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Cancer Cachexia

Prevalence and Predictors in Treatment-naïve Patients

A thesis submitted for the degree of Doctor of Philosophy

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For Joanne

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. I agree to deposit this thesis in the University's open access institutional repository or allow the Library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement of the author.

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Summary

Cancer cachexia is a common wasting syndrome leading to devastating consequences for the individual in terms of physical functioning, quality and quantity of life. Currently the most widely accepted definition is a multifactorial syndrome characterised by ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Prevalence is variable and may be impacted by primary cancer site, disease stage and/or the diagnostic criteria applied. This thesis aims to report the prevalence of cancer cachexia in treatment-naïve patients and to explore the impact cachexia may have on these patients longitudinally. Oncology healthcare professionals' perceptions of cachexia and its impact on patients are also investigated.

Chapter 2 examines weight change in a treatment-naive, mixed tumour population and its impact on survival by means of a retrospective review of 4258 cancer cases from a tertiary cancer centre. More than half (58%) of patients had weight loss in the 6 months prior to diagnosis. Analyses demonstrated that any amount of weight loss prior to diagnosis increased the risk of further weight loss. Prevalence of cachexia, defined in this study as unintentional weight loss > 5% in the previous 6 months, was 8%. Poorest survival was associated with ≥ 10% body weight gain or loss at diagnosis.

While **Chapter 2** highlights under-recognition and under-diagnosis of cachexia in an international setting, **Chapter 3** investigates the familiarity of Irish oncology healthcare professionals with cancer cachexia and its sequelae and the importance placed on nutrition following a cancer diagnosis using a national survey. A definitive sample size was not available; a sample size of n=364 was estimated. A total of 124 valid responses

were received. Poor understanding of cachexia and its associated burden, which may in part be due to the lack of nutritional education at undergraduate level, may limit oncology healthcare professionals in their management of patients.

Chapter 4 and **Chapter 5** focus on gynaecological cancer, for which the prevalence of cachexia is unknown. **Chapter 4** is a systematic review of the literature designed to report prevalence of cachexia in treatment-naïve patients with gynaecological cancer. A total of 7894 records were reviewed for eligibility. Two studies commented on prevalence of cachexia in cervical cancer patients; Poulsen et al stated that none of the participants in their study population met the applied criteria for cachexia, while Aredes et al reported a prevalence of 32.4%. Although it is difficult to draw definitive conclusions on cachexia in treatment-naïve gynaecological populations, this review highlights the limited research conducted in this population to date. **Chapter 5** is an exploratory study of newly diagnosed gynaecological cancer patients. A total of 94 participants were recruited from the Gynaecology Oncology service at St James's Hospital, the largest treatment provider for gynaecological malignancy in the Republic of Ireland. Clinical and anthropometric characteristics of patients at diagnosis were described. Using the criteria for cancer cachexia outlined by Fearon et al, prevalence of cachexia was 21.4%. This was highest in patients with cervical cancer. The impact of cachexia on clinical and patient-reported outcomes was also investigated. While weight loss in the previous month was predictive of developing cachexia, low albumin and anorexia were associated with cachexia, although neither reached significance. Cachectic patients were more symptomatic and had lower functional status in almost all quality of life categories compared to the non-cachectic patients.

Chapter 6 provides a summary of this thesis, which investigated cachexia in treatment-naïve cancer populations. In addition, future research and clinical applications are included.

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Table of Contents

Declaration ……...ii
Summary ……iii
Acknowledgements ……vi
Table of Contents ……..viii
List of Tables ……xiii
List of Figures ……....xiv
List of Appendices ……....xvi
Communications arising from this thesis…….…….xvii

CHAPTER 1

Introduction and Literature Review

1.1 Cachexia.....2
1.1.1 Related Terminology 3
1.2 Cancer Cachexia 5
1.2.1 Defining Cancer Cachexia 6
1.2.2 Diagnosis and Classification.....7
1.2.3 Pathophysiology.....15
1.2.4 Clinical Sequelae of Cancer Cachexia 17
1.2.4.1 Anorexia..... 17
1.2.4.2 Systemic Inflammation 18
1.2.4.3 Weight Loss 20
1.2.4.4 Sarcopenia..... 22
1.3 Management of Cancer Cachexia 23
1.4 Gynaecological Cancer 26
1.4.1 Incidence and Epidemiology.....27
1.4.2 Staging 29
1.4.3 Treatment ……...29
1.5 Gynaecological Cancer and Cachexia 29
1.6 Rationale for Thesis 43
1.7 Thesis Structure and Aims 43
1.8 References.....46

CHAPTER 2

Clinical Significance of Weight Changes at Diagnosis in Solid Tumours

2.1 Introduction 68

2.2 Aim and Objectves 71

2.2.1 Aim 71

2.2.2 Objectives 71

2.3 Methods 71

2.3.1 Ethical Approval 71

2.3.2 Study Design 72

2.3.3 Eligibility Criteria 72

2.3.4 Data Collection and Handling 72

2.3.5 BMI and Weight History 73

2.3.6 Data Analysis 74

2.4 Results 75

2.5 Discussion 85

2.6 Conclusions 89

2.7 References 91

CHAPTER 3

Nutritional Status in Cancer: Perspectives of Irish Healthcare Professionals

3.1 Introduction 97

3.2 Aims 100

3.3 Methods 101

3.3.1 Ethical Approval 101

3.3.2 Study Design 101

3.3.3 Study Participants 101

3.3.4 Data Collection and Handling 101

3.3.5 Statistical Analysis 102

3.4 Results 103

3.5 Discussion 111

3.6 Conclusions 115

3.7 References 116

CHAPTER 4

Prevalence of Cachexia in Treatment-naïve Patients with Gynaecological Cancer: A Systematic Review

4.1 Introduction 121
4.2 Aim 122
4.3 Methods 122
4.3.1 Eligibility Criteria 123
4.3.2 Search Strategy 123
4.3.3 Title and Abstract Screening and Full Text Review 125
4.3.4 Data Extraction and Quality Appraisal 125
4.3.5 Data Synthesis 126
4.4 Results 126
4.4.1 Search Results 126
4.4.2 Study Characteristics 126
4.4.3 Diagnosis and Prevalence of Cachexia 127
4.4.4 Quality of Studies 127
4.5 Discussion 132
4.6 Conclusions 135
4.7 References 136

CHAPTER 5

Cachexia in Treatment-naïve Gynaecological Oncology Patients: Prevalence, Predictors and Clinical Associations

5.1 Introduction 140
5.2 Aim and Objectives 143
5.2.1 Aim 143
5.2.2 Objectives 143
5.3 Methods 144
5.3.1 Ethical Approval 144
5.3.2 Study Design 144
5.3.3 Recruitment Procedure 144
5.3.4 Data Collection 145

5.3.5 Cachexia ……..…..…..140
5.3.5.1 Weight Loss 140
5.3.5.2 BMI 140
5.3.5.3 CT-measured Sarcopenia 140
5.3.1 Ethical Approval 136
5.3.2 Study Design 136
5.3.3 Recruitment Procedure 136
5.3.4 Data Collection ……..…..…..……137
5.3.5 Cachexia ……..……...148
5.3.5.1 Weight Loss 148
5.3.5.2 BMI 148
5.3.5.3 CT-measured Sarcopenia 149
5.3.6 Inflammation-based Prognostic Scores 152
5.3.7 Functional Assessment (Handgrip Strength) ……...……153
5.3.8 Quality of Life ...……...…155
5.3.6 Data Handling 156
5.3.7 Statistical Analysis 156
5.4 Results 157
5.4.1 Population Characteristics 157
5.4.2 Population Quality of Life 163
5.4.3 Cachexia 167
5.4.3.1 Prevalence 167
5.4.3.2 Characteristics of Patients with Cachexia at Baseline 170
5.4.3.3 Association between Cachexia and Clinical Outcomes 174
5.4.3.4 Association between Cachexia and Patient-reported Outcomes ……175
5.4.3.5 Predictors of Cachexia……...….179
5.5 Discussion 180
5.6 Conclusions 189
5.7 References 191

CHAPTER 6

Discussion and Conclusions

6.1 Discussion 199
6.2 Strengths and Limitations 203
6.3 Future Work 204
6.4 Conclusions 205
6.5 References 206

List of Tables

Table 1.1 Body mass index and associated nutritional status……8

Table 1.2 Summary of cachexia-related studies in gynaecological cancer populations..32

Table 1.3 Summary of cachexia-related studies in mixed cancer populations ……37

Table 2.1 Demographics and clinical characteristics at diagnosis and final visit……78

Table 2.2 Variation in weight change categories between diagnosis and final visit……79

Table 2.3 Predictive value of categorical variables in a multivariable model at diagnosis……..80

Table 2.4 Predictive value of categorical variables in a multivariable model (final visit)…….81

Table 2.5 Survival (months) based on weight loss grading system……..85

Table 3.1 Characteristics of participants……...…….104

Table 3.2 Have you had any formal education in nutrition as part of your qualification…..105

Table 3.3 Nutritional risk as perceived by healthcare professional category……106

Table 4.1 Search terms for cancer cachexia and gynaecolgical cancer ……..124

Table 4.2 Summary of general characteristics of included studies…….131

Table 4.3 JBI Critical Appraisal Checklist for included studies ……..…..132

Table 5.1 Inclusion and Exclusion Criteria ……...……145

Table 5.2 Demographics and clinical characteristics at baseline ……..160

Table 5.3 Anthropometric and nutritional parameters at baseline……..161

Table 5.4 Clinical characteristics of patients with cachexia……..171

Table 5.5 Comparison of anthropometric, nutritional and inflammatory markers for cachectic and non-cachectic patients……...……..…172

Table 5.6 Logistic regression model of associations with presence of cachexia at baseline……..179

List of Figures

Figure 1.1 Proposed stages of cancer cachexia ……12

Figure 1.2 Pathogenesis of cancer cachexia……....16

Figure 1.3 Female external genitalia (vulva)……27

Figure 2.1 Kaplan-Meier plot of overall survival by weight change category at diagnosis and final visit……...83

Figure 2.2 Kaplan-Meier plot of overall survival by percentage weight loss category and percentage weight gain category at diagnosis…….……84

Figure 3.1 Respondents' familiarity with consensus definition……107

Figure 3.2 Do you routinely refer cancer patients to a dietetic colleague for assessment at diagnosis?.....109

Figure 3.3 When should the dietitian be part of the treatment plan for patients with cancer?..110

Figure 4.1 PRISMA flow chart……..…130

Figure 5.1 Representative axial CT slice taken at the mid-level of the third lumbar vertebral body (L3)……150

Figure 5.2 Representative axial CT slice taken at the mid-level of the third lumbar vertebral body (L3) with tissue type demarcation……..152

Figure 5.3 JAMAR® Plus + Digital Hand Dynamometer……....154

Figure 5.4 Variation in weight change category across three encounters: baseline and matched analyses for T_0 to T_1 and T_1 to T_2 ……162

Figure 5.5 Global health status / QoL by primary tumour site at baseline ……..….165

Figure 5.6 Global health status / QoL by primary tumour site at each encounter ..…….166

Figure 5.7 Prevalence of cachexia at T_0 based the classification system established by an expert group consensus……..…….. 168

Figure 5.8 Prevalence of cachexia at T_0 by gynaecological cancer site……...…….. 169

Figure 5.9 BMI distribution of cachectic patients at baseline ……...173

Figure 5.10 Global QoL for cachectic and non-cachectic patients at T_0-T_2.....176

Figure 5.11 Physical function for cachectic and non-cachectic patients at T_0-T_2.....177

Figure 5.12 Role function for cachectic and non-cachectic patients at T_0-T_2…….177

Figure 5.13 Emotional function for cachectic and non-cachectic patients at T_0-T_2……177

Figure 5.14 Symptom scsales for cachectic and non-cachectic patients at T_0 178

List of Appendices

Appendix I	Gynaecological cancer
Appendix II	Clinical significance of weight changes at diagnosis in solid tumours
Appendix III	Odds Ratio Tables
Appendix IV	Ethics for Nutritional Survey
Appendix V	Sample Nutritional Survey Questionnaire
Appendix VI	Ethics Approval for Cancer Cachexia Gynaecological Oncology Study
Appendix VII	Participant Information Leaflet and Consent Form
Appendix VIII	Scored Patient-Generated Subjective Global Assessment (PG-SGA)
Appendix IX	American Society of Anesthesiologists Score (ASA)
Appendix X	Clavien-Dindo Classification
Appendix XI	Normative Grip Strength Data
Appendix XII	EORTC QLQ-C30
Appendix XIII	EORTC QLQ-CX24
Appendix XIV	EORTC QLQ-EN24
Appendix XV	EORTC QLQ-OV28
Appendix XVI	EORTC QLQ-VU34
Appendix XVII	Additional nutritional data
Appendix XVIII	Distribution of mean global health status / QoL scores at all three encounters
Appendix XIX	Gynaecological cancer and individual symptom scales
Appendix XX	Nutritional impact symptoms at baseline

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Kenny C, Uí Dhuibir P, **O'Donoghue N**, Barrett M, Parkes C, Daly S, Thirion P, Walsh D. Wireless intra-oral measurement of dynamic tongue pressures: A clinical utility pilot study. Dysphagia 32, 2017 (1) 147.

Chapter 1

Introduction and Literature Review

1.1 Cachexia

Cachexia is a wasting syndrome distinct from starvation occurring as a consequence of underlying disease (1). The most pronounced clinical feature is involuntary weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders) (2). Associated characteristics include anorexia, increased muscle protein catabolism and inflammation, all of which may occur to varying degrees.

Cachexia is described since ancient times, with references to it found in works attributed to Hippocrates (3). It is - as it was then - recognised as a common feature of many acute and chronic pathological conditions including cancer, untreated autoimmune deficiency syndrome, chronic heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD), cystic fibrosis, rheumatoid arthritis and tuberculosis (4-6). It may also develop in the elderly in the absence of any symptoms of disease (7). It is a marker of unfavourable prognosis in all diseases. Although most commonly associated with advanced disease, the presence of cachexia in and of itself can confer a poor prognosis irrespective of the stage of the disease process (8).

Estimated prevalence is high, ranging from 5-15% in chronic heart failure, chronic kidney disease and COPD to 60-80% in advanced cancer (1). Mortality associated with these conditions also varies when cachexia co-exists; 15-25% annual mortality in COPD patients and 20-40% in patients with chronic heart failure and chronic kidney disease (1). Mortality in some advanced cancers may be as high as 80% per year (9).

1.1.1 Related Terminology

Definitions and/or defining diagnostic criteria can support healthcare professionals in disease recognition and in the diagnostic process. However, the risk of confusion is high when terms are used interchangeably, despite relating to distinct but overlapping processes. This has been the case at times with terms such as disease-related malnutrition, cachexia, sarcopenia and sarcopenic obesity.

Disease-related malnutrition is malnutrition due to any underlying disease, which may or may not involve an inflammatory response. It can lead to anorexia, reduced body weight and changes in physical function. Cachexia is a multifactorial syndrome characterized by severe loss in body weight and increased muscle protein catabolism due to underlying disease. It is similar to disease-related malnutrition with respect to loss of body weight being the primary feature, although the source of tissue loss may vary. All cachectic patients suffer from malnutrition; however, the reverse does not apply (10).

Sarcopenia may be broadly defined as clinically significant loss of muscle mass and function. It frequently co-exists with cachexia. It may be categorised as primary sarcopenia or secondary sarcopenia based on aetiology. Primary sarcopenia is age-associated decline in skeletal muscle mass and function and is characterised by low muscle mass and strength, and poor physical performance (11). The aging process starts in the thirties and progressively increases over time (12). Sarcopenia is an important cause of frailty, disability and loss of independence in the elderly (13) and is associated with all-cause mortality (14). Assessment of muscle may be performed in various ways e.g. hand dynamometry, the chair stand test. Hand dynamometry measures handgrip strength, which is an objective measure of muscle function (15) and a proxy for global

muscle strength (16). It is a simple and inexpensive means of assessment (17) and can be applied in both clinical and research settings (18). The chair stand test measures the time taken by a patient to rise five times from a seated position without the use of his/her arms. It reflects leg (quadriceps) muscle strength and endurance (11). Physical performance may also be assessed in a variety of ways including gait speed and the timed up and go test (11). Gait speed may be measured using the 4-metre usual walking test with a cut-off of <0.8 m/s indicating severe sarcopenia (11). The timed up and go test measures the time taken in seconds by a patient to stand from a standard arm chair, walk a distance of 3 metres, turn, walk back to the chair and sit down (19).

Secondary sarcopenia occurs as a result of factors other than ageing, such as systemic disease, physical inactivity or undernutrition. However, it may co-exist with age-related sarcopenia. Several imaging-based modalities including appendicular skeletal muscle index obtained from dual energy x-ray absorptiometry (DEXA), cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) and whole body fat-free mass index determined by bioelectrical impedance analysis (BIA) can be used to quantify muscle mass. The use of CT or MRI for muscle mass assessment in patients with cancer is currently in vogue (20). CT scans are the preferred choice as they are routinely performed for cancer diagnosis, disease staging, monitoring response to treatment and disease progression and are easily accessible with no additional burden to the patient. Different tissue types can be distinguished based on tissue attenuation characteristics. Images taken at the mid-level of the third lumbar vertebral body (L3) correlate with whole body muscle (21). Serial CT scans can be used to detect small changes in muscle and fat including depletion of skeletal muscle.

Age-related shifts in body composition demonstrate a tendency for muscle mass to decline with an associated increase in adipose (fat) tissue and infiltration of this tissue into muscle. Sarcopenic obesity is a condition where severe muscle wasting and excess adiposity co-exist. It combines the risks associated with both sarcopenia and obesity. Muscle loss in these patients may go unnoticed due to increased adiposity. With increased infiltration of fat into muscle (11), sarcopenic obesity is associated with lower functional status and is recognised as an independent predictor of poorer outcomes, when compared to obese, non-sarcopenic cohorts (22). Outcomes can be further worsened by surgical interventions (23), as lean body mass in these patients may be comparable to that of underweight patients (22).

The feature common to disease-related malnutrition, cachexia, sarcopenia and sarcopenic obesity is loss of body muscle and fat to varying degrees, which can lead to adverse outcomes for patients and negatively impact health economic outcomes (1, 11, 24). Familiarity with these conditions would support early identification and management of high risk patients by clinicians and so reduce the burden associated with an untreated population.

1.2 Cancer Cachexia

Cancer cachexia is the most common paraneoplastic syndrome (25). Approximately half of all patients with advanced cancer develop cachexia (26), but this may reach as high as 86% in the final weeks of life (27). The principal clinical characteristic is involuntary weight loss, mainly due to loss of muscle. Other symptoms include anorexia, chemosensory changes, dysphagia, early satiety, fatigue and functional impairment (28).

The changes in body composition which occur lead to increased treatment-related toxicity, reduced quality of life, psychosocial distress and poor prognosis (29-31). In addition to the associated morbidity, cachexia is the cause of up to 20% of cancer-related deaths (9, 32). Much of the research to date has focused on advanced cancer (33-36) but cachexia can arise at any stage earlier in the disease pathway. This shifts the focus towards early recognition of signs of cachexia in cancer patients at diagnosis, even in the absence of weight loss, when interventions may be most beneficial.

1.2.1 Defining Cancer Cachexia

Various definitions for cancer cachexia are in use throughout the literature (2, 10, 20, 34, 37). While each of these apply specifically to cancer, the definition provided by Evans et al (2) relates to cachexia in any chronic illness, which may include cancer. Currently the most widely used definition for cancer cachexia is that proposed by Fearon et al which describes it as "a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (20). This definition and the associated diagnostic criteria and classification of cancer cachexia (see Section 1.2.2 below) were established by an expert group. The group employed a Delphi process, a method for collecting and collating the opinions of participants who are selected based on their expertise in a particular area (38). Although this method can facilitate international collaboration to explore areas of controversy or where a lack of clarity exists, it is important to acknowledge that it is ultimately expert opinion and does not purport to be definitive and therefore may change or evolve with time.

1.2.2 Diagnosis and Classification

Diagnostic criteria for cancer cachexia (20) are:

unintentional weight loss > 5% over the past 6 months

or

unintentional weight loss > 2% in those with a body mass index (BMI) < 20 kg/m^2

or

unintentional weight loss >2% in those with evidence of sarcopenia

A weight history must be taken in order to determine percentage (%) weight loss, which may then be calculated with the formula:

$$\textbf{\% Weight loss} = \frac{\text{initial weight - current weight}}{\text{initial body weight}} \times 100$$

In many instances a measured weight may not be available and so a self-reported weight history should be sought from the patient. The reliability of self-reported weight has come into question, as inherent bias may exist due to difficulty with re-call or a desire to confirm with social norms (39), particularly in overweight and obese populations, leading to underestimation of weight (40). However, there is evidence of the reliability of self-reported weight in the literature (41), demonstrated by the high correlation between self-reported weight and measured weight (42).

Body mass index is the most widely used measure of adiposity in adults. It is considered an indicator of nutritional status and is defined as an individual's weight in kilograms divided by the square of the individual's height in metres (kg/m^2). It is usually categorised into one of four groups as per the World Health Organisation (WHO) BMI Classification (Table 1.1) (43).

Table 1.1 Body mass index and associated nutritional status (43)

BMI	Nutritional status
<18.5 kg/m^2	Underweight
18.5 - 24.9 kg/m^2	Normal weight
25.0 - 29.9 kg/m^2	Overweight (pre-obese)
≥ 30 kg/m^2	Obese

Adipose tissue is a highly active metabolic and endocrine organ (44). It is generally distributed into two compartments: subcutaneous and visceral. Subcutaneous adipose tissue is stored under the skin, while visceral adipose tissue accumulates around the internal organs and is associated with obesity-related diseases. Distribution patterns can vary by age, gender and ethnicity and may be further influenced by factors such as hormones, nutritional intake and physical activity. Adult females have a higher percentage of adipose tissue compared to adult males and tend to deposit it in the hips, thighs and buttocks. In contrast, men typically have a more central or abdominal distribution.

Weight gain generates excess adipose tissue which is associated with low grade systemic inflammation (45), a factor which may promote cancer and a feature of cancer cachexia.

Excess visceral adipose tissue, evident in overweight and obesity, is an established risk factor for the development of a number of malignancies including breast (post-menopausal), colorectal, endometrial, oesophageal (adenocarcinoma), ovarian and prostate (46-50). There is now strong evidence to suggest that being overweight or obese during adulthood is a risk factor for the development of a number of cancer types including endometrial and ovarian cancer (50). Arem et al reported that higher pre-diagnosis BMI is associated with higher cancer-specific mortality in endometrial cancer survivors (51). A recent systematic review and meta-analysis highlighted that increased BMI in early adulthood (18-25 years) and weight gain between young adulthood and middle age are associated with increased endometrial cancer risk (48). Similarly, weight gain in early adulthood and post-menopausal obesity are associated with an increased risk of post-menopausal breast cancer (52). The relationship between obesity and cancer survival and disease recurrence has also been established for a number of cancers (53). In endometrial cancer, normal-weight women have better survival when compared to obese women (54). The association between overweight/obesity and cachexia with low grade systemic inflammation (45) may account for this. While a similar pattern has been noted in patients with cervical cancer, with overweight and obese patients having poorer survival than normal weight patients, underweight BMI is also associated with poorer survival in this cohort (55). Kim et al reported that underweight BMI after treatment - as opposed to prior to treatment - in advanced ovarian cancer patients was associated with more unresectable tumours and a greater risk of disease progression and so could be considered a marker of poor prognosis (56). Other studies including a number with ovarian cancer cohorts have found no association between obesity and survival or suggested that obesity may confer an advantage when compared to normal weight cancer

patients ("obesity paradox") (57-60). However, these results may simply be due methodological limitations (61) including the use of BMI to define obesity (62).

BMI is a crude measure and using it alone risks overlooking some cachectic patients, as it is not considered sufficient for accurate identification of cachexia (63, 64). It cannot detect differences and changes in body composition, which may occur during treatment or as a result of disease progression (65). Segura et al reported that while more than 70% of the cancer patients included in their study had unintentional weight loss, only 6.5% had an underweight BMI (< 18.5 kg/m^2) (64). As a result, the use of imaging modalities which can objectively measure body composition including muscle, visceral and subcutaneous adipose tissue has proved invaluable.

Muscle mass accounts for 60% of the body's protein stores (10). As with adipose tissue, skeletal muscle demonstrates gender-based variations primarily due to the action of sex hormones (66)**.** Adult males have a greater total lean muscle mass compared to adult females due to the anabolic effect of testosterone (67). Differences are also evident in individual muscle fibre size, enzymatic activity and expression of genes (68). Primary sarcopenia in females coincides with oestrogen withdrawal at the onset of menopause and it is associated with an accelerated loss of muscle tissue during the transition into menopause (69). However, the rate of muscle loss subsequently slows, such that a slower rate of muscle loss is observed in older females compared with older males (67).

Within the context of the diagnostic criteria for cancer cachexia (20), sarcopenia is defined as appendicular skeletal muscle index < 7.26 kg/m^2 in males and < 5.45 kg/m^2 in females determined by DEXA, whole body fat-free mass index without bone < 14.6

kg/m^2 in males and < 11.4 kg/m^2 in females determined by BIA (20) and lumbar skeletal muscle index < 43 cm^2/m^2 in males with underweight and normal weight BMI or < 53 cm^2/m^2 in males with overweight and obese BMI and < 41 cm^2/m^2 in females determined by CT imaging (70). The use of the CT modality in particular has resulted in substantial progress being made in cachexia, and sarcopenia, research due to the exploitation of these easily accessible images.

Cancer cachexia is a pathological spectrum that develops from subtle manifestations initially (29). Three stages of clinical relevance have been proposed: pre-cachexia, cachexia and refractory cachexia (20). Not all patients experience the entire spectrum (Figure 1.1). Risk of progression is associated with cancer type and stage, extent of systemic inflammation and degree of response to anticancer treatment. Severity is classified by the rate of ongoing weight loss combined with level of energy store and body protein depletion (20).

In pre-cachexia, early clinical and metabolic signs, including anorexia and unintentional weight loss ≤ 5% occur. The negative sequelae associated with cachexia are not evident at this stage but patients are at high risk of developing cachexia. It is at this stage that intervention would be of most benefit, to stabilise weight and functional status (71). As the syndrome advances, progressive weight loss occurs (> 5%) and patients meet the criteria for cachexia as outlined above. Unfortunately effective treatments are as yet unavailable. Refractory cachexia, typically associated with very advanced or unresponsive disease, is characterised by low performance status and a life expectancy < 3 months (20). There is a presumed irreversibility at this stage. Aggressive artificial nutritional support may yet prove to be an option in some cases either alone or in

combination with other treatments. For now, the burden of an aggressive approach to nutritional treatments is seen to outweigh any potential benefit in very advanced disease (20) when the priority shifts from cure and control of disease to improvement or maintenance of quality of life through palliation of symptoms (27).

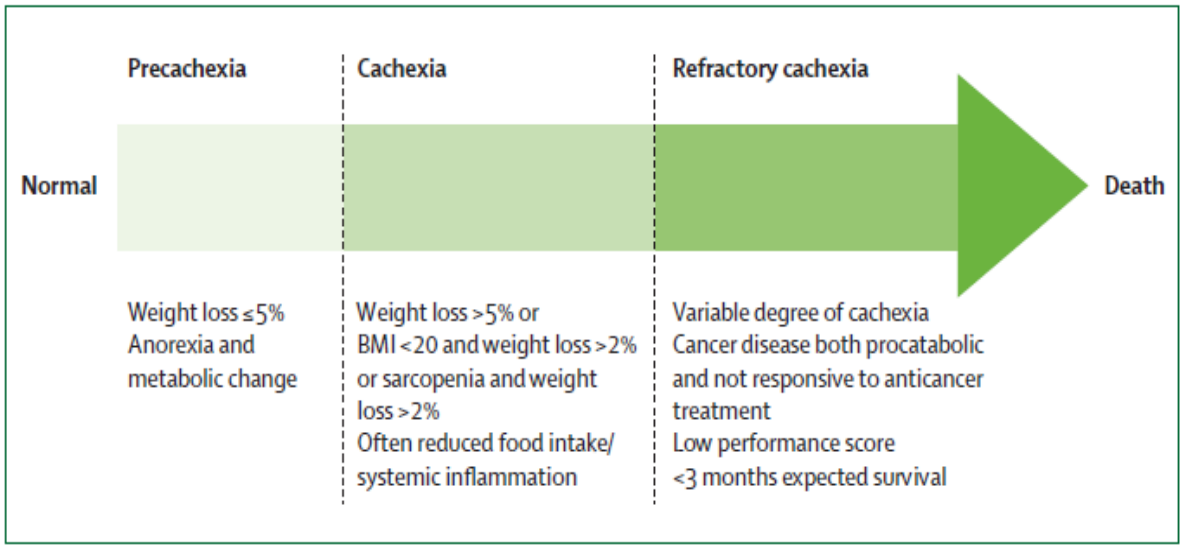

Figure 1.1 Proposed stages of cancer cachexia (Reprinted from The Lancet Oncology, 12(5), Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al., Definition and classification of cancer cachexia: an international consensus, Page No. 491, Copyright (2011), with permission from Elsevier.)

Reported prevalence of cachexia is variable (72-74). Although strongly associated with cancer type and stage, there are documented variations within these too. Cachexia is most prevalent in pancreatic, gastric, oesophageal, hepatic, colorectal, lung, and head and neck cancers (75, 76); pancreatic or gastric cancers have the highest frequency. It is worth noting however that not all patients with these tumours will develop cachexia (77). A tumour arising from any of these sites may impact on an individual's ability to acquire adequate nutrition. Direct encroachment of the tumour itself or metastatic deposits can lead to dysphagia, odynophagia, obstruction, malabsorption and/or deranged metabolism (78-81). Fearon et al reported the presence of cachexia in 20-25% of

patients with pancreatic cancer, 80% of whom had already lost at least 10% of their body weight at diagnosis (34). Approximately 80% and 60% of patients with upper gastrointestinal cancer and lung cancer respectively have already had significant weight loss at diagnosis (82). Prevalence of cachexia at diagnosis in head and neck cancer patients has been reported to be as high as 42% (83).

Patients with other solid tumours, such as breast and prostate, or haematological malignancies, have often demonstrated lower prevalence of cachexia (74, 84, 85). Regardless of this, it is important to be vigilant, as signs of cachexia may be present even in the absence of overt weight loss. Also, cachexia may develop as a late complication of malignancy (86).

The true prevalence of cachexia is still unknown for some cancer cohorts and may be underestimated in others (87). There are a number of confounding factors which may contribute to this, the main one likely to be the lack of consensus on the definition of cachexia until relatively recently. This resulted in different criteria for cachexia being applied by different research groups (20, 34, 37, 87-89). Early recognition of cachexia is also challenging. It is under-recognised in the clinical setting primarily because weight loss is not routinely assessed (88) and the soaring rates of obesity, evident even in patients with malignancy, may mask signs and symptoms of overt cachexia.

Small sample size and heterogeneous populations, whether they be mixed cancer types, stages of disease or treatment, or cohorts from different clinical settings e.g. inpatient and outpatient, may contribute to contradictory results (90), making it difficult at times to draw clear conclusions on prevalence. Much of the research to date has focused on

patients with advanced cancer and so many participants will have received at least one line of treatment prior to inclusion in any study. Cachexia may impact surgical outcomes (26); it is associated with increased post-operative complications and mortality (91). Chemotherapy and radiotherapy can lead to or exacerbate cachexia, further compromising tolerance to treatment, quality of life and overall survival. Malnutrition continues to be a common but underdiagnosed problem in hospital inpatients, with at least one in four patients admitted to Irish hospitals affected by it (92, 93). Oncology patients are a particularly vulnerable group. Reported prevalence ranges from 19% to more than 70%, with variations attributed to patient age, cancer type and stage (94). Bozzetti et al reported that 32% of oncology outpatients screened were at nutritional risk (95), while Muscaritoli et al found that 43% were at nutritional risk and 9% were overtly malnourished at their initial medical oncology appointment (96). Early assessment is important as poor nutritional status is associated with more complications following surgery, decreased tolerance of oncology treatments and reduced quality of life (65, 97).

Although cachexia is common in both male and female cancer patient cohorts, there are differences in how each respond at a physiological and metabolic level (69, 98). Hypogonadism is a recognised complication in male cancer patients (99) and there is evidence that cachectic male patients may be more symptomatic, demonstrating greater weight loss (100), including muscle loss (101), and greater deficits in handgrip strength when compared to cachectic female patients (102). However, whether this is generalisable to all cancers given the variability of cachexia prevalence and severity across and within primary cancer sites and disease stage remains to be seen.

It is vital that well designed studies continue to be conducted in all target populations in order to further the collective knowledge of cachexia. Researchers need to highlight the significant burden cachexia inflicts on patients, their families and carers. A heightened awareness should lead to the development of treatments and in doing so support patient stratification and prognostication. Stratification facilitates allocation of patients to the most appropriate treatment pathway i.e. surgical, oncological or palliative (103). Prognostication is a difficult but important undertaking for clinicians in advanced cancer, as it provides an opportunity for meaningful decision-making and end of life planning with patients and their families and carers (35, 104).

1.2.3 Pathophysiology

Cancer cachexia is an energy wasting syndrome, which affects many of the body's metabolic pathways (9). Pathophysiology is characterised by progressive depletion of body reserves due to a combination of reduced food intake and abnormal metabolism. Weight loss, or more specifically the process of losing weight, is the principal clinical feature and this has been extensively investigated (74, 105-107). Cachexia is an entity distinct from simple starvation. During prolonged starvation, adipose tissue reserves are used preferentially, while in cachexia it is loss of protein from skeletal muscle that results in weakness, reduced mobility and, ultimately, death through impairment of respiratory muscle function (75). Although skeletal muscle tissue is a major target of cachexia, other tissues and organs including adipose tissue are also negatively impacted (7).

The interplay between the tumour and host in addition to cancer surgery, chemotherapy and radiotherapy all play a role in the development and progression of cachexia (Figure 1.2) (84).

The physical presence of a tumour leads to activation of the host's inflammatory response, which is at least in part mediated by tumour-derived pro-inflammatory cytokines (76). Changes in metabolism are a recognised feature (29); systemic inflammation and the acute phase response lead to increased protein degradation, reduced protein synthesis and lipolysis. The result is a negative protein-energy balance. Neuroendocrine mediators increase resting energy expenditure, further promoting the established catabolic milieu. Patients experience weight loss, metabolic dysfunction and limited response to nutritional support as a result of these overlapping processes.

