using computed tomography (CT) at the third lumbar vertebrae.[13] It can also be identified using other assessments of body composition or measures of muscle strength such as grip strength and chair stands.[11] Nutrition plays a pivotal role in sarcopenia. Poor oral intake is associated with a loss of muscle mass[14], with protein being a particularly important nutrient for muscle maintenance.[15] Any symptoms that may reduce the intake of energy and protein can exacerbate sarcopenia.

Sarcopenia is present in over a third of patients with cancer.[16] Incidence differs depending on the cancer type and the diagnostic criteria used to identify sarcopenia. Incidence in older cancer patients ranges from 18.5-83%.[17] This is higher than the review by the European Working Group on Sarcopenia in Older People (EWGSOP) which focused on older adults, suggesting a close association with cancer.[18] There is an increased incidence of sarcopenia post oncological treatment[17], further indicating the impact of surgery, radiation therapy, immunotherapy, chemotherapy and hormonal therapy on muscle mass.

A recent systematic review that contained data on 6894 participants found independent associations between pre-therapeutic sarcopenia and severe post operative complications, increased chemotoxicity and shorter survival.[16] The negative impact of pre-therapeutic sarcopenia was present in both surgical and chemotherapy interventions. Sarcopenia is associated with impaired quality of life

(QoL), fatigue and low muscle strength.[19] It is also more prevalent in males than females.[19, 20]

1.1.4.2 Malnutrition

The onset of malnutrition is as a result of a lack of nutritional intake or absorption of nutrients that results in unintentional weight loss.[21] Its prevalence in cancer ranges from 20% to more than 70%.[22] Malnutrition is a serious burden on the healthcare system.[23] In Ireland, it was estimated to cost an additional €1.4 billion[24] which is likely higher now given this estimation is from more than a decade ago.

All patients with cancer should be screened for malnutrition. Valid nutrition screening tools should be used to detect it.[25] The Global Leadership Initiative on Malnutrition has published criteria for the diagnosis of malnutrition that includes the use of validated screening tools.[26] A multidisciplinary team is recommended to identify, prevent, and treat malnutrition in cancer.[27, 28] The aetiology of malnutrition is multifactorial and is influenced by factors such as tumour type, treatment side effects, functional performance and symptoms that limit nutritional intake.[29, 30] Malnutrition is associated with poorer clinical outcomes, QoL, higher healthcare cost, and increased mortality.[29, 31]

1.1.4.3 Cachexia

Cachexia is present in many conditions such as chronic obstructive pulmonary disease, chronic kidney disease, chronic heart failure, multiple sclerosis, and cancer. Cancer cachexia (CC) is a syndrome where there is a continuous loss of skeletal muscle that cannot be reversed by conventional nutritional support

resulting in a poor functional status.[32] It is considered a form of chronic malnutrition.

CC continues to be a difficult syndrome to define and have agreed diagnostic criteria. One of the first attempts to define cachexia was in 2006 at a consensus conference on cachexia. It was defined as ‘a complex metabolic syndrome associated with underlying illness and characterised by muscle loss with or without loss of fat mass’.[33] It is diagnosed according to the agreed diagnostic criteria in Figure 1.1. It is of particular importance as approximately 30% of patients die as a result of cachexia rather than the cancer itself.[34] The mechanism by which CC develops is complicated, often including a variety of systems. As weight plays an important role in CC, any reduction in nutritional intake may result in the development of CC.

- Weight loss >5% over past 6 months (in absence of simple starvation); or
- BMI <20 and any degree of weight loss >2%; or
- Appendicular skeletal muscle index consistent with sarcopenia (males <7.26kg/m^2; females <5.45kg/m^2) and any degree of weight loss >2%

Figure 1.1 Diagnostic criteria for cancer cachexia[32]

1.1.5 Nutrition Impact Symptoms

The above nutrition disorders are further compounded by nutrition impact symptoms (NIS). These are a spectrum of symptoms that impede nutritional intake in various conditions, including cancer.[35] NIS are common as most patients with cancer experience between 8 and 12 concurrent symptoms.[36-38] NIS are

present across the spectrum of cancer care from both patients yet to commence treatment[39], and those receiving end of life care.[40] These symptoms may be a result of both cancer treatment, and the tumour itself.[39, 41]

Anorexia is one of the most common NIS and is commonly associated with the above nutritional issues. Anorexia is a decrease in the desire to eat that reduces nutritional intake. The exact cause is unclear, however, cytokines[42] and anorectic gut hormones[43] have been suggested. Another is an alteration in the metabolism of key nutrients such as carbohydrates, proteins and fats.[44] Early satiety is another common NIS in cancer that has received very little attention and yet is a key component of the nutrition disorders discussed above. It is important to distinguish between these symptoms as while they often occur in tandem, they are distinct symptoms and can also occur independently of eachother.[45] One of the main differentiating factors is that those with early satiety may report a normal appetite.[46] Before exploring early satiety in detail (Section 1.3), below is a review of normal appetite regulation.

1.2 Appetite

The terminology surrounding appetite regulation is often confused and it is important to separate it into each of its components. It is divided into four processes:[47]

- Appetite: covers a wide spectrum of food preferences, motivations, selection
- Hunger: the mental urge to eat
- Satiation: the termination of an eating episode
- Satiety: the inhibition of further eating episodes

Satiation is an important area of interest. The lack of satiation has been a potential feature of the current obesity epidemic. The point of satiation is determined by a variety of bodily responses including neural and hormonal alterations which bring about meal termination. The term ‘satiety signals’ has been given to these which is an inaccurate description as they induce satiation and meal termination rather than delay subsequent eating.[48]

Energy balance is achieved through the complex regulation of energy intake and energy expenditure. This regulation of energy intake is done via two pathways: the homeostatic and the hedonic pathways. It is important to note that appetite differs from hunger. Hunger is the need to eat and is driven by the body’s homeostatic regulation of food intake with physiological drivers that influence hunger. Some of the symptoms of hunger are dizziness, fatigue, and poor concentration. Appetite is the desire to eat. It is driven by the hedonic regulation of food intake in the body.

Actual food intake is the result of several factors including hunger, appetite, satiation, and satiety. The role of appetite in food intake can be seen with the growing numbers of overweight and obese individuals throughout the world. If food intake was completely governed by the homeostatic need for energy alone, once the point of satiation was reached, then no more food would be consumed until the onset of hunger. We know that this is not the case and that there are a multitude of factors that regulate food intake, including both internal and external stimuli. Consumption may be over what is required when the food is particularly palatable.

1.2.1 Neural Appetite Regulation

1.2.1.1 ***Hypothalamic Regulation***

In the hypothalamus, the arcuate nucleus (ARC) is the primary centre for the homeostatic regulation of food intake. Different areas of the hypothalamus control different aspects of appetite. Both the cocaine and amphetamine related transcript (CART) and proopiomelanocortin (POMC) express anorectic neuropeptides.[49] The second group of neuron clusters are the neuropeptide Y (NPY) and agouti-related protein (AgRP) which express orexigenic neuropeptides.[49] The lateral hypothalamus and perifornical nucleus regulate hunger while the ventromedial nucleus and the paraventricular nucleus regulate satiety. Appetite regulation however is not as straightforward as hedonic factors such as the emotional response to eating or how visually appealing a food is also influences appetite.

1.2.1.2 The Vagus Nerve

Gastrointestinal (GI) functions are controlled through the autonomic nervous system. The intestines are capable of functioning without input from the central nervous system (CNS), whereas the upper portion of the GI tract is significantly more dependent on neural inputs.[50, 51] The GI tract is innervated by neurons from both the sympathetic and parasympathetic nervous systems. Parasympathetic innervation to the GI tract is provided by the vagus nerve. The vagus nerve is a major nerve with both efferent and afferent components. It plays a key role in the gut-brain axis by transporting sensory information from peripheral systems and organs to the brain while also conveying functions through efferent pathways.[52]

The vagus nerve appears to be particularly important in the homeostatic regulation of nutritional intake. Vagal nerve efferents play a key role in the motility of a food bolus through the GI tract. Vagal afferents are sensitive to stretching and transmit valuable information about the volume of ingested food.[53, 54] Ghrelin and the vagus nerve are closely interlinked in appetite and digestion.[55] In rat studies, vagotomy resulted in decreased gastric acid secretion, even with ghrelin administration.[56, 57] It appears that most gut hormones rely on their activation of receptors on vagal afferent nerve endings to mediate their control of GI function.[58-60] Despite the breadth of vagal afferents throughout the GI tract and the key role of the vagus nerve in appetite regulation, the full extent of its role is not fully understood. This is highlighted by the fact that total vagotomy does not cause significant hyperphagia and stimulation of the vagus nerve does not decrease nutritional intake.[61, 62]

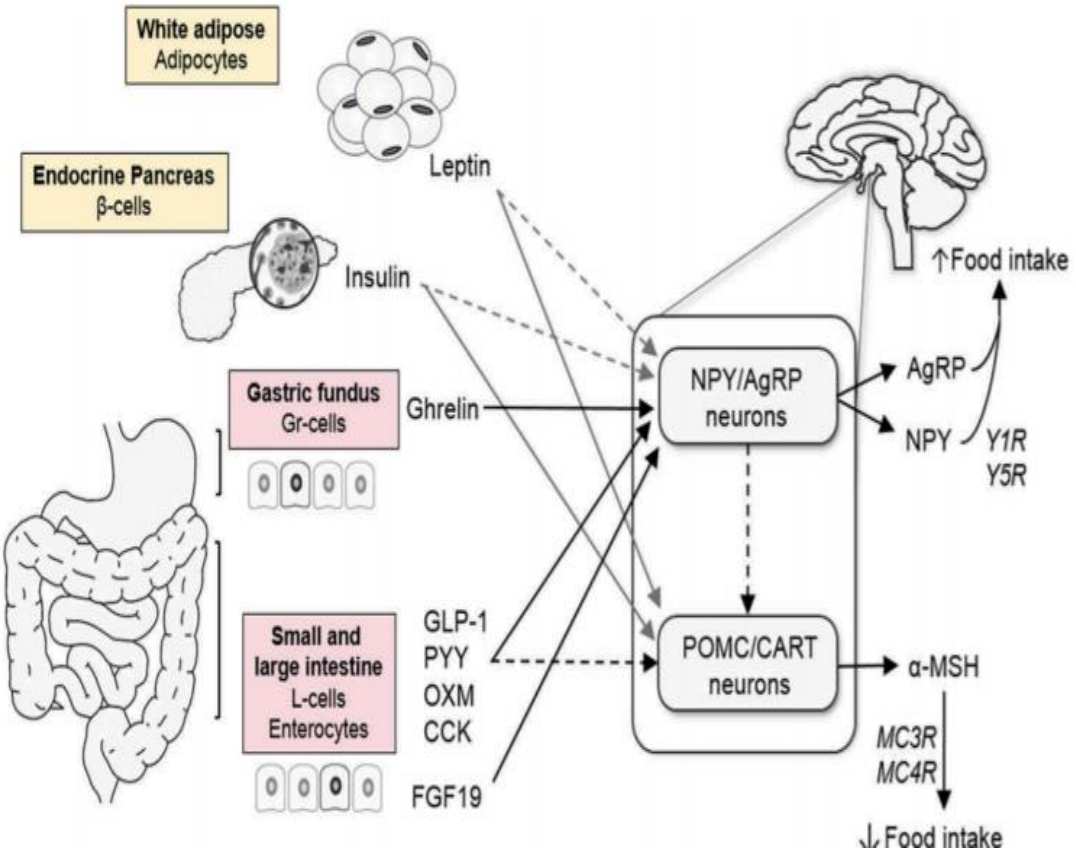


Figure 1.2 Appetite regulation via enteroendocrine system[63]

AgRP, agouti-related peptide; CART, cocaine and amphetamine regulated transcript; CCK, cholecystokinin; FGF19, fibroblast growth factor 19; GLP-1, glucagon-like peptide 1; MCR, melanocortin receptor; NPY, neuropeptide Y; OXM, oxyntomodulin; POMC, pro-opiomelanocortin; PYY, peptide YY; YR, Y receptor

1.2.2 Hormonal Appetite Regulation

1.2.2.1 ***Ghrelin***

Ghrelin is a 28-amino acid octanoylated orexigenic gut hormone.[64] It is predominantly secreted via the Gr-cells of the gastric fundus of the stomach. It was found to influence energy balance[65] via hypothalamic circuits.[66] The effects of ghrelin are mediated through a specific growth hormone secretagogue receptor (GHSR) known as the GHSR-1A which is highly expressed throughout the CNS.[67] Ghrelin has been shown to play a role in several pathologies including obesity

and depression[68], anxiety and memory retention[69, 70] as well as increasing cardiac output and contractility.[71] Formations of ghrelin have also been found in a variety of other organs outside of the stomach including the ovaries[72], kidneys[73], small intestines[74], lymphocytes[75], pancreas[76] and the testes.[77] The relevance of this expression has yet to be determined.

The site that produces the second most ghrelin is the CNS, predominantly the hypothalamus. The expression of ghrelin in the brain was first documented by Kojima et al.[64] The main site of action for ghrelin within the hypothalamus is the ARC.[66] In this study, the authors demonstrated that ghrelin increased the firing rate of NPY/AgRP neurons and inhibited the POMC neurons through the release of γ-amino butyric acid and NPY. This was further confirmed by Chen et al.[78] through molecular genetic studies. These studies demonstrated that the influence of ghrelin on the hypothalamus and appetite was through the manipulation of NPY release from ARC neurons. Despite its role, it is also unknown whether the central nervous system produces ghrelin at a physiologically relevant level.[79] Ghrelin production decreases in response to intake of carbohydrates, fibre, fats, and protein.[80]

In relation to appetite and digestion, ghrelin has several central and peripheral actions. These include the modulation of gut motility[81] and the stimulation of gastric acid secretion.[82] Ghrelin levels increase before nutritional intake and decrease postprandially, indicating a role in appetite regulation.[83] Ghrelin is secreted in two forms: acyl ghrelin and des-acyl ghrelin. Historically, total plasma ghrelin has been measured rather than differentiating the two forms of ghrelin. There has been a recent increase in interest in the different forms of ghrelin,

despite being discovered in 1999. Ghrelin levels also increase due to food deprivation, as well as intentional and unintentional weight loss.[84, 85]

Contrary to expectations, research has shown that those with obesity exhibit lower levels of ghrelin. There is in fact a negative correlation between plasma ghrelin levels and body mass index (BMI).[65, 86] In a recent systematic review and meta-analysis by Wang et al[87], obese individuals showed a lower baseline plasma concentration of both AG and DAG, postprandial levels of AG declined and AG was suppressed for less time in obesity compared to healthy individuals.[87] Administration of ghrelin has been shown to increase nutritional intake.[88] There may be a competitive interaction between ghrelin and leptin in the regulation of appetite.[89] Similarly to leptin, its secretion appears to be reflective of the body's energy stores. Circulating ghrelin is inversely related to body weight, with levels increasing as a result of weight loss.[83]

1.2.2.2 Leptin

Leptin was discovered in 1994[90] with its presence predicted for more than 40 years based on studies involving *ob/ob* and *db/db* mice. Leptin is a 167 amino acid peptide with a molecular weight of 16KD derived from the *lep* gene.[91] Several receptors are present in different areas of the brain involved in appetite regulation with a high number present in the hypothalamus.[92] Leptin is primarily produced by white fat and its production is correlated to overall fat mass in the body.[93] Leptin results in an increase in POMC release through its interaction with POMC neurons.[94] Leptin also interacts with the orexigenic neurons of the ARC and reduces the secretion of NPY and AgRP by inhibiting neural activity at these sites.[95]

1.2.2.3 Glucagon Like Peptide 1

Glucagon Like Peptide 1 (GLP-1) is an anorexic gut hormone secreted via the L-cells of the intestines. They are positioned to be available for direct interaction with nutrients that pass through the gastrointestinal tract. However, GLP-1 secretion is biphasic in nature.[96] It is released within 15 minutes of ingestion of a food source. This is particularly interesting since most L-cells appear to be present in the distal gut.[97] Therefore, GLP-1 secretion may not be solely based on nutrient detection leading to other theories of L-cell activation and GLP-1 secretion.

There is a possible role for Gastric Inhibitory Polypeptide (GIP) in the secretion of GLP-1. The expression of GIP is most notable in the proximal gut. GIP levels appear to increase with the delivery of nutrients.[98, 99] One possible theory as to how GIP influences GLP-1 secretion involves the role of the vagus nerve.[100]. This was highlighted in a rat model where subdiaphragmatic vagotomy did not result in GIP production. To further highlight the role of the vagus nerve, once the subdiaphragmatic vagus nerve was stimulated manually, there was a marked increase in GIP. However, this is not a universally agreed theory. In a study by Little et al., GLP-1 was only secreted when >60cm of the small intestine was exposed to glucose.[101] This was not the case for GIP. This was also seen with Schirra et al. where GIP secretion was earlier than GLP-1 and peak GLP-1 secretion was achieved sooner with higher glucose ingestion and faster gastric emptying.[102] This implies again it is the exposure of glucose to the enteroendocrine cells that stimulates the secretion of GLP-1. Therefore, it is not fully understood what causes the release of GLP-1 but its anorexic properties are well established. GLP-1 receptors can be found in the intestines, central and

peripheral nervous systems.[103] The GLP-1 receptors appear to be most abundant in the ARC and PVN of the hypothalamus.[103, 104] These receptors are how GLP-1 influences appetite and gastric motility.

1.2.2.4 Peptide YY

Peptide YY (PYY) similar to GLP-1 is also released from the L cells of the small intestines.[105] Its secretion appears to be dependent on the intake of calories.[105] It is secreted in response to the intake of carbohydrates, fibre, fats and protein.[80] Its secretion is dependant also on each of these components with a high fat meal resulting in the highest secretion of PYY.[106] Interestingly this was only seen in normal weight and not obese models suggesting a potential attenuation of PYY in obesity. Similar to GLP-1, its release is biphasic in nature.[107] This indicates that there is a secondary cause for release besides direct nutrient sensing. It circulates in two forms: PYY_{1-36} and PYY_{3-36}.[108]

1.2.2.5 Cholecystokinin

Cholecystokinin (CCK) is secreted from the L-cells of the small intestine[109] in response to carbohydrates, fibre, fats and proteins.[80] CCK may also be a regulator in gastric emptying with a dose dependent response of CCK to gastric emptying time.[110] Its effect on gastric emptying appears to be via vagal fibres.[111] Injection of CCK has been shown to reduce nutritional intake in both rodent[112] and animal models[113]

1.2.2.6 Oxyntomodulin

Oxyntomodulin (OXM) is a gut peptide which is also secreted from the L cells within the intestines. It has been shown to have an anorectic effect with a

decrease in nutritional intake and improved weight loss.[114, 115] In fact, OXM appears to have a similar anorectic effect compared to GLP-1 when administered centrally.[116] Interestingly, OXM also appears to increase energy expenditure when active but does not affect resting energy expenditure.[117]

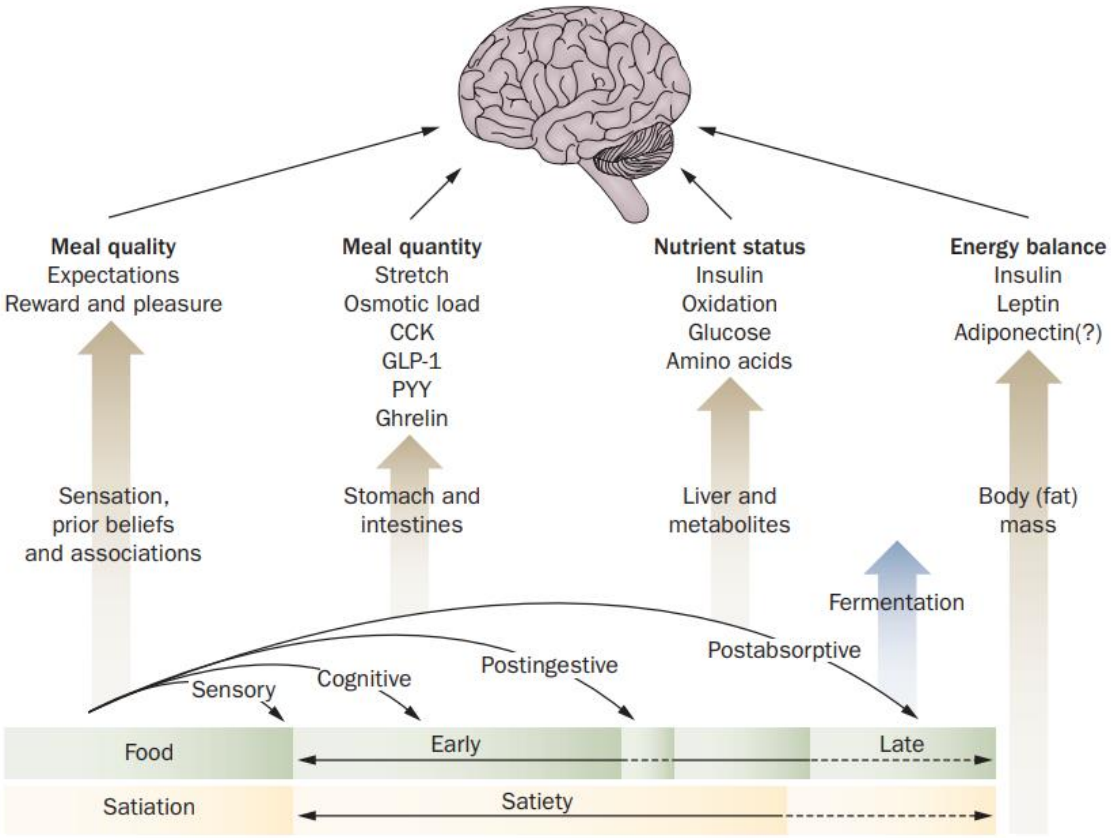


Figure 1.3 Satiety Cascade depicting the relationship between satiation and satiety[118]

1.2.3 Satiation and Satiety

There are a number of factors that dictate satiation and satiety as discussed above. The specific impact of macronutrients, food texture and taste on these components of appetite regulation are discussed below.

1.2.3.1 Carbohydrates

Carbohydrates are a major source of energy in most diets throughout the world. Carbohydrates are often subdivided into monosaccharides, disaccharides and oligosaccharides which vary based on chain length. Carbohydrates have a lower satiating effect than protein.

Aside from investigating simple sugars as discussed above, there has also been an increase in the focus on glycaemic index (GI). This is defined as the "incremental area under the blood glucose curve of a test food containing 50g of carbohydrate, expressed as a percentage of the response to a portion of the reference food containing 50g of carbohydrate, taken by the same subject on a different day".[119, 120] It was first introduced by Jenkins et al in 1981.[121] A high GI is generally accompanied by a high insulin response as it is absorbed into the blood faster than a low GI food. The ingestion of low GI foods has been suggested to prolong satiety.[122] There are mixed results concerning this given low GI did not increase subjective reports of satiety.[123] Carbohydrates have been shown to elicit secretion of GIP, GLP-1 and CCK.[124]

1.2.3.2 Protein

Protein has the most satiating effect of all macronutrients. This is one of the reasons it is a key component in a diet targeted for weight loss. High protein diets

have been shown to reduce body weight, improve blood lipid profiles and reduce blood pressure.[125, 126]

Protein intake results in a decrease in the plasma concentrations of ghrelin.[88] There also appears to be a dose related response to satiety hormones when protein is consumed. In a study by Belza et al[127], three different percentages of total energy intake through protein were evaluated: normal (14%), medium-high (25%) and high (50%). The high protein meal resulted in a 20%, 14% and 116% increase in GLP-1, PYY and glucagon respectively compared to normal protein. It also increased CCK and insulin while also decreasing ghrelin. There was a statistically significant increase in GLP-1 and PYY related to each increasing dose of protein. With increasing protein, there was an increase in subjective fullness and a decrease in hunger. There was however no effect on ad libitum food intake 4 hours after the test meal. This increase in satiety hormones[128-130] but no change in ad libitum food intake has also been shown by others.[129] However, this is not unanimous with some showing decreased energy intake after protein preload.[128, 131] It may also be gender dependent with protein having a less pronounced effect on satiety in women than men.[132] Therefore, the effect on satiation and hunger ratings appears to be more common than a change in satiety when protein is consumed.

1.2.3.3 Fibre

Dietary fibre refers to compounds which when consumed, reach the colon undigested. The effect of fibre on satiation and satiety varies depending on the properties of the fibre consumed, namely its hydration, viscosity and absorption. Fibre has traditionally been solid foods, but there have been some advances in

fibres that can be added to foods or drinks. These isolated compounds are often called functional fibre.[133]

Diets high in fibre have been shown to increase the viscosity and density of a food bolus[134] resulting in slower gastric emptying[135] and decreased gastric transit time through the GI tract[136] This is likely to result in the onset of satiation with fewer overall calories consumed. It is believed that this is mediated through afferent vagus nerve signals.[137, 138] More viscous fibres have been shown to decrease subjective appetite and energy intake more than less viscous fibres.[138] The actual influence of fibres on satiation, satiety and food intake remains somewhat unknown.[139, 140] This may be a result of a multitude of different fibre types and dosages used in interventional trials and warrants further evaluation.

1.2.3.4 Fat

Fat elicits its effect on satiety signals via the uptake of triacylglycerols into the small intestine.[141] The satiating effect of this uptake in the ileum appears to be greater than that of the duodenum.[142] Fat is the least satiating macronutrient, despite it having the highest kcal/kg.[143] It has been suggested that this may be one of the significant factors in the increasing rates of obesity.[144] Longer fatty acid chains appear to elicit greater gut hormone secretion and subsequent appetite suppression, namely via the stimulation of GLP-1 and CCK secretion.[145] There is currently mixed evidence as to whether the degree of saturation has any effect on the satiating potency of fats.[146]

1.2.3.5 Taste

Taste can alter appetite primarily via the hedonic regulation of appetite. Sensory-specific satiety (SSS) is an important concept to consider when discussing taste

and appetite regulation. This is the declining pleasure experienced when eating the same/similar food or flavour over time in comparison to new foods. This is also called taste fatigue. This may therefore have an influence on both food liking and food wanting. One study found that a four-course meal with four differing courses resulted in a 60% increase in intake when compared to all courses being the same food. Interestingly there was also a change in the perceived pleasantness of foods in the same category. When savoury foods were eaten, savoury foods that were uneaten were perceived as less desirable than sweet foods. The converse was also true.[147] Other studies have demonstrated evidence that continued exposure to the same food results in a decrease in overall consumption[148] and appetitive behaviour.[149] It is also seen that limiting food variety results in better weight control,[150] possibly mediated by an earlier point of satiation achieved in these participants. SSS has been demonstrated in amnesic participants indicating that SSS can exist outside of the awareness of previously eating.[151] Interestingly, Smeets et al. found that the consumption of foods that promote SSS increases satiety while merely chewing on these foods did not.[152] When the food was chewed, the desire to eat was less however hunger was unchanged. Therefore, it may be concluded that chewing on foods may achieve SSS however ingestion of nutrients is needed to induce satiation and satiety. There appears to be no effect on satiation or satiety in adults exposed to differing sweetness intensities.[153]

1.2.3.6 Texture

The texture of food can have major influences on appetite. As a general rule of thumb, the more mastication or processing of the food that is required, the more satiating that food is which ultimately results in lower intake.[154, 155] The reason is

that there is that decreased oro-sensory exposure to processing the food in the mouth results in a reduction in the cephalic phase response.[156, 157] This is not limited to satiation. There appears to be a relationship between oro-sensory exposure and satiety. This is highlighted in a study by Spetter et al.[158] Participants were given the same volume of 500ml of water or chocolate milk. The study was a cross over design with three separate sessions: nasogastric infusion of 500ml of water, nasogastric infusion of 500ml of chocolate milk and oral administration of 500ml of chocolate milk. Appetite ratings were significantly reduced in oral administration. Total ghrelin decreased and insulin increased more in the nasogastric infusion than the oral administration indicating a role in oro-sensory exposure and gut hormone release. Similarly, in a study by Cecil and Reed[159], there was a greater decrease in appetite when the test meal was consumed orally over intragastric administration. There was an even greater difference when compared to intraduodenal administration where there was no significant decrease in appetite despite administration at a rate similar to normal gastric emptying.

Expected satiety is highlighted in an interesting study by Cassady et al.[160] Participants were given test foods on four occasions. On one of the days, participants were informed that the test food would be given as a liquid and remain liquid once ingested. On the second day, they were informed the liquid would become solid on ingestion, despite being the same as the previous day. On the third day, participants consumed similar flavoured gelatine cubes and were told this would turn to liquid once ingested. Finally, on the fourth day they were informed that once the gelatine cube (same as the previous day) was ingested, it would remain as a solid in the stomach. Of note, the correct response

was that it would be liquid in the stomach. Despite this, when perceived that it would be a solid once consumed, postprandial subjective feelings of fullness increased, and hunger decreased. Interestingly, the perception of a more “solid” food being in the stomach increased gastric emptying time and expression of satiety gut hormones.

1.2.3.7 Measuring Satiation And Satiety

The measurement of these processes is often quite difficult given the complex nature of appetite regulation and the multiple interplay of systems required. Satiation is most commonly measured using an ad libitum meal experimental design. The goal of an ad libitum meal to measure satiation should be to limit the number of variances in the conditions as well as outside influences. One preferred option for this is to have a buffet style meal rather than a single test meal. One reason for this is the concept of taste fatigue. Another important factor to consider when preparing an ad libitum meal is taste preference. Unsurprisingly, participants are likely to have different food preferences when compared to each other. It is therefore best to use foods that are similarly liked. Palatability plays a key role in ad libitum intake in both normal[161, 162] and laboratory conditions.[163, 164]

Satiety is a more challenging concept to measure due to its subjective nature. Each individual has a non-standardised perception of satiety sensations. As a result, visual analogue scales remain the most frequently used measure of satiety.[165] There has also been the suggestion of using a satiety quotient as a measure of the satiating effects of foods and the resulting food intake. The satiety quotient was calculated by dividing the difference into visual analogue scales in relation to motivation to eat pre and post eating and dividing the result by the energy content of the food.[166] The appropriateness of this measure has been

brought to question given subjective reports do not accurately reflect appetite control and nutritional intake.[167]

1.3 Early Satiety

As previously discussed, Blundell's definition of satiation is the point of meal termination and satiety is the inhibition of further eating.[47] Satiation and Satiety may also be described as intra-meal satiety and inter-meal satiety respectively.

Early satiety is an important NIS associated with a wide variety of illnesses. It occurs when a person experiences a feeling of fullness and satisfaction after consuming less food than it would normally take to reach this point. It is characterised by a premature feeling of fullness which may occur before an individual has consumed an adequate amount to meet their needs. Although highly prevalent and widely reported by multiple disease groups, there is no agreed definition. Attempts to describe the symptom include 'the desire to eat associated with the subsequent inability to eat (except for small amounts) due to a sense of fullness'.[168]

With the previous definitions of satiation and satiety, it could be argued that early satiation rather than early satiety better describes the symptom. However, early satiety has become the term of choice in clinical practice and the literature. There is certainly the question as to the appropriateness of this. The ROME IV criteria for the diagnosis of gastroduodenal disorders specifically reference early satiation rather than early satiety.[169] It is important to distinguish that satiety refers to feelings of fullness between meals while satiation is the feeling of fullness during a meal. This distinction may prove important as they may reflect different mechanisms and or different symptoms.

Early satiety is identified by the American College of Gastroenterology as one of the symptoms to screen for when assessing gastric emptying in clinical practice.[170]

1.3.1 Prevalence

The prevalence of early satiety varies depending on the condition. It is among the most common symptoms of cancer with a prevalence ranging from 15%-52%.[171-173] In advanced cancer, the prevalence of early satiety appears to be higher and ranges from to 51%-77%[174-177] and is often among the most prevalent symptoms. It is also present in those yet to commence their oncological treatment[39], as well as cancer survivors[178] which suggests it is a symptom found at all cancer stages.

Interestingly it may be affected by sex as it is more common in females.[177] A difficulty associated with determining the prevalence is that there are no objective markers of early satiety. It may also be confused with other NIS (e.g. bloating, nausea, anorexia) by both the patient and the healthcare professional. Prevalence also appears to vary depending on the description of early satiety used.[46]

Its prevalence in gastroparesis is between 60 to 86%.[179] It is also seen as one of the most common GI symptoms amongst the general population with almost 1 in 4 people complaining of early satiety.[180] In a retrospective review of older adults referred to a dietitian, it was the most common symptom at 84%.[181] It is also present in Parkinson's disease,[182] chronic obstructive pulmonary disease,[183] end stage renal failure[184] and heart failure.[185]

1.3.2 Screening for Early Satiety in Cancer

Early satiety is not routinely screened for in many instances either clinically or in research. It is rarely provided as a symptom when asked an open-ended question.[186] This is made more difficult as most symptom assessments, including many nutrition screening tools do not include early satiety as a symptom. This is highlighted in a systematic review of symptoms experienced in incurable cancer. In this review, a total of 5 studies were identified which assessed the symptom of early satiety. This resulted in a low number of total participants in relation to the other symptoms and a confidence interval of >50%.[187]

This further exemplifies a lack of understanding of the symptom given that it is more common than many of the other symptoms included in the tools. Examples of screening tools that do ask about early satiety are the abridged Patient Generated Subjective Global Assessment (ab-PGSGA), Functional Assessment of Anorexia/Cachexia Treatment (FAACT) and the Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM). Without routine assessment of early satiety and inclusion in symptom assessment tools, it is difficult to determine the true prevalence in a wide variety of conditions. It must also be noted that these tools investigate the prevalence of early satiety but give no information on characteristics or severity.

Similarly to the screening for early satiety, there are no assessments validated for evaluating the impact of early satiety. This is done through subjective measures, predominately using categories (i.e. mild, moderate) which have no measured value for what represents these categories. Overall nutritional intake in relation to early satiety, and likely other NIS, is currently the only evaluation

and this is also most often done subjectively in a clinical setting. The evaluation may prove difficult for early satiety given its close association and confusion with multiple NIS.

1.3.3 Pathophysiology

The exact pathophysiology of early satiety in cancer is not understood. There have been several suggestions as to the possible pathophysiology including central and peripheral causes. Some are discussed below. The potential causes of early satiety are outlined in Figure 1.4.

1.3.3.1 ***Gastric Dysmotility***

To fully understand this, it is important to know about normal gastric function. The stomach, like many other organs in the GI tract, has secretary and muscular functions. The smooth muscles of the stomach are orientated in three directions: oblique, circular, and longitudinal muscle layers. These muscle layers are involved in the muscular breakdown of food. Ingested food first enters the fundus of the stomach. Vagal nerve stimulation via the parasympathetic nervous system relaxes the fundus for receiving the ingested food. Through peristaltic contractions, the food is then transported to the corpus and antrum. Here, the food bolus is broken down (trituration) into more easily digestible and transportable chyme. This is done via the contraction and relaxation of the oblique muscle layer. The time taken for this trituration varies based on the size and composition of the food particles upon ingestion. The goal of trituration is to create food particles of 1-2mm in diameter. This peristaltic movement for trituration occurs on a cyclical 3 per minute. Once the bolus is broken down into chyme, the circular and longitudinal muscle layers allow for the moving of the bolus through

the pyloric sphincter and into the duodenum. In healthy populations, a pleasant sensation of fullness is felt, and hunger subsides. Between meals, there are strong contractions to ensure any indigestible pieces are removed from the stomach. This process is known as the migrating motor complex.[188]

Early satiety is a common symptom of gastroparesis[189] indicating there may be some delay in gastric emptying in diseases apart from diabetes where early satiety is present. In cancer patients, it has been suggested that early satiety is related to a reduction in gastric motility.[190] This could be a symptom of malignancy-associated gastroparesis.[191] It is important to note that many frequently used medications in oncology may delay gastric emptying. These include anticholinergics, antiemetics, antidepressants, opioids, and proton pump inhibitors.[176]

Impaired gastric accommodation (GA) is also associated with early satiety and weight loss in functional dyspepsia[192, 193] and idiopathic gastroparesis.[194] Gastric barostat is the gold standard for assessing GA[195], while gastric scintigraphy[196] and Magnetic Resonance Imaging[197] are also useful techniques. Sensitivity to gastric hyperextension is also related to early satiety.[194] There is also the potential that the gastric distribution of a meal may result in the onset of different symptoms. In a study of patients with gastroparesis, those with an immediate and 1-hour distal distribution of food contents were more likely to have early satiety. Those with a longer distribution time were more likely to have nausea and vomiting.[198]

1.3.3.2 Autonomic Dysfunction

As highlighted, the ANS plays a key role in the regulation of nutritional intake. Where there is a dysregulation of this process it is known as autonomic dysfunction (AD). This phenomenon has been described in several conditions including diabetic gastroparesis[199, 200], functional dyspepsia[201] and chronic unexplained nausea and vomiting.[202] One possibility is that early satiety in cancer is related to AD[203], especially given it is a common disorder in cancer.[204] AD is associated with loss of appetite[205] and nausea[206], therefore there is a possibility it is also associated with early satiety.

1.3.3.3 Gut Hormones

There may also be merit in the investigation into how gut hormones may induce early satiety. This thought is further emphasised by the effects of GLP-1 receptor agonists. These medications have been so effective at reducing nutritional intake that they have been approved as weight loss medications.[207] Its effect on insulin secretion results in the onset of symptoms to reduce nutritional intake such as decreased appetite and early satiety.[208] There have also been several studies in bariatric surgery that have shown increased concentrations of anorectic gut hormones that promote the earlier onset of satiety.[209-211] In this cohort, this is a desired effect.

There is significantly less evidence as to the changes in gut hormone secretion in cancer. Much of the research investigated the concentrations of these hormones post-surgical intervention in cancer.[212] Elevated anorectic gut hormones are associated with early satiety post oesophagectomy and attenuation of these hormones results in a reduction in early satiety

prevalence.[213] There is also mixed evidence as to whether gut hormones play a role in the proliferation of cancer cells.[214] There is no information on baseline gut hormone concentrations in cancer and their subsequent associations with NIS.

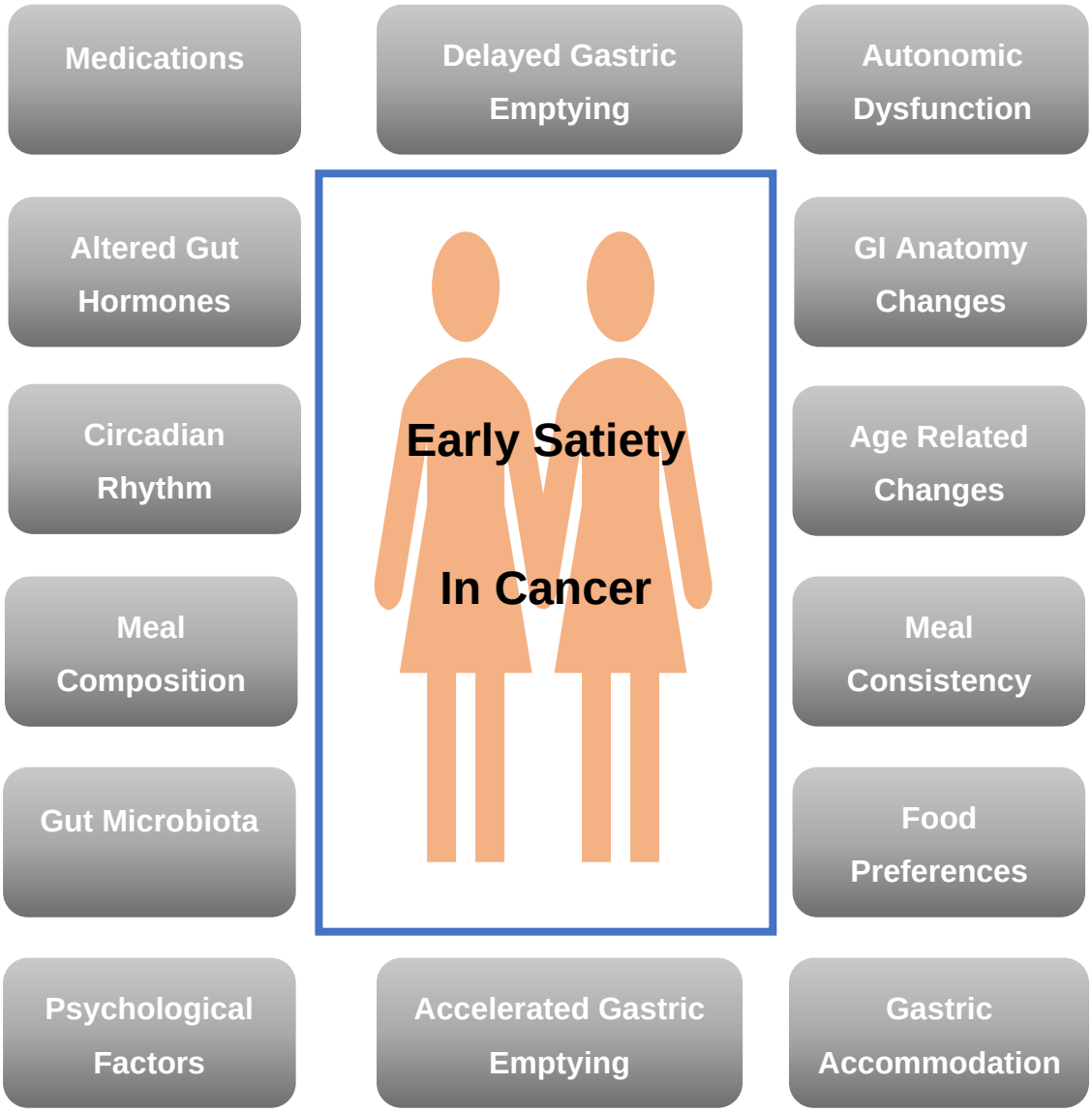


Figure 1.4 Possible causes of early satiety in cancer

1.3.4 Impact of Early Satiety

1.3.4.1 ***Symptoms***

Early satiety is distinct from anorexia as it can occur in individuals in the absence of anorexia.[45] Hunger ratings in those with anorexia or early satiety may be similar. However, after a period of fasting, reported hunger may be similar to that of a normal appetite when early satiety is present in the absence of anorexia.[46] While early satiety is itself distinct from anorexia, there appears to be an association between the two. They are part of the same symptom cluster.[215] This is unsurprising as those who report early satiety as moderate to severe, seem to do so with anorexia also present.[168]

A 22-item questionnaire was given to 95 patients reporting anorexia to determine the severity of anorexia and the prevalence of concurrent GI symptoms. In this study, early satiety was the most common symptom associated with anorexia (82%), followed closely by weight loss (79%) and changes in taste (69%).[216] Early satiety was also shown to be positively correlated with worsening anorexia. Early satiety has also been shown to result in food aversions.

Early satiety appears to be associated with several co-occurring symptoms outside of cancer too. For example, it is associated post prandial fullness, nausea, vomiting and anorexia in gastroparesis.[217] It also appears to routinely occur with bloating in those with gastroparesis.[217, 218]

1.3.4.2 ***Physical***

The physical impact of early satiety is highlighted since Fearon et al. used early satiety as one of the defining characteristics of cancer cachexia.[219] In oncology,

early satiety is associated with several nutritional side effects. It is associated with an increased risk of malnutrition, cachexia and sarcopenia in cancer.[34, 42, 220] Early satiety has been suggested as a predictive symptom of several cancers.[221]

In gastroparesis, early satiety is associated with poorer physical health and a lower body mass index.[217] Early satiety is associated with a statistically significant decrease in calories consumed in functional dyspepsia.[192] In this study, participants were asked to rate their early satiety severity and consume a caloric drink at 15ml/min in both healthy volunteers and patients with dyspepsia. Logistic regression analysis showed low caloric intake was significantly associated with early satiety ($p<0.001$).[192]

1.3.4.3 Psychological

Early satiety is a highly distressing symptom. In fact, it is among the most distressing symptoms in advanced cancer, more so than anorexia.[46] Its association with distress is also present in reflux disease.[222] Early satiety is also associated with anxiety and depression in those with diabetes.[223, 224] Early satiety also reduces QoL in cancer survivors up to 5 years post oncological treatment.[225] This impact of early satiety on QoL is not limited to cancer as it also reduces QoL in both gastroparesis and functional dyspepsia.[217, 218, 226]

1.3.5 Treatment

Currently, there is no universally agreed treatment for the symptom of early satiety. This is likely related to its poorly understood pathophysiology. Some possible treatments are discussed below.

1.3.5.1 Prokinetics

Prokinetics are medications that enhance the contractions and coordination of the muscles in the gastrointestinal tract, thus encouraging timely emptying of the stomach contents. The current ESPEN guidelines for cancer recommend using prokinetics in the treatment of early satiety.[27] They state the level of evidence is moderate. From a search of the literature, there were no trials that investigated the benefit of prokinetic agents on early satiety in cancer. Instead, this recommendation was based on the presence of early satiety in gastroparesis. Metoclopramide and domperidone are often the prokinetics of choice in the treatment of early satiety.[227] It is unclear as to whether these are appropriate agents. The effectiveness of prokinetics may be difficult to determine based on publication bias.[228]

Here are some commonly used prokinetic medications for treating early satiety:

1. Metoclopramide: This medication increases the contractions of the stomach and small intestine, thereby improving gastric emptying. It also helps reduce nausea and vomiting associated with gastroparesis. Metoclopramide is available in both oral and intravenous forms.
2. Domperidone: Domperidone works by blocking the action of dopamine, which can improve gastric motility. It is available in oral form and is often used as an alternative to metoclopramide when side effects are a concern.
3. Erythromycin: Although erythromycin is an antibiotic, it also has prokinetic properties. It stimulates the muscles of the gastrointestinal tract, including the stomach, and can help improve gastric emptying. It is usually

prescribed in low doses for its prokinetic effects rather than its antibiotic properties.

1.3.5.2 Appetite Stimulation

There is currently no evidence to support the use of appetite stimulants in the treatment of early satiety. However, in some cases, healthcare professionals may consider using appetite stimulants as part of a comprehensive treatment plan. These medications can help increase a person's overall appetite and food intake, which may indirectly alleviate the symptoms of early satiety by encouraging them to consume more food. Some commonly used appetite stimulants include:

1. Megestrol acetate: This medication is a progestin that can increase appetite and promote weight gain in individuals with decreased appetite or unintended weight loss. It is often used in cancer patients or those with HIV/AIDS. This has been shown to improve appetite in patients with advanced cancer.[229, 230] Caution is advised when using megestrol acetate as it may reduce endocrine secretions and cause a slight increase in thrombophlebitis risk.[229]
2. Dronabinol/Nabilone: Dronabinol and nabilone are synthetic forms of THC, the active compound found in cannabis. It can help stimulate appetite in individuals with conditions such as cancer, HIV/AIDS, or anorexia. These medications may cause abdominal pain, haemodynamic instability, nausea and vomiting as well as a perceived ‘high’.[231, 232] While there is growing interest in the use of cannabinoids in cancer, there is insufficient evidence for their use in treating early satiety.[233]

3. Mirtazapine: Although primarily an antidepressant, mirtazapine has appetite-stimulating effects and is sometimes used off-label to improve appetite in individuals experiencing weight loss or decreased appetite. Mirtazapine has been shown to improve early satiety in functional dyspepsia[234], but there is no evidence for its use in cancer.
4. Corticosteroids: Corticosteroids have been used throughout the cancer trajectory to treat NIS. The appetite stimulating effect of corticosteroids also appears to be transient.[235] Ultimately, the long-term use of corticosteroids is not recommended secondary to the adverse effects of extended use such as loss of bone mass and immunosuppression.[236] The efficacy of these medications in treating early satiety has not been established.
5. Anamorelin: Anamorelin is a selective agonist of the ghrelin hormone secretagogue receptor. It stimulates ghrelin receptors which increases appetite and nutritional intake. It is currently still in testing, but early results show improve gastric motility in patients with gastroparesis.[237, 238] It has been shown to reduce gastroparesis symptoms, including early satiety.[237] Most of its testing in cancer is in an effort to treat CC.

1.3.5.3 Food Selection

The rate foods empty from the stomach are partially influenced by the nutrients, consistency and calorific value of foods consumed. It is likely therefore that foods ingested may exacerbate or ease the symptom of early satiety.[239] Fibre results in a decrease in the gastric emptying of a meal.[240] Fats and fibre can reduce gastric emptying and so may exacerbate early satiety. Exclusion of these foods may therefore improve early satiety. These are part of the recommended treatments

for functional dyspepsia and gastroparesis. Caution is advised as a reduction in fibre may result in the onset of constipation and a lack of fat may result in nutritional requirements not being met, thus leading to malnutrition.

There may also be merit in the alteration of food consistency. Liquids empty from the stomach via gravity and do not require antral contraction.[241] While the transition to a fully liquidised or pureed diet would prove far too limiting, the use of more liquid calories when they most often experience early satiety during the day may be beneficial. There are currently no studies into this treatment however liquids do result in a greater energy intake compared to solids by generating less of a satiation and satiety response.[157, 242, 243]

There is also some information to be garnered from the attempts to induce satiety, particularly in obesity studies. Results from Rolls et al showed that incorporating water into a meal reduced overall energy consumption.[244] There was also no change in subsequent nutritional intake to compensate for this reduced intake.[245] As a result, there is likely merit in opting for more nutrient dense foods to improve outcomes in those early satiety, however there is no research on this in cancer. It is unlikely to improve the symptom itself but may offset some of the reduced energy and protein intake associated with early satiety.

1.3.5.4 Eating Pattern

Encouraging small meals throughout the day rather than three meals may result in a greater overall calorie and protein intake. This approach is routinely recommended in conditions where patients are nutritionally at risk, including cancer.[246] While this is the case, few nutritional guidelines discuss the recommendation of small frequent meals in early satiety management.[247] While

this may be some benefit, there are no trials that have investigated this eating pattern and whether it influences early satiety.

It may also be beneficial to experiment with meal timing. There are significant individual differences in appetite throughout the day.[248] Some individuals may find it helpful to consume most of their calories when they feel most hungry. There is also evidence that consuming the majority of calories late in the day improves overall intake, however this study was not performed in those with early satiety.[249]

1.3.5.5 Complementary and Alternative Medicine

Complementary and Alternative Medicine (CAM) has become more popular in recent years with a global usage in the general population between 9.8%-76.0%.[250] The use of CAM in cancer patients has also grown in popularity with over a third of patients using some form of CAM.[251, 252] There is very little evidence regarding the efficacy of CAM therapies for the treatment of early satiety of any type, let alone in cancer. Qigong has been suggested to be beneficial to patients with early satiety in cancer.[253] Rikkunshito has also been suggested to improve early satiety in functional dyspepsia.[254] A Cochrane review reported that eicosapentaenoic acid showed no improvement in symptoms associated with cachexia.[255]

A meta-analysis of the use of acupuncture in functional dyspepsia reported improvement in symptoms, however it did not reference early satiety.[256] A further review reported insufficient evidence for the recommendation.[257] While some have shown improvement in early satiety[258, 259], there is insufficient evidence for the recommendation of acupuncture to treat early satiety in dyspeptic disease, while there is no evidence in relation to early satiety in cancer.

While it is clear that there is a desire for CAM, much of the desire likely reflects the ineffective management of early satiety in several medical conditions. There is currently insufficient evidence to recommend CAM, which is unsurprising given the limited evidence for medical based interventions in early satiety management.

1.3.5.6 Other

Buspirone was assessed for a potential treatment for patients with early satiety in gastroparesis. There was however no improvement in early satiety noted.[260] In functional dyspepsia, there was an improvement in early satiety in those taking buspirone.[261] There was also a trial of H. Pylori therapy to reduce symptoms in functional dyspepsia. While it improved epigastric pain, there was no improvement in early satiety.[262] Eosinic duodenitis is also associated with early satiety[263, 264], however there are no studies that investigated the treatment effect on early satiety.

1.4 Conclusion

As can be seen, there is a paucity of information about early satiety in cancer. This is despite this being a symptom that many experience during their disease. It appears to be a symptom that is prevalent throughout cancer and highly impactful. Despite this, there are many pieces of information that are lacking to fully understand early satiety. With this in mind, several questions arose that would be beneficial to explore within this thesis.

- What information has been published about early satiety in cancer and what are the knowledge gaps?
- How prevalent is early satiety at different stages of cancer?
- How is early satiety best identified?
- With what demographic and nutritional factors is early satiety associated with?
- How do patients with early satiety describe their symptom?
- Does early satiety influence functional capacity or quality of life?

1.4.1 Thesis aim

To assess the physical/psychological impact, as well as the individualised experiences of early satiety at multiple stages of cancer treatment

1.4.2 Chapter aims

The individual aims for each chapter of this thesis are detailed at the beginning of each chapter.

1.4.3 Thesis changes

Given the nature of this thesis, COVID-19 had a significant impact on the planned studies. It was planned to complete a study in which a new methodology for

inducing satiety, firstly in healthy volunteers, and then patients with cancer. Ad libitum intake and gut hormone concentrations would be measured. This study had a protocol, funding, and ethical approval. Unfortunately, access to the lab where this study was due to take place was limited to the researchers already established in that lab, and therefore this study could not progress.

It was also planned to explore the ‘symptom experience of early satiety’ in 3 different cohorts, in patients receiving specialist palliative care, with pancreatic cancer and patients post bariatric surgery. It was hoped to compare the desired ‘early satiety’ post bariatric surgery to the symptom experienced in cancer. This study was granted full ethical approval but could not continue as access to the hospital was limited to essential staff.

There were also changes facilitated for reasons outside of COVID-19. During the pandemic, the candidate returned to the wards while off-books. Prior to this, there was a planned database study to explore the prevalence of early satiety. Much of this data was paper based. The candidate was inputting this data onto an electronic record. While off-books, the hardcopy records were not retained.

Finally, it was originally planned explore the physical and psychological impact of early satiety in a different hospital. This had received full ethical approval and was due to commence. The legal team then informed the candidate that a research contract would have to be agreed upon given the association with Trinity College Dublin. This was reportedly due to be a lengthy process and so in order to complete the thesis in a timely manner, this study did not progress.

2 THESIS METHODS

2.1 Patient Selection

This thesis explored the impact and symptom experience of early satiety in patients in two different cohorts, those with advanced disease receiving specialist palliative care and those actively receiving anticancer treatment.

2.1.1 Participants with Advanced Cancer

Participants were recruited from Our Lady's Hospice & Care Services (OLH&CS) in Harold's Cross. This hospice has a dedicated specialist palliative care inpatient unit with 36 beds. In this cohort are patients with advanced cancer. Eligible patients for inclusion were identified at weekly multidisciplinary team meetings. A member of the medical team then gave potential participants a brief introduction to the study. Those participants who agreed to further discussion were then given a Participants Information Leaflet (PIL), and any questions participants had before inclusion were answered. Once consented, participants were assigned a study number and proceeded with all assessments. The explanation, giving of the PIL, consent, and assessments all occurred on the same day. This decision was made given the ever-changing health of these patients which meant that if assessments were delayed, they may no longer be well enough to participate.

2.1.2 Participants Undergoing Active Treatment

The Oncology Day Ward (ODW) at Tallaght University Hospital includes medical, radiation, surgical oncology, and palliative medicine services. Participants were recruited while attending their treatment. The nurse/doctor who reviewed the patient assessed their suitability for study inclusion and dictated which participants were suitable to approach. All potential participants received a short synopsis of the study, a PIL, and consent forms. If participants were interested, they were given the opportunity to read the PIL and consider participating. Those

deemed unsuitable by the nurse/doctor were not approached. Once consented, participants were assigned a study number and proceeded with all assessments. The explanation, giving of the PIL, consent, and data collection all occurred on the same day. This decision was made as the assessments did not impact their treatment and potential participants were able to consider whether they were willing to participate and complete the necessary assessments, besides the physical assessments, while receiving their treatment. On occasion, participants requested to take the PIL home and discuss the study with their families. These participants were then approached on their next visit to the ODW.

2.2 Ethics

Ethical approval was sought from relevant clinical sites. Ethical approval was granted for the advanced cancer cohort from the research and ethics committee in OLH&CS and St Vincent's Healthcare Group Ethics and Medical Research Committee. Ethical approval for the recruitment of patients receiving anticancer treatment was granted by St James's Hospital/Tallaght University Hospital Joint Research Ethics Committee. All letters of approval are included in the Appendices (Appendix 1).

2.3 Scoping review

Given the nature of scoping reviews and the specific protocols used in evaluating the results, the methodology and results of the scoping review are included in one chapter (Chapter 3). For ease of reference, the assessments for each Chapter are in Figure 2.1.

CHAPTER	ASSESSMENTS
3 - Clinical Characteristics Of Early Satiety In Cancer: A Scoping Review Of Available Quantitative And Qualitative Evidence	• Detailed in Chapter 3
4 - Screening For Early Satiety And Associated Malnutrition In Cancer	• Open Symptom Questionnaire (Appendix 3) • AbPG-SGA (Appendix 4) • GLIM Malnutrition
5 - Piloting Of The Symptom Experience Of Early Satiety Questionnaire	• AbPG-SGA (Appendix 4) • SEES Version 1 (Appendix 5) • Feedback Questionnaire (Appendix 6)
6 – The Symptom Experience Of Early Satiety In Patients With Cancer	• SEES Version 2 (Appendix 7)
7 - Quality Of Life, Physical Health, And Functional Ability In Cancer And The Impact Of Early Satiety	• Visual Analogue Scale (Appendix 8) • EORTC QLQ-C30 (Appendix 9) • Handgrip Strength • Sit to Stand • Timed Up and Go • Bioelectrical Impedance Analysis

Figure 2.1 Details of assessments used for data collection with the corresponding chapters and appendices

abPG-SGA, abridged patient generated subjective global assessment; EORTC QLQ-C30, European organisation for research and treatment of cancer quality of life questionnaire – core questionnaire; SEES, symptom experience of early satiety

2.4 Demographic/Clinical Data

Basic demographic and clinical data were gathered on all participants from either their physical or electronic medical records. This information included their sex,

age in years, and whether there was past medical history related to early satiety (gastroparesis, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, Parkinson's Disease). Whether there was a history of cognitive impairment was also established. Details of the primary cancer site, the extent of disease progression, as well as current and planned treatments were also collected. These were then grouped into Breast, Lung, Lower Gastrointestinal (GI), Melanoma, Upper GI, Urological, and other. The presence of certain medications that may relate to early satiety was also collected, such as opioids, corticosteroids, prokinetics, appetite stimulants, vitamins, and complementary medicines. Data that may have eased identification, such as date of birth, specific anticancer treatments, or hospital numbers, were not gathered.

2.5 Assessment of Functional Status

2.5.1 Handgrip Strength

Handgrip strength has been recommended in both a research and clinical setting by the European Working Party on Sarcopenia in Older People.[265] It has also been recommended by the American Society for Parenteral and Enteral Nutrition (ASPEN) as one of the 2 clinical characteristics for diagnosing malnutrition.[266]

Handgrip strength was determined using a hydraulic Jamar hand dynamometer (Figure 2.2). The dynamometer has a dual scale readout that displays isometric grip force from 0-90 kg (0-200 lb). The outer dial registers the result in kg, and the inner dial registers the result in lb. It has a peak hold needle which automatically retains the highest reading until the device is reset. The use of the dynamometer was demonstrated to the participant before use.

Figure 2.2 Jamar hand dynamometer used to assess hand grip strength in patients receiving anticancer treatment on the Oncology Day Ward

The participant was in a seated position (not in a standing position). The participant was advised to be comfortably seated in a chair without armrests, with feet fully resting on the floor, hips as far back in the chair as possible, and the hips and knees positioned at approximately 90 degrees. The gripping arm was to be in the following position: shoulder adducted, elbow flexed 90 degrees, and forearm and wrist in a neutral position. The wrist was positioned between 0-30 degrees of extension (dorsiflexion) and between 0 and 15 degrees of ulnar deviation. All participants were advised to keep their wrist in a neutral position and at 0 degrees for best results[267] however where participants were unable to do so, the above ranges were deemed acceptable.

After it was demonstrated how to hold the device, the dynamometer was placed in the participant's hand, where the researcher gently supported the base of the instrument or rested it on the participant's leg to prevent accidental dropping. Participants were advised to apply the grip force smoothly, without rapid wrenching or jerking motion. Participants were encouraged to give maximum

effort. No visual or auditory feedback was provided; therefore, the dynamometer dial was turned away from participants so they could not see the display. The grip duration was to last at least 3 seconds. Results were recorded to the nearest kg.

Each participant performed the test three times with each arm. The arm was alternated to limit fatigue in each reading. All three measures were documented, and an average was calculated. The dominant hand was also documented for implementation in the reference equations in Table 2.1. Participants with mean HGS less than their predicted were deemed to have low HGS.

Its simplicity, low cost, accessibility, prognostic and associative value meant the HGS was an ideal tool for use on the ODW. A lower HGS has been associated with increased mortality[268, 269], For this study, its function as a marker of overall body strength was used.[270] Lower HGS has also been associated with poorer overall mobility, such as standing from a chair, walking, and climbing stairs.[271, 272]

Table 2.1 Reference equations for grip strength for dominant hands based on sex, adapted from Wang et al.[273]

SEX	REFERENCE EQUATION
MALE	-29.959 – (3.095 x 10^{-5}) x (age in years^3) + 38.719 x (height in metres) + 0.113 x (weight in kg)
FEMALE	-22.717 – (1.920 x 10^{-5}) x (age in years^3) + 30.360 x (height in metres) + 0.048 x (weight in kg)

2.5.2 Sit To Stand

The 30-second sit-to-stand test (STS) is administered using a chair without arms, with a seat height of 46 cm. The chair, with rubber tips on the legs, was placed against a wall to prevent it from moving.

The participant was seated in the middle of the chair, back straight; feet approximately shoulder width apart, and placed on the floor at an angle slightly back from the knees, with one foot slightly in front of the other to help maintain balance. Arms were crossed at the wrists and held against the chest.

The task was demonstrated both slowly and quickly. The participant was encouraged to practice a repetition before completing the test. If a participant required the use of their arms to complete the test, they were scored 0.

At the ‘go’ signal, the participant rose to a full stand (body erect and straight) and then returned to the initial seated position. The participant was encouraged to complete as many full stands as possible in 30 seconds. The participant was instructed to fully sit between each stand. While monitoring the performance to ensure proper form, each correct stand was counted silently. The score was the total number of stands in 30 seconds (more than halfway up at the end of 30 seconds counted as a full stand). Incorrectly executed stands were not counted.[274] The same style of chair was used throughout, as chair height has been shown to significantly influence results.[275]

This version of the STS also potentially introduces some measure of endurance given the multiple repetitions in a longer period than the five repetition STS. This version of the STS was chosen as it was believed that a longer time would allow

a wider assessment of ability levels. While participants are undergoing treatment, they were still outpatients, and it was believed that they would be capable of the more difficult test.

Figure 2.3 Example of Sit to Stand Assessment

Reference values for STS are lacking in younger adults. For Chapter 7, a below average STS for participants 20-59 years was calculated as below 1.5SD of the mean proposed by McKay et al.[276] This decision was taken as all but one participant met the criteria for 1SD and the values for 2SD were less than those recommended by the centre for disease control and prevention values for >60 years, based on data from Rikli and Jones.[277] The values for men and women used are in Table 2.2. A score below these values was considered a risk of falls.

Table 2.2 Definition of below average 30 second sit to stand values differentiated by sex and age range

Age (years)	Male (number of stands)	Female (number of stands)
20-59	<15	<13
60-64	<14	<12
65-69	<12	<11
70-74	<12	<10
75-79	<11	<10

2.5.3 Timed Up And Go

The 'timed up and go' (TUG) was designed to identify frail elderly by assessing mobility.[278] It is a modified version of the Get up and Go test.[279] A long TUG score has been associated with a higher risk of early death.[280]

Participants were asked to sit in a standard armchair (height 46cm), placing their back against the chairs. Any assistive device used for walking was nearby, but participants were advised that arms should not be placed on the device prior to starting the test. Regular footwear and customary walking aids were used. The test was explained and demonstrated to each participant. The same prompt was used as 'Ready, Set, Go'. The participant walked to a line that was 3 metres (9.8 feet) away, turned around at the line, walked back to the chair and sat down.[278] The test ended when the participant sat back down. Participants were instructed to use a comfortable and safe walking speed. A stopwatch was used to time the test (in seconds) to the 100th of a second and was documented. A cut-off score of 13.5 seconds has previously been used to identify those at an increased risk of falls.[281] For this study, a time of >12 seconds was used as the cut-off for

increased falls risk as recommended in the American Society of Clinical Oncology (ASCO) guidelines for geriatric oncology.[282] The TUG is also recommended as a routine screening method for falls risk by both the American and British Geriatric Society.[283] Longer TUG times have been associated with shorter survival in cancer.[280] Longer TUG times have also been shown to predict chemotherapy related toxicity in older patients with cancer.[284] Outside of cancer, there is more evidence of a slower TUG time being associated with increased mortality.[268, 285]

2.6 Nutritional Assessment

2.6.1 Weight, Height, and BMI

When an objective weight measurement was collected, a calibrated scale was used and recorded to one decimal point. Height was collected using a stadiometer. Participants were asked to stand with the heels flush to the wall while ensuring that the head was in the Frankfort plane. Where objective weight and height were unavailable, subjective measurements were used from the abPG-SGA. Weight loss was calculated by subtracting current weight from usual/previous weight within the past six months and multiplying by 100. Body mass index (BMI) was calculated by dividing current weight by height in metres squared. WHO classifications for BMI were used as shown in Table 2.3.[286]

Table 2.3 WHO classifications of Body Mass Index (BMI)

WHO CLASS	BODY MASS INDEX (KG/M^2)
UNDERWEIGHT	<18.5
NORMAL WEIGHT	18.5 – 24.9
OVERWEIGHT	
PRE-OBESE	25.0 – 29.9
OBESE CLASS I	30.0 – 34.9
OBESE CLASS II	35.0 – 39.9
OBESE CLASS III	>40.0

2.6.2 Open Symptom Questionnaire

Participants were asked an open question to describe their NIS. This is referenced as the Open Symptom Questionnaire (OSQ) throughout the thesis. The researcher always read this aloud to the participants. It was also always completed before participants received any other assessments to reduce the risk of response bias. The OSQ was used as it mimics routine clinical practice, where symptom assessment checklists are not commonplace. The question was as follows:

> What problems have you had that have kept you from eating enough during the past two weeks?

The question asked also uses the same time frame (past two weeks) as used in the abridged patient generated subjective global assessment. This allowed for comparisons between the symptoms reported in an OSQ and a symptom checklist. Responses were documented verbatim. When a description of a

symptom was used rather than a name, these descriptions were carefully categorised as a symptom. The OSQ was not validated and there were no specific criteria to identify the risk of malnutrition.

2.6.3 Abridged Patent Generated Subjective Global Assessment

The Abridged Patent Generated Subjective Global Assessment (abPG-SGA) was used to evaluate malnutrition risk and presence of nutrition impact symptoms. This assessment tool is also known as the patient generated subjective global assessment short form. As the name suggests, it is derived from the PG-SGA, which itself is a well-recognised assessment of nutritional status in cancer patients[287, 288], predominantly in clinical research. The abPG-SGA forgoes the physical exam, disease/condition and metabolic considerations found in the PG-SGA, thus removing the need for trained medical personnel. This in turn allowed the tool to be completed solely by the participant.

The abPG-SGA is divided into 4 boxes for participants to complete:

1) self-reported height, weight, weight history (1 month; 6 months prior)

2) dietary intake in the past month

3) 14 nutrition impact symptoms (NIS) including ‘feeling full quickly’ (which was considered to be early satiety)

4) current physical activity levels and daily function

The score for that of abPG-SGA is the same as the PG-SGA without physical assessment. Scores vary for each section, with symptoms scoring proportionately higher than others. Scoring was as follows: box 1 (0-5), box 2 (0-4), box 3 (0-23) and box 4 (0-4). Total score ranges from 0-36. Boxes 1 and 3 are additive,

whereas boxes 2 and 4 are not. A copy of the abPG-SGA is in Appendix 4. The abPG-SGA differs from the SGA as the scoring of the SGA was considered as categorical (A= well nourished, B= moderately malnourished/suspected malnutrition, C= severely malnourished), whereas the abPG-SGA is considered continuous. However, for analysis scores were grouped into risk of malnutrition categories: low (<4), moderate (4-8), high (≥9).[289-291]

For participants with advanced cancer in hospice, the abPG-SGA was read aloud to participants, to which they answered verbally. Their responses were documented on a copy of the abPG-SGA. This was done at the request of the research ethics committee, which felt that the completion of the tool by the participants would be too burdensome. For the anticancer treatment cohort, participants themselves completed the tool. Given that these participants were on active treatment, the research ethics committee considered them to be more suitable for self-completion of the tool. Before leaving participants of the study to complete the tool, each section was explained, paying particular attention to explain the recall time frame of each section and all were advised to read all options carefully. This was to minimise confusion, which has previously been shown with the tool.[292]

The abPG-SGA is a valid tool for assessing nutrition risk in cancer patients.[287, 293] The abPG-SGA also has the benefit of being among a select number of assessment tools that cover the recommended domains for diagnosing malnutrition in both ESPEN and ASPEN guidelines.[294] Given the increased focus on patient centred care, the abPG-SGA is also beneficial as it allows for more patient autonomy. It also allowed for nutritional screening without removing the participant for objective nutritional assessment while on their treatment. It was

also selected as it could be used to detect early satiety given it is one of the few tools that assess symptoms. The abPG-SGA was used throughout this thesis to identify the presence of early satiety.

2.6.4 Bioelectrical Impedance Analysis

Body composition was measured using a medical body composition analyser (Tanita BC-418 model). Bioimpedance analysis (BIA) is a rapid, non-invasive measure of body composition. Body composition is analysed based on the principle that the human body is considered an electrical conductor in an alternating current circuit and this current (impedance) is measured. It is measured in Ohms (Ω)

To begin, the estimated weight for participants was entered using the numerical keys. When the data input was completed, the data was displayed as a minus number.

Body type was selected from Standard Male, Standard Female, Athletic Male, and Athletic Female. Tanita defines ‘athlete’ as a person involved in intense physical activity of at least 10 hours per week and who has a resting heart rate of approximately 60 beats per minute or less. Tanita’s athlete definition includes ‘lifetime of fitness’ individuals who have been fit for years but currently exercise less than 10 hours per week. Tanita’s athlete definition does not include ‘enthusiastic beginners’ who are making a real commitment to exercising at least 10 hours per week but whose bodies have not yet changed to require the Athlete mode.

The age and height of the participants were entered. Measured height was taken from participant medical records which were completed by nursing staff with a stadiometer.