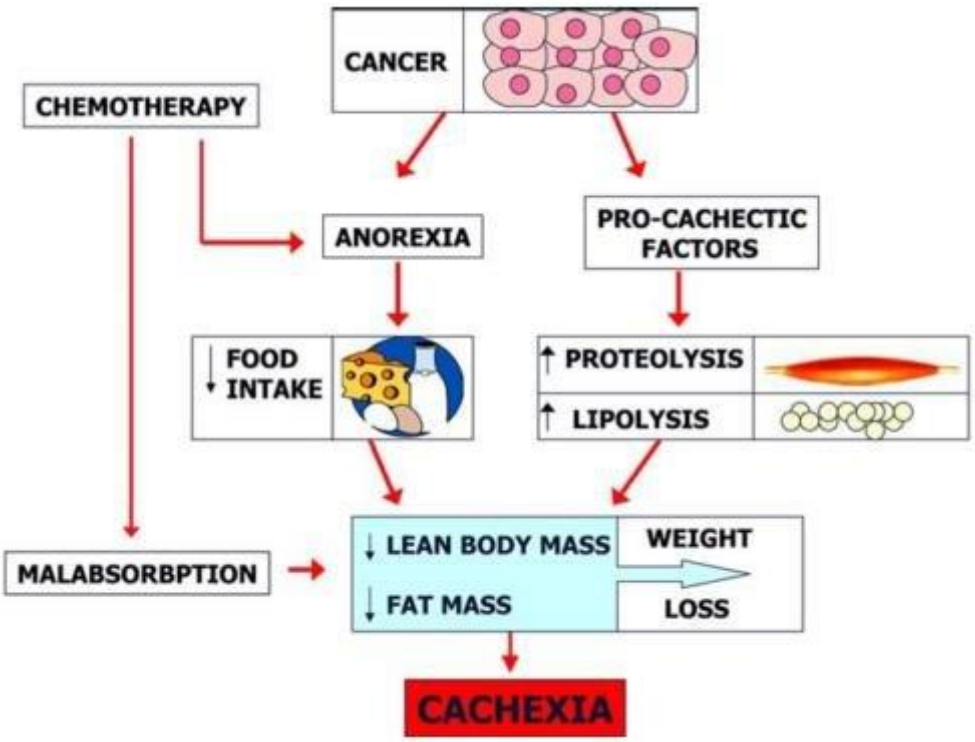

Figure 1.2 Pathogenesis of cancer cachexia (84)

1.2.4 Clinical Sequelae of Cancer Cachexia

1.2.4.1 Anorexia

Patients with cancer frequently experience anorexia or loss of appetite (75); it is present in half of newly diagnosed cancer patients (7). Although a major component of cancer cachexia (108), anorexia is not singularly responsible for the development of the syndrome (77, 109). If it were, nutritional support might be sufficient to reverse it. Not all cachectic patients have anorexia, suggesting that other pro-catabolic mediators may also be at play (77, 110). However, when present, anorexia is associated with a poor prognosis (111).

Anorexia can occur with other symptoms (112). Mariani et al reported that severe anorexia occurred in 17.2% of patients with $\geq$ 20% weight loss. Protracted low oral intake is associated with altered perception of appetite and satiety (113). Early satiety – feeling full after ingestion of only a small amount of food – is a presenting symptom in advanced ovarian cancer due to the presence of ascites and metastatic disease in the omentum or bowel and is frequently reported by patients with anorexia (77). Constipation is also common in patients with pelvic and abdominal disease. Dysphagia is a common and important diagnostic symptom in patients with head and neck and upper gastrointestinal cancer (114, 115). However, it has also been observed in patients with tumours located outside of these regions, where loss of whole-body skeletal muscle mass is implicated (116, 117). Chemosensory dysfunction can aggravate anorexia. Alteration in taste and smell perception is a recognised side-effect of chemotherapy (118) and radiotherapy (119), known to negatively impact appetite, but it can arise in treatment-naïve patients as well (120). Other common side effects of chemotherapy and radiotherapy which can cause or aggravate anorexia include nausea, vomiting and mucositis.

Psychological factors may play a role in anorexia: anxiety, depression and pain are common symptoms among cancer patients (27) and can result in reduced food intake (79). Although anorexia may not in or of itself cause distress to patients, the consequences – fatigue, reduced physical function, poor quality of life – may trigger considerable distress. Lack of appetite may also cause friction with family members or carers (121, 122).

1.2.4.2 Systemic Inflammation

Chronic inflammation and chronic activation of the immune system are both associated with the development of malignancy (123). Systemic inflammation is a hallmark of cancer (124) and a recognised feature and mediator of cachexia (2, 125, 126). Indirect measurement of inflammation is routine throughout the cancer trajectory by measuring cell counts (i.e. neutrophils, lymphocytes, platelets) and levels of acute phase proteins (e.g. C-reactive protein (CRP), albumin). Combinations of these markers of systemic inflammation e.g. neutrophil lymphocyte ratio (NLR), Glasgow Prognostic Score (GPS) also have a recognised prognostic value (103, 127, 128). The activated inflammatory response in cancer comprises a complex interplay of tumour, host and tumour-host interaction factors, ultimately resulting in altered metabolism and accelerated proteolysis and lipolysis.

a) Tumour-derived factors

Tumour cells produce pro-inflammatory and pro-cachectic factors (77), which activate the host's systemic inflammatory response. Two such tumour-derived factors are lipid-mobilising factor (LMF) and proteolysis-inducing factor (PIF) (129), both of which directly stimulate breakdown of their respective target tissue i.e. adipose tissue and

skeletal muscle. Mobilisation of adipose tissue may involve increased oxidation of released fatty acids via induction of uncoupling protein (UCP) expression (130). PIF activates the ubiquitin-proteasome pathway which leads to muscle degradation (126) and inhibition of protein synthesis in muscle cells (129) suggestive of a cachexia-inducing factor. Although preliminary work proposed a similar mechanism in weight-losing cancer patients (131), further attempts have yet to confirm an association between PIF and clinical outcomes such as weight loss and survival in cancer patients (126).

b) Tumour-host interactions

Catabolic, pro-inflammatory cytokines are produced within the tumour microenvironment, although it is not clear whether the source is primarily from tumour or host inflammatory cells (126). These include interleukin (IL)-1, IL-6 and tumour necrosis factor alpha (TNF-α), all of which are known to have a negative effect on appetite (77). These cytokines activate the host inflammatory response as outlined in the section below. Elevated circulating levels of IL-6 are associated with weight loss (81) and reduced survival in cancer patients (132). TNF-α mediates skeletal muscle wasting; like PIF, it can both increase proteolysis while also suppressing protein synthesis (126).

c) Host response

Inflammatory changes occur within the host in direct response to the tumour but also in response to the tumour-host microenvironment. Cytokines are released into the bloodstream and these lead to the acute phase protein response (APPR), the body's response to homeostatic disturbance (133). APPR is associated with hypermetabolism (126); Fearon et al reported that 50% of cancer patients are hypermetabolic (81). The liver increases its production of positive acute phase proteins (133). CRP is one such

protein and is the most commonly used marker of systemic inflammation (134). It is an important prognostic marker in cancer (135) and a key feature of cancer cachexia (136). CRP is primarily produced by IL-6-dependent hepatic biosynthesis, but also by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes (137). Elevated CRP is associated with lung, melanoma, multiple myeloma, lymphoma, ovarian, renal, pancreatic, gastro-oesophageal and colorectal cancers (133) and may be elevated at the time of diagnosis (138). Wallengren et al demonstrated that elevated CRP in cancer populations is adversely associated with functionality, quality of life and overall survival (136). In contrast to the shift in positive acute phase protein levels, hypoalbuminaemia is also common. Although rate of synthesis of this negative phase reactant does not appear to change, it is postulated that mechanisms such as increased vascular permeability may lead to a fall in its plasma concentration (133). It is this rise in CRP and fall in albumin which forms the basis for the inflammation-based score, the Glasgow Prognostic Score.

1.2.4.3 Weight Loss

Weight loss is common; up to half of all cancer patients experience muscle and adipose tissue loss (75). This often precedes reduced food intake, so anorexia cannot entirely account for the weight loss (139). Patients with upper gastrointestinal cancer, lung cancer, pancreatic cancer and head and neck cancer have frequently already experienced significant weight loss at time of diagnosis (75, 82, 83). About 80% of patients with advanced cancer experience weight loss (76).

Unintentional weight loss is an important prognostic (74, 91) and predictive (140) indicator in cancer. Survival is directly related to total weight loss and rate of weight loss

(7). However, there is a lack of agreement on the amount of weight loss considered clinically significant (141). DeWys' seminal paper nearly four decades ago demonstrated the prognostic effect of weight loss >5% prior to commencement of chemotherapy; it was associated with increased risk of poor response to treatment and shortened survival, independent of cancer stage and performance status (74). Unintentional weight loss >5% is included in the proposed diagnostic criteria for cancer cachexia (20). However, there is now evidence that weight loss < 5% is related to decreased survival in cancer patients (7, 30, 70, 142). Despite this, the National Cancer Institute's Common Toxicity Criteria (143) classifies the total degree of weight loss relative to baseline as follows:

Grade 1: 5 - < 10% from baseline, intervention not indicated;

Grade 2: 10 - < 20% from baseline, nutritional support indicated;

Grade 3: ≥ 20% from baseline, tube feeding or total parenteral nutrition indicated;

Grade 4: life-threatening, toxicity not defined;

Grade 5: death related to adverse event, toxicity not defined;

The recommendation for intervention only for weight loss greater than 10% may be inappropriate.

Current weight (and height) are routinely measured in the oncology clinic, primarily for calculation of chemotherapy dose, which is calculated according to body surface area. However, weight history and assessment of nutritional status and/or nutritional impact symptoms are not routinely recorded.

The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines on nutrition in cancer recommend the early detection of nutritional problems through screening, and nutritional assessment when the screening result is abnormal (144). Quantification of weight loss is part of many common screening tools which may be used to identify those at nutritional risk including the Malnutrition Universal Screening Tool (MUST), the Malnutrition Screening Tool (MST), abridged Patient Generated Subjective Global Assessment (aPG-SGA) and the mini-nutritional assessment (MNA). The lack of consensus on which tool is best for use in the cancer population makes it difficult for healthcare professionals, who may have limited or no formal nutritional education, to identify those most at risk. In the UK, a survey of specialist oncology trainees found that 80% expressed uncertainty or a lack of confidence in their ability to identify malnutrition (141). And so despite the well-documented morbidity and mortality associated with unintentional weight loss in the cancer population (113), nutritional screening and assessment, which would include weight history, are not routine in many oncology clinics.

1.2.4.4 Sarcopenia

Sarcopenia has a profound effect on physical function and quality of life. With more than half of new cancer cases diagnosed in people aged ≥ 65 years (145), primary and secondary sarcopenia may co-exist in many patients. Irrespective of aetiology, sarcopenia is an important prognostic factor in several cancers (70, 146-148) and its influence on morbidity and mortality in patients treated with chemotherapy or major surgery has been investigated (149-152). There is evidence that sarcopenia is negatively associated with progression-free survival and overall survival in cervical cancer patients undergoing concurrent chemoradiotherapy (151). Kuroki et al investigated the impact of sarcopenia

in patients with endometrial cancer (150). While progression–free survival was negatively impacted, overall survival was not. Older age and a greater number of co-morbidities were noted to be more frequently associated with sarcopenic patients compared to non-sarcopenic patients (150).

Sarcopenia is a common feature of cancer cachexia. The European School of Oncology recommends the early recognition of cachexia (153), but this has proved challenging with the ever increasing rate of obesity (32, 154). The emaciated appearance, previously synonymous with malignancy, is today frequently masked by adiposity that obscures weight loss and/or muscle wasting, even in advanced disease. Sun et al reported that cancer patients with cachexia were more likely to have their cachexia diagnosed if they were underweight rather than overweight or obese (155). The severe muscle wasting and excess adiposity seen in sarcopenic obesity results in a cumulative risk profile and is associated with a higher risk of dose-limiting toxicity (70), surgical complications and reduced survival (156).

1.3 Management of Cancer Cachexia

Management of cancer cachexia is a challenging, but evolving area. For many years the lack of consensus on the definition and diagnostic criteria for cachexia was considered an impediment to the development of potential treatment options (2, 10). More recently, the notion that cachexia may develop as an early rather than late or unavoidable consequence of cancer has garnered support and is reflected in recent trials. However, there is no widely approved standard of care for cancer cachexia (31). Early screening of nutritional status in cancer patients is recommended starting at diagnosis (94), so that signs of cachexia may be promptly identified. This provides clinicians with an

opportunity to treat any existing nutritional deficits and to allow reversible causes of weight loss to be addressed.

A number of randomised controlled trials have investigated single or combined pharmacological and non-pharmacological interventions for cancer cachexia. These have included appetite stimulants, anabolic agents, cytokine modulators, non-steroidal anti-inflammatory drugs (NSAIDS), nutritional supplements and exercise.

Trials have shown the effectiveness of low dose glucocorticoids to stimulate appetite and improve fatigue in cancer patients (157, 158) but side effects can include immune suppression, muscle myopathy and insulin resistance. ROMANO-1 and ROMANO-2 randomised patients with stage III and IV non-small cell lung cancer (NSCLC) and cachexia to anamorelin 100 mg or placebo daily for 12 weeks (159). Anamorelin is a selective ghrelin agonist with appetite-enhancing and anabolic effects. Cachexia was defined as ≥5% loss of body weight or body mass index < 20 kg/m2. Lean body muscle increased but no improvement in physical function, measured with handgrip strength, or survival was reported.

Wright et al randomised patients with advanced or recurrent squamous cell carcinoma of the cervix or head and neck, who were undergoing chemotherapy and chemoradiation to testosterone enanthate 100 mg or placebo weekly for 7 weeks (99). Testosterone is the primary male sex hormone and an anabolic steroid. Participants were eligible if they had at least 5% loss of body mass in the previous 12 months. Treatment with testosterone improved lean body mass, physical performance and patient-reported quality of life but

did not improve 1-year survival. The authors recommended that future studies should include a larger sample size, treated at earlier stages in their cancer treatment.

Trials investigating the effectiveness of cytokine modulators such as etanercept (160), infliximab (161) and thalidomide (162), all of which act by inhibiting TNF-α, proved disappointing with the associated risks outweighing the benefits in some cases.

Mantovani et al randomized advanced cancer patients with cachexia to receive one of five treatments (163): medroxyprogesterone 500 mg/day or megestrol acetate 320 mg/day; oral nutritional supplement with eicosapentaenoic acid (EPA) 2.2 g/day; L-carnitine 4g/day; thalidomide 200 mg/day or a combination of the all therapies for 4 months. The combination therapy was most effective, resulting in an increase in lean body muscle, improvement in appetite and performance status and a decrease in resting energy expenditure, fatigue, IL-6 and TNF-α. Similarly, a trial was conducted in patients with advanced gynaecological malignancy and cachexia. Patients were randomized to either a combination of megestrol acetate 320 mg/day, L-carnitine 4 g/day, celecoxib 300 mg/day and antioxidant agents, lipoic acid 600 mg/day and arbocysteine 2.7 g/day or megestrol acetate 320 mg/day alone for 4 months (164). The combination therapy resulted in improvements in lean body mass, fatigue and patient-reported quality of life.

Non-pharmacological interventions including nutritional counseling, oral nutritional supplements, antioxidants and exercise have also formed the basis for a number of studies. The nature of these interventions has made it possible to include patients at an earlier stage in their disease, while receiving active cancer treatment. Uster et al investigated the efficacy of nutritional counselling and an individualised nutritional plan

for severely undernourished or “at high risk” for undernutrition outpatients over a 3 month period. Undernutrition/high risk for undernutrition was defined as a score ≥3 on the Nutritional Risk Screening 2002 tool. Nutritional intervention significantly improved energy and protein intake, but it did not improve nutritional or physical function, measured with handgrip strength, sit-to-stand test and leg strength measures, or quality of life. Poor baseline nutritional status may have contributed to the limited efficacy in this patient population. A multi-centre, randomised controlled trial investigating the efficacy of a multimodal intervention to prevent the development or progression of cachexia in patients with advanced NSCLC lung cancer and pancreatic cancer compared to standard care is currently open for recruitment. The 6-week intervention will comprise nutritional counseling, oral nutritional supplements, ibuprofen (NSAID) 1200mg/day and a home-based aerobic and resistance exercise programme.

The development of treatments that improve or maintain functionality, and in doing so quality and possibly even quantity of life, should be a clinical research priority. Given the complexity of cancer cachexia, it is envisaged that this may only be achieved through a multimodal approach (76) administered prior to or concurrently with cancer treatment. Further research is required in larger and more homogenous populations to fully realise the potential of such an intervention and to establish optimal timing, dose and duration of treatment.

1.4 Gynaecological Cancer

Gynaecological cancer accounts for 1 in 8 cancers in Irish women and 1 in 12 cancer-related deaths. It is the collective term used for the five cancers which can originate in the female reproductive system that is, arising from the cervix, the endometrium, the

ovary, the vagina and the vulva (Figure 1.3). A general overview is provided below, however incidence, epidemiology, diagnosis, staging and treatment options for each of the gynaecological malignancies are outlined in detail in Appendix I.

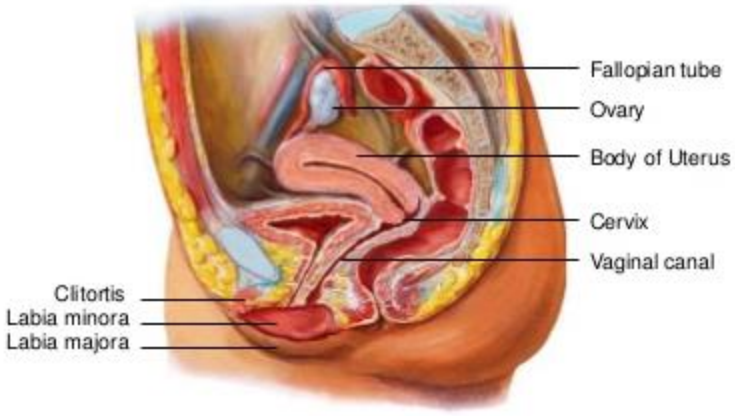

Figure 1.3 Female reproductive system (sagittal view)

1.4.1 Incidence and Epidemiology

Cervical cancer ranks as the fourth most commonly diagnosed and is a leading cause of cancer death in women worldwide (165). In Ireland, approximately 284 new cases are diagnosed and 87 deaths occur per year (166). The most significant cause is persistent human papillomavirus (HPV) infection. HPV 16 and 18 are the most common oncogenic subtypes. The Papanicolaou (pap) test, a cytology-based test, is currently the standard method for cervical cancer screening in Ireland. A HPV-based cervical screening test is being introduced. Primary prevention is now available through immunisation with HPV vaccines.

Endometrial cancer is the most common gynaecological cancer in developed countries. Its incidence is increasing, which may at least in part be due to rising obesity rates. More than 500 new cases are diagnosed per year in Ireland (166), with more than 90% of cases occurring in women > 50 years. The main risk factor is unopposed endogenous or exogenous oestrogen exposure. It is associated with obesity, diabetes and tamoxifen. Genetic predisposition also plays a role in approximately 5% of cases; Lynch syndrome, an autosomal dominant syndrome, accounts for the majority of inherited endometrial cancers (167). The life time risk of developing endometrial cancer with Lynch syndrome is up to 60%.

Ovarian cancer is the sixth most common cancer in women with more than 400 news cases each year in Ireland (166). It is associated with the worst prognosis and highest mortality rate amongst the gynaecological cancers with a 5-year overall survival rate of 25-35%. The majority of cases are in women over 50 years. Pre-disposition to developing ovarian cancer doubles by having a first degree relative with breast or ovarian cancer. Inherited germline mutations in BRCA 1 or BRCA 2 genes increase the risk of ovarian cancer in carriers. BRCA 1 confers an overall risk of 16-39%, while carriers of the BRCA 2 germline mutation have an overall risk of 11-16% of ovarian cancer. Women with Lynch syndrome have a 6 - 8% lifetime risk of ovarian cancer (168).

Vaginal cancer is very rare; it accounts for only 1-2% of gynaecological cancers (169). Previously more common in elderly and postmenopausal women, incidence of vaginal cancer is rising in younger women, mainly due to the increase in persistent high-risk HPV infections, particularly with the HPV 16 subtype (170).

Vulval cancer is uncommon, accounting for 2-5% of all gynecological malignancies worldwide (171). Like vaginal cancer, previously considered a disease of post-menopausal women, a shift in incidence and age of presentation has occurred due to persistent HPV infections (171).

1.4.2. Staging

The most widely used staging system is the tumor node metastasis (TNM) system maintained collaboratively by the American Joint Committee on Cancer and the International Union for Cancer Control. However, gynaecological cancer staging systems are determined by the International Federation of Gynecology and Obstetrics (FIGO) with site-specific staging systems.

1.4.3 Treatment

Surgery is the cornerstone of management for most patients with gynaecological cancer and it is the most effective treatment if the diagnosis is made at an early stage. However, when primary surgery is not possible, whether due to the extent of disease or the patient's physical condition, other treatments including neoadjuvant chemotherapy, primary chemoradiation, radiotherapy, hormone and targeted treatments may be used as alternatives either in combination with surgery, with each other or alone.

1.5 Gynaecological Cancer and Cachexia

Despite considerable progress in recent years in cachexia research, gynaecological cancers remain under-represented in the literature. There are as yet no published studies which have principally focused on cachexia in gynaecological cancer populations. Instead prognostic parameters including body composition and inflammatory markers,

known to be important features of cachexia, have been investigated in terms of the patient outcomes (127, 172-176). The presence of these features highlight patients with a high risk profile who warrant greater surveillance by clinicians. These studies are summarised in Table 1.2.

Unintentional weight loss is common in advanced ovarian cancer (173), but is a poor indicator of disease status. Ovarian cancer is frequently diagnosed at an advanced stage, when ascites and oedema are already established, making it impossible to measure body composition by means of weight measurement or BMI alone. The precision of CT imaging has enabled clinical researchers to quantify muscle mass and adipose tissue and, through serial CT imaging, identify changes in body composition over time. Currently, there is no agreed cut-off for low skeletal muscle index (SMI) or CT-measured sarcopenia in gynaecological populations. Bronger et al reported an 11% prevalence of sarcopenia in treatment-naïve patients with advanced ovarian cancer (Stage III-IV) with a cut-off point of SMI $\leq$38.5 cm^2/m^2 for sarcopenia, the cut-off used in respiratory and gastrointestinal malignancies. Progression-free survival and overall survival were significantly shorter in the sarcopenic patient group. Other studies applied a cut-off of SMI <41.5 cm^2/m^2 and reported prevalence of 50.4% (Stage II-IV) and 27.8% (Stage I-IV) in treatment-naïve patients with ovarian cancer (172, 173). Results from both reported no significant association between reduced SMI at baseline and survival. However, patients with skeletal muscle loss during neoadjuvant chemotherapy had worse survival when compared to those patients who maintained or gained skeletal muscle (173). Sarcopenia is an important component of cachexia but gender, ethnicity and disease specific cut-offs are essential to identify patients most at risk and to accurately determine prevalence in gynaecological cancers. Multimodal interventions similar to

those outlined in Section 1.3 may attenuate the deleterious effects associated with reduced muscle mass in ovarian cancer patients.

Bandera et al (60) investigated the impact of BMI on survival in ovarian cancer patients using a patient database held by a care consortium in the United States. Obese patients with localised disease had worse survival compared to normal weight patients. However, obese patients with advanced disease had better survival compared to normal weight patients with advanced disease. This finding is consistent with the obesity paradox. Although BMI is a widely used measure of obesity, it is a crude tool and unable to detect changes in body composition. Cachexia was defined in this study by the International Classification of Disease (ICD), a diagnostic classification system which codes for and defines diseases and other health-related conditions. Using this system, cancer cachexia was reported in 7% of patients. However, this may not be generalisable to ovarian cancer cohorts, given the potential misclassification of cachexia due to the timing and use of the ICD diagnostic label (177).

Table 1.2 Summary of cachexia-related studies in gynaecological cancer populations

Author, year	Primary purpose	Study design	Population	Cachexia Features, Diagnostic Criteria and/or Prevalence	Outcome
Hefler-Frischmuth et al, 2010 (176)	To evaluate the association between GPS and survival in patients with cervical cancer	Retrospective	Vulval cancer patients N=93 Mean age ±SD: 69.7 (14.8) Stage IA – IV Treatment-naïve	Hypoalbuminaemia (<35g/L) associated with cachexia Cachexia prevalence not reported	mGPS is not a predictor for survival in patients with vulvar cancer
Polterauer et al, 2010 (127)	To evaluate the association between GPS and survival in patients with cervical cancer	Retrospective	Cervical cancer patients n=244 Mean age ±SD: 50.1 ±13.9 Stage IA1 – IVB Treatment-naïve	Hypoalbuminaemia (<35g/L) associated with cachexia Cachexia prevalence not reported	GPS is a predictor for progression-free and overall survival in patients with cervical cancer
Maccio et al, 2012 (164)	To establish the safest and most effective treatment for cachexia comparing megestrol acetate + L-carnitine + celecoxib + antioxidants (Arm 1) with megestrol acetate (Arm 2)	Open-label RCT prospective trial	Ovarian, endometrial, cervical cancer patients with cachexia **Arm 1** n=61 Mean age ±SD: 62.6 ±12.3 Stage IIIC (ovary) 2 Stage IV 59 **Arm 2** n= 63 Mean age (±SD): 58.44 ±13.3 Stage IIIC (ovary) 3 Stage IV 60 Pre-treated	Cachexia defined as loss of ≥ 5% pre-illness body weight in the previous 3 months	Stated primary endpoints for cachexia - LBM, REE, fatigue and QoL were evaluated. Toxicity was negligible and comparable between treatment arms. Arm 1 improved all.

Table 1.2 Summary of cachexia-related studies in gynaecological cancer populations (continued)

Author, year	Primary purpose	Study design	Population	Cachexia Features, Diagnostic Criteria and/or Prevalence	Outcome
Aust et al, 2015 (172)	To investigate the prognostic value of BCMs assessed by pre-operative CT in patients with ovarian cancer	Retrospective	Ovarian cancer (epithelial) patients n=140 Mean age ±SD : 60 years ±13 Stage I-IV Treatment-naïve	MA - marker of cachexia Low MA: n=49 Cachexia prevalence not reported	Low MA associated with poorer nutritional status, systemic inflammatory status and reduced survival.
Rutten et al, 2016 (173)	To investigate overall survival in patients with ovarian cancer related to changes in SM mass and body composition during NACT	Retrospective	Ovarian cancer patients n=123 Mean age ±SE [range] : 66.5 ±0.8 [39-86] Stage IIB-IV Treatment-naïve	Muscle-associated weight-loss Cachexia prevalence not reported	Patients who maintained or gained SM during NACT had a better prognosis than those who lost SM.
Bronger et al, 2017 (174)	To determine the prevalence of sarcopenia and its association with PFS and OS in patients with ovarian cancer	Retrospective	Ovarian cancer (serous) patients n=105 Median age [range]: 65 [33-85] Stage III-IV Treatment-naive	Sarcopenia - feature of cachexia Prevalence of sarcopenia: 11% (n=12) Cachexia prevalence not reported	Baseline sarcopenia independent predictor of poor PFS and OS. Prevalence of sarcopenia lower in ovarian cancer compared to other cancers.

Table 1.2 Summary of cachexia-related studies in gynaecological cancer populations (continued)

Author, year	Primary purpose	Study design	Population	Cachexia Features, Diagnostic Criteria and/or Prevalence	Outcome
Bandera et al, 2017 (60)	To evaluate the impact of BMI on survival and to examine effects by key clinical characteristics	Health insurance cancer registry cohort	Ovarian cancer (epithelial) patients n=1157 Mean age (±SD): 62.6 ±12.6 Stage I-IV Cachexia documented from 3 years before diagnosis to end of follow-up	Cachexia defined by ICD-9: 799.4 Prevalence of cachexia: 7% (n=82)	The association of obesity with ovarian cancer survival varied by stage; worse survival - localised disease, better survival -advanced disease
Aredes et al, 2018 (175)	To assess impact of CRT on nutritional status, functional capacity and QoL and to assess relationship between baseline characteristics and chemotherapy toxicity	Prospective, observational	Cervical cancer N=49 Mean age 45 ±13.8 years Stage I-III Treatment-naïve	WL > 5% in 6 months or WL > 2% + BMI <20 kg/m^2 or WL >2% + sarcopenia Prevalence of cachexia: 32.4% (n=11)	%WL, cachexia and sarcopenia were associated with interruption of chemotherapy. 83% of pts who had a chemotherapy interruption had cachexia at presentation

Abbreviations: BCM: body composition measurements; BMI: body mass index; CRT: chemoradiotherapy; CT: computed tomography; GPS: Glasgow Prognostic Score; ICD: International Classification of Disease; LBM: lean body mass; MA: mean muscle attenuation; NACT: neoadjuvant chemotherapy; OS: overall survival; PFS: progression-free survival; QoL: quality of life; RCT: randomised controlled trial; REE: resting energy expenditure; SD: standard deviation; SE: standard error of mean; SM: skeletal muscle; WL: unintentional weight loss.

Poor nutritional status is common in ovarian cancer patients (178-181), but it is also prevalent in cervical cancer patients, especially in advanced disease (182, 183). Concurrent chemoradiation which is used in the treatment of locally advanced and advanced stage disease is associated with gastrointestinal and haematological toxicity. Therefore, the nutritional status of the patient at baseline may influence tolerability to treatment. Aredes et al demonstrated that percentage weight loss, cachexia and sarcopenia were significantly associated with the interruption of chemotherapy (165). Prevalence of cachexia as defined by Fearon et al (20) was 32.4% at baseline; 83% of these patients had a chemotherapy interruption.

Systemic inflammation is associated with poorer prognosis and reduced quality of life in cancer patients (144). It is implicated in the development and progression of cancer (184) and is associated with both cachectic and obese phenotypes. While the inflammation-based score, the Glasgow Prognostic Score, demonstrated prognostic value in cervical cancer patients (127), the modified version was not a predictor of survival in patients with vulval cancer (176).

Maccio et al compared the safety and efficacy of two treatment regimens for cachexia: a single-agent, appetite-stimulant treatment and a multi-targeted option directed at symptoms of cachexia including lean body mass and fatigue (164). The study included pre-treated, patients with established cachexia and a diagnosis of cervical, endometrial or ovarian cancer. Although the treatment arms were comparable in relation to toxicity, the multi-targeted option proved superior in the improvement of symptoms.

Published cachexia-related studies in mixed cancer populations which included gynaecological cancer cohorts are summarised in Table 1.3. It is difficult to draw any firm conclusions regarding cachexia in gynaecological cancer from these studies for a number of reasons. The

gynaecological cancer cohorts were invariably small relative to the total sample size (range 1-82). Study outcomes were generally not reported on a primary site by site basis. As cachexia was an eligibility criterion for a number of studies (185-187), this precluded prevalence of cachexia being reported. Eight studies reported prevalence of cachexia (155, 186, 188-193); three commented on prevalence by primary site (155, 190, 191). Disease stage, treatment status and method to diagnose cachexia varied between studies. Prevalence in gynaecological cancers ranged from 36.4 - 43.8% and 36.4 - 43.8% for cervical and ovarian cancer patients respectively (155, 191). Poulsen et al did not diagnose cachexia in their cervical cancer cohort (190).

Table 1.3 Summary of cachexia-related studies in mixed cancer populations including gynaecological cancer cohorts

Author, year	Primary purpose	Study design	Population	Cachexia Features, Diagnostic Criteria and/or Prevalence	Outcome
Mantovani et al, 2004 (194)	To assess efficacy and safety of an integrated treatment in an advanced cancer population with cachexia	Open non-randomised phase II study	Any advanced cancer with cachexia n=25 [ovarian n=3; uterine sarcoma n=1] Mean age ±SD: 58.2 ±9.0 Stage II-IV Intervention: Diet, ONS, NSAID, anti-TNF-α antibody Previously treated with chemotherapy or hormone therapy or receiving supportive care.	Cachexia defined as ≥ 5% weight loss from pre-illness weight in previous 3 months ± abnormal pro-inflammatory cytokines, ROS and anti-oxidant enzymes	Interim results: Objective response of 14 patients following 4 months of treatment: Improved: 5 patients Unchanged: 3 patients Worsened: 6 patients
Mantovani et al, 2010 (163)	Randomised Phase III Clinical Trial of Five Different Arms of Treatment in 332 Patients with Cancer Cachexia **Primary Endpoints:** 1. Increase in LBM 2. Decrease in REE 3. Decrease in fatigue **Secondary Endpoints:** 1. Appetite 2. Grip strength 3. IL-6 and TNF-α serum levels 4. GPS 5. REE 6. PS	Phase III randomised controlled trial	Any advanced cancer with cachexia n=332 [ovarian n=26; uterine n=10] Mean age: overall mean not provided Stage: Specified only as advanced Arm 1: medroxyprogesterone 500 mg/day or megestrol acetate 320 mg/day; Arm 2: ONS with EPA 2.2 g/day; Arm 3: L-carnitine 4g/day; Arm 4: Thalidomide 200 mg/day Arm 5: Combination of all Previously treated; concomitant chemotherapy or hormone therapy with palliative intent or supportive care.	Features considered predictive of cachexia: ≥ 5% weight loss from pre-illness weight in previous 3 months ± abnormal pro-inflammatory cytokines, ROS and anti-oxidant enzymes	Arm 5 - most effective treatment for improvement in primary end points and secondary endpoints (appetite, IL-6, TNF-α, GPS, PS) A multi-targeted intervention likely to be most successful.

Table 1.3 Cachexia-related studies in mixed cancer populations including gynaecological cancer cohorts (continued)

Author, year	Primary purpose	Study design	Population	Cachexia Features, Diagnostic Criteria and/or Prevalence	Outcome
Poulsen et al, 2014 (190)	To investigate the effect of intensive individual dietary counselling for patients receiving radiotherapy and/or chemotherapy	Randomised control trial	Patients with oesophageal, gastric, and gynaecological cancer referred for palliative or preoperative chemotherapy and/or radiation therapy n= 61 [gynaecological: n=11] Median age [range]: 62 (53-68) intervention group 64 (57-70) control group Stage: I (cervical) Treatment-naive	Cachexia defined as >5% weight loss Prevalence of cachexia: Cervical cancer: Not identified (Not reported in paper, correspondence with author)	Nutritional intervention resulted in less WL during treatment (44% v 72%, $p<0.05$)) but not between end of treatment and follow-up
Dev et al, 2015 (185)	To compare rate of weight loss, symptom burden, CRP and survival in cachectic cancer patients with normal REE and hypermetabolic cachectic cancer patients with normal REE	Retrospective review	Any advanced cancer with cachexia n=60 [gynaecological cancer: n=3] Median age [range]: 60 [57.0-62.9] Stage: Specified only as advanced Previously treated with chemotherapy and/or radiation therapy	Cachexia defined as >5% weight loss or poor appetite	Hypermetabolism common in patients with weight loss. No strong association between velocity of weight loss, symptom burden, CRP and survival and patients with elevated REE

Table 1.3 Cachexia-related studies in mixed cancer populations including gynaecological cancer cohorts (continued)

Author, year	Primary purpose	Study design	Population	Cachexia Features, Diagnostic Criteria and/or Prevalence	Outcome
Naing et al, 2015 (195)	To determine safety and optimal dose of olanzapine in patients with advanced cancer and to assess the metabolic impact of olanzapine on changes in IL-6, leptin, ghrelin, growth hormone, and weight	Single-centre, open-label, dose escalation study	Any advanced cancer with cachexia n=39 [ovarian n=4; endometrial n=1; cervical n=1] Median age [range]: 57 [28-84] Stage: Specified only as advanced Intervention: 2.5mg - 20mg Concurrent chemotherapy or radiation therapy	Cachexia defined as 10% weight loss in previous 6 months	Recommended dose (20mg) of olanzapine was safe and tolerable. Modest effect in changing weight loss trajectory. Changes in cytokine levels did not correlate to clinical benefit.
Sun et al, 2015 (155)	To assess prevalence of cachexia in advanced cancer patients using the international consensus diagnostic criterion and analyse physician diagnosis and treatment of cachexia	Single centre epidemiological survey	Any advanced cancer Mean age ±SD: 52.1 ±11.7 n=390 [cervical n=11; ovarian n=6] Stage: Specified only as advanced Previously treated	Cachexia defined as WL >5% in 6 months or BMI <20 and WL >2% or sarcopenia and WL >2%. Prevalence of cachexia: All cancers: 35.9% Cervical cancer 36.4% Ovarian cancer 33.3%	Prevalence of cachexia in advanced cancer patients was high but rarely recognized or actively managed. Lack of guidelines, knowledge and awareness regarding early diagnosis are provided as potential reasons for this.
Rotty et al, 2017 (191)	To determine the incidence of cancer anorexia cachexia syndrome in a mixed cancer population	Retrospective	Patients attending centre for chemotherapy n= 206 [ovarian n = 38; cervical n = 32; endometrial n = 2] Mean age ±SD: Not reported Stage: All stages Pre-treatment and post-treatment analysis.	Cachexia assessed by PG-SGA category C - WL> 5% within 1 month or > 10% in 6 months Prevalence of cachexia: Ovarian cancer: 36.84% Cervical cancer: 43.75% Endometrial cancer: NA	Incidence of CACS more common with advanced stage and co-morbidities Improvement in nutritional status of patients after 6 months of chemotherapy Significant association between CACS and stage and co-morbidities

Table 1.3 Cachexia-related studies in mixed cancer populations including gynaecological cancer cohorts (continued)

Author, year	Primary purpose	Study design	Population	Cachexia Features, Diagnostic Criteria and/or Prevalence	Outcome
Vagnildhaug et al, 2017 (196)	To confirm prognostic validity of WLGS and validity of WLGS in relation to cachexia domains and to evaluate if WLGS predicts cachexia progression	Prospective, observational	Patients with incurable cancer enrolled in a palliative care programme N=1406 [gynaecological n=82] Median age [range]: 66 [57–74 Stage: Any, if incurable Pre-treatment and concurrent	Cachexia domains were anorexia, dietary intake, performance status, and physical and emotional functioning	WLGS predictive of survival Cachexia domains improved prognostic accuracy
Ní Bhuachalla et al, 2017 (186)	To assess whether MUST, MST and NRI detect nutritional vulnerable patients	Prospective	Patients with mixed tumours attending for chemotherapy N=725 [gynaecological n=31] Median age [range]: 64.3 [55.9–71.0] Stage: All stages On treatment	Prevalence of cachexia: 41.5% (all cancers)	MUST, MST and NRI were unable to reliability identify all at risk patients.
Keane et al, 2017 (193)	To identify factors affecting prognosis in a cohort of advanced cancer patients receiving HPN	Retrospective	Advanced cancer patients discharged on HPN n=107 [breast, ovarian, endometrial, cervical: n=37] Mean age ±SD: 57 ± 12 Stage: Advanced Previously treated with surgery or chemotherapy	Cachexia defined as WL >5% or BMI < 20kg/m^2 and any degree of WL >2% Prevalence of cachexia: 87.1%	Performance status, GPS and PN requirements may predict survival in patients with advanced cancer receiving HPN

Table 1.3 Cachexia-related studies in mixed cancer populations including gynaecological cancer cohorts (continued)

Author, year	Primary purpose	Study design	Population	Cachexia Features, Diagnostic Criteria and/or Prevalence	Outcome
Wright et al, 2018 (99)	Efficacy of testosterone to limit loss of body mass in advanced cancer patients	Prospective	Advanced or recurrent SCC cervix or head and neck cancer patients n=21 [cervical=9] Intervention for 7 weeks: Arm 1: Testosterone 100 mg Arm 2: Placebo Chemotherapy and chemoradiation	Cachexia defined as ≥ 5% loss in body mass in 12 months measured with DEXA	Improved lean body mass, physical performance and patient-reported quality of life with testosterone No improvement in 1-year survival.
Vagnildhaug et al, 2018 (188)	Assess prevalence of cachexia in an unselected cancer population and assess patient-perceived need of attention to cachexia.	Cross-sectional	All cancer patients (inpatients and outpatients) at 3 hospitals n=386 [gynaecological n=4] Median age [range]: 65 [56–72] Stage: All stages Treatment-naïve and treated*	Cachexia defined as WL > 5% in 6 months or WL >2% in 6 months and BMI < 20 kg/m^2. Prevalence of cachexia: 51% (inpatients) 22% (outpatients)	Cachexia - prevalent condition in unselected sample of patients with cancer. A substantial number of patients expressed a need for increased attention to the condition, particularly in cachectic patients

*including at least 3 of the 4 gynaecological patients

Table 1.3 Cachexia-related studies in mixed cancer populations including gynaecological cancer cohorts (continued)

Author, year	Primary purpose	Study design	Population	Cachexia Features, Diagnostic Criteria and/or Prevalence	Outcome
Zhou et al, 2018 (189)	To develop a clinically applicable cachexia score for staging cancer cachexia	Prospective	Patients with advanced cancer n=259 [gynaecological cancer n=33] Mean age ±SD: 50.6 ± 12.6 Stage: III-IV Unclear if patients previously treated (no reply from corresponding author)	Cachexia staging score consists of: weight loss in 6 months (score range 0-3) Muscle function and sarcopenia assessment (score range 0-3) ECOG (score range 0-2) Appetite loss (score range 0-2) Abnormal biochemistry (score range 0-2) Prevalence of cachexia: 47.1%	New clinical tool developed for classifying cachexia stage
Vagnildhaug et al, 2019 (192)	To identify predictors of cachexia development and to create and evaluate accuracy of a predictive model based on these predictors.	Secondary analysis of a prospective, observational, multicentre study	Patients with incurable cancer n= 628 [gynaecological cancer n=36] Median age [range]: 65 [17] Stage: Any, if incurable Treated	Cachexia defined as WL > 5% in previous 6 months or WL > 2% in previous 6 months and current BMI < 20 kg/m^2. Prevalence of cachexia: All cancers: 25%	WL, cancer type, appetite loss and COPD are significant and independent predictors of cachexia in patients with incurable cancer

Abbreviations: BMI: body mass index; CACS: cancer anorexia cachexia syndrome; CRP: C-reactive protein; COPD: chronic obstructive pulmonary disease; DEXA: dual energy x-ray absorptiometry; ECOG: Eastern Co-operative Oncology Group; GPS: Glasgow Prognostic Score; HPN: home parenteral nutrition; IL-6: interleukin-6; LBM: lean body mass; MUST: Malnutrition Universal Screening Tool; MST: Malnutrition Screening Tool; NA: Not available; NRI: Nutritional Risk Index; NSAID: non-steroidal anti-inflammatory drugs: ONS: oral nutritional supplements; OS: overall survival; PFS: progression-free survival; PN: parenteral nutrition; REE: resting energy expenditure; ROS: reactive oxygen species; SD: standard deviation; SCC: squamous cell cancer; TNF-α: tumour necrosis factor-alpha; WL: unintentional weight loss; WLGS: weight loss grading system.

1.6 Rationale for Thesis

Cachexia is a pervasive burden on cancer patients. It permeates all aspects of the person and can lead to progressive functional impairment, psychological distress and poor prognosis. Although enormous progress has been made in recent years in the area of cachexia research, given its almost ubiquitous nature particularly in advanced cancer, research to date could still be considered limited relative to the scale of the problem.

The need for early recognition and diagnosis should not be underestimated. We know that oncological treatments can exacerbate cachexia and in studies of patients with advanced disease the vast majority will have had at least one line of treatment. Few studies have been conducted investigating prevalence of cachexia in treatment-naïve cancer patients or its prognostic value across the cancer trajectory. As a result, clinical, nutritional and inflammatory characteristics, known to increase susceptibility to changes in behaviour, metabolism and body composition leading to cachexia, need to be comprehensively elucidated at the pre-treatment stage. The prevalence of the early manifestations of cachexia at diagnosis of cancer is also unclear. Defining and establishing this may be of benefit. There is a critical need to support the early identification of those patients most at risk of developing cachexia in the expectation that they would most likely be the cohort to benefit from intervention. This combined with the apparent absence of gynaecological cancer in published cachexia literature compelled me to undertake research in a treatment-naïve gynaecological oncology population.

1.7 Thesis Structure and Aims

The central theme of this thesis is cancer cachexia in treatment-naïve populations. Each study contributes to this narrative from a distinct perspective. Using a widely accepted definition for cancer cachexia i.e. >5% weight loss in 6 months, Study 1 (Chapter 2) retrospectively reports

the prevalence of cachexia in a treatment-naïve mixed tumour outpatient population. It also examines the impact weight change prior to diagnosis has on overall survival. The need for awareness and recognition of cancer cachexia amongst healthcare professionals is highlighted in this study. Poor understanding of the condition and its associated burden may limit healthcare professionals in their management of patients. Consequently, Study 2 (Chapter 3) explored current knowledge of cancer cachexia among Irish oncology healthcare professionals and how this may influence their practice in cancer patient management. Much of the research to date has focused on cachexia in mixed cancer populations. Gynaecological cancer has been under-represented in cachexia literature; the lack of dedicated studies is evident from the literature review, with a limited number including mixed solid malignancy populations with small gynaecological cancer cohorts as seen in Study 1 (Chapter 2) i.e. 5% endometrial cancer. Study 3 (Chapter 4) and Study 4 (Chapter 5) focus on cachexia in treatment-naïve gynaecological cancer populations. Study 3 is a systematic review of the literature designed to examine the prevalence of cachexia in treatment-naïve patients with gynaecological cancer. Study 4 describes an exploratory study in a de novo Irish gynaecological cancer population, which investigates the prevalence of cachexia and its impact on validated clinical and patient-reported outcomes.

In an effort to support the early identification of those most at risk of developing cachexia, a thorough understanding of its prevalence, predictors and its associated burden over time is necessary. Figure 1.6 outlines the overarching aim for the thesis and each study. Detailed aims and objectives for each study are outlined in the relevant chapter.

Thesis Aim

The overall aim of this thesis was to investigate cancer cachexia, in terms of awareness amongst oncology healthcare professionals, prevalence in treatment-naïve patients and its relationship to clinical and patient-reported outcomes, first in a mixed tumour population and then focusing on a gynaecological cancer cohort.

Mixed tumour population

Oncology healthcare professionals

Gynaecological cancer cohorts

Study 1

Aim

To retrospectively examine the prevalence of cachexia and the prognostic value of weight change in treatment-naïve patients with solid tumour malignancy

Study 2

Aim

To determine the importance placed on nutrition following a cancer diagnosis by oncology healthcare professionals and to establish their familiarity with cancer cachexia

Study 3

Aim

To report the prevalence of cancer cachexia in treatment-naïve patients with gynaecological cancer in published literature

Study 4

Aim

To estimate the burden of cachexia in a de novo Irish gynaecological cancer population and prospectively investigate its impact on clinical and patient-reported outcomes

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Chapter 2

Clinical Significance of Weight Change at Diagnosis in Patients with Solid Tumours

2.1 Introduction

Weight changes (loss or gain) may occur throughout the cancer trajectory. Most research has examined weight changes in patients after treatment (1-3) and in those with advanced cancer (2, 4). A landmark study quantified weight loss in patients at diagnosis and demonstrated an association with lower response to chemotherapy and shorter survival (5). Recent evidence has revealed that weight loss before treatment is associated with increased treatment side effects (6-8). Despite this, weight loss is infrequently assessed or actively managed (9, 10) and the high prevalence of obesity is not considered. As a consequence, the clinical significance of weight change in patients at diagnosis remains unclear.

Unintentional weight loss is common in people with cancer and is a predictor of disease outcome (5, 11). It is associated with increased morbidity and mortality. Weight loss is the predominant characteristic of cancer cachexia, a syndrome associated with ongoing loss of skeletal muscle mass (with or without fat), progressive functional impairment and deranged metabolism (12). Awareness and understanding of cancer cachexia amongst healthcare professionals varies (13, 14) and there is no consensus on the degree of weight loss considered clinically significant (15, 16).

With the global trend towards overweight and obesity (17), it is increasingly difficult to clinically identify malnourished individuals. Excess adiposity is a recognised risk factor for many cancers including endometrial and ovarian cancer (18). Cancer patients frequently present with an overweight or obese body mass index (BMI) even in the context of advanced disease (19, 20). This may mask muscle wasting (sarcopenia) (21, 22). Muscle wasting associated with simultaneous adiposity (sarcopenic obesity) has a

negative survival impact (2, 3). The effect of obesity is complex (23). Although usually associated with greater all-cause mortality relative to normal BMI (24), it may confer a survival advantage in cancer (25). Weight gain during treatment is a positive prognostic factor in ovarian cancer (1, 26). However, obesity at breast cancer diagnosis (27, 28) and weight gain amongst breast cancer survivors (29, 30) are both associated with poorer outcomes. Obesity is associated with worse outcomes in colon cancer in the adjuvant setting (31).

A recent study supported the concept that severity of weight loss depends on simultaneous adipose tissue and muscle reserve depletion (25). It demonstrated that self-reported weight loss, adjusted for BMI, predicted survival; patients with a low degree of weight loss (<2.5%) and a high BMI (≥28) had the best prognosis, while those with a high degree of weight loss (≥15%) and a low BMI (<20) had the worst prognosis. Thus, by combining weight loss and BMI, a cancer-associated weight loss grading system ranging from 0 to 4 was proposed. Previous work had demonstrated that weight gain was prognostic of reduced survival in advanced cancer (32). However, this recent study focused on weight stable and weight loss groups, citing the difficulty associated with elucidating the true nature of weight gain as the reason for its exclusion (25). The same uncertainty exists with regard to how much weight loss is specifically tumour-driven. Although it is important to recognise the impact of weight loss, the consequences of weight gain should also be examined.

The clinical significance of weight changes at cancer diagnosis and throughout the cancer trajectory is therefore unclear and warrants investigation. Greater clarity may prompt

early recognition by oncology healthcare professionals of those most at risk, thus providing an opportunity to intervene and improve patient outcomes.

This study has been published in Supportive Care in Cancer (Appendix II).

2.2 Aim and Objectives

2.2.1 Aim

To retrospectively examine the prevalence of cachexia and the prognostic value of weight change in treatment-naïve outpatients with solid tumour malignancy.

2.2.2 Objectives

- To describe the clinical characteristics of a treatment-naïve solid tumour patient population;
- To measure prevalence of weight change patterns in this population by:
    - weight gain and weight loss categories and
    - percentage weight change increments i.e. 0.1-2.4%; 2.5-5%; 5.01-9.9%; ≥ 10%
- To report prevalence of cancer cachexia at diagnosis in a mixed solid tumour outpatient population;
- To determine predictors of weight change at diagnosis;
- To investigate the prognostic value of weight change across the cancer trajectory;
- To identify predictors of survival across the cancer trajectory;

2.3 Methods

2.3.1 Ethical Approval

Institutional Review Board approval was granted and the study met the criteria for waiver of informed consent as no protected health information was collected.

2.3.2 Study Design

This was a retrospective review of a dataset, extracted from the electronic medical record of patients with cancer held at the Taussig Cancer Institute, Cleveland Clinic. It included patients with a solid tumour diagnosis from 2009 to 2011 inclusive. The Taussig Cancer Institute is a tertiary cancer centre in the United States.

2.3.3 Eligibility Criteria

Inclusion Criteria

1. Primary diagnosis of solid tumour malignancy
2. Age $\geq$ 18 years
3. Two outpatient weight measurements at the Cleveland Clinic Taussig Cancer Institute from 1 January 2009 to 12 December 2011.

Exclusion Criteria

1. Primary diagnosis of haematological malignancy
2. Patients with a single recorded visit at the Cleveland Clinic Taussig Cancer Institute
3. Patients who were reviewed at or were inpatients in other Cleveland Clinic facilities
4. Patients who attended for non-clinical encounters

2.3.4 Data Collection and Handling

Data were extracted from the electronic medical record by the Cleveland Clinic eResearch Team, a clinical informatics research technology group responsible for clinical data warehousing and electronic data extraction. It was downloaded to a Microsoft Excel

spreadsheet (Microsoft Office Professional Plus 2013, Microsoft Corporation, Redmond, WA). Institutional regulations were followed for safe data storage and monitoring.

Those with a pre-diagnosis weight (T_0) recorded within 6 months of diagnosis date, a weight at diagnosis (T_1), and a final weight recorded ≥7 days after diagnosis date (T_2) were identified. 'Final weight' refers to the last encounter within the study period when weight was measured.

At T_0, only weight data were extracted. At T_1 and T_2, age, gender, primary cancer site, metastatic disease, number of metastatic sites, treatment received, BMI, 'Abnormal Weight Loss' as per the International Classification of Diseases, 9th Revision (ICD-9) Code 783.21 and date of death data were extracted where available. 'Date of death' was obtained from the electronic medical record; if unavailable, it was verified by Social Security Disability Insurance number. Patients were excluded if a secondary cancer was entered in 'Primary Cancer Site'; if 'Primary Cancer Site' was not specified as either primary or secondary; if BMI data were missing; if a discrepancy existed between electronic medical record 'Date of Death' and Social Security Disability Insurance 'Date of Death' or if recorded data were invalid.

2.3.5 BMI and Weight History

BMI was calculated with the formula: current weight (kg)/height (m^2) and categorised into four groups as per the World Health Organisation (WHO) BMI Classification (33): Underweight (<18.5), Normal (18.5-24.9), Overweight (25.0-29.9), Obese (≥30). Cancer cachexia was defined as weight loss > 5% in the previous 6 months.

Weight at each time point was recorded in kilograms (kg) to one decimal point. Percentage (%) weight change was calculated with the formula: [(current weight (kg) – previous weight (kg)/previous weight (kg)] x 100. A body weight change of ±2.4% is considered reflective of diurnal or daily variation and is often used as a weight stable category in clinical research. However, factors which may influence diurnal variation e.g. sleep pattern, diet, mood, hormone levels, which are frequently dysregulated in cancer, are not considered. Unintentional weight loss >5% is diagnostic of cancer cachexia, but weight loss <5% may confer an increased risk of developing cancer cachexia. Therefore, weight change was categorised into four weight change increments namely 0.1-2.4%; 2.5-5%; 5.01-9.9%; ≥ 10% for both weight gain and weight loss; a weight stable category (no change) was also documented. A categorical weight variable indicated weight loss, gain or stable between time points.

2.3.6 Data Analysis

Demographic and clinical characteristics were analysed to establish if an association with weight change existed. All variables including age (< 65 years; ≥ 65 years) and weight change were analysed as categorical variables using Chi-square test. Odds ratios were used to assess strength of bivariate associations between likelihood of weight loss with primary cancer site and metastatic disease, and also cachexia and metastatic disease. Overall survival was defined as the number of months from T_1 to date of death. All patients were observed to death or censored at T_2. Mean survival time with standard error was calculated. Median survival time could not be used due to the number of patients censored. Survival analyses were calculated using Kaplan-Meier method (comparisons with Cox-Mantel log rank tests). Cox proportional-hazards regression with estimated hazard ratios [HRs] and 95% confidence intervals [CIs] was used to investigate the

association between categorical variables and survival. Appropriate reference categories for categorical predictor variables were chosen and are indicated in each model. Using the cancer-associated weight loss grading system described by Martin et al, a score of 0-4 was assigned by combining weight loss and BMI. A score of 0 represents best survival, while a score of 4 represents worst survival. Survival time was calculated for combined weight loss and BMI categories to test applicability of the grading system in this population.

Analyses were completed using Microsoft Excel (Microsoft Office Professional Plus 2013, Microsoft Corporation, Redmond, WA), IBM SPSS Statistics for Windows Version 23 (SPSS, Chicago IL) and Stata Statistical Software: Release 14 (StataCorp. 2015. College Station, TX: StataCorp LP). Results were considered statistically significant if $p < 0.05$.

2.4 Results

A total of 4258 records were included in the analysis. Demographic and clinical characteristics are presented in Table 2.1. Over half were male (54.4%) and more than three quarters (76.7%) were white. The mean age at diagnosis was 61 ± 12.5 years. The four most common primary sites (lung, breast, prostate and colorectal) accounted for 50% of all cases. 15% (n=652) had metastatic disease. The median days from diagnosis to final visit was 180 days [range 7-1055]. Twenty three percent (n=981) mortality occurred during the study. Mean survival time was 24.4 ± 0.3 months.

Weight changes were nearly universal (98%) at T_1 (mean % weight change, -0.7 ± 3.7%). More than half (58%) had weight loss but only 3% were underweight and 8% cachectic.

Three percent had 'Abnormal Weight Loss' recorded at T_1. Most (69%) were either overweight (35%) or obese (34%). Twenty six patients had ≥ 10% weight gain; nearly two-thirds (65.1%; n=17) of these were overweight or obese at T_1. There was no significant association with primary site or metastatic disease in this group. Although endometrial cancer only constituted 5% (n=194) of the total population, 73.2% (n=142) of these patients were overweight or obese at T_1. Weight change was also prevalent (99%) at T_2; mean % weight change was more than twice that at T_1 (mean % weight change, -1.6 ± 8.3%). Most (59%) had weight loss at T_2. Of those who had weight loss at T_1, 71% continued to lose weight (Table 2.2). Forty-two percent of those who had weight gain at T_1, had weight loss at T_2. Despite this most (65%) were still overweight or obese at T_2. Only 4% were underweight and 14% cachectic.

Those with head & neck (OR=5.54, $p<0.001$) or upper gastrointestinal (GI) malignancy (OR=4.46, $p<0.001$) were most at risk of weight loss, followed by lung (OR=2.125, $p<0.01$) and endometrial cancer (OR=2.121, $p<0.001$), compared to those with breast cancer. Patients with metastatic disease were also more likely to have weight loss (OR=1.68, $p<0.001$) or be cachectic (OR=1.36, $p<0.05$) than those without metastatic disease at T_1 (Appendix III).

Cox multivariate analysis identified independent predictors of survival at T_1 (Table 2.3) and T_2 (Table 2.4) after controlling for known risk factors. Age (<65 years), gender (male), primary site (breast, prostate) and loco-regional disease independently predicted better survival at T_1 and T_2. A weight gain of 0.1-2.4% at T_1 and > 5% weight gain at T_2 were also predictive of better overall survival. Brain, lung and upper GI malignancies had the shortest survival.

Survival analysis based on weight change (gain or loss) alone showed that those with weight gain at T_1 or T_2 (Figure 2.1) had a better overall outcome compared to those who had WL. When individual % weight change bands were analysed, the worst survival was associated with ≥ 10% weight loss and ≥ 10% weight gain (Figure 2.2).

Table 2.1 Demographics and clinical characteristics at diagnosis (T_1) and final visit (T_2) (n=4258)

Characteristic	Diagnosis (T_1)		Final (T_2)		Δ
	N	%	N	%	N
Gender					
Male	2315	54.4			
Female	1943	45.6			
Ethnicity					
White	3264	76.7			
Black	664	15.6			
Other [a]	79	1.8			
No response	251	5.9			
Primary Site					
Breast	725	17			
Prostate	664	16			
Lung	599	14			
Upper GI	470	11			
Head & Neck	320	8			
Endometrial	194	5			
Brain	191	4			
Kidney	165	4			
Colon	133	3			
Melanoma	104	2			
Other	693	16			
Treatment [b]					
Radiotherapy			2065	48	
Chemotherapy			1868	44	
Hormonal therapy			771	18	
Biological modifier			762	18	
Monoclonal antibodies			282	7	
Age at diagnosis, years					
Mean (±SD)	61 (±12.5)		62 (±12.5)		1
Weight, kg					
Mean (± SD)	82.7 (±21.2)		81.2 (±21.4)		-1.5
BMI, kg/m^2					
Mean (±SD)	28.5 (±6.5)		28.1 (± 6.8)		
BMI					
< 18.5	110	3	172	4	62
18.5-24.9	1240	29	1319	31	79
25.0-29.9	1468	34	1374	32	-94
≥ 30	1440	34	1393	33	-47
Weight change, %[c]					
Mean (±SD)	-0.7 (±3.7)		-1.6 (±8.3)		-0.9
Weight change, %[c]					
≥ 10% WL	65	1.5	673	15.8	608
5.01 -9.9% WL	255	5.9	619	14.5	364
2.5-5.0% WL	542	12.7	497	11.7	-45
0.1-2.4% WL	1592	37.4	719	16.9	-873
0 (stable)	99	2.3	26	0.6	-73
0.1-2.4% WG	1232	28.9	654	15.4	-578
2.5-5.0% WG	335	7.9	456	10.7	121
5.01-9.9% WG	112	2.6	401	9.4	289
≥ 10% WG	26	0.6	213	5	187

[a]American Indian/Alaskan Native (9); Asian (25); Asian/Pacific Islander (11); Hispanic/Latino (18); Multiracial/Multicultural (19); Native Hawaiian/Pacific Islander (2); [b] > 1 treatment possible [c] Percentage weight change based on weight recorded in previous 6 months

Table 2.2 Proportion with variation in weight changes category between diagnosis (T_1) and final visit (T_2)

	Weight Loss (T_2)	Weight Stable (T_2)	Weight Gain (T_2)	Total (%)
Weight Loss (T_1)	71.1	0.5	28.4	100
Weight Stable (T_1)	53.5	1.0	45.5	100
Weight Gain (T_1)	41.6	0.8	57.6	100

Table 2.3 Predictive value (survival) of categorical variables in a multivariable model at diagnosis

Variable	B	SE	Wald	df	*p*	HR	95% CI for HR	
							Lower	Upper
Gender								
Male								
Female	0.06	0.07	0.67	1	0.41	1.06	0.92	1.22
Primary Site								
Breast			468.38	10	<0.001			
Lung	1.99	0.19	110.67	1	<0.001	7.36	5.07	10.67
Prostate	0.02	0.26	0.01	1	0.93	0.98	0.59	1.62
Upper GI	2.55	0.19	175.72	1	<0.001	12.83	8.80	18.72
Head & Neck	0.86	0.23	13.53	1	<0.001	2.36	1.49	3.74
Kidney	1.62	0.23	49.00	1	<0.001	5.03	3.19	7.89
Brain	2.85	0.21	182.02	1	<0.001	17.29	11.43	26.17
Endometrial	1.44	0.29	24.03	1	<0.001	4.21	2.37	7.48
Colon	1.33	0.26	27.24	1	<0.001	3.79	2.29	6.26
Malignant melanoma	1.48	0.29	27.08	1	<0.001	4.41	2.52	7.71
Other	1.74	0.19	81.56	1	<0.001	5.69	3.90	8.30
Metastatic disease								
Yes	0.80	0.07	119.49		<0.001	2.23	1.930	2.57
No								
Weight change, %								
≥10% WL			36.80	8	<0.001			
5.01-9.9% WL	0.61	0.22	7.93	1	0.01	0.55	0.36	0.83
2.5-5.0 % WL	0.59	0.20	8.59	1	<0.001	0.55	0.37	0.82
0.1-2.4% WL	0.87	0.19	19.70	1	<0.001	0.42	0.28	0.61
Stable	0.91	0.32	8.12	1	<0.001	0.40	0.21	0.75
0.1-2.4% WG	0.93	0.20	21.27	1	<0.001	0.39	0.27	0.59
2.5-5.0 % WG	0.78	0.22	12.54	1	<0.001	0.46	0.29	0.71
5.01-9.9% WG	0.59	0.29	4.21	1	0.04	0.56	0.32	0.97
≥10% WG	0.19	0.37	0.26	1	0.61	0.83	0.40	1.70
BMI								
Underweight (< 18.5)			23.57	3	<0.001			
Normal (18.5-24.9)	0.31	0.16	3.80	1	0.05	0.73	0.54	1.00
Overweight (25-29.9)	0.59	0.16	13.29	1	<0.001	0.55	0.40	0.76
Obese (≥ 30)	0.55	0.17	11.17	1	<0.001	0.58	0.42	0.79
Age								
< 65								
≥ 65	0.44	0.07	43.24	1	<0.001	1.55	1.36	1.77

Reference categories: male, breast, metastatic disease, underweight body mass index, age < 65 years

Table 2.4 Predictive value (survival) of categorical variables in a multivariable model (final visit)

Variable	B	SE	Wald	df	*p*	HR	95% CI for HR	
							Lower	Upper
Gender								
Male								
Female	0.05	0.07	0.46	1	0.49	1.05	0.91	1.21
Primary Site								
Breast			445.18	10	<0.001			
Lung	2.17	0.20	113.88	1	<0.001	8.71	5.86	12.97
Prostate	0.02	0.27	0.01	1	0.93	0.98	0.58	1.65
Upper GI	2.52	0.21	143.93	1	<0.001	12.36	8.19	18.64
Head & Neck	0.94	0.25	13.78	1	<0.001	2.55	1.56	4.18
Kidney	1.75	0.25	49.64	1	<0.001	5.77	3.54	9.39
Brain	3.11	0.23	183.05	1	<0.001	22.49	14.33	35.31
Endometrial	1.52	0.30	25.24	1	<0.001	4.56	2.52	8.25
Colon	1.50	0.27	30.86	1	<0.001	4.50	2.65	7.65
Malignant melanoma	1.59	0.29	28.47	1	<0.001	4.91	2.74	8.81
Other	1.83	0.21	76.25	1	<0.001	6.20	4.12	9.34
Metastatic disease								
Yes	0.73	0.08	86.66	1	<0.001	2.07	1.78	2.41
No								
Biological therapy								
Yes								
No	0.01	0.09	0.01	1	0.92	1.01	0.85	1.21
Radiotherapy								
Yes								
No	0.31	0.07	17.69	1	<0.001	0.73	0.64	0.85
Monoclonal therapy								
Yes								
No	0.15	0.13	1.49	1	0.22	0.86	0.67	1.09
Chemotherapy								
Yes								
No	0.05	0.08	0.35	1	0.55	0.96	0.82	1.11
Hormonal therapy								
Yes								
No	0.24	0.10	5.41	1	0.02	1.27	1.04	1.56

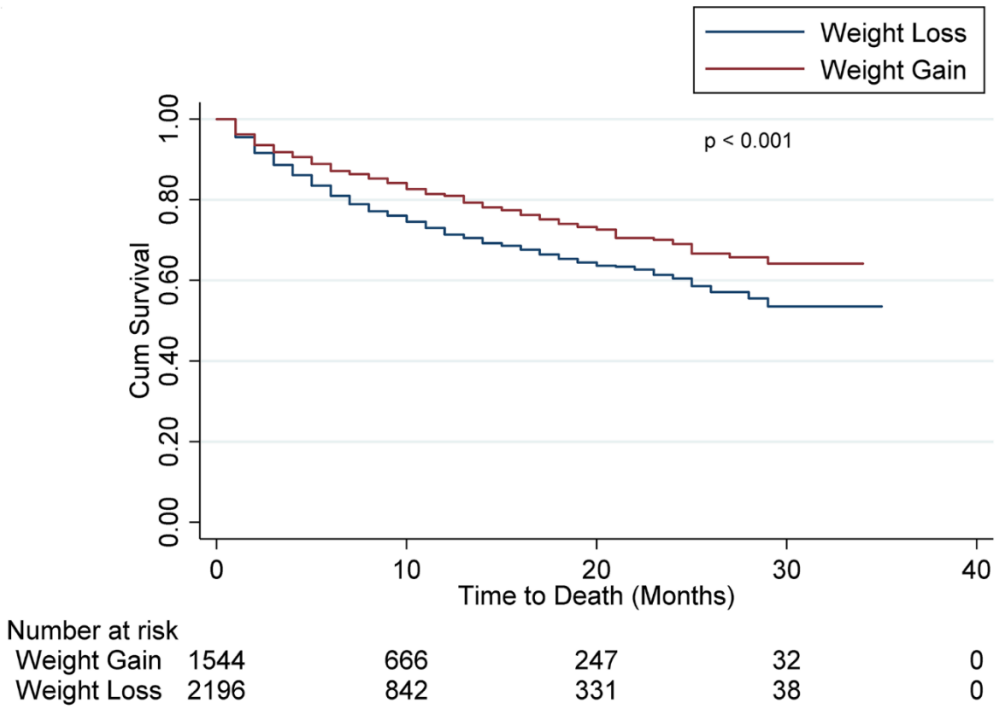
Reference categories: male, breast, metastatic disease, biological therapy, radiotherapy, chemotherapy, hormonal therapy, weight change ≥ 10% WL, underweight body mass index, age < 65 years

Table 2.4 Predictive value (survival) of categorical variables in a multivariable model (final visit) (continued)