For clarity, the process of stepping onto the Tanita and the holding of the grips were demonstrated highlighting that the grips just need to be held rather than squeezed. Participants were asked to step on the weighing platform in bare feet. Heels were placed on the posterior electrodes, and the front part of the feet were in contact with the anterior electrodes. Once completed, participants were advised to step off. When there was an issue with obtaining a reading, each participant was asked if it was possible to try a further reading. Each participant was asked for a reading three times. If a reading was still unobtainable, it was considered missing data. The printout of information was removed and included with the participants' data. Each participant was asked if they were interested in being told their body fat percentage. The equipment was disinfected after each participant.

To ensure the most accurate measurement possible, the following criteria were followed:

- Measurements were not taken after vigorous exercise.
- Participants were asked to empty their bladder before assessment.
- Participants were advised to keep both arms straight while the measurement was taken.
- Measurements were made in the same room.
- Participants were asked to ensure their arms were not touching their sides and their thighs were not touching.

- Shoes were removed to reduce the risk that dirt interfered with the current.
- Measurements were not taken on individuals who had consumed excess fluids (for example if advised for ease of venous access).
- Mobile phones were stored away from the machine to limit the risk of interference.

Gold standard methods for body composition assessment are through computed tomography (CT), Magnetic Resonance Imaging (MRI), or dual-energy X-ray absorptiometry (DEXA). Although BIA is not as accurate, compared to these options, it is cheaper, more accessible, and does not expose participants to radiation. It was a significantly more practical option for body composition in a busy oncology day ward. It has the added benefit of removing operator bias when compared to other methods of body composition measurement, such as skinfold thickness.

Figure 2.4 Tanita BC-418 used for bioelectrical impedance analysis

2.6.5 Diagnosis of Malnutrition

The Global Leadership Initiative on Malnutrition (GLIM) was established in January 2016. Its goal was to reach a global consensus on the diagnosis of malnutrition in the clinical setting.[26] The GLIM criteria are a two-step process with initial risk screening using any validated tools and subsequent diagnostic assessment. The abPG-SGA was used as the tool for risk screening. The second step consists of an assessment of two etiological and three phenotypic criteria. Those with one etiological and one phenotypic criterion are diagnosed with malnutrition. Figure 2.5 shows the GLIM criteria and the process to diagnose malnutrition.

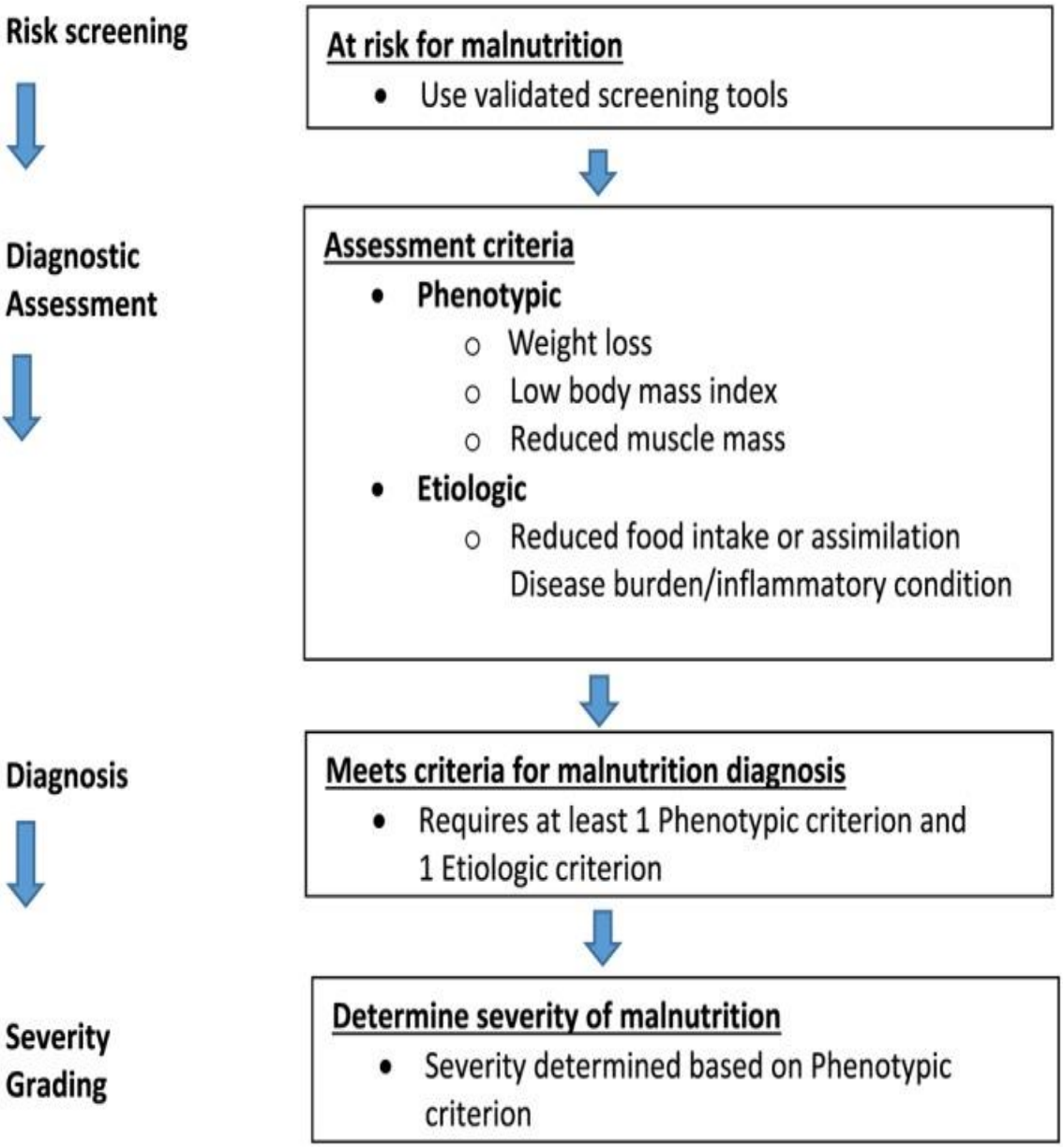


Figure 2.5 Global Leadership Initiative on Malnutrition (GLIM) criteria for screening, assessing diagnosing, and grading malnutrition

For the phenotypic criteria, weight loss was calculated using weights obtained from medical records. Where possible a weight in the past 3-6 months was used. Where this was not possible (as the available records were specific to the ODW), the weight reported weight was used. BMI was calculated using measurements from ODW assessment. Fat free mass index (FFMI) was calculated by dividing

fat free mass values from bioelectrical impedance analysis by measured height in metres squared. This was used to identify low reduced muscle mass.

For etiologic criteria, box 2 of the abPG-SGA was used to determine reduced food intake and CRP was obtained from medical records, which was occasionally assessed at their visit to the ODW. When this was unavailable, the presence of metastatic disease was considered inflammatory. This decision was made as the assignment of inflammation due to a cancer diagnosis and no other criteria is not recommended for the etiologic criterion.[295] Phenotypic and etiologic criteria for the diagnosis of malnutrition used for Chapter 4 are in Table 2.4.

Table 2.4 Phenotypic and etiologic criteria for the diagnosis of malnutrition in the Global Leadership Initiative on Malnutrition (GLIM) criteria.[26]

Phenotypic Criteria	
Weight Loss (%)	>5% in past 6 months >10% beyond 6 months
Low Body Mass Index (kg/m^2)	<20 if <70 years old <22 if >70 years
Reduced Muscle Mass (kg/m^2)	FFMI <17 in males FFMI <15 in females
Etiologic Criteria	
Reduced Food Intake	Reduced intake in Box 2 of the ab PG-SGA
Inflammation	Where available, CRP >5 Presence of metastatic disease

2.7 Symptom Experience of Early Satiety

2.7.1 Questionnaire Development

The Symptom Experience of Early Satiety (SEES) questionnaire was developed within the ADPM research team to assess the symptom experience of early satiety. After extensive reading of the literature, multiple areas with respect to early satiety were determined to have minimal evidence associated with it. Early satiety was reformulated to 'feeling full quickly', as described in the abPG-SGA. This questionnaire was discussed at several research meetings within the ADPM and was discussed with all supervisors. The ADPM and supervisors comprised

of consultants, previous PhD supervisors, current PhD students, and research nurses. The final agreed version of the questionnaire for the pilot (SEES Version 1) can be seen in Appendix 5

2.7.2 SEES Piloting

The SEES questionnaire underwent a pilot (Chapter 5) where feedback was sought from participants. On completion of the SEES questionnaire, a 7-item participant feedback questionnaire (Appendix 6) was administered. These questions asked for participants views on the following:

1) the time needed to complete the SEES questionnaire

2) the wording of questions

3) its suitability to describe the symptom of early satiety.

There was also an opportunity to make suggestions on what improvements (if any) could be made. After this review process, including the feedback from participants, a new draft of the questionnaire was sent to Irish oncology dietitians for their review. With the combined feedback of both the participants and the oncology dietitians, the SEES was edited accordingly. The finalised version of the SEES can be seen in Appendix 7.

2.7.3 SEES in Patients With Cancer

When evaluating the symptom experience of early satiety in Chapter 6, participants were invited to complete the updated SEES Version 2 questionnaire if they reported early satiety in either the open question or the abPG-SGA. Participants self-completed the SEES questionnaire unless they requested/required assistance. The most common need for assistance was due

to their intravenous line for their treatment being placed in their writing arm, impeding their writing ability, or being too fatigued to read the SEES.

The SEES questions were grouped into different themes to allow for ease of analysis. These themes can be seen in Table 2.5

Table 2.5 Thematic grouping of the symptom experience of early satiety questions

THEME	QUESTIONS
TIMING	2,3,4,5,6
SEVERITY	7,8,9,10,11
MANAGEMENT	12,13, 14, 15
INFLUENCE ON INTAKE	16,17,18,19,20,21
EFFECT ON QOL	22,23
MISCELLANEOUS	1,24,25

2.8 Quality of Life

Participants on the ODW (Chapter 7) completed a validated symptom and quality of life questionnaire. All completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire (EORTC QLQ-C30)(Appendix 9).[296] This is a widely used research tool that contains multiple scales. The scales with the corresponding questions are detailed in Table 2.6. The thresholds for clinical importance are also listed based on those identified by Giesinger et al.[297] These have been proposed for use when using the EORTC QLQ-C30 as a screening tool in clinical practice to identify the most significant impairments for individual patients.

Table 2.6 Scoring guidance for each scale in the EORTC QLQ-C30 questionnaire. Thresholds for clinical importance (TCI) are based on Giesinger et al.[297]

	NUMBER OF ITEMS	ITEM RANGE	ASSOCIATED QUESTIONS	TCI
GLOBAL HEALTH/QOL	2	6	29, 30	N/A
FUNCTIONAL SCALES				
PHYSICAL FUNCTIONING	5	3	1 to 5	< 83
ROLE FUNCTIONING	2	3	6, 7	<58
EMOTIONAL FUNCTIONING	4	3	21 to 24	<71
COGNITIVE FUNCTIONING	2	3	20, 25	<75
SOCIAL FUNCTIONING	2	3	26, 27	<58
SYMPTOM SCALES				
FATIGUE	3	3	10, 12, 18	>39
NAUSEA AND VOMITING	2	3	14, 15	>8
PAIN	2	3	9, 19	>25
DYSPNOEA	1	3	8	>17
INSOMNIA	1	3	11	>50
APPETITE LOSS	1	3	13	>50
CONSTIPATION	1	3	16	>50
DIARRHOEA	1	3	17	>17
FINANCIAL DIFFICULTIES	1	3	28	>17

The raw score (RS) for each scale was calculated as the mean for each scale. A linear transformation was used to standardise the raw score on each scale. All scales had a score (S) that ranged from 0 to 100.

Functional Scales: $S = (1 – ((RS-1) / range)) X 100$

Symptom and QoL Scales: $S = ((RS – 1) / range) X 100$

A higher score in functional scales represented a higher-level functioning and a high score in the QoL scale represented a high QoL. A higher score on the symptom scaler represented a high level of symptom burden. To correct for this, an inverse transformation of the scores was performed so that higher scores

represented a lower symptom burden (100 – S). Summary scores were reported that summarise the symptom and functional components of the questionnaire, as recommended by the EORTC Quality of Life Group.[298] A symptom score was also calculated as a summary of the symptom components of the questionnaire.

2.9 Visual Analogue Scale Assessment

Participants in Chapter 7 completed a visual analogue scale (VAS) assessment of hunger, sickness, ability to eat and tiredness with six questions (Appendix 8). Each question was presented with a 10cm line with two anchor responses, one at either end of the line. Participants were instructed to mark with a vertical line through this 10cm line where they felt represented their answer. Most of the questions (5 of the 6) were phrased to allow the same anchor points of ‘not at all’ and ‘extremely’ to be used. This was done to standardise the responses and allow for easier completion for participants. The question that asked, ‘how much do you think you could eat right now’ was anchored with ‘nothing’ and ‘a large amount’. The responses were measured using a standard ruler from the point the participant responses first crossed the 10cm line. Participants who circled either anchor were assumed to respond as 0cm. Responses were measured to 0.1cm.

2.10 Data Protection

Throughout the thesis, data collection and storage were done in compliance with the General Data Protection Regulation 2018.

Before inclusion in all studies, potential participants received a PIL. This PIL outlined the study and its components in full, and potential participants were given the opportunity to ask any questions. Written signed informed consent forms were obtained from all those included. All participants received a copy of the PIL and a signed consent with the relevant contact details to allow them to contact the investigator as required. It was made clear that their inclusion was voluntary, that they could refuse to take part, that they could remove themselves at any point of the study, and that there would be no change in their current treatment as a result of any of the above.

All participants were assigned a study number upon signing the consent form. The keycode was only accessible to members of the research team. For the recruitment of the advanced cancer population, the keycode was stored in a locked cabinet within the ADPM. For the recruitment of the active treatment cohort, the keycode was stored in a locked filing cabinet in an office only accessible to research staff supervised by Professor Conlon. In all instances, the keycode was stored separately from the collected data to ensure confidentiality. All data gathered was justified to the research ethics, and non-essential data were not gathered. To ensure this, a data collection form was used throughout this thesis which was agreed upon by the appropriate research ethics committees. All paper copies of the data were stored per the Trinity College Dublin data retention policy.

2.11 Statistical Analysis

Statistical analysis was completed using Microsoft Excel 2016 and the IBM Statistical Package for Social Sciences (SPSS version 27, Chicago, IL USA). All results were entered into Excel. In all cases, a P value <0.05 was considered statistically significant. Descriptive analysis was performed for participant demographics and medical history of the participants. The mean differences were compared using sample t tests. Where distributions were non-normal, the Mann-Whitney U test was used to compare medians. Pearson Chi-Square compared the frequencies of categorical variables. One-way analysis of variance (ANOVA) was used to compare normally distributed continuous variables.

2.12 Qualitative Analysis

Qualitative analysis was done on open questions in the SEES. In questions 13 (what methods have worked for early satiety management?) and 21 (what foods cause early satiety?), a content analysis approach was chosen as the responses were factual to a direct question. The framework described by Bengtsson was used.[299]

In questions 24 (In your own words, please describe what you experience when you feel full quickly) and 25 (Do you have any further comments?), inductive thematic analysis was used based on the recommendations of Vaismoradi[300] as well as Braun & Clarke.[301]

3 CLINICAL CHARACTERISTICS OF EARLY SATIETY IN CANCER: A SCOPING REVIEW OF AVAILABLE QUANTITATIVE AND QUALITATIVE EVIDENCE

3.1 Introduction

Evidence based medicine (EBM) refers to the use of the best available published evidence to provide the most effective, efficient, and ethical patient care. It has been shown to dramatically improve patient outcomes when implemented.[302] It also ensures cost effectiveness in healthcare. Reviewing all available publications is key to determining EBM. Some symptoms in cancer have significant published research to ensure appropriate screening and treatment. Others, such as early satiety, have minimal available knowledge.

3.1.1 Early Satiety

Early satiety was discussed in more detail in Chapter 1. It is unclear whether early satiety is different within the different conditions in which it is common. As discussed, much of our knowledge surrounding early satiety comes from research into gastrointestinal disorders. It is a symptom of gastroparesis and forms part of the diagnostic criteria for functional dyspepsia. Early satiety in cancer is both under recognised and poorly understood. Early satiety in cancer has been described as an 'orphan symptom'.[303] There has been no systematic or scoping review on early satiety in cancer despite being a common symptom.

3.1.2 What Is A Scoping Review?

With the growing recognition that EBM is the benchmark in healthcare, there has been an increase in the reviewing and collation of primary research. Systematic reviews have become the most desirable form of evidence to guide healthcare practice.[304] As a result, there has been an increased focus on reviews with a systematic and repeatable search with no signs of this trend stopping.[305]

A scoping review is a type of literature review with a systematic and repeatable search similar to a systematic review but without a narrow range. Scoping reviews

are an invaluable style of evidence synthesis. They are used to answer broad questions and are deemed especially useful in areas where there is less research or where less is known on a topic. They allow for a less specific but broader understanding of existing evidence. This approach was used in my study to summarise published research findings, identify the knowledge gaps surrounding early satiety and devise research questions for further studies.

A key aspect of a scoping review is its systematic design allowing for reproducibility. To allow for this, Levac et al.[306] suggest a six stage framework that builds upon the work of Arksey and O'Malley.[307]

1) **Identify the research question:** In this review, the research question underwent repeated drafting after consultation with the research team. The goal of this was to ensure understanding among the research team and determine the need for further clarification.
2) **Identify relevant studies:** Here, it was important to balance breadth and comprehensiveness. Five different databases were searched for this review while also searching the reference lists of all included studies and all review articles identified.
3) **Study selection:** This was an iterative process. Proposed inclusion and exclusion criteria were then discussed and agreed upon by members of the research and supervisor team.
4) **Charting the data:** Data were charted using a self-designed extraction spreadsheet within Microsoft Excel ™ (Microsoft® Excel® for Microsoft 365). The author of this thesis and the second reviewer independently extracted the data from seven randomly selected studies (10%) to refine

the extraction spreadsheet and ensure that the extracted data reflected the research question.

5) **Collating, summarising, and reporting the results:** Results were first analysed individually and then were input into a spreadsheet with all other studies. The results were then summarised in text to give context to the extracted material. To ensure the usefulness of this review in a broader context, the results of this review were also analysed in the context of clinical practice with predictors of early satiety alongside its impact on patients. The results were given a separate section on their impact on clinical practice.
6) **Consultation:** Throughout this review, there was regular consultation between the two reviewers. Preliminary results were discussed to determine an appropriate layout and focus for these results. Finally, all members of the research team met to discuss the implications of this review and how best to use the results to guide future studies of this thesis.

There have also been other attempts to further develop scoping review methodology.[308] Based on the recommendations from Colquhoun et al[309], the framework described above was used.

3.1.3 Systematic Review Vs Scoping Review

As discussed, there are similarities and differences between systematic and scoping reviews. Guidance on which factors influence a decision to choose a scoping review is not clearly defined. A key distinction between scoping and systematic reviews lies in the purpose or research question for the review. Scoping reviews, as the name suggests, have a much broader ‘scope’, and therefore will also have less strict inclusion/exclusion criteria. As discussed

above, these reviews serve different purposes. Unlike systematic reviews, there is no critical appraisal of included studies to address a specific question. Due to this, the assessment of bias is not routinely done in scoping reviews.

Before opting for a scoping review, the pros and cons of the methodology were carefully evaluated. The cons were that a scoping review is limited in the depth of its results potentially leading to limited recommendations from the review. Another con that was considered was that the lack of quality assessment may have resulted in some potentially biased information being included. These were important because one of the indications for this review was to obtain useful information for clinical practice. The pros of the scoping review ultimately outweighed the cons. The breadth of the information gathered may be considered a con by some given the lack of specificity but was deemed a pro in the evaluation for which style of review to choose. From research into the literature, a systematic review in this area would have been too narrow in scope to capture the relevant information. This is due to a lack of basic information on early satiety such as a definition and pathophysiology. A quality appraisal of a select number of studies with a narrow focus was less important than mapping the available literature and identifying where there is a lack of research with a broader scope. The goal was then to identify knowledge gaps and highlight areas that need to be addressed in future research. This was a more important goal than answering a specific question and would allow a greater emphasis on research into early satiety in cancer in the future.

3.2 Methods

3.2.1 Ethical Considerations

Ethical approval was not required, as this is a scoping review of published literature. The reason is that this review accessed publicly accessible data for which consent was obtained from the authors. No new patient data or new secondary analysis was performed on published data.

This scoping review was undertaken using the methodological framework set out by Arksey and O'Malley[307] and enhanced by Levac et al.[306] This methodology suggests a six-step framework. Given the nature of a scoping review, quality was not assessed, and quantitative synthesis was inappropriate.

3.2.2 Identifying The Research Question

The research question in a scoping review guides all further framework stages, and thus an appropriate research question is key. The research question should remain broad in nature as the goal of the review is to summarise a breadth of evidence. Levac et al[306] recommend that the question for the review needs to clearly identify the scope of the review.

Based upon the recommendation from the Joanna Briggs Institute, the population, concept, context framework was used to devise the research question.[310] Based on this framework, the research question was set as:

> *What are the clinical characteristics of early satiety in all cancers excluding animal studies?*

This research question led to the definition of key objectives for this review. Similar to the above research question, these were agreed upon among the research team. The objectives were as follows:

1. Systematically search the available peer reviewed literature for early satiety in cancer.
2. Identify the range of tools used to screen for early satiety and the descriptions used in the literature.
3. Identify the key characteristics of early satiety in cancer including predictors, impact, pathophysiology, and available treatments.
4. Identify existing knowledge gaps and propose recommendations to address these gaps while simultaneously highlighting the importance of future research in this area.

3.2.3 Identifying Relevant Studies

The process is a difficult balance between comprehensiveness and breadth. To ensure breadth, multiple databases were included which all focus on healthcare but include papers from multiple professions with the hope of gaining information from different perspectives.

The search strategy was developed in tandem with a specialist librarian in OLH&CS and a research nurse in the ADPM, both with previous experience in conducting scoping reviews. An initial pilot search was conducted in PubMed. Due to the broad nature of the search, the number of returned studies was high. Search results were screened to determine the accuracy of the search using known key papers in the area. From this, several descriptors for early satiety were noted. It was also noted that some additional cancer descriptors and more colloquial language on early satiety like descriptions used on common screening tools would be beneficial. Subject headings of fullness, satiation, satiety, cancer, neoplasm, and oncology were used to ensure the most thorough search and to

capture the different descriptors used. Postprandial fulness was excluded as it is a different symptom. Early satiety is the feeling of fullness when eating, while postprandial fullness is a prolonged unpleasant feeling of fullness in the stomach after eating. While there is a possibility that some data were missed, since early satiety may have been inappropriately described as postprandial fullness, it would have been difficult to differentiate which described early satiety.

Cochrane, EBSCOhost, Embase, PubMed, and Web of Science databases were searched for this review. Searches were carried out on each database on a trial basis to ensure reproducibility and accuracy. The final searches in all databases were completed on 10/09/2021 (Appendix 2), and the results were saved. Inclusion/exclusion criteria are listed in Table 3.1. Search results were exported from relevant databases, including abstracts where possible, imported into Covidence^{TM}, and deduplicated.

Table 3.1 Inclusion/exclusion criteria for scoping review using Population/Concept/Context framework[310]

	Included	Excluded
Study Details	All study types reporting original data i.e. RCT, observational, cohort studies, case-control, case series/case reports Studies with English full text	Review articles Editorials Systematic/scoping reviews Grey literature Conference abstracts Studies with a full text other than English
Population	Human studies All cancers	Animal studies
Concept	Early satiety due to cancer	Early satiety due to any other condition (i.e. diabetes)
Context	All healthcare/research settings	Participants with known pre-existing gastroparesis

Whether to include conference abstracts and grey literature was discussed among all involved. While they may have included some relevant information, they were excluded from this review. From our initial search, the conference abstracts and grey literature that were screened did not include the description of early satiety used which was a study objective. There was also a hope that the

information from this review would be of clinical relevance and to ensure patient safety, we only included peer-reviewed articles.

3.2.4 Search

Title and abstract screening was conducted by two independent researchers. Studies were included if they discussed gastrointestinal symptoms, a tool known to assess early satiety or named early satiety in the abstract. Inclusion conflicts were resolved through discussion and consensus, after full text review if necessary. In cases where consensus could not be reached, an independent third researcher with specialist knowledge of the area was available to decide on inclusion or exclusion. Review articles were screened for relevant references but were otherwise excluded.

The full text screening was also carried out by two researchers with the same process for resolution of the conflict. Follow up studies and dual reports from the same trial were grouped and highlighted in the extraction table as appropriate. References and citations for each included study were also reviewed to ensure that no relevant articles were omitted.

3.2.5 Data Extraction

Data extraction was completed in Microsoft Excel™ (Microsoft® Excel® for Microsoft 365) using a data charting form that was developed and updated in an iterative process. No quality assessment or meta-analysis was conducted. No appraisal of bias in individual studies or across studies was undertaken. This is due to the broad nature of the study design. The author of this thesis extracted all of the data from included papers with 10% of the extraction results double checked by an independent researcher to ensure accuracy of extraction. This

10% of the search results was randomly selected through a random number generator.

The review has been reported following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist and associated guidelines.

3.3 Results

3.3.1 Search Results

Screening results are shown in the PRISMA diagram (Figure 3.3). A total of 5585 studies were imported for screening. At this point, Covidence removed 2130 leaving 3455 studies for screening. 176 full-text studies were assessed for eligibility. Ultimately, 64 studies were included, with seven additional studies added by hand-searching the review papers and the reference list of included studies.

3.3.2 Study Characteristics

A full list of studies with extracted data can be found in Table 3.2. As discussed, searches were not limited by year of publication. Included studies spanned 41 years of publication. A breakdown of the number of publications by year can be seen in Figure 3.1. Early satiety/early satiation was a keyword in only 6% of publications.[311-314]

Relevant studies for this scoping review were published between 1980 and 2021. Most (n=43) publications were cross-sectional[39, 46, 174, 175, 177, 216, 312, 314-349], 12 longitudinal[313, 350-360], 8 trials[190, 361-367], 6 retrospective[368-373], one audit[311] and one qualitative study[374] were also included.

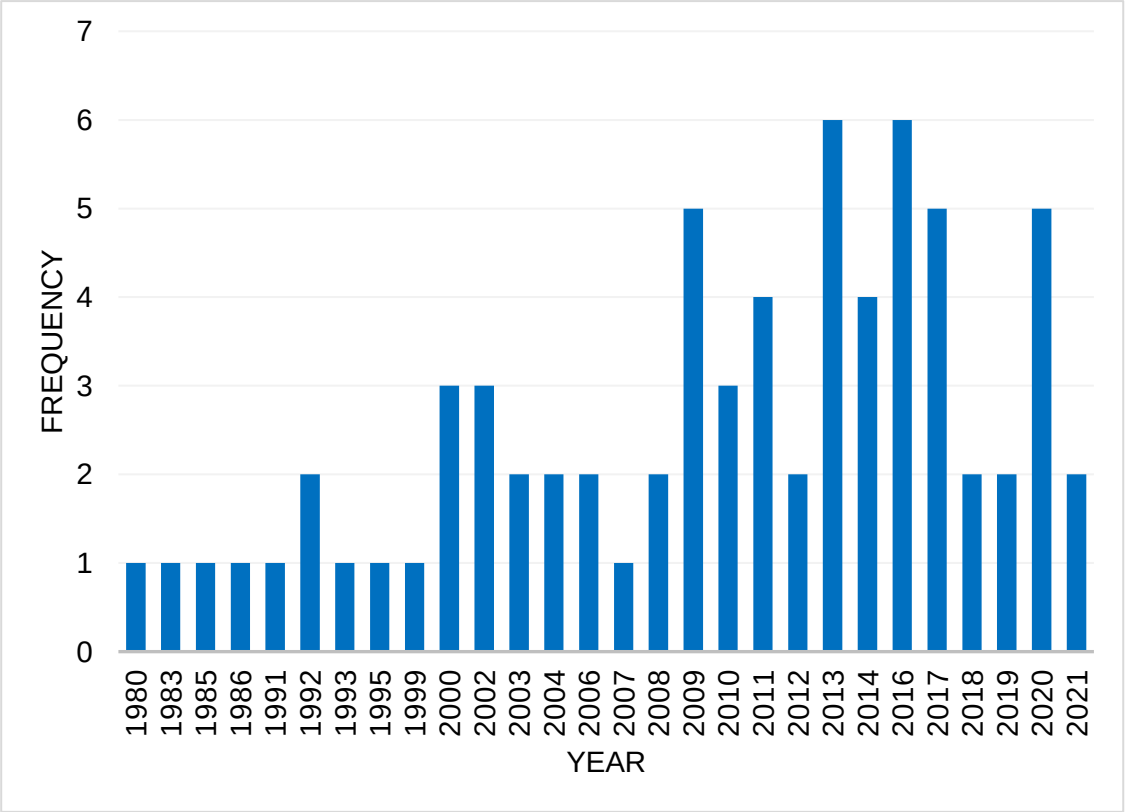


Figure 3.1 Frequency of publications included in the scoping review per year

Publications from across the world were included. The United States of America, United Kingdom, and The Netherlands were the countries with the most publications. Regarding continents engaged in the research of early satiety in cancer, Europe had a majority at 52 publications (48%), with North America having 32 (30%) Asia had 12 (11%), South America 9 (9%) and Australia 2 (2%). A full breakdown of publication sites can be seen in Figure 3.2.

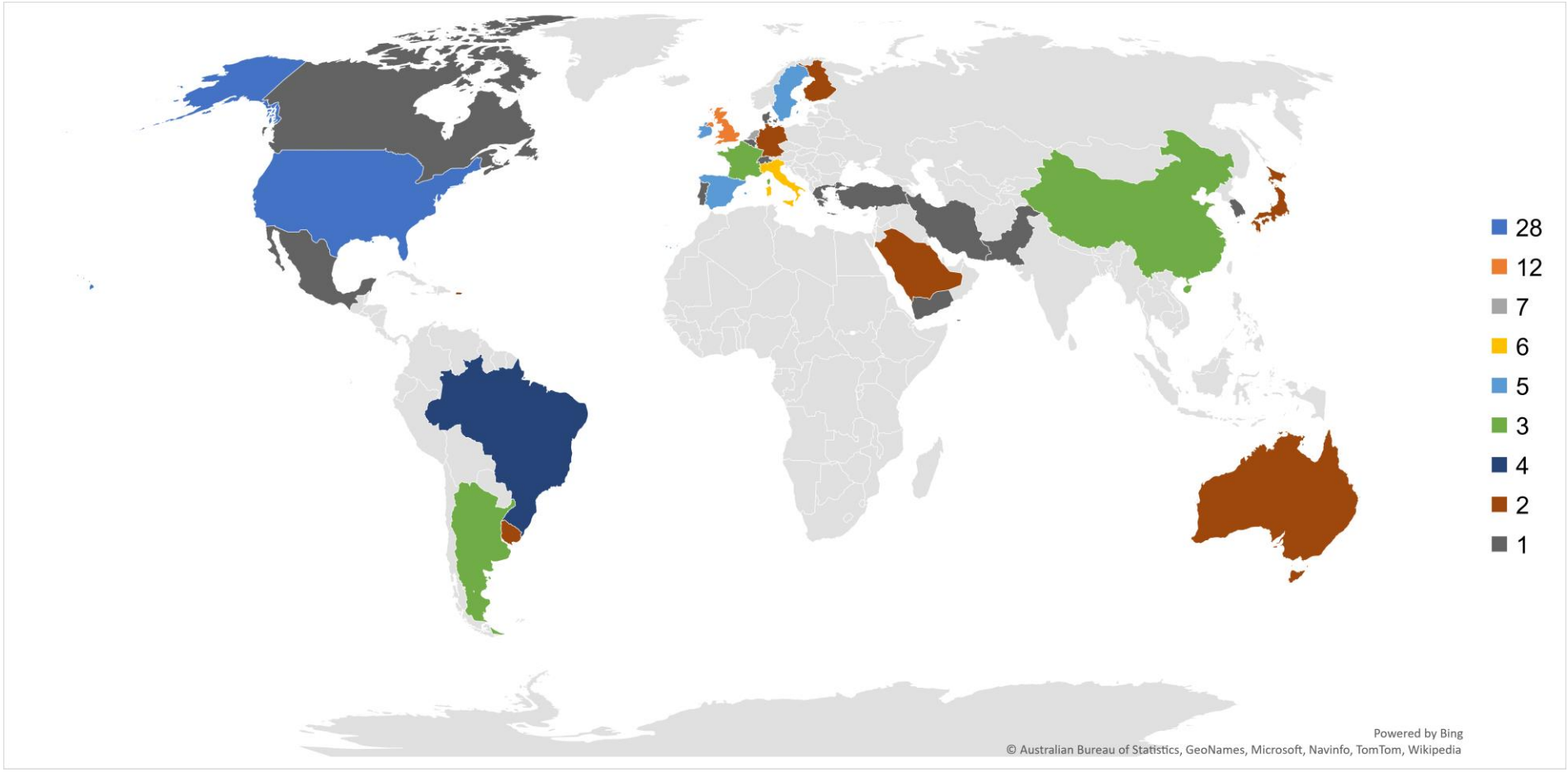


Figure 3.2 Frequency of publications included in the scoping review per country

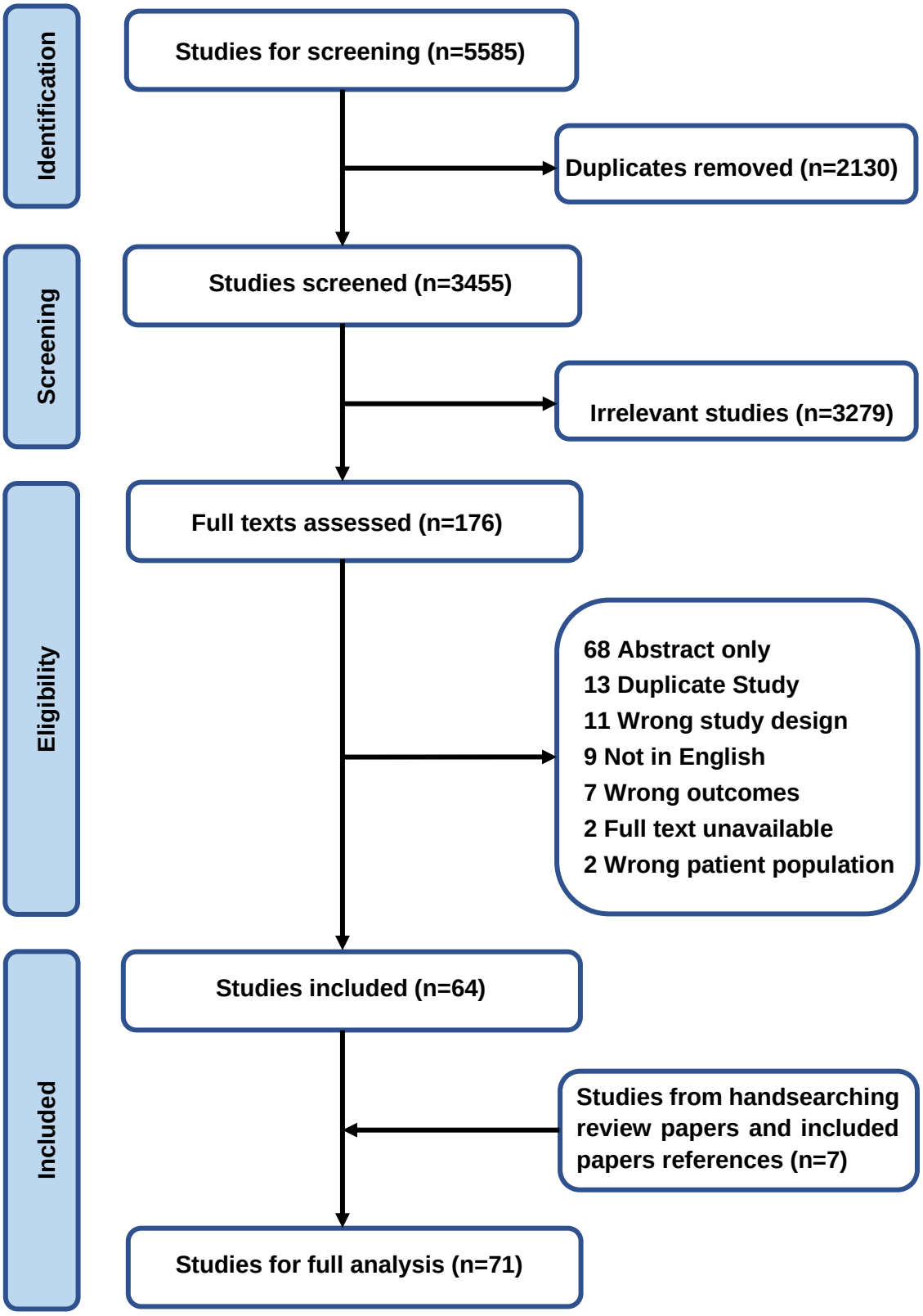


Figure 3.3 PRISMA diagram of the selection process for including studies in the scoping review

Table 3.2 Data extraction table for included studies

First Author, Year	Title, Journal and DOI	Study Design (Keyword Y/N)	Total n (M/F) and Cancer	Tool to identify (Validated Y/N)	Description	Prevalence (%)	Results
Adachi, 2003[350]	**Subjective and functional results after total gastrectomy: prospective study for longterm comparison of reconstruction procedures** Gastric Cancer 10.1007/s101200300003	Longitudinal (N)	30 (23/7) Gastric	Unknown (N)	Unknown	R-Y 20,10,0 P-Y 10,30,50 P-I 50,40,0 (at 1 year, 3 years, and 5 years post gastrectomy respectively)	Early satiety within 30 minutes after starting a meal. No rates were statistically significantly different
Aktas, 2014[315]ϕ	**Cancer symptom clusters: an exploratory analysis of eight statistical techniques** Journal of Pain and Symptom Management 10.1016/j.jpainsymman.2014.02.006	Cross-Sectional (N)	999 (553/446) Mixed	Researcher question (N)	Unknown	51	Early satiety part of the fatigue/anorexia-cachexia symptom cluster with anorexia, dry mouth, fatigue, lack of energy, taste changes, weakness, weight loss (>10%)

Alsirafy, 2016[316]	**Voluntary reporting to assess symptom burden among Yemeni cancer patients: common symptoms are frequently missed** Journal of Community and Supportive Oncology 10.12788/jcso.0178	Cross-Sectional (N)	50 (19/31) Mixed	Researcher designed assessment (N)	Unknown	Total 28 Mild 10 Moderate 10 Severe 8	Early satiety was never voluntarily reported in an open question. Early satiety 12th most reported symptom
Andrew, 2008[311]	**Audit of symptoms and prescribing in patients with the anorexia-cachexia syndrome** Pharmacy World & Science 10.1007/s11096-008-9192-9	Audit (Y)	23 (11/12) Mixed	PG-SGA (Y)	Feel full quickly	70	Early satiety 3rd most common symptom. One of the most commonly untreated symptoms
Andreyev, 2020[359]	**The FOCCUS study: a prospective evaluation of the frequency, severity and treatable causes of gastrointestinal symptoms during and after chemotherapy** Supportive Care in Cancer 10.1007/s00520-020-05610-x	Longitudinal (N)	248 (150/98) Mixed	Modified GSRS questionnaire (N)	Feeling full after small amount of food	Pre chemo 24* 3 months 18* 6 months 18* 12 months 12*	Reported less frequently with chemotherapy (no statistical significance test done)

Armes, 1992[46]	**A study to investigate the incidence of early satiety in patients with advanced cancer** British Journal of Cancer 10.1038/bjc.1992.98	Cross-Sectional (N/A)	61 (47/14) Mixed	Unknown (N)	Unknown	10	The hunger rating for early satiety was similar to normal appetite. Significant difference in hunger, mood, mental activity, and emptiness between those with anorexia/-early satiety and anorexia/+early satiety. All with early satiety had small or very small food intake compared to normal appetite. (SS) All with early satiety had anorexia.
Bankhead, 2008[317]	**Identifying symptoms of ovarian cancer: a qualitative and quantitative study** British Journal of Obstetrics and Gynaecology 10.1111/j.1471-0528.2008.01772.x	Cross-Sectional (N)	124 (0/124) Ovarian	Qualitative interview (N)	N/A	41	Early satiety independent variable associated with ovarian cancer. Adjusted odds ratio (95%CI) 5.0 (1.6-15.7)

Barajas Galindo, 2017[318]	**Appetite disorders in cancer patients: Impact on nutritional status and quality of life** Appetite 10.1016/j.appet.2017.03.020	Cross-Sectional (N)	128 (84/44) Mixed	Researcher question (N)	A precocious sensation of fullness when eating that impeded a complete intake of a meal	Total 30. Men 21.4 (8.3 Early satiety, 13.1 Early satiety and anorexia) Women 47.7 (22.7 Early satiety, 25% with Early satiety and anorexia)	Early satiety was significantly more common in women, patients with cachexia, and those without radiation therapy. No differences according to age, chemotherapy, previous surgery or tumour type. Associated with significantly decreased grip strength compared to normal appetite. Showed no significant decrease in dietary intake. Early satiety + anorexia showed significant decreases in protein intake in g compared to normal appetite. Early satiety alone showed no difference in quality of life. Early satiety + anorexia showed a significant

							difference in global health, physical function, role function, emotional function, cognitive function and fatigue. Early satiety alone and early satiety with anorexia associated with significantly worse nutritional status
Borre, 2018[319]	**Nutritional status and nutritional risk in patients with neuroendocrine tumors** Scandinavian Journal of Gastroenterology 10.1080/00365521.2018.1430848	Cross-Sectional (N)	186 (92/94) Mixed	Disease related appetite questionnaire (N)	When I eat I feel full after eating 1/4 of the meal or less. When I eat I feel full after eating approximately half of the meal.	Total 23 After 1/4 meal 8 After 1/2 meal 15	Early satiety was significantly associated with lower handgrip strength, increased nutritional risk, weight loss, and impaired function
Boshier, 2020[320]	**Assessment of Health Related Quality of Life and Digestive Symptoms in Long-term, Disease Free Survivors After Esophagectomy** Annals of Surgery 10.1097/SLA.0000000000003829	Cross-Sectional (N)	171 (138/33) Oesophageal	Researcher question (N)	Do you get full easily when you eat?	Total 81.3 <1 year 91.7 1-5 year 81.7 >5 year 90.8	Early satiety most common symptom irrespective of timeframe

Bozzetti, 2009[321]	**Defining and Classifying Cancer Cachexia: A Proposal by the SCRINIO Working Group** Journal of Parenteral and Enteral Nutrition 10.1177/0148607108325076	Cross-Sectional (Y)	1307 (830/461) Mixed	Researcher designed scale (N)	Unknown	Total 38 Mild 20 Moderate 14 Severe 4	N/A
Bozzetti, 2009[312]	**Screening the nutritional status in oncology: a preliminary report on 1,000 outpatients** Supportive Care in Cancer 10.1007/s00520-008-0476-3	Cross-Sectional (N)	1000 (643/357) Solid Tumours	Researcher designed scale (N)	Unknown	Total 41.4 Mild 21.7 Moderate 15.0 Severe 4.6	N/A
Cense, 2004[322]	**Quality of life after colon interposition by necessity for esophageal cancer replacement** Journal of Surgical Oncology 10.1002/jso.20132	Cross-Sectional (N)	14 (12/2) Oesophageal	Modified Rotterdam Symptom Checklist (N)	Unknown	Total 92.8 A bit 42.85 Somewhat 42.85 Very much 7.1	Early satiety most frequent symptom
Cerchietti, 2004[361]	**Effects of celecoxib, medroxyprogesterone, and dietary intervention on systemic syndromes in patients with advanced lung adenocarcinoma: a pilot study** Journal of Pain and Symptom Management	Trial (N)	15 (11/4) Lung	Unknown (N)	Unknown	Pre-treatment 53.3 Post treatment 6.7	Significant decrease in Early satiety post treatment

	10.1016/j.jpainsymman.2003.05.010						
Christensen, 2021[323]	**Tobacco use in the Myeloproliferative neoplasms: symptom burden, patient opinions, and care** BMC Cancer 10.1186/s12885-021-08439-7	Cross-Sectional (N)	435 (111/324) Mixed Haematological	MPN-10 (Y)	Filling up quickly when you eat	Total 63. Current/former smokers 68.5 non-smokers 58.3	Smoking was significantly associated with an increased risk of Early satiety
Churm, 2009[324]	**A questionnaire study of the approach to the anorexia-cachexia syndrome in patients with cancer by staff in a district general hospital** Supportive Care in Cancer 10.1007/s00520-008-0486-1	Cross-Sectional (N)	100 (70 Nurses and 30 doctors)* N/A	Researcher question (N)	Early Satiety	N/A	Management: Self-help (44) Do not know/do nothing (29) medical assessment (21) Dietitian and/or supplement drinks (21) Prescription medication (7). Self-help measures included small frequent meals, less fluid at mealtimes, and food with high energy content. Medical assessment included referral to doctors (9) or staging disease, gastroscopy or blood tests (12). Medications to

							prescribe would be metoclopramide (5), corticosteroids (1) and proton pump inhibitor (1). 29% reported being unable to recognise or treat early satiety. Early satiety is routinely assessed by 14
Collard, 1992[325]	**Quality of life three years or more after esophagectomy for cancer** The Journal of Thoracic and Cardiovascular Surgery N/A	Cross-Sectional (N/A)	17 (13/4) Oesophageal	Researcher question (N)	Do you have early thoracic or epigastric fullness when eating	65	Early satiety most common residual symptom. 9/17 with early satiety reduced amount of food ingested at a single meal and to take snacks between meals (no significance data)
Davis, 2012[362]	**A Phase II dose titration study of thalidomide for cancer-associated anorexia** Journal of Pain and Symptom Management 10.1016/j.jpainsymman.2011.03.007	Trial (N)	33 (17/16) Mixed	Researcher designed scale (N)	Sense of fullness after meals	N/A	Early satiety improved (1.2=+/-1.1 to 0.8+/-1.0, p <0.05). CI overlapped and therefore could not conclude was secondary to treatment

De Boer, 2000[351]	**Quality of life in long-term survivors after curative transhiatal oesophagectomy for oesophageal carcinoma** British Journal of Surgery 10.1046/j.1365-2168.2000.01600.x	Longitudinal (N)	35 (28/7) Oesophageal	Modified Rotterdam Symptom Checklist (N)	Unknown	Total 79.4 A bit 32.4 Somewhat 38.2 Very much 8.8	Early satiety most frequent symptom
Del Fabbro, 2011[368]	**Clinical outcomes and contributors to weight loss in a cancer cachexia clinic** Journal of Palliative Medicine 10.1089/jpm.2011.0098	Retrospective (N/A)	151 (65/56) Mixed	Researcher designed with symptoms derived from PG-SGA (N)	Unknown	62	Metoclopramide given to treat early satiety in 79%. Early satiety was the most common symptom
Dias do Prado, 2013[326]	**Nutritional status of patients with gastrointestinal cancer receiving care in a public hospital; 2010-2011** Nutricion Hospitaleria 10.3305/nh.2013.28.2.6305	Cross-Sectional (N)	143 (100/43) Gastrointestinal	PG-SGA (Y)	Feel full quickly	7	Early satiety significantly more common in malnourished patients over non malnourished
Donnelly, 1995[327]ϕ	**The symptoms of advanced cancer: Identification of clinical and research priorities by assessment of prevalence and severity** Journal of Palliative Care 10.1177/082585979501100105	Cross-Sectional (N/A)	999 (553/446) Mixed	Researcher question (N)	Unknown	51	Early satiety significantly more common in females. Early satiety mild in 27%, Moderate 47% and severe 23%*

Dressler, 2016[369]	**Long-term functional outcomes of laparoscopic resection for gastric gastrointestinal stromal tumors** Surgical Endoscopy 10.1007/s00464-015-4384-6	Retrospective (N)	36 (20/16) Gastric	Researcher designed survey (N)	How much food does it take to become "full" compared to before the surgery	N/A	32.4% reported worsening early satiety compared to pre surgery. These reported generally normal Gastrointestinal Quality of Life Index
Elliott, 2017[352]	**Weight Loss, Satiety, and the Postprandial Gut Hormone Response after Esophagectomy: A Prospective Study** Annals of Surgery 10.1097/SLA.0000000000001918	Longitudinal (N)	13 (9/4) Oesophageal	QLQ-OG25 (N)	Have you felt full up too quickly after beginning to eat	N/A	Significant increase in Early satiety postoperatively at three months. Early satiety persists at all timepoints. Early satiety strongly associated with GLP-1 response at 3 months. Early satiety associated with increased composite eating symptom scores
Emanuel, 2012[328]	**Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with**	Cross-Sectional (N/A)	1433 (589/774) Mixed Haematological	MPN-SAF (Y)	Filling up quickly when you eat	Total 64 ET 59 PV 64 MF 77	Second highest symptom intensity

	MPNs Journal of Clinical Oncology 10.1200/JCO.2012.42.3863						
Fanelli, 1986[329]	**Plasma tryptophan and anorexia in human cancer** European Journal of Clinical Oncology 10.1016/0277-5379(86)90346-9	Cross-Sectional (N/A)	45 (22/23) Mixed	Researcher question (N)	Unknown	47	In anorectic patients, early satiety 70%. Plasma free TRP significantly higher in those with Early satiety vs controls. Non significantly different in those in non-anorectic cancer patients. Plasma molar ratio of free tryptophan higher in Early satiety vs controls
Ferreira, 2013[330]	**Acceptance of hospital diets and nutritional status among inpatients with cancer** Einstein (Sao Paulo) 10.1590/s1679-45082013000100008	Cross-Sectional (N)	100 (59/41) Mixed	PG-SGA (Y)	Feel full quickly	14	Significantly higher early satiety in malnourished vs well nourished
Flórez Almonacid, 2013[353]	**Evaluation of the nutritional profile of patients with total laryngectomy** e-SPEN Journal 10.1016/j.clnme.2013.07.004	Longitudinal (N)	40 (38/2) Laryngeal	Researcher question (N)	Unknown	Admission 22.5 7 days post op 80 14 days post op 72.5	Consumed 248 less calories at 14 days postoperatively than those without early satiety (significant). 7 days consumed

							117.7 kcal less (not significant)
Georgina Turcott, 2020[331]	**Baseline Dysgeusia in Chemotherapy-Naive Non-Small Cell Lung Cancer Patients: Association with Nutrition and Quality of Life** Nutrition and Cancer 10.1080/01635581.2019.1633362	Cross-Sectional (N/A)	65 (38/27) Lung	PG-SGA (Y)	Feel full quickly	With Dysgeusia 86 No Dysgeusia 32	Early satiety significantly more common in those with dysgeusia vs without
Geyer, 2013[354]	**Ruxolitinib in Clinical Practice for Therapy of Myelofibrosis: Single USA Center Experience After FDA Approval** Leukemia & Lymphoma 10.3109/10428194.2013.789507	Longitudinal (N/A)	28 (19/9) Mixed Haematological	Researcher question (N)	Unknown	25	Improved early satiety (71%) (no significance calculations)
Greene, 2014[370]	**Long-term quality of life and alimentary satisfaction after esophagectomy with colon interposition** The Annals of Thoracic Surgery 10.1016/j.athoracsur.2014.06.088	Retrospective (N/A)	63 (53/10) Oesophageal	Researcher question (N)	Unknown	40	Early satiety the most common postprandial symptom. Vagal-sparing esophagectomy had significantly less early satiety (20% vs 58%)

Haverkort, 2010[313]	**Presence and Persistence of Nutrition-Related Symptoms During the First Year Following Esophagectomy with Gastric Tube Reconstruction in Clinically Disease-Free Patient** World Journel of Surgery 10.1007/s00268-010-0786-8	Longitudinal (Y)	Total 96 (73/23) Completed one year follow-up (60) Oesophageal	Researcher questionnaire (N)	Early satiety	1 week 89 3 months 87 6 months 87 12 months 90	Early satiety most common symptom
Iivonen, 1999[363x]	**Emptying of the jejunal pouch and Roux-en-Y limb after total gastrectomy-a randomised, prospective study** The European Journal of Surgery 10.1080/11024159950189500	Trial (N)	45(26/19) Gastric	Researcher question (N)	Unknown	3 month (Roux 67 Pouch 33) 6 month (Roux 52 Pouch 17) 15 month (Roux 48 Pouch 25)	Early satiety was significantly more frequent in the Roux-en-Y group 6 months after operation
Iivonen, 2000[364x]	**Long-term follow-up of patients with jejunal pouch reconstruction after total gastrectomy. A randomized prospective study** Scandinavian Journal of Gastroenterology 10.1080/00365520075002 3327	Trial (N)	34 (12/22) Gastric	Researcher questionnaire (N)	Unknown	1 year (Pouch 20 Roux 63) 3 year (Pouch 5 Roux 86) 8 (year Pouch 57 Roux 65)*	Early satiety significantly more common in Roux-en-Y at 3 months, 1 year and 3 years. Early satiety reduced 3 or more years after total gastrectomy vs Roux-en-Y (no

							statistical significance test done)
Johansson, 2011[332]	**Association between quality of life and clinical parameters in patients with myeloproliferative neoplasms** Leukemia & Lymphoma 10.3109/10428194.2011.619608	Cross-Sectional (N)	114 (60/54) Mixed Haematological	MPN-SAF (Y)	Filling up quickly when you eat	Total 55 ET 49 PV 66 PMF 63	Significantly worse in those with no vascular events. Significant correlation between Early satiety and age
Kang, 2016[333]	**A Study on the Dietary Intake and the Nutritional Status among the Pancreatic Cancer Surgical Patients** Clinical Nutrition Research 10.7762/cnr.2016.5.4.279	Cross-Sectional (N)	31 (15/16) Pancreatic	Researcher question (N)	Unknown	32	Early satiety third most common symptom
Khalid, 2006[334]	**Symptoms and weight loss in patients with gastrointestinal and lung cancer at presentation** Supportive Care in Cancer 10.1007/s00520-006-0091-0	Cross-Sectional (N)	151 (85/66) Solid Tumours	abPG-SGA (Y)	Feel full quickly	27	Early satiety second most common symptom. No significant difference in early satiety between gastrointestinal and lung cancers
Khan, 2014[335]	**Gastric carcinoma: Presentation at a tertiary care hospital in Peshawar** Pakistan Journal of Medical and Health	Cross-Sectional (N)	113 (75/38) Gastric	Unknown (N)	Unknown	33.6	N/A

	Sciences N/A						
Kirkova, 2010[336]	**Symptom severity and distress in advanced cancer** Palliative Medicine 10.1177/0269216309356380	Cross-Sectional (N)	181 (unknown) Mixed	Researcher questionnaire/ Volunteered symptom (N)	Feeling full after a few bites of food	50	6th most common symptom 67% with symptom found it distressful. Early satiety significantly more common in ≤65 years old and more distressful in this group
Komurcu, 2002[175]	**Gastrointestinal symptoms among inpatients with advanced cancer** The American Journal of Hospice & Palliative Care 10.1177/104990910201900513	Cross-Sectional (N)	50 (29/21) Mixed	Survey questionnaire (N)	Do you feel full after eating only a small amount of food	71	Early satiety third most prevalent symptom. Early satiety significantly associated with weight loss and bloating
Konishi, 2016[314]	**Impaired Gastrointestinal Function Affects Symptoms and Alimentary Status in Patients After Gastrectomy** World Journal of Surgery 10.1007/s00268-016-3613-z	Cross-Sectional (Y)	51 (40/11) Gastric	Researcher questionnaire (N)	Unknown	Total 29 TGRY 27 DGBI 47 DGRY 16	Early satiety not associated with delayed gastric emptying or reservoir capacity. Early satiety significantly associated with increased water load drink test score

Krech, 1991[337]ϕ	**Symptoms of pancreatic cancer** Journal of Pain and Symptom Management 10.1016/0885-3924(91)90027-2	Cross-Sectional (N)	39 (16/23) Pancreatic	Researcher questionnaire (N)	Unknown	62	Early satiety third most common symptom
Lasheen, 2009[360]ϕ	**The cancer anorexia-cachexia syndrome: myth or reality?** Supportive Care in Cancer 10.1007/s00520-009-0772-6	Longitudinal (N)	484 (unknown) Solid Tumours	Researcher questionnaire (N)	Unknown	Total 51 +Anorexia/-weight loss 63 +Weight loss/-anorexia 39 -No anorexia/-weight loss 17 +Weight loss/+anorexia 70	Early satiety significantly more common in cancer anorexia-cachexia syndrome. Early satiety significantly more common in those with anorexia and no significant weight loss compared to with cachexia and no anorexia
Lin, 2011[371]	**Clinical characteristics of early onset pancreatic adenocarcinoma: A medical center experience and review of the literature** Pancreas 10.1097/MPA.0b013e318214fe56	Retrospective (N/A)	25 (unknown) Pancreatic	Unknown (N)	Unknown	12	N/A

Lindsey, 1985[355]	**Anorexia and weight loss: Indicators of cachexia in small cell lung cancer** Nutrition and Cancer 10.1080/01635588509513841	Longitudinal (N/A)	10 (10/0) Lung	Researcher questionnaire (N)	Feeling full after having eaten only a little bit	Time from diagnosis >2 weeks 20 3-6 weeks 10 11-14 weeks 10 15-18 weeks 12.5 19-22 weeks 37.5	N/A
Lorton, 2019[338]	**Late referral of cancer patients with malnutrition to dietitians: a prospective study of clinical practice** Supportive Care in Cancer 10.1007/s00520-019-05042-2	Cross-Sectional (N)	200 (119/81) Mixed	Researcher questionnaire (N)	Unknown	27	Early satiety third most common symptom
Markar, 2021[339]	**Patient-reported outcomes after oesophagectomy in the multicentre LASER study** The British Journal of Surgery 10.1093/bjs/znab124	Cross-Sectional (N)	876 (559/166) Oesophageal	LASER questionnaire (Y)	Early feeling of fullness after eating	1-2 years 34.4 3-4 years 29 >5 years 28*	Early satiety second most commonly classified as severe (30%). Early satiety most common symptom in first 2 years after surgery (34.4%). Clustered with dysphagia and hiccoughs. Significantly associated with increased age. Early satiety associated with being male,

							having hybrid minimally invasive surgery based on odds ratio (significance test not done)
McGettigan, 2019[174]	**Subjective and Objective Assessment of Taste and Smell Sensation in Advanced Cancer** The American Journal of Hospice & Palliative Care 10.1177/1049909119832836	Cross-Sectional (N)	30 (9/21) Mixed	abPG-SGA (Y)	Feel full quickly	66	N/A
McGreevy, 2014[356]	**Characteristics of taste and smell alterations reported by patients after starting treatment for lung cancer** Supportive Care in Cancer 10.1007/s00520-014-2215-2	Longitudinal (N)	89 (40/49) Lung	PG-SGA (Y)	Feel full quickly	Total 18 With TSA 23 Without TSA 7	N/A

Mehran, 2011[340]	**Minimally invasive esophagectomy versus open esophagectomy, a symptom assessment study** Diseases of the Esophagus 10.1111/j.1442-2050.2010.01113.x	Cross-Sectional (N)	88 (83/5) Oesophageal	Researcher questionnaire (N)	Do you have early satiety	Total 50 MIE 59 Open 41	Early satiety was the most common symptom
Mesa, 2018[341]	**Patient-Reported Outcomes Data From REVEAL at the Time of Enrollment (Baseline): A Prospective Observational Study of Patients With Polycythemia Vera in the United States Clinical Lymphoma** Myeloma & Leukemia 10.1016/j.clml.2018.05.020	Cross-Sectional (N)	2309 (1247/1062) Polycythaemia Vera	MPN-SAF (Y)	Filling up quickly when you eat	60.9	Early satiety second most common symptom and second highest mean severity score
Mitra, 2013[372]	**Symptom burden and splenomegaly in patients with myelofibrosis in the United States: a retrospective medical record review** Cancer Medicine 10.1002/cam4.136	Retrospective (N)	180 (114/66) Mixed Haematological	Physician questioning (N)	Unknown	Total 65 With splenomegaly 79 Without splenomegaly 47	Early satiety significantly more likely with splenomegaly. Early satiety associated with higher international prognostic scoring system score (No significance test done)

Movahed, 2020[342]	**Nutritional Status in Patients with Esophageal Cancer Receiving Chemoradiation and Assessing the Efficacy of Usual Care for Nutritional Managements** Asian Pacific Journal of Cancer Prevention 10.31557/APJCP.2020.21.8.2315	Cross-Sectional (N)	71 (33/38) Oesophageal	PG-SGA (Y)	Feel full quickly	25	N/A
Nielsen, 1980[343]	**Influence of food odors on food aversions and preferences in patients with cancer** The American Journal of Clinical Nutrition 10.1093/ajcn/33.11.2253	Cross-Sectional (N/A)	133 (59/74) Mixed	Researcher questionnaire (N)	Do you get full with less food	62	Chemotherapy not associated with early satiety. Cancer dx not associated with Early satiety prevalence. Early satiety significantly associated with presence of food aversions (80% with vs 49% without). With Early satiety found coffee, pork, and ham odours less pleasant (significant)

Nelson, 1993[190]	**Assessment of upper gastrointestinal motility in the cancer-associated dyspepsia syndrome** Journal of Palliative Care N/A	Experimental (N/A)	20 (13/7) Mixed	Unknown (N)	Unknown	N/A	80% with early satiety had reduced upper GI motility, 10% with cancer and no Early satiety had reduced motility. Early satiety associated with higher symptom scores
Sarhill, 2003[344]	**Evaluation of nutritional status in advanced metastatic cancer** Supportive Care in Cancer 10.1007/s00520-003-0486-0	Cross-Sectional (N)	352 (180/172) Mixed	Researcher questionnaire (N)	Unknown	69	Early satiety third most common symptom
Scotch, 2017[345]	**Symptom burden profile in myelofibrosis patients with thrombocytopenia: Lessons and unmet needs** Leukemia Research 10.1016/j.leukres.2017.10.002	Cross-Sectional (N)	418 (198/220) Mixed Haematological	MPN-SAF (Y)	Filling up quickly when you eat	Total 72.7 No thrombocytopenia 71 With thrombocytopenia 79*	Significantly higher Early satiety symptom score in those with thrombocytopenia
Seker, 2013[373]	**Clinicopathologic features of gastric cancer in young patients** The Saudi Journal of Gastroenterology 10.4103/1319-3767.120876	Retrospective (N)	82 (44/38) Gastric	Unknown (N)	Unknown	23.1	N/A

Shivshanker, 1983[365]	**Tumor-associated gastroparesis: Correction with metoclopramide** American Journal of Surgery 10.1016/0002-9610(83)90067-3	Trial (N/A)	10 (unknown) Pancreatic	Researcher designed scale (N)	Unknown	N/A	Improvement in early satiety within 48 hours (no significance stats done)
Simpson, 2009[366]	**Does the use of nizatidine, as a pro-kinetic agent, improve gastric emptying in patients post-oesophagectomy?** Journal of Gastrointestinal Surgery 10.1007/s11605-008-0736-z	Trial (N)	20 (15/5) Oesophageal	Researcher questionnaire (N)	Unknown	80	Early satiety most common symptom
Spotten, 2016[39]	**Subjective taste and smell changes in treatment-naive people with solid tumours** Supportive Care in Cancer 10.1007/s00520-016-3133-2	Cross-Sectional (N)	40 (23/17) Mixed	abPG-SGA (Y)	Feel full quickly	40	Early satiety fourth most common symptom. Early satiety significantly associated with taste and smell changes
Verschuur, 2006[346]	**Experiences and expectations of patients after oesophageal cancer surgery: an explorative study** European Journal of Cancer Care	Cross-Sectional (N)	30 (21/9) Oesophageal	Researcher questionnaire (N)	Unknown	97	Early satiety most common symptom and most reported that patients expect care from professionals for (67%)

	10.1111/j.1365-2354.2006.00659.x						
Vidra, 2016[347]	**Detailed Dietary Assessment in Patients with Inoperable Tumors: Potential Deficits for Nutrition Care Plans** Nutrition and Cancer 10.1080/01635581.2016.1213867	Cross-Sectional (N/A)	84 (70/14) Solid Tumours	Researcher question (N)	Unknown	34.5	N/A
Wainwright, 2007[374]	**Remapping the Body: Learning to Eat Again After Surgery for Esophageal Cancer** Qualitative Health Research 10.1177/1049732307302021	Qualitative (N)	11 (8/3) Oesophageal	Researcher Interview (N)	Unknown	N/A	The gap between feeling comfortably full and experiencing discomfort, pain, nausea, or even vomiting and diarrhoea had narrowed. Did not realise that their stomach was full until they experienced these symptoms. Adaptation to surgery entailed remapping the embodied sensations of eating,

							learning new limits to what and how much could be eaten, and investing signs and symptoms like nausea and vomiting with new meanings as indicators of satiety or the unsuitability of certain foods
Walsh, 2000[177]ϕ	**The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients** Supportive Care in Cancer 10.1007/s005200050281	Cross-Sectional (N)	999 (553/446) Mixed	Researcher question (N)	Unknown	51	Early satiety more common in females (Odds ratio)
Walsh, 2002[357]ϕ	**Symptoms and prognosis in advanced cancer** Supportive Care in Cancer 10.1007/s00520-001-0318-z	Longitudinal (N)	549 (299/250) Unknown	Researcher question (N)	Unknown	49	Having early satiety is associated with an increased risk of death (odds ratio)
Wiegert, 2017[358]	**Performance of Patient-Generated Subjective Global Assessment (PG-SGA) in Patients with Advanced Cancer in Palliative Care** Nutrition in Clinical Practice	Longitudinal (N)	120 (49/71) Mixed	PG-SGA (Y)	Feel full quickly	27.5	Early satiety 8th most common symptom. No significant association with early satiety and death within 30 days

	10.1177/0884533617725071						
Williams, 2020[348]	**Association of malnutrition with geriatric assessment impairments and health-related quality of life among older adults with gastrointestinal malignancies** Cancer 10.1002/cncr.33122	Cross-Sectional (N)	336 (191/145) Mixed	abPG-SGA (Y)	Feel full quickly	Total 29.1 Pancreatic 52.4 Gastroesophageal 36.1 Hepatobiliary 23 Colorectal 19 Other 14*	Early satiety most common symptom
Wilson, 2002[367]	**Long-term safety and clinical effectiveness of controlled-release metoclopramide in cancer-associated dyspepsia syndrome: a multicentre evaluation** Journal of Palliative Care N/A	Trial (N/A)	48 (25/23) Mixed	Unknown (N)	Unknown	69	Early satiety 4th most common symptom

Yavuzsen, 2009[216]	**Components of the anorexia-cachexia syndrome: gastrointestinal symptom correlates of cancer anorexia** Supportive Care in Cancer 10.1007/s00520-009-0623-5	Cross-Sectional (N)	95 (49/46) Mixed	Researcher questionnaire (N)	Feeling full after a few bites of food	82	Early satiety most common symptom. Early satiety statistically associated with worsening anorexia and food aversions.
Zhou, 2017[349]	**Differences in Symptom Burden Among Cancer Patients With Different Stages of Cachexia** Journal of Pain and Symptom Management 10.1016/j.jpainsymman.2016.12.325	Cross-Sectional (N)	306 (172/134) Mixed	Researcher question (N)	Unknown	Total 25 Non cachexia 15.1 Pre cachexia 14.3 Cachexia 34.4 Refractory cachexia 42.3	Those with cachexia and pre-cachexia had significantly higher symptom scores in Early satiety. Cachexia stages significantly associated with early satiety in terms of symptom severity and prevalence

ϕ Data from the same database with multiple publications.

ˣ Data from the same database with multiple publications.

* Estimates of prevalence based on graphs

3.3.3 Screening Tools

Validated tools for identifying early satiety were used by 17 (24%) of the publications. In studies that did not document how early satiety was assessed, their method was considered unvalidated. Those used were the Patient Generated Subjective Global Assessment (PG-SGA)[311, 326, 330, 331, 342, 356, 358], the Abridged PG-SGA (abPG-SGA)[39, 174, 334, 348], Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)[328, 332, 341, 345], Myeloproliferative Neoplasm 10 (MPN10)[323] and LAsting Symptoms after Esophageal Resection (LASER)[339]. The PG-SGA and the abPG-SGA use the same descriptor for early satiety in both. As a result, the most common description of early satiety in the literature asked participants if they 'feel full quickly' in the past two weeks.

Less than half (46%) of the included publications documented how early satiety was described to the participants. Of the 33 that had included the description of early satiety, 17 were unique. Filling up quickly or a feeling of fullness were the most common themes in the descriptions of early satiety. Some referenced how much food could be consumed before experiencing a feeling of fullness.[175, 216, 319, 336, 355, 369] Two used the participants previous nutritional intake as the reference point to compare how quickly participants become full now.[343, 369]

3.3.4 Prevalence

Prevalence was the most reported and extracted clinical characteristic. The prevalence of early satiety ranged from 7-97%. When studies with mixed cancers were analysed, the median prevalence was 50% (range 10-71%).

There was a strong association between early satiety and gastrointestinal surgery for cancer treatment. A quarter of the included studies investigated early satiety post-surgical intervention for cancer. It was universally the most common symptom post-surgical intervention.[313, 320, 322, 325, 339, 340, 346, 351, 366, 370] Its prevalence ranged from 25-97%. Not only was it the most common symptom post-surgery, but with a prevalence of 91% over five years post-surgery[320], it is a chronic symptom for patients post-surgery.

Early satiety was also common post gastrectomy. Two studies found a statistically significant association between Roux-en-Y and increased early satiety incidence.[363, 364] Early satiety was also present post-surgical intervention for pancreatic[333] and laryngeal cancer.[353] In the former, early satiety was the third most common symptom. In the study of laryngeal cancer, symptom prevalence was not compared however early satiety increased almost threefold post-surgery when compared to pre surgery prevalence. The type of surgical intervention affected prevalence; vagal sparing surgery had less early satiety than non-vagal sparing surgery.[370]

3.3.5 Pathophysiology

Three publications provided information about the potential pathophysiology of early satiety in cancer. Two investigated the association between early satiety and gastric emptying. They were contradictory: one reported a strong association with delayed gastric emptying[190] while another found none.[314] Another found it was strongly associated with the anorectic gut hormone GLP-1 post oesophagectomy.[352]

3.3.6 Clinical Associations

Early satiety appears to be a more common complaint in females.[177, 327, 359] One study did report it being associated with being male.[339] It is also unclear as to the association between early satiety and age. Old age[332, 339], being younger[336] and no association with age[318] have been demonstrated. Demographic predictors of early satiety appear mixed given the above and that type of cancer diagnosis is also not associated with it.[318, 343]

A noteworthy result is that early satiety is not necessarily caused by oncological treatment. Studies showed that early satiety is also present in treatment naïve cancer patients.[39, 331] Both studies included non-gastrointestinal cancer patients indicating that the physical pressure of a GI cancer was not the cause. Chemotherapy was associated with decreased early satiety.[359] The association with chemotherapy was not universal however as no association between early satiety and chemotherapy was also seen.[318, 343] Instead they demonstrated decreased early satiety with having radiation therapy.