Variable	B	SE	Wald	df	*p*	HR	95% CI for HR	
							Lower	Upper
Weight change, %								
≥10% WL			62.89	8	<0.001			
5.01-9.9% WL	0.14	0.09	2.24	1	0.14	1.15	0.96	1.38
2.5-5.0 % WL	0.19	0.12	2.63	1	0.11	0.83	0.66	1.04
0.1-2.4% WL	0.17	0.12	1.93	1	0.17	0.85	0.67	1.07
Stable	0.38	0.51	0.56	1	0.46	1.47	0.54	3.99
0.1-2.4% WG	0.22	0.12	3.03	1	0.08	0.81	0.63	1.03
2.5-5.0 % WG	0.45	0.15	9.42	1	<0.001	0.64	0.48	0.85
5.01-9.9% WG	0.75	0.16	21.82	1	<0.001	0.47	0.35	0.65
≥10% WG	0.91	0.18	25.17	1	<0.001	0.40	0.28	0.57
BMI								
Underweight (< 18.5)			29.76	3	<0.001			
Normal (18.5-24.9)	0.24	0.12	3.84	1	0.05	0.79	0.62	1.00
Overweight (25-29.9)	0.54	0.13	16.93	1	<0.001	0.58	0.45	0.75
Obese (≥ 30)	0.58	0.14	17.77	1	<0.001	0.56	0.42	0.73
Age								
< 65								
≥ 65	0.27	0.07	15.46	1	<0.001	1.30	1.14	1.49

Reference categories: male, breast, metastatic disease, biological therapy, radiotherapy, chemotherapy, hormonal therapy, weight change ≥ 10% WL, underweight BMI, age < 65 years

(a)



(b)

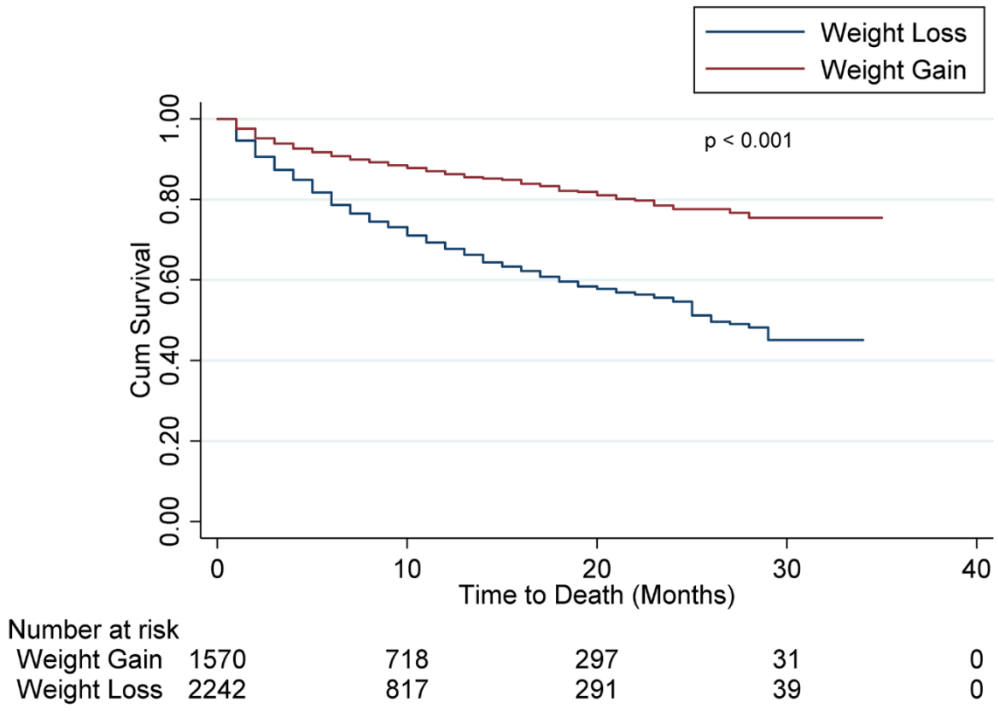
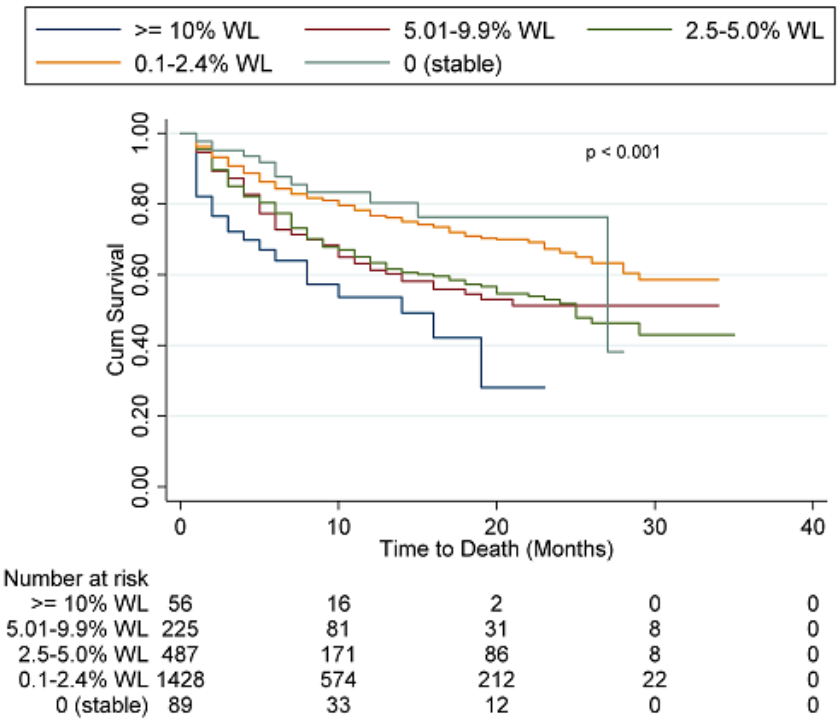


Figure 2.1 Kaplan-Meier plot of overall survival by weight change category at (a) diagnosis (T_1) and (b) final visit (T_2)

(a)



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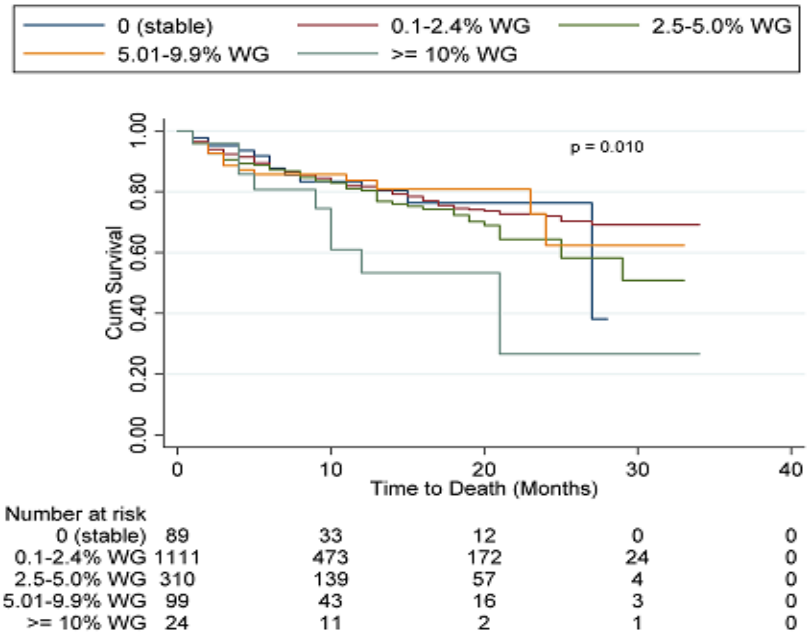

Figure 2.2 Kaplan-Meier plot of overall survival by (a) percentage weight loss category and (b) percentage weight gain category at diagnosis (T_1)

Table 2.5 presents survival data based on the cancer-associated weight loss grading system categories described by Martin et al (25). The results from the current study did not align fully with the weight loss grading system, however there was a trend towards poorer survival in patients with weight loss ≥ 15% and a trend towards better survival with smaller degrees of weight loss i.e. <2.5.

Table 2.5 Survival (months) based on weight loss grading system

		≥28	**25-27.9**	**22-24.9**	**20-21.9**	**< 20**
		Survival (months)	**Survival (months)**	**Survival (months)**	**Survival (months)**	**Survival (months)**
% Weight Loss	**<2.5**	34	33	29	25	18
	2.5-5.9	35	18	19	15	11
	6-10.9	15	27	15	7	7
	11-14.9	23	18	4	16	20
	≥ 15	2	2	2	No Cases	16

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4

By combining weight loss and BMI, a weight loss grade score of 0-4 was given.

2.5 Discussion

Weight change at T_1 was highly prevalent. Weight loss was nearly universally undiagnosed or under-documented, despite an option to record 'Abnormal Weight Loss' in the electronic medical record. Those who had weight loss at T_1 continued to have further weight loss by T_2, but most were still overweight or obese. More than two thirds of adults in the United States are overweight or obese (34) and both are increasingly seen in the cancer population (21, 35), a trend also evident in this study. When weight change was considered in isolation, those who had weight gain were more likely to have longer

survival compared to weight loss with one exception: ≥10% weight gain at T_1. The majority of these patients were overweight or obese. BMI provides a measure of adiposity in adults, but it is unable to detect differences or changes in body composition. Excess visceral adiposity is an established risk factor for many cancers and sarcopenia, which may co-exist with obesity, can have a negative impact on survival. Given that primary cancer site and metastatic disease were not significantly associated with this group, underlying changes in body composition, which were not recorded in this data set, may have been a contributing factor.

Head & neck and upper GI cancers were most likely to be associated with any weight loss. Nutritional deficits are common with these tumours: their location can cause dysphagia and metabolic changes which may alter appetite and chemosensation. In this study, those with head & neck and upper GI cancers were also more likely to be cachectic at both T_1 and T_2. Cachexia is associated with increased treatment toxicity, reduced quality of life and poorer survival. However, as weight history is not routinely assessed at diagnosis, it is likely that this would go undetected before treatment particularly in those with a high BMI. Given that treatment modality can further impact weight change, this again emphasises the critical need for early recognition of those most at risk to ensure delivery of appropriate supportive care and ongoing surveillance.

This study supports previous evidence of weight loss as a predictor of survival (5, 11). It also highlights the role weight gain (which may mask sarcopenia) plays in sub-optimal identification of undernourished patients which may impair their survival. Weight gain and loss have both been linked with disease progression. In this study, those with metastatic disease were less likely to have weight gain at T_1 and significantly more likely

to be cachectic at T_1 and T_2 than those with loco-regional disease. Although there was minimal change in the number who were overweight or obese from T_1 to T_2, those who were cachectic almost doubled. Cancer treatment and disease progression may both account for this. It seems weight loss alone is an insufficient marker based on the proposed cancer-associated weight loss grading system (25). Median survival in this population deviated from that expected based on the cancer-associated weight loss grading system described by Martin et al. Low patient numbers, less advanced disease and a broader range of primary cancer sites compared to those included by Martin et al may have been contributory factors. Validation in various populations is likely needed to improve applicability of this grading system for different primary sites, cancer stage and possibly ethnicities.

Clinicians may be lured into a false sense of security in those with lesser degrees of weight loss or weight gain. This study shows that any weight loss at diagnosis (including those traditionally considered weight stable i.e. ±2.5%) are at high risk of further weight loss. ESPEN Guidelines (36) recommend identification of 'nutritional disturbances' through regular evaluation of weight change and BMI beginning at cancer diagnosis. Although the clinician's instinct may be to prioritise those with weight loss, based on our results weight gain also warrants attention.

Perhaps in reality it is the early identification of any weight change which is important for identification of those most at risk. The optimal time is at diagnosis if the opportunity to intervene with timely, targeted interventions is to be taken. Given the negative relationship between survival and ≥ 10% weight gain observed (Figure 2b), perhaps a spectrum of cancer-associated weight change should be established with stages of weight

gain (i.e. pre-obese, obese, refractory obesity) similar to the proposed weight loss spectrum (12). The diagnostic criteria for cachexia (12) provided an initial framework and expanded beyond simple weight loss with the inclusion of muscle mass measurement. More recent research has built on this with the proposed cancer-associated weight loss grading system (36). Further insight may be gained through refinement of this concept to incorporate various stages of disease and the inclusion of other factors like inflammatory markers. Age and gender may also require further examination.

This study had several strengths. The data were representative of the most common primary cancer sites. It focused on the significance of weight change at diagnosis. This is important given the increased risk of additional weight loss for those who had already weight loss at diagnosis, further increasing the risk of cachexia. Also, uniquely, it included a true weight stable i.e. no weight gain or loss.

There were also limitations to this study. Small patient numbers in some weight loss categories make it difficult to draw any definitive conclusions. Electronic medical records are designed to support clinical and/or billing systems and so may lead to unexpected challenges when they are used for research purposes. The extent and accuracy to which the electronic medical record is completed will inevitably affect output. In this study, patients who did not have a pre-diagnosis weight recorded in the electronic medical record were excluded, potentially introducing selection bias. Performance status and tumour stage are recognised prognostic factors (1, 5, 32). Weight change may be disproportionately associated with poorer performance status and more advanced disease stage. Refractory cachexia is associated with a low performance status score, which negatively impacts response to systemic treatment and survival (5), while tumour stage

frequently dictates treatment options. Neither performance status nor disease stage were available in this dataset. Inclusion of these variables could have enabled greater stratification at diagnosis of those most at risk of weight change. Similarly, body composition was not measured or reported. The generalisability of the results is also limited by this.

To help identify those most at risk, greater emphasis should be placed on the evaluation of more individualised outcomes by diagnosis and disease stage. This will support the recognition of cancer-associated weight change early in the disease trajectory and allow the effectiveness of targeted treatments to be determined. Future studies should include comprehensive information not just on weight change but also performance status, stage of disease and body composition.

2.6 Conclusions

Many newly diagnosed patients with solid tumours had evidence of clinically significant, yet frequently undiagnosed, weight changes. Worst survival was seen with ≥ 10% weight gain or ≥ 10% weight loss. Survival analysis based on weight change alone showed that those who had weight gain at diagnosis or later had a better overall survival compared to weight loss. Any weight loss at diagnosis increased the chance of further weight loss with the additional risk of treatment toxicities and worse survival. Consideration should be given to the use of a weight change spectrum, which would reflect risk associated with various weight loss and weight gain bands. A detailed weight history at diagnosis and at each subsequent visit for every cancer patient is essential to promptly identify and intervene for those most at risk. Such research would be enhanced by in-depth analysis

of the interplay between disease stage, performance status, body composition, and inflammatory markers.

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Chapter 3

Nutritional Status in Cancer:

Perspectives of Irish Healthcare Professionals

3.1 Introduction

Good nutrition is fundamental for optimal health. Deficiency and excess in dietary intake can increase susceptibility to or exacerbate chronic illness. Nutritional symptoms are common in cancer patients (1) and may occur as a result of the disease itself or the treatments given (2). Symptoms such as nausea and vomiting, anorexia, mucositis, diarrhoea and constipation can result in inadequate food intake and/or absorption and may lead to cancer-related malnutrition. Although there is some variation in terminology, the terms cancer-related malnutrition and cancer cachexia are often used interchangeably (3). Both are characterised by systemic inflammation (2) and metabolic derangement leading to reduced food intake, muscle mass loss and subsequent loss of function. While cancer-related malnutrition is a more encompassing term, cancer cachexia has been defined by an international consensus of experts as a "multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass with or without loss of fat mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (4). Irrespective of the terminology this condition can further compromise cancer patients, leading to increased morbidity and mortality, reduced response to treatments, greater treatment toxicity and poorer quality of life (2, 4, 5).

Cancer-related malnutrition is common (6), yet it often goes under-recognised and under- treated (7, 8). It has an estimated prevalence of 15 – 80% (5, 9) and is the cause of up to 20% of cancer-related deaths (8, 10). Primary tumour site, cancer stage and anti-cancer treatment contribute to the broad prevalence range. Gastrointestinal, head and neck, liver and lung cancer, advanced disease and previous/current chemotherapy or radiotherapy are all associated with higher prevalence of malnutrition (11-14).

Unfortunately rates of cancer-related malnutrition have changed little since the publication of DeWys' seminal paper nearly four decades ago (14). However, what has changed dramatically is the phenotype of the cancer patient; the wasted appearance previously synonymous with malignancy has been replaced by overweight and obesity, even in those with advanced disease, and this can mask weight loss or muscle wasting.

Research has shown that more than 25% of patients admitted to Irish hospitals are malnourished (15) and between 63% and 84% are at risk of malnutrition (16). A large international study (n=1453) which screened oncology outpatients for nutritional risk reported that 32% were at risk (17). More recently another study (n=1952) found that 43% were at nutritional risk and 9% were overtly malnourished at initial medical oncology appointment (12). Recognition and effective management of those at risk is essential if the associated deleterious consequences are to be avoided. The Department of Health and Children in Ireland has issued guidelines on the prevention of malnutrition in acute hospitals to increase awareness of the problem and to highlight the importance of nutritional assessment (16). Nutritional risk screening is recommended within 24 hours of hospital admission (16). More specifically, the European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines on nutrition in cancer recommended early detection of nutritional problems through screening, with an abnormal screening result leading to nutritional assessment (3). However, neither screening nor assessment are routine in oncology outpatients. In the UK, a survey of specialist oncology trainees found that 80% expressed uncertainty or a lack of confidence in their ability to identify malnutrition (18). A number of tools are available to identify those at nutritional risk, however there is no consensus or gold standard. Common tools used to screen for malnutrition in oncology patients include the

Malnutrition Universal Screening Tool (MUST), the Malnutrition Screening Tool (MST), abridged Patient Generated Subjective Global Assessment (aPG-SGA) and the mini-nutritional assessment (MNA). MUST is recommended by ESPEN (3) and it combines body mass index (BMI), unintentional weight loss and effect of acute illness to give an overall malnutrition risk score. MST, also recommended by ESPEN (3), includes questions on unintentional weight loss and appetite and it is validated in oncology patients receiving radiotherapy (19). Completed by the patient, the aPG-SGA focuses on weight history, recent dietary intake, nutritional impact symptoms and functional status. It has been validated in chemotherapy outpatients (20) and is useful for the early detection and characterisation of cachexia (21). In addition to questions on dietary intake, weight loss, mobility, BMI and acute disease, the MNA includes a question on neuropsychological issues. The lack of consensus on which tool is best for use in the cancer population makes it difficult for healthcare professionals, who may have limited or no formal nutritional education, to identify those most at risk. Additional challenges for clinicians in the identification of malnutrition include the lack of agreement on the amount of weight loss considered clinically significant, third spacing of fluid in body cavities and limbs which can result in weight gain rather than weight loss even at presentation of some cancers such as ovary and the high and increasing rate of overweight and obesity in the population (8, 22).

Greater clarity about professional knowledge and practice may help us to understand the reasons why those most at risk continue to fall under the radar until an advanced, often irreversible, stage is reached. Identifying and addressing deficits in professional knowledge and expertise may improve early recognition and support the development of effective treatments. This study aimed to determine the importance placed on

nutrition following a cancer diagnosis by healthcare professionals and to establish their familiarity with nutritional screening and assessment tools and national and local nutritional care policies.

3.2 Aims

The aims of this study are:

- To investigate education received by oncology healthcare professionals in the areas of nutrition in cancer;

- To determine the level of importance placed on the role of the oncology dietitian and nutrition following a cancer diagnosis by Irish oncology healthcare professionals;

- To establish familiarity amongst oncology healthcare professionals with:

    (i) nutritional screening and assessment tools;

    (ii) national and local nutritional care policies;

- To explore awareness and current knowledge of cancer cachexia among Irish healthcare professionals and how this may influence their practice;

- To establish perceived barriers to providing optimal nutritional care to cancer patients;

3.3 Methods

3.3.1 Ethical Approval

Ethical approval was granted by Trinity College School of Medicine Research Ethics Committee (Appendix IV).

3.3.2 Study Design

A 32-item, semi-structured questionnaire was designed to capture the importance placed on nutrition by oncology healthcare professionals throughout the cancer continuum and to examine their knowledge of nutritional screening and assessment, and local and national polices that inform nutritional care (Appendix V). A mixed-methods approach integrating quantitative and qualitative methods was used.

3.3.3 Study Participants

Target participants included Oncology Dietitians, Oncology Nurse Specialists, Consultants and Specialist Registrars (SpRs) in Haematology, Medical Oncology, Palliative Medicine, Radiation Oncology and Surgical Oncology. As there is no sub-specialty of surgical oncology, it was not possible to provide a definitive sample size. A conservative estimated sample size of n=364 was made.

3.3.4 Data Collection and Handling

Questionnaires were created and managed with Survey Monkey (SurveyMonkey.com, LLC, San Mateo, CA, USA), an online survey design and distribution tool. Potential participants were invited to complete an anonymous online questionnaire, which was delivered as a hyperlink embedded in an email. Completion of the questionnaire was regarded as consent to participate. The questionnaire was piloted with a sample

population of healthcare professionals (n=9) in order to identify any operational issues with delivery and completion of the online format and to ensure comprehensiveness of the questions. Minor changes were made to the survey following the pilot, largely in order to improve fluidity and overall succinctness of the questions. No major structural changes were recommended. Those who participated in the pilot were excluded from the study sample. The study itself was conducted from February to August 2017. Distribution was facilitated by specialist training bodies, Cancer Trials Ireland and medical, surgical, dietetic and nursing bodies.

The questionnaire had a maximum of 32 questions, with logic incorporated into the design which allowed for 'skip' options as appropriate. Demographic and professional information such as years in chosen speciality, training and/or continuing professional development (CPD) in nutrition in cancer, familiarity with national guidelines on nutritional care and local nutritional screening and assessment policies were included in the questionnaire. A clinical scenario, which required respondents to determine the level of malnutrition risk, was also included. This scenario provided information usually collected by MUST. MUST is the most commonly used nutritional screening tool in the UK and is used to identify adults who are malnourished, at risk of malnutrition or obese. Participants were asked about their familiarity with the consensus definition for cancer cachexia as outlined by Fearon et al (4).

3.3.5 Statistical Analysis

Analyses were completed using Microsoft Excel (Microsoft Office Professional Plus 2013, Microsoft Corporation, Redmond, WA, USA) and IBM SPSS Statistics for Windows Version 23 (SPSS, Chicago, IL, USA). Descriptive statistics were used to

calculate response frequency and to describe population characteristics. Chi squared and Fisher's exact test were used to determine associations. Results were considered statistically significant at the $p < 0.05$ level.

3.4 Results

A total of 124 valid responses were received. Participant characteristics are presented in Table 3.1. Participants were 40 (32%) physicians, 36 (29%) dietitians, 20 (16%) surgeons, 22 (18%) oncology nurses/advanced nurse practitioners and 6 (5%) other.

Eighty-eight (70.9%) respondents were not dietitians; 65 (74%) of these reported no nutritional education during their formal training (Table 3.2). Sixty-two (71%) of the non-dietitians thought it would be helpful. Twenty of the 23 (91.3%) who had received formal education in nutrition reported that they felt confident they could give nutritional advice compared to 61 of 65 (93.8%) respondents who had not received any formal nutritional education ($p < 0.05$). Fifty (40%) respondents had undertaken postgraduate and/or CPD training relating to nutrition in cancer within the previous 12 months. Training was optional for 46 (92%) of these. Those who had not undertaken CPD thought it would be helpful in their current role.

Table 3.1 Characteristics of participants (n=124)

Characteristic	N	%
Profession		
Medical doctor	40	32
Dietitian	36	29
Surgeon	20	16
Oncology nurse/advanced nurse practitioner	22	18
Other[1]	6	5
Speciality[2]		
Medical oncology	55	44
Surgical oncology	39	32
Haematology	38	31
Palliative medicine	35	28
Radiation oncology	23	19
Highest healthcare qualification		
Bachelor degree	37	30
Postgraduate diploma	33	27
Masters degree	31	25
Doctorate	19	15
Other[3]	4	3
Years since qualification		
< 5	10	8
5-10	32	26
11-15	36	29
16-20	21	17
>20	25	20
Workplace[2]		
Public hospital	97	
Hospice	13	
Private hospital	12	
Community	2	

[1] Radiation Therapist (4); Prostate co-ordinator (1); Pharmacist (1)
[2] More than one possible
[3] Specialist Fellowship; Postgraduate Specialist Training

Table 3.2 Have you had any formal education in nutrition as part of your qualification?

Nutrition education	N	%
Undergraduate education in nutrition (n=88; excluding dietitians)	23	26
Postgraduate education in nutrition in cancer in previous 12 months (n=124; all respondents)	50	40

Presented with a case study of a patient at high risk of malnutrition based on the MUST tool criteria, 62 of 109 (56.9%) respondents correctly identified the patient's high risk category. Table 3.3 shows the risk assignment by professional group. Correct assignment ranged from 20-77%. The nutritional risk category was underestimated by 47 (43.1%) respondents, including more than half of oncology nurses and half of dietitian respondents.

When asked to define cachexia in free text, 28 (22%) provided the consensus definition. Seventy-four (60%) included muscle wasting/loss, some in combination with terms such as reduced appetite (n=4; 3.2%), anorexia (n=1; 0.8%), increased catabolism (n=1; 0.8%) and no response to nutrition (n=1; 0.8%). 31% (n=39) defined cachexia simply as weight loss or malnutrition or a combination of the two. Figure 3.1 show familiarity with the consensus definition (4). Twenty-two (18%), predominantly dietitians (n=18), were very familiar with it.

Table 3.3. Nutritional risk as perceived by healthcare professional category (n=109)

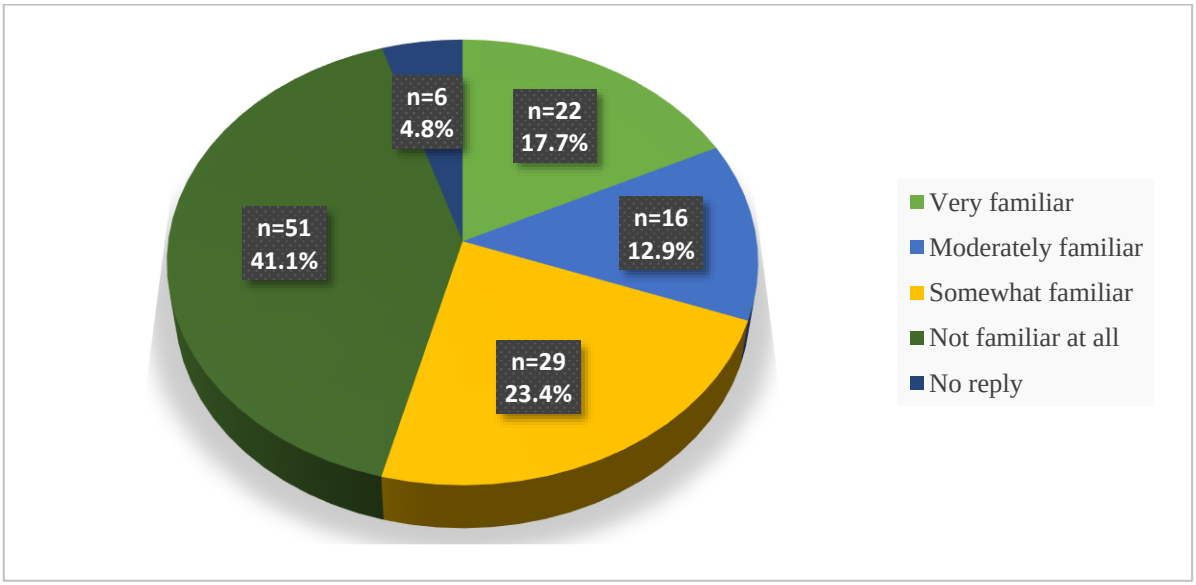
Case study details:

65 year old male with colorectal cancer admitted for surgical resection. Current weight 55kg, BMI 18kg/m^2, no reported weight loss or recent change in appetite and intake.

Correct answer: patient at high nutritional risk based on MUST criteria

Response by healthcare professional category	Low	Medium	High
	N (%)		
Dietitian (n=30)	1 (3.3%)	14 (46.6%)	15 (50%)
Physician (n=37)	2 (5.4%)	11 (29.7%)	24 (64.8%)
Oncology Liaison Nurse (n=20)	2 (10%)	9 (45%)	9 (45%)
Surgeon (n=17)	1 (6%)	3 (18%)	13 (77%)
Other (n=5)	0	4 (80%)	1 (20%)
All respondents (n=109)	6 (5.5%)	41 (37.6%)	62 (56.9%)

Figure 3.1 Respondents' familiarity with consensus definition (n=124)



Fifty-five (44%) of 124 respondents reported that a dietitian attended the multi-disciplinary team meeting. One hundred and eleven (89.5%) respondents reported that patients in their care had some access to a dietitian. Full-time and part-time access varied according to clinical setting (inpatient or outpatient). Full-time access to a dietitian in outpatient and inpatient settings was available to 65 of 121 (54%) practitioners but was restricted to inpatient only for 27 (22.3%) respondents. Six (4.8%) respondents reported no patient access to an oncology dietitian; three (2.4%) of these worked in a designated National Cancer Control Programme (NCCP) cancer centre. A further three (2.4%) did not know if a dietitian was available to cancer patients in their workplace.

The 88 non-dietetic respondents reported that they refer their cancer patients to a dietetic colleague for assessment at diagnosis "always" 13 (15%), "often" 34 (39%), "occasionally" 24 (27%), "never" 7 (8%) (Figure 3.2). Ten (11%) did not respond; of

these, 8 (9%) had previously stated that patients had access to a dietitian in their workplace. Figure 3.3 shows when individual healthcare professional groups consider a dietetic referral should be made for patients with cancer. Healthcare professionals favoured involving the dietitian at diagnosis (43.5%). The >5% weight loss option, a criterion for cancer cachexia, was selected by a fifth of respondents.

In relation to national guidelines and local policies, 16 (13%) respondents stated that the Department of Health and Children Guidelines for Preventing Under-nutrition in Acute Hospitals were always implemented in their workplace; 59 (49%) were either unfamiliar with or did not know if these guidelines were used. Sixty-eight (55%) reported that a local nutritional screening policy was in place; 55 (62%) reported that a screening tool was in use. Nutritional screening took place at diagnosis (15%; n=19), on admission to hospital (25%; n=31), while on treatment (11%; n=14), if weight loss occurred (10%; n=12), on patient request (2%; n=3), on completion of treatment (2%; n=2) and (6%; n=2) did not know. Participants were allowed to provide more than one response to this question. Screening tools used were MUST (44%; n=24), MST (29%; n=16), aPG-SGA (6%; n=3) and other/unspecified (16%; n=9). Three did not respond. The screening tool was most frequently completed by the inpatient Cancer Nurse Specialist (34%; n=25), followed by the dietitian (30%; n=22).

The respondents identified the following items as barriers to providing optimal nutrition to cancer patients: lack of dietetic services (64%; n=79), time constraints limiting ability to perform screening (54%; n=67), inadequate training in recognising cachexia risk (50%; n=62), lack of guidelines (48%; n=60), inadequate training in screening tool

(39%; n=49), difficulty identifying those at nutritional risk (37%; n=46) and other (6%; n=8).