Early satiety appears to be associated with multiple other common NIS in cancer. It forms part of the same symptom cluster as anorexia, dry mouth, fatigue, taste changes, weakness, and clinically significant weight loss.[315] Other studies showed an association with weight loss, bloating[175], anorexia[46, 216, 360], dysphagia and hiccoughs.[339] Interestingly, early satiety was shown to be most commonly associated with changes to taste and smell.[39, 216, 331, 343]

3.3.7 Impact Of Early Satiety

Multiple studies have shown an association between early satiety and the presence and severity of cachexia[318, 349, 360] highlighting it as an important component in cancer anorexia-cachexia syndrome. Early satiety is also

associated with poorer nutritional outcomes with reduced handgrip strength[318, 319], greater nutritional risk[319, 326, 330, 352] and reduced nutritional intake.[318, 325, 353] Finally, early satiety is also associated with poorer quality of life[318, 336] and poorer prognosis.[357, 372]

Early satiety appears to be a symptom that patients rarely volunteer. Open questions associated with symptoms yielded very few reporting early satiety.[316] Once they were assessed using systematic symptom assessment, prevalence increased significantly. This may highlight the difficulty of differentiating it from other NIS, which we see as even healthcare professionals find it difficult and oftentimes don't assess early satiety.[324] This results in a disparity between patient and healthcare provider with early satiety also being the most common symptom patients expect care from their healthcare professionals for [346] despite not voluntarily reporting it. All of the above results in early satiety being a rarely identified and one of the least treated symptoms.[311]

3.3.8 Treatment

Seven of the included publications investigated treatment effect on early satiety. Some described the current landscape of early satiety treatment/management[311, 324, 368] while others investigated interventions and changes in early satiety.[354, 361, 362, 365, 366] Prokinetic agents were often prescribed for treatment,[311, 324, 368] and were beneficial for malignant gastroparesis*[365] in which early satiety is common. The other trials showed an improvement in early satiety using a multimodal intervention of diet, celecoxib, and medroxyprogesterone in lung cancer[361], thalidomide[362] and ruxolitinub as treatment in myelofibrosis.*[354] The final trial showed no improvement in early satiety using nizatidine post oesophagectomy.[366] Some non-pharmacological interventions described were

small frequent meals, less fluid at mealtimes and food with high energy content.[324] Some patients altered their eating pattern as a result of early satiety.[325, 374] None investigated the effectiveness of non-pharmacological interventions.

3.4 Discussion

This scoping review demonstrated the published evidence spanning any time period related to early satiety and cancer. No meta-analysis was possible. From review of the results, there are some common themes surrounding early satiety which emerge.

3.4.1 Limited Research For Early Satiety In Cancer

One theme that has become evident from this search is that there is in fact limited research on early satiety in cancer. Despite broad search terms, multiple large databases, no publication time limitations, and no limitation on the information provided, only 71 included studies highlight how this symptom is under researched. It was surprising to find that the publications related to early satiety in cancer were less than two annually. The is despite early satiety being a known issue for patients as far back as 1980, meaning it is not a new symptom. Many studies showed conflicting results, few used the same tool to identify early satiety, and most results were not shown outside of a single study. Oftentimes, the only available result to extract was prevalence. This may have been due to non-significant findings or limited statistical analysis around early satiety. Finally, most did not list early satiety or early satiation as keywords in their publications. With all of the above, it is clear that early satiety in relation to cancer has received very little research focus despite being a highly impactful symptom.

3.4.2 Minimal Qualitative Data

An area that requires further research is a qualitative exploration of early satiety. With only one study being qualitative in nature[374], this highlights a gap in the literature to understand how patients with early satiety describe the symptom. Although the numbers in this study are small given its design, it sheds light on

some useful data that were not identified in the qualitative data included. One finding of interest is that the early satiety described occurs simultaneously with other NIS of nausea or sometimes vomiting and diarrhoea. In fact, these symptoms were used as indicators of fullness rather than participants feeling normal cues of satiety. This resulted in participants having to adapt their eating to be wary of these symptoms as markers of satiety and that they manifest more quickly. This presents the possibility that early satiety is not only an earlier sensation of fullness, but also a reduction in the amount consumed between being comfortably and uncomfortably full. More qualitative data on the patient's experience of early satiety would be beneficial in determining both a definition and guiding the investigation into suitable treatments, which may need to focus not only treating it, but also educating individuals on the revised sensations of satiety.

3.4.3 Absence Of Definition

With less than a quarter of studies using a validated assessment tool to identify early satiety, multiple descriptors were used. The lack of validated assessment tools used is unsurprising given early satiety is often not on the most frequently used symptom assessment tools in cancer.[303] Most descriptions of early satiety were vague and gave no reference point for the participant when evaluating their feeling of fullness. Some gave more detail and used quantities of food consumed before being full as part of their descriptor. This allows the participant to have a reference point as to when they feel full that they can reflect on. One difficulty however is that it does not necessarily consider the amount of food consumed which is normal for the participant. The approach of the two studies which used previous nutritional intake as a reference point is worth further exploration when

determining a description for early satiety. This method may be beneficial as it clearly looks at a change in satiety for the individual rather than a generic discussion of fullness. This allows the participant to understand whether their sense of fullness or satiety is indeed ‘early’ for them rather than being compared to others or comparing what they would eat to what the general population would eat.

3.4.4 Early Satiety Is Highly Prevalent

The wide range of early satiety prevalence is likely attributed to the heterogeneous collection of study populations and the various stages of cancer included. With a median prevalence of 50%, there appears to be a high prevalence of early satiety among mixed cancers. Future studies investigating the prevalence of early satiety in different cancer diagnoses would be beneficial. Although it is clear that early satiety in all cancers is important given its high prevalence, knowing the cancers in which it is most prevalent and impactful would allow for fewer missed diagnoses and, in turn fewer negative outcomes resulting from early satiety.

Some of the highest prevalence of early satiety was found in those post-surgical intervention for cancer. Interestingly, the type of surgical intervention appears to have a strong association with the presence of early satiety. With all of this in mind, evaluation of the presence of early satiety should be done at all points post-surgical intervention for cancer. This would allow a greater understanding of how the type of surgery influences the symptoms experienced post-surgery.

3.4.5 Early Satiety Is Clinically Important

Early satiety is a well-established component of cachexia, and the association between early satiety and cachexia found in this review was unsurprising. Details

on cancer cachexia were discussed in more detail in Chapter 1. The negative impact of cachexia on cancer patients is well documented and is responsible for up to 20% of cancer deaths.[375] Patients with cancer should be better educated about cachexia and associated factors, one of which is early satiety to promote awareness and encourage early intervention.[376]

Early satiety was also associated with other clinically relevant symptoms and risk factors. Low HGS in cancer is associated with increased depression[377], cachexia[378] and fatigue.[379] Early satiety is likely to make managing low HGS more difficult as it appears to influence nutritional intake. Without adequate protein and calorie intake, muscle strength and mass are likely to continue to decline and increase the risk associated with them in cancer.

With early satiety itself as well as malnutrition[380], lower handgrip strength[381], cachexia[382] and poorer QoL[383] all being associated with shorter prognosis, the impact of early satiety is clear. With this in mind, all patients with cancer would benefit from being screened for early satiety.

3.4.6 Unknown Pathophysiology

As discussed previously, the exact cause of early satiety is unknown and appears multifactorial. In diabetes, it is associated with gastroparesis.[217] It remains unclear whether early satiety in cancer is caused by delayed gastric emptying given the conflicting results of the included studies. Given the high prevalence caused by delayed gastric emptying in gastroparesis[384], there is merit in investigations into delayed gastric emptying as a potential cause. This is further strengthened by undiagnosed autonomic dysfunction in cancer.[385]

Of note, the role in the vagus nerve and the development of early satiety in cancer should be explored in future studies. One reason is the significant difference in

prevalence between vagal-sparing and non-vagal-sparing surgery. A further reason for this research is that early satiety was associated with other NIS, of particular interest is the strong association with changes in taste and smell in cancer. The exact mechanism by which these NIS are linked remains unclear, however if any of these symptoms are present then assessment of whether there is concurrent early satiety is justified. Finally, as discussed in Chapter 1, the vagus nerve plays an important role in appetite regulation and research into it has been a primary focus in managing obesity and promoting weight loss. Research into aiding the opposite in cancer by determining whether it has a role in early satiety is an important area for future focus. There may also be merit in an evaluation of gastric accommodation and hypersensitivity to gastric distension, as early satiety is more prevalent in idiopathic gastroparesis.[194]

3.4.7 No Clear Suitable Treatment

A total of seven showed a treatment effect on early satiety. Some described how it is treated currently while others investigated improvements in early satiety through a trial study design, none of which had changes in early satiety severity or prevalence as a key objective. Prokinetic agents are most commonly prescribed to treat early satiety. The use of prokinetic agents to treat early satiety is in line with current ESPEN clinical nutrition in cancer guidelines.[386] There is however limited evidence justifying its use with only one trial being included. This is reflected in the ESPEN guidelines, where the strength of the recommendation is weak and the level of evidence is moderate. Whether this is an appropriate treatment is further questioned given the lack of consensus on whether early satiety in cancer is caused by delayed motility as previously described. As can

be seen, the lack of information provided on treatment is reflected by early satiety being one of the most commonly untreated symptoms.[311]

A key area that has not been investigated in the literature is a non-pharmacological treatment for early satiety. The benefit of a non-pharmacological would be to reduce polypharmacy within cancer patients. Given there are several consequences of polypharmacy including adverse drug reactions[387], functional ability, cognition, and malnutrition.[388] Another benefit of a nutrition related treatment for early satiety is that patients are more engaged as it provides them with a sense of control in a condition where most of their treatment is out of their control.[389] One difficulty is that limiting protein intake is mostly inappropriate in this cohort given the increased risk of malnutrition and cachexia. Limiting fibre may be more appropriate however care should also be given as opioids, which are commonly prescribed in cancer, may delay GI motility and cause constipation. The most appropriate action to determine the appropriate treatment for early satiety in cancer is to first determine the pathophysiology. With this information, both a pharmacological and a non-pharmacological intervention could be explored for early satiety. Without this information, interventions are based on presumed causes of early satiety.

This review highlights the need for continued research into early satiety in cancer. With so few results included with a broad search, it justifies the decision to undertake a scoping review. It also highlights that a systematic review in this area is unlikely to yield results of interest given the insufficient amount of research on this highly prevalent and important symptom in cancer.

3.4.8 Strengths and Limitations

A strength of the above review was that the search was broad with no limitations on the search. This allowed for any published literature within the chosen databases to be assessed. A further strength was that the search was designed in tandem with a specialist librarian and research nurse with previous experience in scoping reviews. Finally, another strength is that two independent researchers screened the results.

A limitation of the above review was the inability to perform a formal quality assessment due to the heterogeneity and broad nature of the included studies. This is a feature of the scoping review study design rather than this review specifically. As discussed previously, the lack of formal quality appraisal allows for a broader approach and ultimately less risk of missing important information in an area that has minimal research associated with it, as in this case.

Another limitation is the exclusion of conference abstracts and grey literature. Due to resources or publication bias, these were not published as full papers. While these may have had valuable information, the decision to exclude these was taken based on the fact that a complete data extraction could not be performed on them. It is unlikely that validated assessment tools for early satiety would be published outside peer-reviewed sources, though it cannot be ruled out that there may indeed be novel and important information on early satiety within these sources. The exclusion of articles not in English was a further limitation. Every effort was made to identify the full text in English. The nine excluded papers may have contained pertinent information on early satiety however we did not have the resources to translate these.

Efforts were made to contact the corresponding authors for the two publications in which full text articles could not be found. It is unclear as to whether these publications were relevant or not however further efforts through postal or telephone follow up may have been more successful. Similarly, where a publication discussed early satiety but did not differentiate cancer and non-cancer participants, follow up with the authors to retrieve the data specific to cancer would have been preferred. However, neither was done due to time constraints.

3.4.9 Clinical Implications

Given the nature of this scoping review and that there was no assessment of bias, the recommendations for clinical practice are more limited than a systematic review. Despite this, there were some clear trends in the selected studies. First, while this study reports on a heterogeneous population, early satiety was present in a variety of cancer diagnoses. With its prevalence and lack of clear predictive characteristics for those with early satiety, all cancer patients should be regularly screened for early satiety. Most importantly, all those who undergo gastrointestinal surgery should be routinely screened for early satiety given it is among the most prevalent symptoms and appears to linger long after the surgery. To ensure that early satiety is correctly identified, the use of validated screening tools or the description used on a validated tool when asking about early satiety is recommended. Given the difficulty in differentiating from other symptoms by healthcare professionals and patients, a clear description should be used.

Unfortunately, no clear recommendation for treating early satiety can be drawn. Although improvements in early satiety were observed, no study investigated treating the symptom directly and none investigated non-pharmaceutical interventions. Consideration for inclusion of a prokinetic agent should be

considered based on the most recent guidelines, however this should be done on a case-by-case basis with regular reviews of whether early satiety improves with their inclusion. Maximising nutritional intake should also form part of the treatment plan for early satiety given it is likely to reduce overall nutritional intake. The implementation of a high protein, high calorie diet and potentially oral nutritional supplementation should be explored in those with early satiety.

3.5 Conclusions

A variety of descriptors for early satiety were used, with most studies not including how it was described to patients or using a validated tool. This is expected while there continues to be no agreed definition for early satiety. Tools that include early satiety should be developed and used in this cohort. At a minimum, symptom assessment tools that contain early satiety should be used. For the research presented in this thesis, the abridged patient generated assessment tool was used throughout to comply with the most used tool in the literature. No validated self-assessment tool for early satiety was identified. There is evidence that early satiety is a common NIS across a variety of cancers. early satiety is also present through the spectrum of cancer care from treatment naïve to advanced disease. Early satiety is often the most common symptom after surgical intervention for cancer. It should be regularly screened for given its clinical importance. Early satiety is associated with reduced nutritional intake, increased risk of malnutrition and sarcopenia, and poorer prognosis. There is no clear pathophysiology or appropriate treatment for early satiety.

4 SCREENING FOR EARLY SATIETY AND ASSOCIATED MALNUTRITION IN CANCER

4.1 Introduction

Cancer patients often suffer from malnutrition with a varied prevalence of 30-50% in Europe[390-392], depending on several parameters, such as the tool used to assess malnutrition. Both the anticancer treatment, as well as cancer itself, can cause physiological changes such as impaired metabolism as well as Nutrition Impact Symptoms (NIS), which all contribute towards malnutrition. Increased morbidity, mortality, and reduced physical capacity are all associated with malnutrition in cancer.[393-396]

ESPEN guidelines state that all patients with cancer should be screened for malnutrition using validated screening tools.[386] While there is a broad agreement that early recognition of malnutrition is important, screening continues to be poorly implemented in daily clinical practice.[397] One challenge with implementation is that there is a plethora of validated screening tools to choose from. To help guide the diagnosis of malnutrition, the use of the agreed Global Leadership Initiative on Malnutrition (GLIM) criteria has been recommended.[386]

As highlighted previously, early satiety is a common symptom experienced across the spectrum of cancer care from treatment naïve to advanced disease. The prevalence of early satiety in patients receiving active treatment is 23-69%[171, 338, 398] and up to 77% in advanced cancer.[176] Despite this, it continues to be underreported and certainly under-researched. It is a key symptom to detect, particularly in patients receiving active treatment given its association with malnutrition, cachexia, and sarcopenia, all of which have negative impacts on patient outcomes. It is however not just early satiety that should be screened for, but also other NIS. Symptom evaluation remains an integral part of the oncological decision-making process.[399] If there is an increased symptom

burden, it may indicate poor response to treatment or possibly disease progression.

What remains unclear is the most appropriate assessment for screening for symptoms. It has been well established that the clinician's judgment of symptoms is inaccurate.[400] The use of open symptom enquiry has previously been shown to generate significantly fewer symptoms than through systematic evaluation in patients with advanced cancer.[186] It is important to assess multiple symptoms as there is often a 'symptom burden' associated with multiple simultaneous symptoms that may not be identified using open questioning. With this in mind, this study set out to evaluate symptoms in patients with cancer comparing an open question on symptoms and a validated screening tool.

4.2 Aims And Research Questions

4.2.1 Aims

- Compare an open question with a validated questionnaire to assess nutritional impact symptoms
- Determine the risk of malnutrition using the abPG-SGA in patients with cancer
- Diagnose malnutrition using GLIM criteria in patients with cancer receiving active treatment
- Determine the prevalence of early satiety in patients with cancer

4.2.2 Research Questions

- What is the prevalence of early satiety in patients receiving active treatment for cancer?
- What is the prevalence of early satiety in patients with advanced cancer receiving palliative care?
- What percentage of patients receiving active treatment are diagnosed with malnutrition using the GLIM criteria?
- Is early satiety impactful on malnutrition?

4.3 Methods

4.3.1 Patient Selection

Recruitment took place in the Oncology Day Ward (ODW) of Tallaght University Hospital Dublin for patients receiving active treatment and the Palliative Care Unit in OLH&CS for those with advanced cancer. The inclusion criteria for both cohorts were similar and are presented in Table 4.1.

Table 4.1 Inclusion and Exclusion criteria for recruitment

INCLUSION CRITERIA
• Diagnosis of cancer receiving anticancer treatment OR specialist palliative care (advanced cancer)
• Age > 18 years old
• Able to understand and speak English
• Able to provide witnessed signed consent
EXCLUSION CRITERIA
• Current or previous diagnosis of gastroparesis
• Unable to complete study assessments
• Diagnosis of dementia
• Participation deemed inappropriate by the consultant or nurse

4.3.2 Recruitment

The methodology for this chapter is discussed in more detail in Chapter 2. The participants were identified as potentially suitable by nursing staff on the ward after the initial review. Then, the suggested patient's medical records were screened to ensure compliance with inclusion and exclusion criteria. Participants were asked an open symptom questionnaire (OSQ) about their symptoms. As discussed previously, abPG-SGA was utilised as it is the most used validated tool to identify early satiety according to Chapter 3. Early satiety is termed 'feel full quickly' on the tool. Participants who reported a symptom that appeared to be early satiety in the open question or who 'feel full quickly' in abPG-SGA were deemed to have early satiety.

4.4 Results

4.4.1 Demographics

4.4.1.1 ***Active Treatment***

In total, 122 participants were approached to participate in this study after being suggested by nursing staff at the ODW. Of this, 50 agreed to participate. The recruitment flow chart for this study is in Figure 4.2.

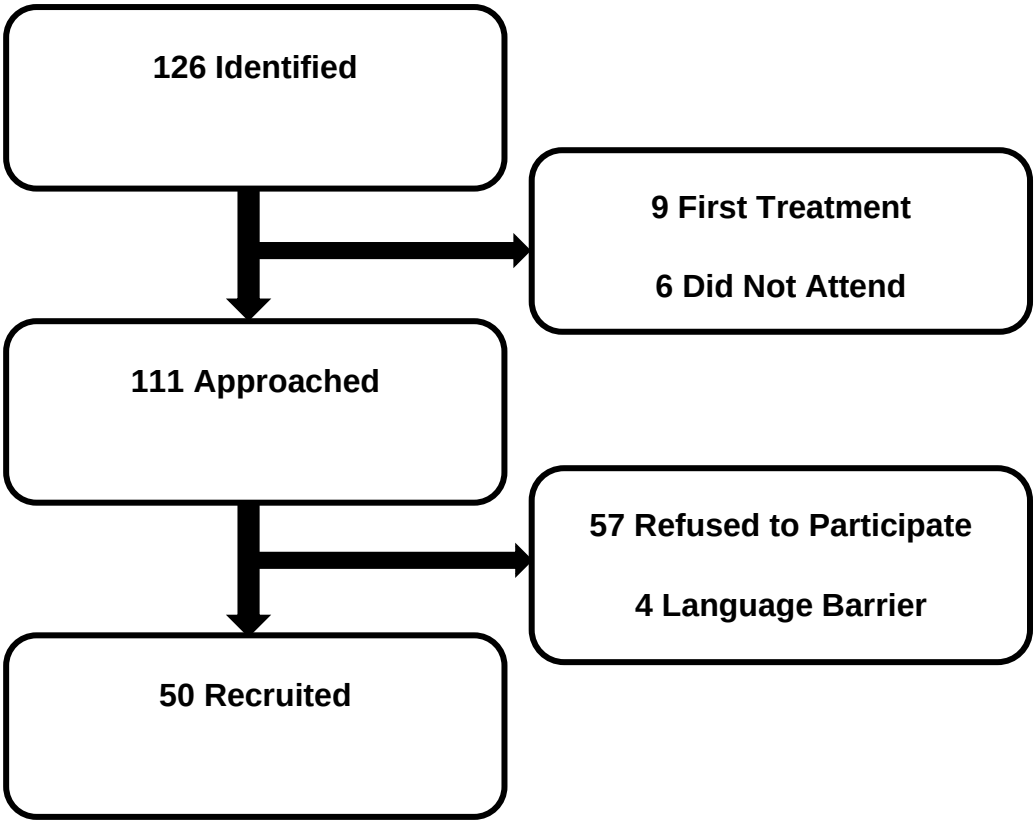


Figure 4.1 Recruitment process of participants identified by nurses on the Oncology Day Ward

Demographic data are presented in Table 4.2 for the recruited participants. Data regarding the prevalence of early satiety for each demographic, along with significance, are also listed. Six participants had T2DM, three of whom had early satiety. There was no association between being over 65 years old (p=1.00) or the presence of metastatic disease (p=0.135) and early satiety. In fact, the presence of metastatic disease was not associated with abPG-SGA symptoms. There was no association between early satiety and sex (p=0.605) or age (p=0.772). Those with upper GI and melanoma cancers tended to have early satiety more often than not. There was an association between early satiety and lymph nodes metastases (p=0.017). There were no correlations between early satiety and most medications. Interestingly, the only correlation was between regular prokinetic use and early satiety (p=0.035). It should be noted that the n for this was small (n=2) and both had early satiety. There was no association between previous or planned anticancer treatments and early satiety.

Table 4.2 Demographic data for the total cohort and those with early satiety for patients receiving anticancer treatment (n=50)

	Total Cohort		Early Satiety		
Variable	**n**	**%**	**n**	**% of total**	**P value**
Sex					
Male	35	70	11	31	0.605
Female	15	30	4	27	0.597
Age (median, range)	64	27-78	66	(27-78)	0.772
Over 65 Years	25	50	8	32	1
Type 2 Diabetes	6	12	3	50	0.314
Cancer type					
Urological	20	40	5	25	0.386
Upper GI	11	22	6	55	0.07
Lower GI	11	22	1	9	0.065
Lung	4	8	1	25	0.754
Melanoma	4	8	3	75	0.055
Metastatic disease	37	74	14	38	0.135
Lymph Nodes	14	28	8	57	0.017*
Lung	11	22	4	36	0.725
Liver	8	16	3	38	0.716
Bone	8	16	3	38	0.716
Brain	1	2	1	100	0.141
Previous Treatment					
Chemotherapy	31	62	11	35	0.5
Surgery	21	42	4	19	0.095
Radiotherapy	10	20	4	40	0.544
Immunotherapy	3	6	1	33	0.959
Current Treatment					
Chemotherapy	40	10	13	33	0.88
Immunotherapy	11	22	4	36	0.725
Radiotherapy	3	6	1	33	0.959
Surgery	3	6	2	67	0.184
Hormone	1	2	1	100	0.141
Medications					
Corticosteroid	29	58	9	31	0.863
Vitamins	16	32	4	25	0.467
Opioid	7	14	3	43	0.507
Prokinetic	2	4	2	100	0.035*

4.4.1.2 Advanced Cancer

In total, 20 participants agreed to participate in this study. A total of 13 participants met the criteria for the completion of the SEES. Table 4.3 compares demographics between those with early satiety (n=13) and those without early satiety (n=7) as well as combined data. There were no significant differences between sex and the presence of early satiety (p=0.094).

The median age of those who participated was 66.5 years (range 40-78). Liver metastases were the most common in eight participants. Seven participants had lung or bone metastases. Brain metastases were present in two. Almost all were no longer receiving anticancer treatment. There was one participant each receiving chemotherapy, radiation therapy, and immunotherapy. The remainder were associated with palliative care for supportive therapy. None had T1DM or Parkinson's Disease. Three participants were diagnosed with T2DM. Two of these three had early satiety.

Almost all (95%) were on regular opioid medications. Twelve participants were taking corticosteroids, four of whom reported early satiety. Four participants were taking regular metoclopramide; three of them had early satiety. No one was taking Megace. Five participants were taking extra vitamins, of which only two had early satiety. There were no significant differences in demographics based on early satiety.

Table 4.3 Demographic data for the total cohort and those with early satiety for patients with advanced cancer (n=20)

	Total Cohort		Early Satiety		
Variable	**n**	**%**	**n**	**% of total**	**Significance**
Sex					
Male	8	40	7	88	0.093
Female	12	60	6	50	0.371
Age (median, range)	66.5	(40-78)	64	(40-77)	0.639
Over 65 Years	11	55	6	55	0.291
Type 2 Diabetes	3	15	1	33	0.949
Cancer type					
Lung	5	25	4	80	0.429
Breast	4	20	3	75	0.493
Lower GI	4	20	2	50	0.648
Upper GI	3	15	1	33	0.172
Urological	3	15	2	66	0.648
Gynae	1	5	1	100	0.463
Metastatic disease	18	90	13	72	0.135
Liver	8	40	6	75	0.456
Bone	7	35	5	71	0.286
Lung	6	30	5	83	0.165
Lymph Node	3	15	2	66	0.323
Brain	2	10	2	100	0.286
Previous Treatment					
Chemotherapy	11	55	7	64	0.890
Radiotherapy	9	45	5	56	0.435
Surgery	7	35	5	71	0.666
Immunotherapy	4	20	2	50	0.493
Supportive	2	10	1	50	0.648
Current Treatment					
Supportive	17	85	11	65	0.949
Immunotherapy	1	5	1	100	0.463
Chemotherapy	1	5	1	100	0.463
Radiotherapy	1	5	0	0	0.173
Medications					
Opioid	19	95	13	68	0.173
Corticosteroid	12	60	8	66	0.852
NSAID	7	35	6	86	0.165
Prokinetic	4	20	3	75	0.648

4.4.2 Open Symptom Questionnaire Screening

4.4.2.1 ***Active Treatment***

All participants answered the open question questionnaire (OSQ) about their NIS. 'None' was the most common response, with almost half (46%) reporting no NIS. This resulted in 27 participants with a minimum of one NIS. Ten participants reported more than one symptom. Of those who reported symptoms, the mean per person was 1 symptom. The most reported symptoms were nausea, anorexia, and taste changes. Early satiety was reported by three. A third (n=3) of those who reported anorexia in the open question did not report it in the abPG-SGA. All participants that reported early satiety in the open question also reported it in the abPG-SGA. The descriptions used were 'not eating full dinner at once', 'fullness', and 'stomach telling me I'm full'.

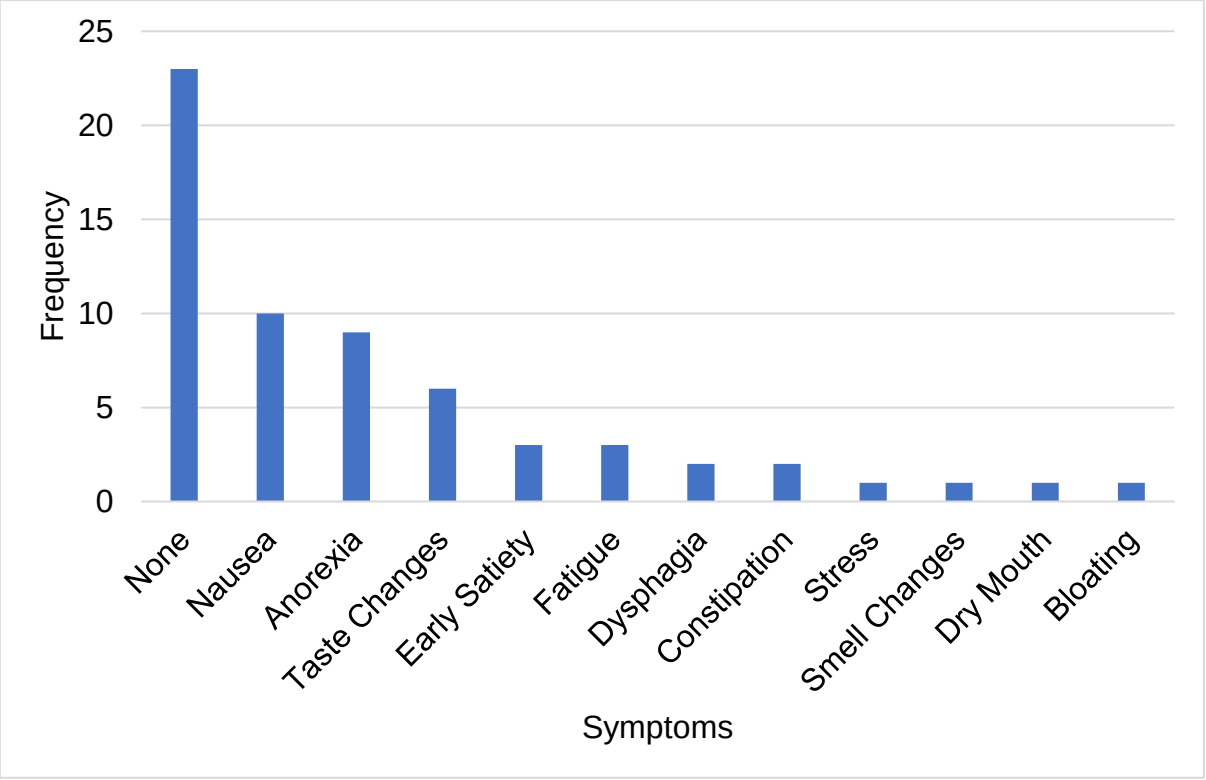


Figure 4.2 Frequency of nutrition impact symptoms reported in the open symptom questionnaire in patients on active treatment

Participants who reported symptoms in the OSQ were more likely to be at risk of malnutrition (p=0.002) and have a higher total abPG-SGA score (p=<0.001). They were also less likely to be considered at low risk of malnutrition (p=0.002). The number of symptoms reported was also associated with an increased total abPG-SGA score (p=<0.001). Median abPG-SGA scores were significantly higher (p=0.047) in those who reported symptoms (median=9, range 0-18) compared to those who did not (median=1.5, range 0-10). While there was a significant association between reporting ≥2 symptoms in the OSQ and risk of malnutrition (p=0.006), it should also be noted that the OSQ identified less than a third (32%) of those identified at risk of malnutrition in the abPG-SGA.

4.4.2.2 Advanced Cancer

The open question that asked about NIS in the past two weeks was answered by all. Of the 20 participants, 14 gave a minimum of one symptom. Almost half (n=6) of those who responded reported more than one NIS. The most common reported symptom was anorexia (n=3). Three also reported problems with food selection. Pain, smell changes, and nausea were all reported by two. None reported any description of early satiety in the open question. The average number of symptoms in open questioning was less than one (0.95). 'None' was the most reported nutritional issue. The frequency of responses is in Figure 4.3.

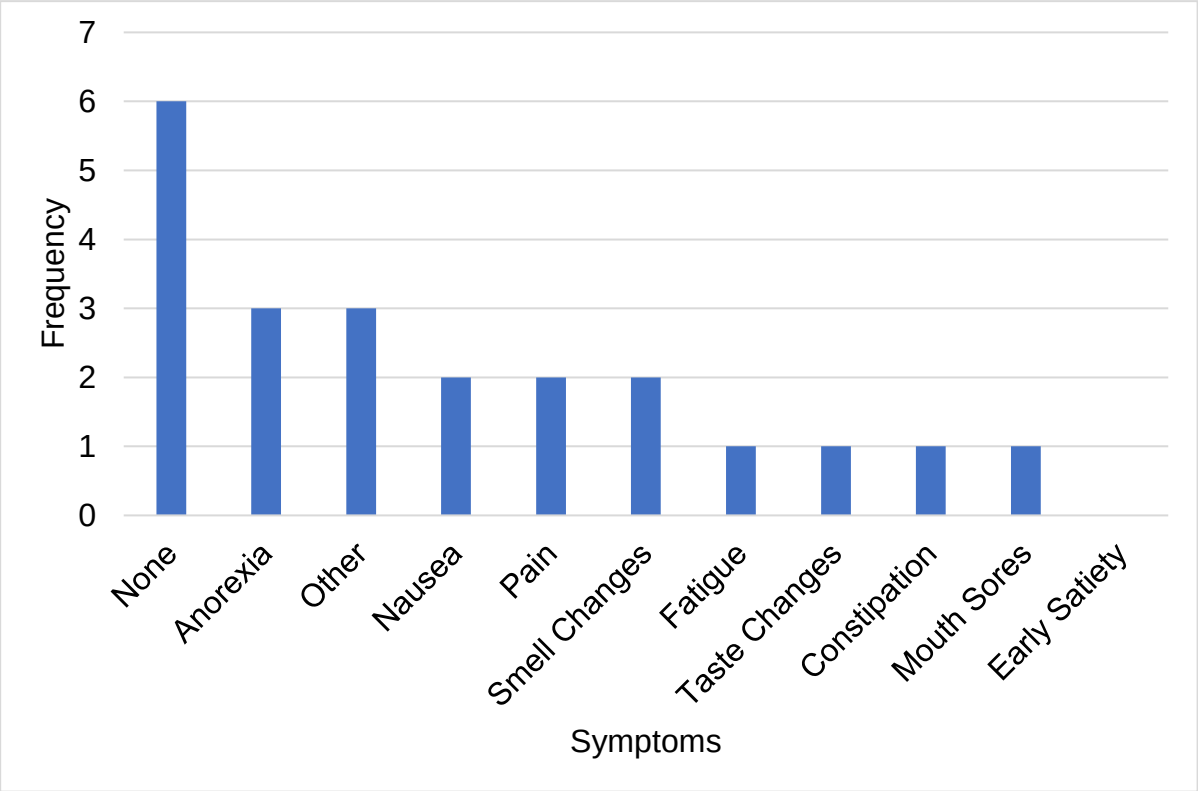


Figure 4.3 Frequency of nutrition impact symptoms reported in the open symptom questionnaire in patients with advanced cancer

4.4.3 Abridged Patient-Generated Subjective Global Assessment

4.4.3.1 ***Active Treatment***

Most participants reported at least one symptom. The most common symptoms were taste changes (34%), early satiety (32%) and anorexia (26%). The average number of symptoms in those who reported NIS was 4. The average number of symptoms in all recruited was 2.

More than a third (36%) of the participants reported no symptoms. Interestingly, 22% of those who reported no symptoms in the abPG-SGA did describe having symptoms in the open question. The symptoms reported that did not correspond to the abPG-SGA assessment were anorexia (n=1), fatigue (n=1), nausea (n=1), and taste changes (n=1).

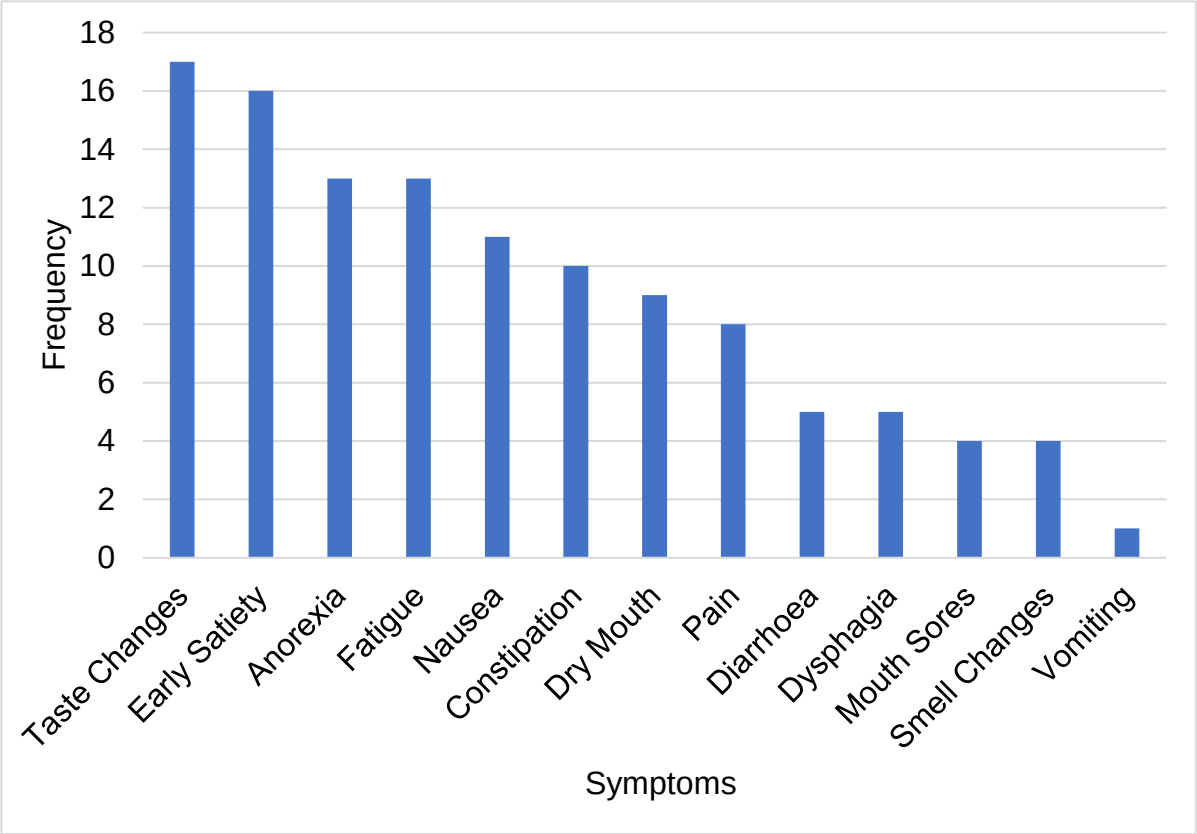


Figure 4.4 Frequency of nutrition impact symptoms reported in the abPG-SGA in patients on active treatment

The mean number of symptoms identified via the abPG-SGA was higher in those with early satiety (4.2) than in those without (3.1). When early satiety is removed, there was no significant difference between the average number of symptoms (3.2).

Early satiety was associated with several other symptoms. These included anorexia (p=0.007), taste changes (p=0.022), and fatigue (p=<0.001). Early satiety tended toward a significant association with smell changes (p=0.057). Of note, early satiety was not associated with nausea (p=0.732). Other associations between symptoms are presented in Table 4.4. Being female was associated with an increased risk of dry mouth (p=0.007). There were no significant differences between sex and any other symptoms. Participants over 65 years old were more

likely to have mouth sores (p=0.038) while less likely to have smell changes (p=0.038).

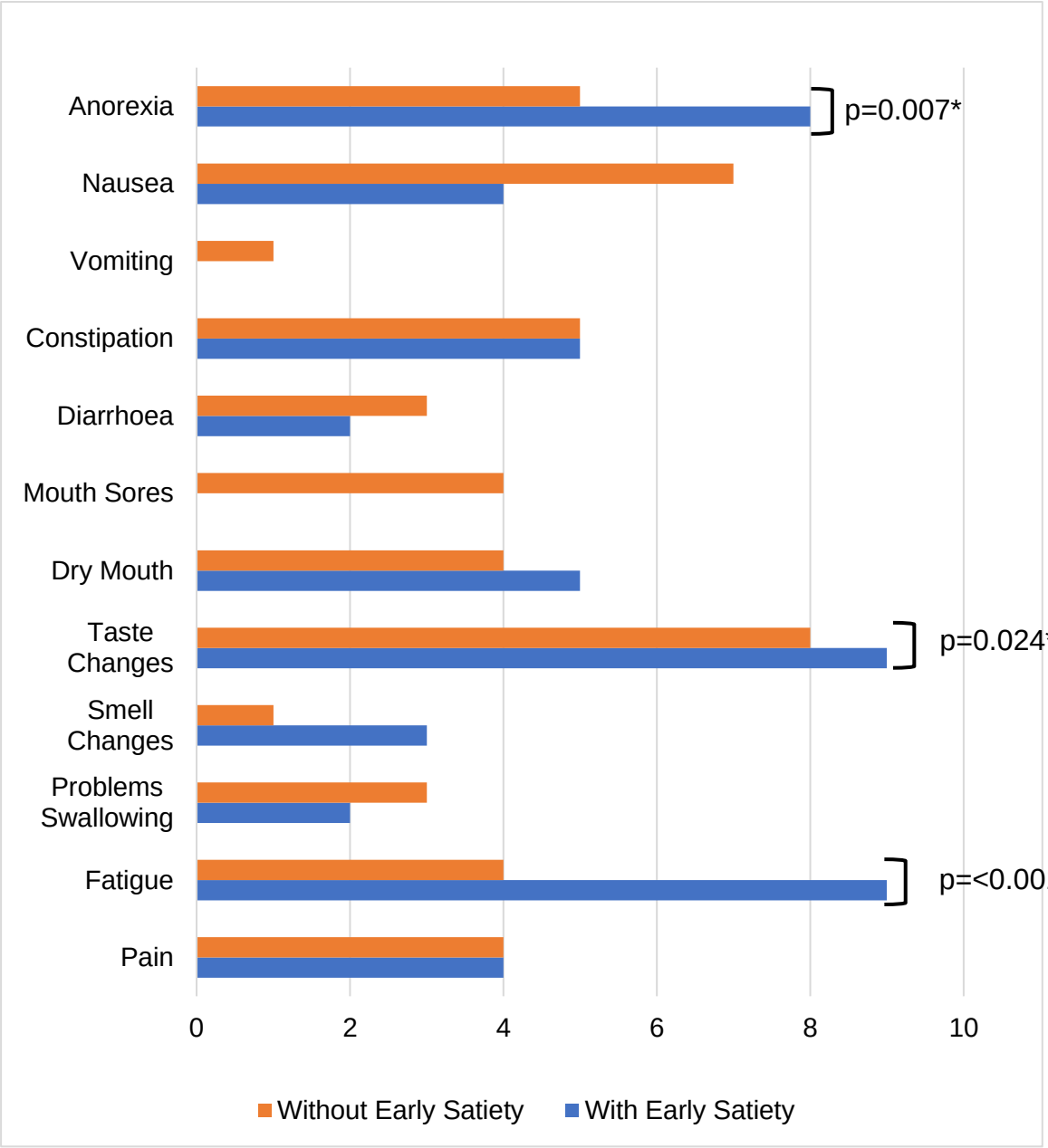


Figure 4.5 Frequency of nutrition impact symptoms reported in the abPG-SGA differentiated by the presence of early satiety in patients on active treatment

Table 4.4 Correlation coefficients and p values between nutrition impact symptoms assessed by the abPG-SGA in active treatment

	Anorexia	Nausea	Vomit	Constipation	Diarrhoea	Mouth Sores	Dry Mouth	Taste Changes	Smell Changes	Dysphagia	Early Satiety	Fatigue	Pain
Anorexia	-	0.346* (0.014*)	0.241 N/S	0.274 N/S	0.106 N/S	-0.007 N/S	0.316* (0.026*)	0.537** (<0.001**)	0.329* (0.019*)	-0.046 N/S	0.375** (0.007**)	0.272 N/S (0.056)	-0.010 N/S
Nausea	0.346* (0.014*)	-	0.269 N/S	0.097 N/S	-0.097 N/S	0.377** (0.007**)	0.003 N/S	0.230 N/S	0.377** (0.007**)	0.306* (0.031*)	0.50 N/S	0.125 N/S	-0.100 N/S
Vomiting	0.241 N/S	0.269 N/S (0.059)	-	-0.071 N/S	-0.048 N/S	-0.042 N/S	-0.067 N/S	0.199 N/S	-0.042 N/S	-0.048 N/S	-0.098 N/S	-0.085 N/S	-0.062 N/S
Constipation	0.274 N/S	0.097 N/S	-0.071 N/S	-	0.333* (0.018*)	0.221 N/S	0.416** (0.003**)	0.063 N/S	-0.147 N/S	0.000 N/S	0.193 N/S	0.046 N/S	0.191 N/S
Diarrhoea	0.106 N/S	-0.097 N/S	-0.048 N/S	0.333* (0.018*)	-	0.393* (0.005**)	0.191 N/S	0.042 N/S	-0.098 N/S	-0.111 N/S	0.057 N/S	0.258 N/S	0.400** (0.004**)
Mouth Sores	-0.007 N/S	0.377** (0.007**)	-0.042 N/S	0.221 N/S	0.393* (0.005**)	-	0.246 N/S	0.100 N/S	-0.087 N/S	0.147 N/S	-0.202 N/S	0.161 N/S	0.273 N/S
Dry Mouth	0.316* (0.026*)	0.003 N/S	-0.067 N/S	0.416** (0.003**)	0.191 N/S	0.246 N/S	-	0.323* (0.022*)	0.054 N/S	0.017 N/S	0.237 N/S	0.197 N/S	0.080 N/S
Taste Changes	0.537** (<0.001**)	0.230 N/S	0.199 N/S	0.063 N/S	0.042 N/S	0.100 N/S	0.323* (0.022*)	-	0.255 N/S	0.042 N/S	0.322* (0.022*)	0.152 N/S	0.147 N/S
Smell Changes	0.329* (0.019*)	0.377** (0.007**)	-0.042 N/S	-0.147 N/S	-0.098 N/S	-0.087 N/S	0.054 N/S	0.255 N/S (0.074)	-	0.098 N/S	0.272 N/S	0.161 N/S	-0.129 N/S
Dysphagia	-0.046 N/S	0.306* (0.031*)	-0.048 N/S	0.000 N/S	-0.111 N/S	0.147 N/S	0.017 N/S	0.042 N/S	0.098 N/S	-	0.057 N/S	-0.046 N/S	0.036 N/S
Early Satiety	0.375** (0.007**)	0.050 N/S	-0.098 N/S	0.193 N/S	0.057 N/S	-0.202 N/S	0.237 N/S	0.322* (0.022*)	0.272 N/S	0.057 N/S	-	0.473** (<0.001**)	0.168 N/S
Fatigue	0.272 N/S	0.125 N/S	-0.085 N/S	0.046 N/S	0.258 N/S (0.070)	0.161 N/S	0.197 N/S	0.152 N/S	0.161 N/S	-0.046 N/S	0.473** (<0.001**)	-	0.239 N/S
Pain	-0.010 N/S	-0.100 N/S	-0.062 N/S	0.191 N/S	0.400** (0.004**)	0.273 N/S	0.080 N/S	0.147 N/S	-0.129 N/S	0.036 N/S	0.168 N/S	0.239 N/S	-

Significance values are shown in parentheses. When significant (p=<0.05), values are marked with *. N/S indicates non-significance

4.4.3.2 Advanced Cancer

The abPG-SGA was completed by all. Everyone gave an estimated height; however, some found completing current and previous weights difficult. Most reported that their weight was unchanged (n=8) with the same number reporting an increase or decreased weight (n=6). The percentage weight loss ranged from 2% - 12.5% in the past month and 2% - 40.6% in the past six months. Only three participants completed their current weight, their weight one month ago, and their weight six months ago. In participants with adequate detail (n=14), six participants had clinically significant weight loss.

More than half reported eating less than usual (n=11), five reported eating more than usual, and four reported that it was unchanged. Almost all who reported eating less than usual reported eating normal foods, but less of them. Two reported eating little solid foods and one only taking liquids. Those who took little solid foods had lung and oesophageal cancer while the participant taking only liquids had cholangiocarcinoma.

Those with early satiety had reduced food intake more often than those without early satiety (69% vs 28%) (p=0.089). Reduced food intake was the most common response in those with early satiety, while unchanged intake was the most common response in those without early satiety. Inversely, those without early satiety were more likely to report an increase in nutritional intake than those with early satiety (28% vs. 15%), however, it was not statistically significant (p=0.800).

All participants who reported no nutrition impact symptoms when asked via the open question reported symptoms in the abPG-SGA. Fatigue, dry mouth, and constipation were the symptoms reported most frequently among all participants.

Early satiety was the fourth most common symptom ahead of anorexia and nausea, among others. The symptoms reported in the abPG-SGA are shown in Figure 4.6. The average number of symptoms per person, when evaluated through the abPG-SGA, was 6.45.

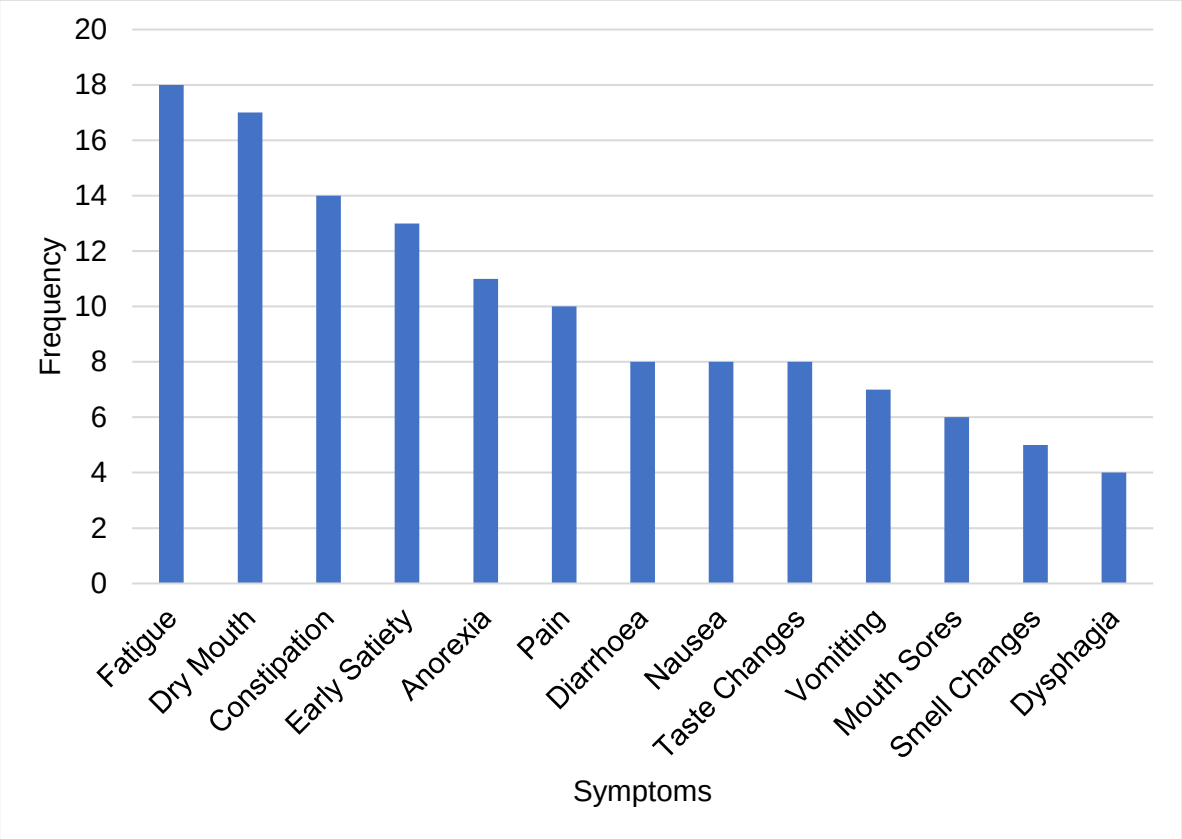


Figure 4.6 Frequency of nutrition impact symptoms reported in the abPG-SGA in patients with advanced cancer

The symptoms reported by those with and without early satiety are shown in Figure 5.3. Those with early satiety were significantly more likely to have a higher symptom burden (p=0.002). It should be noted that nausea, vomiting, and dysphagia were only found in those with early satiety; however, only nausea (p=0.005) and vomiting (p=0.014) reached statistical significance. The correlations between each of the symptoms are presented in Table 4.5.

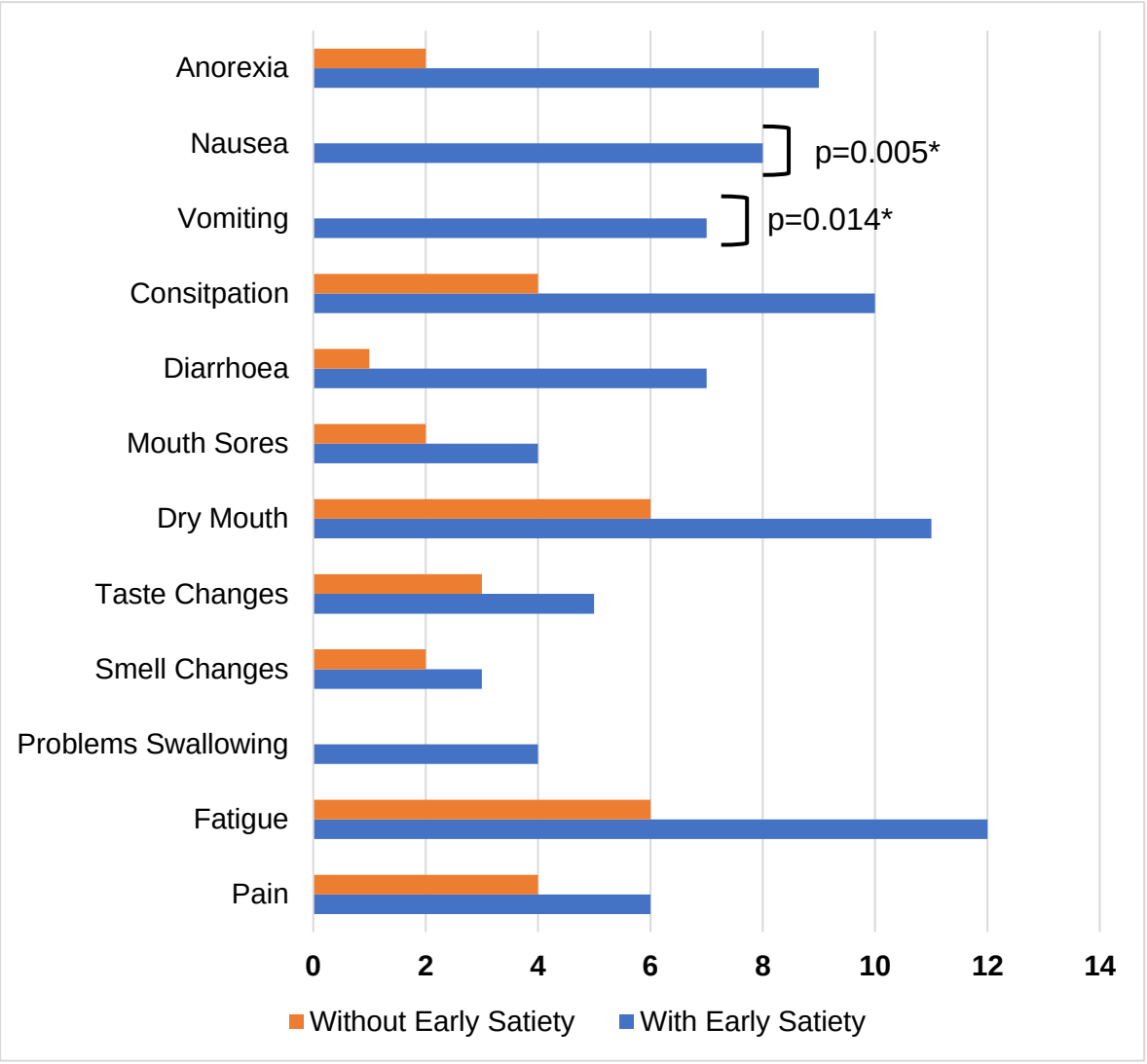


Figure 4.7 Frequency of nutrition impact symptoms reported in the abPG-SGA differentiated by presence of early satiety in patients with advanced cancer

More than two-thirds of the participants (n=14) reported their physical activity and function as ‘able to do little activity and spend most of the day in bed or in a chair’. The remaining six reported they were ‘not my normal self, but able to be up and about with fairly normal activities’. There was no statistical difference in the activity level between those with and without early satiety (p=0.924).

Table 4.5 Correlation coefficients between nutrition impact symptoms assessed by the abPG-SGA in advanced cancer

	Anorexia	Nausea	Vomit	Constipation	Diarrhoea	Mouth Sores	Dry Mouth	Taste Changes	Smell Changes	Dysphagia	Early Satiety	Fatigue	Pain
Anorexia	-	0.328 N/S	0.242 N/S	-0.154 N/S	0.328 N/S	-0.066 N/S	0.183 N/S	0.328 N/S	0.290 N/S	0.452* (0.045*)	0.390 N/S	-0.302 N/S	-0.101 N/S
Nausea	0.328 N/S	-	0.685** (<0.001**)	0.089 N/S	0.167 N/S	-0.089 N/S	0.343 N/S	0.167 N/S	0.236 N/S	0.102 N/S	0.599** (0.005**)	0.272 N/S	-0.408 N/S
Vomiting	0.242 N/S	0.685** (<0.001**)	-	1.00 N/S	0.089 N/S	0.206 N/S	0.015 N/S	0.257 N/S	0.303 N/S	0.157 N/S	0.538* (0.014*)	0.245 N/S	-0.105 N/S
Constipation	-0.154 N/S	0.089 N/S	1.00 N/S	-	0.089 N/S	-0.048 N/S	0.031 N/S	-0.356 N/S	-0.126 N/S	-0.218 N/S	0.206 N/S	0.509* 0.022*	-0.218 N/S
Diarrhoea	0.328 N/S	0.167 N/S	0.089 N/S	0.089 N/S	-	-0.089 N/S	0.057 N/S	0.167 N/S	0.00 N/S	0.102 N/S	0.385 N/S	-0.068 N/S	0.00 N/S
Mouth Sores	-0.066 N/S	-0.089 N/S	0.206 N/S	-0.048 N/S	-0.089 N/S	-	-0.336 N/S	0.167 N/S	0.00 N/S	0.218 N/S	0.023 N/S	0.355 N/S	0.00 N/S
Dry Mouth	0.183 N/S	0.343 N/S	0.015 N/S	0.031 N/S	0.057 N/S	-0.336 N/S	-	0.343 N/S	0.243 N/S	-0.140 N/S	-0.015 N/S	-0.140 N/S	-0.420 N/S
Taste Changes	0.328 N/S	0.167 N/S	0.257 N/S	-0.356 N/S	0.167 N/S	0.167 N/S	0.343 N/S	-	0.707** (<0.001**)	0.102 N/S	-0.043 N/S	-0.068 N/S	0.00 N/S
Smell Changes	0.290 N/S	0.236 N/S	0.303 N/S	-0.126 N/S	0.00 N/S	0.00 N/S	0.243 N/S	0.707** (<0.001**)	-	0.00 N/S	0.061 N/S	0.192 N/S	0.115 N/S
Dysphagia	0.452* (0.045*)	0.102 N/S	0.157 N/S	-0.218 N/S	0.102 N/S	0.218 N/S	-0.140 N/S	0.102 N/S	0.00 N/S	-	0.367 N/S	0.167 N/S	-0.250 N/S
Early Satiety	0.390 N/S	0.599** (0.005**)	0.538* (0.014*)	0.206 N/S	0.385 N/S	0.023 N/S	-0.015 N/S	-0.043 N/S	-0.061 N/S	0.367 N/S	-	0.105 N/S	1.00 N/S
Fatigue	-0.302 N/S	0.272 N/S	0.245 N/S	0.509* 0.022*	-0.068 N/S	0.355 N/S	-0.140 N/S	-0.068 N/S	0.192 N/S	0.167 N/S	0.105 N/S	-	-0.333 N/S
Pain	-0.101 N/S	-0.408 N/S	-0.105 N/S	-0.218 N/S	0.00 N/S	0.00 N/S	-0.420 N/S	0.00 N/S	0.115 N/S	-0.250 N/S	1.00 N/S	-0.333 N/S	-

Significance values are shown in parentheses. When significant (p=<0.05), values are marked with *. N/S indicated non-significance.

4.4.4 Malnutrition

4.4.4.1 ***Active Treatment***

Over half of the participants (62%) were at risk of malnutrition. Early satiety was associated with a risk of malnutrition (p=0.011). Early satiety was associated with an increased number of symptoms both when early satiety was included (median=4 vs 0) (p=<0.001) and excluded (median=3 vs 0) (p=0.003) in the total number of symptoms. The frequency of each category of malnutrition is shown in Figure 4.8 Participants with early satiety were more likely to have moderate or high risk of malnutrition (p=0.010). There was no significant association between the risk of malnutrition and age (p=0.560). There was no significant difference in symptom burden between those under and over 65 years of age (p=0.647). The presence an upper GI cancer was associated with being at risk of malnutrition (p=0.025). No other cancer types showed a significant relationship with risk of malnutrition. The percentages of patients of each cancer type at risk of and diagnosed with malnutrition respectively are as follows; Lower GI (55%, 18%), Lung (25%, 25%), Melanoma (50%, 50%), Upper GI (64%, 45%), and Urological (50%, 25%).

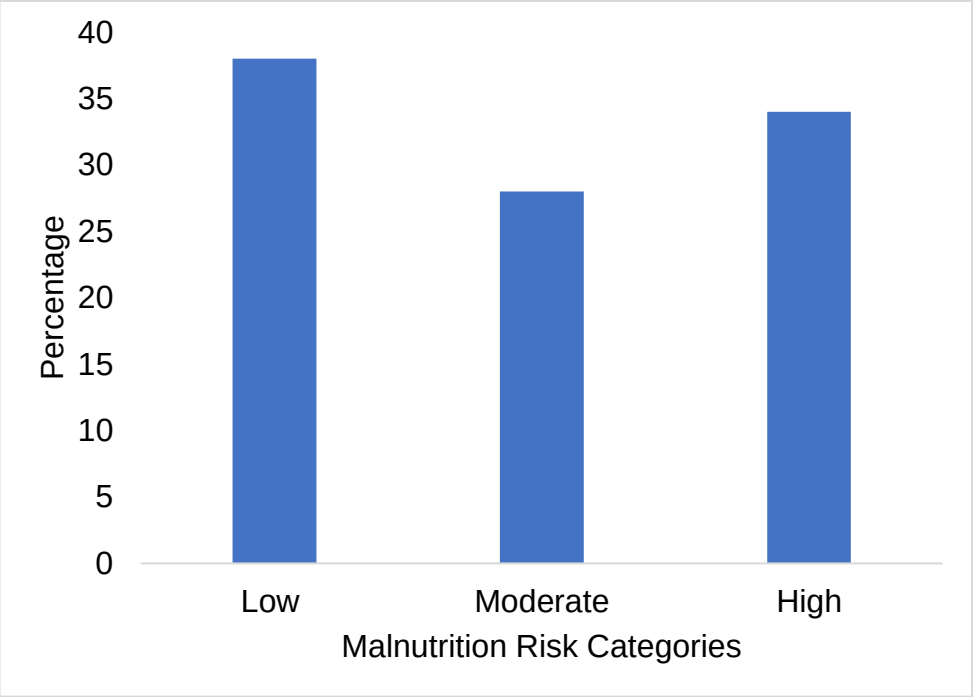


Figure 4.8 Percentage of patients on active treatment in each malnutrition risk category based on the abPG-SGA

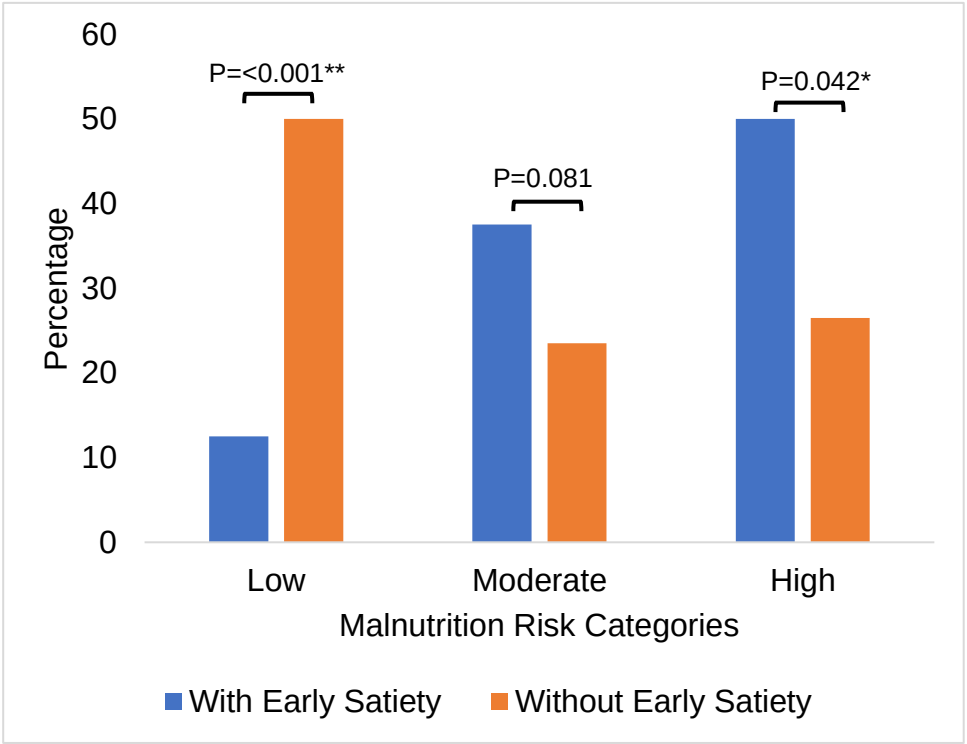


Figure 4.9 Malnutrition risk categories based on the abPG-SGA differentiate by presence of early satiety in patients receiving active treatment

Diagnosed Malnutrition

In this cohort, 10 participants (20%) were diagnosed with malnutrition using a positive abPG-SGA score and GLIM criteria. There was no significant difference in malnutrition between males and females (p=0.440) or being over 65 (p=0.480). There were no significant differences in malnutrition in each cancer group. Presence of early satiety was associated with the diagnosis of malnutrition (p=0.035). Participants with nausea (p=0.017) and dysphagia (p=0.018) were also more likely to be diagnosed with malnutrition.

4.4.4.2 Advanced Cancer

The average score for the abPG-SGA was 19 (range 6-25). All participants were at risk of malnutrition with most (85%) being at high risk. Unsurprisingly, most of the scoring was weighted towards the symptom assessment of the abPG-SGA. The median score for those with early satiety was higher (19) than for those without early satiety (10) (p=0.002). Early satiety was associated with a score >12 (p=0.001), which is a marker of prognosis. All participants with early satiety were at high risk of malnutrition. There was no significant difference in malnutrition category based on sex (p=0.135). Females had a lower median nonsignificant abPG-SGA score (12 vs 18, p=0.456). There was also no difference in the total abPG-SGA scores based on being over 65 years old (p=0.670).

4.5 Discussion

This study confirms that a high percentage of patients with cancer continue to be at risk of malnutrition and a fifth of patients have diagnosable malnutrition that remains underdiagnosed. In addition, despite being one of the most common symptoms in this cohort, early satiety is rarely volunteered as a symptom when assessed with an open question. Unsurprisingly, there was a huge disparity between the number of symptoms volunteered when assessed in open questions compared to a validated screening tool.

4.5.1 Malnutrition Risk

The risk of malnutrition in active treatment was similar to the prevalence identified in the literature.[401-403] The risk of malnutrition in those with advanced cancer was also similar to previous reports.[404] While not evaluated, it is possible some were not referred to the dietitian. There are several potential negative implications for this. Firstly, malnutrition can cause impaired immune function, and this may result in delayed recovery. This is especially a concern for those on active treatment, as delays in treatment can have huge repercussions on patient health. A delay of four weeks in treatment increases the mortality risk by approximately 10%.[405] Untreated malnutrition may also exacerbate the side effects of treatment, such as several NIS. This may result in a vicious cycle of poor nutrition and increased treatment toxicity. There is also the risk of decreased QoL in those with untreated malnutrition.

An unexpected result of this study was that there was no difference in the risk of malnutrition based on age. This differs from the literature where older patients with cancer have a higher risk of malnutrition compared to younger patients.[172]

While identification of malnutrition is key for all patients with cancer, malnutrition may have a greater impact on younger patients. As discussed previously, cancer increases the metabolic demand on the body and thus results in increased energy and nutrient requirements. This may be particularly challenging for those under 65 years of age as they generally have higher activity levels.[406, 407] Younger individuals may also be suitable to undergo more aggressive anticancer treatments such as high-dose chemotherapy.[408] These treatments often have increased risk of NIS, which can lead to increased malnutrition. Coping with a cancer diagnosis and undergoing treatment can be emotionally and psychologically demanding, with younger adults experiencing this more than older adults.[409] Stress, anxiety, and depression can negatively affect appetite, food intake, and overall nutrition.[410, 411] Younger individuals may experience unique psychological challenges due to disruption of their personal and professional lives, potentially exacerbating the risk of malnutrition. With all the above in mind, younger people with cancer can be particularly vulnerable to the effects of malnutrition.

The management of malnutrition in cancer patients is crucial to their physical and psychological well-being. Although not assessed in this study, patients with malnutrition have up to a 5 times greater risk of dying.[31, 412, 413] A multidisciplinary approach is essential to develop appropriate intervention plans to optimise patient outcomes. One challenge associated with this is the difficulty in identifying symptoms and the risk of malnutrition, which is not limited to these wards and is an issue in the healthcare system.

4.5.2 Missed Therapeutic Opportunities

There was an underreporting of early satiety in OSQ in both cohorts. Some reported their early satiety in the active treatment cohort, unlike in the advanced cancer cohort, where none reported it. This result is similar to that of Homse et al.[186] where closed questioning resulted in a higher incidence of early satiety compared to open questioning. The difference here is that early satiety was extensively mentioned extensively throughout the PIL and the consent process. Despite hearing the terms 'feel full quickly' and early satiety, it continued to be unreported when asked through an open question. It is reasonable to believe that this is likely to reflect oncology practice where systematic symptom assessment is not commonplace. Even when a questionnaire is used, it is unlikely to include early satiety.[303] Therefore, in clinical practice, it is best to use closed questions when trying to determine symptoms, particularly early satiety.

There may also be a benefit in assessing the degree of bothersome symptoms in this cohort rather than just prevalence and severity. Hoekstra et al[414] analysed the prevalence and severity in patients with advanced cancer. The patients were also given the opportunity to report their 'most troubling symptom'. In a third of the sample, the most troublesome symptom was not ranked as the most severe and resulted in possible missed opportunities for treatment.

This disparity in early satiety reporting is not a result of patients with advanced cancer being less symptomatic. This is evidenced both in the literature[415, 416] and also in the fact that the mean number of symptoms in the advanced cancer cohort was higher than the active treatment cohort here when evaluated with the abPG-SGA. This results in a disparity between OSQ in the active treatment cohort compared to the advanced cancer cohort. There are several possible

explanations for this. One is that there may be some adaptation to their symptoms in advanced cancer. They may have normalised their symptoms and do not think about the impact of their symptoms in the same way. Another possibility is the increased risk of cognitive decline since advanced disease is associated with older age. Finally, it may be due to those with advanced disease receiving palliative care. With the focus of palliative care on improving QoL through symptom management and the provision physical, psychological, and spiritual support, these patients may manage their symptoms better than those on active treatment. It may also be that, given they have stopped their anti-cancer treatment; their symptoms are less severe.

Anorexia was reported more often in the open question than any other NIS. However, in abPG-SGA, it was the fifth most common symptom in active treatment and the third in advanced cancer, behind early satiety in both cohorts. This is in agreement with further studies in advanced cancer.[174, 176] This raises the possibility that those who reported anorexia may have other symptoms that they group together with anorexia, such as early satiety. The simple description of 'feel full quickly' may more accurately reflect their situation, and instead they reported a loss of appetite. Another possibility is that participants found remembering their symptoms in the open question difficult. Similarly, it may be because participants feel that symptoms are common in advanced cancer and don't report them to be 'strong by not complaining'[417], suggesting a social desirability bias.

Other studies that have used the PG-SGA focused on its potential as a prognostic indicator. One such study by Wiegart et al. did not show early satiety as a prognostic indicator when the PG-SGA was used.[358] In a study by Feng et al.[418],

a score of >12 was associated with greater risk of death, which is significantly lower than Weigert (>20). It should be noted that this was limited to patients with advanced lung cancer. In this Chapter, early satiety was associated with a score of >12 suggesting a possible role in predicting survival. Other studies have shown that higher PG-SGA scores are associated with greater risk of death[288, 419, 420]; however, these were performed shortly after admission, which was not controlled in this study. It would be beneficial to evaluate survival rates of those recruited in a longitudinal study and see if early satiety is related to death as suggested by Walsh et al.[357]

4.5.3 Implementation of Nutritional Screening

There were some benefits to OSQ. One is the time associated with answering an open question about symptoms compared to a complete screening with a validated tool. While this is the case, there is also evidence that the abPG-SGA is a more effective screening tool. Firstly, there was a significant disparity between those that reported symptoms in the OSQ and those identified as at risk of malnutrition in the abPG-SGA and diagnosed with malnutrition by the GLIM. This highlights that open ended symptom assessment is a poor predictor of malnutrition risk in cancer and is not specific. Secondly, the management of NIS is an important aspect of care both during active treatment to minimise malnutrition and in palliative care to enhance QoL. The OSQ was not as effective in identifying the NIS present as the abPG-SGA. The use of the abPG-SGA is also aligned with ESPEN guidelines where the use of open questions for symptom assessment is not.[386] While it is important to identify these risks, there should also be appropriate treatment. This is not always done, as more than a third of patients with a significantly reduced oral intake do not receive nutritional

advice, ultimately exacerbating the malnutrition.[421, 422] Instead, the use of a validated screening tool is preferred, particularly one that includes an evaluation of NIS.

The use of abPG-SGA is suitable in the active treatment cohort not only for the above associations, but also because it is patient completed and therefore does not add additional stress on staff or require extra equipment which have been barriers to implementation.[423] There are insufficient data on the suitability in the PCU as the questionnaire was not self-completed. However, the evaluation of symptoms through open questions may result in missed therapeutic opportunities in this cohort. As a result of the above, when considering the use of closed questioning, it may be of most benefit to have a routine assessment with a validated tool where the participant can complete it without the physician present. This is also important, as clinicians may not allow adequate descriptions of the patient's symptoms[424], possibly as a result of their workload. The disparity between self-reported and systemic questioning in palliative care has previously been shown, with further recommendations to consider closed questions in symptom assessment.[425]

4.5.4 Impact of Early Satiety

The association between early satiety and other NIS has been well established in the literature. In this study, it was associated with the presence of anorexia.[426] An association that has been demonstrated less often in previous research is that of fatigue and early satiety. These symptoms have been shown to be part of the same symptom cluster in advanced cancer.[427] One reason for the lack of evidence is again that early satiety remains an orphan symptom and is not assessed in most studies. Many symptom cluster analyses have shown that

appetite disturbances and fatigue are part of the same symptom clusters[428-430], however they did not evaluate early satiety. The association found here between early satiety and fatigue may therefore reflect symptom clustering. The association between the two may be due to the impact of cancer related fatigue on nutritional intake. Those with cancer related fatigue have low energy and chronic exhaustion, which may result in less motivation to eat.[431] It may also relate to decreased speed in eating which may result in earlier onset of satiety.[432, 433] It may also be related to the psychological burden of fatigue such as increased stress and anxiety.[434] This may lead to alterations in eating patterns[435] which may relate to early satiety and hypophagia. Regardless of the cause of the association, those with fatigue should also be assessed for early satiety and treatment of both symptoms would improve overall well-being.

Early satiety was one of the few symptoms associated both with an increased risk of malnutrition and with diagnosed malnutrition. This was similar to the literature where early satiety is associated with risk of malnutrition.[319] Of particular interest is that despite the fact that symptoms are often confused for each other, anorexia did not show this association. Participants who reported anorexia in the OSQ but did not in the abPG-SGA all reported early satiety in the abPG-SGA. This suggests that the description of ‘feel full quickly’ more accurately represents their symptom than ‘no appetite, just did not feel like eating’. This difficulty in distinguishing symptoms may lead to inappropriate and unnecessary interventions, which may result in no improvement in early satiety and thus have a psychological impact on patients. This further justifies the importance of distinguishing the two symptoms. They are unique symptoms and while both are impactful, if early satiety remains to be underreported, there is unlikely to be

appropriate progression in research and these patients will continue to suffer from its impact.

The association between early satiety and nausea in advanced cancer is interesting, and the association has been shown along with chemosensory dysfunction.[436] Despite a statistically significant association, most did not report nausea that occurs in tandem with early satiety in SEES. It would be interesting to determine whether nausea follows early satiety rather than with early satiety, particularly with several references to bloating by participants. It also further highlights the potential association between early satiety and autonomic dysfunction given the research done in functional dyspepsia which was discussed extensively in Chapter 1. There is also the potential that the association is not related to pathophysiology and, instead, another factor, as early satiety and nausea are part of different symptom clusters in advanced cancer, suggesting different a pathophysiology or psychological relationship. On the contrary, in a study of diabetic patients, early satiety was the only symptom that remained statistically more prevalent compared to controls after adjustment for anxiety and depression, possibly indicating a somatic origin.[437] Further research on this symptom association would benefit from a clearer potential pathophysiology of early satiety first.

As shown, those with early satiety appeared to be more symptomatic than those without, suggesting a higher symptom burden with early satiety. The increased number of symptoms present when there is also early satiety suggests that it may be clustered with other symptoms. Symptom clusters have been previously suggested. An increased number of symptoms is associated with poorer physical and mental health[438, 439], suggesting that those with early satiety may have poorer

physical and mental health. Further evaluation of QoL in advanced cancer would have proven beneficial, however this assessment was considered too burdensome at the time of designing the study. Evaluation of QoL was performed in the active cancer cohort and results are described in Chapter 7.

4.5.5 Clinical Implications

One of the key findings related to clinical practice is how simply asking patients about what symptoms they suffer from is not only likely to result in underreporting of symptoms but is also a poor indicator of malnutrition risk. Instead, as per the ESPEN guidelines, patients with cancer should be routinely screened for malnutrition using a validated screening tool. Although there are many suitable screening tools that exist, there are several advantages to the abPG-SGA. One of the main advantages of this tool is that it is self-completed. Self-completion allows patients to answer questions about their nutrition and symptoms privately. Patients may be more likely to provide honest and accurate information on account of reduced social desirability bias and bias from the presence of healthcare professionals. This may have been present and may explain the disparity in reported symptoms in the OSQ compared to the abPG-SGA. This is especially relevant since nutrition is often a sensitive topic for people. A further advantage is that where a validated tool is used, the questions and scoring are standardised, allowing for consistency and comparability across both individuals and settings. It could also be used to help gauge the impact of nutritional interventions if used in a prospective manner. Finally, it also allows for the comparison between established norms, while also allowing for appropriate gathering of data for retrospective analyses in the future.

It should be noted that there are some limitations to the self-completion of nutrition screening tools. Namely, they may introduce inaccuracies due to self-reporting or incomplete information. They may also be challenging for those with difficulty in understanding English, those with cognitive impairment or with limited health literacy. It should also be noted that it should be used as a nutritional screening tool and not as a method to diagnose malnutrition. Instead, a complete evaluation of the patient, possibly using a nutrition-focused physical exam should be performed on all those identified as malnourished by a registered dietitian.

A further recommendation for clinical practice is to consider the presence of early satiety in patients with cancer where there is not a screening tool in place that assesses NIS. In this study it was the second most common symptom and impactful on QoL and malnutrition. While it is recommended to use a validated tool, it should at a minimum be added to the routine symptom evaluation in patients with cancer. This symptom is evidently impactful and, if left unidentified and untreated, may lead to difficulties in adherence, tolerance and as shown in the literature, early death.

4.5.6 Strengths and Limitations

To our knowledge, this is the first study to assess the prevalence of early satiety in cancer patients receiving anti-cancer treatment comparing two identification methods and assessing the impact of early satiety. A comparison of methods to identify symptoms, including early satiety, has been evaluated in patients with advanced cancer previously. There was a validated tool used in this present study however. One strength of this study is the thorough assessment of the nutritional status used and the use of the GLIM criteria for diagnosing malnutrition.

A further strength is this study shows a clear disparity between using OSQ and validated screening tools for malnutrition risk, further justifying the ESPEN guidelines. This study also had very few exclusion criteria, which allowed this cohort to mimic that of cancer patients in its heterogeneity. Furthermore, all assessments were carried out by the same researcher, which reduced potential variability.

Regarding the GLIM criteria, it should be noted that information on inflammatory status was not present for most in this study. Therefore, as highlighted in the methods, the presence of metastatic disease was considered to meet the criteria for the etiological 'inflammatory condition'. Participants did not routinely have their CRP assessed at each visit to the ODW. It would be of interest to assess inflammation through CRP and determine whether early satiety is still associated with diagnosed malnutrition in this cohort. It should also be noted that while diagnosis of cancer is not useful as a broad indicator of inflammation, some have suggested that inflammation is one of the newer hallmarks of cancer.[440] In the most recent review by Hanahan however, they highlighted the importance of inflammation but did not implicate it as a hallmark of cancer.[441] While it is therefore clear that those with cancer are likely in an inflammatory state, a blanket positive diagnosis for 'inflammatory condition' in all with cancer is not useful in differentiating malnutrition diagnosis. This would result in all meeting the etiologic criteria based on their cancer diagnosis. This may be further compounded by the result that early satiety was not associated with risk of malnutrition when assessed with the abPG-SGA, however it did trend towards significance. Those with early satiety were however more likely to be at moderate to high risk of

malnutrition than those without, suggesting that it does play a role in malnutrition risk.

This cohort was also limited by the access to patients through nursing staff who determined their suitability. Patients who were more ill were considered unsuitable for inclusion. It is likely that those who were more ill would likely be more at risk of malnutrition given the acute change in their condition.

The final limitation for this data reflects the exploratory nature of the statistical analysis. Due to the sample size, the data could not be effectively controlled for. As a result, correlations highlighted are unadjusted. With a larger sample size, other factors such as demographics and treatments could be controlled for and there would be scope for regression analysis. It is hoped that given these crude yet significant findings and highlighting both the clinical and research importance of this symptom, that larger studies into early satiety will take place and these correlations can be explored further.

4.6 Conclusions

This study assessed the prevalence and impact of early satiety in patients with cancer at two stages of cancer. The use of an open question to assess NIS resulted in significantly fewer identified than the closed questions of the validated abPG-SGA. Early satiety was the second and fourth most common symptoms in active treatment and advanced cancer cohorts, respectively. The presence of early satiety was associated with concurrent anorexia, fatigue, nausea, taste changes, and vomiting. It was also associated with being at risk of malnutrition and being diagnosed with malnutrition. Early satiety was also associated with a significantly increased symptom burden. More than half of the participants in the active treatment cohort were at risk of malnutrition, 20% of the cohort being diagnosed with malnutrition. All those in the advanced cancer cohort were at risk of malnutrition. Systematic screening for malnutrition using a validated tool, in which we highly recommend the abPG-SGA for its thorough evaluation, is necessary for all patients with cancer. While early satiety was extremely common, there was still some confusion in its reporting, which further exemplifies the need for more research into this impactful symptom, particularly how patients describe it given the disparity in OSQ and abPG-SGA prevalence of the symptom.

5 PILOTING OF THE SYMPTOM EXPERIENCE OF EARLY SATIETY QUESTIONNAIRE

5.1 Introduction

From Chapter 4, early satiety was an extremely common and impactful symptom. Yet, from Chapter 3, there is very little qualitative data surrounding early satiety. There are several methods to gather information on the patient's experience, one being a questionnaire. This evaluation of patient experience is used throughout healthcare, namely for patient satisfaction analysis.[442]

The use of questionnaires to collect data has increased significantly in recent years.[443] This likely reflects the increased emphasis on evidence-based medicine, as highlighted in Chapter 3. Another possibility is the ease of data collection and interpretation, decreased risk of interviewer bias, and the standardisation of the assessment.[444, 445]

Patient and Public Involvement (PPI) refers to the need for research goals to be refocused on being carried out 'with' members of the public rather than 'to' or 'for' them. PPI in cancer research is an ever-expanding area and is growing in popularity.[446] In fact, patients in palliative care are becoming increasingly involved with PPI.[447, 448] One example of PPI is the inclusion of patient feedback when developing new research materials, including questionnaires. Therefore, to obtain information on the experience of patients with early satiety, a new questionnaire was tested in patients with advanced cancer. These patients gave feedback on this questionnaire for implementation in future research studies. This PPI approach is classified as 'consultation'.[449] this chapter therefore piloted a newly designed Symptom Experience of Early Satiety (SEES) questionnaire that aimed to shed a light on the experience of those with early satiety for the first time.

5.2 Aims And Research Questions

5.2.1 Aims

- Determine the feasibility of exploring the symptom experience through a questionnaire.
- Gain feedback from patients with early satiety on the components of the SEES
- Gain feedback from oncology and palliative care experts on the components of the SEES

5.2.2 Research Questions

- How suitable is the SEES questionnaire to assess the symptom experience?
- Are patients with advanced cancer suitable to further explore the symptom experience of early satiety?
- Does the SEES require further modification to accommodate patients with advanced cancer?

5.3 Methods

This chapter describes the development and piloting of a 30-item symptom experience of early satiety (SEES) questionnaire (SEES V1, Appendix 5). An in-depth description of the process is in Chapter 2 (section 2.7)

5.3.1 Patient Selection

Participants were recruited from the palliative care unit of Our Lady's Hospice & Care Services (OLH&CS). All participants had advanced cancer and were receiving specialist palliative care.

5.3.2 Recruitment

As described in Chapter 2, recruitment involved participants receiving a PIL, signing a consent form, and completing the relevant questionnaires and assessments. Any participant who reported 'feel full quickly' (early satiety) in the abPG-SGA was given the SEES. As discussed, all assessments were read aloud to participants as required by the research ethics committee. Inclusion and exclusion criteria are outlined in Table 5.1.

Table 5.1 Inclusion and exclusion criteria for questionnaire pilot

INCLUSION CRITERIA
• Diagnosis of cancer receiving specialist palliative care (advanced cancer)
• Age > 18 years old
• Able to understand and speak English
• Able to provide witnessed signed consent
EXCLUSION CRITERIA
• Current or previous diagnosis of gastroparesis
• Unable to complete study assessments
• Diagnosis of dementia
• Australia-modified Karnofsky Performance Scale (AKPS) < 30%
• Participation deemed inappropriate by the consultant or nurse

5.4 Results

5.4.1 Recruitment

Participants were identified at multidisciplinary team meetings for inclusion in this study. Of these, 18 consented to participate in this study. Recruitment took place in two stages as a result of COVID-19 limiting access to participants on the ward. Ten participated during stage one, and eight were recruited subsequently. Ten of these participants reported early satiety in the abPG-SGA and completed the SEES V1 and the subsequent feedback questionnaire.

5.4.2 Demographics

Eighteen patients with cancer participated in this study. Demographic and clinical data can be seen in Table 5.1. The median age of participants was 75.5 years (range 38-89). The median AKPS score was 50%. All participants were admitted to the hospice with supportive care as the treatment goal. None were admitted for end-of-life care. All participants had some form of metastatic disease. Two participants had a medical history of hypothyroidism, and one had a history of type 2 diabetes.

Table 5.2 Demographic data for the total cohort and those with early satiety for questionnaire piloting

	Total Cohort		Early Satiety	
Variable	**n**	**%**	**n**	**% of total**
Sex				
Male	10	56	4	40
Female	8	44	6	75
Age (Median/Range)	76 (36-89)		77 (38-89)	
Over 65 Years	15	83	9	60
Primary Diagnosis				
Urological	7	39	2	29
Lung	4	22	3	75
GI	3	17	2	66
Other	4	22	3	75
Metastatic disease				
Bone	9	50	3	33
Lymph Node	4	22	2	50
Liver	3	17	1	33
Peritoneum	3	17	3	100
Brain	2	11	2	100
Lung	2	11	1	50
AKPS (%)				
30	1	6	0	0
40	4	22	4	100
50	9	50	5	56
60	4	22	1	25

5.4.3 Questionnaire Feedback

All those with early satiety completed the SEES V1. The median time to complete the questionnaire was 12 minutes and 54 seconds. The shortest time to complete was 5:44 and the longest was 21:07. Participants that were well enough to hold a copy of the SEES V1, completed the questionnaire in less time and with a reduced need to repeat questions.

All ten participants with early satiety completed the feedback questionnaire after finishing the SEES V1. Seven felt that the questions adequately captured their

experience of early satiety while three said they didn't know. Half of the participants felt that some of the questions were irrelevant, with four stating that there were no irrelevant questions. No specific questions were identified as irrelevant. Four felt that all required areas were addressed in the questionnaire, two felt some areas were not addressed and four felt they didn't know. The questionnaire was deemed too long by five participants. Three felt the length of time to complete was appropriate and the remainder didn't know.

Most participants (n=8) found the wording of the questions clear. When asked if there were areas that required further expansion, one participant said yes and that the questionnaire 'needed a lot of concentration'. Most (n=8) said that the instructions for filling in the questionnaire were clear.

From the researcher's perspective, participants found the differentiation between early satiety and other symptoms difficult. Participants required repeated prompting and refocusing to answer all questions based on early satiety. The most common symptoms confused with early satiety were anorexia and bloating.

The SEES V1 was sent to six dietitians with research and oncology experience for review. Most (n=4) reported that they felt the SEES was appropriate. Two gave more detailed feedback regarding the SEES. The prompt 'The questions below ask about Feel Full Quickly in detail' was removed, as it was similar to the previous sentence. In Question 1, 'Many' was changed to 'Very' for grammatical precision.

5.5 Discussion

The most common cause for a questionnaire to fail is that the target population does not understand, can't complete, or becomes fatigued while completing the questionnaire. Although the ADPM proved invaluable in the development of the SEES, they were not suitable to predict difficulties of comprehension in a cancer cohort. As a result, the SEES V1 was piloted in patients with advanced cancer receiving specialist palliative care. This cohort was chosen as they are likely to have the most difficulty in questionnaire completion given their physical health. It was believed that if this cohort deemed the SEES suitable, it could be implemented in other cancer cohorts.

5.5.1 Representative Cohort

This sample of patients with advanced cancer all had solid tumours and was representative in age to published literature.[450] All participants were at risk of malnutrition based on the abPG-SGA. This is a similar result to that of Chapter 4. Participants appeared to have poorer physical health given the lower median AKPS compared to the literature[451], although it is difficult to determine whether this was a true finding or related to the sample size.

The majority of participants with early satiety were female. The sample size was too small to infer any statistically significant association between gender and early satiety prevalence. Previous research has shown that there is a greater prevalence of early satiety in females[177], however, the result is not unanimous based on Chapter 3. Another result from this study that differed from Chapter 3 was that early satiety was not common in gastrointestinal cancers.

Research within palliative care can often be challenging. This is due to advanced disease, low-performance status, and high symptom burden. Despite these

challenges, all who reported early satiety were able and willing to complete the SEES and provide feedback on the questionnaire. This, along with the high prevalence of early satiety, further justifies future research into early satiety in this cohort.

5.5.2 Questionnaire Review

Since this study was the first to use the SEES questionnaire, participant feedback and suggested changes were crucial. Participant feedback was positive, and participants reported that this questionnaire adequately captured their experience of early satiety, and that the formulation of the questions was clear. Based on the feedback obtained from the participants, we had three goals for reviewing the SEES:

- Reduce the time to complete the questionnaire.
- Remove some repetitive/irrelevant questions.
- Maintain the language and instructions.

With this in mind, five questions were removed from the SEES. The questions that were removed were:

13. In what ways have you tried to manage this symptom?

25. How would you rate your overall quality of life during the past week?

26. How would you rate your overall health during the past week?

27. Did you ever ‘feel full quickly’ before your diagnosis/treatment?

28. Describe what you felt was the cause of your early satiety? (e.g., anxiety, pregnancy)

Question 13 asked about how participants have tried to manage their early satiety. This question caused some difficulties for the participants. Given that the

questionnaire was administered verbally, the participants found it difficult to remember all available responses. Participants needed the options repeated and prompting to give detail on their responses. This question yielded some interesting responses as to what methods have been employed to manage early satiety. It was deemed that identifying the methods that proved useful was more important than identifying those that were not. With this, the fact that it caused difficulties and took a long time to complete resulted in it being removed.

Questions 25 and 26 were also removed from the SEES. One of the key goals of the SEES was to establish whether early satiety was associated with quality of life (QoL). These questions were included given their validity in the EORTC-QLQ30. There also appeared to be some challenges in answering the question as the anchors had to be repeated for several participants. Given the need to reduce the length of the questionnaire, these questions were also removed. This was further strengthened by the fact that questions removed from a validated tool do not remain validated in isolation. A full quality of life assessment was deemed more appropriate and was performed for Chapter 7.

As stated, questions 27 and 28 were similar to question 2 on review. These were initially included to determine whether participants had experienced similar experiences of early satiety for any other reason besides cancer. When this question was answered, only one participant indicated of when else they felt caused early satiety. Given the confusion surrounding these questions and that there was minimal information gathered, they were removed.

While administering the questionnaire, participants seemed to find differentiating between early satiety and other symptoms a challenge. The suggestion of taking time at the beginning of the SEES to ascertain the participants' knowledge of

early satiety and to clarify with the participant what symptom we were asking about was discussed. Ultimately this suggestion was rejected as this may result in contamination of the participants' responses with the words or phrases used to describe early satiety to the participant. Instead, the reference to early satiety was exaggerated when the SEES V2 was used in Chapter 6. This confusion further reinforces the need for a definition of early satiety. This issue will likely remain among patients and healthcare professionals without a definition.

5.5.3 The Challenges of Don't Know

Several participants selected 'don't know' in their responses. It is possible that there was an element of 'satisficing' within the responses.[452] This theory was outlined by Krosnick where participants take shortcuts in responses to reduce the cognitive effort and so do not report accurate information.[453] There are several reasons why this may have occurred. One was that the SEES was too long, and so participants became fatigued and gave the answer that required the least amount of thought. Another possibility is that they responded with the last option given to them. During the design of the SEES, options for 'don't know' were included due to the difficulty of some questions for those with some memory issues, however, there is much debate as to the suitability of this practice.[454] These options were always placed as the last option to limit the possibility of satisficing when completing the questionnaire. In actuality, this may have facilitated it in some capacity as 'don't know' was always the last option presented to participants when the questionnaires were read aloud. Those that responded with 'don't know' often took longer to answer and so their response may be a combination of satisficing and uncertainty.[455] In this present study, however, time to respond to individual questions, or time to complete the feedback questionnaire

was not assessed. Another possibility is that participants were uncertain due to a potential lack of knowledge surrounding early satiety.[456] The responses don't appear to be related to the formatting and wording of the SEES as this was deemed clear by almost all participants. While it continues to be a challenge to decipher the meaning of 'don't know' responses, they were neither considered positive nor negative for this pilot. The shortened questionnaire may reduce satisficing in future uses of the tool. Most of this also occurred during the feedback questionnaire, rather than the SEES V1 itself.

5.5.4 Influences On Questionnaire Suitability

The quality of the data collected when using a questionnaire is dependent on several factors, one of which is the length and time to complete. The time taken to complete a questionnaire is a key component of its suitability for use. There is significantly more evidence surrounding the completion of individual components, but the total completion time of a questionnaire is also important for the accuracy of responses.[457] The median completion time resulted in each question taking approximately 30 seconds to read and complete. One key finding is that even at the highest range, the SEES V1 was completed within the recommended time of less than 30 minutes for a questionnaire.[458, 459] For transparency in future PILs, it was stated that the questionnaire would take approximately 15 minutes to complete.

Another key factor is the length of the questionnaire. This differs slightly from the time to complete a questionnaire, as it can be impacted by the visual design of the questionnaire. It is a difficult balance to ensure a thorough evaluation of the symptom experience while not being too long to reduce the quality of data gathered. The impact of questionnaire length is seen in a study by Iglesias and

Torgerson who reported an increased length of questionnaire resulted in a significant reduction in response rate.[460] There is further evidence of this in the literature where the short version of a questionnaire results in more responses compared to a longer questionnaire.[461-463] Therefore, one of the key objectives based on the feedback was to shorten the SEES V1. As a result, we reduced the length by 17%. Although this may not have been as relevant for those with advanced cancer, those undergoing active treatment were in a position to self-complete the questionnaire and ensuring appropriate engagement was key. This also resulted in the SEES V2 (Appendix 7) being condensed into two pages (one A4 sheet) which helped maximise the response rate.[464]

Questions in a questionnaire can be categorised into two major forms of closed and open questions.[465] For this questionnaire, both forms of questions were used. Closed questions are generally used where there is less scope for a wide variety of answers and where it is easy to categorise potential responses. They may result in a decreased variety of responses and the included options may not accurately reflect the participant's response. Many of the questions included in the SEES were quite specific in what was asked, and therefore most are designed as closed questions. Where a topic required a greater understanding of the individuality of responses, open questions were used.

A clear example of this is within the theme of early satiety management. There is a closed question that asks whether participants have tried to manage their early satiety. This is a yes/no question and allows for a simple, quantitative assessment of how often those with early satiety try to manage their symptom. The following question asked what methods have worked for them. Given the lack of knowledge

on early satiety management found in Chapter 3, it was imperative that this question be open. This allowed for a number of responses to be recorded.

5.5.5 Questionnaire Vs Interview

A questionnaire was the chosen method to explore the symptom experience of patients with early satiety in this cohort. There are several reasons for this decision. Firstly, questionnaires are structured with mostly predetermined questions and responses.[465] This allowed more focused questions to be asked of a cohort that has an extremely high prevalence of fatigue.[466] This fatigue may explain the number of participants that reported 'don't know' during the feedback questionnaire. Although there are benefits to a qualitative interview to gather more nuanced information, this cohort would likely have become far too fatigued during the process[467], and responses to questions may have been biased.

The questionnaire also allowed data to be gathered from a larger sample of participants. Initial plans were for a large-scale study into the symptom experience of early satiety in multiple cohorts, however, this had to be altered due to the pandemic limiting patient access. While it was not part of the initial decision process, it was beneficial that the questionnaire was chosen to allow continued, albeit limited recruitment during the COVID-19 pandemic. It was also hoped that the results of the questionnaire might help guide qualitative research in the future. This would be done by identifying relevant topics surrounding early satiety in cancer that require deeper investigation, which is highlighted in Chapter 6 of this thesis.

5.5.6 Strengths & Limitations

This study is the first to pilot a questionnaire that aimed to investigate the prevalence, characteristics, and severity of early satiety. Despite the small

sample, it was clear from the SEES V1 responses that early satiety is a highly individualised symptom. A further strength of this study was that, although some repetition and focusing were necessary, all participants were able to complete the SEES V1. As highlighted, there was a risk that participants would not be able to, given the physical health of this cohort. The feedback was positive overall regarding the questionnaire. Therefore, there is merit in using the SEES, specifically the updated SEES V2, in a larger sample and different cohorts.

Another strength is that it further highlighted the issues associated with a lack of qualitative data on early satiety. Participants found it challenging to differentiate early satiety from other NIS. Part of this challenge is likely related to the lack of definition and the inability to tailor questions and possible responses to accurately reflect early satiety. This highlights a lack of focus on early satiety from both research and a patient standpoint.

One clear limitation of the above study was that the process was not a validation study. One of the key reasons for that is the lack of a gold standard to compare the SEES. There is no objective measure or gold standard for the evaluation of symptom experience to compare this questionnaire to. It is hoped that this questionnaire could be validated in the future. Another limitation is that the symptom experience of early satiety was limited to being assessed in those who have the appropriate literacy skills. This is not a requirement in most interviews, as they primarily require listening skills and the ability to respond to questions. A further limitation is that it was challenging to differentiate the causes of where participants found the questionnaire difficult. Given the low performance status, it was unclear whether the challenges were related to the participant or the

questionnaire. The use of the feedback questionnaire helped to somewhat correct this difficulty.

5.6 Conclusions

This study was the first to pilot a questionnaire to examine the symptom experience in patients with early satiety. Early satiety was one of the most reported symptoms, suggesting those with advanced cancer should be included in any further evaluation of early satiety. All participants with early satiety completed the SEES V1 and provided full feedback on the questionnaire. Most of the feedback was positive and the questionnaire adequately captured the experience of early satiety. Some suggested that the SEES V1 was too long and somewhat repetitive, which resulted in the redraft of the SEES to accommodate this feedback (SEES V2). Participants often found differentiating early satiety from other NIS a challenge. Given that early satiety was highly prevalent, advanced cancer was deemed a suitable cohort to further explore the symptom experience of early satiety, as well as those on active treatment using the revised SEES V2.

6 THE SYMPTOM EXPERIENCE OF EARLY SATIETY IN PATIENTS WITH CANCER

6.1 Introduction

The importance of the patient voice is evident throughout cancer research from the growing interest in qualitative research[468] to patient-reported outcomes becoming more commonplace in randomised control trials.[469] A detailed exploration of a patient's experience of a symptom is a cornerstone to ensure adequate management of that symptom. Additionally, patients want to better engage with their healthcare providers regarding their symptoms and their management.[470] A tailored approach to symptom management is preferred by both patients and healthcare professionals.[471] By understanding the unique aspects of an individual's symptom experience, healthcare providers can offer personalised care that is specific to the individual taking into account patient preferences, goals, and well-being. One challenge with effective management is that each individual's experience may be different.

Individualised experiences of symptoms is not a novel concept. Decades ago, Chapman and Jones identified that when using a standardised pain stimulus, subjective pain reports varied greatly.[472] Pain is one of the most researched subjective symptoms in oncology, and this individualised nature has been shown extensively throughout the literature. The symptom experience is influenced by several factors including biological, psychological, and psychosocial factors.[473] This in-depth investigation into the individualised nature of a symptom has not been performed on most symptoms. Early satiety is one such symptom. There is no information on how patients with cancer describe this symptom. One of the major challenges to this is that there is a lack of instruments to measure symptom experience.[474] This Chapter discusses the individual experiences of those with

early satiety in two cancer cohorts, those receiving active anticancer treatment, and those with advanced cancer.

6.2 Aims And Research Questions

6.2.1 Aims

- Determine differences and commonalities in the way patients with cancer receiving treatment describe early satiety.
- Compare the experiences of those with early satiety receiving anticancer treatment and those with advanced disease.
- Document descriptions of early satiety by patients with cancer.

6.2.2 Research Questions

- How do patients with early satiety describe their experience?
- How does the experience of early satiety differ depending on disease stage?

6.3 Methods

This chapter describes the implementation of Chapter 5's updated Symptom Experience of Early Satiety (SEES) questionnaire on patients receiving anticancer treatment and those with advanced cancer admitted to the PCU (SEES V2, Appendix 7). This questionnaire contained 25 questions on the patient's experience of early satiety.

6.3.1 Patient Selection

Recruitment was carried out in the Oncology Day Unit at Tallaght University Hospital Dublin for patients receiving active treatment and the Palliative Care Unit in OLH&CS for those with advanced cancer.

6.3.2 Recruitment

The recruitment involved participants receiving a PIL, signing a consent form, and completing the relevant questionnaires and assessments. Participants that reported early satiety (feel full quickly) on the abPG-SGA or reported it in the open question were given the SEES. Participants in the active treatment cohort were given the opportunity to self-complete the SEES. If participants were unable to do so, for example, if their intravenous access was inserted into the arm used for writing, they received a copy of each of the questionnaires, and their responses were documented in a separate copy. All data from the advanced cancer cohort were collected with this method because self-completion of the SEES was deemed too burdensome by the research ethics committee.

6.4 Results

6.4.1 Demographics

Demographic data are presented in Chapter 5 (5.4.1) for both the treatment and the advanced cancer cohorts.

As highlighted in Chapter 5, 16 of the participants reported early satiety in the abPG-SGA or open question in the active treatment cohort. All 16 completed the SEES questionnaire. No participants in the advanced cancer group reported early satiety in the open question and only reported it using abPG-SGA (n=13).

6.4.2 Timing and Duration of Early Satiety in Cancer

When participants experienced early satiety first varied across the cancer trajectory. During treatment was reported most frequently as the point at which participants first reported early satiety. After treatment was reported most often in the advanced cancer cohort. The most common treatment associated with early satiety was chemotherapy (n=12) followed by immunotherapy (n=2) radiation therapy (n=2) and surgery (n=2). Determining when early satiety was first experienced was a challenge with the second most common response being ‘don’t know’.

Most participants reported that early satiety occurred in the evening (n=7). This was the most common response for those in the active treatment cohort. There appeared to be a more varied response in those with advanced cancer with equal responses for ‘morning’, ‘afternoon’ and ‘all the time’ (n=3). None reported early satiety occurred at night. ‘All the time’ was the second most common response. When participants experienced early satiety appeared to vary with most participants selecting ‘varies’. The second most reported was ‘after starting to eat’. There was a greater variety of responses from the advanced cancer cohort.

With regards to how often participants experienced early satiety, ‘often’ was by far the most common response (n=17). ‘Occasionally’ and ‘almost constantly’ were equally reported (n=5). ‘Rarely’ was the least reported and was only reported by those with advanced cancer. Overall, the responses from the advanced cancer cohort varied more than the active treatment cohort.

The length of time that participants reported that early satiety was lasting also varied greatly. This was evident in both cohorts. The most common response was that it lasts 1-2 hours. The advanced cancer cohort reported it lasted less time than the active treatment cohort, with <30 minutes being the most commonly reported duration.

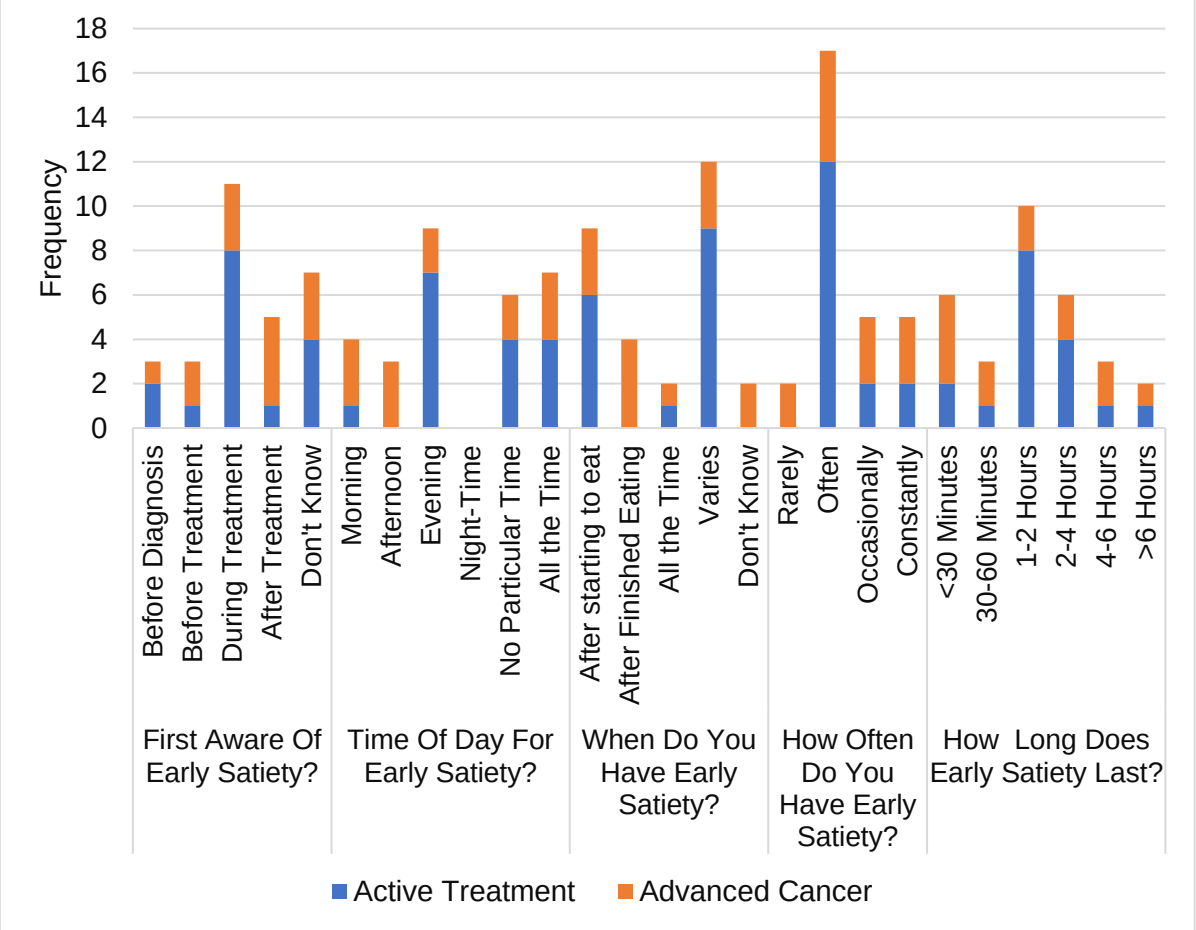


Figure 6.1 Distribution of responses under the theme of timing of early satiety differentiated by stage of cancer (n=29)

6.4.3 Severity of Early Satiety in Cancer

The severity of early satiety was not universal. The most common response was 'moderate' (n=15). This was the most common response in both cohorts. 'Varied' severity was the second most common response. Only the advanced cancer cohort reported their early satiety was 'severe'.

There were equal reports as to whether early satiety co-occurred with other symptoms. Those with advanced cancer were slightly more likely to report co-occurring symptoms. There were 13 symptoms that reportedly co-occurred with early satiety. The most common symptoms to occur with early satiety were fatigue, dry mouth, and nausea (Figure 6.2).

Figure 6.2 Frequency of co-occurring symptoms with early satiety in cancer

Most participants reported their early satiety had changed throughout their cancer (n=16). There were almost the same number that reported no changes in their early satiety (n=13). It appeared that participants undergoing active treatment were more likely to report changes in early satiety.

The most common changes reported were that early satiety became ‘worse’ and occurred ‘more often’. This was the case for both cohorts. Only those undergoing treatment reported any improvements in early satiety.

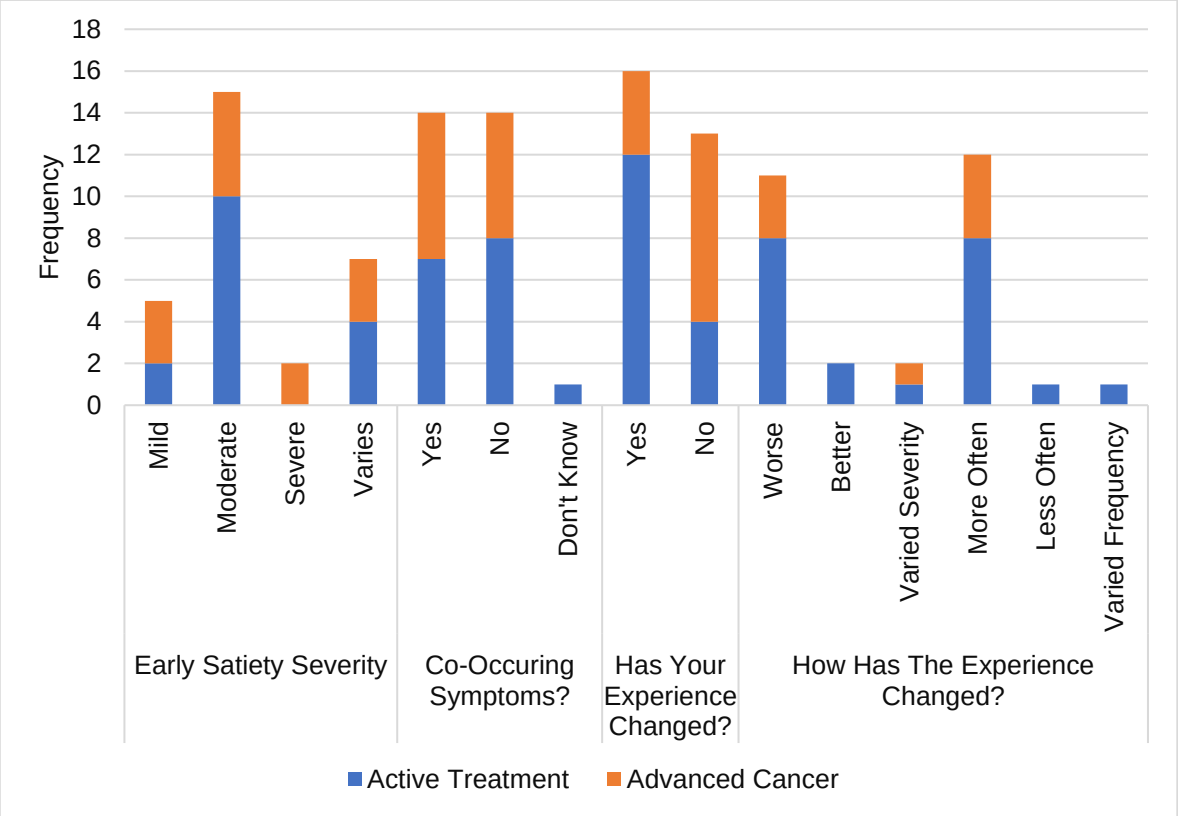


Figure 6.3 Distribution of responses under the theme of severity of early satiety differentiated by stage of cancer (n=29)

6.4.4 Management of Early Satiety in Cancer

Most attempted to manage their early satiety (n=20) while the remainder (n=9) made no attempt. A little and often eating pattern appeared to be the most beneficial, with eight reporting that it proved beneficial. More than a third of those who tried to manage their early satiety reported that they were unsuccessful.

A majority (n=17) had not reported early satiety to their doctor or health and social care professional (HSCP) and the remaining 12 reported they had informed their doctor/HSCP. None in either cohort reported that a doctor or HSCP had previously asked them if they had early satiety/feel full quickly before the study.

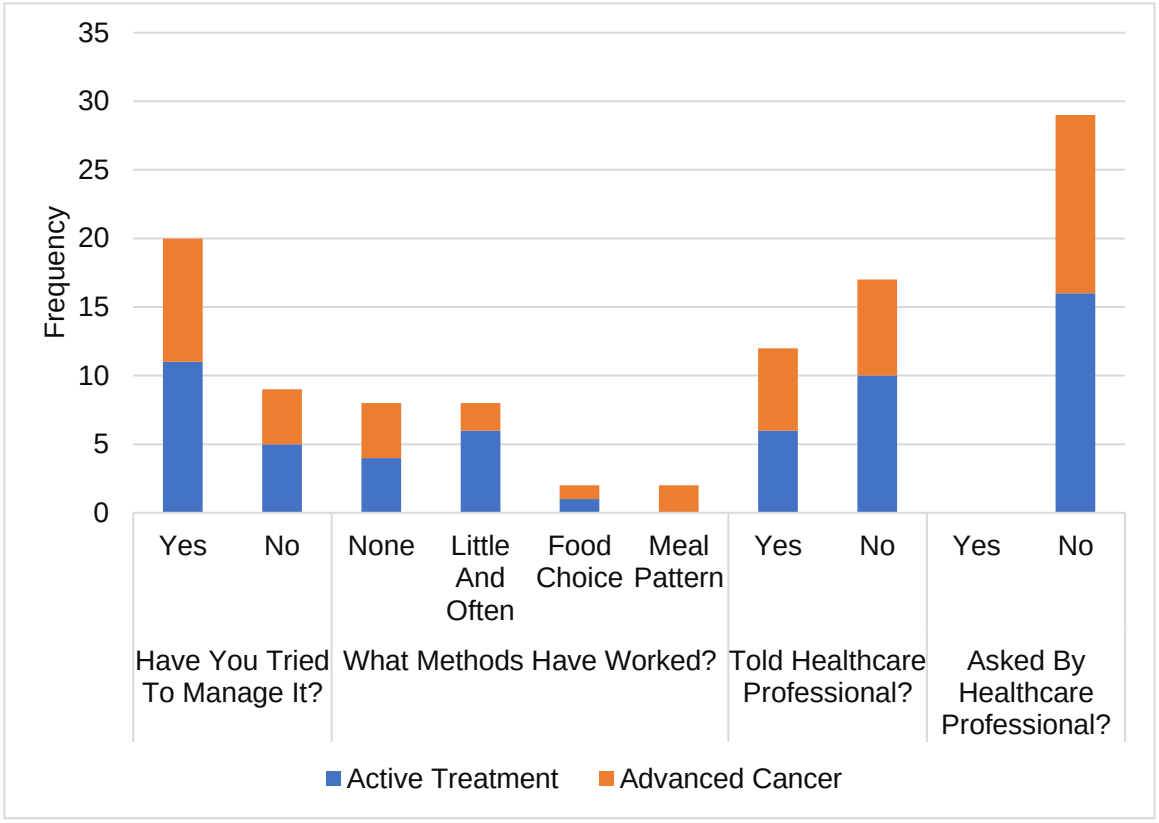


Figure 6.4 Distribution of responses under the theme management of early satiety differentiated by stage of cancer (n=29)

6.4.5 Influence of Early Satiety on Nutritional Intake

Early satiety appears to directly, but not universally, impact nutritional intake. Most (n=24) reported that early satiety reduced nutritional intake, while three reported that it did not. One participant reported that early satiety sometimes affected their intake in both cohorts. All those with advanced cancer reported it reduced their nutritional intake.

Early satiety appeared to reduce nutritional intake by ‘a lot’ in most. ‘Moderately’ was the second most common response. It was also the joint most common response with ‘a lot’ in the advanced cancer cohort.

Most participants were unable to finish their meals with the onset of early satiety (n=17). This was by far the most common response in those with advanced cancer. In participants undergoing active treatment, there were more equal responses given to ‘yes’ and ‘sometimes’, however the majority did report they were unable to finish their meals. Interestingly, despite the prompt of ‘if yes’, 14 participants responded to whether it takes long to complete their meals. ‘Quite a bit’ (n=6) and ‘a little’ (n=4) were the most common responses. In those who had reported yes, there were equal responses for ‘not at all’, ‘a little’ and ‘quite a bit’ (n=2), with one reporting they ‘don’t know’.

Most (n=16) participants did not report specific foods/drinks that caused early satiety. Eight reported that certain foods caused early satiety. The most common foods were bread, carbonated drinks and any food (n=2). Other responses included dry meat, potatoes, oral nutritional supplements, dinners and greasy food. One person who responded no reported that ‘all foods’ cause early satiety.

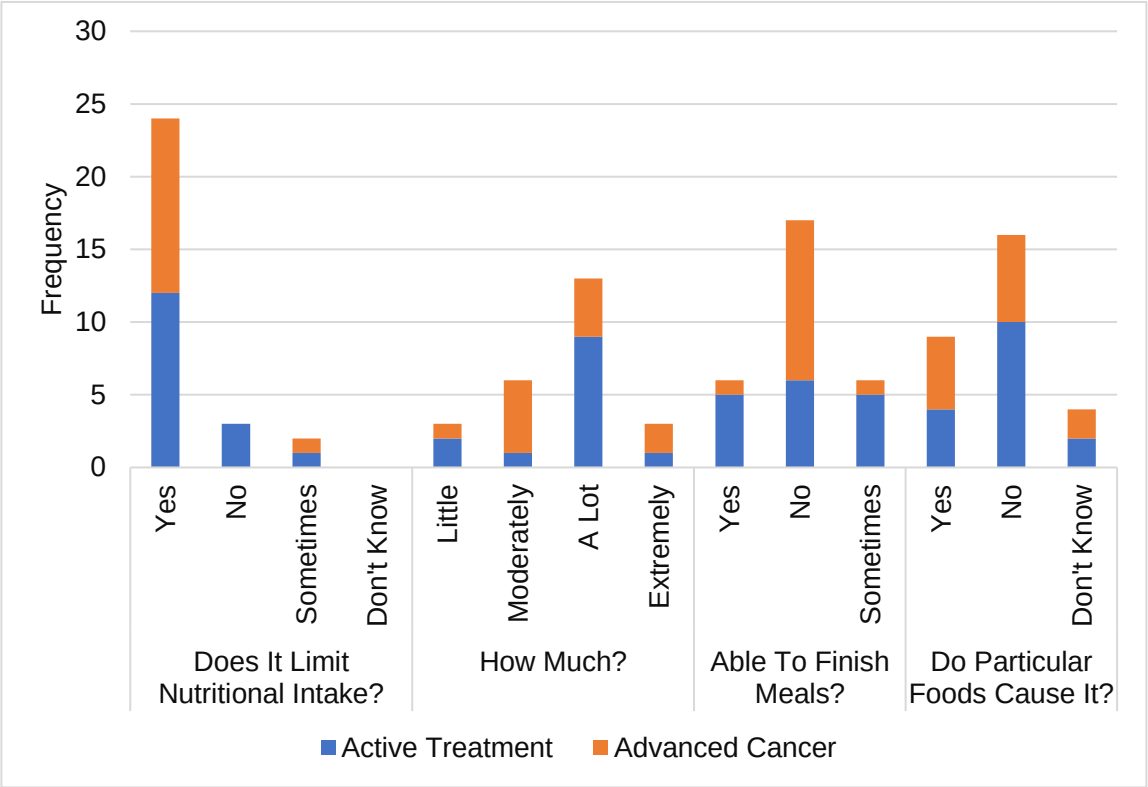


Figure 6.5 Distribution of responses under the theme of influence of early satiety on nutritional intake differentiated by stage of cancer (n=29)

6.4.6 Effect of Early Satiety on Quality of Life

Early satiety caused distress in most participants (n=18). There was mixed severity of distress caused. 'A little bit' and 'quite a bit' were reported most (n=7). Somewhat was reported by four participants. Not at all was the most common response for both cohorts combined. In advanced cancer it was the most common response while in those on active treatment, 'a little' was most commonly reported. None reported that early satiety distressed them 'very much'.

There were also mixed reports as to whether early satiety reduced QoL. Most reported that it did reduce QoL (n=16) while there was almost an equal report of early satiety not reducing QoL (n=13). Early satiety reduced QoL most often in the advanced cancer cohort while it did not in the active treatment cohort. There is a more thorough evaluation of the impact of early satiety on QoL in Chapter 7.

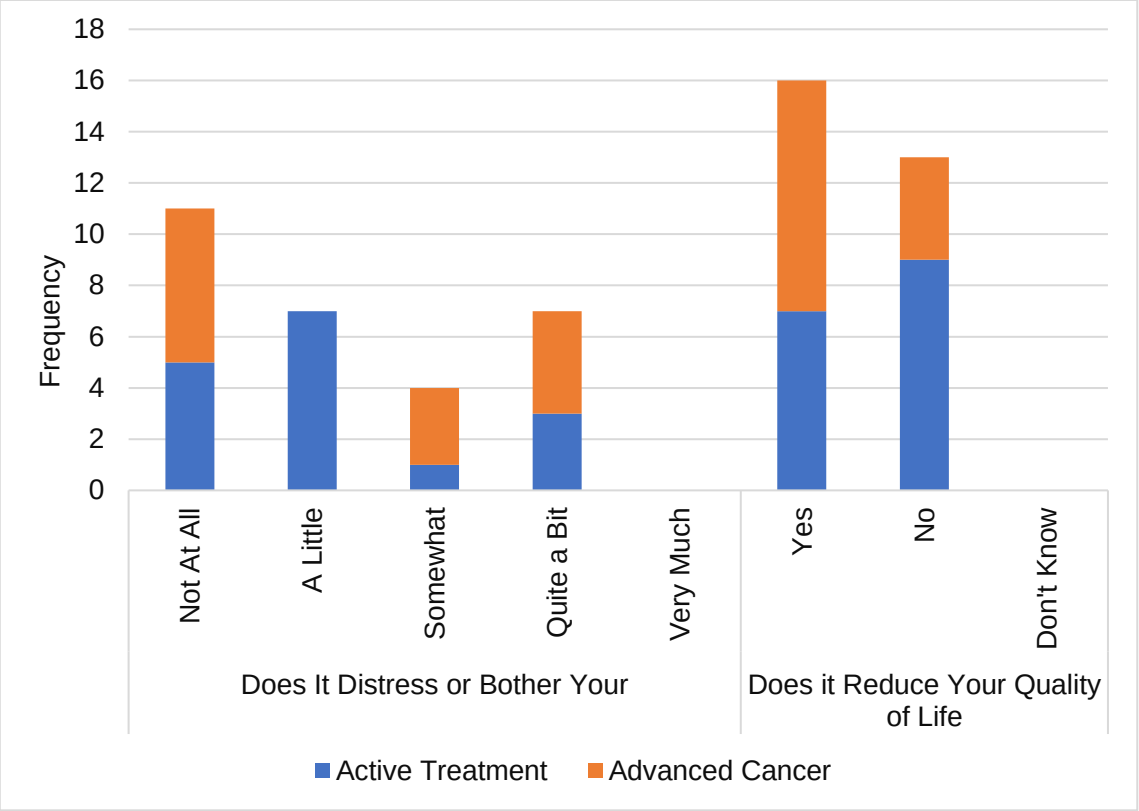


Figure 6.6 Distribution of responses under the theme of influence of early satiety on quality of life differentiated by stage of cancer (n=29)

6.4.7 Descriptions of Early Satiety in Cancer

Many of the themes identified in the SEES, where participants were given the opportunity to describe their early satiety experience, were the same across both cohorts. Distress, lack of enjoyment, bloating, and inability to eat were all identified in both cohorts. Unsurprisingly in the active treatment cohort, another theme identified was quotes related to health concerns.

An 'inability to eat' was the most common theme identified (n=16). Most of the descriptions of this inability to eat were quite direct.

'I have enough of that and push it aside',

'I feel very full',

‘I have enough in a few minutes’

‘I might pick at it’ and

‘Not able to eat like you used to be’.

Early satiety also caused distress in participants in both cohorts. Distress was the most common theme identified in those with advanced cancer. Some references to this were direct, with it being described as

‘Distressing’,

‘Uncomfortable’,

‘I get stressed’ and

‘Feel anxious when it happens’.

Some participants described how it caused distress by forcing them to think about their health.

‘Reminds me that I’m sick’,

‘If I don’t stop it causes pain’ and

‘Mind turns to the progression of disease and things getting worse’.

Early satiety also appeared be related to bloating in many experiences of early satiety. Some gave basic descriptions of being ‘totally bloated’ while others gave more detail like:

‘Ready to burst’,

‘Feel full to the throat’,

‘Feel very uncomfortable and bloated’ and

‘Bloated. I need to move my position’.

Some had more extreme descriptions of bloating related to early cancer.

> ‘Like someone inflated your stomach’,
>
> ‘Feels like I will explode’,
>
> ‘Like having a 10-course meal’ and
>
> ‘I feel my whole eating way is full right up to my throat’.

The theme of ‘loss of enjoyment’ of eating was the fourth most common (n=13). Participants described how they were often ‘looking forward’ to a meal and unable to enjoy it due to their early satiety. Others described how eating no longer has the same joy now with early satiety. They described how they:

> ‘Get no satisfaction from eating’,
>
> how early satiety has ‘taken the joy away from eating’,
>
> and how they wish they could ‘enjoy food all the time’.

There was also a social impact, with participants describing

> ‘When we go out, I'm finished earlier than others. I try to talk myself out of going for meals to avoid it’
>
> and ‘I suggest going for coffee over a meal to avoid embarrassment.’

Those with early satiety were often ‘forcing’ themselves to eat to ensure they remained in good health despite their discomfort as a result of early satiety. They focused on the desire to meet their nutritional requirements rather than their enjoyment.

> ‘I sometimes put pressure on myself to try harder to eat more as a requirement to keep my weight and strength up.’

and ‘even though you have eaten a small amount, you know it is not enough for your body’.

There were also descriptions that were categorised as miscellaneous since their theme was not repeated by others. Such descriptions included:

‘Surprising’,

‘Suddenly your breathing is more difficult’ and

‘Grease and fat make it worse. Lying down makes it worse.’

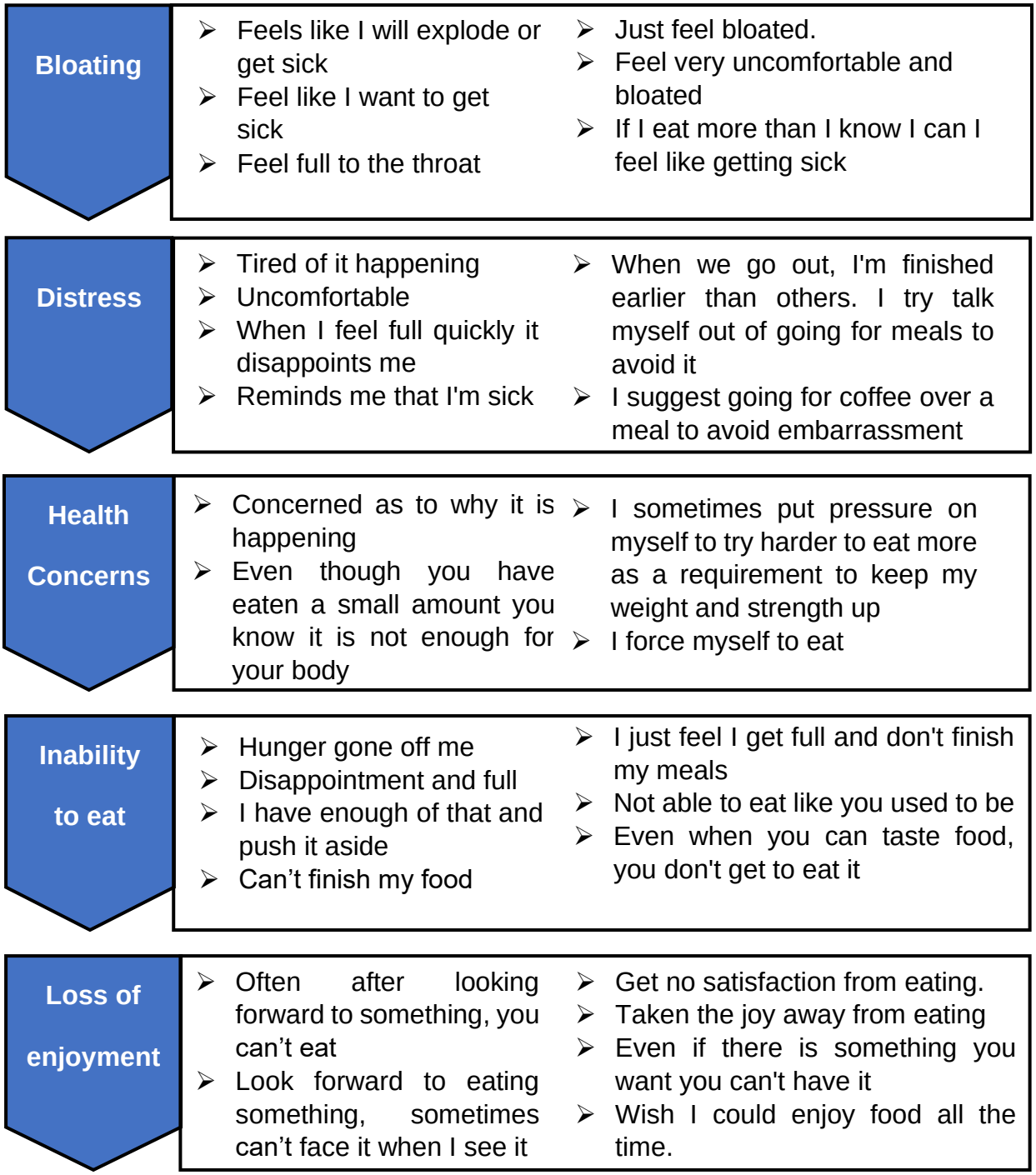


Figure 6.7 Verbatim quotes about early satiety in patients receiving anticancer treatment, grouped by theme

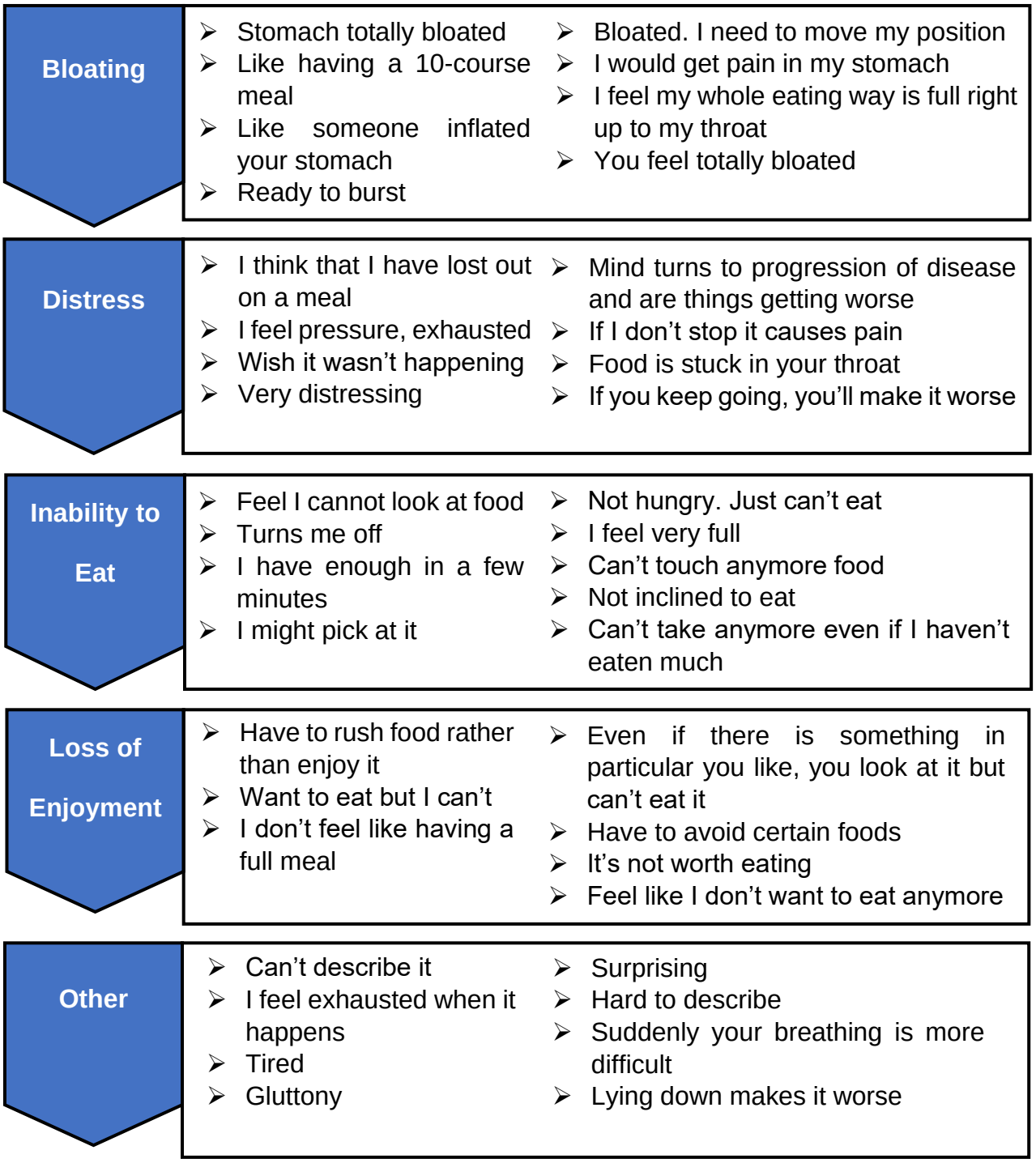


Figure 6.8 Verbatim quotes on early satiety in advanced cancer, grouped by theme

Table 6.1 Most common responses for the symptom experience of early satiety questions of patients with advanced cancer and receiving active treatment compared

Question	Advanced Cancer	Active Treatment
When Were You First Aware?	After Treatment (Chemotherapy)	During Treatment (Chemotherapy)
What Time of Day Do You Have It?	Morning, Afternoon, All the time	Evening
How Often Does Early Satiety Occur?	Often	Often
How Long Does Early Satiety Last?	<30 Minutes	1-2 Hours
How Severe Is Your Early Satiety?	Moderate	Moderate
Does It Co-Occur With Symptoms?	Yes	Yes
Which Symptoms?	Fatigue, Nausea, Heartburn, Difficulty Breathing	Stomach Pain, Nausea, Bloating, Dry Mouth
Did Your Experience Change Throughout Your Illness?	Yes (Worse, More Often)	Yes (Worse, More Often)
Have You Tried To Manage It?	No	Yes
What Methods Worked?	None	Little and Often
Ever Told Doctor/HSCP?	No	No
Ever Been Asked By Doctor/HSCP?	No	No
Does It Affect How Much You Eat?	Moderately, A Lot	Moderately
Able To Finish Meals With Early Satiety?	No	No
Take Longer To Finish Meals With Early Satiety?	Quite a Bit	Quite a Bit
Do Particular Foods Cause Early Satiety?	No	No
Which Foods/Drinks?	Fatty Food, Fizzy Drinks	Bread, Meat, Potatoes
Does Early Satiety Cause Distress?	Not at All	A Little Bit
Does Early Satiety Affect Quality of Life?	Yes	No

6.5 Discussion

This study was the first to explore the symptom experience of early satiety in participants on active anticancer treatment. It showed that there are not only individual experiences of early satiety, but also similarities and differences in the experiences between those receiving anticancer treatment and those receiving palliative care.

6.5.1 Similarities In Experiences

Although the experiences of those with early satiety ultimately appear to be unique for all, there were some similarities between the experience of those with advanced cancer and those on anticancer treatment here.

Unfortunately, one commonality between both cohorts is that these patients are not screened for early satiety at any point during their cancer. This is likely to be more impactful on those receiving treatment than advanced disease. This is due to the importance of maintaining weight to ensure the optimal tolerability and efficacy of the cancer treatment. However, it is important to identify and manage early satiety, despite the treatment goals being different. The reason for not being asked about early satiety is difficult to pinpoint. As highlighted extensively, it is an orphan symptom and not part of several symptom assessments. With neither patients on active treatment, nor with advanced cancer being assessed for it, there may be a lack of knowledge surrounding early satiety and its impact.

An association in both cohorts is between fatigue and early satiety. Fatigue was the most commonly reported symptom to co-occur with early satiety in the SEES in advanced cancer and was statistically associated with early satiety in both the abPG-SGA and the EORTC QLQ-C30. Despite this, fatigue was not the most common symptom to co-occur with early satiety in the SEES. This may be related

to the higher baseline prevalence of fatigue in the advanced cancer group compared to those receiving active treatment.[475] The reason for this is likely multifactorial with disease progression resulting in higher tumour burden, treatment side effects from multiple treatment modalities, sleep disturbances, and poor nutritional intake. Although the association with early satiety was significant in the active treatment cohort, there was a higher baseline fatigue in the advanced cancer group. It is therefore difficult to determine whether fatigue cooccurs with early satiety or is significantly associated with the presence of early satiety.

Another commonality between both cohorts was that most with early satiety could not finish their meals. This inadequate nutritional intake is likely to lead to poor nutritional status as well as psychological impacts. This risk is likely higher, as most also report that it took them longer to eat their meals. Slow eating has been shown to increase fullness and decrease nutritional intake.[476, 477] Both of these factors likely contribute to the association between early satiety and malnutrition found in Chapter 4. Although this is important in both cohorts, it is important to note that the care goals for both cohorts are different. There is scope for more aggressive management of early satiety in the cohort receiving anticancer treatment, as nutritional status is an important aspect of their care. In the advanced cancer group, the emphasis is more on improving QoL. Take for example that patients with early satiety are not finishing their meals. In the active treatment group, it would be recommended to tailor the meal to be high in protein and dense in calories to maximise protein and energy consumption in as small a meal as possible. In the advanced cancer group, patients would be encouraged to choose a meal they enjoy and eat to maximise QoL, which may include focusing on the nutrient-dense components of their meal. Therefore, while it is a

common theme in both, the impact on the treatment plan is likely different in both cohorts.

6.5.2 Differences In Experiences

Despite not being screened for it and therefore not receiving nutritional advice from a registered dietitian for early satiety, participants in the active treatment cohort were more likely to try to self-manage their early satiety than those with advanced disease. One possible cause is that those undergoing anticancer treatment are likely to be more focused on meeting their nutritional requirements to ensure treatment efficacy. This is less of a concern for those with advanced cancer. It may also be related to the increased symptom burden in those with advanced cancer. Management of physical, emotional, and psychosocial symptoms simultaneously can be challenging and those with advanced cancer may find it overwhelming and uncertain about which symptoms to prioritise. There continues to be no clear consensus on which methods for early satiety management worked. In both cohorts, a little and often eating approach was reported to be beneficial on some occasions. Physiologically, it remains unclear whether this would be an effective intervention.

If early satiety remains untreated, the burden of an untreated symptom, as well as the potential impact of the resulting weight loss, can cause undue psychological distress. This can result in a reduced QoL, inability to engage in decisions about their treatment as well as making coping with their cancer more challenging.[478, 479] This is especially relevant given that most reported their early satiety did cause distress. This was not the same in the advanced cancer group, where they reported that it did not cause distress. Another possible explanation is that those with advanced cancer have greater baseline distress than those at

an earlier stage of cancer, possibly as a result of their anticipated death.[480] This results in those with advanced disease being more concerned about their death than current nutritional symptoms. This is further evidenced by only participants in the advanced cancer cohort describing their early satiety as 'severe'.