Figure 3.2 Do you routinely refer cancer patients to a dietetic colleague for assessment at diagnosis? (n=88; non-dietitian respondents only)

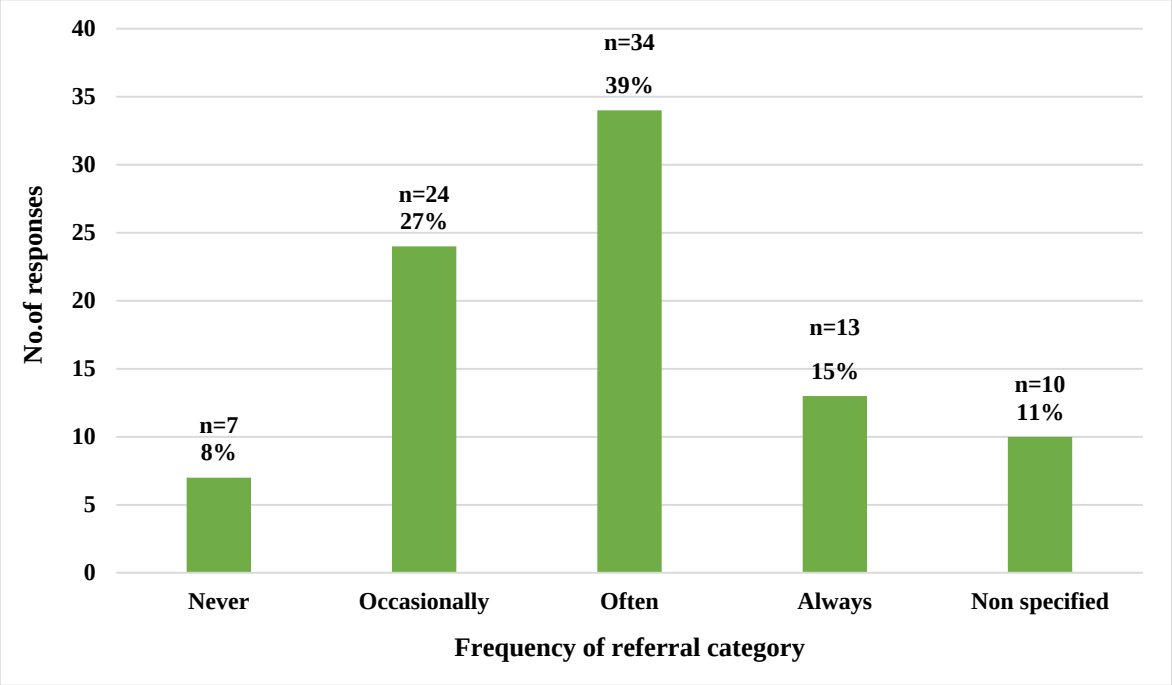
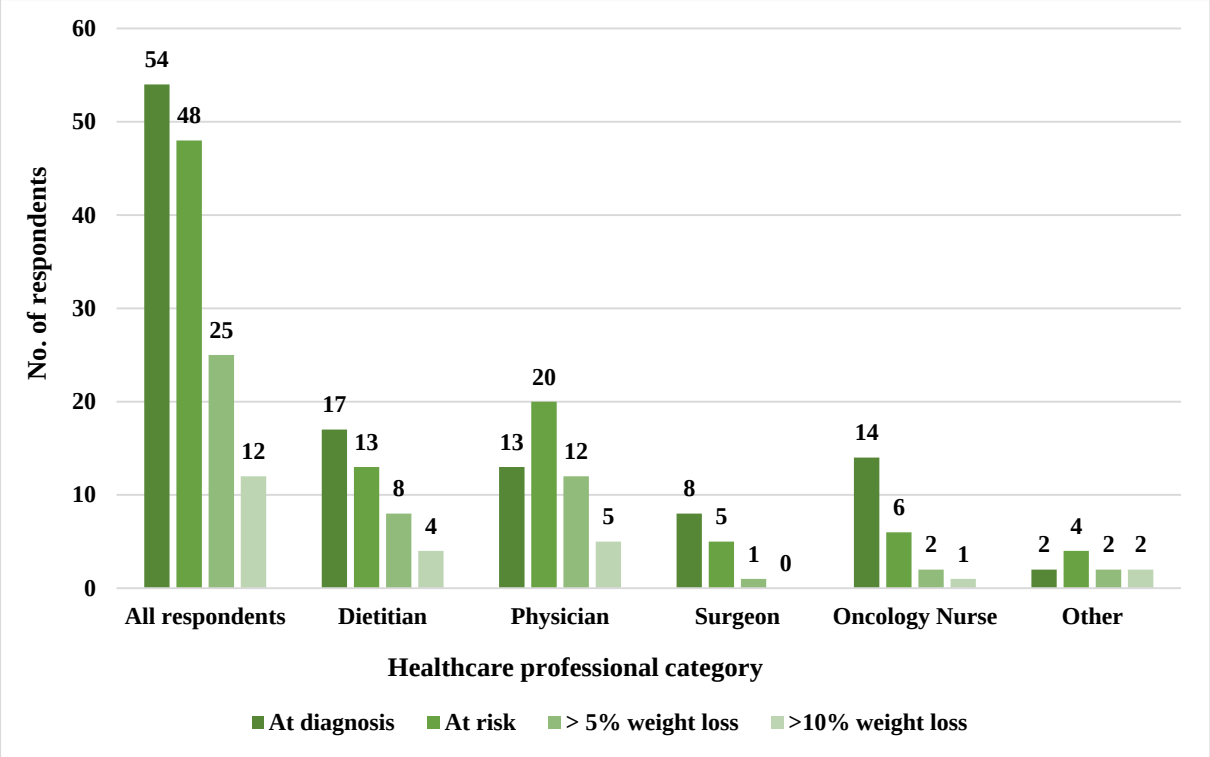


Figure 3.3 In your opinion, when should the dietitian be part of the treatment plan for patients with cancer? (n=124; more than one response allowed)



Response by healthcare professional category	Diagnosis	At Risk	5% Weight Loss	10% Weight Loss
	N (%)			
All respondents	54 (43.5%)	48 (38.6%)	25 (20.2)	12 (9.6%)
Dietitian	17 (13.7%)	13 (10.5%)	8 (6.5%)	4 (3.2%)
Physician	13 (10.5%)	20 (16.1%)	12 (9.7%)	5 (4.0%)
Surgeon	8 (6.5%)	5 (4.0%)	1 (0.8%)	0
Oncology Nurse	14 (11.3%)	6 (4.8%)	2 (1.6%)	1 (0.8%)
Other	2 (1.6%)	4 (3.2%)	2 (1.6%)	2 (1.6%)

3.5 Discussion

Survey responses have been on the decline for the past decade in the field of health-related research (23) and notably doctors are a group with low survey response rate (23). Previous studies have demonstrated that when a topic is of high interest, potential respondents are more likely to reply to the survey. Despite considerable evidence of the high prevalence of cancer-related malnutrition (20, 24, 25) and its associated morbidity and mortality, nutrition following a cancer diagnosis may not as yet be considered a high priority by all oncology healthcare professionals. However, it is important to seek input from healthcare professionals to determine knowledge base and familiarity with current policies. This will inform updates to both current and new policies. Surveys are a means to gather such information but also raise awareness. This survey yielded 124 valid responses from a country with a population of 4.8 million and over 33,000 new cancer cases/year (26).

In this survey, three quarters of non-dietitian respondents reported no formal education in nutrition. Doctors are perceived as a trusted source of knowledge and there is an expectation for them to provide guidance on nutrition and a level of nutritional care in chronic illnesses (27). This is reasonable given that a healthy lifestyle is generally associated with reduced morbidity and mortality. However, there is a deficiency in nutritional education in undergraduate medical education. Although minor differences between medical schools may exist, the teaching of human nutrition is largely absent from undergraduate medical curricula. Standards for medical education in the Republic of Ireland are set by the Irish Medical Council. A recent review of the undergraduate medical curriculum in six countries (Australia, Canada, Ireland, New Zealand, UK,

USA) revealed that Ireland was the only country in which no specific nutrition guidelines were identified (27).

Forty percent of non-dietetic respondents had undertaken postgraduate education of their own volition in the majority. This suggests that healthcare professionals acknowledge the deficiency in nutritional education in their formal programmes. There is a need and growing desire across medical and surgical disciplines to have access to education in nutrition. Nutrition education can never replace the specialist oncology dietitian, but for other oncology healthcare professionals there should at the very least be an appreciation of the importance of optimal nutrition at all stages in the cancer journey.

The role of the oncology dietitian cannot be underestimated. Not only do they assess and actively manage patients with nutritional symptoms, they are involved in the development of policy and guidelines for the management of malnutrition and the education of other healthcare professionals. Optimising patient care is a core tenet of the multi-disciplinary team. It is a useful platform for cross-disciplinary education and should be expanded to incorporate allied health professionals. Less than half of respondents reported that a dietitian attended the multi-disciplinary team meeting. Non-attendance at the multi-disciplinary team meeting may be due to scarcity of numbers. With only 33 whole time equivalent dietitians, this means there is only one dietitian to approximately 4,500 patients with cancer in Ireland (28). It is reassuring that most healthcare professionals recognised the importance of referral at time of diagnosis. With the exception of physicians, who mostly thought referral should be made when the patient was considered at nutritional risk, the majority within each discipline considered

diagnosis to be the most appropriate time for referral. Yet only a small proportion reported “always” referring to a dietetic colleague. Early dietitian involvement ensures that nutrition is optimised from cancer diagnosis and throughout the cancer continuum.

This survey revealed that less than two-thirds of respondents had access to nutritional screening despite international best practice guidelines (3). The most commonly applied screening tool was MUST, a simple tool which derives a malnutrition risk score from a combination of BMI, unintentional weight loss and effect of acute illness on oral intake for > 5 days. Although it is validated in a range of healthcare settings (29) and recommended by ESPEN, it may not be the most appropriate means to identify those most at risk. Body composition abnormalities such as sarcopenia are not considered within the framework of this or a number of other screening tools. A recent study demonstrated that MUST, MST and the Nutritional Risk Index (NRI) tool were neither sensitive nor specific in detecting sarcopenia in chemotherapy patients which resulted in the misclassification of many nutritionally vulnerable cancer patients (30). A recent study by Lorton et al reported errors arising from incorrect calculations using this tool (31).

The National Institute for Health and Clinical Excellence (NICE) recommends that screening for malnutrition and risk of malnutrition should be carried out by a suitably trained healthcare professional for all hospital outpatients at their first clinic appointment and all hospital inpatients (32). Body mass index, percentage unintentional weight loss and nutrient intake should be assessed with screening. ESPEN recommends that these factors be evaluated first at cancer diagnosis and then repeated as per clinical need (3).

Identification of nutritional risk through screening should prompt a full nutritional assessment. This would enable the oncology dietitian to determine the level of intervention required on a patient by patient basis. Referral when a patient is considered at nutritional risk may pose a challenge given that 43% were unable to recognise high nutritional risk in the clinical scenario presented. Overweight and obesity, which is increasingly common in the cancer population, may further compound this. Poor nutritional status can impact tolerance to cancer treatment, quality of life and overall survival (2). The greater the amount of weight loss, the greater the challenge to reverse it. Previous research has shown that any weight loss prior to diagnosis puts a patient at greater risk of further weight loss (33). This implies an inevitability (almost) to weight loss and ties in with the concept of cancer cachexia as a progressive condition (4). It further highlights the importance of a detailed weight history at diagnosis, part of the oncology dietitian's remit, and at each subsequent visit for every cancer patient in order to identify and treat those most at risk in a timely manner.

Spiro et al (18) reported that lack of healthcare professional knowledge was the principal barrier between the at-risk patient and optimal nutrition. Our healthcare professionals reported lack of dietetic service, but their response to the case study suggest that the knowledge base of healthcare professionals themselves may be the main barrier. In addition, understanding of cancer cachexia was variable. Poor recognition of patients at risk must be a substantial contributing factor. It is of some concern that in the case study administered nutritional risk category was underestimated by a substantial number of HCPs including half of dietetic respondents. Healthcare professional education programmes need to address this deficiency at undergraduate and postgraduate level.

The study had a number of limitations. The sample size was small and as we have no measure of the eligible population of healthcare professionals, the exact response rate is unknown. Some respondents may have been working within the same institution and this may have spuriously influenced responses to questions on site-specific protocols and practices or access to dietetic support. The self-volunteer basis for survey response inevitably introduces bias, as one would expect those with most interest in the area to respond. We would caution that the true knowledge of nutritional risk associated with cancer may be even worse than reported in this study. To the best of our knowledge, this is the first survey of the views of Irish healthcare professionals working in oncology on nutrition in cancer.

3.6 Conclusions

Healthcare professionals working in oncology have a unique opportunity to screen cancer patients for malnutrition/risk of malnutrition. However, there is an absence of nutritional education at undergraduate level across disciplines. Some healthcare professionals choose to engage in postgraduate education in nutrition and cancer, but more needs to done to enhance understanding across different disciplines. Optimal timing of dietetic referral should be clear; oncology dietitians should be involved in patient management from the time of cancer diagnosis. Limited dietetic resources, time constraints and difficulty identifying cancer-related malnutrition are among the obstacles highlighted in this study. Screening for malnutrition/risk of malnutrition should be mandatory for all cancer patients at first presentation to medical and/or surgical oncology services. Inclusion of nutrition-specific components within the medical and nursing curricula and greater familiarity with the role of the oncology dietitian would lead to improved multi-disciplinary care of the cancer patient.

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Chapter 4

Prevalence of Cachexia in Treatment-naïve Patients with Gynaecological Cancer: A Systematic Review

4.1 Introduction

Cachexia is considered by many to be an inevitable consequence of advanced cancer. Although much of the research to date has concentrated on patients with advanced disease (1-4), cancer cachexia may occur at any stage of disease. The progressive nature of the syndrome has also been acknowledged. This has led to a shift in focus towards the characterisation of early manifestations of cachexia, when greater scope for reversibility and interventions may exist. Various definitions and diagnostic criteria for cachexia have been reported in the literature (2, 5-7). These are outlined in Chapter 1. Although there are variations, each recognises weight loss, mainly due to loss of muscle, as the principal clinical characteristic. Currently the most widely accepted definition is that proposed by expert consensus in 2011 (8).

Gynaecological cancer is a leading cause of premature death and disability worldwide (9). It encompasses a number of distinct malignancies arising from the female reproductive system, namely the cervix, the endometrium, the ovary, the vagina and the vulva. In 2018, an estimated half a million new cases of cervical cancer alone were recorded globally (10). Approximately 85% of women diagnosed with cervical cancer and 88% of women who die from cervical cancer live in low to middle income countries (9). Although most evident amongst women living in these countries, which receive as little as 5% of global spending on cancer (11), disparities also exist within and between high income countries (12). In addition to inequities in gender, geography and socioeconomic status, ethnicity and more recently the surge in migration due to conflict have collectively increased womens' risk of developing certain cancers and has also affected their ability to gain access to optimal treatment.

A measure of prevalence can be useful for many reasons. At a global and national level, it can inform governments and policy makers on the burden and changing trends of particular diseases over time, while locally it is useful for healthcare professionals to better understand diseases and their symptoms. This can in turn help to optimise patient management in terms of stratification and prognostication. In comparison to other cancers, gynaecological cancer has not featured extensively in published cachexia literature. Where research exists, patients with gynaecological cancer are usually represented by a small cohort within a larger mixed tumour study, as demonstrated in Chapter 2, or the focus has been on symptoms which may constitute a component or aspect of cachexia e.g. anorexia, sarcopenia. Prevalence of cachexia in this population is therefore unclear. Chemotherapeutic treatments can cause or exacerbate cachexia, so there is value in the study of treatment-naïve cohorts in order to establish prevalence based on the natural history of cachexia without previously received treatments confounding the results.

4.2 Aim

- To report the prevalence of cachexia, as defined by previously published definitions or diagnostic criteria, in patients with gynaecological cancer prior to treatment;

4.3 Methods

The review protocol was registered in the PROSPERO database (ref: CRD42018104758) (13). Title and abstract screening was through Covidence (14). All subsequent review steps were manual. The preferred reporting items for systematic review and meta-analysis (PRISMA) guided the review (15) and the Joanna Briggs Institute (JBI) Critical Appraisal

Checklist for Studies Reporting Prevalence Data was chosen as the quality appraisal tool (16).

4.3.1 Eligibility Criteria

All published adult population-based studies which presented original data on the prevalence of cachexia in treatment-naive patients with gynaecological cancer or where prevalence could be calculated from available data were considered for inclusion. Gynaecological cancer was defined as cancer of the cervix, endometrium, ovary, vagina or vulva. All previously published definitions or diagnostic criteria for cachexia were accepted, once the definition and/or criteria used were clearly stated or where the author could confirm which definition and/or criteria had been used. For studies involving mixed tumour sites, data on gynaecological cancer patients had to be separately extractable. No date or language restrictions were applied.

Studies where prevalence of cachexia was not reported or if it was unclear when cachexia was diagnosed, and if the authors could not be contacted to clarify these details, were excluded. Studies which only reported prevalence of sarcopenia or malnutrition, or used a tool designed to identify malnutrition or malnutrition risk were excluded. Cancer cachexia is a syndrome comprised of many symptoms, which can include sarcopenia and malnutrition but neither alone automatically confer a diagnosis of cachexia. Animal and paediatric studies were also excluded, as were case reports, editorials, and review articles (including systematic reviews).

4.3.2 Search Strategy

CINAHL, Cochrane Library, EMBASE, MEDLINE Ovid, Scopus and Web of Science were searched from inception up to 26 March 2018. The search strategy was developed

by clinical and library staff (David Mockler) and combined key words and related database-specific subject terms. The MEDLINE Ovid search terms are detailed in Table 4.1. The electronic database search was updated on 3 April 2019.

Additional relevant articles were identified by hand searching a number of key journals namely Journal of Cachexia, Sarcopenia and Muscle, Gynecologic Oncology, International Journal of Gynecological Cancer and European Journal of Gynaecological Oncology from 2011-2018 inclusive. This included the review of published abstracts from any conference proceedings indexed by these journals. The reference lists of included full-text articles were also searched. Search results were exported to EndnoteX8 (17) and then to Covidence (14). De-duplication of search results was conducted using Covidence (14).

Table 4.1 Search terms for cancer cachexia and gynaecological cancer

1. CACHEXIA/ OR (Cachexia OR cachectic OR cancer anorexi*)

2. Genital Neoplasms, Female/ OR (cervi* OR endometr* OR ovar* OR vagina* OR vulva* OR peritoneal OR gyne* OR gynae* OR cervix OR cervical OR female genital OR pelvi* OR uter* OR fallopian*)

3. cancer* OR tumor* OR tumour* OR neoplas* OR carcinoma* OR malignan* OR metasta* OR micrometasta* OR carcinogen* OR adenocarcinoma* OR carcinosarcoma* OR squamous* OR adenosquamous

4.3.3 Title and Abstract Screening and Full Text Review

Both screening (Niamh O'Donoghue and Brenda O'Connor) and full text review steps were independently conducted by two reviewers (Niamh O'Donoghue and Claire Thompson). All titles and abstracts resulting from the search were screened for eligibility for full review using Covidence. Those which did not meet the inclusion criteria were excluded and the remainder went forward for full-text review in order to find relevant studies which met the inclusion criteria.

Full text review was performed manually. Differences in decisions relating to eligibility were discussed until agreement was reached. If agreement could not be reached, a third reviewer adjudicated (Noreen Gleeson). Where full-text articles were identified as potentially eligible for analysis but further information required, the corresponding authors were contacted electronically. In the event the corresponding author did not respond after a three week period, a further email was sent. If after this there was still no acknowledgement of the correspondence, the study was excluded.

4.3.4 Data Extraction and Quality Appraisal

A data extraction form was developed by the lead reviewer (Niamh O'Donoghue). It was independently piloted by two reviewers on a single study and its comprehensiveness discussed. They confirmed no changes were required. Following this, the form was used to extract equivalent information from each full-text article which met the inclusion criteria, again independently performed by two reviewers. Extracted data related to study design, characteristics of the population sampled, outcomes and prevalence estimates.

Quality and risk of bias was assessed using the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data (16). This appraisal tool contains nine criteria to assess the methodological quality of a study and to determine the extent to which it has addressed the likelihood of bias in its design, conduct and analysis. Two reviewers independently appraised the quality of the included studies. Unanimous agreement was required for both data extraction and quality appraisal.

4.3.5 Data Synthesis

A narrative synthesis was performed in order to integrate the findings from the included studies. An initial synthesis which included details of the search and a summary of the included studies was presented in tabulated format. Following this, the results were structured around the following themes: study characteristics, criteria used for cachexia diagnosis and prevalence of cachexia.

4.4 Results

4.4.1 Search Results

The search identified a total of 8832 records. After removing duplicates, the titles and abstracts of 7894 articles were screened. Following this, 7833 were excluded as they did not meet the eligibility criteria. A total of 61 articles had the full-text reviewed for eligibility. Of these, two studies were identified as eligible for inclusion in the review. The results of the search strategy are shown in Figure 4.1.

4.4.2 Study Characteristics

Table 4.1 provides a summary of the study characteristics including year of publication, study design, population characteristics, prevalence of cachexia and outcome. Neither

study was designed with the primary purpose being to estimate prevalence of cachexia in treatment-naïve patients with gynaecological cancer. Aredes et al (18) investigated the influence of chemoradiotherapy on nutritional status, functional capacity, quality of life and toxicity of treatment for patients with cervical cancer. Participants with stage I-III cervical cancer were prospectively recruited in a study conducted in Brazil. Poulsen et al (19) recruited a mixed cohort of patients with a diagnosis of gastric, oesophageal or gynaecological (stage I cervical) cancer to a randomized control trial which investigated the effects of a nutritional intervention in cancer patients. The intervention involved nutritional counselling and patients were offered Forticare, a high-protein (33.8g) oral nutritional supplement containing 2.2g eicosapentaenoic acid (EPA). Nutritional counselling took place at baseline. The oral nutritional supplement was taken daily for 5 to 12 week duration depending on diagnosis and treatment schedule. Follow-up was performed three months after completion of treatment. The study was conducted in Denmark.

4.4.3 Diagnosis and Prevalence of Cachexia

Aredes et al applied the three diagnostic criteria (3) proposed by the international expert consensus as outlined in Chapter 1 (8) and reported a prevalence of 32.4%. Poulsen et al used the criterion of ≥ 5% weight loss prior to treatment and did not diagnose cachexia in any of their cervical cancer study participants.

4.4.4 Quality of Studies

A quality appraisal was performed on the two studies which met the inclusion criteria (Table 4.2). Appraisals were reported using the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data (20). Both studies included women who were

expected to receive treatment for cervical cancer; Aredes et al recruited patients from the pre-cancer treatment group counselling session but excluded those who had certain conditions which may influence nutritional status and/or the bioelectrical impedance measures. Poulsen et al recruited from patients who were referred to the Department of Oncology for palliative or neoadjuvant chemotherapy and/or radiation treatment. Patients were then randomised by the researchers to either a control or intervention group. Both studies used a prospective study design, which is an appropriate choice to determine the effect of an intervention or treatment. One study was a randomised control trial.

The sample size was small in both studies. Although adequate to gather information for the stated purpose of each study i.e. the influence of chemoradiation treatment on patient outcome (Aredes et al) and the effect of a nutritional intervention on patients attending for treatment (Poulsen et al), the small size is less useful in determining prevalence. Aredes et al exclusively enrolled patients with cervical cancer (n=49). Poulsen et al recruited a mixed tumour site population for their trial with seven gynaecological (cervical) patients included; four were randomised to the nutritional intervention arm, three to the control arm.

Aredes et al described the included population sufficiently well to determine that they were treatment-naïve gynaecological (cervical) patients. Disease stage I-III were included. Poulsen et al were contacted to clarify the type (cervical) and stage of gynaecological cancer (stage I) of their patients. Aredes et al applied the diagnostic criteria for cachexia as proposed by the 2011 expert group consensus. Poulsen used a single criterion i.e. $\geq$ 5% weight loss, which may have resulted in an underestimation of prevalence. Of the 61 patients randomised in the Poulsen et al study, one was lost to follow up and five died. It is not clear if any of these were from the gynaecological sub-

population. Aredes et al invited a total of 52 women to take part; only three refused. Of the 49 enrolled patients, analysis including cachexia evaluation was only performed on participants who completed treatment (n=34).

Figure 4.1 PRISMA Flow Chart

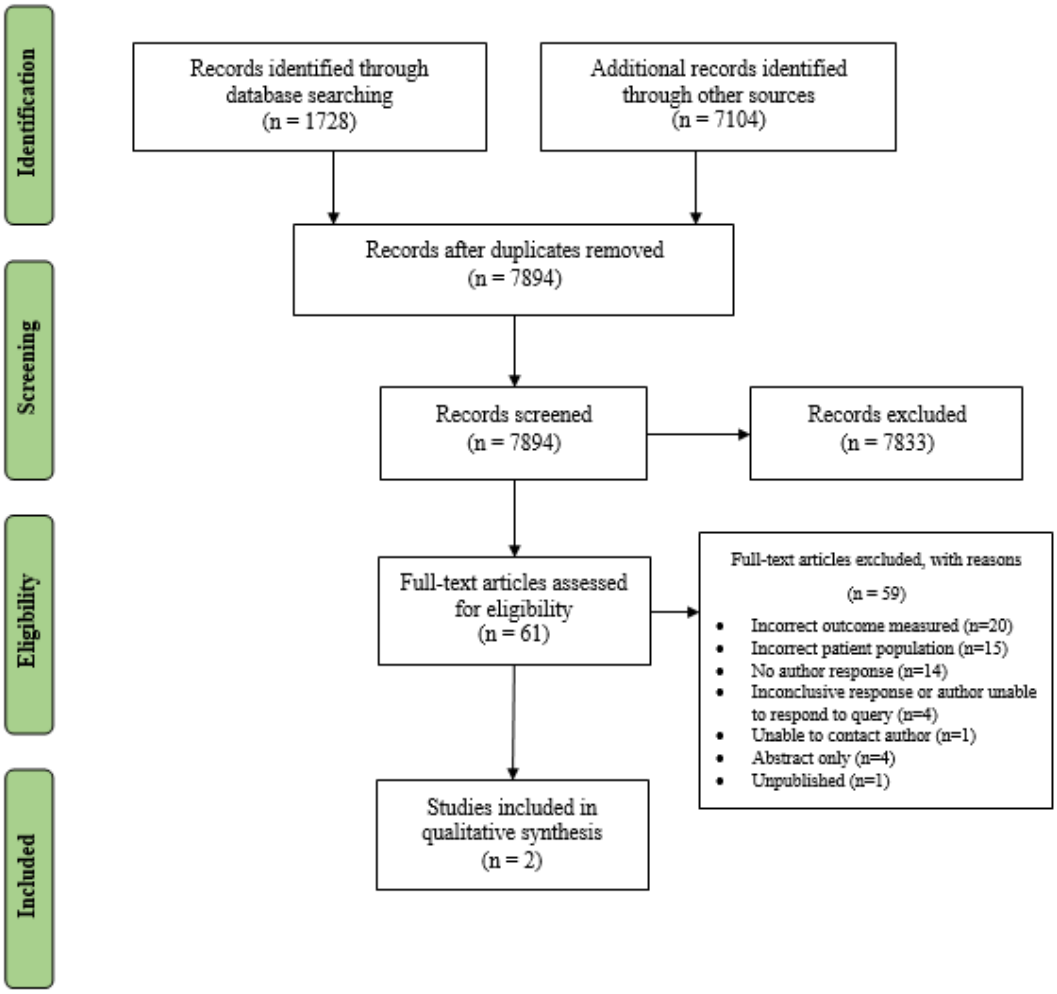

Table 4.2 Summary of General Characteristics of Included Studies

Author, year	Cancer type, %	Country	Study design	Population characteristics	Diagnostic criteria used	Prevalence of cachexia	Outcome
Aredes et al, 2018	Cervical, 100	Brazil	Prospective, observational	N = 49 (N=34 completed treatment) Mean age: 45±13.8 years Stage: I-III Outpatients Treatment intent: curative	UWL > 5% in previous 6 months **or** UWL > 2% and BMI < 20 kg/m^2 **or** UWL >2% and sarcopenia	32.4% (n=11)	%WL, cachexia and sarcopenia were associated with interruption of chemotherapy. 83% of pts who had a chemotherapy interruption had cachexia at presentation
Poulsen et al, 2014	Mixed cancer sites Oesophageal, 23 Gastric, 66 Gynaecological, 11	Denmark	Randomised control trial	N= 61 (N=61 evaluated) Median age: 62 (53-68) intervention group 64 (57-70) control group Stage: I (cervical) Outpatients Treatment intent: mixed Intervention: Nutritional counselling and high-protein ONS containing n-3 fatty acids	≥ 5% weight loss	No participants with cachexia	Dietary counselling resulted in less WL during treatment (44 v 72%, p<0.05) but not between end of treatment and follow-up

Abbreviations: BMI: body mass index; ONS: oral nutritional supplement; UWL unintentional weight loss

Table 4.3 JBI Critical Appraisal Checklist for Included Studies

	Aredes et al	Poulsen et al
Was the sample frame appropriate to address the target population?	●	●
Were study participants sampled in an appropriate way?	●	●
Was the sample size adequate?	●	●
Were the study subjects and the setting described in detail?	●	●
Was the data analysis conducted with sufficient coverage of the identified sample?	●	●
Were valid methods used for the identification of the condition?	●	●
Was the condition measured in a standard, reliable way for all participants?	●	●
Was there appropriate statistical analysis?	●	●
Was the response rate adequate, and if not, was the low response rate managed appropriately?	●	●

● **Yes** ● **No** ● **Not applicable**

4.5 Discussion

Reported prevalence of cachexia in cancer patients varies considerably. Cachexia is strongly associated with cancer site and stage but the use of different diagnostic criteria has at times confounded outcomes. This review aimed to report the estimated prevalence of cachexia in treatment-naïve patients with gynaecological cancer in studies which used defined cachexia criteria.

There is a dearth of published literature investigating cachexia in treatment-naïve patients with gynaecological cancer. No studies specifically designed to establish prevalence of

cachexia as an endpoint in this patient population were identified by this review. Studies which reported on malnutrition or sarcopenia exclusively or used the Patient Generated Subjective Global Assessment (PG-SGA) to diagnose cachexia were excluded. The definition of malnutrition is broad and highly variable both in the literature and in clinical practice. Although all cachectic patients are malnourished, the reverse is not necessarily true (7). Equally sarcopenia is a key feature of cachexia and is useful to highlight at risk individuals but it does not automatically confer a diagnosis of cachexia. Similarly the PG-SGA is a valuable tool for the subjective reporting of aspects of cachexia but was not designed for to diagnose it.

Of the two eligible studies included, only Aredes et al was conducted exclusively in a gynaecological population. Prevalence varied between the included studies. Given the very small sample of gynaecological cancer patients recruited in Poulsen et al, in which women had only stage I disease, compared with Aredes et al which recruited women with stage I-III cervical cancer, this is not entirely unexpected. Cachexia is strongly associated with advanced disease and most of the research to date has focused on this relationship. However, there is an increasing interest in and promotion of the early identification of cachexia and its' forerunner pre-cachexia (21). This is supported by a growing body of evidence that any unintentional weight loss < 5% prior to cancer diagnosis increases the risk of further weight loss and so can negatively impact overall survival. Poulsen et al reported that none of the gynaecological cancer patients included in their trial were cachectic, however, all had weight loss <5% prior to treatment (correspondence with author). Identification of the early manifestations of cachexia may allow for more timely treatment and/or interventions to be applied and in doing so potentially provide women with optimal cancer care. Recognising that a tangible clinical benefit may be achievable

may encourage a shift in the all too frequent nihilistic mind-set of healthcare professionals towards cancer cachexia. Furthermore, the proposed classification system for cancer cachexia was not intended to be definitive but was instead to provide a framework which could be built upon (8). However, the use of only one criterion to diagnose cachexia by Poulsen et al compared with three by Aredes et al may have led to an underestimation of prevalence by the former. As a result, the prevalence of cachexia in this population remains unclear.

Previous research has shown that although patients recognise the importance of clinical research, participation in clinical trials can be perceived as burdensome (22), with randomised trials viewed less favourably (23). The low dropout rate in both studies suggests that these patients may have considered their participation low burden and/or beneficial to either themselves or others. Both studies also demonstrated the relevance and feasibility of establishing prevalence of cachexia and how it can easily be incorporated into a broader study in both middle and high income countries. However, there is an urgent need for governments and policy makers to endorse dedicated studies including more gynaecological cancer sites and stages in order to estimate the prevalence and truly appreciate the burden of cachexia in all gynaecological cancers in a global context.

There are several strengths and limitations to this systematic review. Prevalence of cachexia in treatment-naïve patients with gynaecological cancer appears to have been grossly understudied to date. To our knowledge, this is the first review to focus on cachexia in this population. This systematic review, which was executed in a rigorous and reproducible manner, highlights the research gaps in the area of cachexia in

gynaecological cancer. In addition it demonstrates the feasibility of investigating cachexia across all countries irrespective of economic stratum. That being said, the lack of studies limits our ability to establish a true prevalence of cancer cachexia in this patient population. Only full-text articles which discussed cachexia and reported on its prevalence were included in the review. Also the included studies were not sufficiently comparable to perform a meta-analysis.

4.6 Conclusions

Cancer cachexia is associated with significant morbidity and mortality. However, its prevalence in treatment-naive patients with gynaecological cancer has been poorly addressed in published literature. In order to counter this, cachexia as an endpoint should be included in well-designed and robust studies in this patient population. Universal application of the cachexia diagnostic criteria would help to streamline clinical research in this area. This would allow the true prevalence of cachexia to be quantified and support the early identification of pre-cachectic patients for whom interventions may be most beneficial.

4.7 References

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Chapter 5

Cachexia in Treatment-naïve Gynaecological Cancer Patients:

Prevalence, Predictors and Clinical Associations

5.1 Introduction

Gynaecological cancers – cancer of the cervix, the endometrium, the ovary, the vagina and the vulva – account for at least 16% of all cancer diagnoses (excluding non-melanoma of skin) in women worldwide (1) and for 1 in 12 cancer-related deaths in Irish women (2). There is considerable morbidity associated with a gynaecological cancer diagnosis and with its treatment. Pain, fatigue and anorexia are commonly experienced by cancer patients (3). Women with gynecological cancer are also confronted with disease-specific challenges such as loss of fertility, treatment-induced menopause, bowel and bladder dysfunction, sexual dysfunction, lower limb lymphoedema and the complex psychological impact on body image and sexuality (4).

The clinical significance of any medical condition depends on how common it is in a population and its impact on the health of affected individuals. The reported prevalence of cachexia in cancer populations is highly variable (5, 6). Disease-specific factors such as tumour type and disease stage may account for some of this variability but the use of different criteria to diagnose cachexia must also be considered a factor. For patients with cachexia, there is a substantial associated physical burden but also a psychosocial one, making estimation of its prevalence not only useful but important. When compared with other cancer populations, there is a paucity of published literature investigating the prevalence of cachexia in treatment-naïve gynaecological oncology populations as highlighted in Chapter 4. Given that cachexia is present in at least 50% of patients with advanced cancer (7) and that up to 20% of cancer-related deaths may be attributed to cachexia (8), it is reasonable to assume that at least some gynaecology oncology patients will be affected by cancer cachexia.

While literature pertaining to cachexia in gynaecological cancer is limited, some of the clinical and pathophysiological aspects of cachexia have been investigated in gynaecological oncology populations. Weight history or patterns of weight change may be more important than current weight in identifying at-risk populations. Unintentional weight loss, the most recognisable clinical feature of cachexia, is a poor indicator of disease status in ovarian cancer patients, who may experience an artificial weight gain due to accumulation of fluid in the peritoneal and pleural cavities and lower limbs. At the other end of the spectrum, long-term obesity increases the risk of developing endometrial cancer and it is associated with increased all-cause and endometrial cancer-specific mortality (9). Weight gain in both of these malignancies may mask weight loss from muscle and fat depletion. As a result, it is important to assess weight history and body composition rather than body weight alone in these patients.

Malnutrition has prognostic value regarding post-operative morbidity including surgical complications, post-operative infections and delayed post-operative discharge (10-12). Ovarian cancer patients are at high risk of disease-related malnutrition (11, 13), being 19 times more likely to be malnourished compared to those with benign conditions (13). Reported prevalence of malnutrition in cervical cancer patients ranges from 4 – 60% depending on disease stage (14). Albumin is often used as a marker of nutritional status (15); hypoalbuminaemia is associated with malnutrition and systemic inflammation (16, 17). It has demonstrated prognostic value in endometrial, ovarian and more recently vulval cancer (17). There is increasing evidence that systemic inflammation is associated with clinical decline in cancer patients (16, 18); it increases metabolic demand while simultaneously depleting muscle through increased protein catabolism. Elevated CRP

levels are positively correlated with weight loss (19), which has treatment implications for cancer patients.

Sarcopenia (reduced muscle mass and strength) is associated with frailty, post-operative complications and reduced quality of life (20, 21). The relationship between sarcopenia and reduced overall survival has been demonstrated in many cancers including cervical cancer (22-24). This relationship is less clear in ovarian cancer (25, 26). A recent systematic review highlighted the lack of available standardized cut-offs to define sarcopenia in ovarian cancer populations as a potential reason for the contradictory findings (27).

The aim of the current research was to devise a study that would not only allow an estimation of cachexia to be made in gynaecological cancer patients, but also provide information regarding the clinical characteristics which may co-exist with or as part of the cachexia syndrome and in those at risk of the condition. Simply put, I wished to determine the prevalence of cachexia in de novo gynaecological cancer patients and to investigate the relationship between pre-treatment cachexia and parameters of clinical performance including post-operative length of stay and Clavien-Dindo Classification, both measures of peri-operative patient performance, and also patient-reported quality of life. Identification of at-risk populations, or sub-populations, is a clinical priority in order to enable healthcare professionals to optimise patient management.