Another difference was that early satiety appeared to usually last less time in those on active treatment compared to advanced cancer. One possible cause of this is the multiple medications used in advanced cancer, including opioid analgesia, that slow gastric emptying[481], which may result in higher severity of early satiety.[482] It may also perhaps be due to the baseline higher symptom severity in those with advanced cancer.[483] The ability of admission to a palliative care unit to reduce symptom severity should also be noted.[484] While early satiety was unlikely to be directly treated, the treatment of other symptoms or reduction in psychological distress may have reduced the severity of early satiety and there may have been a greater disparity in length of time if participants were assessed on admission to the PCU. While there are age-related changes in appetite regulation, the median ages for both cohorts were similar and therefore it was unlikely to be a factor.

6.5.3 Descriptions of Early Satiety

While many of the individual components of early satiety are different between the two cohorts, the themes identified in the description of early satiety provided by both cohorts were similar. Both had themes of 'distress', 'bloating', 'loss of enjoyment', and 'inability to eat'. These final two themes are likely to have a major psychological impact. Eating is an incredibly significant part of people's daily lives and is often part of social meetings or celebrations.[485] There may also be some psychological impact of bloating, as issues surrounding self-esteem and body

image have been shown to have major psychological implications.[486-488] Finally, distress has been shown to affect patient outcomes in cancer.[489, 490]

The direct association between early satiety and distress has not previously been established in the literature. Other NIS, such as nausea and anorexia, have been shown to precipitate distress in cancer. They have also been shown to affect caregivers for the patient with cancer. This distress in caregivers can cause them to encourage more nutritional intake, which can cause some conflict.[491] It is difficult to determine the impact of early satiety on distress, as while it was a common theme identified in patient descriptions, it did not appear to universally cause distress.

Interestingly, participants receiving active treatment also highlighted the theme of 'health concerns' related to their early satiety. As a result of this concern, some force themselves to eat more than their point of satiation. Therefore, this theme is likely associated with that of 'loss of enjoyment'. For those concerned with their health, eating is no longer about enjoyment, but instead about maximising nutritional intake to try and maximise treatment potential. This is likely to cause more psychological stress while fixated on maximising intake. While this approach may help minimise the impact of early satiety on nutritional status, although this has not been investigated, it does not address the hedonic or social components of eating.

6.5.4 The Need For Treatment For Early Satiety

Although it is likely to be of benefit to patients to have individualised advice from a dietitian, staffing difficulties and timely referral are a challenge in this regard. Therefore, some general evidence-based advice could also be beneficial, particularly for those living with advanced cancer outside of the hospice setting.

For those with advanced cancer, it is particularly important that this advice is based on a non-pharmaceutical intervention. This is because polypharmacy is commonplace in this cohort already with prevalence between 13% and 92%[492] and adding to this may prove counterproductive. Not only is polypharmacy common, but oftentimes patients with advanced cancer are left on unnecessary medications.[493] This is especially important given the negative associations between polypharmacy and poorer health scores[494], falls,[495] hospitalisation[496], poorer nutritional status[388] and mortality.[497, 498]

Drug-to-drug interactions are also a risk in cancer, further justifying the need for nonpharmaceutical intervention studies. This is particularly relevant given that the current ESPEN guidelines recommend the start of prokinetic agents.[386] Metoclopramide has the potential to interact with commonly used medications in palliative care, such as causing a higher and earlier peak of levodopa[499], reducing the mean AUC of digoxin[500] and increasing aspirin absorption of aspirin resulting in salicylate toxicity.[501] Careful consideration is needed in the prescribing of these medications for early satiety.

With this in mind, the most effective management based on this study was adopting a little and often approach to eating. This is similar to the current advice for management of anorexia where a high-protein, high-calorie, nutrient-dense diet is recommended.[502] It would be beneficial to investigate whether this intervention would be beneficial for early management of satiety. One difficulty with this is that nutritional support for cancer patients in palliative care is somewhat controversial. Given that the focus in palliative care is to maximise QoL for patients and their families,[503] there are ethical considerations for interventional trials in this cohort. ESPEN guidelines recommend offering nutritional support in

patients with advanced cancer only after careful consideration and discussion with the patient and evaluating the burden of nutritional support.[27] There are proven emotional issues surrounding patients and their families around eating in advanced cancer[504, 505] and so enrolling these patients in an interventional trial would need to be carefully considered. It may be beneficial to trial an intervention in those with early satiety at an earlier stage of disease, like the above cohort of patients receiving anticancer treatment. Once there is a non-pharmaceutical intervention identified, it is justifiable to then trial in advanced disease and evaluate any improvement in QoL in the patient or their families.

6.5.5 Clinical Implications

A clear implication from the results of this study is that early satiety is highly individual across the cancer trajectory. Several aspects of early satiety were unique to the participant. While gaining that level of detail regarding a single symptom is not practical, and arguably not an appropriate use of time, certain aspects were highly individualised that may impact the advice given. Such factors include at what time of day they experience it, co-occurring symptoms, do certain foods induce early satiety more than others and what methods have they tried previously. These are useful pieces of information to help tailor management advice. This individualised, patient-centred approach has been shown to improve health outcomes and reduce the cost of healthcare services.[506-508]

Acknowledgement of the importance of early satiety not only in clinical outcomes but also in psychological impact is important for clinical practice. As discussed above, the importance of eating goes beyond the physical need for nutrition. This also goes beyond that of early satiety and encompasses all NIS associated with cancer. Changes in food choices, avoiding social gatherings due to fear of NIS

impacting intake, loss of enjoyment of eating, and that these NIS cause distress and fear for their health are all as important as the physical impact of these NIS. Further qualitative research into the influence of these NIS on psychological health is needed to better understand the needs of patients with cancer. This research should not be limited to those undergoing treatment, but also a longitudinal assessment of the impact of long-term symptoms post-treatment. With this information, nurses, physicians, and dietitians can provide the appropriate information to manage the physical and psychological impact of these NIS. There may also be a benefit to a symptom management and rehabilitation clinic for those with cancer to address these NIS.

While not evaluated in this study, there may be some benefit in evaluating the distress caused by NIS in cancer. There are several tools for assessing the intensity of individual symptoms such as pain[509], fatigue[510], and nausea.[511] Some tools assess distress related to the individual symptoms, but there are fewer that assess distress of multiple symptoms. Examples of some scales that do assess distress include: Symptom Distress Scale[512, 513], Memorial Symptom Assessment Scale[514], and the Rotterdam Symptom Checklist.[515] These scales however, do not include all potential symptoms that may cause distress, namely early satiety is not included in any. The development of a symptom assessment measure that includes early satiety would prove to be beneficial for patients with cancer. There are challenges associated with this as if a patient is asked to rate too many symptoms, they me feel overwhelmed and do not accurately report their distress. Therefore, the tool in question may be limited to NIS or may even be a verbal report of 0-10 on how they would rate the distress caused by NIS identified in the abPG-SGA.

6.5.6 Strengths and Limitations

This questionnaire was designed to extract the individual experiences of those who suffer from early satiety. It was designed to be a quick tool that could be administered to patients with cancer that could be easily completed while also gathering enough information to be relevant. This allowed for information to be gathered in significantly less time, and being less of a burden, compared to a qualitative interview. A further benefit of this tool was that it could be administered while participants were on their treatment and allowed all study assessments to be completed in one day. Finally, from a practical perspective, asking participants to come to a hospital on days they were not scheduled for qualitative assessment was considered especially difficult during COVID-19.

The main limitation of this tool is that it is not validated. No similar tool has been developed to gather the patient experience of a symptom in this detail, let alone of early satiety. As discussed, qualitative interviews were considered but deemed impractical by the research group. In addition to this, it was hoped that the data extracted from this tool could guide questions to be asked during qualitative assessments in the future. Another limitation of this tool is that it requires recall ability. To combat participants not completing the questionnaire or giving an answer that they were not confident in, “don’t know” options were included as a possible response. The development of a tool that assesses early satiety while the participant feels it or after it is induced may also prove beneficial for those who may not be able to recall it in detail.

6.6 Conclusions

Experiences of early satiety not only differ individually but show different trends depending on the cancer stage. One commonality is that patients are not routinely screened for early satiety and are inconsistent in their self-reporting of the symptom. Common themes across the cancer trajectory are that early satiety is related to ‘distress’, ‘bloating’, ‘loss of enjoyment’, and ‘inability to eat’. Those receiving anticancer treatment were also concerned about the health implications of early satiety. This study further demonstrates that everyone’s experience of early satiety is different, and that generic management advice is unlikely to benefit everyone with early satiety. Instead, individualised, patient centred care is preferred and so all patients should be screened for early satiety and receive individualised nutrition counselling from a registered dietitian. Not only should patients with cancer be screened for early satiety, among other NIS, but there is likely benefit in examining distress caused by these symptoms.

7 QUALITY OF LIFE, PHYSICAL HEALTH, AND FUNCTIONAL ABILITY IN CANCER AND THE IMPACT OF EARLY SATIETY

7.1 Introduction

This Chapter reports on findings from a study that examined the impact of early satiety on Quality of Life (QoL) and physical function in patients with cancer attending for their anticancer treatment. Since early satiety appeared to influence malnutrition in Chapter 4, a deeper exploration of the impact on physical function seemed intuitive. Early satiety also caused some to have reduced QoL in Chapter 6 and thus an evaluation with a validated tool allowed for a more accurate measure of the association between early satiety and QoL.

Quality of life in cancer is a multidimensional concept that carefully evaluates four key areas of physical, functional, emotional, and social well-being.[516] Measurement of QoL in cancer plays a potentially key role in many components of cancer care. First, it aids in clinical decision-making. It has also gained increasing popularity as a key patient-reported outcome in clinical trials. Decreased QoL is influenced by several factors in cancer and is present in all types of cancer and at all stages of cancer care.[517, 518] Symptoms play a huge role in determining QoL in cancer patients.[519] There is some evidence that the treatment of NIS can improve QoL.[520] The direct impact of early satiety on QoL was highlighted in Chapter 3, early satiety only reduced QoL when accompanied by anorexia.[318] A second investigation into the effect of early satiety on QoL seemed appropriate.

Quality of life is, by definition, a subjective experience. This makes it a challenging aspect of cancer care to assess as it cannot be quantified by an objective assessment. This is further highlighted by Tchekmedyian and Cella, who admit that QoL is impossible to validly assess given the subjective nature of QoL. Therefore, it is analysed using a set of defined quantifiable aspects. There are

several tools that evaluate QoL, but for this Chapter, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was used as it is one of the most widely used assessments.[521]

Another uncertainty is the impact of early satiety on physical function in patients with cancer. While early satiety affects HGS and physical strength, little is known about its effect on physical function. This is a key indicator of overall patient health status and prognosis.[522] Patients with a greater symptom burden are associated with decreased functional capacity[523], thus this study aimed to investigate the association between a single symptom of early satiety and physical function.

7.2 Aims And Research Questions

7.2.1 Aims

- Evaluate QoL and functional status of patients with cancer receiving active treatment.
- Determine which symptoms, including early satiety, impact QoL.
- Determine which symptoms, including early satiety, impact functional capacity.

7.2.2 Research Questions

- What is the QoL in patients receiving anticancer treatment?
- Are patients receiving anticancer treatment at risk of functional impairment?
- What impact does early satiety have on QoL and functional ability in patients receiving active treatment for cancer?

7.3 Methods

7.3.1 Patient Selection

Recruitment took place in the Oncology Day Unit at Tallaght University Hospital Dublin for patients receiving active treatment. These evaluations were deemed too burdensome for patients with advanced cancer and therefore were not performed. Inclusion and exclusion criteria are presented in Table 7.1.

Table 7.1 Inclusion and exclusion criteria for Chapter 7

INCLUSION CRITERIA
• Diagnosis of cancer receiving anti-cancer treatment
• Age > 18 years old
• Able to understand and speak English
• Ability to provide signed witnessed signed consent
EXCLUSION CRITERIA
• Current or previous diagnosis of gastroparesis or dementia
• Presence of a pacemaker
• Unable to complete study assessments
• Participation deemed inappropriate by the consultant or nurse

7.3.2 Recruitment

Details on the methodology for data collection are discussed in Chapter 2. QoL was assessed using the EORTC QLQ-C30 assessment. Function was assessed using multiple assessments that included handgrip strength (HGS), a 30-second sit to stand (STS) and a timed up and go (TUG) test. Body composition was assessed using the Tanita model BC-418. Additional information regarding hunger, fatigue, and ability to eat was gathered using a visual analogue scale (VAS)

7.4 Results

7.4.1 Demographics

The demographics for this cohort are similar to that of Chapter 4. This chapter only refers to those receiving active treatment. Not all participants who were considered suitable completed the physical assessments. Some were unable due to the space dedicated for the assessments being used at the time of participation, and some reported that they felt too weak for them. Most (n=41) were able to complete the HGS, STS, and TUG. Of the nine unable to complete the physical assessment, three had early satiety and six did not. Demographic data for those able to complete the physical assessments are presented in Table 7.2. All participants (n=50) completed the VAS and the EORTC QLQ-C30.

Table 7.2 Demographic data for those that completed the functional assessments (n=41)

	Total Cohort		Early Satiety	
Variable	**n**	**%**	**n**	**% of total**
Sex				
Male	29	71	11	38
Female	12	29	2	17
Age (median, range)	65	(27-78)	68	(27-78)
Over 65 Years	20	49	7	35
Type 2 Diabetes	5	12	3	60
Cancer type				
Urological	16	39	5	31
Upper GI	11	27	6	55
Lower GI	8	20	0	0
Lung	3	7	0	0
Melanoma	3	7	2	66
Metastatic disease	29	71	11	38
Lymph Nodes	10	24	6	60
Lung	10	24	3	30
Bone	7	17	3	43
Liver	5	12	2	40
Previous Treatment				
Chemotherapy	26	63	9	35
Surgery	17	41	3	18
Radiation Therapy	10	24	4	40
Immunotherapy	3	7	1	33
Current Treatment				
Chemotherapy	31	76	10	32
Immunotherapy	11	27	4	36
Surgery	3	7	2	66
Radiation Therapy	2	5	0	0
Hormone	1	2	1	100
Medications				
Corticosteroid	22	54	8	36
Vitamins	12	29	3	25
Opioid	5	12	2	40
Prokinetic	2	5	0	0

7.4.2 Visual Analogue Scale

7.4.2.1 ***'How Hungry Do You Feel Right Now?'***

The median response to Question 1 in the entire cohort was 2.1 cm (range 0-10). The median response from those with early satiety was higher (2.15cm) than those without (1.75 cm), however, it was not significant (p=0.546). There were no significant differences in the response based on sex (p=0.916), being over 65 years of age (p=0.719), or the presence of metastatic disease (p=0.660). There was no difference in responses from those who were and were not at malnutrition risk (p=0.992). There was a trend toward those with low STS reporting decreased hunger (p=0.071).

7.4.2.2 ***'How Sick Do You Feel Right Now?'***

The median response for the cohort was 0.3 cm (range 0-7.5). Those with early satiety had higher responses (0.65cm) compared to those without (0.3cm) (p=0.418). There were no significant differences in response based on sex (p=0.748), being over 65 years of age (p=0.427), or the presence of metastatic disease (p=0.236). There was no difference in responses from those who were and were not at malnutrition risk (p=0.176). Participants with a higher QoL score reported significantly reduced sickness (p=0.005). Those who reported nausea (p=0.102) or vomiting (p=0.115) were no more likely to report sickness.

7.4.2.3 ***'How Pleasant Would It Be To Eat Right Now?'***

The median response for all was 3.85 cm (range 0-10). Median responses for participants with early satiety were higher (4.25 cm), but not significant (p=0.231) compared to those without early satiety (3.1cm). There were no significant differences in response according to sex (p=0.849), being over 65 years old (p=0.669), and the presence of metastatic disease (p=0.816). There was no

difference in responses from those who were and were not at malnutrition risk (p=0.449)

7.4.2.4 'How Much Do You Think You Could Eat Right Now?'

The median of all participants was 3.2cm (range 0-10). Those with early satiety had a lower response (2.8cm) compared to those without (4.05cm), however it was non-significant (p=0.779). There was no significant difference in response based on sex (p=0.340), being over 65 years of age (p=0.907), presence of metastatic disease (p=0.557). There was no difference in responses from those who were and were not at malnutrition risk (p=0.0.786). Participants with low STS reported less ability to eat (p=0.022).

7.4.2.5 'How Full Do You Feel Right Now?'

The median response for all was 4.2 cm (range 0-10). There was no significant difference (p=0.640) between those with early satiety (4.1cm) and those without it (4.2 cm). Although not significant (p=0.061), females reported a higher median response compared to males, being over 65 years old (p=0.662), and the presence of metastatic disease (p=0.765). There were no differences in responses from those who were and were not at risk of malnutrition (p=0.332)

7.4.2.6 'How Sleepy Do You Feel Right Now?'

The median response for the cohort was 2.6 cm (range 0-10). There were no significant differences (p=0.843) in responses from those with (2.0cm) and without (2.6cm) early satiety. There was no significant difference in response according to sex (p=0.124). Participants over 65 years of age (p=0.035) and those with metastatic disease (p=0.022) were less likely to report being tired. There were no differences in responses of those who were and were not at risk of malnutrition (p=0.954). Those with an increase in QoL reported feeling less

sleepy (p=0.011). There was no association between those who reported fatigue on abPG-SGA and reported sleepiness (p=0.802).

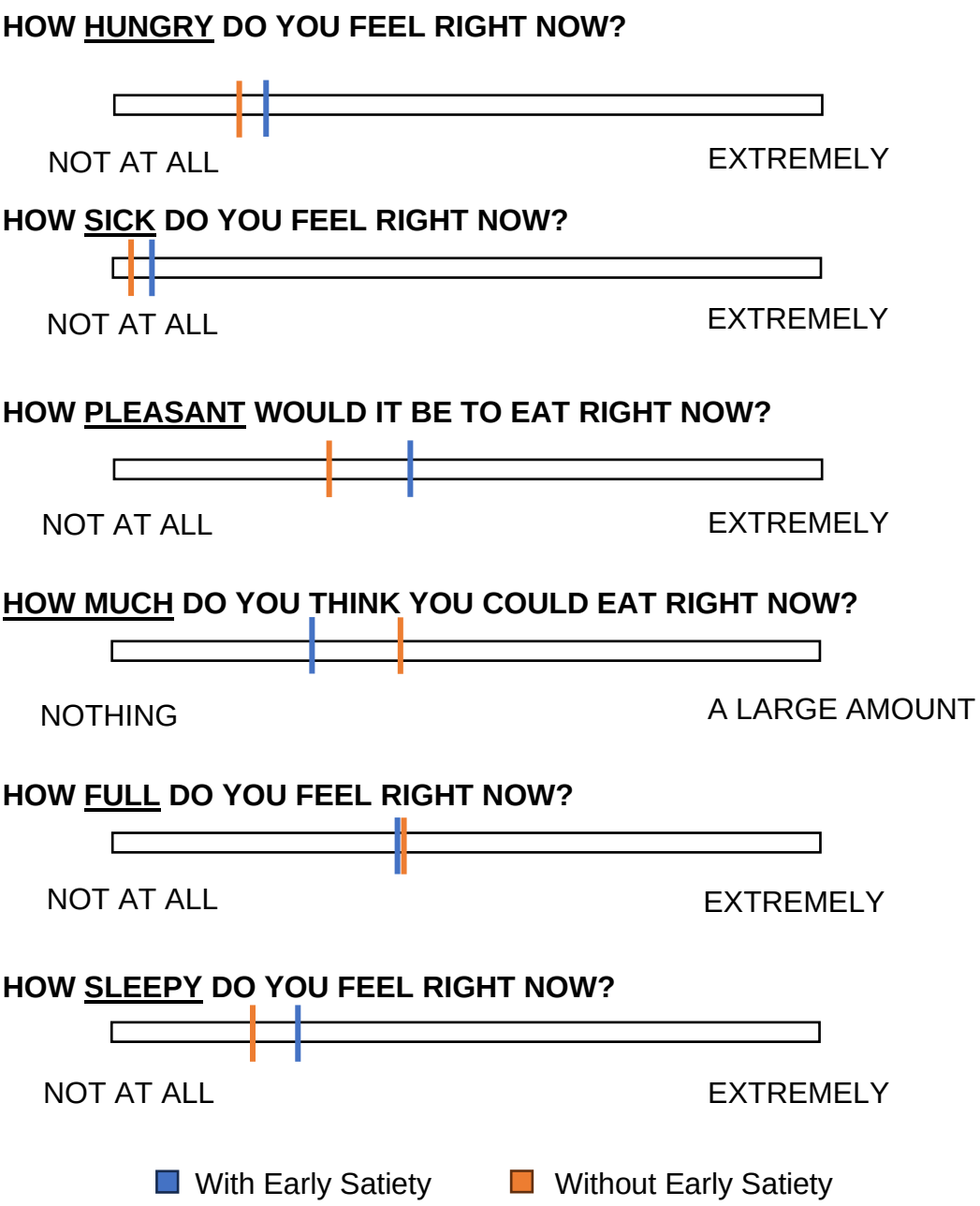


Figure 7.1 Median visual analogue scale responses differentiated by early satiety

7.4.3 Functional Capacity

As highlighted, the functional capacity assessment was conducted separately to the questionnaire-based assessments to ensure standardisation of assessment conditions. Due to this space also being used by other members of the ODW, these assessments were not possible for all participants, however most (n=41) successfully completed the assessments.

Table 7.3 Functional assessment results of the total cohort, as well as those with and without early satiety

	Total Cohort		With Early Satiety		Without Early Satiety	
Variable	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**
Handgrip Strength (kg)	31	(12-54)	29	(18-49)	31	(12-54)
Low EWGSOP2	25	(12-29)	25	(18-29)	17	(12-25)
Low Predicted	29	(12-49)	29	(18-49)	30	(12-47)
Sit to Stand (n)	11	(7-25)	11	(8-25)	11	(7-14)
Low STS	10	(7-14)	10	(8-14)	10	(7-14)
Timed Up and Go (sec)	8.28	(4.94-16.71)	8.28	(5.75-10.28)	8.18	(4.94-16.71)
Fat Free Mass Index (kg/m^2)	16.7	(12.6-21.8)	17.4	(12.6-21.8)	16.2	(13.7-21.8)

7.4.3.1 ***Handgrip Strength***

Mean HGS for males in this cohort was 36kg (SD=7.66) while for females it was 19kg (SD=3.37). There was no significant difference in HGS between those with and without early satiety (p=0.504).

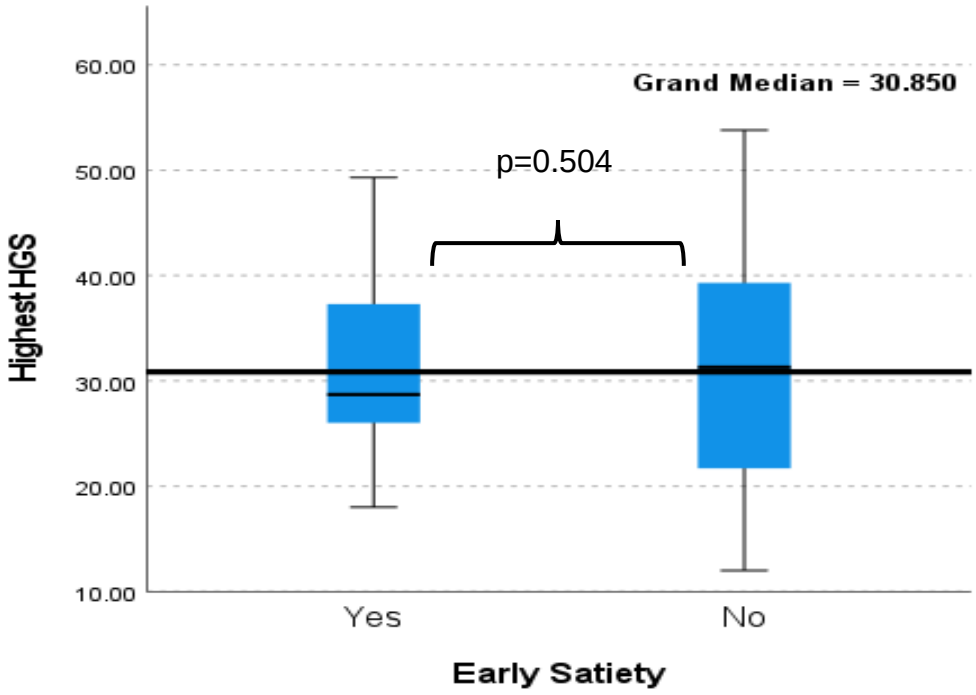


Figure 7.2 Distribution (median and range) for the highest handgrip strength differentiated by presence of early satiety

There were no significant differences between mean left (p=0.099), mean right (p=0.055) or highest (p=0.057) HGS scores based on the risk of malnutrition. Male participants had significantly higher grip strength compared to females (p=<0.001). The HGS values were significantly higher in those under 65 years of age (36.1 kg) than in participants >65 years of age (27.1 kg) (p=0.006). Neither being over 65 years of age (p = 0.211) nor having early satiety (p=0.204) were associated with low HGS based on the EWGSOP2 cutoff values. There were no significant differences in HGS between the types of cancer (p=0.424). Participants with low HGS according to EWGSOP2 were more likely be malnourished (p=0.029), however, low HGS from predicted values were not (p=0.760).

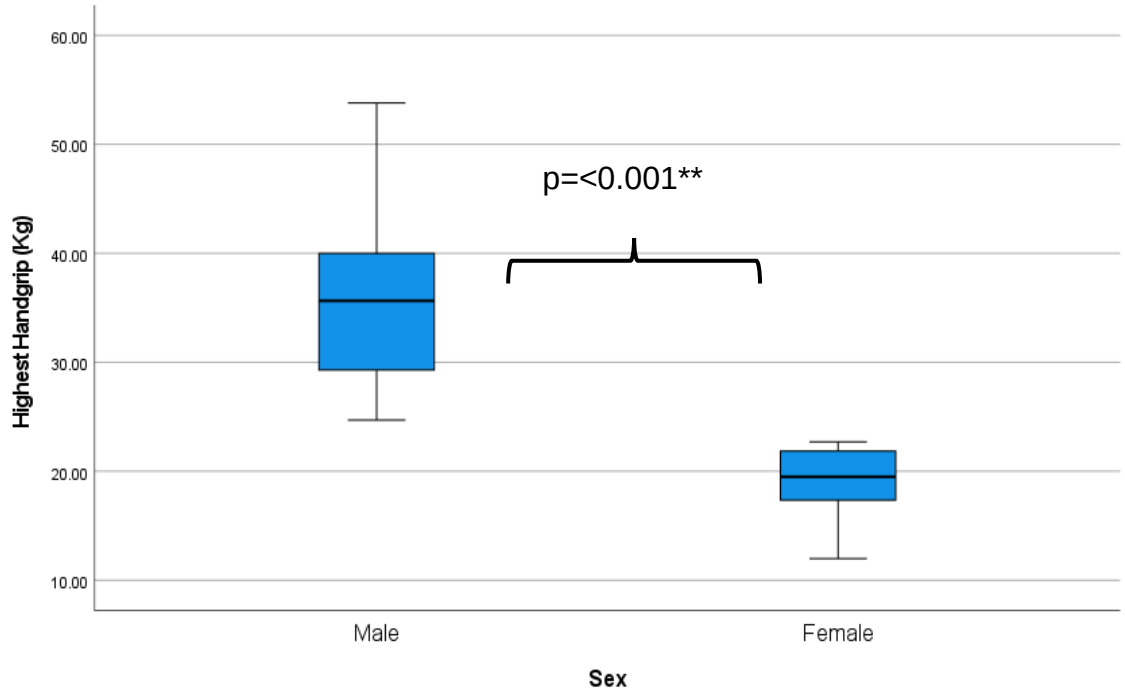


Figure 7.3 Distribution (median and range) for the highest handgrip strength differentiated by sex

HGS based on predictive equations ranged from 29-51kg for males and 16-28kg for females. More than a quarter (27%) had met their predicted HGS based on their age, weight, and height, resulting in most being classed as low HGS. Neither sex (p=0.387) nor age (p=0.748) was associated with low predicted HGS. The presence of early satiety was not associated with low predicted HGS (p=0.262). Low predicted HGS was not associated with risk of malnutrition in this cohort (p=0.746). Low predicted HGS was not associated with a higher number of symptoms in the OSQ (p=0.054) or the number of symptoms in the abPG-SGA (p=0.712). It was associated with the reporting of any symptoms in the OSQ (p=0.023). Low predicted HGS was not associated with low STS (p=0.180).

7.4.3.2 Sit to Stand

The median STS value for those with early satiety was 11 (range 8-25) and without early satiety was also 11 (range 7-14). The median for the entire cohort was also 11. There were no significant differences in STS between those with and without early satiety (p=0.940).

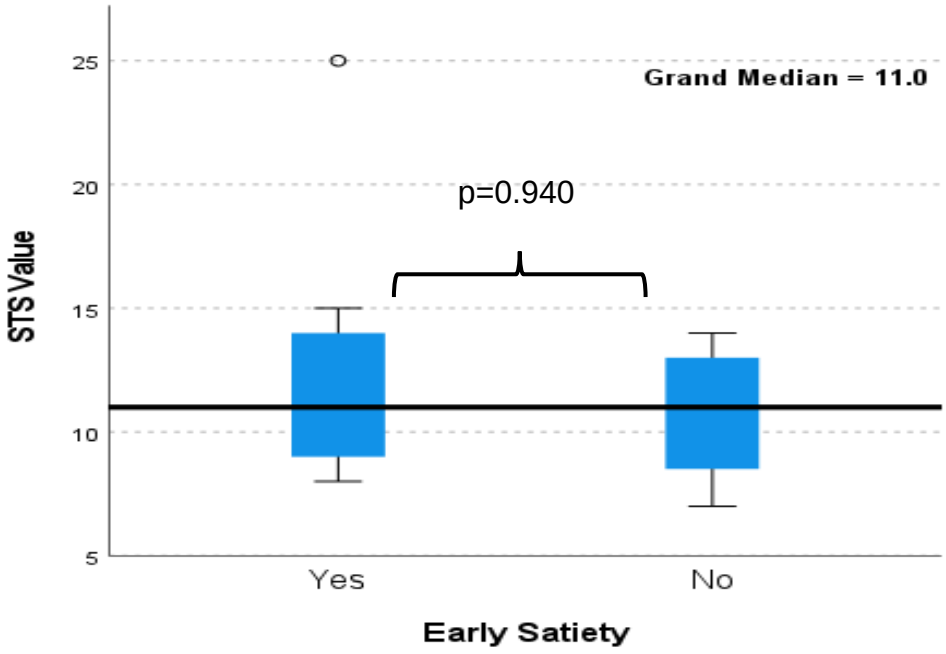


Figure 7.4 Distribution (median and range) for Sit to Stand values differentiated by presence of early satiety

Males had significantly higher STS compared to females (p=0.025). The median STS value for participants >65 years of age (10) was significantly lower than those under 65 (12) (p=0.029). The median value for those younger than 60 years was also 12.

Most (70.7%) of participants appeared to be at risk of falls due to their low STS. There was no significant difference in the risk based on STS between those with

and without early satiety (p=0.868). Although not significant (p=0.081), there was a trend toward participants over 65 and having a low STS. There were no significant differences in the low STS values based on the EWGSOP2 cut-off points for sarcopenia in those with or without early satiety (p=0.824). While not significant (p=0.052), there was a trend toward females being more likely to have low STS based on the EWGSOP2 cut offs for sarcopenia. Low STS was not associated with malnutrition (p=0.599).

7.4.3.3 Timed Up and Go

Almost all participants (93%) were classified as having normal TUG. None of the three with a low TUG reported early satiety. The median TUG time was 8.24s. The median TUG times for those with (8.28s) and without (8.18s) early satiety were not significantly different (p=0.544). Females had a longer TUG time (8.91s) compared to males (7.91s); however, it was not significant (p=0.258). Unsurprisingly, those >65 years of age had a significantly longer TUG compared to participants under 65 years old (p=0.018). Participants with and without metastatic disease had similar TUG times (p=0.915). There were no significant differences in TUG time based on risk of malnutrition (p=0.268), HGS (p=0.238), or diagnosed malnutrition using GLIM (p=0.828). No participants reached the EWGSOP2 cut off (≥20s) for low TUG.

7.4.3.4 Bioelectrical Impedance

Due to some technical issues with the bioelectrical impedance analysis machine, as well as challenges with space on the ODW, not all participants were able to complete the BIA. Of the 50 participants, half were able to complete the BIA (19 males and 6 females). Of the 16 participants with early satiety, 7 completed their

BIA. The median percentage body fat for the cohort was 36.3%. For males it was 33.1% and for females it was 36.1%. This difference was non-significant (p=0.121). Median FFMI (FFM (kg) / height $(m)^2$) for males was 17.41kg/m^2 and for females, it was 15.39kg/m^2. The FFMI was significantly higher in males than females (p=0.011). FFMI did not differ significantly between those with and without early satiety (p=0.440). There was also no difference in FFMI based on malnutrition (p=0.374).

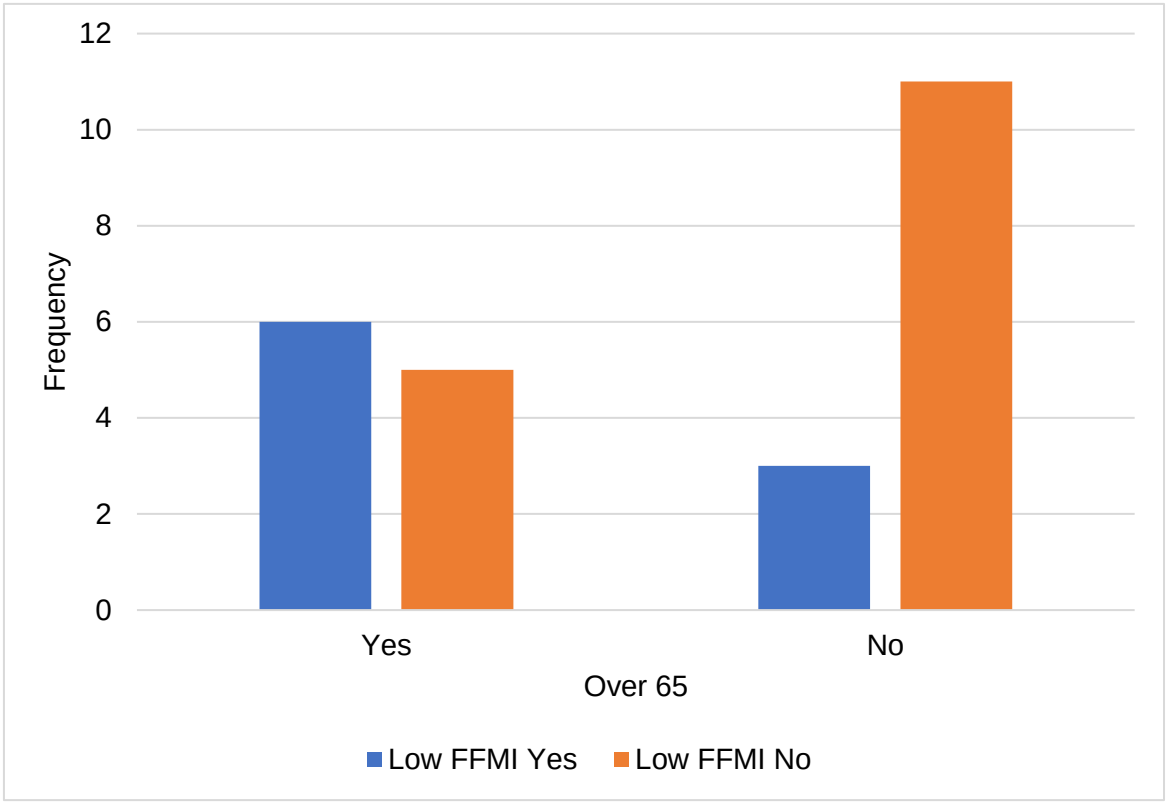


Figure 7.5 Presence of a low fat free mass index differentiated by being over 65 years old

7.4.4 Quality of Life

Quality of life data for the cohort are presented in Table 7.4. The scores for most domains were similar to reference values for both mean and median. Mean scores for physical functioning, nausea and vomiting, pain, dyspnoea and financial difficulties reached the threshold for clinical importance. Only the domains of pain and dyspnoea reached the threshold for being clinically important using median scores.

Table 7.4 Components of the EORTC QLQ-C30 compared to reference values for all cancers from Scott et al.[524]

QoL Domain	Ref Mean	Cohort Mean	Clinical Importance	Ref Median	Cohort Median	Clinical Importance
Global health	61	64	N/A	67	67	N/A
Functional Scales						
Physical Functioning	77	82	Yes	80	87	No
Role Functioning	71	72	No	83	67	No
Emotional Functioning	71	80	No	75	83	No
Cognitive Functioning	83	84	No	83	83	No
Social Functioning	75	69	No	83	67	No
Symptom Scales						
Fatigue	35	35	No	33	33	No
Nausea And Vomiting	9	9	Yes	0	0	No
Pain	27	26	Yes	17	35	Yes
Dyspnoea	21	21	Yes	0	33	Yes
Insomnia	29	31	No	33	33	No
Anorexia	21	24	No	0	33	No
Constipation	18	17	No	0	0	No
Diarrhoea	9	16	No	0	0	No
Financial Difficulties	16	23	Yes	0	0	No

Table 7.5 shows the breakdown of each scale of the EORTC QLQ-30 where those with and without early satiety were compared. Participants with early satiety did not report significantly lower global health (p=0.129). There was a trend towards a significant association between early satiety and median EORTC QLQ-C30 score (rho=0.276), however, it did not reach statistical significance (p=0.052). The median score for those with early satiety was 67 while for those without it was 78 (p=0.010). They also had significantly higher symptoms scores (p=0.001). There were no significant differences in QoL (p=0.252) between those who reported early satiety did and did not reduce their QoL in the SEES.

Table 7.5 Components of the EORTC QLQ-C30 compared by the presence of early satiety

	EARLY SATIETY			
QOL DOMAIN	**Yes**	**No**	**Significance**	**Clinical Importance**
Global Health	50	67	0.129	N/A
Functional Scales				
Physical Functioning	80	87	0.140	Yes
Role Functioning	58	80	0.011*	Yes
Emotional Functioning	79	83	0.933	No
Cognitive Functioning	83	83	0.859	No
Social Functioning	67	67	0.542	No
Symptom Scales				
Fatigue	56	78	<0.001**	Yes
Nausea And Vomiting	100	100	0.233	No
Pain	67	92	0.016*	Yes
Dyspnoea	67	83	0.372	Yes
Insomnia	67	67	0.790	No
Anorexia	67	88	<0.001**	No
Constipation	83	100	0.087	No
Diarrhoea	100	100	0.547	No
Financial Difficulties	100	67	0.544	No

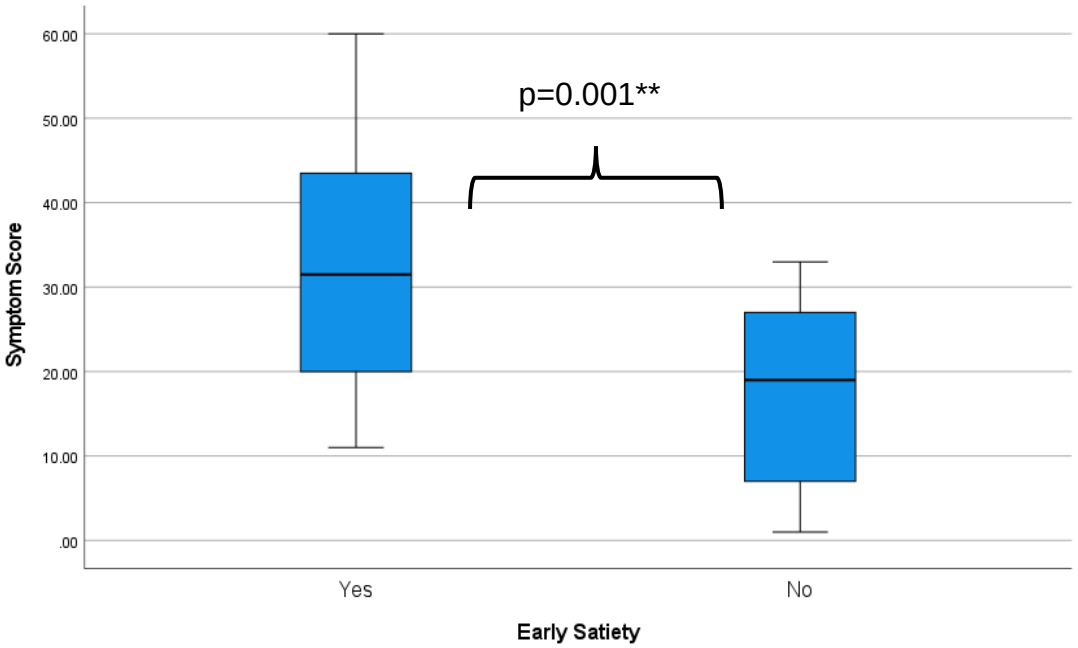


Figure 7.6 Distribution (median and range) for the EORTC QLQ-C30 symptom score stratified by the presence of early satiety

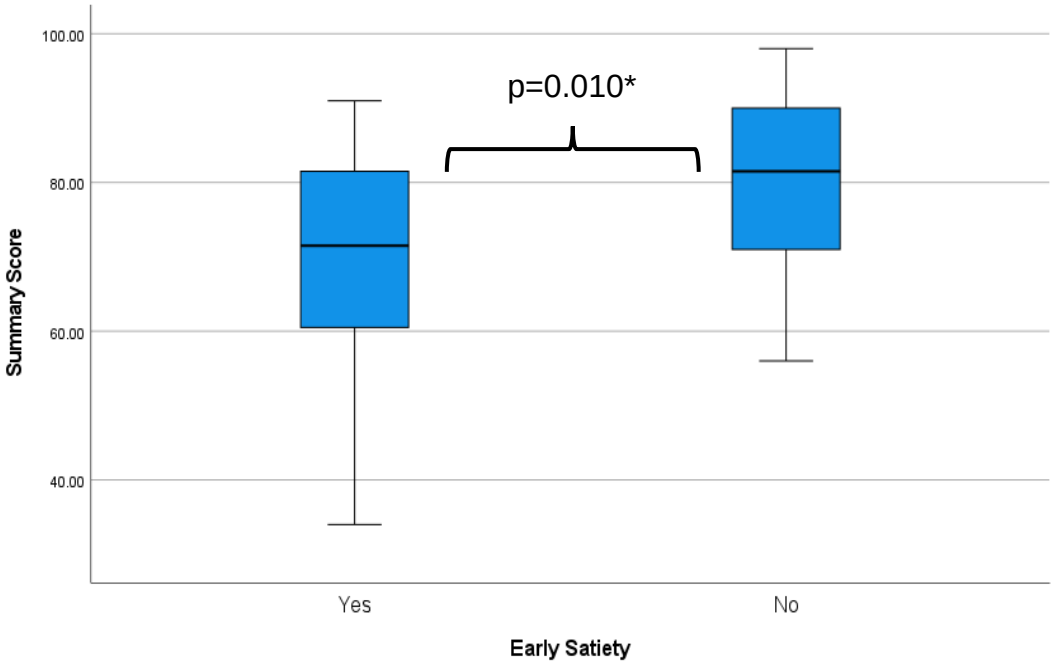


Figure 7.7 Distribution (median and range) for the EORTC QLQ-C30 summary score stratified by the presence of early satiety

There was practically no difference in QoL between males and females. The physical function domain was significantly reduced in females (p=0.027). Nausea and vomiting, dyspnoea and financial difficulties all reached the threshold for clinical importance in males. Physical functioning, nausea and vomiting, pain diarrhoea, and financial difficulties reached clinical importance in females (Table 7.6).

Table 7.6 Components of EORTC QLQ-C30 compared to the general population based on normative data from Nolte et al.[525]

	MALES			FEMALE		
QOL DOMAIN	**Reference**	**Present**	**Clinical Importance**	**Reference**	**Present**	**Clinical Importance**
Global Health	68	65	N/A	66	59	N/A
Functional Scales						
Physical Functioning	86	85	No	85	74	Yes
Role Functioning	84.5	75	No	84	65.5	No
Emotional Functioning	77	83	No	74	74	No
Cognitive Functioning	85	82	No	85	86	No
Social Functioning	84	70	No	86	64	No
Symptom Scales						
Fatigue	27	34	No	29.5	36	No
Nausea And Vomiting	6	8	Yes	6	10	Yes
Pain	22	22	No	23.5	34	Yes
Dyspnoea	15.5	23	Yes	16	15.5	No
Insomnia	24	30	No	27	31	No
Anorexia	10	24	No	10	24	No
Constipation	11	19	No	12.5	13	No
Diarrhoea	10	14	No	9.5	20	Yes
Financial Difficulties	10	20	Yes	11	31	Yes

Younger participants appeared to have a reduced QoL compared to those over 65 years. They reported a greater impact of all symptoms but constipation and in almost all functional scales, except physical functioning. Only the differences in insomnia (p=0.012) and emotional functioning (p=0.09) reached significance. There were no significant differences in any aspect of QoL based on the presence of metastatic disease or type of cancer. QoL summary score was significantly reduced in participants with anorexia (p=0.001), nausea (p=0.002), smell changes (p=0.003), and fatigue (p=0.028). The p values for demographics, symptoms, malnutrition, and functional capacity are outlined in Table 7.7.

Table 7.7 Quality of life scores compared by participant factors with subsequent p values

Variable	Quality of Life Domain	Summary Score	Symptom Score
Demographics			
Sex	N/S	N/S	N/S
Age	N/S	N/S	N/S
Metastatic Disease	N/S	N/S	N/S
Symptoms			
Anorexia	0.032*	<0.001**	0.001*
Nausea	N/S	0.002*	<0.001**
Vomiting	N/S	N/S	N/S
Constipation	N/S	N/S	0.036*
Diarrhoea	N/S	N/S	0.037*
Mouth Sores	N/S	N/S	N/S
Dry Mouth	N/S	N/S	N/S
Taste Changes	N/S	N/S	N/S
Smell Changes	0.002*	0.006*	0.008*
Dysphagia	N/S	N/S	N/S
Fatigue	N/S	0.028*	0.007*
Pain	N/S	N/S	N/S
Malnutrition			
Risk (abPG-SGA)	N/S	<0.001**	0.004*
Diagnosed (GLIM)	N/S	N/S	N/S
Functional Capacity			
Low Handgrip	N/S	N/S	N/S
Low Timed Up and Go	N/S	N/S	N/S
Low Sit To Stand	N/S	N/S	N/S
Low FFMI	N/S	N/S	N/S

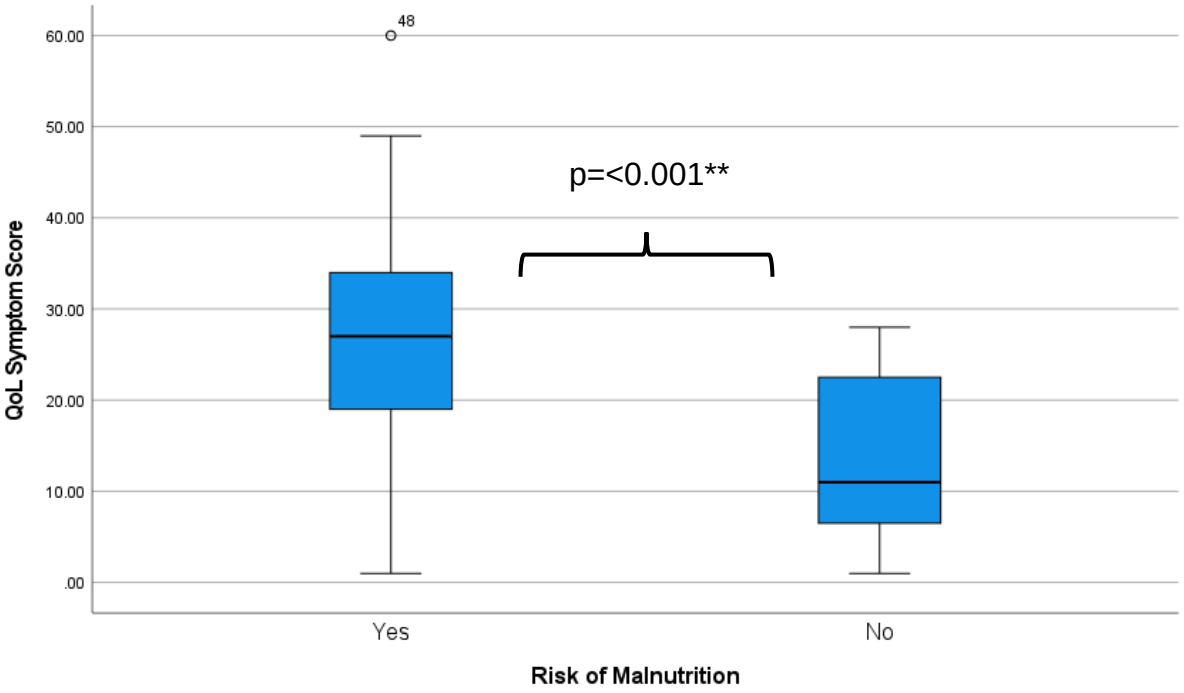


Figure 7.8 Distribution (median and range) for the EORTC QLQ-C30 symptom score stratified by risk of malnutrition

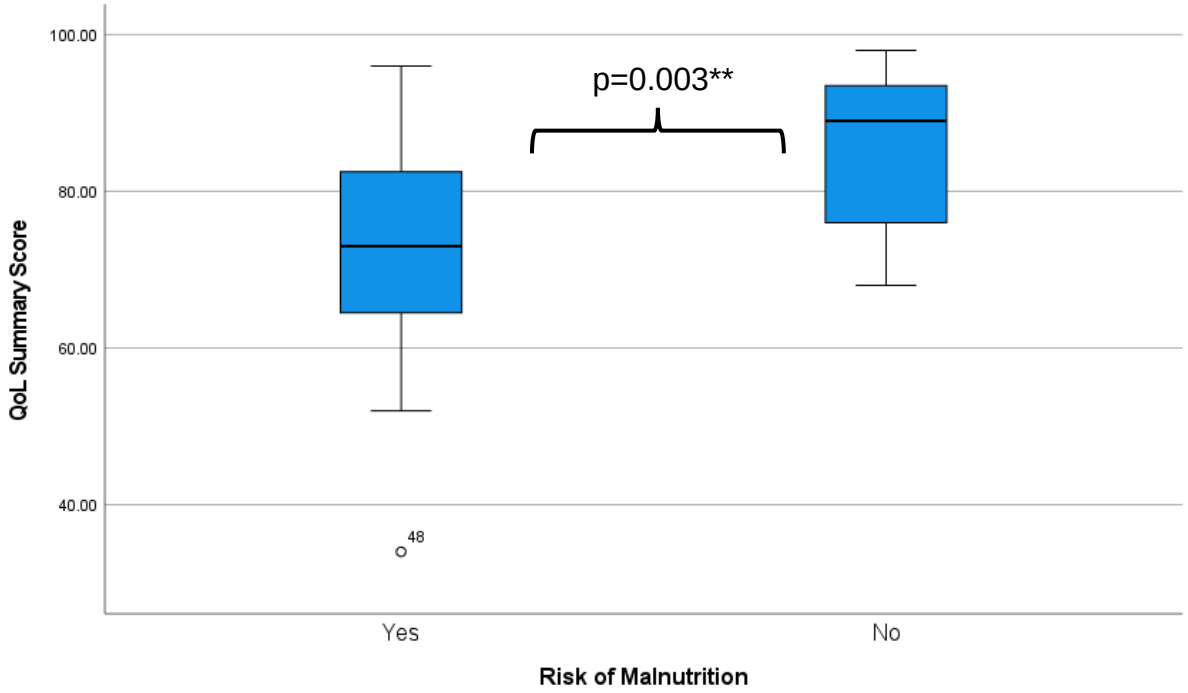


Figure 7.9 Distribution (median and range) for the EORTC QLQ-C30 summary score stratified by risk of malnutrition

7.5 Discussion

7.5.1 Functional Capacity

While not all the assessments of functional capacity showed significant results, there are still some associations worth exploring. One such assessment was the TUG. The times taken to complete this assessment were significantly shorter than previously described in the literature.[526, 527] This result is unlikely related to the younger cohort as those >65 had a shorter TUG time compared to what has been suggested for increased mortality and falls risk. One possibility is that the participants in this present study were at a relatively early stage of their cancer treatment. A likely cause is that older patients who may have scored higher TUG times were not recruited as they were deemed inappropriate by healthcare staff.

A surprising finding was the high number of participants at risk of falling according to STS. Unsurprisingly, older age is associated with an increased probability of falls.[528] There is a significant amount of research on the impact of falls on older people, including changes in oncological treatment[529], admission to a nursing home[530] and increased mortality.[531] One possible explanation for this high risk is that participants were fatigued when being evaluated. This is because the physical assessments were most often conducted post anti-cancer treatment. This is relevant given that chemotherapy, the most common treatment in this cohort, is related to a decrease in balance[532-534], which may have impacted STS.

While one limitation of the STS used here is that normative values for younger people are limited, the value chosen was only 1 stand greater than the value for those over 60 years old. Given the functional decline associated with aging, it was unexpected that younger adults would not meet this recommended threshold. With the median STS value for younger adults equal to the risk

threshold in those 70-74 years, the STS was significantly lower than expected. Research on the risk of falls in younger adults is limited compared to older adults. Possible causes of this risk of falls may include physical deconditioning due to their illness and treatment side effects as highlighted above.[535, 536] It is a key risk to identify in younger adults as many of them may continue to work during their treatment to financially support their families and they are more independent than older adults.[537] Loss of this independence due to injuries related to falls as well as the fear of falling may impact QoL.[538]

7.5.2 Impact of Cancer on Quality of Life

In this study, QoL was decreased compared to the general population. A cancer diagnosis can have a significant and multifaceted impact on QoL. It can also impact their loved ones. All domains of patient QoL can be impacted by both the malignancy and subsequent treatment. One is that there are several side effects of treatment that may reduce QoL, including symptom burden.[539] Another is that oncological treatment results in recurring hospital visits for an extended period of time.[540] Cancer can also lead to social withdrawal and feelings of isolation. This isolation can lead to feelings of loneliness and reduced social support. Cancer also places a huge financial burden on patients and their families which may also reduce QoL.[541]

There was a trend in the above results from this study that younger participants reported a poorer QoL compared to their older counterparts. Although not explored as part of this thesis, there are a number of potential explanations for this. First, younger individuals may face unique psychological challenges when given a cancer diagnosis. Cancer is perceived as common in later life and an

early diagnosis may lead to disruptions in life plans. It is also likely that their diagnosis will have a greater impact on their social relationships. It is also not surprising that there was a difference in the financial domain given the impact of cancer on younger adults.[542] Although insomnia is more common in older adults[543], it was more impactful on younger adults in this cohort. The cause of this impact was not assessed but may be related to the younger person having a greater requirement for sleep and that insomnia is closely associated with emotional and mental health issues. This is also likely why there was a greater impact on emotional function. Younger adults are also more aware of their emotional well-being compared to older adults. This trend is likely to change in the future given the increase in health promotion of mental health.[544]

This is important not only for psychological well-being but also physiological condition. Distress has been shown to increase stress hormones[545] which alter immune function[546] and may impact treatment tolerance. Furthermore, better QoL is associated with improved adherence to treatment in multiple conditions[547, 548], including cancer.[549, 550] QoL is also an important factor for prognostication.[551] Finally, as evidenced in the current study, patients at risk of malnutrition appeared to have a significantly reduced QoL. This association was not significant when assessed with diagnosed malnutrition. GLIM-diagnosed malnutrition has been shown to be closely related to QoL extensively in the literature which was not shown in this study.[552, 553] This is likely related to the small sample of patients with diagnosed malnutrition using the GLIM criteria. There was a greater disparity between abPG-SGA and GLIM malnutrition than in previous literature.[554, 555] Those with moderate to severe risk of malnutrition did have a statistically significant decrease in QoL which was an expected result.[556, 557]

7.5.3 Early Satiety And Quality Of Life

The impact of early satiety on QoL has also been shown previously in the literature.[218, 318, 332, 558] There are a number of possible reasons for this. One possibility is that the reduction in nutritional intake may lead to malnutrition, weight loss, decreased energy levels and increased susceptibility to infections, all of which may negative affect QoL.[559] Another possibility is that early satiety may impact the enjoyment of meals. This has been explained in more detail in Chapter 6 where this was one of the most common themes of the symptom experience for those with early satiety. Another possibility is that early satiety may limit their ability to engage in social eating interactions, such as sharing food or eating out. This leads to feelings of isolation and exclusion. Patients with early satiety may feel like they cannot attend events where food is the central focus as a result. This is a concern, as social isolation increases the risk of malnutrition[560], decreases nutritional intake[561] and results in earlier satiation during meals.[562] It may be due to the emotional impact of reduced nutritional intake. There is a well-established association between food and emotions, as well as the symbolic relevance of food for many.[563]

Early satiety may invoke negative emotions such as frustration or disappointment in their inability to eat. These emotions as a result of early satiety may reduce the psychological well-being of cancer patients. Finally, early satiety was associated with an increased symptom burden. Although this does not explain the direct association, a higher symptom burden has been shown to reduce QoL.[564] With this in mind, treatment of early satiety should be a priority to improve QoL.

7.5.4 Clinical Implications

In this study, QoL was assessed at a single timepoint and did yield some interesting results. There is however much more benefit in routinely assessing QoL. The QoL is transient and subject to change depending on a number of factors as highlighted previously. Therefore, evaluation of QoL should be repeated throughout their treatment. Given the multidimensional nature of QoL, it is recommended that valid and reliable tools be used rather than the development of a new assessment. Therefore, we recommend the continued use of the EORTC QLQ-C30. Patients can complete a copy of this assessment while on their oncological treatment as it is a short but thorough assessment. It may also be benefit to the QoL assessment prior to attending for treatment to allow appropriate treatment of the issues that reduce QoL. This could be done through an electronic portal for oncological patients. A recent randomised control trial of electronic monitoring of symptoms and QoL results in better symptom management, improved QoL and survival compared to usual care.[565]

Quality of life has become one of the most popular outcomes to evaluate in clinical research. Despite this, it is not routinely assessed in clinical practice. The benefits of assessing QoL in terms of patient outcomes were discussed previously. While there is undoubtedly benefit to further evaluation of QoL, there are some challenges with implementation in a clinical setting. For one, there is a lack of knowledge of the potential benefits of QoL assessment in clinical decision making.[566] In fact, patients themselves often consider maintaining QoL more important than survival time.[567] There has also historically been scepticism with regards to the specificity of QoL assessment.[568] Prior to implementing QoL assessment, the tool should also allow for easy to read and understand results.

That is one of the challenges of the EORTC QLQ-C30 is the need to convert raw scores to a scale of 0-100 to be understood clearly. There has been some work on identifying clinically relevant scores for domains within the EORTC QLQ-C30[569], however, more research is needed.

Although it was not significant in this study, there are benefits to the evaluation of HGS in cancer patients. It is a quick and cost-effective evaluation of muscle strength and, by proxy, nutritional status. Due to the limited space in most hospitals, the use of the STS and TUG evaluation in clinical practice is unsuitable. These tests also limit who can be assessed given the need for mobility to perform.

Finally, this study further highlights the impact of early satiety in patients with cancer. Not only was it impactful in terms of malnutrition and symptom burden in Chapter 4, but here it was associated with reduced QoL. There were also a number of other symptoms that significantly reduced QoL. As highlighted extensively in this thesis, the limited screening for symptoms in clinical practice is impactful and if not implemented, may result in continued decreases in the QoL of patients with cancer.

7.5.5 Strengths and Limitations

Although the 'gold standard' for a detailed QoL is an interview, this is not practical in most research settings. Therefore, we used a well-established and validated QoL tool. The use of the tool was also important since physician evaluations of QoL are normally less accurate.[570] Further strengths include the use of a dedicated area for assessment which allowed standardisation of equipment, distance and setting for evaluation. Another strength, similar to that of Chapter 4, was the use of clinically relevant/useful evaluations. While there was no formal evaluation of suitability for each of the assessments used, it allowed for a 'proof

of concept' to be carried out on the ODW to establish the appropriateness of further investigations into using these assessments in daily clinical practice.

There were some limitations with respect to the assessments and tools used. One clear limitation is that not all participants had the opportunity to complete all assessments due to space on a busy oncology unit and the equipment occasionally not working. A further limitation to the use of BIA is that the equations used for the estimation of body composition are highly specific for the device used. It possibly could be more beneficial to calculate the phase angle, which has recently become a popular BIA output due to its use in determining nutritional status and prognostication.[571] Body composition analysis was only taken at one time point, which is also a limitation. It would be interesting to see the longitudinal impact of early satiety on body composition.

This version of the STS also potentially introduces some measure of endurance given the multiple repetitions in a longer period than the five repetition STS. This version of the STS was chosen because it was believed that the longer time would allow for a wider assessment of ability levels. There are no normative values for STS in cancer patients, particularly those >65 years of age. A limitation in the analysis here is that below average STS is estimated rather than based on published values. The ability of the TUG to predict falls remains an area of contention.[572-574] It is noteworthy that these reviews included heterogeneous populations, varying length of follow up for predictive falls risk, and often had small cohorts.

Similar to the results presented previously, the statistical analysis of this data is predominantly exploratory in nature. Further exploration of these findings with a larger sample, controlling for confounders to QoL and functional capacity

assessments may yield alternative results. Despite this, these are relevant findings for the justification of exploring early satiety further in research while also highlighting the potential of early satiety to influence QoL.

7.6 Conclusions

This study investigated the impact of symptoms, including early satiety, on QoL and functional capacity in patients receiving active oncological treatment. Patients with cancer had a reduced QoL compared to their non-caner counterparts. Females had reduced, but nonsignificant, QoL compared to males. Symptoms of anorexia, early satiety, fatigue, nausea and smell changes were all associated with decreased QoL. Early satiety was associated with clinically important domains of emotional functioning, role functioning, fatigue, pain and dyspnoea. Patients at risk of malnutrition had a decreased QoL, but there was no difference when limited to those diagnosed with malnutrition using the GLIM criteria. This cohort had a significantly reduced TUG score and was subsequently identified as at risk for falls. There was no significant difference in HGS based on the presence of early satiety. There were no significant differences in VAS reports of hunger, fatigue, or ability to eat based on presence of early satiety. This study further exemplifies the impact of early satiety on patients with cancer.

8 CONCLUDING SUMMARY

8.1 Thesis Overview

Patients with cancer experience multiple symptoms throughout their cancer care that have both physical and psychological consequences. The author of this thesis noted that these patients often underreported their symptoms to their healthcare provider and reported more symptoms when assessed in detail. One symptom which patients reported on the ward routinely but had no name for, and instead described as ‘getting full after eating less than usual’ was common. Multiple different descriptions were used which fell under the term early satiety. When asked, no patients had heard of that term before. This led to an interest in determining how patients with early satiety in cancer described their experience of it, how is it best identified in a cancer cohort, and how impactful is it.

This thesis used a diverse suite of research methodologies and assessments, from a thorough evaluation of published literature using validated guidelines for scoping reviews to direct patient contact. Information was also collected on several aspects of cancer that early satiety may impact, including malnutrition, symptoms, physical health, and quality of life. No specific types of cancer were chosen to highlight that this symptom is present in a wide variety of cancers.

Chapter 3 was the first review using validated guidelines that looked at early satiety in cancer. The purpose of the scoping review was to organise any information relating to this symptom, as in the initial search, there was insufficient information to conduct a systematic review. Even with the nature of the scoping review, very little information was found relating to early satiety in cancer using broad search criteria. Although there were several key findings of the search, one of the biggest concerns that arose was the lack of a standardised assessment. This resulted in the risk that much of the information provided did not reflect the

results of true early satiety. Another key finding was that the PG-SGA was the most commonly used tool to identify early satiety where a validated tool was used. The abPG-SGA was therefore selected as the tool to identify early satiety throughout the thesis. It was also somewhat unclear as to the impact of early satiety in cancer.

This led to the development of a tool to assess how patients with early satiety described their symptom in Chapter 5. This tool was developed in collaboration with researchers and dietitians in the fields of oncology and palliative care. It was then piloted on patients admitted to the PCU and they also provided feedback on the questionnaire. Patients engaged well with the questionnaire and could take part in the research on this symptom. They provided feedback on the questionnaire length and reflected on its ability to truly capture their experience of early satiety.

This information led to the revision of the SEES and subsequent use in patients with advanced cancer and patients receiving active treatment for their cancer in an oncology day ward (Chapter 6). One key query was whether these cohorts at different stages of cancer describe the symptom in different ways. What we found instead was that there were individual differences in the symptom experience within the same cohorts. There were some commonalities in the experiences among individuals, but each patient's experience was unique to them.

Although we were keen to establish how patients described early satiety, we were also keen to establish the clinical importance of early satiety in cancer. In Chapter 4 whether there was a significant difference in symptom reporting in open symptom questioning and a symptom checklist was established. The risk of malnutrition via the abPG-SGA was also determined. This result was then used

to diagnose malnutrition using the GLIM criteria. Physical functioning and quality of life were measured in Chapter 7. The impact of early satiety on each of the above factors was established. The assessments that were chosen were the quickest and least burdensome for patients to minimise delay in leaving the ODW post-treatment.

8.2 Thesis Discussion

This thesis is the first body of work that we know of that investigated early satiety in detail. Chapter 3 provided a summary of the literature on early satiety in cancer. This was the first scoping or systematic review to examine early satiety. Arguably, the starkest result of this review was that despite the absence of limits in years, cancer type, population, or tool, there were so few studies identified that discussed early satiety in cancer. The author of this thesis was aware of the lack of clinical focus on this symptom, but the poor research focus further justified the investigation of this symptom in detail for this thesis.

One key result of the scoping review was multiple tools were used throughout the literature to identify early satiety. The most common validated tool was the PG-SGA. As a result, the abPG-SGA was used to identify early satiety throughout this thesis. This decision to use the abPG-SGA instead of the full PG-SGA was to better replicate a tool that could be implemented on a ward. It was used not only as a tool to identify early satiety but also to determine the risk of malnutrition. Finally, it is one of the recommended tools for appropriate use of the GLIM criteria[26], which allowed for the diagnosis of malnutrition. Another key finding was that early satiety was present at all cancer stages. This therefore allowed for the comparison of the symptom experience between advanced cancer and active treatment cohorts. Early satiety was not associated with cancer treatment, disease extent, or cancer site. Instead, not only was it present in all cancer types and stages, but it was also among the most common symptoms. In fact, much of the evidence found for Chapter 3 was in non-solid tumours. This suggests that early satiety is not just related to the tumours physically altering the GI tract, but also cancer itself as well as treatments.

An interesting result was that patients were not assessed for early satiety by their healthcare professionals. As a result, we compared the reporting of symptoms from open symptom questioning with the symptom checklist of the abPG-SGA. Symptoms are typically assessed using an unstructured discussion[575], similar to the OSQ. There were significantly fewer symptoms reported in the OSQ, which suggests the possibility of underreporting of symptoms in clinical practice, which has been shown in the literature.[576, 577] Despite early satiety being discussed throughout each PIL, there was a huge discrepancy between the frequency with which early satiety was reported in the OSQ compared to when assessed via the abPG-SGA. This is similar to the work by Homsi et al.[186], where systematic assessment resulted in significantly more symptoms. Another interesting consideration is that the list of symptoms used in this thesis was one-quarter of the length used by Homsi et al., and yet showed similar results that systematic assessment of symptoms yields more symptoms and information compared to patient-reported symptoms.

Despite how prevalent the symptom was in both cohorts of cancer patients, the lack of knowledge surrounding the importance of this symptom is clear. In a systematic review of symptom assessment tools, early satiety is rarely screened for. In a systematic review to identify the core set of symptoms that the National Cancer Institute recommends screening for during cancer trials[578], early satiety was neither recommended nor considered. Similar results were found in their recommendations for head and neck cancer.[579] In a review of the National Cancer Organisations' websites, significant gaps in information on early satiety were found, further compounding the point that there is little focus on the symptom despite its prevalence. Until early satiety is recognised as a symptom that

requires screening, there is unlikely to be any change in the clinical impact of early satiety. While there is no ideal symptom assessment tool, it is important to ensure that patients themselves are involved in the trialling of new tools on the ward.

Having patients actively participate in their nutritional care has been shown to increase energy and protein intake.[580] Despite this, there is often an underreporting of their nutritional status and concerns to healthcare staff.[389] There is strong evidence to suggest that many of these patients had not received nutrition counseling[581], however, it was not evaluated as part of this thesis. While referrals to the dietitian were not evaluated, early satiety was unanimously never assessed by healthcare staff. No patients with early satiety in either the active treatment or the advanced cancer cohort had been asked about their early satiety prior to engagement in this thesis. Most had also not reported their early satiety to their healthcare provider, which is in accordance with the literature. This suggests that the management tactics used were potentially not evidence-based and either self-derived or taken from media sources such as the Internet. [582, 583]

A key reason for the identification of the patient experience is that healthcare staff are often poor at predicting symptom severity compared to patient self-report.[584-586] This is a longstanding, important area for both patient satisfaction and outcomes.[587-590] Part of the difficulty in addressing the disparity is that both cohorts have different goals for reporting/identifying symptoms. Patients may report their symptoms to reduce the burden on their quality of life. For healthcare staff, the identification of symptoms is often to confirm a possible diagnosis, evaluate disease progression, investigate treatment compliance, and inform the treatment plan. Healthcare staff may not have screened for early satiety for

multiple reasons. One is that it is rarely included in screening tools. Another may be the result of a perceived lack of importance of early satiety. Another possibility is that it is underreported due to it being a subjective symptom. There appears to be a better reporting of objective symptoms than subjective symptoms.[591]

Early satiety was screened for using the terminology of 'feel full quickly' in the abPG-SGA. There were also 12 other NIS screened for that impacted nutritional intake in the last 2 weeks. Early satiety was significantly associated with the occurrence of anorexia, fatigue, nausea, taste changes, and vomiting. In the advanced cancer cohort, the associations were with nausea and vomiting, while anorexia trended toward significance (p=0.089). This differs from the results of Walsh and Rybicki[427] who reported that early satiety was in the 'Fatigue: Anorexia-Cachexia Cluster', while nausea and vomiting formed their own cluster. There is no consensus on the definition of symptom clusters in methodology or concept, and therefore it is difficult to determine the true symptom clusters. It is important to note that symptoms that cluster together do not necessarily share a common etiology.[592] It is challenging to compare the presence of early satiety as in a systematic review of symptom clustering in advanced cancer by Dong et al.[593], in the 33 studies identified, only two studies evaluated early satiety, and they also shared the same sample.

This is more challenging in patients receiving active treatment, where there is even less information on the associations between early satiety and other symptoms. In a systematic review of symptom clusters in head and neck cancers by Mathew et al.[594], where again in Chapter 3 early satiety was the most common symptom post oesophagectomy, early satiety was not evaluated in any of the identified studies for the review. This further highlights the poor screening for this

symptom in research. These co-occurring symptoms are a key component of cancer care as they have a greater effect on patient outcomes, including prognosis and quality of life compared to individual symptoms.[595-597] As a result, it would be beneficial to further investigate symptom clusters that include early satiety. It would be especially interesting to include other symptoms, alongside NIS, to assess the association between early satiety and a wide variety of common symptoms in cancer, not just those related to nutrition.

One major finding from Chapter 3 was that there was very little qualitative data on early satiety published. As a result, Chapters 5 and 6 focused on the development and implementation of the SEES to capture how patients with early satiety describe it. This allowed for these chapters to be the first to explore the symptom experience of patients with early satiety in detail. As highlighted in Chapter 2, the SEES was divided into several themes. Some of the questions and themes showed little variability. One was that early satiety reduced nutritional intake in almost all who completed the SEES. Another that has been described extensively throughout was that none with early satiety had ever been screened for the symptom during their cancer. The need for screening of this symptom is likely to be beneficial across the cancer trajectory as it is a potential early symptom of cancer to aid cancer detection while also a source of distress in advanced cancer. If these symptoms continue to be underreported, there is a huge missed therapeutic opportunity for these patients.

The theme that appeared to vary most was that of the timing of early satiety. It started for patients at all stages of cancer from before diagnosis to after their treatment ceased. The time of day and length of time the symptom lasted was also highly variable. Under the theme of impact on nutritional intake, whether

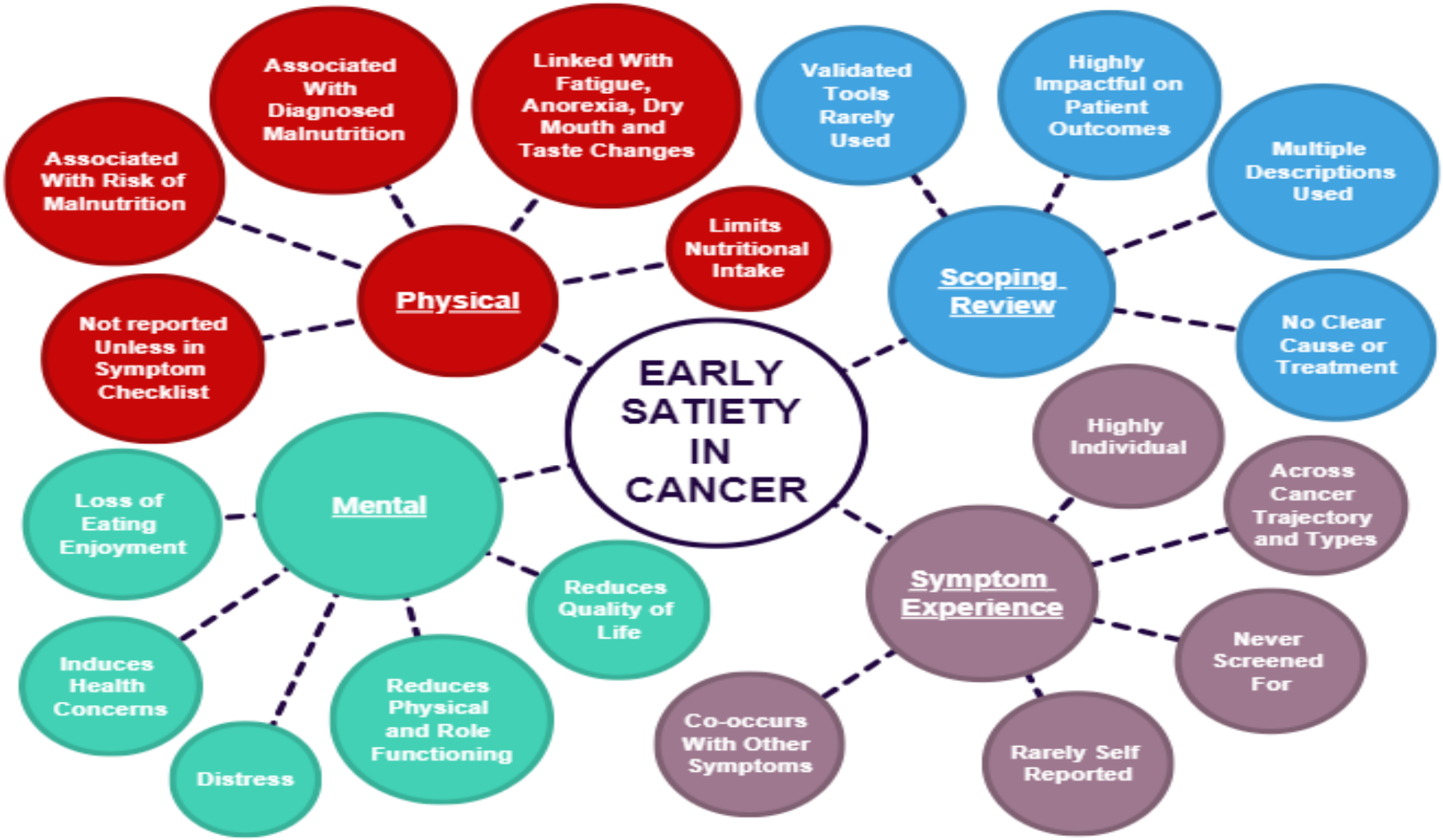
specific foods cause early satiety was also highly variable. The use of interviews or focus groups to gather detailed accounts of how patients perceive their symptom would allow for a greater understanding of this symptom.

An unfortunate finding throughout this thesis was the challenges of early satiety management. In Chapter 3, no clear pathophysiology or treatment was found for early satiety in cancer. This is made more challenging given the ESPEN guidelines for early satiety management suggest the use of prokinetics to treat early satiety.[386] No research into the use of these medications to treat early satiety in cancer was found in the scoping review. Another difficulty in recommending this approach was that many participants in both cohorts were taking prokinetics, and still reported early satiety. Prior to the design of a randomised trial for early satiety intervention, it is necessary to understand the pathophysiology of early satiety is needed. As highlighted, there may be some merit to the trial of a little and often eating pattern, as this was suggested as effective for some in both cohorts. Unfortunately, as it stands, most who have tried to self-manage their early satiety have been unsuccessful.

Overall, this thesis highlights that early satiety is worthy of both clinical and research attention. It can significantly impact nutritional status, quality of life, and overall well-being. Allowing early satiety to remain an orphan symptom with little focus will allow for it to continue as a highly impactful symptom, with little or no information to guide healthcare providers on the best management strategies. Clinically, it is crucial to take early satiety seriously, identify the underlying cause, and provide appropriate support to address the symptom and its consequences. We hope that this work helps to address some of the misconceptions surrounding early satiety and ensure a more accurate understanding of it among healthcare

providers, patients experiencing the symptom and the public. It is important to note that there is much research work to be done prior to an effective management strategy being identified, which will result in continued challenges in management and a burden on patients.

8.3 Summary Of Thesis Findings



8.4 Strengths And Limitations

A strength of the work outlined in this thesis is that it is the first to explore early satiety in cancer in detail. Very few studies investigated it as a primary outcome despite how common it is. To better understand this symptom, quantitative and qualitative data were gathered. Early satiety was screened for using two methods, one of which was the most widely used in the literature. The research generated a substantial amount of data and important findings for both research and clinical purposes are described throughout.

A further strength is that it has a strong clinical focus. No elaborate methodology or complicated assessments were used. Instead, tools that could be used in clinical practice were used throughout this thesis. The OSQ was chosen as it most accurately reflects clinical practice in the settings explored here. The abPG-SGA was used as it was not only the most commonly used tool found in Chapter 2, but also has several potential benefits for its implementation in a ward setting. It avoids the common challenges of implementing new tools, namely adding to the workload of healthcare professionals. Handgrip strength assessment is a cheap, quick, and validated strength assessment that could be easily implemented. The tools used for the study are also those that are most important to patients, including quality of life.

There were some limitations in the tools used in this thesis, namely the SEES questionnaire. No such tool exists currently, and this thesis aimed to gain some qualitative data on early satiety. Given the challenges of a full qualitative assessment due to COVID-19, the SEES was deemed more suitable. While it was not validated, it was successfully piloted on a cohort that it was hoped to use the tool. There was also input from experts in palliative care, oncology, and

research practice to guide the development of the tool. It would be beneficial to validate the tool in the future.

Another limitation is the sample sizes for each chapter. There were several challenges with recruitment, namely that it was done during the COVID-19 pandemic. These participants were also especially vulnerable to COVID-19 since they were immunocompromised, so every effort was made to have participants as safe as possible. Another explanation for the sample size was that the planned studies had to be significantly altered during the course of the thesis. Unfortunately, 4 potential studies were planned and had been awarded ethical approval but could not proceed due to COVID-19. Therefore, new studies that could be carried out during the pandemic were planned and ethical approval was sought during this time which ultimately meant time to recruit was significantly reduced.

Due to the limited sample, certain findings may be under or over-represented in terms of their significance as the samples did not reach the calculated power sample. Therefore, it would be beneficial to replicate this research over a longer period or in different centres. As described above, this could be done retrospectively for some components if symptom screening became standard practice.

8.5 Implications For Clinical Practice

The first recommendation from this research is that a comprehensive symptom checklist or malnutrition screening tool that contains a symptom checklist, such as the abPG-SGA should be implemented across all cancer stages. The abPG-SGA has been evaluated by patients previously and was easy to understand and has an appropriate length.[598] Before the implementation of such a tool, it would be beneficial to get patient feedback from those attending the ODW. The use of these assessments allows for a much more comprehensive evaluation of symptom burden. If patients are asked an open question and to list their symptoms, there are likely symptoms that will be missed. One such symptom that was rarely reported in open questioning but was highly prevalent was early satiety.

Another clear recommendation is that early satiety should be screened for regularly. This recommendation is for patients at all stages of cancer. The SEES found that some reported their early satiety before they were diagnosed, while in this thesis it was among the most common symptoms in those receiving anticancer treatment and in those receiving palliative care. This symptom proved to be impactful on both physical and psychological health. It was related to malnutrition whereas other more commonly assessed symptoms, such as anorexia and vomiting were not. It also reduced nutritional intake and quality of life. This highly impactful symptom however has not been screened for in any of the patients with early satiety previously, but we hope this thesis encourages it to be assessed in the future.

When assessing early satiety, it is important to factor in that each patient's experience of the symptom may be different. Therefore, it is important to ask

further questions regarding their symptom. Based on the results from the SEES, some universal results do not require clarification such as does it reduce nutritional intake. Instead, questions that showed a larger variance in responses should be asked, as these details may influence the nutrition counselling provided. Such factors include at what time of day they experience it, co-occurring symptoms, do certain foods induce early satiety more than others and what methods have they tried previously. Manipulation of the diet based on these factors may help to limit the impact of early satiety in cancer patients, both on active treatment and those receiving palliative care.

8.6 Future Directions

As discussed throughout this thesis, there are several areas regarding early satiety that are lacking. One of the key pieces of information missing is a definition. From the scoping review, there were many different descriptions of early satiety used throughout, and not all were documented. There are several benefits to an agreed definition of early satiety. The main advantage is that it would ensure that healthcare professionals, researchers, and patients can communicate more clearly regarding early satiety. It also allows for a consistent assessment or screening of the symptom. This in turn allows for more reliable comparisons between individuals or studies. It would also facilitate the development of future screening tools that include early satiety, the importance of which has been shown extensively throughout this thesis.

To develop a definition for early satiety, a key piece of research missing is qualitative interviews with patients who report early satiety. Patient input is crucial to understanding the lived experience of the symptom. To guide the qualitative interview, it would be beneficial to use the SEES in a larger cohort to better understand some of the commonalities and differences in experiences. When this information is collected, there is also a benefit to patient involvement in the development of the definition, namely to ensure the definition reflects their experience and is compliant with patient-centred care. This, along with a consensus-building model such as the Delphi technique, along with validity and reliability assessments, would allow for an agreed definition.

With this definition, the next step would be to determine the pathophysiology of early satiety in cancer. The definition ensures that those with true early satiety are being assessed. One possible study, which was planned as part of the thesis

originally, is to induce satiety in patients with early satiety and assess the concentrations of anorectic gut hormone. Based on the results of this thesis, this is very much still a relevant study and would be beneficial to further understand early satiety. It would also be beneficial to assess whether those with early satiety have delayed gastric emptying. The identification of pathophysiology would allow for the development of an evidence-based treatment. Neural signalling and sensory processing are also possible causes that warrant investigation. This is a key component of early satiety that is missing, especially given the number of patients that reported they tried to manage their symptom but failed. It would also be beneficial to investigate long-term outcomes using longitudinal studies to investigate changes in early satiety based on cancer stage, health outcomes, and influence on prognosis.

In addition to these important aspects for the identification and treatment of early satiety, the social impact of early satiety should be investigated. To date, there has been no research to examine the psychosocial impact of early satiety. In the SEES, there were several references to how patients lost their enjoyment of meals. Others were unable to ‘eat out’ as a result of their early satiety, suggesting that early satiety may affect cultural, interpersonal, and social relationships. This is especially true given the importance of food and drink in celebrations. If early satiety was to limit the possibility to engage in these daily activities, it may adversely affect those with cancer who already experience a high psychosocial burden from their cancer diagnosis and treatment.

Exploring early satiety using the same methodology, but with a larger sample size would be beneficial. There was originally a larger study planned (as outlined in section 1.4.3) that was also powered. This would allow for a significantly more in-

depth evaluation of the correlations between early satiety and other NIS as well as the physical and psychological impact of the symptom. Changes in the symptom throughout the disease trajectory would also be interesting.

Although this thesis focused on early satiety in the context of cancer, as discussed in Chapter 2, it is a common symptom in several other diseases and conditions. Given the lack of available research, the data may not be generalisable to those outside of cancer. Therefore, it would be of interest to determine whether the symptom is the same in different disease states. Of particular interest is functional dyspepsia given its prevalence. Another is bariatric surgery, where ‘early satiety’ is a desired outcome post-surgery. This was a planned study that could not be completed due to COVID-19 and is still a relevant comparison.

While the above recommendations for future directions are needed, it is hoped that the results of this study at a minimum highlight the high prevalence and importance of early satiety in cancer. Some of the information within this thesis has already been disseminated, as referenced at the beginning of this thesis. It is hoped that the results of this thesis will be further disseminated not only to healthcare staff and journals, but also to the public to raise awareness of the importance of reporting early satiety.

8.7 Overall Conclusions

The work carried out for this thesis has advanced the current understanding of early satiety in cancer and has highlighted the importance of future research into the symptom. Early satiety was among the most common symptoms among cancer patients receiving anticancer treatment and palliative care. It was more common than anorexia, nausea, and vomiting in both cohorts. Patients underreport symptoms, including early satiety, when asked via an open question that mimics normal clinical practice, compared to a symptom checklist. Early satiety is associated with an increased risk of malnutrition, diagnosed malnutrition, and reduced quality of life. Individual experiences of early satiety are highly individualised; however, one commonality is that patients are frequently not reporting their early satiety and are never asked by their healthcare provider about early satiety. This thesis has highlighted the research areas that need to be examined in future work to ensure adequate identification and treatment of this highly impactful orphan symptom.

9 References

1. National Institutes of Health. Understanding Cancer. *NIH Curriculum Supplement Series* 2007.

2. National Cancer Registry Ireland. Cancer in Ireland 1994-2017 with estimates for 2017-2019: Annual Report of the National Cancer Registry. 2019.

3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians* 2021; **71**(3)**:** 209-249. doi: https://doi.org/10.3322/caac.21660

4. O'Connor M, O'Donovan B, Donnelly C. P77 Unmet needs of cancer survivors in ireland: a scoping review of the existing evidence. *Journal of Epidemiology and Community Health* 2019; **73**(Suppl 1)**:** A106-A106. doi: 10.1136/jech-2019-SSMabstracts.228

5. Maddams J, Utley M, Møller H. Projections of cancer prevalence in the United Kingdom, 2010-2040. *British journal of cancer* 2012; **107**(7)**:** 1195-1202. e-pub ahead of print 2012/08/14; doi: 10.1038/bjc.2012.366

6. World Health Organisation. Palliative Care. In, 2020.

7. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA *et al.* Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; **363**(8)**:** 733-742. e-pub ahead of print 2010/09/08; doi: 10.1056/NEJMoa1000678

8. Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leighl N, Oza A *et al.* Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet (London, England)* 2014; **383**(9930)**:** 1721-1730. e-pub ahead of print 2014/02/25; doi: 10.1016/s0140-6736(13)62416-2

9. Bakitas MA, Tosteson TD, Li Z, Lyons KD, Hull JG, Li Z *et al.* Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial. *J Clin Oncol* 2015; **33**(13)**:** 1438-1445. e-pub ahead of print 2015/03/25; doi: 10.1200/jco.2014.58.6362

10. Yabroff KR, Wu XC, Negoita S, Stevens J, Coyle L, Zhao J *et al.* Association of the COVID-19 Pandemic With Patterns of Statewide Cancer Services. *J Natl Cancer Inst* 2022; **114**(6)**:** 907-909. e-pub ahead of print 2021/06/29; doi: 10.1093/jnci/djab122

11. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T *et al.* Sarcopenia: revised European consensus on definition and diagnosis.

Age Ageing 2019; **48**(1)**:** 16-31. e-pub ahead of print 2018/10/13; doi: 10.1093/ageing/afy169

12. Falcon LJ, Harris-Love MO. Sarcopenia and the New ICD-10-CM Code: Screening, Staging, and Diagnosis Considerations. *Fed Pract* 2017; **34**(7)**:** 24-32. e-pub ahead of print 2017/09/05;

13. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 2008; **33**(5)**:** 997-1006. e-pub ahead of print 2008/10/17; doi: 10.1139/h08-075

14. Nieuwenhuizen WF, Weenen H, Rigby P, Hetherington MM. Older adults and patients in need of nutritional support: review of current treatment options and factors influencing nutritional intake. *Clin Nutr* 2010; **29**(2)**:** 160-169. e-pub ahead of print 2009/10/16; doi: 10.1016/j.clnu.2009.09.003

15. Kaiser M, Bandinelli S, Lunenfeld B. Frailty and the role of nutrition in older people. A review of the current literature. *Acta Biomed* 2010; **81 Suppl 1:** 37-45. e-pub ahead of print 2010/06/04;

16. Pamoukdjian F, Bouillet T, Lévy V, Soussan M, Zelek L, Paillaud E. Prevalence and predictive value of pre-therapeutic sarcopenia in cancer patients: A systematic review. *Clin Nutr* 2018; **37**(4)**:** 1101-1113. e-pub ahead of print 2017/07/25; doi: 10.1016/j.clnu.2017.07.010

17. Sun Q, Jiang X, Qin R, Yang Y, Gong Y, Wang K *et al.* Sarcopenia among older patients with cancer: A scoping review of the literature. *Journal of Geriatric Oncology* 2022. doi: https://doi.org/10.1016/j.jgo.2022.03.008

18. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y *et al.* Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). *Age Ageing* 2014; **43**(6)**:** 748-759. doi: 10.1093/ageing/afu115

19. Morishita S, Kaida K, Tanaka T, Itani Y, Ikegame K, Okada M *et al.* Prevalence of sarcopenia and relevance of body composition, physiological function, fatigue, and health-related quality of life in patients before allogeneic hematopoietic stem cell transplantation. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2012; **20**(12)**:** 3161-3168. e-pub ahead of print 2012/04/25; doi: 10.1007/s00520-012-1460-5

20. Nipp RD, Fuchs G, El-Jawahri A, Mario J, Troschel FM, Greer JA *et al.* Sarcopenia Is Associated with Quality of Life and Depression in Patients with Advanced Cancer. *The oncologist* 2018; **23**(1)**:** 97-104. e-pub ahead of print 2017/09/25; doi: 10.1634/theoncologist.2017-0255

21. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP *et al.* ESPEN expert group recommendations for action against cancer-related malnutrition. *Clin Nutr* 2017; **36**(5)**:** 1187-1196. e-pub ahead of print 2017/07/12; doi: 10.1016/j.clnu.2017.06.017

22. Beirer A. Malnutrition and cancer, diagnosis and treatment. *memo - Magazine of European Medical Oncology* 2021; **14**(2)**:** 168-173. doi: 10.1007/s12254-020-00672-3

23. Khalatbari-Soltani S, Marques-Vidal P. The economic cost of hospital malnutrition in Europe; a narrative review. *Clinical Nutrition ESPEN* 2015; **10**(3)**:** e89-e94. doi: https://doi.org/10.1016/j.clnesp.2015.04.003

24. Rice N, Normand C. The cost associated with disease-related malnutrition in Ireland. *Public Health Nutrition* 2012; **15**(10)**:** 1966-1972. e-pub ahead of print 2012/02/08; doi: 10.1017/S1368980011003624

25. Castillo-Martínez L, Castro-Eguiluz D, Copca-Mendoza ET, Pérez-Camargo DA, Reyes-Torres CA, Ávila EA *et al.* Nutritional Assessment Tools for the Identification of Malnutrition and Nutritional Risk Associated with Cancer Treatment. *Rev Invest Clin* 2018; **70**(3)**:** 121-125. e-pub ahead of print 2018/06/27; doi: 10.24875/ric.18002524

26. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T *et al.* GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. *J Cachexia Sarcopenia Muscle* 2019; **10**(1)**:** 207-217. e-pub ahead of print 2019/03/29; doi: 10.1002/jcsm.12383

27. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F *et al.* ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* 2017; **36**(1)**:** 11-48. e-pub ahead of print 2016/09/18; doi: 10.1016/j.clnu.2016.07.015

28. McGrath P. Reflections on nutritional issues associated with cancer therapy. *Cancer Pract* 2002; **10**(2)**:** 94-101. e-pub ahead of print 2002/03/21; doi: 10.1046/j.1523-5394.2002.102007.x

29. Datema FR, Ferrier MB, Baatenburg de Jong RJ. Impact of severe malnutrition on short-term mortality and overall survival in head and neck cancer. *Oral Oncol* 2011; **47**(9)**:** 910-914. e-pub ahead of print 2011/08/02; doi: 10.1016/j.oraloncology.2011.06.510

30. Silva FR, de Oliveira MG, Souza AS, Figueroa JN, Santos CS. Factors associated with malnutrition in hospitalized cancer patients: a croos-sectional study. *Nutr J* 2015; **14:** 123. e-pub ahead of print 2015/12/15; doi: 10.1186/s12937-015-0113-1

31. Pressoir M, Desné S, Berchery D, Rossignol G, Poiree B, Meslier M *et al.* Prevalence, risk factors and clinical implications of malnutrition in French Comprehensive Cancer Centres. *Br J Cancer* 2010; **102**(6)**:** 966-971. e-pub ahead of print 2010/02/18; doi: 10.1038/sj.bjc.6605578

32. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL *et al.* Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011; **12**(5)**:** 489-495. e-pub ahead of print 2011/02/08; doi: 10.1016/s1470-2045(10)70218-7

33. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D *et al.* Cachexia: a new definition. *Clin Nutr* 2008; **27**(6)**:** 793-799. e-pub ahead of print 2008/08/23; doi: 10.1016/j.clnu.2008.06.013

34. von Haehling S, Anker SD. Cachexia as major underestimated unmet medical need: facts and numbers. *Int J Cardiol* 2012; **161**(3)**:** 121-123. e-pub ahead of print 2012/10/23; doi: 10.1016/j.ijcard.2012.09.213

35. Kubrak C, Olson K, Jha N, Jensen L, McCargar L, Seikaly H *et al.* Nutrition impact symptoms: key determinants of reduced dietary intake, weight loss, and reduced functional capacity of patients with head and neck cancer before treatment. *Head Neck* 2010; **32**(3)**:** 290-300. e-pub ahead of print 2009/07/25; doi: 10.1002/hed.21174

36. Chang VT, Hwang SS, Feuerman M, Kasimis BS. Symptom and quality of life survey of medical oncology patients at a veterans affairs medical center: a role for symptom assessment. *Cancer* 2000; **88**(5)**:** 1175-1183. e-pub ahead of print 2000/03/04; doi: 10.1002/(sici)1097-0142(20000301)88:5<1175::aid-cncr30>3.0.co;2-n

37. Lobchuk MM, Degner LF. Symptom experiences: perceptual accuracy between advanced-stage cancer patients and family caregivers in the home care setting. *J Clin Oncol* 2002; **20**(16)**:** 3495-3507. e-pub ahead of print 2002/08/15; doi: 10.1200/jco.2002.01.153

38. Donovan HS, Hartenbach EM, Method MW. Patient-provider communication and perceived control for women experiencing multiple symptoms associated with ovarian cancer. *Gynecol Oncol* 2005; **99**(2)**:** 404-411. e-pub ahead of print 2005/08/23; doi: 10.1016/j.ygyno.2005.06.062

39. Spotten L, Corish C, Lorton C, Dhuibhir PU, O'Donoghue N, O'Connor B *et al.* Subjective taste and smell changes in treatment-naive people with solid tumours. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2016; **24**(7)**:** 3201-3208. e-pub ahead of print 2016/03/08; doi: 10.1007/s00520-016-3133-2

40. Hui D, Dev R, Bruera E. The last days of life: symptom burden and impact on nutrition and hydration in cancer patients. *Curr Opin Support Palliat Care* 2015; **9**(4)**:** 346-354. e-pub ahead of print 2015/10/29; doi: 10.1097/spc.0000000000000171

41. Sommariva S, Pongiglione B, Tarricone R. Impact of chemotherapy-induced nausea and vomiting on health-related quality of life and resource

utilization: A systematic review. *Crit Rev Oncol Hematol* 2016; **99:** 13-36. e-pub ahead of print 2015/12/25; doi: 10.1016/j.critrevonc.2015.12.001

42. Durham WJ, Dillon EL, Sheffield-Moore M. Inflammatory burden and amino acid metabolism in cancer cachexia. *Curr Opin Clin Nutr Metab Care* 2009; **12**(1)**:** 72-77. doi: 10.1097/MCO.0b013e32831cef61

43. Bing C, Taylor S, Tisdale MJ, Williams G. Cachexia in MAC16 adenocarcinoma: suppression of hunger despite normal regulation of leptin, insulin and hypothalamic neuropeptide Y. *J Neurochem* 2001; **79**(5)**:** 1004-1012. e-pub ahead of print 2001/12/12; doi: 10.1046/j.1471-4159.2001.00639.x

44. Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. Cachexia and sarcopenia: mechanisms and potential targets for intervention. *Curr Opin Pharmacol* 2015; **22:** 100-106. e-pub ahead of print 2015/05/15; doi: 10.1016/j.coph.2015.04.003

45. Theologides A. Anorexia-producing intermediary metabolites. *Am J Clin Nutr* 1976; **29**(5)**:** 552-558. e-pub ahead of print 1976/05/01; doi: 10.1093/ajcn/29.5.552

46. Armes PJ, Plant HJ, Allbright A, Silverstone T, Slevin ML. A study to investigate the incidence of early satiety in patients with advanced cancer. *British journal of cancer* 1992; **65**(3)**:** 481-484.

47. Blundell J, de Graaf C, Hulshof T, Jebb S, Livingstone B, Lluch A *et al.* Appetite control: methodological aspects of the evaluation of foods. *Obes Rev* 2010; **11**(3)**:** 251-270. e-pub ahead of print 2010/02/04; doi: 10.1111/j.1467-789X.2010.00714.x

48. Cummings DE, Overduin J. Gastrointestinal regulation of food intake. *The Journal of clinical investigation* 2007; **117**(1)**:** 13-23. doi: 10.1172/JCI30227

49. Valassi E, Scacchi M, Cavagnini F. Neuroendocrine control of food intake. *Nutrition, Metabolism and Cardiovascular Diseases* 2008; **18**(2)**:** 158-168. doi: https://doi.org/10.1016/j.numecd.2007.06.004

50. Browning KN, Travagli RA. Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. *Compr Physiol* 2014; **4**(4)**:** 1339-1368. e-pub ahead of print 2014/11/28; doi: 10.1002/cphy.c130055

51. Berthoud HR, Carlson NR, Powley TL. Topography of efferent vagal innervation of the rat gastrointestinal tract. *Am J Physiol* 1991; **260**(1 Pt 2)**:** R200-207. e-pub ahead of print 1991/01/01; doi: 10.1152/ajpregu.1991.260.1.R200

52. Richards P, Thornberry NA, Pinto S. The gut-brain axis: Identifying new therapeutic approaches for type 2 diabetes, obesity, and related disorders.

Mol Metab 2021; **46:** 101175. e-pub ahead of print 2021/02/07; doi: 10.1016/j.molmet.2021.101175

53. Berthoud HR. The vagus nerve, food intake and obesity. *Regul Pept* 2008; **149**(1-3)**:** 15-25. e-pub ahead of print 2008/05/17; doi: 10.1016/j.regpep.2007.08.024

54. Phillips RJ, Powley TL. Tension and stretch receptors in gastrointestinal smooth muscle: re-evaluating vagal mechanoreceptor electrophysiology. *Brain Res Brain Res Rev* 2000; **34**(1-2)**:** 1-26. e-pub ahead of print 2000/11/22; doi: 10.1016/s0165-0173(00)00036-9

55. Sakurada T, Ro S, Onouchi T, Ohno S, Aoyama T, Chinen K *et al.* Comparison of the actions of acylated and desacylated ghrelin on acid secretion in the rat stomach. *J Gastroenterol* 2010; **45**(11)**:** 1111-1120. e-pub ahead of print 2010/06/24; doi: 10.1007/s00535-010-0269-6

56. Yakabi K, Ro S, Onouhi T, Tanaka T, Ohno S, Miura S *et al.* Histamine mediates the stimulatory action of ghrelin on acid secretion in rat stomach. *Digestive diseases and sciences* 2006; **51**(8)**:** 1313-1321. e-pub ahead of print 2006/07/14; doi: 10.1007/s10620-005-9002-3

57. le Roux CW, Neary NM, Halsey TJ, Small CJ, Martinez-Isla AM, Ghatei MA *et al.* Ghrelin does not stimulate food intake in patients with surgical procedures involving vagotomy. *J Clin Endocrinol Metab* 2005; **90**(8)**:** 4521-4524. e-pub ahead of print 2005/05/26; doi: 10.1210/jc.2004-2537

58. Owyang C. Physiological mechanisms of cholecystokinin action on pancreatic secretion. *Am J Physiol* 1996; **271**(1 Pt 1)**:** G1-7. e-pub ahead of print 1996/07/01; doi: 10.1152/ajpgi.1996.271.1.G1

59. Raybould HE. Mechanisms of CCK signaling from gut to brain. *Curr Opin Pharmacol* 2007; **7**(6)**:** 570-574. e-pub ahead of print 2007/10/24; doi: 10.1016/j.coph.2007.09.006

60. Takahashi T, Owyang C. Mechanism of cholecystokinin-induced relaxation of the rat stomach. *J Auton Nerv Syst* 1999; **75**(2-3)**:** 123-130. e-pub ahead of print 1999/04/03; doi: 10.1016/s0165-1838(98)00181-7

61. Koren MS, Holmes MD. Vagus nerve stimulation does not lead to significant changes in body weight in patients with epilepsy. *Epilepsy Behav* 2006; **8**(1)**:** 246-249. e-pub ahead of print 2005/12/14; doi: 10.1016/j.yebeh.2005.10.001

62. L'Heureux-Bouron D, Tomé D, Rampin O, Even PC, Larue-Achagiotis C, Fromentin G. Total subdiaphragmatic vagotomy does not suppress high protein diet-induced food intake depression in rats. *J Nutr* 2003; **133**(8)**:** 2639-2642. e-pub ahead of print 2003/07/31; doi: 10.1093/jn/133.8.2639

63. Elliott JA, Reynolds JV, le Roux CW, Docherty NG. Physiology, pathophysiology and therapeutic implications of enteroendocrine control

of food intake. *Expert Review of Endocrinology & Metabolism* 2016; **11**(6)**:** 475-499. doi: 10.1080/17446651.2016.1245140

64. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* 1999; **402**(6762)**:** 656-660. e-pub ahead of print 1999/12/22; doi: 10.1038/45230

65. Tschop M, Smiley DL, Heiman ML. Ghrelin induces adiposity in rodents. *Nature* 2000; **407**(6806)**:** 908-913. e-pub ahead of print 2000/11/01; doi: 10.1038/35038090

66. Cowley MA, Smith RG, Diano S, Tschop M, Pronchuk N, Grove KL *et al.* The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. *Neuron* 2003; **37**(4)**:** 649-661. e-pub ahead of print 2003/02/25; doi: 10.1016/s0896-6273(03)00063-1

67. Zigman JM, Jones JE, Lee CE, Saper CB, Elmquist JK. Expression of ghrelin receptor mRNA in the rat and the mouse brain. *J Comp Neurol* 2006; **494**(3)**:** 528-548. e-pub ahead of print 2005/12/02; doi: 10.1002/cne.20823

68. Schellekens H, Finger BC, Dinan TG, Cryan JF. Ghrelin signalling and obesity: at the interface of stress, mood and food reward. *Pharmacol Ther* 2012; **135**(3)**:** 316-326. e-pub ahead of print 2012/07/04; doi: 10.1016/j.pharmthera.2012.06.004

69. Carlini VP, Monzón ME, Varas MM, Cragnolini AB, Schiöth HB, Scimonelli TN *et al.* Ghrelin increases anxiety-like behavior and memory retention in rats. *Biochem Biophys Res Commun* 2002; **299**(5)**:** 739-743. e-pub ahead of print 2002/12/10; doi: 10.1016/s0006-291x(02)02740-7

70. Diano S, Farr SA, Benoit SC, McNay EC, da Silva I, Horvath B *et al.* Ghrelin controls hippocampal spine synapse density and memory performance. *Nat Neurosci* 2006; **9**(3)**:** 381-388. e-pub ahead of print 2006/02/24; doi: 10.1038/nn1656

71. Tesauro M, Schinzari F, Caramanti M, Lauro R, Cardillo C. Metabolic and cardiovascular effects of ghrelin. *Int J Pept* 2010; **2010**. e-pub ahead of print 2010/08/28; doi: 10.1155/2010/864342

72. Caminos JE, Tena-Sempere M, Gaytán F, Sanchez-Criado JE, Barreiro ML, Nogueiras R *et al.* Expression of ghrelin in the cyclic and pregnant rat ovary. *Endocrinology* 2003; **144**(4)**:** 1594-1602. e-pub ahead of print 2003/03/18; doi: 10.1210/en.2002-221058

73. Mori K, Yoshimoto A, Takaya K, Hosoda K, Ariyasu H, Yahata K *et al.* Kidney produces a novel acylated peptide, ghrelin. *FEBS Lett* 2000; **486**(3)**:** 213-216. e-pub ahead of print 2000/12/20; doi: 10.1016/s0014-5793(00)02308-5

74. Date Y, Kojima M, Hosoda H, Sawaguchi A, Mondal MS, Suganuma T *et al.* Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology* 2000; **141**(11)**:** 4255-4261. e-pub ahead of print 2000/11/23; doi: 10.1210/endo.141.11.7757

75. Hattori N, Saito T, Yagyu T, Jiang BH, Kitagawa K, Inagaki C. GH, GH receptor, GH secretagogue receptor, and ghrelin expression in human T cells, B cells, and neutrophils. *J Clin Endocrinol Metab* 2001; **86**(9)**:** 4284-4291. e-pub ahead of print 2001/09/11; doi: 10.1210/jcem.86.9.7866

76. Volante M, Allìa E, Gugliotta P, Funaro A, Broglio F, Deghenghi R *et al.* Expression of ghrelin and of the GH secretagogue receptor by pancreatic islet cells and related endocrine tumors. *J Clin Endocrinol Metab* 2002; **87**(3)**:** 1300-1308. e-pub ahead of print 2002/03/13; doi: 10.1210/jcem.87.3.8279

77. Tanaka M, Hayashida Y, Nakao N, Nakai N, Nakashima K. Testis-specific and developmentally induced expression of a ghrelin gene-derived transcript that encodes a novel polypeptide in the mouse. *Biochim Biophys Acta* 2001; **1522**(1)**:** 62-65. e-pub ahead of print 2001/11/24; doi: 10.1016/s0167-4781(01)00304-9

78. Chen HY, Trumbauer ME, Chen AS, Weingarth DT, Adams JR, Frazier EG *et al.* Orexigenic action of peripheral ghrelin is mediated by neuropeptide Y and agouti-related protein. *Endocrinology* 2004; **145**(6)**:** 2607-2612. e-pub ahead of print 2004/02/14; doi: 10.1210/en.2003-1596

79. Cabral A, López Soto EJ, Epelbaum J, Perelló M. Is Ghrelin Synthesized in the Central Nervous System? *Int J Mol Sci* 2017; **18**(3). e-pub ahead of print 2017/03/16; doi: 10.3390/ijms18030638

80. Karhunen LJ, Juvonen KR, Huotari A, Purhonen AK, Herzig KH. Effect of protein, fat, carbohydrate and fibre on gastrointestinal peptide release in humans. *Regul Pept* 2008; **149**(1-3)**:** 70-78. e-pub ahead of print 2008/05/06; doi: 10.1016/j.regpep.2007.10.008

81. Masuda Y, Tanaka T, Inomata N, Ohnuma N, Tanaka S, Itoh Z *et al.* Ghrelin stimulates gastric acid secretion and motility in rats. *Biochem Biophys Res Commun* 2000; **276**(3)**:** 905-908. e-pub ahead of print 2000/10/12; doi: 10.1006/bbrc.2000.3568

82. Date Y, Nakazato M, Murakami N, Kojima M, Kangawa K, Matsukura S. Ghrelin acts in the central nervous system to stimulate gastric acid secretion. *Biochem Biophys Res Commun* 2001; **280**(3)**:** 904-907. e-pub ahead of print 2001/02/13; doi: 10.1006/bbrc.2000.4212

83. Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP *et al.* Plasma ghrelin levels after diet-induced weight loss or gastric bypass

surgery. *N Engl J Med* 2002; **346**(21)**:** 1623-1630. e-pub ahead of print 2002/05/25; doi: 10.1056/NEJMoa012908

84. Nagaya N, Uematsu M, Kojima M, Date Y, Nakazato M, Okumura H *et al.* Elevated circulating level of ghrelin in cachexia associated with chronic heart failure: relationships between ghrelin and anabolic/catabolic factors. *Circulation* 2001; **104**(17)**:** 2034-2038. e-pub ahead of print 2001/10/24; doi: 10.1161/hc4201.097836

85. Otto B, Cuntz U, Fruehauf E, Wawarta R, Folwaczny C, Riepl RL *et al.* Weight gain decreases elevated plasma ghrelin concentrations of patients with anorexia nervosa. *Eur J Endocrinol* 2001; **145**(5)**:** 669-673. e-pub ahead of print 2001/11/27;

86. Shiiya T, Nakazato M, Mizuta M, Date Y, Mondal MS, Tanaka M *et al.* Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion. *J Clin Endocrinol Metab* 2002; **87**(1)**:** 240-244. e-pub ahead of print 2002/01/15; doi: 10.1210/jcem.87.1.8129

87. Wang Y, Wu Q, Zhou Q, Chen Y, Lei X, Chen Y *et al.* Circulating acyl and des-acyl ghrelin levels in obese adults: a systematic review and meta-analysis. *Sci Rep* 2022; **12**(1)**:** 2679. e-pub ahead of print 2022/02/19; doi: 10.1038/s41598-022-06636-3

88. Wren AM, Seal LJ, Cohen MA, Brynes AE, Frost GS, Murphy KG *et al.* Ghrelin enhances appetite and increases food intake in humans. *J Clin Endocrinol Metab* 2001; **86**(12)**:** 5992. e-pub ahead of print 2001/12/12; doi: 10.1210/jcem.86.12.8111

89. Elliott JA, Reynolds JV, le Roux CW, Docherty NG. Physiology, pathophysiology and therapeutic implications of enteroendocrine control of food intake. *Expert Rev Endocrinol Metab* 2016; **11**(6)**:** 475-499. e-pub ahead of print 2016/11/01; doi: 10.1080/17446651.2016.1245140

90. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994; **372**(6505)**:** 425-432. e-pub ahead of print 1994/12/01; doi: 10.1038/372425a0

91. Münzberg H, Morrison CD. Structure, production and signaling of leptin. *Metabolism: clinical and experimental* 2015; **64**(1)**:** 13-23. e-pub ahead of print 2014/09/28; doi: 10.1016/j.metabol.2014.09.010

92. Elmquist JK, Bjørbaek C, Ahima RS, Flier JS, Saper CB. Distributions of leptin receptor mRNA isoforms in the rat brain. *J Comp Neurol* 1998; **395**(4)**:** 535-547. e-pub ahead of print 1998/06/10;

93. Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y *et al.* Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat Med* 1995; **1**(11)**:** 1155-1161. e-pub ahead of print 1995/11/01; doi: 10.1038/nm1195-1155

94. Cowley MA, Smart JL, Rubinstein M, Cerdán MG, Diano S, Horvath TL *et al.* Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. *Nature* 2001; **411**(6836)**:** 480-484. e-pub ahead of print 2001/05/25; doi: 10.1038/35078085

95. Enriori PJ, Evans AE, Sinnayah P, Jobst EE, Tonelli-Lemos L, Billes SK *et al.* Diet-induced obesity causes severe but reversible leptin resistance in arcuate melanocortin neurons. *Cell Metab* 2007; **5**(3)**:** 181-194. e-pub ahead of print 2007/03/07; doi: 10.1016/j.cmet.2007.02.004

96. Herrmann C, Goke R, Richter G, Fehmann HC, Arnold R, Goke B. Glucagon-like peptide-1 and glucose-dependent insulin-releasing polypeptide plasma levels in response to nutrients. *Digestion* 1995; **56**(2)**:** 117-126. e-pub ahead of print 1995/01/01; doi: 10.1159/000201231

97. Eissele R, Goke R, Willemer S, Harthus HP, Vermeer H, Arnold R *et al.* Glucagon-like peptide-1 cells in the gastrointestinal tract and pancreas of rat, pig and man. *European journal of clinical investigation* 1992; **22**(4)**:** 283-291. e-pub ahead of print 1992/04/01; doi: 10.1111/j.1365-2362.1992.tb01464.x

98. Orskov C, Wettergren A, Holst JJ. Secretion of the incretin hormones glucagon-like peptide-1 and gastric inhibitory polypeptide correlates with insulin secretion in normal man throughout the day. *Scand J Gastroenterol* 1996; **31**(7)**:** 665-670. e-pub ahead of print 1996/07/01; doi: 10.3109/00365529609009147

99. Brubaker PL. Regulation of intestinal proglucagon-derived peptide secretion by intestinal regulatory peptides. *Endocrinology* 1991; **128**(6)**:** 3175-3182. e-pub ahead of print 1991/06/01; doi: 10.1210/endo-128-6-3175

100. Rocca AS, Brubaker PL. Role of the vagus nerve in mediating proximal nutrient-induced glucagon-like peptide-1 secretion. *Endocrinology* 1999; **140**(4)**:** 1687-1694. e-pub ahead of print 1999/03/31; doi: 10.1210/endo.140.4.6643

101. Little TJ, Doran S, Meyer JH, Smout AJPM, O'Donovan DG, Wu K-L *et al.* The release of GLP-1 and ghrelin, but not GIP and CCK, by glucose is dependent upon the length of small intestine exposed. *American Journal of Physiology-Endocrinology and Metabolism* 2006; **291**(3)**:** E647-E655. doi: 10.1152/ajpendo.00099.2006

102. Schirra J, Katschinski M, Weidmann C, Schäfer T, Wank U, Arnold R *et al.* Gastric emptying and release of incretin hormones after glucose ingestion in humans. *J Clin Invest* 1996; **97**(1)**:** 92-103. e-pub ahead of print 1996/01/01; doi: 10.1172/jci118411

103. Secher A, Jelsing J, Baquero AF, Hecksher-Sorensen J, Cowley MA, Dalboge LS *et al.* The arcuate nucleus mediates GLP-1 receptor agonist

liraglutide-dependent weight loss. *J Clin Invest* 2014; **124**(10)**:** 4473-4488. e-pub ahead of print 2014/09/10; doi: 10.1172/jci75276

104. Richards P, Parker HE, Adriaenssens AE, Hodgson JM, Cork SC, Trapp S *et al.* Identification and characterization of GLP-1 receptor-expressing cells using a new transgenic mouse model. *Diabetes* 2014; **63**(4)**:** 1224-1233. e-pub ahead of print 2013/12/02; doi: 10.2337/db13-1440

105. Adrian TE, Ferri GL, Bacarese-Hamilton AJ, Fuessl HS, Polak JM, Bloom SR. Human distribution and release of a putative new gut hormone, peptide YY. *Gastroenterology* 1985; **89**(5)**:** 1070-1077. e-pub ahead of print 1985/11/01; doi: 10.1016/0016-5085(85)90211-2

106. Batterham RL, Heffron H, Kapoor S, Chivers JE, Chandarana K, Herzog H *et al.* Critical role for peptide YY in protein-mediated satiation and body-weight regulation. *Cell Metab* 2006; **4**(3)**:** 223-233. e-pub ahead of print 2006/09/05; doi: 10.1016/j.cmet.2006.08.001

107. Ekblad E, Sundler F. Distribution of pancreatic polypeptide and peptide YY. *Peptides* 2002; **23**(2)**:** 251-261. e-pub ahead of print 2002/02/05; doi: 10.1016/s0196-9781(01)00601-5

108. Grandt D, Schimiczek M, Beglinger C, Layer P, Goebell H, Eysselein VE *et al.* Two molecular forms of peptide YY (PYY) are abundant in human blood: characterization of a radioimmunoassay recognizing PYY 1-36 and PYY 3-36. *Regul Pept* 1994; **51**(2)**:** 151-159. e-pub ahead of print 1994/05/05; doi: 10.1016/0167-0115(94)90204-6

109. Liddle RA. Cholecystokinin cells. *Annu Rev Physiol* 1997; **59:** 221-242. e-pub ahead of print 1997/01/01; doi: 10.1146/annurev.physiol.59.1.221

110. Liddle RA, Morita ET, Conrad CK, Williams JA. Regulation of gastric emptying in humans by cholecystokinin. *J Clin Invest* 1986; **77**(3)**:** 992-996. e-pub ahead of print 1986/03/01; doi: 10.1172/jci112401

111. Wickbom J, Herrington MK, Permert J, Jansson A, Arnelo U. Gastric emptying in response to IAPP and CCK in rats with subdiaphragmatic afferent vagotomy. *Regul Pept* 2008; **148**(1-3)**:** 21-25. e-pub ahead of print 2008/05/06; doi: 10.1016/j.regpep.2008.03.010

112. Gibbs J, Young RC, Smith GP. Cholecystokinin Decreases Food Intake in Rats1. *Obesity research* 1997; **5**(3)**:** 284-290. doi: 10.1002/j.1550-8528.1997.tb00305.x

113. Lieverse RJ, Jansen JB, Masclee AA, Lamers CB. Satiety effects of a physiological dose of cholecystokinin in humans. *Gut* 1995; **36**(2)**:** 176-179. doi: 10.1136/gut.36.2.176

114. Wynne K, Park AJ, Small CJ, Patterson M, Ellis SM, Murphy KG *et al.* Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects: a double-blind, randomized, controlled trial. *Diabetes*

2005; **54**(8)**:** 2390-2395. e-pub ahead of print 2005/07/28; doi: 10.2337/diabetes.54.8.2390

115. Dakin CL, Small CJ, Batterham RL, Neary NM, Cohen MA, Patterson M *et al.* Peripheral oxyntomodulin reduces food intake and body weight gain in rats. *Endocrinology* 2004; **145**(6)**:** 2687-2695. e-pub ahead of print 2004/03/06; doi: 10.1210/en.2003-1338

116. Dakin CL, Gunn I, Small CJ, Edwards CM, Hay DL, Smith DM *et al.* Oxyntomodulin inhibits food intake in the rat. *Endocrinology* 2001; **142**(10)**:** 4244-4250. e-pub ahead of print 2001/09/21; doi: 10.1210/endo.142.10.8430

117. Wynne K, Park AJ, Small CJ, Meeran K, Ghatei MA, Frost GS *et al.* Oxyntomodulin increases energy expenditure in addition to decreasing energy intake in overweight and obese humans: a randomised controlled trial. *International journal of obesity (2005)* 2006; **30**(12)**:** 1729-1736. e-pub ahead of print 2006/04/19; doi: 10.1038/sj.ijo.0803344

118. Blundell J. Making claims: functional foods for managing appetite and weight. *Nat Rev Endocrinol* 2010; **6**(1)**:** 53-56. e-pub ahead of print 2009/12/17; doi: 10.1038/nrendo.2009.224

119. Arvidsson-Lenner R, Asp N-G, Axelsen M, Bryngelsson S, Haapa E, Järvi A *et al.* Glycaemic Index. *Scandinavian Journal of Nutrition* 2004; **48**(2)**:** 84-94. doi: 10.1080/11026480410033999

120. Benelam B. Satiation, satiety and their effects on eating behaviour. *Nutrition Bulletin* 2009; **34**(2)**:** 126-173. doi: https://doi.org/10.1111/j.1467-3010.2009.01753.x

121. Jenkins DJ, Wolever TM, Taylor RH, Barker H, Fielden H, Baldwin JM *et al.* Glycemic index of foods: a physiological basis for carbohydrate exchange. *The American journal of clinical nutrition* 1981; **34**(3)**:** 362-366. e-pub ahead of print 1981/03/01; doi: 10.1093/ajcn/34.3.362

122. Ball SD, Keller KR, Moyer-Mileur LJ, Ding YW, Donaldson D, Jackson WD. Prolongation of satiety after low versus moderately high glycemic index meals in obese adolescents. *Pediatrics* 2003; **111**(3)**:** 488-494. e-pub ahead of print 2003/03/04; doi: 10.1542/peds.111.3.488

123. Liu AG, Most MM, Brashear MM, Johnson WD, Cefalu WT, Greenway FL. Reducing the glycemic index or carbohydrate content of mixed meals reduces postprandial glycemia and insulinemia over the entire day but does not affect satiety. *Diabetes Care* 2012; **35**(8)**:** 1633-1637. e-pub ahead of print 2012/06/13; doi: 10.2337/dc12-0329

124. Carreiro AL, Dhillon J, Gordon S, Higgins KA, Jacobs AG, McArthur BM *et al.* The Macronutrients, Appetite, and Energy Intake. *Annu Rev Nutr* 2016; **36:** 73-103. e-pub ahead of print 2016/07/20; doi: 10.1146/annurev-nutr-121415-112624

125. Wycherley TP, Moran LJ, Clifton PM, Noakes M, Brinkworth GD. Effects of energy-restricted high-protein, low-fat compared with standard-protein, low-fat diets: a meta-analysis of randomized controlled trials. *The American journal of clinical nutrition* 2012; **96**(6)**:** 1281-1298. e-pub ahead of print 2012/10/26; doi: 10.3945/ajcn.112.044321

126. Santesso N, Akl EA, Bianchi M, Mente A, Mustafa R, Heels-Ansdell D *et al.* Effects of higher- versus lower-protein diets on health outcomes: a systematic review and meta-analysis. *European journal of clinical nutrition* 2012; **66**(7)**:** 780-788. e-pub ahead of print 2012/04/19; doi: 10.1038/ejcn.2012.37

127. Belza A, Ritz C, Sørensen MQ, Holst JJ, Rehfeld JF, Astrup A. Contribution of gastroenteropancreatic appetite hormones to protein-induced satiety. *The American journal of clinical nutrition* 2013; **97**(5)**:** 980-989. e-pub ahead of print 2013/03/08; doi: 10.3945/ajcn.112.047563

128. Bowen J, Noakes M, Clifton PM. Appetite regulatory hormone responses to various dietary proteins differ by body mass index status despite similar reductions in ad libitum energy intake. *J Clin Endocrinol Metab* 2006; **91**(8)**:** 2913-2919. e-pub ahead of print 2006/06/01; doi: 10.1210/jc.2006-0609

129. Bowen J, Noakes M, Clifton PM. Appetite hormones and energy intake in obese men after consumption of fructose, glucose and whey protein beverages. *International journal of obesity (2005)* 2007; **31**(11)**:** 1696-1703. e-pub ahead of print 2007/06/28; doi: 10.1038/sj.ijo.0803665

130. Foltz M, Ansems P, Schwarz J, Tasker MC, Lourbakos A, Gerhardt CC. Protein hydrolysates induce CCK release from enteroendocrine cells and act as partial agonists of the CCK1 receptor. *J Agric Food Chem* 2008; **56**(3)**:** 837-843. e-pub ahead of print 2008/01/24; doi: 10.1021/jf072611h

131. Akhavan T, Luhovyy BL, Brown PH, Cho CE, Anderson GH. Effect of premeal consumption of whey protein and its hydrolysate on food intake and postmeal glycemia and insulin responses in young adults. *The American journal of clinical nutrition* 2010; **91**(4)**:** 966-975. e-pub ahead of print 2010/02/19; doi: 10.3945/ajcn.2009.28406

132. Giezenaar C, Luscombe-Marsh ND, Hutchison AT, Lange K, Hausken T, Jones KL *et al.* Effect of gender on the acute effects of whey protein ingestion on energy intake, appetite, gastric emptying and gut hormone responses in healthy young adults. *Nutrition & Diabetes* 2018; **8**(1)**:** 40. doi: 10.1038/s41387-018-0048-7

133. Jones JM. CODEX-aligned dietary fiber definitions help to bridge the 'fiber gap'. *Nutr J* 2014; **13:** 34. e-pub ahead of print 2014/04/15; doi: 10.1186/1475-2891-13-34

134. Eastwood MA, Morris ER. Physical properties of dietary fiber that influence physiological function: a model for polymers along the gastrointestinal tract. *The American journal of clinical nutrition* 1992; **55**(2)**:** 436-442. e-pub ahead of print 1992/02/01; doi: 10.1093/ajcn/55.2.436

135. Yao M, Roberts SB. Dietary energy density and weight regulation. *Nutrition reviews* 2001; **59**(8 Pt 1)**:** 247-258. e-pub ahead of print 2001/08/24; doi: 10.1111/j.1753-4887.2001.tb05509.x

136. Marciani L, Gowland PA, Spiller RC, Manoj P, Moore RJ, Young P *et al.* Effect of meal viscosity and nutrients on satiety, intragastric dilution, and emptying assessed by MRI. *Am J Physiol Gastrointest Liver Physiol* 2001; **280**(6)**:** G1227-1233. e-pub ahead of print 2001/05/16; doi: 10.1152/ajpgi.2001.280.6.G1227

137. Ho IH, Matia-Merino L, Huffman LM. Use of viscous fibres in beverages for appetite control: a review of studies. *Int J Food Sci Nutr* 2015; **66**(5)**:** 479-490. e-pub ahead of print 2015/05/23; doi: 10.3109/09637486.2015.1034252

138. Wanders AJ, van den Borne JJ, de Graaf C, Hulshof T, Jonathan MC, Kristensen M *et al.* Effects of dietary fibre on subjective appetite, energy intake and body weight: a systematic review of randomized controlled trials. *Obes Rev* 2011; **12**(9)**:** 724-739. e-pub ahead of print 2011/06/17; doi: 10.1111/j.1467-789X.2011.00895.x

139. Clark MJ, Slavin JL. The Effect of Fiber on Satiety and Food Intake: A Systematic Review. *Journal of the American College of Nutrition* 2013; **32**(3)**:** 200-211. doi: 10.1080/07315724.2013.791194

140. Warrilow A, Mellor D, McKune A, Pumpa K. Dietary fat, fibre, satiation, and satiety—a systematic review of acute studies. *European journal of clinical nutrition* 2019; **73**(3)**:** 333-344. doi: 10.1038/s41430-018-0295-7

141. Maljaars J, Romeyn EA, Haddeman E, Peters HP, Masclee AA. Effect of fat saturation on satiety, hormone release, and food intake. *The American journal of clinical nutrition* 2009; **89**(4)**:** 1019-1024. doi: 10.3945/ajcn.2008.27335

142. Comparison of ileal and duodenal brake mechanisms on satiety and gastrointestinal transport. *Gastroenterology*. WB SAUNDERS CO-ELSEVIER INC 1600 JOHN F KENNEDY BOULEVARD, STE 1800 …, 2007.

143. Blundell JE, Burley VJ, Cotton JR, Lawton CL. Dietary fat and the control of energy intake: evaluating the effects of fat on meal size and postmeal satiety. *The American journal of clinical nutrition* 1993; **57**(5 Suppl)**:** 772S-777S; discussion 777S-778S. e-pub ahead of print 1993/05/01; doi: 10.1093/ajcn/57.5.772S

144. Austin GL, Ogden LG, Hill JO. Trends in carbohydrate, fat, and protein intakes and association with energy intake in normal-weight, overweight, and obese individuals: 1971-2006. *The American journal of clinical nutrition* 2011; **93**(4)**:** 836-843. e-pub ahead of print 2011/02/12; doi: 10.3945/ajcn.110.000141

145. Feltrin KL, Little TJ, Meyer JH, Horowitz M, Smout AJ, Wishart J *et al.* Effects of intraduodenal fatty acids on appetite, antropyloroduodenal motility, and plasma CCK and GLP-1 in humans vary with their chain length. *American journal of physiology. Regulatory, integrative and comparative physiology* 2004; **287**(3)**:** R524-533. e-pub ahead of print 2004/05/29; doi: 10.1152/ajpregu.00039.2004

146. Lawton CL, Delargy HJ, Brockman J, Smith FC, Blundell JE. The degree of saturation of fatty acids influences post-ingestive satiety. *The British journal of nutrition* 2000; **83**(5)**:** 473-482. e-pub ahead of print 2000/08/23;

147. Rolls BJ, Van Duijvenvoorde PM, Rolls ET. Pleasantness changes and food intake in a varied four-course meal. *Appetite* 1984; **5**(4)**:** 337-348. e-pub ahead of print 1984/12/01; doi: 10.1016/s0195-6663(84)80006-9

148. Hetherington MM, Foster R, Newman T, Anderson AS, Norton G. Understanding variety: tasting different foods delays satiation. *Physiology & behavior* 2006; **87**(2)**:** 263-271. e-pub ahead of print 2006/01/13; doi: 10.1016/j.physbeh.2005.10.012

149. Havermans RC, Janssen T, Giesen JC, Roefs A, Jansen A. Food liking, food wanting, and sensory-specific satiety. *Appetite* 2009; **52**(1)**:** 222-225. e-pub ahead of print 2008/10/28; doi: 10.1016/j.appet.2008.09.020

150. Raynor HA, Jeffery RW, Phelan S, Hill JO, Wing RR. Amount of food group variety consumed in the diet and long-term weight loss maintenance. *Obesity research* 2005; **13**(5)**:** 883-890. e-pub ahead of print 2005/05/28; doi: 10.1038/oby.2005.102

151. Higgs S, Williamson AC, Rotshtein P, Humphreys GW. Sensory-specific satiety is intact in amnesics who eat multiple meals. *Psychol Sci* 2008; **19**(7)**:** 623-628. e-pub ahead of print 2008/08/30; doi: 10.1111/j.1467-9280.2008.02132.x

152. Smeets AJ, Westerterp-Plantenga MS. Oral exposure and sensory-specific satiety. *Physiology & behavior* 2006; **89**(2)**:** 281-286. e-pub ahead of print 2006/08/01; doi: 10.1016/j.physbeh.2006.06.011

153. den Boer A, Boesveldt S, Lawlor JB. How sweetness intensity and thickness of an oral nutritional supplement affects intake and satiety. *Food Quality and Preference* 2019; **71:** 406-414. doi: https://doi.org/10.1016/j.foodqual.2018.08.009

154. Bolhuis DP, Forde CG, Cheng Y, Xu H, Martin N, de Graaf C. Slow food: sustained impact of harder foods on the reduction in energy intake over

the course of the day. *PloS one* 2014; **9**(4)**:** e93370. e-pub ahead of print 2014/04/04; doi: 10.1371/journal.pone.0093370

155. Teo PS, Lim AJ, Goh AT, R J, Choy JYM, McCrickerd K *et al.* Texture-based differences in eating rate influence energy intake for minimally processed and ultra-processed meals. *The American journal of clinical nutrition* 2022; **116**(1)**:** 244-254. e-pub ahead of print 2022/03/15; doi: 10.1093/ajcn/nqac068

156. de Graaf C. Texture and satiation: the role of oro-sensory exposure time. *Physiology & behavior* 2012; **107**(4)**:** 496-501. e-pub ahead of print 2012/05/23; doi: 10.1016/j.physbeh.2012.05.008

157. de Graaf C. Why liquid energy results in overconsumption. *Proc Nutr Soc* 2011; **70**(2)**:** 162-170. e-pub ahead of print 2011/03/02; doi: 10.1017/s0029665111000012

158. Spetter MS, Mars M, Viergever MA, de Graaf C, Smeets PA. Taste matters - effects of bypassing oral stimulation on hormone and appetite responses. *Physiology & behavior* 2014; **137:** 9-17. e-pub ahead of print 2014/07/11; doi: 10.1016/j.physbeh.2014.06.021

159. Cecil JE, Francis J, Read NW. Relative contributions of intestinal, gastric, oro-sensory influences and information to changes in appetite induced by the same liquid meal. *Appetite* 1998; **31**(3)**:** 377-390. e-pub ahead of print 1999/01/28; doi: 10.1006/appe.1998.0177

160. Cassady BA, Considine RV, Mattes RD. Beverage consumption, appetite, and energy intake: what did you expect? *The American journal of clinical nutrition* 2012; **95**(3)**:** 587-593. e-pub ahead of print 2012/01/20; doi: 10.3945/ajcn.111.025437

161. de Graaf C, Cardello AV, Matthew Kramer F, Lesher LL, Meiselman HL, Schutz HG. A comparison between liking ratings obtained under laboratory and field conditions: the role of choice. *Appetite* 2005; **44**(1)**:** 15-22. e-pub ahead of print 2004/12/18; doi: 10.1016/j.appet.2003.06.002

162. de Graaf C, Kramer FM, Meiselman HL, Lesher LL, Baker-Fulco C, Hirsch ES *et al.* Food acceptability in field studies with US army men and women: relationship with food intake and food choice after repeated exposures. *Appetite* 2005; **44**(1)**:** 23-31. e-pub ahead of print 2004/12/18; doi: 10.1016/j.appet.2004.08.008

163. De Graaf C, De Jong LS, Lambers AC. Palatability affects satiation but not satiety. *Physiology & behavior* 1999; **66**(4)**:** 681-688. e-pub ahead of print 1999/07/01; doi: 10.1016/s0031-9384(98)00335-7

164. Premavalli KS, Wadikar DD, Nanjappa C. Comparison of the acceptability ratings of appetizers under laboratory, base level and high altitude field conditions. *Appetite* 2009; **53**(1)**:** 127-130. e-pub ahead of print 2009/05/13; doi: 10.1016/j.appet.2009.05.002

165. Forde CG. Chapter 7 - Measuring Satiation and Satiety. In: Ares G, Varela P (eds). *Methods in Consumer Research, Volume 2*. Woodhead Publishing, 2018, pp 151-182.

166. Green SM, Delargy HJ, Joanes D, Blundell JE. A satiety quotient: a formulation to assess the satiating effect of food. *Appetite* 1997; **29**(3)**:** 291-304. e-pub ahead of print 1998/02/20; doi: 10.1006/appe.1997.0096

167. Rakha A, Mehak F, Shabbir MA, Arslan M, Ranjha M, Ahmed W *et al.* Insights into the constellating drivers of satiety impacting dietary patterns and lifestyle. *Front Nutr* 2022; **9:** 1002619. e-pub ahead of print 2022/10/14; doi: 10.3389/fnut.2022.1002619

168. Davis MP, Walsh D, Lagman R, Yavuzsen T. Early satiety in cancer patients: a common and important but underrecognized symptom. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2006; **14**(7)**:** 693-698. doi: 10.1007/s00520-005-0015-4

169. Stanghellini V, Chan FKL, Hasler WL, Malagelada JR, Suzuki H, Tack J *et al.* Gastroduodenal Disorders. *Gastroenterology* 2016; **150**(6)**:** 1380-1392. doi: 10.1053/j.gastro.2016.02.011

170. Camilleri M, Kuo B, Nguyen L, Vaughn VM, Petrey J, Greer K *et al.* ACG Clinical Guideline: Gastroparesis. *Am J Gastroenterol* 2022; **117**(8)**:** 1197-1220. e-pub ahead of print 2022/08/05; doi: 10.14309/ajg.0000000000001874

171. Deftereos I, Yeung JMC, Arslan J, Carter VM, Isenring E, Kiss N *et al.* Assessment of Nutritional Status and Nutrition Impact Symptoms in Patients Undergoing Resection for Upper Gastrointestinal Cancer: Results from the Multi-Centre NOURISH Point Prevalence Study. *Nutrients* 2021; **13**(10)**:** 3349.

172. de Pinho NB, Martucci RB, Rodrigues VD, D'Almeida CA, Thuler LCS, Saunders C *et al.* High prevalence of malnutrition and nutrition impact symptoms in older patients with cancer: Results of a Brazilian multicenter study. *Cancer* 2020; **126**(1)**:** 156-164. doi: https://doi.org/10.1002/cncr.32437

173. Neoh MK, Abu Zaid Z, Mat Daud ZA, Md. Yusop NB, Ibrahim Z, Abdul Rahman Z *et al.* Changes in Nutrition Impact Symptoms, Nutritional and Functional Status during Head and Neck Cancer Treatment. *Nutrients* 2020; **12**(5)**:** 1225.

174. McGettigan N, Dhuibhir PU, Barrett M, Sui J, Balding L, Higgins S *et al.* Subjective and Objective Assessment of Taste and Smell Sensation in Advanced Cancer. *American Journal of Hospice and Palliative Medicine*® 2019; **36**(8)**:** 688-696. doi: 10.1177/1049909119832836

175. Komurcu S, Nelson KA, Walsh D, Ford RB, Rybicki LA. Gastrointestinal symptoms among inpatients with advanced cancer. *Am J Hosp Palliat Care* 2002; **19**(5)**:** 351-355. e-pub ahead of print 2002/09/25; doi: 10.1177/104990910201900513

176. O'Donoghue A, Barrett M, Dhuibhir PU, Kennedy A, O'Leary N, Walsh D. Taste and smell abnormalities in advanced cancer: Negative impact on subjective food intake. *Nutrition in Clinical Practice*; **n/a**(n/a). doi: https://doi.org/10.1002/ncp.10943

177. Walsh D, Donnelly S, Rybicki L. The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2000; **8**(3)**:** 175-179. e-pub ahead of print 2000/05/02;

178. Stavraka C, Ford A, Ghaem-Maghami S, Crook T, Agarwal R, Gabra H *et al.* A study of symptoms described by ovarian cancer survivors. *Gynecologic Oncology* 2012; **125**(1)**:** 59-64. doi: https://doi.org/10.1016/j.ygyno.2011.12.421

179. Camilleri M. Gastroparesis: Etiology, clinical manifestations, and diagnosis. In: Nicholas J Talley SG, (ed).

180. Camilleri M, Dubois D, Coulie B, Jones M, Kahrilas PJ, Rentz AM *et al.* Prevalence and socioeconomic impact of upper gastrointestinal disorders in the United States: results of the US Upper Gastrointestinal Study. *Clin Gastroenterol Hepatol* 2005; **3**(6)**:** 543-552. e-pub ahead of print 2005/06/14; doi: 10.1016/s1542-3565(05)00153-9

181. Jespersen JB, Beck AM, Munk T, Jensen HO, Knudsen AW. Low-intake dehydration and nutrition impact symptoms in older medical patients – A retrospective study. *Clinical Nutrition ESPEN* 2023; **57:** 190-196. doi: https://doi.org/10.1016/j.clnesp.2023.06.030

182. Sung H-Y, Park J-W, Kim J-S. The frequency and severity of gastrointestinal symptoms in patients with early Parkinson's disease. *J Mov Disord* 2014; **7**(1)**:** 7-12. e-pub ahead of print 2014/04/30; doi: 10.14802/jmd.14002

183. Cochrane WJ, Afolabi OA. Investigation into the nutritional status, dietary intake and smoking habits of patients with chronic obstructive pulmonary disease. *Journal of Human Nutrition and Dietetics* 2004; **17**(1)**:** 3-11. doi: 10.1046/j.1365-277X.2003.00478.x

184. Ariffin NFM NL, Pisharam J, Khalil MAM, Tamin N, Chong VH, Tan J. Appetite and Gastrointestinal Symptoms in End Stage Renal Disease Patients. *Journal of Clinical & Experimental Nephrology* 2016; **1**(6). doi: 10.21767/2472-5056.100006

185. Opasich C, Gualco A. The complex symptom burden of the aged heart failure population. *Curr Opin Support Palliat Care* 2007; **1**(4)**:** 255-259. e-pub ahead of print 2008/08/08; doi: 10.1097/SPC.0b013e3282f33f98

186. Homsi J, Walsh D, Rivera N, Rybicki LA, Nelson KA, Legrand SB *et al.* Symptom evaluation in palliative medicine: patient report vs systematic assessment. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2006; **14**(5)**:** 444-453. e-pub ahead of print 2006/01/13; doi: 10.1007/s00520-005-0009-2

187. Teunissen SC, Wesker W, Kruitwagen C, de Haes HC, Voest EE, de Graeff A. Symptom prevalence in patients with incurable cancer: a systematic review. *Journal of pain and symptom management* 2007; **34**(1)**:** 94-104. e-pub ahead of print 2007/05/19; doi: 10.1016/j.jpainsymman.2006.10.015

188. Deloose E, Janssen P, Depoortere I, Tack J. The migrating motor complex: control mechanisms and its role in health and disease. *Nat Rev Gastroenterol Hepatol* 2012; **9**(5)**:** 271-285. e-pub ahead of print 2012/03/28; doi: 10.1038/nrgastro.2012.57

189. Parkman HP, Hallinan EK, Hasler WL, Farrugia G, Koch KL, Nguyen L *et al.* Early satiety and postprandial fullness in gastroparesis correlate with gastroparesis severity, gastric emptying, and water load testing. *Neurogastroenterol Motil* 2017; **29**(4). e-pub ahead of print 2016/10/27; doi: 10.1111/nmo.12981

190. Nelson KA, Walsh TD, Sheehan FG, O'Donovan PB, Falk GW. Assessment of upper gastrointestinal motility in the cancer-associated dyspepsia syndrome. *J Palliat Care* 1993; **9**(1)**:** 27-31. e-pub ahead of print 1993/01/01;

191. Kelly D, Moran C, Maher M, O'Mahony S. Malignancy-associated gastroparesis: an important and overlooked cause of chronic nausea and vomiting. 2014. doi: 10.1136/bcr-2013-201815

192. Tack J, Piessevaux H, Coulie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in functional dyspepsia. *Gastroenterology* 1998; **115**(6)**:** 1346-1352. doi: 10.1016/S0016-5085(98)70012-5

193. Piessevaux H, Tack J, Walrand S, Pauwels S, Geubel A. Intragastric distribution of a standardized meal in health and functional dyspepsia: correlation with specific symptoms. *Neurogastroenterol Motil* 2003; **15**(5)**:** 447-455. e-pub ahead of print 2003/09/26; doi: 10.1046/j.1365-2982.2003.00431.x

194. Karamanolis G, Caenepeel P, Arts J, Tack J. Determinants of symptom pattern in idiopathic severely delayed gastric emptying: gastric emptying rate or proximal stomach dysfunction? *Gut* 2007; **56**(1)**:** 29-36. e-pub ahead of print 2006/07/13; doi: 10.1136/gut.2005.089508

195. Kim DY, Camilleri M. Noninvasive measurement of gastric accommodation by SPECT. *Korean J Intern Med* 2002; **17**(1)**:** 1-6. e-pub ahead of print 2002/05/17; doi: 10.3904/kjim.2002.17.1.1

196. Tomita T, Okugawa T, Yamasaki T, Kondo T, Toyoshima F, Sakurai J *et al.* Use of scintigraphy to evaluate gastric accommodation and emptying: Comparison with barostat. *Journal of Gastroenterology and Hepatology* 2013; **28**(1)**:** 106-111. doi: https://doi.org/10.1111/j.1440-1746.2012.07261.x

197. Choi M-G, Kim BW, Choo KY, Park SH, Jung SE, Lee JM *et al.* Measurement of gastric accommodation and emptying of a solid meal by magnetic resonance imaging. *Gastroenterology* 2000; **118**(4, Part 1)**:** A388-A389. doi: https://doi.org/10.1016/S0016-5085(00)83664-1

198. Silver PJ, Dadparvar S, Maurer AH, Parkman HP. Proximal and distal intragastric meal distribution during gastric emptying scintigraphy: Relationships to symptoms of gastroparesis. *Neurogastroenterology & Motility* 2022; **34**(12)**:** e14436. doi: https://doi.org/10.1111/nmo.14436

199. Campbell IW, Heading RC, Tothill P, Buist TA, Ewing DJ, Clarke BF. Gastric emptying in diabetic autonomic neuropathy. *Gut* 1977; **18**(6)**:** 462-467. e-pub ahead of print 1977/06/01; doi: 10.1136/gut.18.6.462

200. Mohammad MK, Pepper DJ, Kedar A, Bhaijee F, Familoni B, Rashed H *et al.* Measures of Autonomic Dysfunction in Diabetic and Idiopathic Gastroparesis. *Gastroenterology Res* 2016; **9**(4-5)**:** 65-69. e-pub ahead of print 2016/10/28; doi: 10.14740/gr713w

201. Hausken T, Svebak S, Wilhelmsen I, Haug TT, Olafsen K, Pettersson E *et al.* Low vagal tone and antral dysmotility in patients with functional dyspepsia. *Psychosom Med* 1993; **55**(1)**:** 12-22. e-pub ahead of print 1993/01/01; doi: 10.1097/00006842-199301000-00004

202. Hejazi RA, Lavenbarg TH, Pasnoor M, Dimachkie M, Foran P, Herbelin L *et al.* Autonomic nerve function in adult patients with cyclic vomiting syndrome. *Neurogastroenterology & Motility* 2011; **23**(5)**:** 439-443. doi: https://doi.org/10.1111/j.1365-2982.2011.01679.x

203. Wells R, Tonkin A. Clinical approach to autonomic dysfunction. *Internal Medicine Journal* 2016; **46**(10)**:** 1134-1139. doi: https://doi.org/10.1111/imj.13216

204. Stone CA, Kenny RA, Nolan B, Lawlor PG. Autonomic dysfunction in patients with advanced cancer; prevalence, clinical correlates and challenges in assessment. *BMC Palliat Care* 2012; **11:** 3-3. doi: 10.1186/1472-684X-11-3

205. Park H, Lee JY, Shin CM, Kim J-M, Kim TJ, Kim JW. Characterization of gastrointestinal disorders in patients with parkinsonian syndromes.