5.2 Aim and Objectives

5.2.1 Aim

To explore and quantify the presence of cachexia in a de novo Irish gynaecological cancer population and investigate the clinical consequences related to it.

5.2.2 Objectives

- To describe for the first time the clinical, anthropometric and nutritional characteristics of Irish treatment-naïve gynaecological cancer patients;
- To describe quality of life in gynaecological cancer patients prior to and during treatment;
- To describe the prevalence of cachexia in this cohort using the criteria proposed by Fearon et al;
- To describe the clinical, anthropometric and nutritional characteristics of gynaecological cancer patients with cachexia;
- To determine the impact cachexia has on patients in this population over time compared to non-cachectic patients using peri-operative patient performance parameters and patient-reported quality of life measures;
- To investigate the role individual components of the cachexia syndrome i.e. weight loss, BMI, CT-measured sarcopenia and inflammation, have as predictors of cachexia;

5.3 Methods

5.3.1 Ethical Approval

Ethical approval was obtained from the St. James's Hospital/Adelaide and Meath incorporating the National Children's Hospital Joint Research Ethics Committee. A copy of the ethical approval can be found in Appendix VI. Approval was also obtained locally from the Research and Innovation Office, St. James's Hospital.

5.3.2 Study Design

This prospective, exploratory, observational study was conducted at St. James's Hospital (SJH) Gynaecological Cancer Care Centre, the largest treatment provider for gynaecological malignancy in the Republic of Ireland. SJH is accredited by the National Cancer Control Programme for complex radical gynaecological surgeries.

5.3.3 Recruitment Procedure

Eligible participants were identified from the entire population of patients with actual or possible gynaecological malignancy that were referred to a designated cancer centre at St James's Hospital. Potential participants were identified and screened for eligibility at the weekly multidisciplinary meeting, where new gynaecological cancer cases are discussed to confirm diagnosis and establish a consensus on an individual treatment plan for each patient. Other sources included patients identified by Gynaecology Oncologists and Gynaecology Clinical Nurse Specialists (CNS) through inpatient and outpatient referrals and Emergency Department presentations. Eligibility criteria are outlined in Table 5.1.

Table 5.1 Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
1. Recently diagnosed or high probability of gynaecological cancer 2. Treatment-naive 3. ≥ 18 years of age 4. Able to provide witnessed, signed consent 5. Completed staging scan (CT/PET CT/MRI)	1. < 18 years of age 2. Previous or synchronous cancer diagnosis (with the exception of basal cell carcinoma) 3. Haematological malignancy 4. Previous cancer treatment 5. Unable to complete study assessments 6. Participation deemed inappropriate by attending physician

Once eligibility was confirmed, patients were invited to take part in the study by the Gynaecological Oncologist or Gynaecological CNS. For outpatients, this took place at their scheduled outpatient appointment; for inpatients, it occurred at the bedside. Those who were interested in taking part met with the lead researcher (Niamh O'Donoghue) who explained the study in detail to the potential participant and provided written information in the form of a Participant Information Leaflet. Potential participants were given an opportunity to ask questions and were also given contact details for the lead researcher should any questions arise after the initial meeting. Those who agreed to participate signed a consent form in the presence of the lead researcher. The participant was assigned a study number, which ensured confidentiality and the study was commenced on that day. A copy of the Participant Information Leaflet and Consent Form can be found in Appendix VII.

5.3.4 Data Collection

Data collection took place from January 2018 to March 2019 over 3 non-consecutive days. Each encounter consisted of an interview between the lead researcher and the

participant and a review of their medical record. The first encounter, T_0, baseline/pre-treatment was conducted face-to-face with the participant and the dates for the second encounter, T_1, after a 6 week interval and third encounter, T_2, after a 3 month interval were scheduled and agreed with the participant at that time. Each participant was contacted by SMS message on the specified dates to arrange a suitable time to complete the follow-up assessments. T_1 and T_2 were conducted on the phone, unless the participant was attending the hospital for another reason. In this case it was as per participant preference.

Age, date of birth, height, weight, primary diagnosis including stage, extent of disease, date of diagnosis, date of staging scan and planned treatment were collected from the participant's medical record. Co-morbidities such as COPD, heart failure, chronic kidney disease, rheumatoid arthritis were documented if present. Routine first clinic appointment blood results or pre-operative blood results were recorded. Routine bloods included white cell count with neutrophil and lymphocyte differential, platelets, haemoglobin, urea, creatinine, sodium, potassium, albumin, total protein and corrected calcium. Ca 125 and C-reactive protein (CRP) were recorded if available.

Participants completed a questionnaire (Appendix VIII) at each interview which collected the following data: height, weight, weight history, recent dietary intake, nutritional impact symptoms and functional status. Functional status scores were assigned according to patient-reported daily physical function: 0=Normal with no limitations; 1=Not my normal self, but able to be up and about with fairly normal activities; 2=Not feeling up to most things, but in bed or chair less than half the day; 3=Able to do little activity and spend most of the day in bed or chair; 4=Pretty much

bedridden, rarely out of bed. Participants were asked at each interview if they had been prescribed any medications to improve their appetite or weight. These included nutritional supplements, megestrol acetate (progestin), metoclopramide (anti-emetic) or dexamethasone (corticosteroid).

During the T_1 and T_2 interviews, participants were asked if they were on active oncological treatment or if they had surgery since the previous interview. Details were completed by reviewing the patient's electronic medical record. Participants were asked if they had been hospitalised since the previous interview or if there had been a dose reduction or delay in treatment for any reason. If a dietetic review had taken place since the previous interview, this was also recorded. Parameters of physical status and clinical performance including the American Society of Anesthesiologists Score (ASA) (Appendix IX), post-operative length of stay and Clavien-Dindo Classification (Appendix X) were recorded from the electronic medical record. Post-operative length of stay is defined as the time from the end of surgical procedure to discharge from hospital. Pre-operative patient factors e.g. malnutrition, and operative factors can contribute to a prolonged post-operative length of stay, which can impact long term morbidity and mortality.

5.3.5 Cachexia

Cachexia was defined based on the criteria proposed in 2011 (28). Participants who met any of the three criteria listed below were classified as cachectic:

1. Unintentional weight loss > 5% over the past 6 months **or**
2. BMI < 20 kg/m^2 and unintentional weight loss > 2% **or**
3. Skeletal muscle index (SMI) determined by CT imaging consistent with sarcopenia* and unintentional weight loss >2%

* defined as SMI < 41cm^2/m^2 (23)

5.3.5.1 Weight Loss

Weight was measured using a digital scales to within 0.1kg with patients wearing indoor clothing. Height was measured using a stadiometer to within 0.5cm. Weight and height were recorded from patients' medical records. A patient-reported weight and height was also recorded. Unintentional weight loss (%) was calculated as follows: initial weight - current weight x 100/initial body weight.

5.3.5.2 BMI

The World Health Organisation (WHO) BMI Classification (29) categorises BMI into four groups: underweight (<18.5 kg/m^2), normal (18.5 - 24.9 kg/m^2), overweight (25.0 - 29.9 kg/m^2), obese (≥ 30 kg/m^2). BMI was calculated at all three interviews based on the patient-reported height and weight with the formula: current weight in kilograms divided by height in metres squared (weight (kg)/height $(m)^2$). Both were then categorised into one of the four groups as per the WHO BMI Classification.

5.3.5.3 CT-measured Sarcopenia

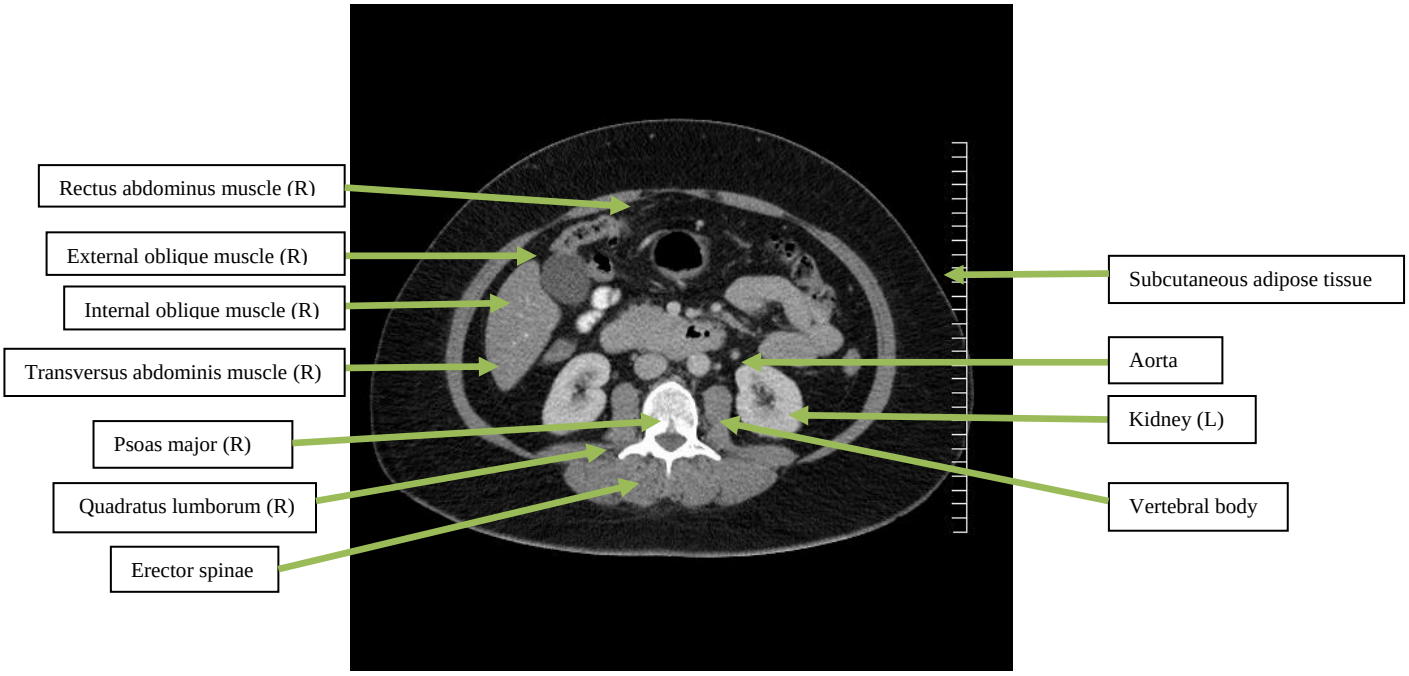
CT Image Acquisition

Electronically stored CT images were used in this study. The imaging studies analysed ranged in date from December 2017 to February 2019. Participants provided written consent for images to be used specifically for body composition analysis. Staging CT scans were preferentially used, as these were closest to T_0. All image acquisition was performed by a radiologically-trained investigator (Dr Charlie Sullivan). The National Integrated Medical Imaging System (NIMIS) records were searched for imaging which related to each study participant. Not all imaging studies were carried out in SJH, however, a unique hospital medical record number pertaining to SJH was used to locate each participant's imaging. Date of birth was subsequently used to search for imaging performed in outside institutions if necessary. Pre-treatment staging CT scans were selected for analysis in each case. The modality used was either CT or the unenhanced CT component of positron emission tomography (PET)/CT studies, depending on which was closer to diagnosis and provided optimal soft tissue contrast. In the event of both being performed at a similar time prior to treatment, contrast-enhanced CT was considered superior to PET/CT. Portal venous contrast phase was used in the contrast-enhanced CT scans.

A single axial image taken at the mid-level of the third lumbar vertebral body (L3) was chosen for analysis in each participant to estimate body composition with particular focus on muscle mass and evidence of sarcopenia. Where available, coronal or sagittal reconstructions were used to verify the location of the axial slice chosen. Axial reconstructions in 5mm slice thickness were used in each patient as these were provided by all outside institutions and as the CT component of PET/CT studies. Each image was

set to display a window width of 400 Hounsfield units (HU) and window level of 40 HU. All identifying information was removed from the image and the participant's study number was assigned to their image (Figure 5.1). The selected image was exported as a Digital Imaging and Communications in Medicine (DICOM) file to an external hard drive in an anonymised format.

Figure 5.1 Representative axial CT slice taken at the mid-level of the third lumbar vertebral body (L3)



CT Image Analysis

Each axial CT slice taken at L3 was analysed by the lead researcher using SliceOmatic Version 5.0 (TomoVision, Montreal, Canada), a specialised body composition analysis software. Following analysis, images were reviewed by a radiologically-trained investigator (Dr Charlie Sullivan). The muscles contained within the L3 region are

psoas, paraspinal muscles (erector spinae, quadratus lumborum) and abdominal wall muscles (transversus abdominus, external and internal obliques and rectus abdominus). Visceral adipose tissue, intra-muscular adipose tissue and subcutaneous adipose tissue are also present. The density of each tissue is represented using the Hounsfield scale and so CT attenuation values are expressed as Hounsfield units (HU). Predefined and previously validated boundaries were used to demarcate and quantify each tissue type (Figure 5.2). The HU thresholds for each tissue type were as follows:

- 29 to 150 HU for skeletal muscle
- 190 to -30 HU for subcutaneous and intramuscular adipose tissue
- 50 to -150 HU for visceral adipose tissue

The muscle and surrounding adipose tissue surface areas were automatically quantified and measured in square centimetres (cm^2). Skeletal Muscle Index (SMI) was calculated by normalising skeletal muscle area for height with the formula: skeletal muscle area (cm^2) divided by the square of the height (m^2). Gender specific cut-off values for sarcopenia obtained by CT imaging have previously been described (23).

Patients were excluded from skeletal muscle analysis for the following reasons: if the image was not retrievable, if no imaging was performed or if the imaging was not performed to a comparable vertebral level e.g. MRI pelvis to a superior limit of L5.

Figure 5.2 Representative axial CT slice taken at the mid-level of the third lumbar vertebral body (L3) with tissue type demarcation

5.3.6 Inflammation-based Prognostic Scores

Haematological components of the systemic inflammatory response may be combined to form prognostic scores which are predictive of cancer-related morbidity and mortality. Three such prognostic scores were applied in this study.

a) Modified Glasgow Prognostic Score (mGPS)

The modified Glasgow Prognostic Score (mGPS) combines routinely collected acute phase proteins, CRP and albumin, to create a prognostic scoring system (30). Higher

mGPS is predictive of overall survival and associated with reduced QoL. The mGPS has scores ranging from 0 to 2 and is calculated as follows:

CRP ≤ 10 mg/L = 0;

CRP > 10 mg/L = 1;

CRP > 10 mg/L and albumin < 35 g/L = 2

b) Neutrophil: Lymphocyte Ratio (NLR)

High neutrophil:lymphocyte ratio values have demonstrated prognostic value in a number of cancers (31, 32). It is considered an accessible, cost-effective alternative for institutions where CRP is not routinely performed (33). There is heterogeneity in published literature regarding cut-offs e.g. 1.4 - 5.25 (32, 34, 35)

c) Platelet: Lymphocyte Ratio (PLR)

High pre-operative platelet:lymphocyte ratio values reflect platelet activation and systemic inflammation. It is a readily available marker of poor prognosis in cancer. Cut-offs are variable depending on the cohort e.g. <150 - >300 (36).

5.3.7 Functional Assessment (Handgrip Strength)

Hand grip strength is associated with changes in function, body composition, nutritional status and inflammation in a number of chronic illnesses. It is considered predictive of survival in advanced cancer (37). Measurement of handgrip strength is considered a surrogate for total muscle strength (38) and an objective measure of muscle function (39). Handgrip strength has been included as a primary endpoint in studies investigating treatment for cachexia (40). It is measured as the amount of static force that the hand

can apply (squeeze) around a hand dynamometer (41). It is a simple and inexpensive way to identify low muscle strength (dynapenia) and demonstrates high inter-rater reliability (42).

A JAMAR® Plus + Digital Hand Dynamometer (Sammons Preston Rolyan, Bolingbrook, IL) was used (Figure 5.3). Participants were asked to take the dynamometer in their dominant hand while seated, either on a chair or in bed, with their elbow flexed at 90 degrees and a neutral wrist position (41). Handle width was adjusted to hand size. Participants were then asked to complete three consecutive isometric contractions with no less than 10 seconds and no more than 30 seconds between each contraction (42). Each reading and the average of the three readings were recorded. The average of the three readings was compared with gender- and age-matched normative grip strength data (Appendix XI).

Figure 5.3 JAMAR® Plus + Digital Hand Dynamometer

5.3.8 Quality of Life

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire (EORTC QLQ-C30 version 3.0) is a 30 item, validated, self-report tool developed to assess quality of life (QoL) in cancer patients (Appendix XII). It comprises both multi-item scales and single-item measures including five functional scales (physical, social, role, cognitive, and emotional), three symptom scales (fatigue, pain, and nausea and vomiting), six single item scales (dyspnoea, sleeping disturbances, appetite loss, constipation, diarrhoea, and financial impact) and a global health status / QoL scale (43). Response choices range from 1 (not at all) to 4 (very much), with the exception of the two items of the global QoL scale, where responses range from 1 (very poor) to 7 (excellent). All scale scores are linearly transformed to a 0-100 scale. For the functioning scales and the global QoL scale, a higher score represents a higher level of functioning or QoL. For the symptom scales, a higher score represents greater symptom burden.

The EORTC Quality of Life Group have also developed a number of supplementary disease and treatment-specific modules which should only be administered in addition to the core questionnaire. These include a number of gynaecological cancer specific modules namely cervical (EORTC QLQ-CX24), endometrial (EORTC QLQ-EN24), ovarian (EORTC QLQ-OV28) and vulva (EORTC QLQ-VU34) (Appendix XIII - XVI); all are fully validated with the exception of the vulva module which is in Phase IV testing i.e. undergoing validation testing.

The EORTC QoL core module and relevant supplementary gynaecological cancer module were completed by the participants at each encounter. Scoring was applied according to the EORTC Manual, with a range from 0-100.

5.3.6 Data Handling

Data privacy and protection protocols complied with the Data Protection Acts of 1988 and 2003. Data were collected on anonymised paper data recording forms and entered into a password-protected Excel spreadsheet (Excel 2013, Microsoft Office Professional Plus 2013, Washington) which was stored on a password protected hard drive. The anonymised CT images were also stored on a password protected hard drive. The hard drive password was changed every 2 months. Paper data sheets and the hard drive were stored in a locked office at SJH.

Participants were assigned a coded study number by the lead researcher at point of entry to the study to maintain confidentiality. The code key was kept by the lead researcher in a locked office at SJH. The study number was used on the Data Recording Form, on electronically stored data and on de-identified radiology images.

5.3.7 Statistical Analysis

Descriptive statistics were used to illustrate patient characteristics. Continuous variables were compared with independent sample t-tests or Mann Whitney U tests, where appropriate. Paired samples t-tests were used to compare differences between baseline self-reported weight and measured weight. Categorical data were analysed using Chi-square. Univariate analysis was used to identify significant associations between variables. Logistic regression was used to model predictors of cachexia, with no

presence of cachexia as a reference category. Predictors included weight change at 1 month, low albumin (<35g/L), presence of metastases, presence of sarcopenia, platelet:lymphocyte ratio ≥ 5.4, presence of anorexia and presence of early satiety. Analyses were completed using Microsoft Excel (Microsoft Office Professional Plus 2013, Microsoft Corporation, Redmond, WA), IBM SPSS Statistics for Windows Version 23 (SPSS, Chicago IL) and Stata Statistical Software: Release 14 (StataCorp. 2015. College Station, TX: StataCorp LP). A p-value of ≤0.05 was considered statistically significant.

5.4 Results

5.4.1 Population Characteristics

From a total population of 354 new gynaecological cancers presenting over a fifteen month period 101 (28.5%) patients were enrolled. Demographic and clinical characteristics are presented in Table 5.2. Seven were excluded after enrollment: six no longer met the inclusion criteria following review of their post-operative histology (metastatic colorectal cancer (1), synchronous ovarian/endometrial malignancies (1), benign (4)) and one became too unwell to complete the assessments. The mean number of days from staging CT scan to recruitment date was 22. Ninety-four patients completed assessments at T_0 prior to treatment; 65 and 60 patients completed T_1 and T_2 assessments, which took place 6 weeks and 12 weeks after T_0 respectively.

The mean age of the study population was 56.7±14.9; 31% (n=29) were over 65 years. Endometrial cancer was the most frequent diagnosis (46.8%), followed by cervical cancer (25.5%) and ovarian cancer (17%).

More than half (60.9%) were FIGO Stage I. 16% of patients had metastatic disease. Most patients reported optimum performance status according to the ECOG performance status tool in the PG-SGA; 44.7% had an ECOG=0. Poor performance status (ECOG=3) at T_0 (9.6%) occurred in patients across each of the gynaecological cancers, FIGO stages and BMI categories. Of the nine patients with ECOG=3, 5 patients were sarcopenic and 4 were cachectic. At T_1 and T_2, most patients reported performance status as ECOG=1.

ASA Class 2 (patient with a mild systemic disease) was most frequently recorded. Most patients (80.8%; n=76) had upfront surgery, either alone (34%) or in combination with other treatments (46.8%). Cachexia-associated co-morbidities were identified in 6 patients (6.4%); they were COPD (3), heart failure (2) and COPD and heart failure (1). Four patients (4.3%) died during the study period; three of these patients were overweight/obese with an ECOG=1, one was underweight and had an ECOG=2 at T_0.

Anthropometric and nutritional parameters at baseline (T_0) are presented in Table 5.3. The average weight of patients at recruitment was 75.6kg; average BMI was 29.8kg/m^2 (overweight). In the six months prior to recruitment, 40% of patients reported unintentional weight loss. The average percentage weight change was 0.68kg ±7.92 (weight loss). More than a tenth of patients had ≥10% weight loss prior to diagnosis; more than half of these had a cervical cancer diagnosis (FIGO IB1-IVB). 7% had 5-10% weight loss and a further 27.1% had ≤ 5% weight loss.

More than a quarter gained weight, with 10.6% reporting a ≥10% weight gain in the previous six months. Of those who remained weight stable, nearly three-quarters

(73.9%; n=17) had an endometrial cancer diagnosis. Nearly a third (31.9%; n=30) were classified as normal weight prior to treatment; nearly two-thirds (63.8%; n=60) were overweight and obese.

Figure 5.4 presents variation by weight change category. Baseline data are included, as are matched cohort data across the three encounters, although the number of participants notably reduced due to attrition. Of those who lost weight prior to diagnosis (42%), all continued to lose weight to T_1. A change in trend was noted at T_2, with nearly half (49.1%) reporting weight gain. There was a trend towards decreasing BMI between T_0 to T_2 assessment.

The mean difference between baseline self-reported and measured weights was 0.56. As no statistically significant difference was identified (p=0.09), self-reported weight was used. This allowed for consistency across all encounters to be maintained, as the majority of encounters at 6 weeks and 12 weeks were conducted over the phone.

Additional information on nutritional supplement and appetite stimulant use, dietetic review, hospitalisation during the study period and dose reduction and/or delay in treatment are included in Appendix XVII.

Table 5.2 Demographics and clinical characteristics at baseline (n=94)

Characteristic	N=94	%
Age at diagnosis, years		
Mean (±SD)	56.7 (±14.9)	
Primary cancer site and histology type		
Endometrial	**44**	**46.8**
Endometrioid adenocarcinoma	37	39.4
Carcinosarcoma	7	7.4
Cervix	**24**	**25.6**
Squamous cell carcinoma	16	17.0
Adenocarcinoma	6	6.4
Large cell neuroendocrine of cervix	1	1.1
Mixed (large and small cell) neuroendocrine of cervix	1	1.1
Ovarian	**16**	**17.1**
High grade serous carcinoma of ovary	13	13.8
Mixed ovarian (clear cell/endometrioid)	1	1.1
Ovarian carcinosarcoma	1	1.1
Mucinous borderline ovary	1	1.1
Vulva	**7**	**7.4**
Squamous cell carcinoma of vulva	7	7.44
Vagina	**3**	**3.3**
Squamous cell carcinoma of vagina	1	1.1
Malignant melanoma	1	1.1
Neuroendocrine carcinoma small cell type of vagina	1	1.1
FIGO stage (n=92)[a]		
I	56	60.9
II	10	10.9
III	13	14.1
IV	13	14.1
Metastatic disease		
Yes	15	16
No	79	84
ECOG		
0	42	44.7
1	36	38.3
2	7	7.4
3	9	9.6
ASA (n=76)[b]		
0	4	5.3
1	8	10.5
2	60	79.0
3	4	5.3
Treatment		
Surgery (primary)	32	34.0
and radiotherapy (pelvic ± brachytherapy)	27	28.7
and adjuvant chemotherapy	12	12.8
and chemoradiation	3	3.2
and adjuvant chemotherapy and radiotherapy	1	1.1
and adjuvant immunotherapy	1	1.1
Primary chemoradiation	10	10.6
Neoadjuvant chemotherapy	1	1.1
and interval cytoreduction	2	2.1
and interval cytoreduction and adjuvant chemotherapy	2	2.1
and radiotherapy	1	1.1
Radiotherapy	2	2.1

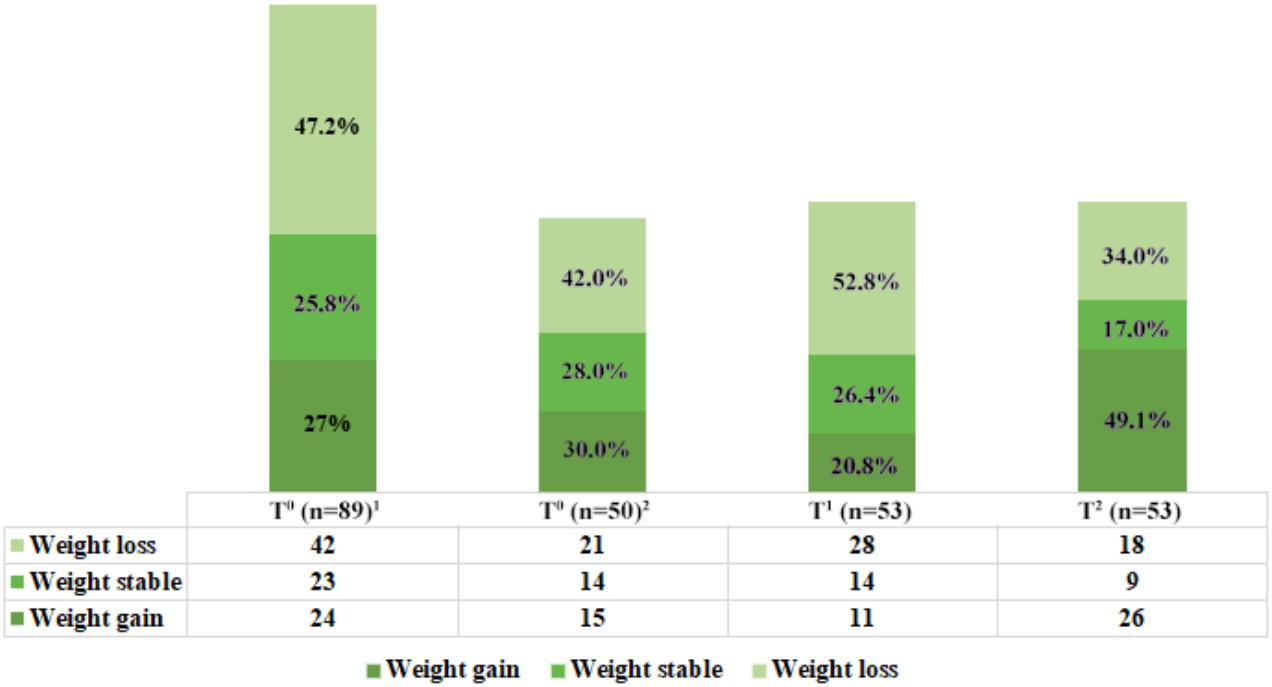
[a] 2 patients were unstaged; [b] primary surgical patients only

Table 5.3 Anthropometric and nutritional markers at baseline (n=94)

Characteristic	N=94	%
Weight, kg		
Mean (SD)	75.6 (± 22.7)	
Height, m		
Mean (SD)	1.60 (± 0.08)	
BMI, kg/m^2		
Mean (SD)	29.8 (± 9.3)	
BMI, category		
Underweight (< 18.5)	4	4.3
Normal (18.5-24.9)	30	31.9
Overweight (25-29.9)	23	24.5
Obese (≥ 30)	37	39.4
Weight change (n=89)		
Weight gain	24	27
Weight stable	23	25.8
Weight loss	42	47.2
Weight change in previous 6 months, %		
Mean (± SD)	-0.68 (±7.92)	
Weight loss (unintentional) in previous 6 months, % (n=85)[a,b]		
≥ 10 WL	9	10.6
5.01 -9.9 WL	6	7.1
2.5-5.0 WL	10	11.8
0.1-2.4 WL	13	15.3
Weight gain in previous 6 months, %		
0.1-2.4 WG	3	3.5
2.5-5.0 WG	6	7.1
5.01-9.9 WG	6	7.1
≥10 WG	9	10.6
Weight stable in previous 6 months, %		
0	23	27.0
Body composition (n=87)[c]		
Skeletal muscle (cm^2)	114.4 (±20.8)	
Skeletal muscle index (cm^2/m^2)	44.9 (±9.4)	
Sarcopenia	32	36.8
Sarcopenic obese	5	5.7
No abnormality detected	44	50.6
Albumin (n=91)[d]		
≥35	85	93.4
<35	6	6.6
Handgrip strength (n=90)[e]		
Normal	44	48.9
Abnormal	46	51.1

[a] 5 patients did not provide weight history
[b] 4 patients were excluded as reported intentional weight loss
[c] Sarcopenia assessment could not be completed for 7 patients as imaging was not accessible available
[d] albumin not recorded for 3 patients
[e] 4 patients did not perform hand grip test

Figure 5.4 Variation in weight change category across three encounters: baseline (T_0) and matched analyses for T_0 to T_1 and T_1 to T_2



	T⁰ (n=89)[1]	T⁰ (n=50)[2]	T¹ (n=53)	T² (n=53)
Weight loss	42	21	28	18
Weight stable	23	14	14	9
Weight gain	24	15	11	26

[1]Missing weight history (n=5)

[2]Missing weight history (n=3)

5.4.2 Population Quality of Life

The distribution of mean global health status / QoL scores measured by the EORTC-C30 at all three encounters can be found in Appendix XVIII. The mean global health status / QoL on a scale of 1 to 100 was 58.3 ±28.04 at T_0. This improved over the subsequent two encounters. Physical functioning demonstrated the highest score at T_0, while emotional functioning scored the lowest. The reverse pattern was seen at T_2. Symptom scale scores were generally low and consistent across all three encounters. Patients reported being most symptomatic with insomnia (36.88 ±35.22; 40 ±33.69; 33.89 ±33.05) and fatigue (33.92 ±26.65; 36.58 ±23.28; 37.04 ±26.27) at each encounter. Anorexia showed most improvement between T_0 and T_2 for all patients.

The global health status / QoL for each of the five gynaecological cancers at baseline and all three encounters are presented in Figures 5.5 and 5.6. Patients with ovarian cancer and vaginal cancer at T_0 reported the lowest and highest global health status / QoL respectively. This trend was also noted at T_2. Patients with endometrial and cervical cancers demonstrated the least amount of variation across the three encounters.

Patients with cancer of the vagina comprised the cohort that reported insomnia most frequently at T_0 and T_2. Ovarian cancer patients were most symptomatic of fatigue and appetite loss at T_0 compared to other gynaecological cancer sites (Appendix XIX).

In relation to the EORTC gynaecological cancer specific modules, endometrial cancer patients were most symptomatic with back and pelvis pain at T_0 and with urological symptoms at T_2. Patients with cervical cancer consistently scored higher for sexual worry across all three encounters. Gastrointestinal symptoms were ranked highest by

ovarian cancer patients at T_0 but these improved over subsequent encounters; chemotherapy associated side-effects, including hair loss, were more frequently scored by this group at T_2. Symptom scores were generally low (<10) for women with vulval cancer at T_0 with the exception of skin changes, vulvo-vaginal discharge and urinary urgency and leakage. Vulval scarring, vulvo-vaginal discharge and swelling were the symptoms ranked highest at T_2.

A third of patients had ≥2 nutritional impact symptoms at baseline. Anorexia (n=36; 34%), early satiety (n=32; 21.2%) and pain (n=20; 13.8%) were the most frequently reported symptoms at T_0 by the PG-SGA (Appendix XX).