Parkinsonism & Related Disorders 2015; **21**(5)**:** 455-460. doi: https://doi.org/10.1016/j.parkreldis.2015.02.005

206. Bruera E, Chadwick S, Fox R, Hanson J, MacDonald N. Study of cardiovascular autonomic insufficiency in advanced cancer patients. *Cancer Treat Rep* 1986; **70**(12)**:** 1383-1387. e-pub ahead of print 1986/12/01;

207. Wang JY, Wang QW, Yang XY, Yang W, Li DR, Jin JY *et al.* GLP-1 receptor agonists for the treatment of obesity: Role as a promising approach. *Front Endocrinol (Lausanne)* 2023; **14:** 1085799. e-pub ahead of print 2023/02/28; doi: 10.3389/fendo.2023.1085799

208. Goodarzi MO, Petrov MS. Diabetes of the Exocrine Pancreas: Implications for Pharmacological Management. *Drugs* 2023. doi: 10.1007/s40265-023-01913-5

209. Jacobsen SH, Olesen SC, Dirksen C, Jørgensen NB, Bojsen-Møller KN, Kielgast U *et al.* Changes in gastrointestinal hormone responses, insulin sensitivity, and beta-cell function within 2 weeks after gastric bypass in non-diabetic subjects. *Obes Surg* 2012; **22**(7)**:** 1084-1096. e-pub ahead of print 2012/02/24; doi: 10.1007/s11695-012-0621-4

210. Laferrère B, Teixeira J, McGinty J, Tran H, Egger JR, Colarusso A *et al.* Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2008; **93**(7)**:** 2479-2485. e-pub ahead of print 2008/04/24; doi: 10.1210/jc.2007-2851

211. Casajoana A, Pujol J, Garcia A, Elvira J, Virgili N, de Oca FJ *et al.* Predictive Value of Gut Peptides in T2D Remission: Randomized Controlled Trial Comparing Metabolic Gastric Bypass, Sleeve Gastrectomy and Greater Curvature Plication. *Obes Surg* 2017; **27**(9)**:** 2235-2245. e-pub ahead of print 2017/04/30; doi: 10.1007/s11695-017-2669-7

212. Harmuth S, Wewalka M, Holst JJ, Nemecek R, Thalhammer S, Schmid R *et al.* Distal gastrectomy in pancreaticoduodenectomy is associated with accelerated gastric emptying, enhanced postprandial release of GLP-1, and improved insulin sensitivity. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2014; **18**(1)**:** 52-59. e-pub ahead of print 2013/09/05; doi: 10.1007/s11605-013-2283-5

213. Elliott JA, Jackson S, King S, McHugh R, Docherty NG, Reynolds JV *et al.* Gut Hormone Suppression Increases Food Intake After Esophagectomy With Gastric Conduit Reconstruction. *Annals of surgery* 2015; **262**(5)**:** 824-829; discussion 829-830. e-pub ahead of print 2015/11/20; doi: 10.1097/sla.0000000000001465

214. Bodén S, Harbs J, Sundkvist A, Fuchs K, Myte R, Gylling B *et al.* Plasma Concentrations of Gut Hormones Acyl Ghrelin and Peptide YY and

Subsequent Risk of Colorectal Cancer and Molecular Tumor Subtypes. *Cancer Prev Res (Phila)* 2023; **16**(2)**:** 75-87. e-pub ahead of print 2022/11/12; doi: 10.1158/1940-6207.Capr-22-0325

215. Walsh D, Rybicki L. Symptom clustering in advanced cancer. *Support Care Cancer* 2006; **14**(8)**:** 831-836. e-pub ahead of print 2006/02/17; doi: 10.1007/s00520-005-0899-z

216. Yavuzsen T, Walsh D, Davis MP, Kirkova J, Jin T, LeGrand S *et al.* Components of the anorexia-cachexia syndrome: gastrointestinal symptom correlates of cancer anorexia. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2009; **17**(12)**:** 1531-1541. e-pub ahead of print 2009/04/08; doi: 10.1007/s00520-009-0623-5

217. Parkman HP, Hallinan EK, Hasler WL, Farrugia G, Koch KL, Nguyen L *et al.* Early satiety and postprandial fullness in gastroparesis correlate with gastroparesis severity, gastric emptying, and water load testing. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society* 2017; **29**(4)**:** 10.1111/nmo.12981. e-pub ahead of print 2016/10/25; doi: 10.1111/nmo.12981

218. Yu D, Ramsey FV, Norton WF, Norton N, Schneck S, Gaetano T *et al.* The Burdens, Concerns, and Quality of Life of Patients with Gastroparesis. *Digestive diseases and sciences* 2017; **62**(4)**:** 879-893. doi: 10.1007/s10620-017-4456-7

219. Fearon KC, Voss AC, Hustead DS. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. *The American journal of clinical nutrition* 2006; **83**(6)**:** 1345-1350. doi: 10.1093/ajcn/83.6.1345

220. de Pinho NB, Martucci RB, Rodrigues VD, D'Almeida CA, Thuler LCS, Saunders C *et al.* Malnutrition associated with nutrition impact symptoms and localization of the disease: Results of a multicentric research on oncological nutrition. *Clinical Nutrition* 2019; **38**(3)**:** 1274-1279. doi: https://doi.org/10.1016/j.clnu.2018.05.010

221. Levitsky A, Pernemalm M, Bernhardson B-M, Forshed J, Kölbeck K, Olin M *et al.* Early symptoms and sensations as predictors of lung cancer: a machine learning multivariate model. *Scientific Reports* 2019; **9**(1)**:** 16504. doi: 10.1038/s41598-019-52915-x

222. Damiano A, Handley K, Adler E, Siddique R, Bhattacharyja A. Measuring Symptom Distress and Health-Related Quality of Life in Clinical Trials of Gastroesophageal Reflux Disease Treatment: Further Validation of the Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS). *Digestive diseases and sciences* 2002; **47**(7)**:** 1530-1537. doi: 10.1023/A:1015815102175

223. Bener A, Ghuloum S, Al-Hamaq AO, Dafeeah EE. Association between psychological distress and gastrointestinal symptoms in diabetes mellitus. *World J Diabetes* 2012; **3**(6)**:** 123-129. e-pub ahead of print 2012/06/28; doi: 10.4239/wjd.v3.i6.123

224. Talley SJ, Bytzer P, Hammer J, Young L, Jones M, Horowitz M. Psychological distress is linked to gastrointestinal symptoms in diabetes mellitus. *Am J Gastroenterol* 2001; **96**(4)**:** 1033-1038. e-pub ahead of print 2001/04/24; doi: 10.1111/j.1572-0241.2001.03605.x

225. Lee SS, Chung HY, Kwon OK, Yu W. Quality of life in cancer survivors 5 years or more after total gastrectomy: A case-control study. *International Journal of Surgery* 2014; **12**(7)**:** 700-705. doi: https://doi.org/10.1016/j.ijsu.2014.05.067

226. Talley NJ, III GRL, Lahr BD, Zinsmeister AR, Tougas G, Ligozio G *et al.* Functional dyspepsia, delayed gastric emptying, and impaired quality of life. *Gut* 2006; **55**(7)**:** 933-939. doi: 10.1136/gut.2005.078634

227. Del Fabbro E, Hui D, Dalal S, Dev R, Nooruddin ZI, Bruera E. Clinical outcomes and contributors to weight loss in a cancer cachexia clinic. *J Palliat Med* 2011; **14**(9)**:** 1004-1008. e-pub ahead of print 2011/07/27; doi: 10.1089/jpm.2011.0098

228. Moayyedi P, Soo S, Deeks J, Delaney B, Innes M, Forman D *et al.* Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database of Systematic Reviews* 2003; (1). doi: 10.1002/14651858.CD001960

229. Ruiz Garcia V, López-Briz E, Carbonell Sanchis R, Gonzalvez Perales JL, Bort-Martí S. Megestrol acetate for treatment of anorexia-cachexia syndrome. *Cochrane Database of Systematic Reviews* 2013; (3). doi: 10.1002/14651858.CD004310.pub3

230. Dev R, Wong A, Hui D, Bruera E. The Evolving Approach to Management of Cancer Cachexia. *Oncology (Williston Park)* 2017; **31**(1)**:** 23-32. e-pub ahead of print 2017/01/17;

231. May MB, Glode AE. Dronabinol for chemotherapy-induced nausea and vomiting unresponsive to antiemetics. *Cancer Manag Res* 2016; **8:** 49-55. e-pub ahead of print 2016/06/09; doi: 10.2147/cmar.S81425

232. Tramèr MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *Bmj* 2001; **323**(7303)**:** 16-21. e-pub ahead of print 2001/07/07; doi: 10.1136/bmj.323.7303.16

233. Arends J, Strasser F, Gonella S, Solheim TS, Madeddu C, Ravasco P *et al.* Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines(☆). *ESMO Open* 2021; **6**(3)**:** 100092. e-pub ahead of print 2021/06/20; doi: 10.1016/j.esmoop.2021.100092

234. Tack J, Ly HG, Carbone F, Vanheel H, Vanuytsel T, Holvoet L *et al.* Efficacy of Mirtazapine in Patients With Functional Dyspepsia and Weight Loss. *Clin Gastroenterol Hepatol* 2016; **14**(3)**:** 385-392.e384. e-pub ahead of print 2015/11/06; doi: 10.1016/j.cgh.2015.09.043

235. Moertel CG, Schutt AJ, Reitemeier RJ, Hahn RG. Corticosteroid therapy of preterminal gastrointestinal cancer. *Cancer* 1974; **33**(6)**:** 1607-1609. e-pub ahead of print 1974/06/01; doi: 10.1002/1097-0142(197406)33:6<1607::aid-cncr2820330620>3.0.co;2-v

236. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Mol Cell Endocrinol* 2011; **335**(1)**:** 2-13. e-pub ahead of print 2010/04/20; doi: 10.1016/j.mce.2010.04.005

237. Lembo A, Camilleri M, McCallum R, Sastre R, Breton C, Spence S *et al.* Relamorelin Reduces Vomiting Frequency and Severity and Accelerates Gastric Emptying in Adults With Diabetic Gastroparesis. *Gastroenterology* 2016; **151**(1)**:** 87-96.e86. e-pub ahead of print 2016/04/09; doi: 10.1053/j.gastro.2016.03.038

238. Camilleri M, McCallum RW, Tack J, Spence SC, Gottesdiener K, Fiedorek FT. Efficacy and Safety of Relamorelin in Diabetics With Symptoms of Gastroparesis: A Randomized, Placebo-Controlled Study. *Gastroenterology* 2017; **153**(5)**:** 1240-1250.e1242. e-pub ahead of print 2017/08/02; doi: 10.1053/j.gastro.2017.07.035

239. Camilleri M. Novel Diet, Drugs, and Gastric Interventions for Gastroparesis. *Clin Gastroenterol Hepatol* 2016; **14**(8)**:** 1072-1080. e-pub ahead of print 2016/01/04; doi: 10.1016/j.cgh.2015.12.033

240. Benini L, Castellani G, Brighenti F, Heaton KW, Brentegani MT, Casiraghi MC *et al.* Gastric emptying of a solid meal is accelerated by the removal of dietary fibre naturally present in food. *Gut* 1995; **36**(6)**:** 825-830. doi: 10.1136/gut.36.6.825

241. Sadiya A. Nutritional therapy for the management of diabetic gastroparesis: clinical review. *Diabetes, Metabolic Syndrome and Obesity* 2012; **5:** 329-335. doi: 10.2147/DMSO.S31962

242. Mattes R. Fluid calories and energy balance: The good, the bad, and the uncertain. *Physiology & behavior* 2006; **89**(1)**:** 66-70. doi: https://doi.org/10.1016/j.physbeh.2006.01.023

243. Tsuchiya A, Almiron-Roig E, Lluch A, Guyonnet D, Drewnowski A. Higher Satiety Ratings Following Yogurt Consumption Relative to Fruit Drink or Dairy Fruit Drink. *Journal of the American Dietetic Association* 2006; **106**(4)**:** 550-557. doi: https://doi.org/10.1016/j.jada.2006.01.004

244. Rolls BJ, Castellanos VH, Halford JC, Kilara A, Panyam D, Pelkman CL *et al.* Volume of food consumed affects satiety in men. *The American journal of clinical nutrition* 1998; **67**(6)**:** 1170-1177. e-pub ahead of print 1998/06/13; doi: 10.1093/ajcn/67.6.1170

245. Rolls BJ. The relationship between dietary energy density and energy intake. *Physiology & behavior* 2009; **97**(5)**:** 609-615. e-pub ahead of print 2009/03/24; doi: 10.1016/j.physbeh.2009.03.011

246. Dashti HS, Mogensen KM. Recommending Small, Frequent Meals in the Clinical Care of Adults: A Review of the Evidence and Important Considerations. *Nutrition in Clinical Practice* 2017; **32**(3)**:** 365-377. doi: https://doi.org/10.1177/0884533616662995

247. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL *et al.* Nutrition and physical activity guidelines for cancer survivors. *CA: A Cancer Journal for Clinicians* 2012; **62**(4)**:** 242-274. doi: https://doi.org/10.3322/caac.21142

248. de Castro JM. Circadian rhythms of the spontaneous meal pattern, macronutrient intake, and mood of humans. *Physiology & behavior* 1987; **40**(4)**:** 437-446. doi: https://doi.org/10.1016/0031-9384(87)90028-X

249. de Castro JM. The time of day of food intake influences overall intake in humans. *J Nutr* 2004; **134**(1)**:** 104-111. e-pub ahead of print 2004/01/06; doi: 10.1093/jn/134.1.104

250. Harris PE, Cooper KL, Relton C, Thomas KJ. Prevalence of complementary and alternative medicine (CAM) use by the general population: a systematic review and update. *Int J Clin Pract* 2012; **66**(10)**:** 924-939. e-pub ahead of print 2012/09/22; doi: 10.1111/j.1742-1241.2012.02945.x

251. Bahall M. Prevalence, patterns, and perceived value of complementary and alternative medicine among cancer patients: a cross-sectional, descriptive study. *BMC Complement Altern Med* 2017; **17**(1)**:** 345. e-pub ahead of print 2017/07/02; doi: 10.1186/s12906-017-1853-6

252. Molassiotis A, Fernadez-Ortega P, Pud D, Ozden G, Scott JA, Panteli V *et al.* Use of complementary and alternative medicine in cancer patients: a European survey. *Annals of Oncology* 2005; **16**(4)**:** 655-663. doi: https://doi.org/10.1093/annonc/mdi110

253. Van Vu D, Molassiotis A, Ching SSY, Le TT. Effects of Qigong on symptom management in cancer patients: A systematic review. *Complementary Therapies in Clinical Practice* 2017; **29:** 111-121. doi: https://doi.org/10.1016/j.ctcp.2017.09.005

254. Tominaga K, Sakata Y, Kusunoki H, Odaka T, Sakurai K, Kawamura O *et al.* Rikkunshito simultaneously improves dyspepsia correlated with anxiety in patients with functional dyspepsia: A randomized clinical trial (the

DREAM study). *Neurogastroenterol Motil* 2018; **30**(7)**:** e13319. e-pub ahead of print 2018/03/03; doi: 10.1111/nmo.13319

255. Dewey A, Baughan C, Dean TP, Higgins B, Johnson I. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. *Cochrane Database of Systematic Reviews* 2007; (1). doi: 10.1002/14651858.CD004597.pub2

256. Zhou W, Su J, Zhang H. Efficacy and Safety of Acupuncture for the Treatment of Functional Dyspepsia: Meta-Analysis. *J Altern Complement Med* 2016; **22**(5)**:** 380-389. e-pub ahead of print 2016/03/31; doi: 10.1089/acm.2014.0400

257. Peng T, Huang X, Zhu M, Hou X, Xiong Y, Fang X *et al.* Effect of different acupuncture and moxibustion methods on functional dyspepsia caused by sequelae of COVID-19: A protocol for systematic review and meta-analysis. *Medicine (Baltimore)* 2022; **101**(38)**:** e30770. e-pub ahead of print 2022/10/06; doi: 10.1097/md.0000000000030770

258. Wang Y, Yang J-W, Hu H, Wang J, Zhao J-J, Zhou W *et al.* [Improvement in dyspepsia related symptoms treated with acupuncture in 278 patients with postprandial distress syndrome: a secondary analysis of a multi-center randomized controlled trial]. *Zhongguo Zhen Jiu* 2021; **41**(6)**:** 583-587. doi: 10.13703/j.0255-2930.20200527-k0001

259. Jin Y, Zhao Q, Zhou K, Jing X, Yu X, Fang J *et al.* Acupuncture for Functional Dyspepsia: A Single Blinded, Randomized, Controlled Trial. *Evidence-Based Complementary and Alternative Medicine* 2015; **2015:** 904926. doi: 10.1155/2015/904926

260. Parkman HP, Yates KP, Sarosiek I, Bulat RS, Abell TL, Koch KL *et al.* Buspirone for early satiety and symptoms of gastroparesis: A multi-centre, randomised, placebo-controlled, double-masked trial (BESST). *Alimentary pharmacology & therapeutics* 2023; **57**(11)**:** 1272-1289. e-pub ahead of print 2023/04/14; doi: 10.1111/apt.17479

261. Tack J, Janssen P, Masaoka T, Farré R, Van Oudenhove L. Efficacy of buspirone, a fundus-relaxing drug, in patients with functional dyspepsia. *Clin Gastroenterol Hepatol* 2012; **10**(11)**:** 1239-1245. e-pub ahead of print 2012/07/21; doi: 10.1016/j.cgh.2012.06.036

262. Lan L, Yu J, Chen YL, Zhong YL, Zhang H, Jia CH *et al.* Symptom-based tendencies of Helicobacter pylori eradication in patients with functional dyspepsia. *World J Gastroenterol* 2011; **17**(27)**:** 3242-3247. e-pub ahead of print 2011/09/14; doi: 10.3748/wjg.v17.i27.3242

263. Walker MM, Aggarwal KR, Shim LS, Bassan M, Kalantar JS, Weltman MD *et al.* Duodenal eosinophilia and early satiety in functional dyspepsia: confirmation of a positive association in an Australian cohort. *J Gastroenterol Hepatol* 2014; **29**(3)**:** 474-479. e-pub ahead of print 2013/12/07; doi: 10.1111/jgh.12419

264. Walker MM, Salehian SS, Murray CE, Rajendran A, Hoare JM, Negus R *et al.* Implications of eosinophilia in the normal duodenal biopsy - an association with allergy and functional dyspepsia. *Alimentary pharmacology & therapeutics* 2010; **31**(11)**:** 1229-1236. e-pub ahead of print 2010/03/13; doi: 10.1111/j.1365-2036.2010.04282.x

265. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F *et al.* Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010; **39**(4)**:** 412-423. e-pub ahead of print 2010/04/13; doi: 10.1093/ageing/afq034

266. White JV, Guenter P, Jensen G, Malone A, Schofield M. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *JPEN J Parenter Enteral Nutr* 2012; **36**(3)**:** 275-283. e-pub ahead of print 2012/04/27; doi: 10.1177/0148607112440285

267. Liao K-H. The effect of wrist posture and forearm position on the control capability of hand-grip strength. *The International Journal of Industrial Engineering: Theory, Applications and Practice* 2014; **21:** 295-303.

268. Chua KY, Lim WS, Lin X, Yuan JM, Koh W-P. Handgrip Strength and Timed Up-and-Go (TUG) Test are Predictors of Short-Term Mortality among Elderly in a Population-Based Cohort in Singapore. *The journal of nutrition, health & aging* 2020; **24**(4)**:** 371-378. doi: 10.1007/s12603-020-1337-0

269. Zhuang CL, Zhang FM, Li W, Wang KH, Xu HX, Song CH *et al.* Associations of low handgrip strength with cancer mortality: a multicentre observational study. *J Cachexia Sarcopenia Muscle* 2020; **11**(6)**:** 1476-1486. e-pub ahead of print 2020/09/11; doi: 10.1002/jcsm.12614

270. Wind AE, Takken T, Helders PJ, Engelbert RH. Is grip strength a predictor for total muscle strength in healthy children, adolescents, and young adults? *Eur J Pediatr* 2010; **169**(3)**:** 281-287. e-pub ahead of print 2009/06/16; doi: 10.1007/s00431-009-1010-4

271. Forrest KYZ, Williams AM, Leeds MJ, Robare JF, Bechard TJ. Patterns and Correlates of Grip Strength in Older Americans. *Curr Aging Sci* 2018; **11**(1)**:** 63-70. e-pub ahead of print 2017/11/19; doi: 10.2174/1874609810666171116164000

272. Sallinen J, Stenholm S, Rantanen T, Heliövaara M, Sainio P, Koskinen S. Hand-grip strength cut points to screen older persons at risk for mobility limitation. *J Am Geriatr Soc* 2010; **58**(9)**:** 1721-1726. e-pub ahead of print 2010/09/25; doi: 10.1111/j.1532-5415.2010.03035.x

273. Wang Y-C, Bohannon RW, Li X, Sindhu B, Kapellusch J. Hand-Grip Strength: Normative Reference Values and Equations for Individuals 18 to 85 Years of Age Residing in the United States. *Journal of Orthopaedic & Sports Physical Therapy* 2018; **48**(9)**:** 685-693. doi: 10.2519/jospt.2018.7851

274. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport* 1999; **70**(2)**:** 113-119. e-pub ahead of print 1999/06/25; doi: 10.1080/02701367.1999.10608028

275. Kuo YL. The influence of chair seat height on the performance of community-dwelling older adults' 30-second chair stand test. *Aging Clin Exp Res* 2013; **25**(3)**:** 305-309. e-pub ahead of print 2013/06/07; doi: 10.1007/s40520-013-0041-x

276. McKay MJ, Baldwin JN, Ferreira P, Simic M, Vanicek N, Burns J *et al.* Reference values for developing responsive functional outcome measures across the lifespan. *Neurology* 2017; **88**(16)**:** 1512-1519. doi: 10.1212/wnl.0000000000003847

277. Rikli RE, Jones CJ. Functional Fitness Normative Scores for Community-Residing Older Adults, Ages 60-94. *Journal of Aging and Physical Activity* 1999; **7**(2)**:** 162-181. doi: 10.1123/japa.7.2.162

278. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991; **39**(2)**:** 142-148. e-pub ahead of print 1991/02/01; doi: 10.1111/j.1532-5415.1991.tb01616.x

279. Mathias S, Nayak US, Isaacs B. Balance in elderly patients: the "get-up and go" test. *Arch Phys Med Rehabil* 1986; **67**(6)**:** 387-389. e-pub ahead of print 1986/06/01;

280. Soubeyran P, Fonck M, Blanc-Bisson C, Blanc JF, Ceccaldi J, Mertens C *et al.* Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. *J Clin Oncol* 2012; **30**(15)**:** 1829-1834. e-pub ahead of print 2012/04/18; doi: 10.1200/jco.2011.35.7442

281. Rose DJ, Jones CJ, Lucchese N. Predicting the Probability of Falls in Community-Residing Older Adults Using the 8-Foot Up-and-Go: A New Measure of Functional Mobility. *Journal of Aging and Physical Activity* 2002; **10**(4)**:** 466-475. doi: 10.1123/japa.10.4.466

282. Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS *et al.* Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. *J Clin Oncol* 2018; **36**(22)**:** 2326-2347. e-pub ahead of print 2018/05/22; doi: 10.1200/jco.2018.78.8687

283. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc* 2011; **59**(1)**:** 148-157. e-pub ahead of print 2011/01/14; doi: 10.1111/j.1532-5415.2010.03234.x

284. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP *et al.* Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol* 2011; **29**(25)**:** 3457-3465. e-pub ahead of print 2011/08/04; doi: 10.1200/jco.2011.34.7625

285. Chun S, Shin DW, Han K, Jung JH, Kim B, Jung H-W *et al.* The Timed Up and Go test and the ageing heart: Findings from a national health screening of 1,084,875 community-dwelling older adults. *European Journal of Preventive Cardiology* 2019; **28**(2)**:** 213-219. doi: 10.1177/2047487319882118

286. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000; **894:** i-xii, 1-253. e-pub ahead of print 2001/03/10;

287. Bauer J, Capra S, Ferguson M. Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *European journal of clinical nutrition* 2002; **56**(8)**:** 779-785. e-pub ahead of print 2002/07/18; doi: 10.1038/sj.ejcn.1601412

288. Rodrigues CS, Lacerda MS, Chaves GV. Patient Generated Subjective Global Assessment as a prognosis tool in women with gynecologic cancer. *Nutrition* 2015; **31**(11-12)**:** 1372-1378. e-pub ahead of print 2015/10/03; doi: 10.1016/j.nut.2015.06.001

289. Banning LBD, ter Beek L, El Moumni M, Visser L, Zeebregts CJ, Jager-Wittenaar H *et al.* Vascular Surgery Patients at Risk for Malnutrition Are at an Increased Risk of Developing Postoperative Complications. *Annals of Vascular Surgery* 2020; **64:** 213-220. doi: https://doi.org/10.1016/j.avsg.2019.10.037

290. Beek Lt, Banning LBD, Visser L, Roodenburg JLN, Krijnen WP, van der Schans CP *et al.* Risk for malnutrition in patients prior to vascular surgery. *The American Journal of Surgery* 2018; **216**(3)**:** 534-539. doi: https://doi.org/10.1016/j.amjsurg.2017.11.038

291. Jager-Wittenaar H, Ottery FD. Assessing nutritional status in cancer: role of the Patient-Generated Subjective Global Assessment. *Curr Opin Clin Nutr Metab Care* 2017; **20**(5)**:** 322-329. doi: 10.1097/MCO.0000000000000389

292. Balstad TR, Bye A, Jenssen CR, Solheim TS, Thoresen L, Sand K. Patient interpretation of the Patient-Generated Subjective Global Assessment (PG-SGA) Short Form. *Patient Prefer Adherence* 2019; **13:** 1391-1400. e-pub ahead of print 2019/09/10; doi: 10.2147/ppa.S204188

293. Gabrielson DK, Scaffidi D, Leung E, Stoyanoff L, Robinson J, Nisenbaum R *et al.* Use of an abridged scored Patient-Generated Subjective Global Assessment (abPG-SGA) as a nutritional screening tool for cancer patients in an outpatient setting. *Nutr Cancer* 2013; **65**(2)**:** 234-239. e-pub ahead of print 2013/02/28; doi: 10.1080/01635581.2013.755554

294. Sealy MJ, Nijholt W, Stuiver MM, van der Berg MM, Roodenburg JL, van der Schans CP *et al.* Content validity across methods of malnutrition assessment in patients with cancer is limited. *J Clin Epidemiol* 2016; **76:** 125-136. e-pub ahead of print 2016/03/05; doi: 10.1016/j.jclinepi.2016.02.020

295. de van der Schueren MAE, Keller H, Cederholm T, Barazzoni R, Compher C, Correia M *et al.* Global Leadership Initiative on Malnutrition (GLIM): Guidance on validation of the operational criteria for the diagnosis of protein-energy malnutrition in adults. *Clin Nutr* 2020; **39**(9)**:** 2872-2880. e-pub ahead of print 2020/06/22; doi: 10.1016/j.clnu.2019.12.022

296. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**(5)**:** 365-376. e-pub ahead of print 1993/03/03; doi: 10.1093/jnci/85.5.365

297. Giesinger JM, Loth FLC, Aaronson NK, Arraras JI, Caocci G, Efficace F *et al.* Thresholds for clinical importance were established to improve interpretation of the EORTC QLQ-C30 in clinical practice and research. *Journal of Clinical Epidemiology* 2020; **118:** 1-8. doi: 10.1016/j.jclinepi.2019.10.003

298. Giesinger JM, Kieffer JM, Fayers PM, Groenvold M, Petersen MA, Scott NW *et al.* Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. *J Clin Epidemiol* 2016; **69:** 79-88. e-pub ahead of print 2015/09/04; doi: 10.1016/j.jclinepi.2015.08.007

299. Bengtsson M. How to plan and perform a qualitative study using content analysis. *NursingPlus Open* 2016; **2:** 8-14. doi: https://doi.org/10.1016/j.npls.2016.01.001

300. Vaismoradi M, Turunen H, Bondas T. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. *Nursing & Health Sciences* 2013; **15**(3)**:** 398-405. doi: https://doi.org/10.1111/nhs.12048

301. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006; **3**(2)**:** 77-101. doi: 10.1191/1478088706qp063oa

302. Melnyk BM, Gallagher-Ford L, Long LE, Fineout-Overholt E. The establishment of evidence-based practice competencies for practicing

registered nurses and advanced practice nurses in real-world clinical settings: proficiencies to improve healthcare quality, reliability, patient outcomes, and costs. *Worldviews Evid Based Nurs* 2014; **11**(1)**:** 5-15. e-pub ahead of print 2014/01/23; doi: 10.1111/wvn.12021

303. Thomas S, Walsh D, Aktas A. Systematic bias in cancer patient-reported outcomes: symptom 'orphans' and 'champions'. *BMJ Support Palliat Care* 2019; **9**(1)**:** 67-74. e-pub ahead of print 2015/12/25; doi: 10.1136/bmjspcare-2014-000835

304. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. *Evidence Based Medicine* 2016; **21**(4)**:** 125-127. doi: 10.1136/ebmed-2016-110401

305. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? *PLoS Med* 2010; **7**(9)**:** e1000326. e-pub ahead of print 2010/09/30; doi: 10.1371/journal.pmed.1000326

306. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implementation Science* 2010; **5**(1)**:** 69. doi: 10.1186/1748-5908-5-69

307. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *International Journal of Social Research Methodology* 2005; **8**(1)**:** 19-32. doi: 10.1080/1364557032000119616

308. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *Int J Evid Based Healthc* 2015; **13**(3)**:** 141-146. e-pub ahead of print 2015/07/03; doi: 10.1097/xeb.0000000000000050

309. Colquhoun HL, Levac D, O'Brien KK, Straus S, Tricco AC, Perrier L *et al.* Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol* 2014; **67**(12)**:** 1291-1294. e-pub ahead of print 2014/07/19; doi: 10.1016/j.jclinepi.2014.03.013

310. Peters MDJ, Godfrey CM, McInerney P, Soares CB, Khalil H, Parker D. *The Joanna Briggs Institute Reviewers' Manual 2015: Methodology for JBI Scoping Reviews*. The Joanna Briggs Institute: Adelaide, Australia, 2015.

311. Andrew I, Kirkpatrick G, Holden K, Hawkins C. Audit of symptoms and prescribing in patients with the anorexia–cachexia syndrome. *Pharmacy World & Science* 2008; **30**(5)**:** 489-496. doi: 10.1007/s11096-008-9192-9

312. Bozzetti F, on behalf of the SWG. Screening the nutritional status in oncology: a preliminary report on 1,000 outpatients. *Supportive Care in Cancer* 2009; **17**(3)**:** 279-284. doi: 10.1007/s00520-008-0476-3

313. Haverkort EB, Binnekade JM, Busch ORC, van Berge Henegouwen MI, de Haan RJ, Gouma DJ. Presence and persistence of nutrition-related

symptoms during the first year following esophagectomy with gastric tube reconstruction in clinically disease-free patients. *World journal of surgery* 2010; **34**(12)**:** 2844-2852. e-pub ahead of print 2010/09/15; doi: 10.1007/s00268-010-0786-8

314. Konishi H, Nakada K, Kawamura M, Iwasaki T, Murakami K, Mitsumori N *et al.* Impaired Gastrointestinal Function Affects Symptoms and Alimentary Status in Patients After Gastrectomy. *World Journal of Surgery* 2016; **40**(11)**:** 2713-2718. doi: 10.1007/s00268-016-3613-z

315. Aktas A, Walsh D, Hu B. Cancer Symptom Clusters: An Exploratory Analysis of Eight Statistical Techniques. *Journal of pain and symptom management* 2014; **48**(6)**:** 1254-1266. doi: 10.1016/j.jpainsymman.2014.02.006

316. Alsirafy SA, Al-Alimi KA, Thabet SM, Al-Nabhi A, Aklan NA. Voluntary reporting to assess symptom burden among Yemeni cancer patients: common symptoms are frequently missed. *J Community Support Oncol* 2016; **14**(3)**:** 117-121. e-pub ahead of print 2016/04/09; doi: 10.12788/jcso.0178

317. Bankhead C, Collins C, Stokes-Lampard H, Rose P, Wilson S, Clements A *et al.* Identifying symptoms of ovarian cancer: a qualitative and quantitative study. *BJOG: An International Journal of Obstetrics & Gynaecology* 2008; **115**(8)**:** 1008-1014. doi: https://doi.org/10.1111/j.1471-0528.2008.01772.x

318. Barajas Galindo DE, Vidal-Casariego A, Calleja-Fernández A, Hernández-Moreno A, Pintor de la Maza B, Pedraza-Lorenzo M *et al.* Appetite disorders in cancer patients: Impact on nutritional status and quality of life. *Appetite* 2017; **114:** 23-27. doi: https://doi.org/10.1016/j.appet.2017.03.020

319. Borre M, Dam GA, Knudsen AW, Grønbaek H. Nutritional status and nutritional risk in patients with neuroendocrine tumors. *Scandinavian Journal of Gastroenterology* 2018; **53**(3)**:** 284-292. doi: 10.1080/00365521.2018.1430848

320. Boshier PR, Klevebro F, Savva KV, Waller A, Hage L, Hanna GB *et al.* Assessment of Health Related Quality of Life and Digestive Symptoms in Long-term, Disease Free Survivors After Esophagectomy. *Annals of surgery* 2020. e-pub ahead of print 2020/02/19; doi: 10.1097/sla.0000000000003829

321. Bozzetti F, Mariani L. Defining and Classifying Cancer Cachexia: A Proposal by the SCRINIO Working Group. *Journal of Parenteral and Enteral Nutrition* 2009; **33**(4)**:** 361-367. doi: https://doi.org/10.1177/0148607108325076

322. Cense HA, Visser MRM, van Sandick JW, de Boer AGEM, Lamme B, Obertop H *et al.* Quality of life after colon interposition by necessity for

esophageal cancer replacement. *Journal of Surgical Oncology* 2004; **88**(1)**:** 32-38. doi: https://doi.org/10.1002/jso.20132

323. Christensen SF, Scherber RM, Mazza GL, Dueck AC, Brochmann N, Andersen CL *et al.* Tobacco use in the Myeloproliferative neoplasms: symptom burden, patient opinions, and care. *BMC Cancer* 2021; **21**(1)**:** 691. doi: 10.1186/s12885-021-08439-7

324. Churm D, Andrew IM, Holden K, Hildreth AJ, Hawkins C. A questionnaire study of the approach to the anorexia–cachexia syndrome in patients with cancer by staff in a district general hospital. *Supportive Care in Cancer* 2009; **17**(5)**:** 503-507. doi: 10.1007/s00520-008-0486-1

325. Collard JM, Otte JB, Reynaert M, Kestens PJ. Quality of life three years or more after esophagectomy for cancer. *J Thorac Cardiovasc Surg* 1992; **104**(2)**:** 391-394. e-pub ahead of print 1992/08/01;

326. Dias do Prado C, Alvares Duarte Bonini Campos J. Nutritional status of patients with gastrointestinal cancer receiving care in a public hospital; 2010-2011. *Nutr Hosp* 2013; **28**(2)**:** 405-411. e-pub ahead of print 2013/07/05; doi: 10.3305/nh.2013.28.2.6305

327. Donnelly S, Walsh D, Rybicki L. The symptoms of advanced cancer: identification of clinical and research priorities by assessment of prevalence and severity. *J Palliat Care* 1995; **11**(1)**:** 27-32. e-pub ahead of print 1995/01/01;

328. Emanuel RM, Dueck AC, Geyer HL, Kiladjian J-J, Slot S, Zweegman S *et al.* Myeloproliferative Neoplasm (MPN) Symptom Assessment Form Total Symptom Score: Prospective International Assessment of an Abbreviated Symptom Burden Scoring System Among Patients With MPNs. *Journal of Clinical Oncology* 2012; **30**(33)**:** 4098-4103. doi: 10.1200/jco.2012.42.3863

329. Fanelli FR, Cangiano C, Ceci F, Cellerino R, Franchi F, Menichetti E *et al.* Plasma tryptophan and anorexia in human cancer. *European Journal of Cancer and Clinical Oncology* 1986; **22**(1)**:** 89-95. doi: https://doi.org/10.1016/0277-5379(86)90346-9

330. Ferreira D, Guimarães TG, Marcadenti A. Acceptance of hospital diets and nutritional status among inpatients with cancer. *Einstein (Sao Paulo)* 2013; **11**(1)**:** 41-46. e-pub ahead of print 2013/04/13; doi: 10.1590/s1679-45082013000100008

331. Turcott JG, Juárez-Hernández E, Sánchez-Lara K, Flores-Estrada D, Zatarain-Barrón ZL, Arrieta O. Baseline Dysgeusia in Chemotherapy-Naïve Non-Small Cell Lung Cancer Patients: Association with Nutrition and Quality of Life. *Nutrition and Cancer* 2020; **72**(2)**:** 194-201. doi: 10.1080/01635581.2019.1633362

332. Johansson P, Mesa R, Scherber R, Abelsson J, Samuelsson J, Birgegård G *et al.* Association between quality of life and clinical parameters in patients with myeloproliferative neoplasms. *Leukemia & Lymphoma* 2011; **53**(3)**:** 441-444. doi: 10.3109/10428194.2011.619608

333. Kang J, Park JS, Yoon DS, Kim WJ, Chung H-y, Lee SM *et al.* A Study on the Dietary Intake and the Nutritional Status among the Pancreatic Cancer Surgical Patients. *Clin Nutr Res* 2016; **5**(4)**:** 279-289.

334. Khalid U, Spiro A, Baldwin C, Sharma B, McGough C, Norman AR *et al.* Symptoms and weight loss in patients with gastrointestinal and lung cancer at presentation. *Supportive Care in Cancer* 2006; **15**(1)**:** 39. doi: 10.1007/s00520-006-0091-0

335. Khan D, Rehman A, Iltaf M. Gastric carcinoma: Presentation at a tertiary care hospital in Peshawar. *Pakistan Journal of Medical and Health Sciences* 2014; **8:** 1053-1056.

336. Kirkova J, Walsh D, Rybicki L, Davis MP, Aktas A, Jin T *et al.* Symptom severity and distress in advanced cancer. *Palliative Medicine* 2010; **24**(3)**:** 330-339. doi: 10.1177/0269216309356380

337. Krech RL, Walsh D. Symptoms of pancreatic cancer. *Journal of pain and symptom management* 1991; **6**(6)**:** 360-367. doi: https://doi.org/10.1016/0885-3924(91)90027-2

338. Lorton CM, Griffin O, Higgins K, Roulston F, Stewart G, Gough N *et al.* Late referral of cancer patients with malnutrition to dietitians: a prospective study of clinical practice. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2019. e-pub ahead of print 2019/09/06; doi: 10.1007/s00520-019-05042-2

339. Markar SR, Sounderajah V, Johar A, Zaninotto G, Castoro C, Lagergren P *et al.* Patient-reported outcomes after oesophagectomy in the multicentre LASER study. *British Journal of Surgery* 2021; **108**(9)**:** 1090-1096. doi: 10.1093/bjs/znab124

340. Mehran R, Rice D, El-Zein R, Huang JL, Vaporciyan A, Goodyear A *et al.* Minimally invasive esophagectomy versus open esophagectomy, a symptom assessment study. *Diseases of the Esophagus* 2011; **24**(3)**:** 147-152. doi: 10.1111/j.1442-2050.2010.01113.x

341. Mesa R, Boccia RV, Grunwald MR, Oh ST, Colucci P, Paranagama D *et al.* Patient-Reported Outcomes Data From REVEAL at the Time of Enrollment (Baseline): A Prospective Observational Study of Patients With Polycythemia Vera in the United States. *Clinical Lymphoma, Myeloma and Leukemia* 2018; **18**(9)**:** 590-596. doi: 10.1016/j.clml.2018.05.020

342. Movahed S, Norouzy A, Ghanbari-Motlagh A, Eslami S, Khadem-Rezaiyan M, Emadzadeh M *et al.* Nutritional Status in Patients with Esophageal Cancer Receiving Chemoradiation and Assessing the

Efficacy of Usual Care for Nutritional Managements. *Asian Pac J Cancer Prev* 2020; **21**(8)**:** 2315-2323. e-pub ahead of print 2020/08/29; doi: 10.31557/apjcp.2020.21.8.2315

343. Nielsen SS, Theologides A, Vickers ZM. Influence of food odors on food aversions and preferences in patients with cancer. *The American journal of clinical nutrition* 1980; **33**(11)**:** 2253-2261. doi: 10.1093/ajcn/33.11.2253

344. Sarhill N, Mahmoud F, Walsh D, Nelson KA, Komurcu S, Davis M *et al.* Evaluation of nutritional status in advanced metastatic cancer. *Supportive Care in Cancer* 2003; **11**(10)**:** 652-659. doi: 10.1007/s00520-003-0486-0

345. Scotch AH, Kosiorek H, Scherber R, Dueck AC, Slot S, Zweegman S *et al.* Symptom burden profile in myelofibrosis patients with thrombocytopenia: Lessons and unmet needs. *Leukemia Research* 2017; **63:** 34-40. doi: https://doi.org/10.1016/j.leukres.2017.10.002

346. VERSCHUUR EML, STEYERBERG EW, KUIPERS EJ, ESSINK-BOT M-L, TRAN KTC, VAN DER GAAST A *et al.* Experiences and expectations of patients after oesophageal cancer surgery: an explorative study. *European journal of cancer care* 2006; **15**(4)**:** 324-332. doi: https://doi.org/10.1111/j.1365-2354.2006.00659.x

347. Vidra N, Kontogianni MD, Schina E, Gioulbasanis I. Detailed Dietary Assessment in Patients with Inoperable Tumors: Potential Deficits for Nutrition Care Plans. *Nutrition and Cancer* 2016; **68**(7)**:** 1131-1139. doi: 10.1080/01635581.2016.1213867

348. Williams GR, Al-Obaidi M, Dai C, Mir N, Challa SA, Daniel M *et al.* Association of malnutrition with geriatric assessment impairments and health-related quality of life among older adults with gastrointestinal malignancies. *Cancer* 2020; **126**(23)**:** 5147-5155. doi: https://doi.org/10.1002/cncr.33122

349. Zhou T, Yang K, Thapa S, Liu H, Wang B, Yu S. Differences in Symptom Burden Among Cancer Patients With Different Stages of Cachexia. *Journal of pain and symptom management* 2017; **53**(5)**:** 919-926. doi: 10.1016/j.jpainsymman.2016.12.325

350. Adachi S, Inagawa S, Enomoto T, Shinozaki E, Oda T, Kawamoto T. Subjective and functional results after total gastrectomy: prospective study for longterm comparison of reconstruction procedures. *Gastric Cancer* 2003; **6**(1)**:** 0024-0029. doi: 10.1007/s101200300003

351. de Boer AGEM, Oñorbe Genovesi PI, Sprangers MAG, van Sandick JW, Obertop H, van Lanschot JJB. Quality of life in long-term survivors after curative transhiatal oesophagectomy for oesophageal carcinoma. *British Journal of Surgery* 2002; **87**(12)**:** 1716-1721. doi: 10.1046/j.1365-2168.2000.01600.x

352. Elliott JA, Docherty NG, Eckhardt HG, Doyle SL, Guinan EM, Ravi N *et al.* Weight Loss, Satiety, and the Postprandial Gut Hormone Response After Esophagectomy: A Prospective Study. *Annals of surgery* 2017; **266**(1)**:** 82-90. e-pub ahead of print 2016/07/28; doi: 10.1097/sla.0000000000001918

353. Flórez Almonacid CI, Jurado Ramos A, Rodríguez Borrego MA. Evaluation of the nutritional profile of patients with total laryngectomy. *e-SPEN Journal* 2013; **8**(5)**:** e229-e234. doi: https://doi.org/10.1016/j.clnme.2013.07.004

354. Geyer H, Cannon K, Knight E, Fauble V, Camoriano J, Emanuel R *et al.* Ruxolitinib in clinical practice for therapy of myelofibrosis: single USA center experience following Food and Drug Administration approval. *Leuk Lymphoma* 2014; **55**(1)**:** 195-197. e-pub ahead of print 2013/05/08; doi: 10.3109/10428194.2013.789507

355. Lindsey AM, Piper BF. Anorexia and weight loss: Indicators of cachexia in small cell lung cancer. *Nutrition and Cancer* 1985; **7**(1-2)**:** 65-76. doi: 10.1080/01635588509513841

356. McGreevy J, Orrevall Y, Belqaid K, Wismer W, Tishelman C, Bernhardson B-M. Characteristics of taste and smell alterations reported by patients after starting treatment for lung cancer. *Supportive Care in Cancer* 2014; **22**(10)**:** 2635-2644. doi: 10.1007/s00520-014-2215-2

357. Walsh D, Rybicki L, Nelson KA, Donnelly S. Symptoms and prognosis in advanced cancer. *Supportive Care in Cancer* 2002; **10**(5)**:** 385-388. doi: 10.1007/s00520-001-0318-z

358. Wiegert EVM, Padilha PdC, Peres WAF. Performance of Patient-Generated Subjective Global Assessment (PG-SGA) in Patients With Advanced Cancer in Palliative Care. *Nutrition in Clinical Practice* 2017; **32**(5)**:** 675-681. doi: https://doi.org/10.1177/0884533617725071

359. Andreyev HJN, Lalji A, Mohammed K, Muls ACG, Watkins D, Rao S *et al.* The FOCCUS study: a prospective evaluation of the frequency, severity and treatable causes of gastrointestinal symptoms during and after chemotherapy. *Supportive Care in Cancer* 2021; **29**(3)**:** 1443-1453. doi: 10.1007/s00520-020-05610-x

360. Lasheen W, Walsh D. The cancer anorexia-cachexia syndrome: myth or reality? *Supportive Care in Cancer* 2009; **18**(2)**:** 265. doi: 10.1007/s00520-009-0772-6

361. Cerchietti LCA, Navigante AH, Peluffo GD, Diament MJ, Stillitani I, Klein SA *et al.* Effects of celecoxib, medroxyprogesterone, and dietary intervention on systemic syndromes in patients with advanced lung adenocarcinoma: a pilot study. *Journal of pain and symptom management* 2004; **27**(1)**:** 85-95. doi: 10.1016/j.jpainsymman.2003.05.010

362. Davis M, Lasheen W, Walsh D, Mahmoud F, Bicanovsky L, Lagman R. A Phase II Dose Titration Study of Thalidomide for Cancer-Associated Anorexia. *Journal of pain and symptom management* 2012; **43**(1)**:** 78-86. doi: 10.1016/j.jpainsymman.2011.03.007

363. Iivonen MK, Koskinen MO, Ikonen TJ, Matikainen MJ. Emptying of the Jejunal pouch and Roux-en-Y limb after total gastrectomy—a randomised, prospective study. *European Journal of Surgery* 1999; **165**(8)**:** 742-747. doi: 10.1080/11024159950189500

364. Iivonen MK. Long-Term Follow-up of Patients with Jejunal Pouch Reconstruction after Total Gastrectomy: A Randomized Prospective Study. *Scandinavian Journal of Gastroenterology* 2000; **35**(7)**:** 679-685. doi: 10.1080/003655200750023327

365. Shivshanker K, Bennett RW, Jr., Haynie TP. Tumor-associated gastroparesis: correction with metoclopramide. *Am J Surg* 1983; **145**(2)**:** 221-225. e-pub ahead of print 1983/02/01; doi: 10.1016/0002-9610(83)90067-3

366. Simpson PJ, Ooi C, Chong J, Smith A, Baldey A, Staples M *et al.* Does the Use of Nizatidine, as a Pro-kinetic Agent, Improve Gastric Emptying in Patients Post-oesophagectomy? *Journal of Gastrointestinal Surgery* 2009; **13**(3)**:** 432-437. doi: 10.1007/s11605-008-0736-z

367. Wilson J, Plourde JY, Marshall D, Yoshida S, Chow W, Harsanyi Z *et al.* Long-term safety and clinical effectiveness of controlled-release metoclopramide in cancer-associated dyspepsia syndrome: a multicentre evaluation. *J Palliat Care* 2002; **18**(2)**:** 84-91. e-pub ahead of print 2002/08/08;

368. Del Fabbro E, Hui D, Dalal S, Dev R, Nooruddin ZI, Bruera E. Clinical outcomes and contributors to weight loss in a cancer cachexia clinic. *J Palliat Med* 2011; **14**(9)**:** 1004-1008. e-pub ahead of print 2011/07/29; doi: 10.1089/jpm.2011.0098

369. Dressler JA, Palazzo F, Berger AC, Stake S, Chaudhary A, Chojnacki KA *et al.* Long-term functional outcomes of laparoscopic resection for gastric gastrointestinal stromal tumors. *Surgical Endoscopy* 2016; **30**(4)**:** 1592-1598. doi: 10.1007/s00464-015-4384-6

370. Greene CL, DeMeester SR, Augustin F, Worrell SG, Oh DS, Hagen JA *et al.* Long-Term Quality of Life and Alimentary Satisfaction After Esophagectomy With Colon Interposition. *The Annals of Thoracic Surgery* 2014; **98**(5)**:** 1713-1720. doi: 10.1016/j.athoracsur.2014.06.088

371. Lin J-C, Chan D-C, Chen P-J, Chu H-C, Chueh T-H, Huang H-H *et al.* Clinical Characteristics of Early Onset Pancreatic Adenocarcinoma: A Medical Center Experience and Review of the Literature. *Pancreas* 2011; **40**(4).

372. Mitra D, Kaye JA, Piecoro LT, Brown J, Reith K, Mughal TI *et al.* Symptom burden and splenomegaly in patients with myelofibrosis in the United States: a retrospective medical record review. *Cancer Medicine* 2013; **2**(6)**:** 889-898. doi: https://doi.org/10.1002/cam4.136

373. Seker M, Aksoy S, Ozdemir N, Uncu D, Zengin N. Clinicopathologic features of gastric cancer in young patients. *Saudi Journal of Gastroenterology* 2013; **19**(6)**:** 258-261. doi: 10.4103/1319-3767.120876

374. Wainwright D, Donovan JL, Kavadas V, Cramer H, Blazeby JM. Remapping the Body: Learning to Eat Again After Surgery for Esophageal Cancer. *Qualitative Health Research* 2007; **17**(6)**:** 759-771. doi: 10.1177/1049732307302021

375. Loberg RD, Bradley DA, Tomlins SA, Chinnaiyan AM, Pienta KJ. The lethal phenotype of cancer: the molecular basis of death due to malignancy. *CA Cancer J Clin* 2007; **57**(4)**:** 225-241. e-pub ahead of print 2007/07/13; doi: 10.3322/canjclin.57.4.225

376. Arends J, Strasser F, Gonella S, Solheim TS, Madeddu C, Ravasco P *et al.* Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines[☆]. *ESMO Open* 2021; **6**(3). doi: 10.1016/j.esmoop.2021.100092

377. Zhang X-M, Zhang Z-B, Chen W, Wu X. The association between handgrip strength and depression in cancer survivors: a cross-sectional study. *BMC Geriatrics* 2022; **22**(1)**:** 111. doi: 10.1186/s12877-022-02795-0

378. Stene GB, Balstad TR, Leer ASM, Bye A, Kaasa S, Fallon M *et al.* Deterioration in Muscle Mass and Physical Function Differs According to Weight Loss History in Cancer Cachexia. *Cancers (Basel)* 2019; **11**(12). e-pub ahead of print 2019/12/11; doi: 10.3390/cancers11121925

379. Kilgour RD, Vigano A, Trutschnigg B, Hornby L, Lucar E, Bacon SL *et al.* Cancer-related fatigue: the impact of skeletal muscle mass and strength in patients with advanced cancer. *J Cachexia Sarcopenia Muscle* 2010; **1**(2)**:** 177-185. e-pub ahead of print 2011/04/09; doi: 10.1007/s13539-010-0016-0

380. Nikniaz Z, Somi MH, Naghashi S. Malnutrition and Weight Loss as Prognostic Factors in the Survival of Patients with Gastric Cancer. *Nutrition and Cancer* 2022**:** 1-6. doi: 10.1080/01635581.2022.2059089

381. Grøntved A, Hu FB. Walking pace and handgrip strength: simple measures of fitness and mortality risk? *Eur Heart J* 2017; **38**(43)**:** 3241-3243. e-pub ahead of print 2017/10/12; doi: 10.1093/eurheartj/ehx497

382. Thoresen L, Frykholm G, Lydersen S, Ulveland H, Baracos V, Prado CMM *et al.* Nutritional status, cachexia and survival in patients with advanced colorectal carcinoma. Different assessment criteria for nutritional status

provide unequal results. *Clinical Nutrition* 2013; **32**(1)**:** 65-72. doi: https://doi.org/10.1016/j.clnu.2012.05.009

383. Kypriotakis G, Vidrine DJ, Francis LE, Rose JH. The longitudinal relationship between quality of life and survival in advanced stage cancer. *Psychooncology* 2016; **25**(2)**:** 225-231. e-pub ahead of print 2015/05/08; doi: 10.1002/pon.3846

384. Soykan I, Sivri B, Sarosiek I, Kiernan B, McCallum RW. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. *Dig Dis Sci* 1998; **43**(11)**:** 2398-2404. e-pub ahead of print 1998/11/21; doi: 10.1023/a:1026665728213

385. Stone CA, Kenny RA, Nolan B, Lawlor PG. Autonomic dysfunction in patients with advanced cancer; prevalence, clinical correlates and challenges in assessment. *BMC Palliat Care* 2012; **11:** 3. e-pub ahead of print 2012/03/03; doi: 10.1186/1472-684x-11-3

386. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H *et al.* ESPEN practical guideline: Clinical Nutrition in cancer. *Clin Nutr* 2021; **40**(5)**:** 2898-2913. e-pub ahead of print 2021/05/05; doi: 10.1016/j.clnu.2021.02.005

387. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: an 11-year national analysis. *Pharmacoepidemiol Drug Saf* 2010; **19**(9)**:** 901-910. e-pub ahead of print 2010/07/14; doi: 10.1002/pds.1984

388. Jyrkkä J, Enlund H, Lavikainen P, Sulkava R, Hartikainen S. Association of polypharmacy with nutritional status, functional ability and cognitive capacity over a three-year period in an elderly population. *Pharmacoepidemiol Drug Saf* 2011; **20**(5)**:** 514-522. e-pub ahead of print 2011/02/11; doi: 10.1002/pds.2116

389. Loeliger J, Dewar S, Kiss N, Drosdowsky A, Stewart J. Patient and carer experiences of nutrition in cancer care: a mixed-methods study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2021; **29**(9)**:** 5475-5485. e-pub ahead of print 2021/03/13; doi: 10.1007/s00520-021-06111-1

390. Marshall KM, Loeliger J, Nolte L, Kelaart A, Kiss NK. Prevalence of malnutrition and impact on clinical outcomes in cancer services: A comparison of two time points. *Clin Nutr* 2019; **38**(2)**:** 644-651. e-pub ahead of print 2018/05/24; doi: 10.1016/j.clnu.2018.04.007

391. Gyan E, Raynard B, Durand JP, Lacau Saint Guily J, Gouy S, Movschin ML *et al.* Malnutrition in Patients With Cancer: Comparison of Perceptions by Patients, Relatives, and Physicians-Results of the NutriCancer2012 Study. *JPEN J Parenter Enteral Nutr* 2018; **42**(1)**:** 255-260. e-pub ahead of print 2018/03/06; doi: 10.1177/0148607116688881

392. Segura A, Pardo J, Jara C, Zugazabeitia L, Carulla J, de las Peñas R *et al.* An epidemiological evaluation of the prevalence of malnutrition in Spanish patients with locally advanced or metastatic cancer. *Clinical Nutrition* 2005; **24**(5)**:** 801-814. doi: https://doi.org/10.1016/j.clnu.2005.05.001

393. Ferrat E, Paillaud E, Laurent M, Le Thuaut A, Caillet P, Tournigand C *et al.* Predictors of 1-Year Mortality in a Prospective Cohort of Elderly Patients With Cancer. *The Journals of Gerontology: Series A* 2015; **70**(9)**:** 1148-1155. doi: 10.1093/gerona/glv025

394. Bourdel-Marchasson I, Diallo A, Bellera C, Blanc-Bisson C, Durrieu J, Germain C *et al.* One-Year Mortality in Older Patients with Cancer: Development and External Validation of an MNA-Based Prognostic Score. *PloS one* 2016; **11**(2)**:** e0148523. doi: 10.1371/journal.pone.0148523

395. Gillis C, Richer L, Fenton TR, Gramlich L, Keller H, Culos-Reed SN *et al.* Colorectal cancer patients with malnutrition suffer poor physical and mental health before surgery. *Surgery* 2021; **170**(3)**:** 841-847. doi: https://doi.org/10.1016/j.surg.2021.04.003

396. Ferreira V, Lawson C, Gillis C, Scheede-Bergdahl C, Chevalier S, Carli F. Malnourished lung cancer patients have poor baseline functional capacity but show greatest improvements with multimodal prehabilitation. *Nutrition in Clinical Practice* 2021; **36**(5)**:** 1011-1019. doi: https://doi.org/10.1002/ncp.10655

397. Green SM, James EP. Barriers and facilitators to undertaking nutritional screening of patients: a systematic review. *Journal of Human Nutrition and Dietetics* 2013; **26**(3)**:** 211-221. doi: https://doi.org/10.1111/jhn.12011

398. Muscaritoli M, Lucia S, Farcomeni A, Lorusso V, Saracino V, Barone C *et al.* Prevalence of malnutrition in patients at first medical oncology visit: the PreMiO study. *Oncotarget* 2017; **8**(45)**:** 79884-79896. e-pub ahead of print 2017/11/08; doi: 10.18632/oncotarget.20168

399. Basch E, Abernethy AP. Supporting clinical practice decisions with real-time patient-reported outcomes. *J Clin Oncol* 2011; **29**(8)**:** 954-956. e-pub ahead of print 2011/02/02; doi: 10.1200/jco.2010.33.2668

400. Fromme EK, Eilers KM, Mori M, Hsieh YC, Beer TM. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. *J Clin Oncol* 2004; **22**(17)**:** 3485-3490. e-pub ahead of print 2004/09/01; doi: 10.1200/jco.2004.03.025

401. Zhang Z, Wan Z, Zhu Y, Zhang L, Zhang L, Wan H. Prevalence of malnutrition comparing NRS2002, MUST, and PG-SGA with the GLIM criteria in adults with cancer: A multi-center study. *Nutrition* 2021; **83:** 111072. doi: https://doi.org/10.1016/j.nut.2020.111072

402. Wang Y, Chen X, Wang Y, Liu Z, Fang Y, Peng Z *et al.* Body Composition Measurement Improved Performance of GLIM Criteria in Diagnosing Malnutrition Compared to PG-SGA in Ambulatory Cancer Patients: A Prospective Cross-Sectional Study. *Nutrients* 2021; **13**(8)**:** 2744.

403. Isenring E, Cross G, Kellett E, Koczwara B, Daniels L. Nutritional Status and Information Needs of Medical Oncology Patients Receiving Treatment at an Australian Public Hospital. *Nutrition and Cancer* 2010; **62**(2)**:** 220-228. doi: 10.1080/01635580903305276

404. Aktas A, Walsh D, Galang M, O'Donoghue N, Rybicki L, Hullihen B *et al.* Underrecognition of Malnutrition in Advanced Cancer: The Role of the Dietitian and Clinical Practice Variations. *American Journal of Hospice and Palliative Medicine®* 2017; **34**(6)**:** 547-555. doi: 10.1177/1049909116639969

405. Hanna TP, King WD, Thibodeau S, Jalink M, Paulin GA, Harvey-Jones E *et al.* Mortality due to cancer treatment delay: systematic review and meta-analysis. *BMJ* 2020; **371:** m4087. doi: 10.1136/bmj.m4087

406. Speakman JR, Westerterp KR. Associations between energy demands, physical activity, and body composition in adult humans between 18 and 96 y of age. *The American journal of clinical nutrition* 2010; **92**(4)**:** 826-834. e-pub ahead of print 2010/09/03; doi: 10.3945/ajcn.2009.28540

407. Hawkins MS, Storti KL, Richardson CR, King WC, Strath SJ, Holleman RG *et al.* Objectively measured physical activity of USA adults by sex, age, and racial/ethnic groups: a cross-sectional study. *Int J Behav Nutr Phys Act* 2009; **6:** 31. e-pub ahead of print 2009/06/06; doi: 10.1186/1479-5868-6-31

408. Foster JA, Salinas GD, Mansell D, Williamson JC, Casebeer LL. How does older age influence oncologists' cancer management? *The oncologist* 2010; **15**(6)**:** 584-592. e-pub ahead of print 2010/05/25; doi: 10.1634/theoncologist.2009-0198

409. Stava CJ, Lopez A, Vassilopoulou-Sellin R. Health profiles of younger and older breast cancer survivors. *Cancer* 2006; **107**(8)**:** 1752-1759. doi: https://doi.org/10.1002/cncr.22200

410. Zhu C, Wang B, Gao Y, Ma X. Prevalence and relationship of malnutrition and distress in patients with Cancer using questionnaires. *BMC Cancer* 2018; **18**(1)**:** 1272. doi: 10.1186/s12885-018-5176-x

411. Britton B, Clover K, Bateman L, Odelli C, Wenham K, Zeman A *et al.* Baseline depression predicts malnutrition in head and neck cancer patients undergoing radiotherapy. *Supportive Care in Cancer* 2012; **20**(2)**:** 335-342. doi: 10.1007/s00520-011-1087-y

412. Maasberg S, Knappe-Drzikova B, Vonderbeck D, Jann H, Weylandt KH, Grieser C *et al.* Malnutrition Predicts Clinical Outcome in Patients with Neuroendocrine Neoplasia. *Neuroendocrinology* 2017; **104**(1)**:** 11-25. e-pub ahead of print 2016/11/03; doi: 10.1159/000442983

413. Aaldriks AA, van der Geest LG, Giltay EJ, le Cessie S, Portielje JE, Tanis BC *et al.* Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy. *J Geriatr Oncol* 2013; **4**(3)**:** 218-226. e-pub ahead of print 2013/09/28; doi: 10.1016/j.jgo.2013.04.001

414. Hoekstra J, Vernooij-Dassen MJ, de Vos R, Bindels PJ. The added value of assessing the 'most troublesome' symptom among patients with cancer in the palliative phase. *Patient Educ Couns* 2007; **65**(2)**:** 223-229. e-pub ahead of print 2006/09/13; doi: 10.1016/j.pec.2006.08.001

415. Kebebew T, Mavhandu-Mudzusi AH, Mosalo A. A cross-sectional assessment of symptom burden among patients with advanced cervical cancer. *BMC Palliat Care* 2021; **20**(1)**:** 190. doi: 10.1186/s12904-021-00883-3

416. Lage DE, El-Jawahri A, Fuh C-X, Newcomb RA, Jackson VA, Ryan DP *et al.* Functional Impairment, Symptom Burden, and Clinical Outcomes Among Hospitalized Patients With Advanced Cancer. *Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw* 2020; **18**(6)**:** 747-754. doi: 10.6004/jnccn.2019.7385

417. Salsman JM, Grunberg SM, Beaumont JL, Rogers M, Paul D, Clayman ML *et al.* Communicating about chemotherapy-induced nausea and vomiting: a comparison of patient and provider perspectives. *J Natl Compr Canc Netw* 2012; **10**(2)**:** 149-157. e-pub ahead of print 2012/02/07; doi: 10.6004/jnccn.2012.0018

418. Feng C, Yu H, Lei H, Cao H, Chen M, Liu S. A prognostic model using the neutrophil-albumin ratio and PG-SGA to predict overall survival in advanced palliative lung cancer. *BMC Palliat Care* 2022; **21**(1)**:** 81. doi: 10.1186/s12904-022-00972-x

419. Kim HS, Lee JY, Lim SH, Cho J, Kim SJ, Jang JH *et al.* Patient-Generated Subjective Global Assessment as a prognosis tool in patients with multiple myeloma. *Nutrition* 2017; **36:** 67-71. e-pub ahead of print 2017/03/25; doi: 10.1016/j.nut.2016.06.009

420. Ge T, Lin T, Yang J, Wang M. Nutritional status and related factors of patients with advanced lung cancer in northern China: a retrospective study. *Cancer Manag Res* 2019; **11:** 2225-2231. e-pub ahead of print 2019/04/10; doi: 10.2147/cmar.S193567

421. Hébuterne X, Lemarié E, Michallet M, de Montreuil CB, Schneider SM, Goldwasser F. Prevalence of malnutrition and current use of nutrition support in patients with cancer. *JPEN J Parenter Enteral Nutr* 2014; **38**(2)**:**

196-204. e-pub ahead of print 2014/04/22; doi: 10.1177/0148607113502674

422. Planas M, Álvarez-Hernández J, León-Sanz M, Celaya-Pérez S, Araujo K, García de Lorenzo A. Prevalence of hospital malnutrition in cancer patients: a sub-analysis of the PREDyCES® study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2016; **24**(1)**:** 429-435. e-pub ahead of print 2015/06/24; doi: 10.1007/s00520-015-2813-7

423. Taipa-Mendes AM, Amaral TF, Gregório M. Undernutrition risk and nutritional screening implementation in hospitals: Barriers and time trends (2019–2020). *Clinical Nutrition ESPEN* 2021; **45:** 192-199. doi: https://doi.org/10.1016/j.clnesp.2021.08.029

424. Berry DL, Wilkie DJ, Thomas CR, Jr., Fortner P. Clinicians communicating with patients experiencing cancer pain. *Cancer Invest* 2003; **21**(3)**:** 374-381. e-pub ahead of print 2003/08/07; doi: 10.1081/cnv-120018228

425. White C, McMullan, D, Doyle, D. "Now that You Mention it, Doctor … ": Symptom Reporting and the Need for Systematic Questioning in a Specialist Palliative Care Unit. *Journal of Palliative Medicine* 2009; **12**(5)**:** 447-450. doi: 10.1089/jpm.2008.0272

426. Bennani-Baiti N, Walsh D. What is cancer anorexia-cachexia syndrome? A historical perspective. *J R Coll Physicians Edinb* 2009; **39**(3)**:** 257-262.

427. Walsh D, Rybicki L. Symptom clustering in advanced cancer. *Supportive Care in Cancer* 2006; **14**(8)**:** 831-836. doi: 10.1007/s00520-005-0899-z

428. Chen ML, Tseng HC. Symptom clusters in cancer patients. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2006; **14**(8)**:** 825-830. e-pub ahead of print 2006/02/24; doi: 10.1007/s00520-006-0019-8

429. Ivanova MO, Ionova TI, Kalyadina SA, Uspenskaya OS, Kishtovich AV, Guo H *et al.* Cancer-related symptom assessment in Russia: validation and utility of the Russian M. D. Anderson Symptom Inventory. *Journal of pain and symptom management* 2005; **30**(5)**:** 443-453. e-pub ahead of print 2005/11/29; doi: 10.1016/j.jpainsymman.2005.04.015

430. de Rooij BH, Oerlemans S, van Deun K, Mols F, de Ligt KM, Husson O *et al.* Symptom clusters in 1330 survivors of 7 cancer types from the PROFILES registry: A network analysis. *Cancer* 2021; **127**(24)**:** 4665-4674. doi: https://doi.org/10.1002/cncr.33852

431. Chan CWH, Molassiotis A. The impact of fatigue on Chinese cancer patients in Hong Kong. *Supportive Care in Cancer* 2001; **9**(1)**:** 18-24. doi: 10.1007/s005200000192

432. Robinson E, Almiron-Roig E, Rutters F, de Graaf C, Forde CG, Tudur Smith C *et al.* A systematic review and meta-analysis examining the effect of eating rate on energy intake and hunger. *The American journal of clinical nutrition* 2014; **100**(1)**:** 123-151. e-pub ahead of print 2014/05/23; doi: 10.3945/ajcn.113.081745

433. Hogenkamp PS, Schiöth HB. Effect of oral processing behaviour on food intake and satiety. *Trends in Food Science & Technology* 2013; **34**(1)**:** 67-75. doi: https://doi.org/10.1016/j.tifs.2013.08.010

434. Borneman T, Piper BF, Koczywas M, Munevar CM, Sun V, Uman GC *et al.* A qualitative analysis of cancer-related fatigue in ambulatory oncology. *Clin J Oncol Nurs* 2012; **16**(1)**:** E26-32. e-pub ahead of print 2012/02/03; doi: 10.1188/12.Cjon.E26-e32

435. Oliver G, Wardle J. Perceived Effects of Stress on Food Choice. *Physiology & behavior* 1999; **66**(3)**:** 511-515. doi: https://doi.org/10.1016/S0031-9384(98)00322-9

436. Hutton JL, Baracos VE, Wismer WV. Chemosensory dysfunction is a primary factor in the evolution of declining nutritional status and quality of life in patients with advanced cancer. *Journal of pain and symptom management* 2007; **33**(2)**:** 156-165. e-pub ahead of print 2007/02/07; doi: 10.1016/j.jpainsymman.2006.07.017

437. de Kort S, Kruimel JW, Sels JP, Arts ICW, Schaper NC, Masclee AAM. Gastrointestinal symptoms in diabetes mellitus, and their relation to anxiety and depression. *Diabetes Research and Clinical Practice* 2012; **96**(2)**:** 248-255. doi: https://doi.org/10.1016/j.diabres.2012.01.021

438. de Ligt KM, Heins M, Verloop J, Ezendam NPM, Smorenburg CH, Korevaar JC *et al.* The impact of health symptoms on health-related quality of life in early-stage breast cancer survivors. *Breast Cancer Res Treat* 2019; **178**(3)**:** 703-711. e-pub ahead of print 2019/09/13; doi: 10.1007/s10549-019-05433-3

439. Voskamp PWM, van Diepen M, Evans M, Caskey FJ, Torino C, Postorino M *et al.* The impact of symptoms on health-related quality of life in elderly pre-dialysis patients: effect and importance in the EQUAL study. *Nephrol Dial Transplant* 2019; **34**(10)**:** 1707-1715. e-pub ahead of print 2018/06/26; doi: 10.1093/ndt/gfy167

440. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 2009; **30**(7)**:** 1073-1081. e-pub ahead of print 2009/05/27; doi: 10.1093/carcin/bgp127

441. Hanahan D. Hallmarks of Cancer: New Dimensions. *Cancer Discovery* 2022; **12**(1)**:** 31-46. doi: 10.1158/2159-8290.Cd-21-1059

442. Beattie M, Murphy DJ, Atherton I, Lauder W. Instruments to measure patient experience of healthcare quality in hospitals: a systematic review. *Systematic Reviews* 2015; **4**(1)**:** 97. doi: 10.1186/s13643-015-0089-0

443. Rattray J, Jones MC. Essential elements of questionnaire design and development. *Journal of Clinical Nursing* 2007; **16**(2)**:** 234-243. doi: https://doi.org/10.1111/j.1365-2702.2006.01573.x

444. Gillham B. *Developing a questionnaire*, A&C Black, 2008.

445. Safdar N, Abbo LM, Knobloch MJ, Seo SK. Research Methods in Healthcare Epidemiology: Survey and Qualitative Research. *Infect Control Hosp Epidemiol* 2016; **37**(11)**:** 1272-1277. e-pub ahead of print 2016/10/22; doi: 10.1017/ice.2016.171

446. Pii KH, Schou LH, Piil K, Jarden M. Current trends in patient and public involvement in cancer research: A systematic review. *Health Expect* 2019; **22**(1)**:** 3-20. e-pub ahead of print 2018/11/01; doi: 10.1111/hex.12841

447. Perkins P, Booth S, Vowler SL, Barclay S. What are patients' priorities for palliative care research? -- a questionnaire study. *Palliat Med* 2008; **22**(1)**:** 7-12. e-pub ahead of print 2008/01/25; doi: 10.1177/0269216307085180

448. Perkins P, Barclay S, Booth S. What are patients' priorities for palliative care research? Focus group study. *Palliat Med* 2007; **21**(3)**:** 219-225. e-pub ahead of print 2007/07/21; doi: 10.1177/0269216307077353

449. Jennings H, Slade M, Bates P, Munday E, Toney R. Best practice framework for Patient and Public Involvement (PPI) in collaborative data analysis of qualitative mental health research: methodology development and refinement. *BMC Psychiatry* 2018; **18**(1)**:** 213. e-pub ahead of print 2018/06/30; doi: 10.1186/s12888-018-1794-8

450. Estapé T. Cancer in the Elderly: Challenges and Barriers. *Asia Pac J Oncol Nurs* 2018; **5**(1)**:** 40-42. e-pub ahead of print 2018/01/31; doi: 10.4103/apjon.apjon_52_17

451. Abernethy AP, Shelby-James T, Fazekas BS, Woods D, Currow DC. The Australia-modified Karnofsky Performance Status (AKPS) scale: a revised scale for contemporary palliative care clinical practice [ISRCTN81117481]. *BMC Palliat Care* 2005; **4**(1)**:** 7. doi: 10.1186/1472-684X-4-7

452. Hamby T, Taylor W. Survey Satisficing Inflates Reliability and Validity Measures: An Experimental Comparison of College and Amazon Mechanical Turk Samples. *Educ Psychol Meas* 2016; **76**(6)**:** 912-932. e-pub ahead of print 2016/12/01; doi: 10.1177/0013164415627349

453. Krosnick JA. Response strategies for coping with the cognitive demands of attitude measures in surveys. *Applied Cognitive Psychology* 1991; **5**(3)**:** 213-236. doi: https://doi.org/10.1002/acp.2350050305

454. Beatty P, Herrmann D, Puskar C, Kerwin J. "Don't know" responses in surveys: is what I know what you want to know and do I want you to know it? *Memory* 1998; **6**(4)**:** 407-426. e-pub ahead of print 1998/11/26; doi: 10.1080/741942605

455. Turner G, Sturgis P, Martin D. Can Response Latencies Be Used to Detect Survey Satisficing on Cognitively Demanding Questions? *Journal of Survey Statistics and Methodology* 2014; **3**(1)**:** 89-108. doi: 10.1093/jssam/smu022

456. Denman DC, Baldwin AS, Betts AC, McQueen A, Tiro JA. Reducing "I Don't Know" Responses and Missing Survey Data: Implications for Measurement. *Med Decis Making* 2018; **38**(6)**:** 673-682. e-pub ahead of print 2018/07/03; doi: 10.1177/0272989x18785159

457. Malhotra N. Completion Time and Response Order Effects in Web Surveys. *Public Opinion Quarterly* 2008; **72**(5)**:** 914-934. doi: 10.1093/poq/nfn050

458. Sharma H. How short or long should be a questionnaire for any research? Researchers dilemma in deciding the appropriate questionnaire length. *Saudi J Anaesth* 2022; **16**(1)**:** 65-68. e-pub ahead of print 2022/03/10; doi: 10.4103/sja.sja_163_21

459. Galesic M, Bosnjak M. Effects of Questionnaire Length on Participation and Indicators of Response Quality in a Web Survey. *Public Opinion Quarterly* 2009; **73**(2)**:** 349-360. doi: 10.1093/poq/nfp031

460. Iglesias C, Torgerson D. Does length of questionnaire matter? A randomised trial of response rates to a mailed questionnaire. *J Health Serv Res Policy* 2000; **5**(4)**:** 219-221. e-pub ahead of print 2001/02/24; doi: 10.1177/135581960000500406

461. Sahlqvist S, Song Y, Bull F, Adams E, Preston J, Ogilvie D. Effect of questionnaire length, personalisation and reminder type on response rate to a complex postal survey: randomised controlled trial. *BMC Med Res Methodol* 2011; **11:** 62. e-pub ahead of print 2011/05/10; doi: 10.1186/1471-2288-11-62

462. Kost RG, de Rosa JC. Impact of survey length and compensation on validity, reliability, and sample characteristics for Ultrashort-, Short-, and Long-Research Participant Perception Surveys. *J Clin Transl Sci* 2018; **2**(1)**:** 31-37. e-pub ahead of print 2018/11/06; doi: 10.1017/cts.2018.18

463. Subar AF, Ziegler RG, Thompson FE, Johnson CC, Weissfeld JL, Reding D *et al.* Is shorter always better? Relative importance of questionnaire length and cognitive ease on response rates and data quality for two dietary questionnaires. *Am J Epidemiol* 2001; **153**(4)**:** 404-409. e-pub ahead of print 2001/02/24; doi: 10.1093/aje/153.4.404

464. Rolstad S, Adler J, Rydén A. Response Burden and Questionnaire Length: Is Shorter Better? A Review and Meta-analysis. *Value in Health* 2011; **14**(8)**:** 1101-1108. doi: https://doi.org/10.1016/j.jval.2011.06.003

465. Slattery EL, Voelker CC, Nussenbaum B, Rich JT, Paniello RC, Neely JG. A practical guide to surveys and questionnaires. *Otolaryngol Head Neck Surg* 2011; **144**(6)**:** 831-837. e-pub ahead of print 2011/04/16; doi: 10.1177/0194599811399724

466. Barnes EA, Bruera E. Fatigue in patients with advanced cancer: A review. *International Journal of Gynecologic Cancer* 2002; **12**(5)**:** 424-428. doi: 10.1136/ijgc-00009577-200209000-00002

467. Sperling CD, Petersen GS, Hølge-Hazelton B, Graugaard C, Winther JF, Gudmundsdottir T *et al.* Being Young and Getting Cancer: Development of a Questionnaire Reflecting the Needs and Experiences of Adolescents and Young Adults with Cancer. *J Adolesc Young Adult Oncol* 2017; **6**(1)**:** 171-177. e-pub ahead of print 2016/09/23; doi: 10.1089/jayao.2015.0063

468. Borreani C, Miccinesi G, Brunelli C, Lina M. An increasing number of qualitative research papers in oncology and palliative care: does it mean a thorough development of the methodology of research? *Health and Quality of Life Outcomes* 2004; **2**(1)**:** 7. doi: 10.1186/1477-7525-2-7

469. Giesinger JM, Efficace F, Aaronson N, Calvert M, Kyte D, Cottone F *et al.* Past and Current Practice of Patient-Reported Outcome Measurement in Randomized Cancer Clinical Trials: A Systematic Review. *Value Health* 2021; **24**(4)**:** 585-591. e-pub ahead of print 2021/04/13; doi: 10.1016/j.jval.2020.11.004

470. Cox KJ, Parshall MB, Hernandez SHA, Parvez SZ, Unruh ML. Symptoms among patients receiving in-center hemodialysis: A qualitative study. *Hemodial Int* 2017; **21**(4)**:** 524-533. e-pub ahead of print 2016/12/19; doi: 10.1111/hdi.12521

471. Chapman EJ, Pini S, Edwards Z, Elmokhallalati Y, Murtagh FEM, Bennett MI. Conceptualising effective symptom management in palliative care: a novel model derived from qualitative data. *BMC Palliat Care* 2022; **21**(1)**:** 17. e-pub ahead of print 2022/02/05; doi: 10.1186/s12904-022-00904-9

472. Chapman WP, Jones CM. VARIATIONS IN CUTANEOUS AND VISCERAL PAIN SENSITIVITY IN NORMAL SUBJECTS. *J Clin Invest* 1944; **23**(1)**:** 81-91. e-pub ahead of print 1944/01/01; doi: 10.1172/jci101475

473. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull* 2007; **133**(4)**:** 581-624. e-pub ahead of print 2007/06/27; doi: 10.1037/0033-2909.133.4.581

474. McDaniel RW, Rhodes VA. Symptom experience. *Seminars in Oncology Nursing* 1995; **11**(4)**:** 232-234. doi: https://doi.org/10.1016/S0749-2081(05)80002-6

475. Al Maqbali M, Al Sinani M, Al Naamani Z, Al Badi K, Tanash MI. Prevalence of Fatigue in Patients With Cancer: A Systematic Review and Meta-Analysis. *Journal of pain and symptom management* 2021; **61**(1)**:** 167-189.e114. e-pub ahead of print 2020/08/10; doi: 10.1016/j.jpainsymman.2020.07.037

476. Angelopoulos T, Kokkinos A, Liaskos C, Tentolouris N, Alexiadou K, Miras AD *et al.* The effect of slow spaced eating on hunger and satiety in overweight and obese patients with type 2 diabetes mellitus. *BMJ Open Diabetes Research & Care* 2014; **2**(1)**:** e000013. doi: 10.1136/bmjdrc-2013-000013

477. Nakamura T, Nakamura Y, Takashima N, Kadota A, Miura K, Ueshima H *et al.* Eating Slowly Is Associated with Undernutrition among Community-Dwelling Adult Men and Older Adult Women. *Nutrients* 2021; **14**(1). e-pub ahead of print 2022/01/12; doi: 10.3390/nu14010054

478. Álvaro Sanz E, Abilés J, Garrido Siles M, Pérez Ruíz E, Alcaide García J, Rueda Domínguez A. Impact of weight loss on cancer patients' quality of life at the beginning of the chemotherapy. *Supportive Care in Cancer* 2021; **29**(2)**:** 627-634. doi: 10.1007/s00520-020-05496-9

479. Head BA, Heitz L, Keeney C, Myers J, Appana SN, Studts JL *et al.* The relationship between weight loss and health-related quality of life in persons treated for head and neck cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2011; **19**(10)**:** 1511-1518. e-pub ahead of print 2010/08/24; doi: 10.1007/s00520-010-0975-x

480. Abu-Odah H, Molassiotis A, Zhao IY, Su JJ, Allsop MJ. Psychological distress and associated factors among Palestinian advanced cancer patients: A cross-sectional study. *Front Psychol* 2022; **13:** 1061327. e-pub ahead of print 2022/12/20; doi: 10.3389/fpsyg.2022.1061327

481. N AL. Opioid-Induced Constipation in Advanced Cancer Patients. *Cureus* 2021; **13**(4)**:** e14386. e-pub ahead of print 2021/04/15; doi: 10.7759/cureus.14386

482. Jehangir A, Parkman HP. Chronic opioids in gastroparesis: Relationship with gastrointestinal symptoms, healthcare utilization and employment. *World J Gastroenterol* 2017; **23**(40)**:** 7310-7320. e-pub ahead of print 2017/11/17; doi: 10.3748/wjg.v23.i40.7310

483. Caterino JM, Adler D, Durham DD, Yeung S-CJ, Hudson MF, Bastani A *et al.* Analysis of Diagnoses, Symptoms, Medications, and Admissions Among Patients With Cancer Presenting to Emergency Departments.

JAMA Network Open 2019; **2**(3)**:** e190979-e190979. doi: 10.1001/jamanetworkopen.2019.0979

484. Tai SY, Lee CY, Wu CY, Hsieh HY, Huang JJ, Huang CT *et al.* Symptom severity of patients with advanced cancer in palliative care unit: longitudinal assessments of symptoms improvement. *BMC Palliat Care* 2016; **15:** 32. e-pub ahead of print 2016/03/13; doi: 10.1186/s12904-016-0105-8

485. Rozin P. The Meaning of Food in Our Lives: A Cross-Cultural Perspective on Eating and Well-Being. *Journal of Nutrition Education and Behavior* 2005; **37:** S107-S112. doi: https://doi.org/10.1016/S1499-4046(06)60209-1

486. Bowie J, Brunckhorst O, Stewart R, Dasgupta P, Ahmed K. Body image, self-esteem, and sense of masculinity in patients with prostate cancer: a qualitative meta-synthesis. *Journal of Cancer Survivorship* 2022; **16**(1)**:** 95-110. doi: 10.1007/s11764-021-01007-9

487. Manier KK, Rowe LS, Welsh J, Armstrong TS. The impact and incidence of altered body image in patients with head and neck tumors: a systematic review. *Neurooncol Pract* 2018; **5**(4)**:** 204-213. e-pub ahead of print 2019/08/07; doi: 10.1093/nop/npy018

488. Fingeret MC, Teo I, Epner DE. Managing body image difficulties of adult cancer patients: Lessons from available research. *Cancer* 2014; **120**(5)**:** 633-641. doi: https://doi.org/10.1002/cncr.28469

489. Hamer M, Chida Y, Molloy GJ. Psychological distress and cancer mortality. *Journal of Psychosomatic Research* 2009; **66**(3)**:** 255-258. doi: https://doi.org/10.1016/j.jpsychores.2008.11.002

490. RYAN H, SCHOFIELD P, COCKBURN J, BUTOW P, TATTERSALL M, TURNER J *et al.* How to recognize and manage psychological distress in cancer patients. *European journal of cancer care* 2005; **14**(1)**:** 7-15. doi: https://doi.org/10.1111/j.1365-2354.2005.00482.x

491. Family Beliefs Regarding the Nutritional Care of a Terminally Ill Relative: A Qualitative Study. *Journal of Palliative Medicine* 2003; **6**(5)**:** 737-748. doi: 10.1089/109662103322515248

492. Maggiore RJ, Gross CP, Hurria A. Polypharmacy in Older Adults with Cancer. *The oncologist* 2010; **15**(5)**:** 507-522. doi: 10.1634/theoncologist.2009-0290

493. Fede A, Miranda M, Antonangelo D, Trevizan L, Schaffhausser H, Hamermesz B *et al.* Use of unnecessary medications by patients with advanced cancer: cross-sectional survey. *Supportive Care in Cancer* 2011; **19**(9)**:** 1313-1318. doi: 10.1007/s00520-010-0947-1

494. Fu AZ, Liu GG, Christensen DB. Inappropriate medication use and health outcomes in the elderly. *J Am Geriatr Soc* 2004; **52**(11)**:** 1934-1939. e-pub ahead of print 2004/10/28; doi: 10.1111/j.1532-5415.2004.52522.x

495. Dhalwani NN, Fahami R, Sathanapally H, Seidu S, Davies MJ, Khunti K. Association between polypharmacy and falls in older adults: a longitudinal study from England. *BMJ Open* 2017; **7**(10)**:** e016358. e-pub ahead of print 2017/10/19; doi: 10.1136/bmjopen-2017-016358

496. Klarin I, Wimo A, Fastbom J. The association of inappropriate drug use with hospitalisation and mortality: a population-based study of the very old. *Drugs Aging* 2005; **22**(1)**:** 69-82. e-pub ahead of print 2005/01/25; doi: 10.2165/00002512-200522010-00005

497. Dhakal P, Lyden E, Muir KE, Al-Kadhimi ZS, Koll T, Maness LJ *et al.* Prevalence and effects of polypharmacy on overall survival in acute myeloid leukemia. *Leuk Lymphoma* 2020; **61**(7)**:** 1702-1708. e-pub ahead of print 2020/03/12; doi: 10.1080/10428194.2020.1737687

498. Lau DT, Kasper JD, Potter DE, Lyles A, Bennett RG. Hospitalization and death associated with potentially inappropriate medication prescriptions among elderly nursing home residents. *Arch Intern Med* 2005; **165**(1)**:** 68-74. e-pub ahead of print 2005/01/12; doi: 10.1001/archinte.165.1.68

499. Morris JG, Parsons RL, Trounce JR, Groves MJ. Plasma dopa concentrations after different preparations of levodopa in normal subjects. *Br J Clin Pharmacol* 1976; **3**(6)**:** 983-990. e-pub ahead of print 1976/12/01; doi: 10.1111/j.1365-2125.1976.tb00347.x

500. Johnson BF, Bustrack JA, Urbach DR, Hull JH, Marwaha R. Effect of metoclopramide on digoxin absorption from tablets and capsules. *Clin Pharmacol Ther* 1984; **36**(6)**:** 724-730. e-pub ahead of print 1984/12/01; doi: 10.1038/clpt.1984.249

501. Volans GN. The effect of metoclopramide on the absorption of effervescent aspirin in migraine. *Br J Clin Pharmacol* 1975; **2**(1)**:** 57-63. e-pub ahead of print 1975/02/01; doi: 10.1111/j.1365-2125.1975.tb00472.x

502. Roeland EJ, Bohlke K, Baracos VE, Bruera E, Fabbro Ed, Dixon S *et al.* Management of Cancer Cachexia: ASCO Guideline. *Journal of Clinical Oncology* 2020; **38**(21)**:** 2438-2453. doi: 10.1200/jco.20.00611

503. Sepúlveda C, Marlin A, Yoshida T, Ullrich A. Palliative Care: the World Health Organization's global perspective. *Journal of pain and symptom management* 2002; **24**(2)**:** 91-96. e-pub ahead of print 2002/09/17; doi: 10.1016/s0885-3924(02)00440-2

504. Reid J, McKenna H, Fitzsimons D, McCance T. Fighting over food: patient and family understanding of cancer cachexia. *Oncol Nurs Forum* 2009; **36**(4)**:** 439-445. e-pub ahead of print 2009/07/08; doi: 10.1188/09.Onf.439-445

505. Reid J, McKenna H, Fitzsimons D, McCance T. The experience of cancer cachexia: a qualitative study of advanced cancer patients and their family members. *Int J Nurs Stud* 2009; **46**(5)**:** 606-616. e-pub ahead of print 2008/12/17; doi: 10.1016/j.ijnurstu.2008.10.012

506. Olsson LE, Jakobsson Ung E, Swedberg K, Ekman I. Efficacy of person-centred care as an intervention in controlled trials - a systematic review. *J Clin Nurs* 2013; **22**(3-4)**:** 456-465. e-pub ahead of print 2012/12/13; doi: 10.1111/jocn.12039

507. McMillan SS, Kendall E, Sav A, King MA, Whitty JA, Kelly F *et al.* Patient-centered approaches to health care: a systematic review of randomized controlled trials. *Med Care Res Rev* 2013; **70**(6)**:** 567-596. e-pub ahead of print 2013/07/31; doi: 10.1177/1077558713496318

508. Stewart M, Brown JB, Donner A, McWhinney IR, Oates J, Weston WW *et al.* The impact of patient-centered care on outcomes. *J Fam Pract* 2000; **49**(9)**:** 796-804. e-pub ahead of print 2000/10/14;

509. Jones KR, Vojir CP, Hutt E, Fink R. Determining mild, moderate, and severe pain equivalency across pain-intensity tools in nursing home residents. *J Rehabil Res Dev* 2007; **44**(2)**:** 305-314. e-pub ahead of print 2007/06/07; doi: 10.1682/jrrd.2006.05.0051

510. Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK *et al.* The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer* 1999; **85**(5)**:** 1186-1196. e-pub ahead of print 1999/03/26; doi: 10.1002/(sici)1097-0142(19990301)85:5<1186::aid-cncr24>3.0.co;2-n

511. Molassiotis A, Coventry PA, Stricker CT, Clements C, Eaby B, Velders L *et al.* Validation and Psychometric Assessment of a Short Clinical Scale to Measure Chemotherapy-Induced Nausea and Vomiting: The MASCC Antiemesis Tool. *Journal of pain and symptom management* 2007; **34**(2)**:** 148-159. doi: https://doi.org/10.1016/j.jpainsymman.2006.10.018

512. McCorkle R, Young K. Development of a symptom distress scale. *Cancer Nurs* 1978; **1**(5)**:** 373-378. e-pub ahead of print 1978/10/01;

513. McCorkle R, Quint-Benoliel J. Symptom distress, current concerns and mood disturbance after diagnosis of life-threatening disease. *Soc Sci Med* 1983; **17**(7)**:** 431-438. e-pub ahead of print 1983/01/01; doi: 10.1016/0277-9536(83)90348-9

514. Portenoy RK, Thaler HT, Kornblith AB, Lepore JM, Friedlander-Klar H, Kiyasu E *et al.* The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *Eur J Cancer* 1994; **30a**(9)**:** 1326-1336. e-pub ahead of print 1994/01/01; doi: 10.1016/0959-8049(94)90182-1

515. de Haes JC, van Knippenberg FC, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. *Br J Cancer* 1990; **62**(6)**:** 1034-1038. e-pub ahead of print 1990/12/01; doi: 10.1038/bjc.1990.434

516. Cella DF. Quality of life: Concepts and definition. *Journal of pain and symptom management* 1994; **9**(3)**:** 186-192. doi: https://doi.org/10.1016/0885-3924(94)90129-5

517. Hanna EY, Mendoza TR, Rosenthal DI, Gunn GB, Sehra P, Yucel E *et al.* The symptom burden of treatment-naive patients with head and neck cancer. *Cancer* 2015; **121**(5)**:** 766-773. doi: https://doi.org/10.1002/cncr.29097

518. Lopes AC, Bacalhau R, Santos M, Pereira M, Pereira MG. Contribution of Sociodemographic, Clinical, and Psychological Variables to Quality of Life in Women with Cervical Cancer in the Follow-Up Phase. *J Clin Psychol Med Settings* 2020; **27**(3)**:** 603-614. e-pub ahead of print 2019/07/12; doi: 10.1007/s10880-019-09644-0

519. Lindqvist C, Slinde F, Majeed A, Bottai M, Wahlin S. Nutrition impact symptoms are related to malnutrition and quality of life – A cross-sectional study of patients with chronic liver disease. *Clinical Nutrition* 2020; **39**(6)**:** 1840-1848. doi: https://doi.org/10.1016/j.clnu.2019.07.024

520. Langius JAE, Zandbergen MC, Eerenstein SEJ, van Tulder MW, Leemans CR, Kramer MHH *et al.* Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo)radiotherapy: a systematic review. *Clinical Nutrition* 2013; **32**(5)**:** 671-678. doi: https://doi.org/10.1016/j.clnu.2013.06.012

521. Fayers P, Bottomley A. Quality of life research within the EORTC—the EORTC QLQ-C30. *European Journal of Cancer* 2002; **38:** 125-133. doi: https://doi.org/10.1016/S0959-8049(01)00448-8

522. Ezzatvar Y, Ramírez-Vélez R, Sáez de Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F, Izquierdo M *et al.* Physical Function and All-Cause Mortality in Older Adults Diagnosed With Cancer: A Systematic Review and Meta-Analysis. *J Gerontol A Biol Sci Med Sci* 2021; **76**(8)**:** 1447-1453. e-pub ahead of print 2021/01/10; doi: 10.1093/gerona/glaa305

523. Pandya C, Magnuson A, Flannery M, Zittel J, Duberstein P, Loh KP *et al.* Association Between Symptom Burden and Physical Function in Older Patients with Cancer. *J Am Geriatr Soc* 2019; **67**(5)**:** 998-1004. e-pub ahead of print 2019/03/09; doi: 10.1111/jgs.15864

524. Scott N, Fayers P, Aaronson N, Bottomley A, de Graeff A, Groenvold M *et al.* EORTC QLQ-C30. *Reference values. Brussels: EORTC* 2008.

525. Nolte S, Liegl G, Petersen MA, Aaronson NK, Costantini A, Fayers PM *et al.* General population normative data for the EORTC QLQ-C30 health-

related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. *European Journal of Cancer* 2019; **107:** 153-163. doi: https://doi.org/10.1016/j.ejca.2018.11.024

526. Hendriks S, Huisman MG, Ghignone F, Vigano A, de Liguori Carino N, Farinella E *et al.* Timed up and go test and long-term survival in older adults after oncologic surgery. *BMC Geriatrics* 2022; **22**(1)**:** 934. doi: 10.1186/s12877-022-03585-4

527. Schmidt M, Eckardt R, Altmeppen S, Wernecke K-D, Spies C. Functional impairment prior to major non-cardiac surgery is associated with mortality within one year in elderly patients with gastrointestinal, gynaecological and urogenital cancer: A prospective observational cohort study. *Journal of Geriatric Oncology* 2018; **9**(1)**:** 53-59. doi: 10.1016/j.jgo.2017.07.011

528. Milanović Z, Pantelić S, Trajković N, Sporiš G, Kostić R, James N. Age-related decrease in physical activity and functional fitness among elderly men and women. *Clin Interv Aging* 2013; **8:** 549-556. e-pub ahead of print 2013/06/01; doi: 10.2147/cia.S44112

529. Sattar S, Alibhai SMH, Spoelstra SL, Puts MTE. The assessment, management, and reporting of falls, and the impact of falls on cancer treatment in community-dwelling older patients receiving cancer treatment: Results from a mixed-methods study. *J Geriatr Oncol* 2019; **10**(1)**:** 98-104. e-pub ahead of print 2018/09/04; doi: 10.1016/j.jgo.2018.08.006

530. Tinetti ME, Williams CS. Falls, Injuries Due to Falls, and the Risk of Admission to a Nursing Home. *New England Journal of Medicine* 1997; **337**(18)**:** 1279-1284. doi: 10.1056/nejm199710303371806

531. Toomey A, Friedman L. Mortality in cancer patients after a fall-related injury: The impact of cancer spread and type. *Injury* 2014; **45**(11)**:** 1710-1716. e-pub ahead of print 2014/04/22; doi: 10.1016/j.injury.2014.03.008

532. Bahcaci U, Demirbuken I. Effects of chemotherapy process on postural balance control in patients with breast cancer. *Indian J Cancer* 2019; **56**(1)**:** 50-54. e-pub ahead of print 2019/04/06; doi: 10.4103/ijc.IJC_47_18

533. Monfort SM, Pan X, Patrick R, Ramaswamy B, Wesolowski R, Naughton MJ *et al.* Gait, balance, and patient-reported outcomes during taxane-based chemotherapy in early-stage breast cancer patients. *Breast Cancer Res Treat* 2017; **164**(1)**:** 69-77. e-pub ahead of print 2017/04/05; doi: 10.1007/s10549-017-4230-8

534. Müller J, Ringhof S, Vollmer M, Jäger LB, Stein T, Weiler M *et al.* Out of balance - Postural control in cancer patients before and after neurotoxic chemotherapy. *Gait Posture* 2020; **77:** 156-163. e-pub ahead of print 2020/02/10; doi: 10.1016/j.gaitpost.2020.01.012

535. Gavotto A, Dubard V, Avesani M, Huguet H, Picot M-C, Abassi H *et al.* Impaired aerobic capacity in adolescents and young adults after treatment for cancer or non-malignant haematological disease. *Pediatric Research* 2023. doi: 10.1038/s41390-023-02477-6

536. Deimling GT, Sterns S, Bowman KF, Kahana B. Functioning and activity participation restrictions among older adult, long-term cancer survivors. *Cancer Invest* 2007; **25**(2)**:** 106-116. e-pub ahead of print 2007/04/25; doi: 10.1080/07357900701224813

537. Sisk BA, Fasciano K, Block SD, Mack JW. Impact of cancer on school, work, and financial independence among adolescents and young adults. *Cancer* 2020; **126**(19)**:** 4400-4406. e-pub ahead of print 2020/07/14; doi: 10.1002/cncr.33081

538. Trombetti A, Reid KF, Hars M, Herrmann FR, Pasha E, Phillips EM *et al.* Age-associated declines in muscle mass, strength, power, and physical performance: impact on fear of falling and quality of life. *Osteoporosis International* 2016; **27**(2)**:** 463-471. doi: 10.1007/s00198-015-3236-5

539. ElMokhallalati Y, Alaloul E, Shatat M, Shneewra T, El Massri S, Shaer O *et al.* The Symptom Burden and Quality of Life in Cancer Patients in the Gaza Strip, Palestine: A Cross-Sectional Study. *PloS one* 2022; **17**(1)**:** e0262512. e-pub ahead of print 2022/01/14; doi: 10.1371/journal.pone.0262512

540. Ramasubbu SK, Pasricha RK, Nath UK, Rawat VS, Das B. Quality of life and factors affecting it in adult cancer patients undergoing cancer chemotherapy in a tertiary care hospital. *Cancer Reports* 2021; **4**(2)**:** e1312. doi: https://doi.org/10.1002/cnr2.1312

541. Alzehr A, Hulme C, Spencer A, Morgan-Trimmer S. The economic impact of cancer diagnosis to individuals and their families: a systematic review. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2022; **30**(8)**:** 6385-6404. e-pub ahead of print 2022/03/03; doi: 10.1007/s00520-022-06913-x

542. Landwehr MS, Watson SE, Macpherson CF, Novak KA, Johnson RH. The cost of cancer: a retrospective analysis of the financial impact of cancer on young adults. *Cancer Medicine* 2016; **5**(5)**:** 863-870. doi: https://doi.org/10.1002/cam4.657

543. Patel D, Steinberg J, Patel P. Insomnia in the Elderly: A Review. *J Clin Sleep Med* 2018; **14**(6)**:** 1017-1024. e-pub ahead of print 2018/06/02; doi: 10.5664/jcsm.7172

544. Trudel-Fitzgerald C, Millstein RA, von Hippel C, Howe CJ, Tomasso LP, Wagner GR *et al.* Psychological well-being as part of the public health debate? Insight into dimensions, interventions, and policy. *BMC Public Health* 2019; **19**(1)**:** 1712. doi: 10.1186/s12889-019-8029-x

545. Chrousos GP. The stress response and immune function: clinical implications. The 1999 Novera H. Spector Lecture. *Ann N Y Acad Sci* 2000; **917:** 38-67. e-pub ahead of print 2001/03/28; doi: 10.1111/j.1749-6632.2000.tb05371.x

546. Webster Marketon JI, Glaser R. Stress hormones and immune function. *Cell Immunol* 2008; **252**(1-2)**:** 16-26. e-pub ahead of print 2008/02/19; doi: 10.1016/j.cellimm.2007.09.006

547. Majeed A, Rehman M, Hussain I, Imran I, Saleem MU, Saeed H *et al.* The Impact of Treatment Adherence on Quality of Life Among Type 2 Diabetes Mellitus Patients - Findings from a Cross-Sectional Study. *Patient Prefer Adherence* 2021; **15:** 475-481. e-pub ahead of print 2021/03/06; doi: 10.2147/ppa.S295012

548. Holt EW, Muntner P, Joyce CJ, Webber L, Krousel-Wood MA. Health-related quality of life and antihypertensive medication adherence among older adults. *Age Ageing* 2010; **39**(4)**:** 481-487. doi: 10.1093/ageing/afq040

549. Cheville AL, Alberts SR, Rummans TA, Basford JR, Lapid MI, Sloan JA *et al.* Improving Adherence to Cancer Treatment by Addressing Quality of Life in Patients With Advanced Gastrointestinal Cancers. *Journal of pain and symptom management* 2015; **50**(3)**:** 321-327. e-pub ahead of print 2015/05/16; doi: 10.1016/j.jpainsymman.2015.03.005

550. Yoder AK, Dong E, Yu X, Echeverria A, Sharma S, Montealegre J *et al.* Effect of Quality of Life on Radiation Adherence for Patients With Cervical Cancer in an Urban Safety Net Health System. *International Journal of Radiation Oncology*Biology*Physics* 2023; **116**(1)**:** 182-190. doi: https://doi.org/10.1016/j.ijrobp.2022.10.013

551. Sloan JA, Zhao X, Novotny PJ, Wampfler J, Garces Y, Clark MM *et al.* Relationship between deficits in overall quality of life and non-small-cell lung cancer survival. *J Clin Oncol* 2012; **30**(13)**:** 1498-1504. e-pub ahead of print 2012/03/29; doi: 10.1200/jco.2010.33.4631

552. Ehrsson YT, Fransson P, Einarsson S. Mapping Health-Related Quality of Life, Anxiety, and Depression in Patients with Head and Neck Cancer Diagnosed with Malnutrition Defined by GLIM. *Nutrients* 2021; **13**(4)**:** 1167.

553. Kaźmierczak-Siedlecka K, Skonieczna-Żydecka K, Folwarski M, Ruszkowski J, Świerblewski M, Makarewicz W. Influence of malnutrition stage according to GLIM 2019 criteria and SGA on the quality of life of patients with advanced cancer. *Nutr Hosp* 2020; **37**(6)**:** 1179-1185. e-pub ahead of print 2020/10/30; doi: 10.20960/nh.03185

554. Zhou L, Fu J, Ding Z, Jin K, Wu R, Ye LX. Comparison of GLIM, SGA, PG-SGA, and PNI in diagnosing malnutrition among hepatobiliary-pancreatic

surgery patients. *Front Nutr* 2023; **10:** 1116243. e-pub ahead of print 2023/02/11; doi: 10.3389/fnut.2023.1116243

555. V IJ-H, Heerschop S, Wanten G, van den Berg M. Evaluation of the Validity and Feasibility of the GLIM Criteria Compared with PG-SGA to Diagnose Malnutrition in Relation to One-Year Mortality in Hospitalized Patients. *J Acad Nutr Diet* 2022; **122**(3)**:** 595-601. e-pub ahead of print 2021/09/01; doi: 10.1016/j.jand.2021.07.011

556. Gupta D, Lis CG, Granick J, Grutsch JF, Vashi PG, Lammersfeld CA. Malnutrition was associated with poor quality of life in colorectal cancer: a retrospective analysis. *Journal of Clinical Epidemiology* 2006; **59**(7)**:** 704-709. doi: https://doi.org/10.1016/j.jclinepi.2005.08.020

557. Maia FdCP, Silva TA, Generoso SdV, Correia MITD. Malnutrition is associated with poor health-related quality of life in surgical patients with gastrointestinal cancer. *Nutrition* 2020; **75-76:** 110769. doi: https://doi.org/10.1016/j.nut.2020.110769

558. Pulley J, Todd A, Flatley C, Begun J. Malnutrition and quality of life among adult inflammatory bowel disease patients. *JGH Open* 2020; **4**(3)**:** 454-460. doi: https://doi.org/10.1002/jgh3.12278

559. Ravasco P. Nutrition in Cancer Patients. *Journal of Clinical Medicine* 2019; **8**(8)**:** 1211.

560. Locher JL, Ritchie CS, Roth DL, Baker PS, Bodner EV, Allman RM. Social isolation, support, and capital and nutritional risk in an older sample: ethnic and gender differences. *Soc Sci Med* 2005; **60**(4)**:** 747-761. e-pub ahead of print 2004/12/02; doi: 10.1016/j.socscimed.2004.06.023

561. Delerue Matos A, Barbosa F, Cunha C, Voss G, Correia F. Social isolation, physical inactivity and inadequate diet among European middle-aged and older adults. *BMC Public Health* 2021; **21**(1)**:** 924. doi: 10.1186/s12889-021-10956-w

562. de Castro JM, de Castro ES. Spontaneous meal patterns of humans: influence of the presence of other people. *The American journal of clinical nutrition* 1989; **50**(2)**:** 237-247. doi: 10.1093/ajcn/50.2.237

563. Canetti L, Bachar E, Berry EM. Food and emotion. *Behavioural Processes* 2002; **60**(2)**:** 157-164. doi: https://doi.org/10.1016/S0376-6357(02)00082-7

564. Wu H-S, Harden JK. Symptom Burden and Quality of Life in Survivorship: A Review of the Literature. *Cancer Nursing* 2015; **38**(1).

565. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P *et al.* Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. *J Clin Oncol* 2016;

34(6)**:** 557-565. e-pub ahead of print 2015/12/09; doi: 10.1200/jco.2015.63.0830

566. King S, Exley J, Parks S, Ball S, Bienkowska-Gibbs T, MacLure C *et al.* The use and impact of quality of life assessment tools in clinical care settings for cancer patients, with a particular emphasis on brain cancer: insights from a systematic review and stakeholder consultations. *Qual Life Res* 2016; **25**(9)**:** 2245-2256. e-pub ahead of print 2016/04/04; doi: 10.1007/s11136-016-1278-6

567. Meropol NJ, Egleston BL, Buzaglo JS, Benson III AB, Cegala DJ, Diefenbach MA *et al.* Cancer patient preferences for quality and length of life. *Cancer* 2008; **113**(12)**:** 3459-3466. doi: https://doi.org/10.1002/cncr.23968

568. Lipscomb J, Gotay CC, Snyder CF. Patient-reported outcomes in cancer: a review of recent research and policy initiatives. *CA Cancer J Clin* 2007; **57**(5)**:** 278-300. e-pub ahead of print 2007/09/15; doi: 10.3322/ca.57.5.278

569. Snyder CF, Blackford AL, Okuyama T, Akechi T, Yamashita H, Toyama T *et al.* Using the EORTC-QLQ-C30 in clinical practice for patient management: identifying scores requiring a clinician's attention. *Qual Life Res* 2013; **22**(10)**:** 2685-2691. e-pub ahead of print 2013/03/28; doi: 10.1007/s11136-013-0387-8

570. Slevin ML, Plant H, Lynch D, Drinkwater J, Gregory WM. Who should measure quality of life, the doctor or the patient? *Br J Cancer* 1988; **57**(1)**:** 109-112. e-pub ahead of print 1988/01/01; doi: 10.1038/bjc.1988.20

571. Arab A, Karimi E, Vingrys K, Shirani F. Is phase angle a valuable prognostic tool in cancer patients' survival? A systematic review and meta-analysis of available literature. *Clinical Nutrition* 2021; **40**(5)**:** 3182-3190. doi: https://doi.org/10.1016/j.clnu.2021.01.027

572. Rydwik E, Bergland A, Forsén L, Frändin K. Psychometric Properties of Timed Up and Go in Elderly People: A Systematic Review. *Physical & Occupational Therapy In Geriatrics* 2011; **29**(2)**:** 102-125. doi: 10.3109/02703181.2011.564725

573. Beauchet O, Fantino B, Allali G, Muir SW, Montero-Odasso M, Annweiler C. Timed Up and Go test and risk of falls in older adults: a systematic review. *J Nutr Health Aging* 2011; **15**(10)**:** 933-938. e-pub ahead of print 2011/12/14; doi: 10.1007/s12603-011-0062-0

574. Barry E, Galvin R, Keogh C, Horgan F, Fahey T. Is the Timed Up and Go test a useful predictor of risk of falls in community dwelling older adults: a systematic review and meta-analysis. *BMC Geriatr* 2014; **14:** 14. e-pub ahead of print 2014/02/04; doi: 10.1186/1471-2318-14-14

575. Stover AM, Basch EM. Implementation of Symptom Questionnaires Into Oncology Workflow. *J Oncol Pract* 2016; **12**(10)**:** 859-862. e-pub ahead of print 2016/09/08; doi: 10.1200/jop.2016.015610

576. Nekolaichuk CL, Bruera E, Spachynski K, MacEachern T, Hanson J, Maguire TO. A comparison of patient and proxy symptom assessments in advanced cancer patients. *Palliat Med* 1999; **13**(4)**:** 311-323. e-pub ahead of print 2000/02/05; doi: 10.1191/026921699675854885

577. Laugsand EA, Sprangers MA, Bjordal K, Skorpen F, Kaasa S, Klepstad P. Health care providers underestimate symptom intensities of cancer patients: a multicenter European study. *Health Qual Life Outcomes* 2010; **8:** 104. e-pub ahead of print 2010/09/23; doi: 10.1186/1477-7525-8-104

578. Reeve BB, Mitchell SA, Dueck AC, Basch E, Cella D, Reilly CM *et al.* Recommended patient-reported core set of symptoms to measure in adult cancer treatment trials. *J Natl Cancer Inst* 2014; **106**(7). e-pub ahead of print 2014/07/10; doi: 10.1093/jnci/dju129

579. Chera BS, Eisbruch A, Murphy BA, Ridge JA, Gavin P, Reeve BB *et al.* Recommended patient-reported core set of symptoms to measure in head and neck cancer treatment trials. *J Natl Cancer Inst* 2014; **106**(7). e-pub ahead of print 2014/07/10; doi: 10.1093/jnci/dju127

580. Pedersen PU. Nutritional care: the effectiveness of actively involving older patients. *J Clin Nurs* 2005; **14**(2)**:** 247-255. e-pub ahead of print 2005/01/27; doi: 10.1111/j.1365-2702.2004.00874.x

581. Hartmuller VW, Desmond SM. Professional and patient perspectives on nutritional needs of patients with cancer. *Oncol Nurs Forum* 2004; **31**(5)**:** 989-996. e-pub ahead of print 2004/09/21; doi: 10.1188/04.Onf.989-996

582. Quaidoo EY, Ohemeng A, Amankwah-Poku M. Sources of nutrition information and level of nutrition knowledge among young adults in the Accra metropolis. *BMC Public Health* 2018; **18**(1)**:** 1323. doi: 10.1186/s12889-018-6159-1

583. Mullee A, O'Donoghue A, Dhuibhir PU, O'Donoghue N, Burke D, McSharry V *et al.* Diet and Nutrition Advice After a Solid Tumor Diagnosis. *JCO Oncology Practice* 2021; **17**(7)**:** e982-e991. doi: 10.1200/op.20.00685

584. Zastrow A, Faude V, Seyboth F, Niehoff D, Herzog W, Löwe B. Risk factors of symptom underestimation by physicians. *J Psychosom Res* 2008; **64**(5)**:** 543-551. e-pub ahead of print 2008/04/29; doi: 10.1016/j.jpsychores.2007.11.010

585. Guimarães M, Pinto M, Resende GG, Machado CJ, Vargas-Santos AB, Amorim RBC *et al.* Discordance between the patient's and physician's global assessment in rheumatoid arthritis: Data from the REAL study-Brazil. *PloS one* 2020; **15**(3)**:** e0230317. e-pub ahead of print 2020/03/14; doi: 10.1371/journal.pone.0230317

586. Basch E, Iasonos A, McDonough T, Barz A, Culkin A, Kris MG *et al.* Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study. *Lancet Oncol* 2006; **7**(11)**:** 903-909. e-pub ahead of print 2006/11/04; doi: 10.1016/s1470-2045(06)70910-x

587. Karpouzas GA, Ramadan SN, Cost CE, Draper TL, Hernandez E, Strand V *et al.* Discordant patient-physician assessments of disease activity and its persistence adversely impact quality of life and work productivity in US Hispanics with rheumatoid arthritis. *RMD Open* 2017; **3**(2)**:** e000551. e-pub ahead of print 2017/11/10; doi: 10.1136/rmdopen-2017-000551

588. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther* 2001; **26**(5)**:** 331-342. e-pub ahead of print 2001/10/27; doi: 10.1046/j.1365-2710.2001.00363.x

589. Starfield B, Wray C, Hess K, Gross R, Birk PS, D'Lugoff BC. The influence of patient-practitioner agreement on outcome of care. *Am J Public Health* 1981; **71**(2)**:** 127-131. e-pub ahead of print 1981/02/01; doi: 10.2105/ajph.71.2.127

590. Tomaselli G, Buttigieg SC, Rosano A, Cassar M, Grima G. Person-Centered Care From a Relational Ethics Perspective for the Delivery of High Quality and Safe Healthcare: A Scoping Review. *Front Public Health* 2020; **8:** 44. e-pub ahead of print 2020/03/27; doi: 10.3389/fpubh.2020.00044

591. Barbara AM, Loeb M, Dolovich L, Brazil K, Russell M. Agreement between self-report and medical records on signs and symptoms of respiratory illness. *Primary Care Respiratory Journal* 2012; **21**(2)**:** 145-152. doi: 10.4104/pcrj.2011.00098

592. Gilbertson-White S, Aouizerat BE, Jahan T, Miaskowski C. A review of the literature on multiple symptoms, their predictors, and associated outcomes in patients with advanced cancer. *Palliative & Supportive Care* 2011; **9**(1)**:** 81-102. e-pub ahead of print 2011/02/25; doi: 10.1017/S147895151000057X

593. Dong ST, Butow PN, Costa DSJ, Lovell MR, Agar M. Symptom Clusters in Patients With Advanced Cancer: A Systematic Review of Observational Studies. *Journal of pain and symptom management* 2014; **48**(3)**:** 411-450. doi: https://doi.org/10.1016/j.jpainsymman.2013.10.027

594. Mathew A, Tirkey AJ, Li H, Steffen A, Lockwood MB, Patil CL *et al.* Symptom Clusters in Head and Neck Cancer: A Systematic Review and Conceptual Model. *Semin Oncol Nurs* 2021; **37**(5)**:** 151215. e-pub ahead of print 2021/09/07; doi: 10.1016/j.soncn.2021.151215

595. Chang VT, Hwang SS, Feuerman M, Kasimis BS. Symptom and quality of life survey of medical oncology patients at a Veterans Affairs medical center. *Cancer* 2000; **88**(5)**:** 1175-1183. doi: https://doi.org/10.1002/(SICI)1097-0142(20000301)88:5<1175::AID-CNCR30>3.0.CO;2-N

596. Degner LF, Sloan JA. Symptom distress in newly diagnosed ambulatory cancer patients and as a predictor of survival in lung cancer. *Journal of pain and symptom management* 1995; **10**(6)**:** 423-431. doi: https://doi.org/10.1016/0885-3924(95)00056-5

597. Aktas A, Walsh D, Rybicki L. Symptom clusters and prognosis in advanced cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2012; **20**(11)**:** 2837-2843. e-pub ahead of print 2012/03/01; doi: 10.1007/s00520-012-1408-9

598. De Groot LM, Lee G, Ackerie A, van der Meij BS. Malnutrition Screening and Assessment in the Cancer Care Ambulatory Setting: Mortality Predictability and Validity of the Patient-Generated Subjective Global Assessment Short form (PG-SGA SF) and the GLIM Criteria. *Nutrients* 2020; **12**(8)**:** 2287.

10 APPENDICES

10.1 Appendix 1 - Ethical Approval Letters

ST. VINCENT'S UNIVERSITY HOSPITAL
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Professor Kevin Conlon
Professor of Surgery
St. Vincent's University Hospital
Elm Park
Dublin 4

13th January 2020

Ref: **RS19-080**
Study title: **The Symptom Experience of Early Satiety**

Documentation:
Cover letter- 23.12.2019. Research Protocol as per submission on 23.12.2019. Patient Information Leaflet as per submission on 23.12.2019. Appendix 5: Data Collection Form as per submission on 23.12.2019. Standard Application form 23.12.2019

Dear Professor Conlon,

I refer to correspondence on 23rd December 2019. Following review of the responses and clarifications received, this study has been granted full Ethics approval.

Please note, it is the responsibility of the Principal Investigator and Sponsor to retain full file copies of all documentation submitted and received in respect of this study application.

Yours sincerely,

Dr. Rachel Crowley
Chairperson
Ethics & Medical Research Committee

Tallaght University Hospital | Ospidéal Ollscoile Thamhlachta

An Academic Partner of Trinity College Dublin

Ospidéal San Séamas – Seirbhís Dé agus A Phobail

Research Office

Project ID: 1919

Mr Aidan O'Donoghue,

Trinity College Dublin

Professor Kevin Conlon, Trinity College Dublin/Tallaght University Hospital

Approval Date: 2 August 2022

Submission Number: 952

Submission Title: Early Satiety: Determining the prevalence, symptom experience and association with functional status in cancer
Submission Date: 08 Jun 2022 18:25

Dear Mr O'Donoghue,

On behalf of the Chair and members of the SJH/TUH Joint Research Ethics Committee I wish to inform you that your study has received **FULL APPROVAL**. Your study can now proceed.

The following comments were made:

Title	Comment
4.1.1.5 Who are the Data Handlers of the study data? (Please refer to the information bubble)	Umair Aleem not listed as Co-I. It is understood that Umair Aleem is a Co-Investigator.

The following documents were reviewed and approved:

Document Type	File Name	Date	Version
Principle Investigator C.V.	Professor Kevin Conlon - CV Sept 2021 NOVEMBER		
Indemnity Proof for Non-TUH	2021-2022 TWIMC		

researchers			
Data Collection Case Report Form	Data collection form V1	25.Mar.2022	1
Protocol	Protocol V1	25.Mar.2022	1
Survey/Questionnaire	Open Symptom Assessment V1	25.Mar.2022	1
Survey/Questionnaire	QLQ-C30	25.Mar.2022	1
Survey/Questionnaire	Abridged PG-SGA	25.Mar.2022	1
Survey/Questionnaire	Visual Analogue Scale	25.Mar.2022	1
Survey/Questionnaire	SEES Questionnaire V2 Post pilot	25.Mar.2022	2
Participant Information Leaflet	PIL Version 2	24.May.2022	2
Participant Consent Form	Consent form V2	25.May.2022	2
Default	Ethics cover letter	25.May.2022	1

Please note that ethical approval for this study is only active under the following conditions:

1. *Applicants must submit an annual report for ongoing projects.*
2. *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
3. *All adverse events must be reported to the JREC.*
4. *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Dr Sadhbh O'Neill

Research Ethics & Clinical Trials Manager,

SJH/TUH Joint Research Ethics Committee

The SJH/TUH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

10.2 Appendix 2 - Scoping Review Searches

Embase

('satiety'/exp OR 'satiety' OR 'satiety response'/exp OR 'satiety response' OR 'early satiety'/exp OR 'early satiety' OR 'premature fullness' OR 'premature satiety' OR 'early fullness' OR 'premature satiation' OR 'early satiation') AND ('malignant neoplasm'/exp OR 'malignant neoplasm' OR 'malignant neoplasm*' OR 'carcinoma'/exp OR 'carcinoma' OR 'carcinoma*' OR 'cancer*' OR 'neoplasm'/exp OR 'neoplasm' OR 'neoplasm*' OR 'oncology'/exp OR 'oncology' OR 'oncology*' OR 'tumour'/exp OR 'tumour' OR 'tumour*' OR 'tumor'/exp OR 'tumor' OR 'tumor*' OR 'malignan*')

Web of Science

TS=((Early satiety OR Early satiation OR early fullness OR premature fullness OR premature satiety OR premature satiation OR satiation OR satiety) AND (C ancer* OR Carcinoma* OR Malignan* OR Neoplas* OR Oncolog* OR Tumour* OR Tumor*))

Pubmed/Medline

((((((((((Early satiety[Title/Abstract]) OR Early satiation[Title/Abstract]) OR early fullness[Title/Abstract]) OR premature fullness[Title/Abstract]) OR premature satiety[Title/Abstract]) OR premature satiation[Title/Abstract])) OR "Satiation"[Mesh])) OR satiation[Title/Abstract]) OR satiety[Title/Abstract])) AND ((((((((((Cancer*[Title/Abstract]) OR Carcinoma*[Title/Abstract]) OR Malignan*[Title/Abstract]) OR Neoplasm*[Title/Abstract]) OR Neoplas*[Title/Abstract]) OR Oncolog*[Title/Abstract]) OR Tumour*[Title/Abstract]) OR Tumor*[Title/Abstract])) OR "Carcinoma"[Mesh]) OR "Neoplasms"[Mesh])

EBSCOhost

((((((((((((((((MH "Satiation") OR TI early satiety) OR AB early satiety) OR TI satiation) OR AB satiation) OR TI early fullness) OR AB early fullness) OR TI early satiation) OR AB early satiation) OR TI premature fullness) OR AB premature fullness) OR TI premature satiety) OR AB premature satiety) OR TI premature satiation) OR AB premature satiation) OR TI satiety) OR AB satiety) AND ((((((((((((((MH "Carcinoma") OR MH "Neoplasms") OR TI Neoplas*) OR AB Neoplas*) OR TI Carcinoma*) OR AB Carcinoma*) OR TI Cancer*) OR AB Cancer*) OR TI malignan*) OR AB malignan*) OR TI Tumour*) OR AB Tumour*) OR TI Tumor*) OR AB Tumor*) OR TI Oncolog*) OR AB Oncolog*)

Cochrane

1. MeSh Descriptor [Satiation] explode all trees
2. MeSh Descriptor [Satiety Response] explode all trees
3. ((early satiety*) or (satiety*) or (satiation*) or (early satiation*) or (fullness*)):ti, ab, kw
4. Or 1-3
5. MeSh Descriptor [Neoplasms] explode all trees
6. MeSh Descriptor [Carcinoma] explode all trees
7. ((oncolog*) or (cancer*) or (neoplasm*) or (carcinoma*) or (tumour*) or (tumor*)
8. Or 5-7
9. 4 and 8

10.3 Appendix 3 - Open Symptom Questionnaire (OSQ)

Open Question Symptoms Assessment

Study Number: _____ **Date:** _____

What problems have you had that have kept you from eating enough during the past two weeks?

_____
_____
_____
_____
_____

10.4 Appendix 4 - Abridged Patient-Generated Subjective Global Assessment (abPG-SGA)

ABRIDGED PATIENT-GENERATED SUBJECTIVE GLOBAL ASSESSMENT (abPG-SGA)

Study Number: _____ **Date:** _____

PLEASE COMPLETE BOXES 1-4

BOX 1: WEIGHT

In summary of my current and recent weight:

I am about _____feet _____inches tall

I currently weigh about: _____stone _____pounds OR _____kg

One month ago I weighed about _____stone ____pounds OR _____kg

Six months ago I weighed about _____stone ____pounds OR _____kg

During the past two weeks my weight has:

Decreased ☐ Not changed ☐ Increased ☐

BOX 2: FOOD INTAKE

As compared to my normal intake, I would rate my food intake during the past month as: (please tick)

☐ Unchanged
☐ More than usual
☐ Less than usual

If "Less than usual":

I am now taking:

☐ Normal food but less than normal amounts
☐ Little solid food
☐ Only liquids
☐ Only nutritional supplements
☐ Very little of anything
☐ Only tube feeding or only nutrition by vein

BOX 3: SYMPTOMS

I have had the following problems that have kept me from eating enough during the past two weeks **(tick all that apply)**:

- ☐ No problems eating
- ☐ No appetite, just did not feel like eating
- ☐ Nausea
- ☐ Vomiting
- ☐ Constipation
- ☐ Diarrhoea
- ☐ Mouth sores
- ☐ Dry mouth
- ☐ Things taste funny or have no taste
- ☐ Smells bother me
- ☐ Problems swallowing
- ☐ Feel full quickly
- ☐ Fatigue
- ☐ Pain: where_____

- ☐ Other*_____

*e.g. depression, money or dental problems

BOX 4: ACTIVITIES AND FUNCTION

Over the past month, I would generally rate my activity as: (please circle)

- ☐ Normal with no limitations
- ☐ Not my normal self, but able to be up and about with fairly normal activities
- ☐ Not feeling up to most things, but in bed or chair less than half the day
- ☐ Able to do little activity and spend most of the day in bed or chair
- ☐ Pretty much bedridden, rarely out of bed

10.5 Appendix 5 - Symptom Experience of Early Satiety (SEES) Version 1 (pre pilot)

Study ID: _____ Date: _____ Signed: _____

You have been asked to fill out this questionnaire because you reported you **'Feel Full Quickly'** in the previous questionnaire. The questions below ask about 'Feel Full Quickly' in detail. Please answer all questions.

1. **How hungry do you feel before your meals?**
   - A little ☐ Moderately ☐ A lot ☐
   - Extremely ☐ Not at all ☐ Varies ☐

2. **When did you first become aware that you 'feel full quickly'?**

Method		Treatment		
Before Diagnosis	☐	Chemotherapy	☐	
Before Treatment	☐	Radiotherapy	☐	
During Treatment	☐	Surgery	☐	Comment_____
After Treatment	☐	Other	☐	Comment_____
I Don't Know	☐			

3. **At what time of the day do you 'feel full quickly'?**
   - Morning ☐ Afternoon ☐ Evening ☐
   - Night-time ☐ No Particular Time ☐ All the time ☐
   - Other_____

4. **When do you 'feel full quickly'?**
   - After starting to eat ☐ After finishing eating ☐ All the time ☐
   - Varies ☐ I Don't Know ☐ Other_____

5. **How often throughout the day, do you 'feel full quickly'?**
   - Rarely ☐ Often ☐ Don't Know ☐
   - Occasionally ☐ Almost Constantly ☐ Other_____

6. **When you 'feel full quickly' how long does it last?**
   - <30 minutes ☐ 30-60 minutes ☐ 1-2 hours ☐
   - 2-4 hours ☐ 4-6 hours ☐ >6 hours ☐

7. **When you 'feel full quickly', is it?**
   - Mild ☐ Moderate ☐ Severe ☐ Varies ☐

8. **Some people who 'feel full quickly' have other symptoms at the same time. Does this happen to you?**
   - Yes ☐ No ☐ I Don't Know ☐

9. **If yes, please tick all that apply**

Nausea	☐	Vomiting	☐	Belching	☐
Stomach Bloating	☐	Stomach Pain	☐	Chest Pain	☐
Heartburn	☐	Difficulty Breathing	☐	Dry Mouth	☐
Fatigue	☐	Difficulty Swallowing	☐	Anxiety	☐
Low mood	☐	Weakness	☐	Other_____	

10. Has your experience of 'feel full quickly' changed throughout your illness?

Yes ☐ No ☐ I Don't Know ☐

11. If yes, how has it changed? (tick all that apply)

Worse ☐ Better ☐ Varied Severity ☐
More Often ☐ Less Often ☐ Varied Frequency ☐
Other_____

12. With regards to this symptom of 'feel full quickly' have you tried to manage it?

Yes ☐ No ☐ Don't Know ☐

13. If yes, in what ways have you tried to manage this symptom?

Method		Description			
Meal Frequency	☐	Less Often	☐	More Often	☐
Portion Size	☐	Smaller	☐	Larger	☐
Meal Texture	☐	Describe_____			
Food Selection	☐	Describe_____			
Sitting Position	☐	Describe_____			
Medications	☐	Describe_____			
Other	☐	Describe_____			

14. What methods of managing have worked for you?

_____
_____
_____

15. Have you ever told your doctor or healthcare professional that you 'feel full quickly'?

Yes ☐ No ☐ I Don't Know ☐

16. Has your doctor or healthcare professional ever asked you if you 'feel full quickly'?

Yes ☐ No ☐ I Don't Know ☐

17. When you 'feel full quickly' does it affect how much you eat?

Yes ☐ No ☐ Sometimes ☐ I Don't Know ☐

18. If yes, how much?

A little ☐ Somewhat ☐ Moderately ☐
A lot ☐ Extremely ☐ I Don't Know ☐

19. Do any particular foods/drinks make you 'feel full quickly'?

Yes ☐ No ☐ I Don't Know ☐

20. If yes, what foods/drinks?

_____
_____
_____

21. When you 'feel full quickly', are you able to complete your meals?

Yes ☐ No ☐ Sometimes ☐ I Don't Know ☐

22. If yes, does it take you a long time to complete your meals?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐
I Don't Know ☐

23. When you 'feel full quickly', does it distress or bother you?

Not at all ☐ A little bit ☐ Somewhat ☐
Quite a bit ☐ Very much ☐

24. When you 'feel full quickly', does it affect your quality of life?

Yes ☐ No ☐ I Don't Know ☐

25. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7
Very poor Excellent

26. How would you rate your overall health during the past week?

1 2 3 4 5 6 7
Very poor Excellent

27. Did you ever 'feel full quickly' before your diagnosis/treatment?

Yes ☐ No ☐ I Don't Know ☐

28. If yes, please describe what you felt was the cause (e.g., anxiety, pregnancy)

_____
_____
_____

29. In your own words, please describe what you experience when you 'feel full quickly'.

_____
_____
_____

30. Do you have any further comments about when you 'feel full quickly'?

_____
_____
_____

Thank you for taking the time to complete this questionnaire

10.6 Appendix 6 – SEES Feedback Questionnaire

SEES Feedback Questionnaire

Study Number_____

Did you feel that the questions captured your experience?

Yes ☐ No ☐ Don't Know ☐

Comment

_____
_____
_____

Did you think any of the questions were irrelevant?

Yes ☐ No ☐ Don't Know ☐

Comment

_____
_____
_____

Were there areas of relevance that you feel were not addressed in the questionnaire?

Yes ☐ No ☐ Don't Know ☐

Comment

_____
_____
_____

Did you think the length of time to complete the questionnaire was appropriate?

Yes ☐ No ☐ Don't Know ☐

Comment

_____
_____
_____

Was the wording of the questions clear?

Yes ☐ No ☐ Don't Know ☐

Comment

_____
_____
_____

Were there areas that required further expansion that weren't offered?

Yes ☐ No ☐ Don't Know ☐

Comment

_____
_____
_____

Were the instructions for filling in the questionnaire clear?

Yes ☐ No ☐ Don't Know ☐

Comment

_____
_____
_____

10.7 Appendix 7 - Symptom Experience of Early Satiety (SEES) Questionnaire Version 2 (post pilot)

Study ID: _____ Date: _____

You have been asked to fill out this questionnaire because you reported you **'Feel Full Quickly'** in the previous questionnaire. Please answer all questions.

1. **How hungry do you feel before your meals?**
   A little ☐ Moderately ☐ Very ☐
   Extremely ☐ Not at all ☐ Varies ☐

2. **When did you first become aware that you 'feel full quickly'?**

When		Treatment		
Before Diagnosis	☐	Chemotherapy	☐	
Before Treatment	☐	Radiotherapy	☐	
During Treatment	☐	Surgery	☐	Comment_____
After Treatment	☐	Other	☐	Comment_____
Don't Know	☐			

3. **At what time of the day do you 'feel full quickly'?**
   Morning ☐ Afternoon ☐ Evening ☐
   Night-time ☐ No Particular Time ☐ All the time ☐

4. **When do you 'feel full quickly'?**
   After starting to eat ☐ After finishing eating ☐ All the time ☐
   Varies ☐ Don't Know ☐

5. **How often throughout the day, do you 'feel full quickly'?**
   Rarely ☐ Often ☐ Don't Know ☐
   Occasionally ☐ Almost Constantly ☐

6. **When you 'feel full quickly' how long does it last?**
   <30 minutes ☐ 30-60 minutes ☐ 1-2 hours ☐
   2-4 hours ☐ 4-6 hours ☐ >6 hours ☐

7. **When you 'feel full quickly', is it?**
   Mild ☐ Moderate ☐ Severe ☐ Varies ☐

8. **Some people who 'feel full quickly' have other symptoms at the same time. Does this happen to you?**
   Yes ☐ No ☐ Don't Know ☐

9. **If yes, please tick all that apply**

Nausea	☐	Vomiting	☐	Belching	☐
Stomach Bloating	☐	Stomach Pain	☐	Chest Pain	☐
Heartburn	☐	Difficulty Breathing	☐	Dry Mouth	☐
Fatigue	☐	Difficulty Swallowing	☐	Anxiety	☐
Low mood	☐	Weakness	☐	Other_____	

10. **Has your experience of 'feel full quickly' changed throughout your illness?**
    Yes ☐ No ☐ Don't Know ☐

11. **If yes, how has it changed? (tick all that apply)**
    Worse ☐ Better ☐ Varied Severity ☐
    More Often ☐ Less Often ☐ Varied Frequency ☐
    Other_____

12. **With regards to this symptom of 'feel full quickly' have you tried to manage it?**
    Yes ☐ No ☐ Don't Know ☐

13. What methods of managing have worked for you?

_____
_____
_____

14. Have you ever told your doctor or healthcare professional that you 'feel full quickly'?

Yes ☐ No ☐ Don't Know ☐

15. Has your doctor or healthcare professional ever asked you if you 'feel full quickly'?

Yes ☐ No ☐ Don't Know ☐

16. When you 'feel full quickly' does it affect how much you eat?

Yes ☐ No ☐ Sometimes ☐ Don't Know ☐

17. If yes, how much?

A little ☐ Somewhat ☐ Moderately ☐
A lot ☐ Extremely ☐ Don't Know ☐

18. When you 'feel full quickly', are you able to complete your meals?

Yes ☐ No ☐ Sometimes ☐ Don't Know ☐

19. If yes, does it take you a long time to complete your meals?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐
Don't Know ☐

20. Do any particular foods/drinks make you 'feel full quickly'?

Yes ☐ No ☐ Don't Know ☐

21. If yes, what foods/drinks?

_____
_____
_____

22. When you 'feel full quickly', does it distress or bother you?

Not at all ☐ A little bit ☐ Somewhat ☐
Quite a bit ☐ Very much ☐

23. When you 'feel full quickly', does it affect your quality of life?

Yes ☐ No ☐ Don't Know ☐

24. In your own words, please describe what you experience when you 'feel full quickly'.

_____
_____
_____

25. Do you have any further comments about when you 'feel full quickly'?

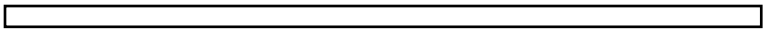
_____
_____
_____

Thank you for taking the time to complete this questionnaire.

10.8 Appendix 8 - VISUAL ANALOGUE SCALE

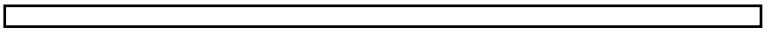
Study: **Patient ID:** **Date:**

HOW <u>HUNGRY</u> DO YOU FEEL RIGHT NOW?



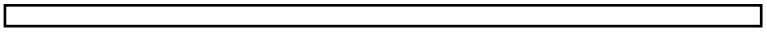
NOT AT ALL EXTREMELY

HOW <u>SICK</u> DO YOU FEEL RIGHT NOW?



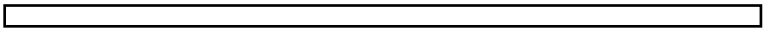
NOT AT ALL EXTREMELY

HOW <u>PLEASANT</u> WOULD IT BE TO EAT RIGHT NOW?



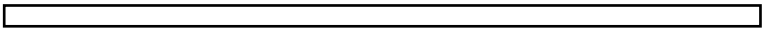
NOT AT ALL EXTREMELY

<u>HOW MUCH</u> DO YOU THINK YOU COULD EAT RIGHT NOW?



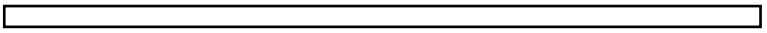
NOTHING A LARGE AMOUNT

HOW <u>FULL</u> DO YOU FEEL RIGHT NOW?



NOT AT ALL EXTREMELY

HOW <u>SLEEPY</u> DO YOU FEEL RIGHT NOW?



NOT AT ALL EXTREMELY

10.9 Appendix 9 - EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling thenumber that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washingyourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or otherleisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 thatbest applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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