Figure 5.5 Global health status / QoL by primary tumour site at baseline

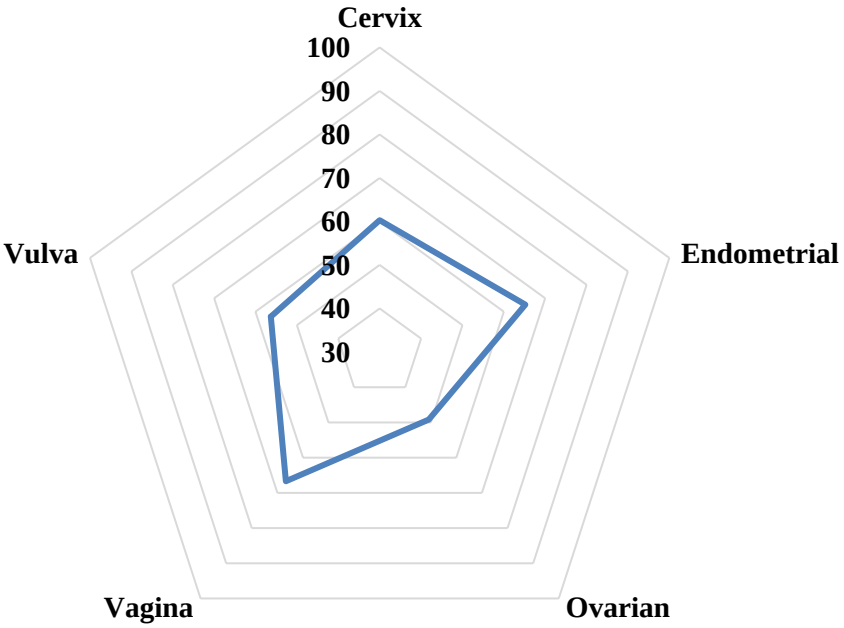
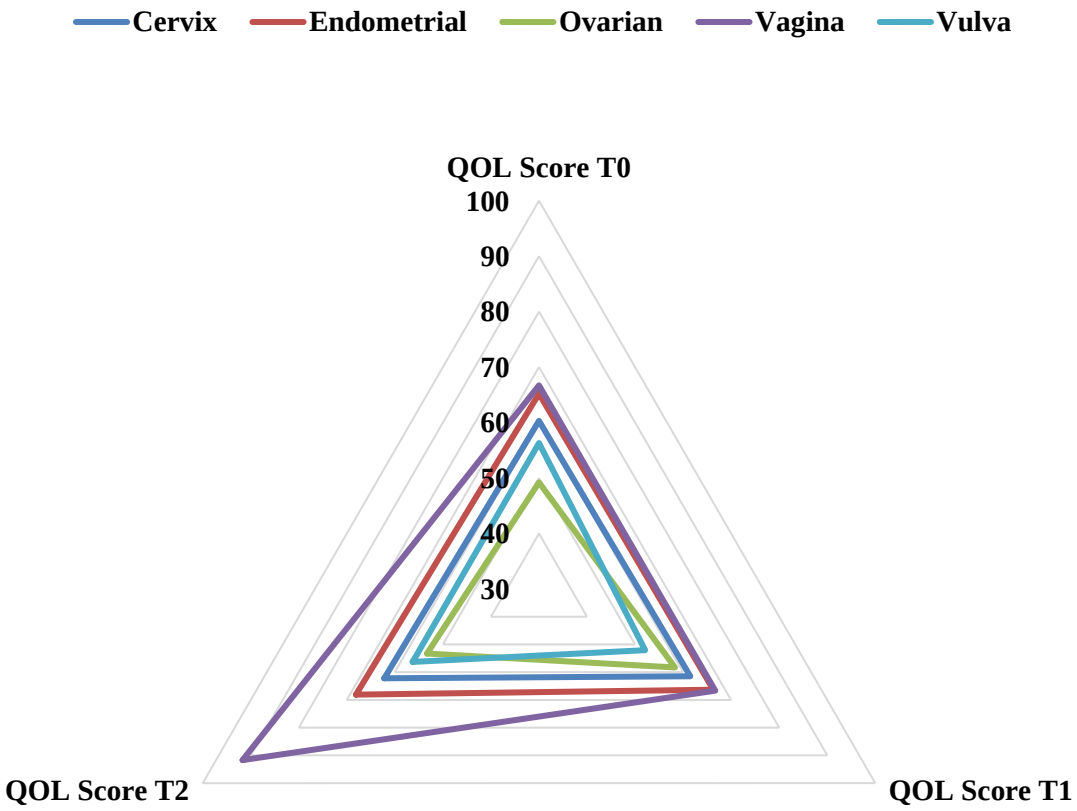


Figure 5.6 Global health status / QoL by primary tumour site at each encounter



5.4.3 Cachexia

5.4.3.1 Prevalence

The criteria presented in the consensus definition and classification of cachexia (28) were applied to the patients in this study. The prevalence of cachexia in patients with gynaecological malignancy prior to receiving any treatment was 21.8% (n=19). More than a third (36.78%; n=32) were sarcopenic. Nearly 80% of the cachectic patients (78.9%; n=15) had weight loss >5%. Three patients with weight loss >2% would not have been identified as cachectic without skeletal muscle index measure. Figure 5.7 illustrates the number of patients identified as cachectic by each criterion.

Cachexia was most prevalent in patients with cervical cancer (37.5%), while patients with endometrial cancer had the lowest rate of cachexia (9.1%) (Figure 5.8). In total 30 patients (34.5%) were classified as cachectic at some time between T_0 and T_2. Sarcopenia was present in patients with vulval cancer (71.4%), cervical cancer (41.6%), endometrial cancer (31.8%) and ovarian cancer (18.6%).

Figure 5.7 Prevalence of cachexia at T_0 based the classification system established by an expert group consensus (n=19)

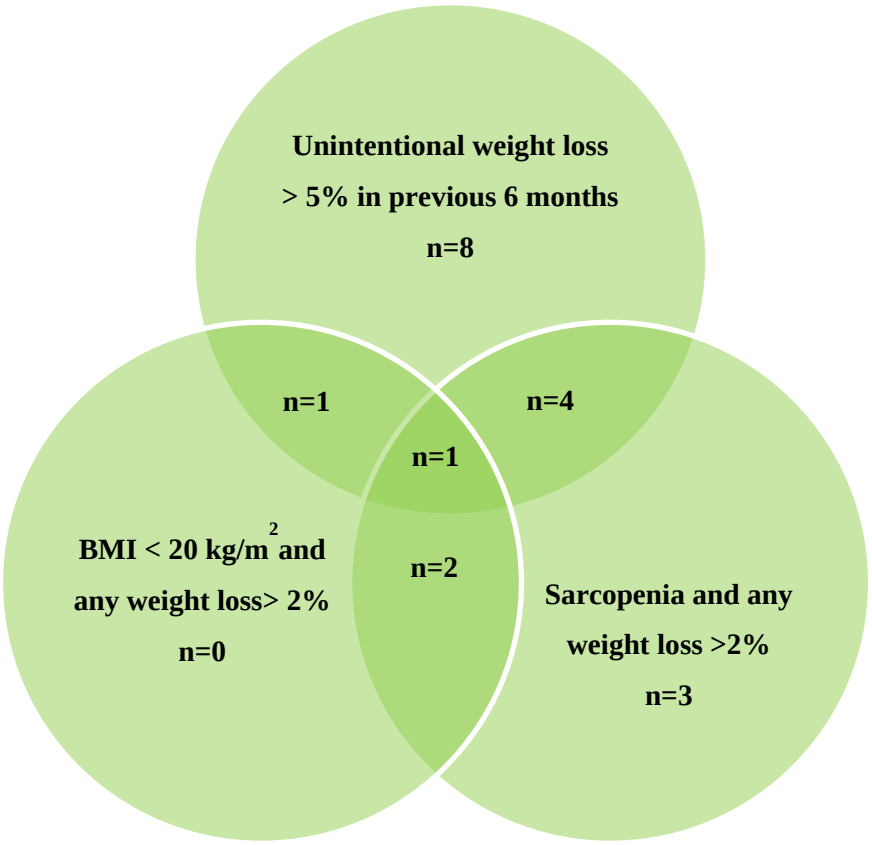
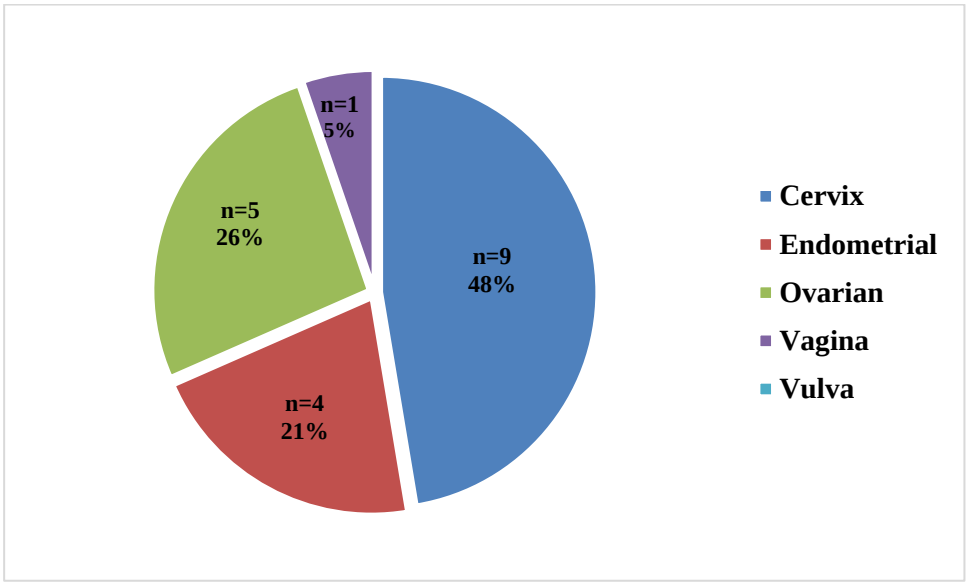


Figure 5.8 Prevalence of cachexia at baseline by gynaecological cancer site (n=19)



5.4.3.2 Characteristics of Patients with Cachexia at Baseline

Table 5.4 presents the clinical characteristics of patients with cachexia. Nearly three-quarters were ≤65 years (73.7%; n=14). There was no significant association between age and the presence of cancer cachexia. Cachexia occurred at all FIGO stages; more than a third of cases were in patients with Stage IV disease. Increasing disease stage ($p < 0.01$) and metastatic disease (<0.001) were both associated with higher rates of cachexia. Poorer performance status was associated with cachexia ($p < 0.05$).

A comparison of anthropometric, nutritional and inflammatory markers for cachectic and non-cachectic patients are presented in Table 5.5. There was a significant difference in weight change one month and six months prior to T_0 in cachectic patients compared with non-cachectic patients ($p < 0.001$). Cachexia (Figure 5.9) and sarcopenia occurred in all BMI categories. BMI was significantly lower in cachectic ($p < 0.05$) and sarcopenic ($p < 0.001$) patients at T_0 compared to non-cachectic/non-sarcopenic patients.

No significant difference between skeletal muscle mass in cachectic and non-cachectic patients was identified but skeletal muscle index was lower in cachectic patients ($p < 0.01$). More than 50% of both cachectic (57.9%; n=11) and sarcopenic (53.1%; n=17) patients had an abnormal handgrip test result; no significant difference was identified between cachectic and non-cachectic patients or sarcopenic and non-sarcopenic patients.

Table 5.4 Clinical characteristics of patients with cachexia (n=19)

Characteristic	Cachectic (n)	Cachectic (%)	p-value
Age[a]	53.8 (±16.8)		0.256
Primary cancer site (n=94)			<0.05
Endometrial (n=44)	4	21.1	
Cervix (n=24)	9	47.4	
Ovarian (n=16)	5	26.3	
Vagina (n=3)	1	5.3	
Vulva (n=7)	0	0	
FIGO stage (%)[b]			<0.01
I (n=56)	5	26.3	
II (n=10)	3	15.8	
III (n=13)	3	15.8	
IV (n=13)	7	36.8	
Metastatic disease (%)	9	47.4	<0.001
ECOG (%)			<0.05
0-1 (n=78)	13	68.4	
≥2 (n=16)	6	31.6	

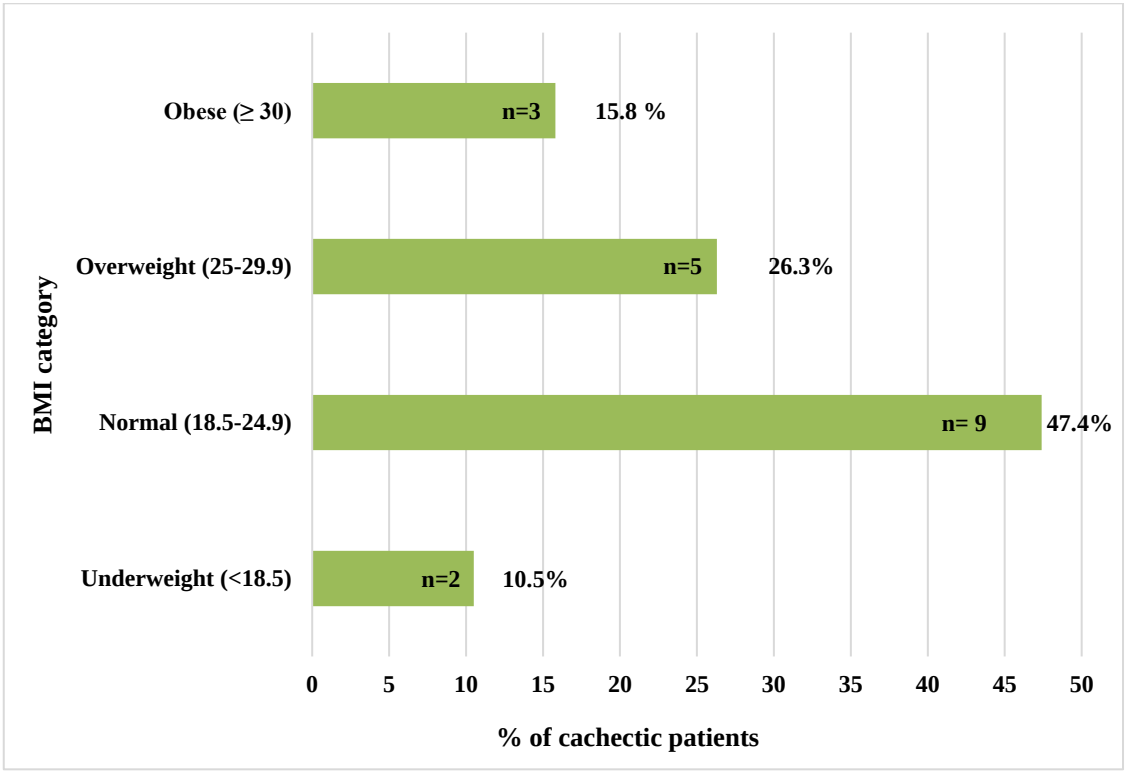
[a] Analysed by independent samples t-test
[b] Stage not recorded for neuroendocrine carcinoma (small cell type) of vagina

Table 5.5 Comparison of anthropometric, nutritional and inflammatory markers for cachectic and non-cachectic patients (n=94)

Variable at T_0	Cachectic (n=19)	Non-cachectic (n=68)	p-value
BMI, kg/m^2 [a]	24.7 (±6.2)	31.4 (±9.9)	<0.05
Weight change in 1 month[a]	-4.39 (±5.5)	0.05 (±3.2)	<0.001
Weight change in 6 months[a]	-9.03 (±6.1)	2.64 (±10.1)	<0.001
Skeletal muscle mass (cm^2)[a]	105.8 (±14.8)	117.7 (±22.0)	0.170
Skeletal muscle index (cm^2/m^2)[a]	40.1 (±6.3)	46.5 (±9.8)	<0.01
Hand grip strength[a]	21.4 (±6.2)	20.8 (±5.1)	0.495
PG-SGA Score[b]	10 [1-22]	4 [1-20]	<0.001
PG-SGA Category (%)			
A (Well nourished)	36.8	76.5	<0.01
B (Moderately malnourished)	36.8	19.1	<0.01
C (Severely malnourished)	26.3	4.4	<0.01
Albumin (g/L)[a]	40.1 (±7.3)	43.3 (±3.6)	<0.001
C-reactive protein (mg/L)[b]	13.0 [<1.0-151.3]	4.5 [<1.0-141.6]	0.122
mGPS=0, %	50.0	78.3	<0.01
mGPS=1 (%)	25.0	21.7	
mGPS=2 (%)	25.0	0	
Neutrophil:Lymphocyte ratio[b]	3.4 [1.4-19.8]	2.5 [0.9-11.2]	0.144
Platelet:Lymphocyte ratio[b]	213.7 [1.4-19.8]	155.2 [-0.89-11.7]	<0.01

[a] expressed as mean ±SD
[b] expressed as median [range]

Figure 5.9 BMI distribution of cachectic patients at baseline (%)



5.4.3.3 Association between Cachexia and Clinical Outcomes

Of the 76 patients who had primary surgery, 10 were cachectic. Cachexia status was unknown for five patients. The median post-operative length of stay for cachectic patients (n=10) was 5 days (range 1-57) compared to 4 days (range 0-27) for non-cachectic patients (n=61) (p=0.682).

Thirty patients had no complication after surgery. Of these, four were cachectic and a further 7 were sarcopenic. Post-operative complications were graded Clavien-Dindo Grade I (30 patients – 3 cachectic, 8 sarcopenic), Grade II (13 patients – 2 cachectic, 3 sarcopenic), Grade III/IV (3 patients – 1 cachectic) While numbers are too small to determine level of significance, 60% of cachectic patients had some post-operative complication.

The results from inflammatory marker analysis showed lower serum albumin in cachexia but no significant change in CRP. Sarcopenia was significantly associated with CRP ($p < 0.05$). mGPS=2 was significantly associated with both cachexia and sarcopenia ($p < 0.01$). Platelet:lymphocyte ratio were significantly associated with cachexia at T_0. Lymphocyte level, neutrophil:lymphocyte ratio and platelet:lymphocyte ratio were associated with cachexia at T_1 (<0.05). Primary cancer site, FIGO stage and treatment received categories were too small for significance testing.

Of the six patients who were hospitalised between T_0 and T_1, two were cachectic and sarcopenic (adenocarcinoma cervix, stage IIA; HGSC ovary, stage IIIC) and a third was sarcopenic (SCC cervix, stage IB2) at T_0. Treatments received since recruitment were chemoradiation, surgery and neoadjuvant chemotherapy. Of the patients hospitalised

between T_1 and T_2, one was sarcopenic (HGSC of ovary, stage IC3) at recruitment and cachectic at T_1 and 2 others (ovarian carcinosarcoma, stage IC3; malignant melanoma of vagina, stage IV)) were cachectic at T_1. Of the four patients who died during the study period, two were cachectic and one was sarcopenic-cachectic.

5.4.3.4 Association between Cachexia and Patient-reported Outcomes

When compared to non-cachectic patients, cachectic patients had poorer global health status / QoL at T_0 and T_1 (Figure 5.10). Cachectic patients scored lower than non-cachectic on all functional scales from T_0 to T_2, with the exception of emotional function on T_2. Physical, role and emotional function are illustrated below (5.11-5.13). Cachectic patients were more symptomatic with fatigue, nausea and vomiting, pain, dyspnoea, appetite loss, constipation, diarrhoea and financial difficulties compared to their non-cachectic counterparts (Figure 5.14). Anorexia (73.7%), early satiety (36.8%) and fatigue (26.3%) were the most commonly reported nutritional symptoms by patients with cachexia at T_0 by the PG-SGA.

Figure 5.10 Global health status / QoL for cachectic and non-cachectic patients at T_0-T_2

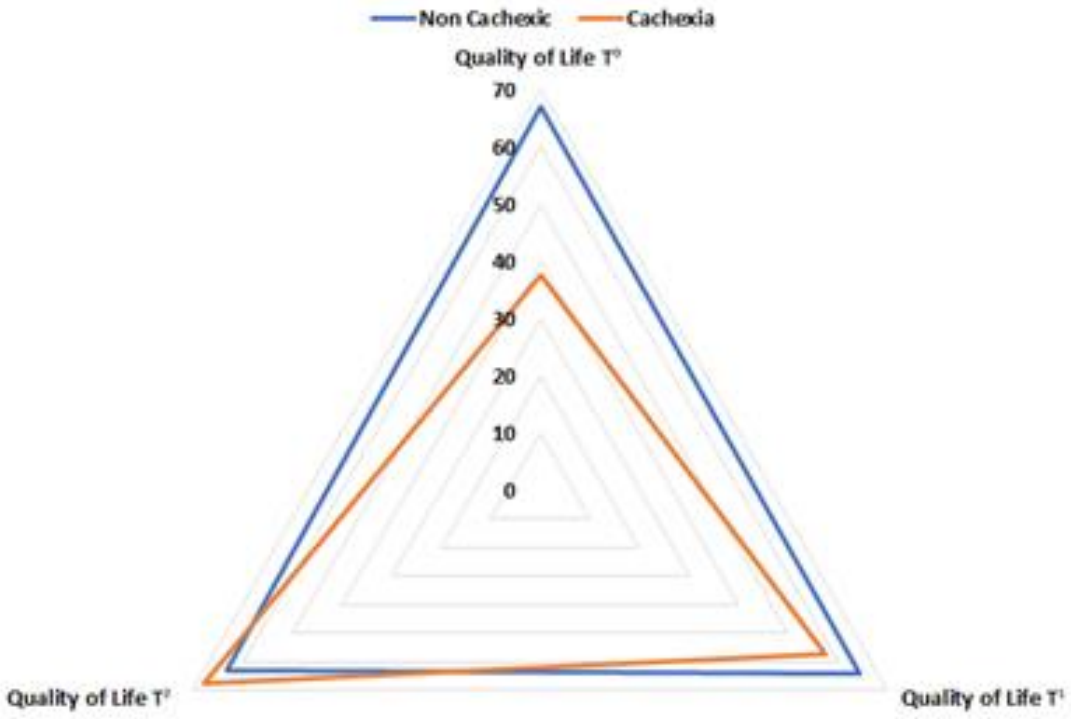


Figure 5.11 Physical function for cachectic and non-cachectic patients at T_0-T_2

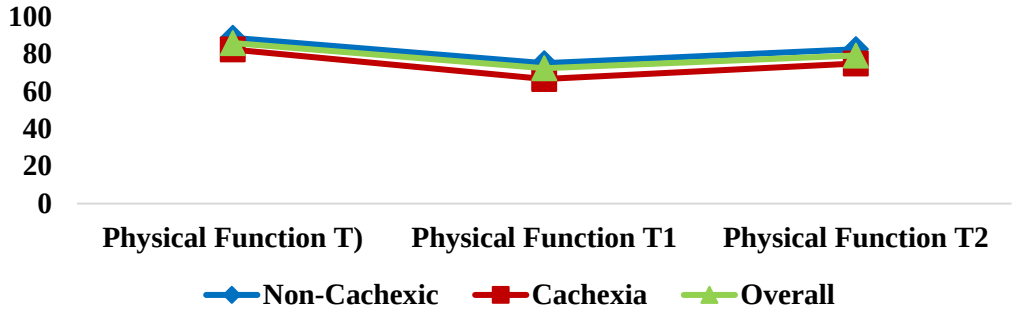


Figure 5.12 Role function for cachectic and non-cachectic patients at T_0-T_2

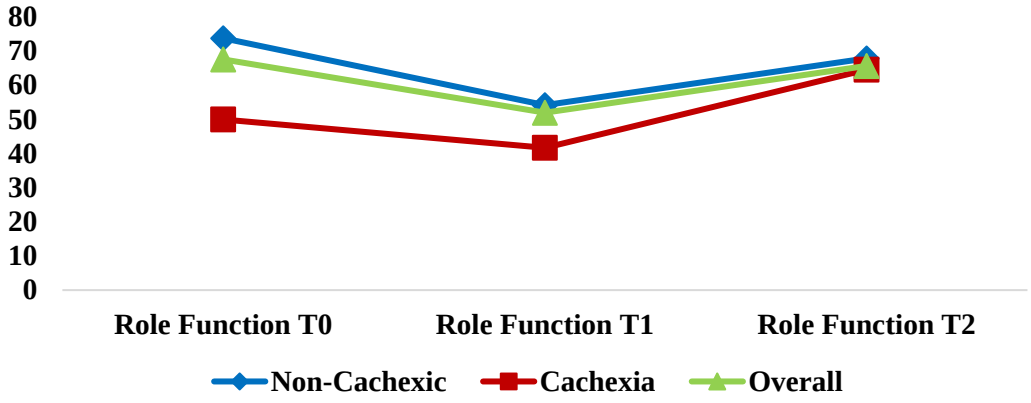


Figure 5.13 Emotional function for cachectic and non-cachectic patients at T_0-T_2

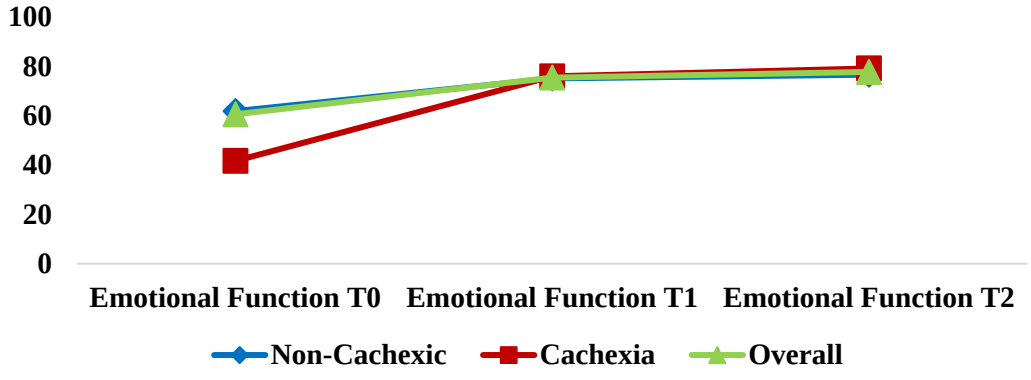
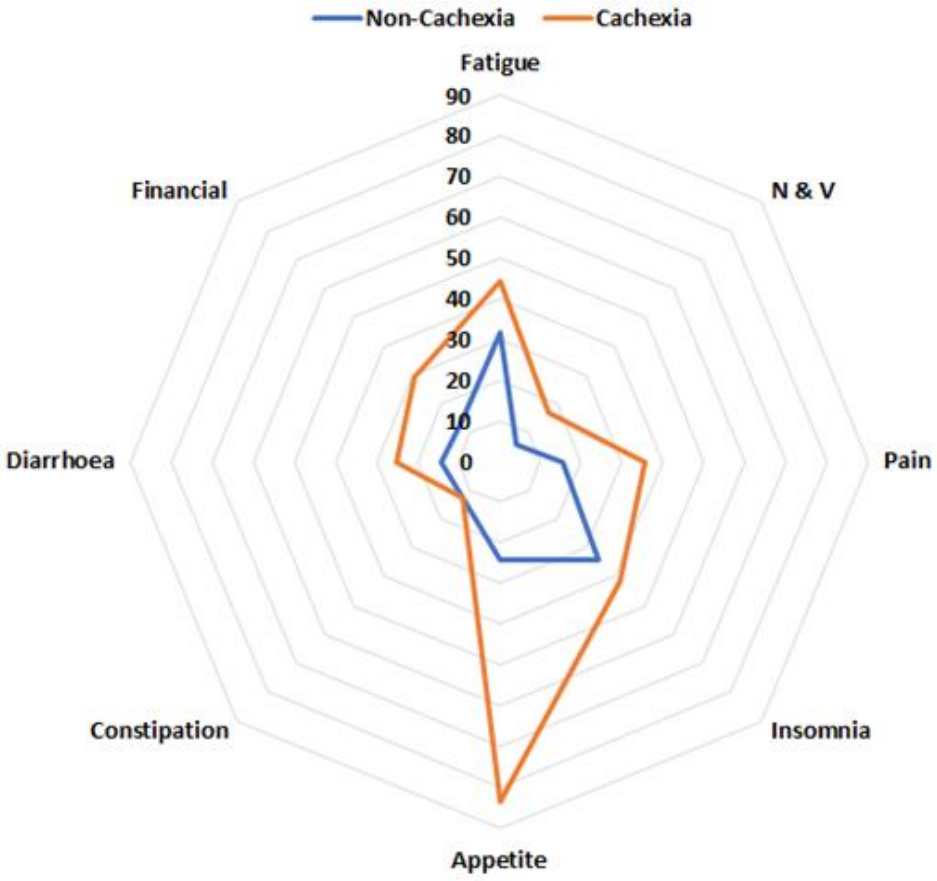


Figure 5.14 Symptom scales for cachectic and non-cachectic patients at T_0



5.4.3.5 Predictors of Cachexia

Using the variables identified by univariate analysis as significantly associated with cachexia, logistic regression analysis was then used to identify potential predictors of cachexia, although this was limited by the small sample size (Table 5.6). Weight change (loss) in previous month was predictive of developing cachexia ($p<0.05$). Low albumin (<35g/L) (OR 4.77, 95%CI 0.22-103.26, p=0.319), compared to normal albumin, and anorexia (OR 3.69, 95%CI 0.86-15.83, p=0. 0.078), compared with no anorexia, showed a positive association with cachexia although neither reached significance.

Table 5.6 Logistic regression model of associations with presence of cachexia at baseline

Variable	OR	95% CI	*p*
Weight change in 1 month	0.78	0.63-0.98	<0.05
Albumin (<35)	4.77	0.22-103.26	0.319
Presence of metastases	2.81	0.44-18.05	0.277
Presence of sarcopenia	2.43	0.60-9.89	0.216
Platelet: Lymphocyte ratio ≥ 5.4	1.31	0.17-10.14	0.799
Anorexia	3.69	0.86-15.83	0.078
Early satiety	1.22	0.22-6.63	0.819

5.5 Discussion

Cachexia is not routinely associated with gynaecological cancer and, as such, has rarely been investigated in this patient population. Weight gain is often a feature of ovarian cancer and patients with endometrial cancer frequently have a history of long-standing obesity. Sarcopenia, a component of cachexia, is prognostic in several cancers and more recently it has been the focus of research in ovarian cancer (25, 44). Using the proposed criteria for the diagnosis of cachexia, we found 21.8% of women with gynaecological cancer were cachectic at presentation. A further 13.5% developed cachexia within three months of diagnosis. This means more than one third of patients with gynaecological cancer were cachectic. The population studied represented more than a quarter of all new gynaecological cancers attending a designated cancer centre. All major genital tract cancers were represented. Cachexia is therefore prevalent in the gynaecological cancer population. However, we expect that our measure of the prevalence of cachexia would be the minimum value for the following reasons. Weight history and evidence of sarcopenia were unknown for some patients. Patients who were very frail may have been excluded by their gynaecological oncologists and those who had been referred to the multidisciplinary meeting for discussion from regional centres but deemed unsuitable surgical candidates may not have attended our cancer centre clinics.

The reported prevalence of cachexia is concerning for a number of reasons. Traditionally cachexia is not seen as characteristic of gynaecological cancer, as evident from its absence in the cachexia literature. Although it can develop at any stage in the cancer continuum, it is most frequently associated with advanced rather than early stage disease. More than 40% of cachectic patients recruited to the current study were FIGO

stage I and II and all of these patients had a cervical or endometrial cancer diagnosis. Sarcopenia was diagnosed in over a third of patients (36.8%) and nearly two-thirds (65.6%) of these were FIGO stage I and II. Sarcopenia is often associated with advancing age but it is not always an inevitable pairing. More than half of participants in this study had an abnormal hand dynamometry result, reflecting primary sarcopenia. Nearly 60% of those with CT-measured sarcopenia were under the age of 65 years; 7.4% were under 50 years. Primary and secondary sarcopenia co-existed in a third of participants. This is important because irrespective of the underlying cause, sarcopenia is associated with frailty and reduced QoL. The negative impact of chemotherapy on weight and muscle mass has been extensively documented but our patient cohort had yet to receive any treatment for their cancer diagnosis at the time of assessment. A recent systematic review (26) reported that although there appears to be an association between skeletal muscle index and survival in ovarian cancer, interpreting it and determining the strength of this association is complicated by the lack of a standardised cut-off. The presence of pre-existing cachexia and sarcopenia in this cohort of gynaecological patients could put these patients at considerable risk of being further compromised once their treatment begins. Although previous emphasis has been on the impact of chemotherapy and radiotherapy, this study suggests that the cachectic label would also identify patients who were likely to develop post-operative complications; 60% of cachectic patients had some post-operative complication as determined by the Clavien-Dindo. Half of the patients hospitalised between T_0 and T_1 were cachectic and/or sarcopenic and three quarters of those who died during the study were cachectic at T_0. Patients with a previous history of cancer were not eligible for this study and the

number of patients with cachexia-associated co-morbidities was low. With the exclusion of these as possible confounders, we conclude that either the tumour itself or other patient factors or both are responsible for the presence of cachexia and sarcopenia. Gynaecological malignancies are a heterogeneous group of cancers and the disease type impacts substantially on the clinical presentation. Ovarian cancer presents with advanced systemic disease outside the pelvis in more than 70% of patients. Typically there is ascites, other effusions and hypoalbuminaemia. By comparison, advanced stage cervical and vaginal cancer remains local to the pelvis in the majority of cases, progressing to involve the bladder, rectum and pelvic sidewall often without impactful distant metastases. Despite these differences in disease pattern and progression, the prevalence of cachexia at presentation was remarkably similar in ovarian cancer (31.3%) and cervix/vaginal cancer (37%) or approximately one third of cases. The majority of endometrial cancers are early stage at diagnosis and 9.1% were cachectic. Vulval cancer is a skin cancer and was not associated with cachexia at presentation. It is likely that skin cancer would be less likely to induce a systemic response.

Baseline or pre-treatment characteristics may increase a patient's susceptibility to developing cachexia. After their diagnosis with cancer, one eighth of our cohort became cachectic. Cachexia and sarcopenia can occur in patients of any weight or BMI. It is important to look at additional parameters because weight and BMI do not reflect body composition. The associated features like systemic inflammation and reduced oral intake can hasten the individual's progression towards a cachectic state in the months after their cancer diagnosis. Our study was consistent with current evidence in that

many of the known associated features of cachexia such as weight loss (including muscle) as a function of time, advanced stage of disease, poor performance status and systemic inflammation were present in some of the patients who developed cachexia over the course of the study. However, our study also demonstrated that cachexia developed in patients with early stage disease, good performance status and no evidence of systemic inflammation.

Nearly 40% of patients in this study were obese at T_0; less than 5% were underweight. Excess weight makes it more difficult to identify patients with weight (muscle) loss, as it is often heavily masked. Obesity is endemic even in cancer populations. It is associated with an increased risk of developing a number of cancers and with cancer recurrence. Post-operative recovery may also be negatively impacted. There is evidence to suggest that despite the high prevalence of overweight and obesity in most of the developed world, healthcare professionals often fail to recognise it (45). Underestimation may in part be due to overweight and obesity being considered the 'norm' and so may go unseen because they are so commonplace (46). Without a high level of surveillance for cachexia by the healthcare professional, it is likely to be missed. Healthcare professionals should routinely weigh their patients and calculate their BMI to monitor any changes relating to underweight, overweight or obesity and counsel their patients accordingly.

Extremes of weight change occurred in this population in the months prior to diagnosis. This has been previously reported as detrimental for patients with cancer (47). Forty

percent of the patients recruited had unintentional weight loss with a tenth losing more than 10% of their body weight. Cervical cancer made up the majority in this group but ovarian cancer and cancer of the vagina also featured in smaller numbers. Unintentional weight loss is synonymous with cancer and it is cited as a red flag symptom for almost all cancers. It was DeWys et al (48) who nearly 40 years ago first described the prognostic effect of weight loss prior to chemotherapy in a mixed cancer cohort. Their study also highlighted the variation in percentage of weight lost across a spectrum of cancers but gynaecological cancers were not included. In our study, more than a quarter had gained weight; a tenth of these gained more than 10% in body weight. This group included patients with endometrial, cervical and ovarian cancer. Large fluctuations in weight gain may reflect tumour burden in the form of third space fluid - ascites, pleural effusions and lower limb oedema and within large pelvic tumours.

Measures of the systemic inflammatory response yielded a significant association between modified Glasgow Prognostic Score (mGPS) and both cachexia and sarcopenia. An increasing mGPS is predictive of reduced survival in cancer in all major cancer types. The individual components, CRP and albumin did correlate with one or other condition. Low albumin was associated with cachexia, while raised CRP was associated with sarcopenia. This is interesting because the cachectic and sarcopenic body composition states are considered inflammatory, yet one is reflected in a negative acute phase protein and the other in a positive acute phase protein response. A larger sample size may help tease out the reasons for this. Given these findings, albumin and CRP should be included in all bloods from diagnosis and the mGPS calculated on each

occasion. Platelet:lymphocyte ratio and neutrophil:lymphocyte ratio also demonstrated an association with cachexia at various stages in the disease trajectory. However, without validated cut-offs for both in this population, we do not recommend their routine use at this time.

Cancer is strongly associated with age. Highest incidence is recorded in older people, with more than a third occurring in those ≥ 75 years. Nearly half of participants in this study had an endometrial cancer diagnosis, while a quarter had a cervical cancer diagnosis. Endometrial and ovarian cancer are most frequently diagnosed in post-menopausal women, although exceptions do occur mainly due to genetic risk factors. Vaginal and vulval cancers, also previously considered diseases of post-menopausal women, have seen an increase in incidence in younger women due to infection with the human papilloma virus. This is also the principal risk factor for cervical cancer, which is predominantly a disease of younger women. The relatively low mean age of the study population reflects the disease-associated age distribution.

Interestingly most (84.2%) patients who were confirmed as cachectic were identified by unintentional weight loss and weight loss in the setting of low BMI. The simplicity of these two (of three) criteria for the classification of patients as cachectic is important because these are measures that can be easily applied in the most basic clinical settings. We recommend that weight, BMI and a comprehensive weight history are included in all clinical assessments and especially at first assessment of all gynaecological cancer patients. Analysis of CT scans is becoming more common in research but it is not as yet

routinely used by clinicians in daily practice to identify sarcopenia or to establish cachexia status. For more remote clinics, where there is no access to CTs or where there is no one to facilitate the analysis of these images, it is reassuring to know that two of the three criteria for cachexia will likely capture a large proportion of gynaecological cancer patients with cachexia. That being said, Laky et al (12) demonstrated that percentage weight loss and BMI alone cannot detect malnutrition in gynaecological cancer patients. The potential risk of some cachectic patients being missed highlights the need for evidence of sarcopenia to be included for completeness. Ovarian cancer patients are prone to weight gain due to third spacing of body fluids. Detecting sarcopenia as a risk factor of cachexia may be especially important in that group. Of note, 18.8% of our ovarian cancer patients were sarcopenic at T_0.

Measuring skeletal muscle mass index is labour intensive in that it requires the acquisition of CT images from the medical institution storage system and demarcation of images using software. But the CT based modality does provide more precise tissue analysis and is less burdensome than other methods of body composition assessment such as dual energy x-ray absorptiometry, ultrasound and bioelectrical impedance. Of course, the ideal would be an automated measure that would be provided as part of the standard radiology report. This would provide baseline skeletal muscle index to the multidisciplinary team at treatment planning and serial assessment of the skeletal muscle index over the course of the disease.

Disappointingly the handgrip strength assessment, which measures primary sarcopenia, did not correlate with CT-measured sarcopenia. We do not recommend its use in this population as a surrogate for CT-measured sarcopenia. Performance status is a global assessment of a patient's level of function (49). It is routinely used in oncology populations to assess fitness for treatment (50) and eligibility for clinical trials (49) and has been shown to correlate with chemotherapy tolerability, quality of life and survival (51, 52). The ECOG is a commonly used performance status assessment tool in research and clinical practice. It describes the level of function in terms of the person's ability to care for themselves, their daily activity and physical ability. The scale ranges from zero ("fully active") through three ("capable of only limited self-care") to five ("dead") (53). There is evidence to show that patients and oncologists assess performance status scores similarly (54). In this study, performance status was assessed at all three encounters using the Activities and Function component of the scored PG-SGA questionnaire, which directly reflects the components of the ECOG Performance Status (53). Scores were assigned according to participants' self-reported daily physical function.

The PG-SGA is designed to assess patients for malnutrition or risk of malnutrition and provides a recommendation for nutritional intervention based on a score > 4. In this study, it was principally used as a means to capture weight history and performance status. Patient-reported anthropometric measures have been previously validated (55, 56). It is worth noting that when compared to the diagnostic criteria for cachexia, the PG-SGA overestimated the nutritional status of many of the cachectic patients. For this

reason, it would not be an appropriate tool to investigate cachexia, as it may not capture all at-risk patients. While this was an observational study, the lead researcher did refer patients to the dietetics services in SJH based on clinical need. This included all cachectic patients. Ideally all cancer patients should be reviewed by a dietitian at diagnosis but this is not feasible given the shortage of specialist oncology dietitians.

In this study, mean symptom scale scores for all participants were generally low. After insomnia, patients were most symptomatic of fatigue and this increased over time. Cancer-related fatigue is commonly reported by patients. It is often more pronounced in advanced disease and/or during active treatment. This was evident in the ovarian cancer patient cohort, the majority of whom had advanced disease and were most symptomatic of fatigue compared to other gynaecological cancers. However, more than half of the participants in this study were FIGO stage I, which may in part account for the low mean symptom scale scores.

Predictably cachectic patients were more symptomatic and had lower functional status in almost all categories across the three encounters compared to their non-cachectic counterparts. It is important to apply some QoL measure at diagnosis and routinely throughout the cancer trajectory. Symptoms such anxiety, depression and pain are common in cancer patients and they may lead to social withdrawal and food refusal. Such behaviours increase the risk of cachexia or may further compound cachexia if already established.

There were a number of strengths and limitations to this study. This is the first known study designed to estimate prevalence of cachexia in a treatment-naïve gynaecological cancer population using the criteria outlined by expert consensus. All gynaecological cancers were represented in this study which was undertaken in a tertiary referral centre. It also explored predictors and clinical associations of cachexia. However, the sample size was small and this made it difficult to undertake significance testing for some outcomes. There is no agreed skeletal muscle index cut-off for assessing sarcopenia in gynaecological cancer populations (38.5–41.5 cm^2/m^2). The cut-off applied in this study is normally used to identify sarcopenia in female patients with lung and gastrointestinal cancers. This may have resulted in an under or over estimation of sarcopenic and so by default cachexia in this study. Patients identified as malnourished or at risk of malnutrition were referred to the team dietitian. Although unlikely to have had an effect on body composition, it may have changed weight and QoL outcomes for some patients. Self-reported weight and height were used in this study. There is evidence in the literature to support and dispute the use of this method. This study almost exclusively comprised Caucasians, and the results therefore are not generalisable to other ethnicities.

5.6 Conclusions

The prevalence of cachexia in a treatment naive gynaecological cancer population is at least 22% based on this representative sample from a designated gynaecological cancer centre. We strongly recommend that screening for cachexia should be included in all clinical assessments. Sarcopenia without weight loss was also common (17%).

Although weight loss and BMI can identify the majority of patients who are cachectic, it is important not to rely only on these measures. Skeletal muscle mass index should also be included where possible. Its incorporation into standard radiology assessment of cancer patients would be optimal. Further research is warranted in a larger population to fully elucidate the predictors of cachexia and disease-specific cut-offs both for sarcopenia and inflammation-based prognostic scores for all five gynaecological cancers. QoL is a useful means to monitor symptoms and functional status which may contribute to or exacerbate cachexia.

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Chapter 6

Discussion and Conclusions

6.1 Discussion

This thesis investigated cancer cachexia, in terms of prevalence in treatment-naïve patients, its relationship to clinical and patient-reported outcomes, and awareness of the syndrome amongst oncology healthcare professionals. The discussion which follows summarises the main findings, provides recommendations based on these findings and offers a foundation for future studies.

Cachexia has long been recognised as a common feature of cancer, yet it remains a poorly understood phenomenon. Approximately half of all patients with advanced cancer develop cachexia (1) but it is unclear why others are spared, even in cancers known to have a high prevalence of cachexia. What is clear is that the processes which result in sustained inadequate nutrition including reduced intake or poor absorption considerably increase a patient's risk for development of cachexia. Perhaps it is the association with advanced cancer which has at times led to the nihilistic attitude amongst some healthcare professionals towards cachexia. Management of cachexia is challenging and trials to date have had limited success as outlined in Chapter 1. There is currently no accepted standard of care. Although not intended to be absolute, the proposed definition and diagnostic criteria have helped streamline research and provided a framework to support the early and prompt recognition of cachexia. Both ESPEN and the European School of Oncology recommend the early recognition of cachexia (3, 4). The early symptoms of cachexia may be subtle, so subtle in fact that they may go unnoticed by the patient themselves. Symptoms such as change in appetite, changes in taste and smell and weight loss may occur but should be sought so that reversible causes of weight loss and nutritional deficits may be addressed.

One particular challenge in cachexia research is the continued lack of consensus on the amount of weight loss considered clinically significant, although it is now believed to be less than the previously suggested >5% weight loss. Loss of lean muscle is implicated in increased chemotherapy related-toxicities and reduced physical functioning, both of which negatively impact quality of life. The retrospective study in Chapter 2 was in part modelled on a study conducted nearly 40 years ago by DeWys et al (2) which investigated weight loss in a treatment-naïve mixed tumour population. The present study investigated the consequences of various weight change increments in the months prior to diagnosis in a mixed tumour population. Although more than half of the patients in our study lost weight prior to treatment, the majority were still overweight and obese. Our study confirmed that even small percentages of weight loss, including amounts (±2.5%) usually considered an acceptable weight fluctuation in healthy individuals, increased the risk of subsequent weight loss. Broadly speaking those who gained weight prior to diagnosis or later had a better overall survival compared to those who lost weight but there was one exception: shortest survival was noted in those with ≥ 10% body weight gain or weight loss. The clinical phenotype of the cachectic patient has changed from one of emaciation to now including patients who are normal weight, overweight and obese. Obesity is one of the strongest risk factors for cancer in the developed world and it is at least in part driving the increasing cancer rates. It also makes the recognition of cachexia a more challenging pursuit. Although weight and BMI alone are not sufficient to reliably identify cachectic patients, they certainly should be routinely measured and monitored for all cancer patients and a weight history taken at first presentation to identify at-risk patients who may benefit from nutritional and lifestyle interventions.

ESPEN recommends the identification of ‘nutritional disturbances’ through regular evaluation of nutritional intake, weight change and BMI beginning at cancer diagnosis. Cancer cachexia is the ultimate nutritional disturbance. So why are at-risk patients not being identified in our oncology clinics? It could be argued that this includes all patients with a cancer diagnosis. Chapter 3 demonstrated that nutritional screening and assessment are not routinely performed in Irish medical or surgical oncology clinics. It also highlighted that not all cancer centres have access to a full-time dietitian and the majority of non-dietetic healthcare professionals have received little to no nutrition-related education as part of their training. This was reflected in the variable awareness of cachexia and its significance within the context of a cancer diagnosis noted across oncology healthcare professionals. Nutritional screening should be mandatory for all cancer patients at first presentation if at-risk cancer patients are to be promptly identified. However, if patient outcomes are to be improved, it is essential that healthcare professionals working in oncology, irrespective of discipline, understand the relevance of this screening and have a greater understanding of the complex relationship between nutrition and cancer. This will only be achieved through the inclusion of nutrition-related material in undergraduate and postgraduate curricula and with ongoing collaboration with our dietetic colleagues.

Patients with advanced disease, particularly cancers associated with overt weight loss, have been the focus for much of the cachexia research to date. Many of the cohorts included in such research will have already received treatment, therefore the prevalence of cachexia at cancer diagnosis is unclear. Given that weight loss is not equal across primary cancer sites, the true burden of cachexia is simply not known. Cachexia and the adverse consequences associated with it are common, lending merit to exploring its

prevalence in cancer cohorts that may not previously have been considered at high risk for developing cachexia. Gynaecological cancer has never been studied specifically in relation to cachexia, hence the attention to newly diagnosed women with genital tract cancer in Chapters 4 and 5. A systematic review of the literature demonstrated the absolute lack of research exploring prevalence of cachexia in treatment-naïve gynaecological cancer patients. Two studies commented on prevalence, both in cervical cancer patients, but neither were explicitly designed with prevalence as an endpoint. This gap in the literature supported the work undertaken in Chapter 5.

A prevalence of 21.8% of cachexia was reported in patients with newly diagnosed gynaecological cancer in Chapter 5. Sarcopenia was present in 32% of patients. While the figure itself is important, we very much need to shift our thinking to appreciate the breadth of the problem and further analyse its true clinical importance. Our study found evidence of cachexia in patients with all gynaecological cancer types with the exception of vulval cancer. Interestingly, over 70% of patients with vulval cancer had evidence of sarcopenia; 60% of these were over 65 years of age. Sarcopenia is associated with frailty and poor quality of life but it also increases the risk of developing cachexia. At least 20% of these patients became cachectic over subsequent encounters. Cervical cancer demonstrated the highest prevalence of cachexia. More than half were FIGO stage I or II. The only comparable published prevalence was reported by Aredes et al (32.4%). That study also used the same diagnostic criteria for cachexia as in our study and included treatment-naïve patients with cervical cancer FIGO stage I-III. Based on our findings it is essential to apply all three of the diagnostic criteria in order to diagnose cachexia in at-risk gynaecological cancer patients. Weight loss and BMI alone were insufficient, as previously reported in other studies.

A number of expected associations with cachexia – advanced disease, poor performance status and systemic inflammation – were demonstrated in this study. Surprisingly though the reverse was also true with patients with early stage disease, good performance status and no evidence of systemic inflammation also being given a diagnosis of cachexia. This further emphasises the importance of using specific criteria to identify at-risk patients so that none are overlooked.

The appeal and novelty of the modified Glasgow Prognostic Score (mGPS) was highlighted in this study. Low albumin, but not elevated CRP, was associated with cachexia. The reverse was true for sarcopenia. The mGPS combined both of these two acute phase proteins to identify at-risk patients. Other haematological prognostic scores have shown some promise and two demonstrated the ability to predict development of cachexia at different stages in the study.

6.2 Strengths and Limitations

Research investigating the prevalence of cachexia in treatment-naïve cancer populations is limited. In addition to estimating the prevalence of cachexia in a large mixed tumour database, this thesis prospectively investigated and reported prevalence of cachexia for the first time in a treatment-naïve gynaecological cancer population using internationally accepted diagnostic criteria. Results of a national survey highlighted the absence of nutritional education at undergraduate level across disciplines, the variable awareness of cachexia and the perceived barriers to identifying cachexia. To the best of our knowledge, this is the first survey to include the views of Irish healthcare professionals working in oncology on nutrition in cancer.

Compared to international studies, the sample size in two of the studies were small, making sub-group analyses challenging at times, particularly in the prospective gynaecological cancer study. With no agreed standardised cut-off for sarcopenia in gynaecological cancer populations, the use of a lung/upper GI cut-off may have led to an under or over estimation of sarcopenia, and by default cachexia, in this population. Similarly the lack of established and validated cut-off for the haematological prognostic scores in the gynaecological cancer populations makes comparison with other studies difficult.

6.3 Future Work

The findings in this thesis have highlighted areas which warrant further investigation. Prospective longitudinal studies in gynaecological cancer populations, which would continue for sufficient time so as to allow survival analyses for each of the five gynaecological cancers to be conducted, should be designed. Prehabilitation (improving the functional capacity of a patient prior to surgery) has improved outcomes in some upper GI cancer cohorts. Prompt identification of sarcopenia on CT staging scans could provide a 'prehabilitation window' for some gynaecological cancer patients. Currently CT-measured muscle mass in an arduous process. Automation would allow muscle mass to be routinely included in the CT staging report.

Personalised models of care in gynaecological cancer rather than a 'one-size-fits all' approach are becoming more commonplace. Based on this research, the assessment for and management of cachexia should be an integral part of this model from diagnosis. Maintaining the ability to shift and re-align with our patients needs as and when they change throughout their disease trajectory should be the priority. It is our hope that these

findings will stimulate and encourage further investigation of patients with gynaecological malignancy who appear to have been a forgotten cohort in cachexia research.

6.4 Conclusions

Cancer cachexia is prevalent in treatment-naïve patients, including gynaecological cancer patients. Its insidious nature leads to considerable patient burden and poorer prognosis when compared to those without cachexia. All healthcare professionals working in oncology have a duty to screen cancer patients for cachexia, however an absence of nutritional education across disciplines has made this challenging. A comprehensive weight history, including nutritional symptoms, body composition analysis and monitoring markers of systemic inflammation are necessary at all clinical encounters but especially at first assessment if those patients most at-risk are to be identified.

6.5 References

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Appendices

Appendix I

Gynaecological Cancer

Gynaecological cancer accounts for 1 in 8 cancers in Irish women and 1 in 12 cancer-related deaths. It is the collective term used for the five cancers which can originate in the female reproductive system (Figures 1 - 4), that is arising from the cervix, the endometrium, the ovary, the vagina and the vulva. Each gynaecological cancer is distinct with different aetiology, risk factors and signs and symptoms.

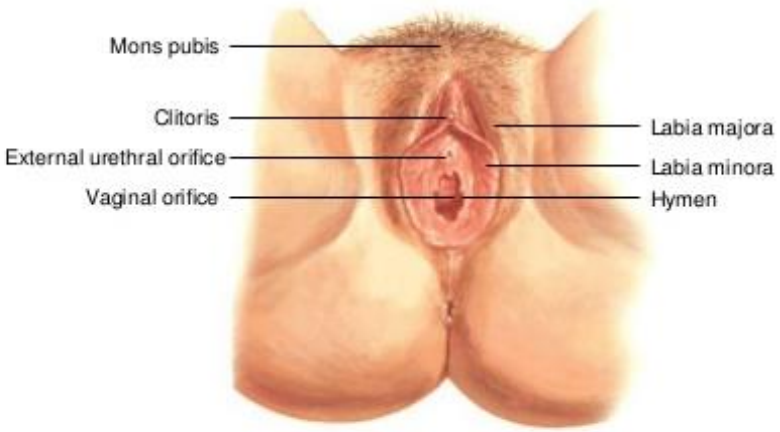

Figure 1. Female external genitalia (vulva) (110)

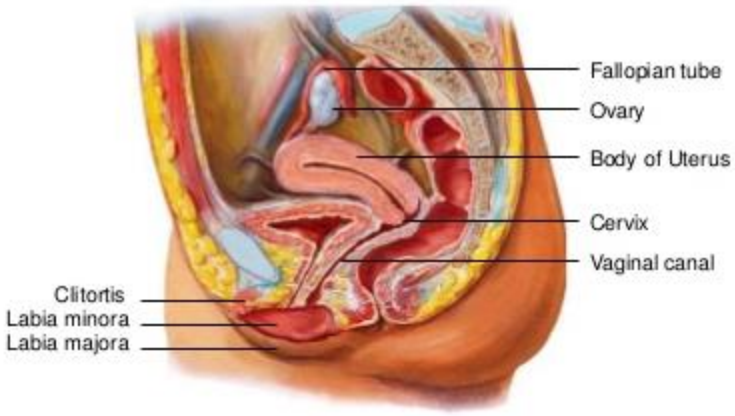

Figure 2. Female reproductive system (sagittal view) (110)

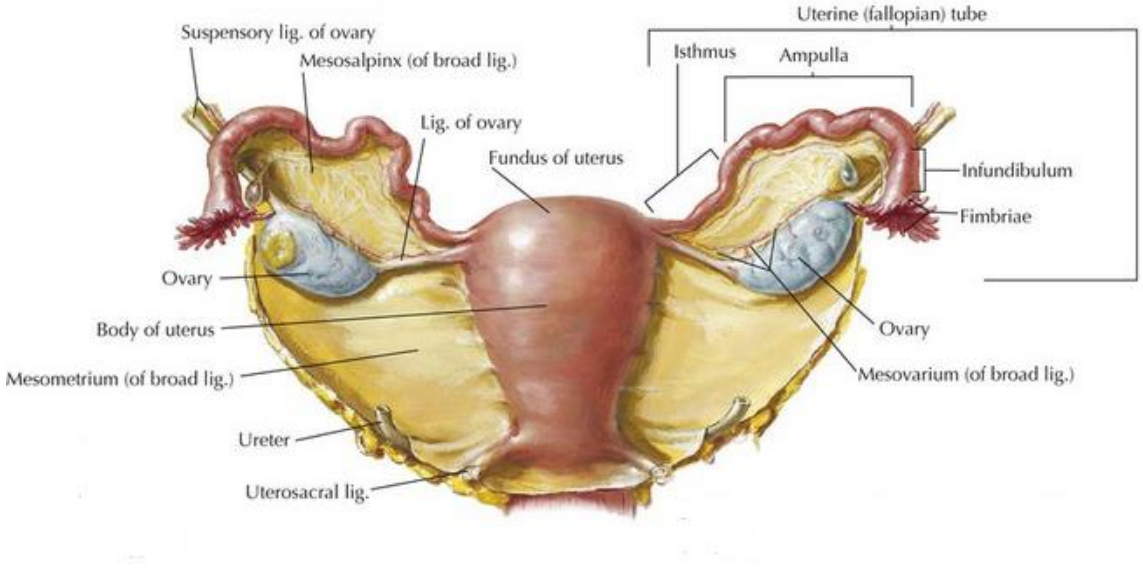

Figure 3. Uterus and adnexa (posterior view) (110)

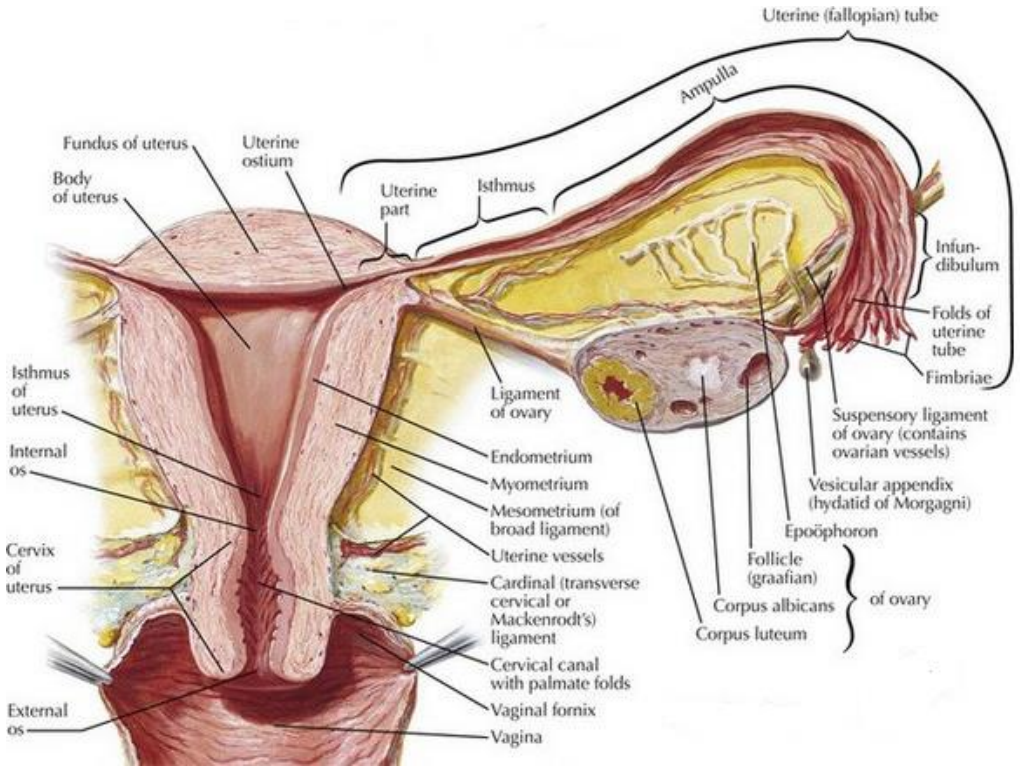

Figure 4. Uterus and adnexa (frontal section) (110)

Surgery is the mainstay of treatment for gynaecological cancer patients (111) and is the most effective treatment if the diagnosis is made at an early stage. Other treatment options are single or combination modality treatments including chemotherapy, radiotherapy, hormone and targeted treatments.

Staging and classification

Cancer staging is the means by which the extent of disease is uniformly described. It is a fundamental aspect of the diagnostic process leading to the most appropriate treatment selection for the patient. The most widely used system is the tumor node metastasis (TNM) system maintained collaboratively by the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) (112):

T - size or extent of the primary tumor

N - absence or presence and extent of cancer in the regional draining lymph nodes

M - absence or presence of distant metastases

For each of T, N, and M categories, the use of increasing values denotes progressively greater extent of disease (112) and include the following values: $T_{[0-4]}$, $N_{[0-3]}$, $M_{[0-1]}$.

Further classification of stage may be designated as follows:

Clinical/pre-treatment stage: cTNM or TNM

Pathologic stage: pTNM

Post-therapy/post-neoadjuvant therapy stage: ycTNM or ypTNM

Retreatment/recurrence classification: rTNM

Autopsy classification: aTNM

Gynaecological cancer s**taging systems** are determined by the International Federation of Gynecology and Obstetrics (FIGO). There are site-specific staging systems, each of which is outlined below in the relevant section. However, in general, there are five stages:

Stage 0: carcinoma in situ (common in cervical, vaginal and vulval cancer);

Stage I: confined to the organ of origin;

Stage II: invasion of surrounding organs or tissue;

Stage III: spread to distant nodes or tissue within the pelvis;

Stage IV: distant metastasis(es);

Cervical Cancer

Incidence and Epidemiology

Cervical cancer ranks as the fourth most commonly diagnosed and the fourth leading cause of cancer death in women worldwide (113). In Ireland, approximately 264 new cases are diagnosed and 88 deaths occur per year (114). The most significant cause is persistent human papillomavirus (HPV) infection, detected in 99% of cervical tumours. HPV 16 and 18 are the most common oncogenic subtypes (115). The Papanicolaou (pap) test, a cytology-based test, is currently the standard method for cervical cancer screening in Ireland. A HPV-based cervical screening test is being introduced; it demonstrates greater sensitivity for pre-cancerous, high-grade cervical intraepithelial neoplasia (CIN 2+) (114) and greater protection against invasive cancer when compared to the pap test (116). Primary prevention is now available through immunisation with HPV vaccines.

Diagnosis and Pathology

When cervical cytology yields a high grade abnormality, colposcopy is indicated to facilitate biopsy and/or excision of the transformation zone of cervix. Early cervical cancer is often asymptomatic. Symptoms of cervical cancer include abnormal vaginal bleeding, discharge, pain and bladder and rectal dysfunction.

Although the WHO describes a number of histological types, it recognises three categories of epithelial tumours of the cervix: squamous, adenocarcinoma and other epithelial, which includes adenosquamous, neuroendocrine and undifferentiated (115). Squamous cell carcinomas account for approximately 70-80%, adenocarcinoma approximately 20-25% (115).

Staging

Cervical cancer is staged using the FIGO and TNM staging classification. The FIGO staging for cervical cancer was updated in 2018. The prospective study outlined in Chapter 4 began recruitment prior to its introduction so the previous version has been used to report disease stage in this study. Both tables have been included for completeness (Tables 2 and 3). FIGO stage is one of the most important prognostic factors (115). Staging is based on tumour size, vaginal or parametrial involvement, bladder/rectal extension and distant metastases (115).

Management

a) Early disease

Surgery is the appropriate treatment for patients with earlier stage disease, that is, up to FIGO IIA. Treatments include conisation or simple trachelectomy for microinvasive disease (IA1) with no lymphovascular space invasion in order to preserve fertility, and simple hysterectomy for patients not requiring fertility preservation. Surgical assessment of lymph nodes, including the sentinel lymph node, should be part of treatment for microinvasive disease with lymphovascular space invasion. Radical surgery excises upper vagina and parametrium at hysterectomy and trachelectomy. Standard treatment for FIGO stage IA2, IB and IIA is radical surgery with pelvic lymphadenectomy.

Adjuvant treatment

A number of risk factors, which are identifiable on the pathological specimen post-hysterectomy, are used as indicators for adjuvant treatment for FIGO stage IA2, IB and IIA. These have been divided into intermediate and high risk factors. Intermediate risk factors include deep cervical stromal invasion (to the middle one-third depth),

lymphovascular space invasion and large tumour size (> 4cm). Individually they do not increase recurrence rate; however, when combined, the risk of recurrence is similar to high risk factors (115). High risk factors include positive or close surgical margins, positive lymph nodes or microscopic parametrial involvement (115). Adjuvant chemoradiotherapy is recommended for these patients as it may improve progression-free survival and overall survival.

b) Locally advanced disease

Concurrent platinum-based chemoradiation therapy is standard treatment for bulky FIGO IB2-IVA. Weekly cisplatin 40mg/m^2 is the most commonly used regimen (115). Pelvic exenteration (surgical removal of all pelvic organs) may also be used in selected cases of stage IVA and recurrent disease.

c) Metastatic disease

For patients with an ECOG performance status < 2 and no contraindications, palliative chemotherapy may be an option in advanced disease for relief of symptoms. Cisplatin and paclitaxel in combination with bevacizumab, an anti-angiogenic monoclonal antibody which targets vascular endothelial growth factor, is the preferred first-line regimen in metastatic or recurrent disease (115). Short course radiotherapy can be effective for symptom palliation.

Cisplatin and paclitaxel in combination with bevacizumab is also the preferred first-line regimen in recurrent disease. Radiotherapy or pelvic exenteration are options for patients who relapse following primary surgery.

Table 1. Staging of cervical cancer by FIGO and TNM classification (115)

FIGO	TNM	Description
	TX	Primary tumour cannot be assessed
	T0	No evidence of primary tumour
	T_{is}	Carcinoma in situ (pre-invasive carcinoma)
I	T1	Tumour confined to the cervix[a]
IA	T1a[b,c]	Invasive cancer diagnosed only by microscopy. Stromal invasion with a maximal depth of 5 mm measured from the base of the epithelium and a horizontal spread of 7 mm or less[d]
IA1	T1a1	Measured stromal invasion ≤ 3 mm in depth and ≤ 7 mm in horizontal spread
IA2	T1a2	Measured stromal invasion > 3 mm and not more than 5mm in depth and a horizontal spread of ≤ 7 mm[d]
IB	T1b	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
IB1	TIB1	Clinically visible lesion 4 cm or less in greatest diameter
IB2	TIB2	Clinically visible lesion more than 4cm in greatest diameter
II	T2	Tumour invades beyond uterus but not to pelvic wall or to lower third of vagina.
IIA	T2a	Tumour without parametrial invasion
IIA1	T2a1	Clinically visible lesion 4 cm or less in greatest diameter
IIA2	T2a2	Clinically visible lesion more than 4cm in greatest diameter
IIB	T2b	Tumour with parametrial invasion
III		Tumour involves lower third of vagina, or extends to pelvic sidewall or causes hydronephrosis or non-functioning kidney
IIIA	T3a	Tumour involves lower third of vagina
IIIB	T3b	Tumour extends to pelvic wall or causes hydronephrosis/non-functioning kidney
IVA	T4	Tumour invades mucosa of the bladder or rectum or extends beyond the true pelvis[e]
	NX[f]	Regional lymph nodes cannot be assessed
	N0[f]	No regional lymph node metastasis
	N1[f]	Regional lymph node metastasis
	M0[f]	No distant metastasis
	M1[f]	Distant metastasis (includes inguinal lymph nodes and intraperitoneal disease). It excludes metastasis to vagina, pelvic serosa and adnexa.

[a] Extension to the corpus uteri should be disregarded
[b] The depth of invasion should be taken from the base of the epithelium, either surface of glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelia-stromal junction of the adjacent most superficial papillae to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification.
[c] All macroscopically visible lesions even with superficial invasion are T1b/IB.
[d] Vascular space involvement, venous or lymphatic, does not affect classification.
[e] Bullous oedema is not sufficient to classify a tumour as T4
[f] No FIGO equivalent

Table 2. Staging of cervical cancer by FIGO 2018 (117)

FIGO	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion < 5 mm[a]
IA1	Measured stromal invasion < 3 mm in depth
IA2	Measured stromal invasion ≥ 3 mm and < 5mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥ 5mm (greater than Stage IA), lesion limited to the cervix uteri[b]
IB1	Invasive carcinoma ≥ 5mm depth of stromal invasion, and < 2cm in greatest dimension
IB2	Invasive carcinoma ≥ 2cm and < 4cm in greatest dimension
IB3	Invasive carcinoma ≥ 4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower 1/3 of the vagina or to the pelvic wall
IIA	Involvement limited to the upper 2/3 of the vagina without parametrial involvement
IIA1	Invasive carcinoma < 4cm in greatest dimension
IIA2	Invasive carcinoma ≥ 4cm in greatest dimension
IIB	With parametrial involvement but not onto the pelvic wall.
III	The carcinoma involves the lower 1/3 of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes[c]
IIIA	The carcinoma involves the lower 1/3 of the vagina but no extension onto pelvic wall.
IIIB	Extension onto the pelvic wall and/or hydronephrosis/non-functioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumour size and extent (with r and p notations)[c]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma had extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder and/or rectum. (A bullous oedema, as such, does not permit a case to be allotted to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

When in doubt the lower staging should be assigned.
[a]Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumour size and extent, in all stages.
[b]The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.
[c]Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC.

Endometrial Cancer

Incidence and Epidemiology

Endometrial cancer is the most common gynaecological cancer in developed countries (118). Its incidence is increasing (119), which may at least in part be due to the rising obesity rates and more sedentary lifestyle. Nearly 500 new cases are diagnosed per year in Ireland, with more than 90% of cases occurring in women > 50 years (120).

The main risk factor is unopposed endogenous or exogenous oestrogen exposure. It is associated with obesity, diabetes and tamoxifen (119). Genetic predisposition also plays a role; Lynch syndrome, an autosomal dominant syndrome, accounts for up to 5% of endometrial cancers. The life time risk of developing endometrial cancer with Lynch syndrome is up to 60% (121) .

Diagnosis and pathology

The majority of endometrial cancers are diagnosed early (80% at stage I) (118, 122), mainly because abnormal uterine bleeding is the presenting red flag symptom in 90% of cases (123). A biopsy of the endometrial lining is the definitive investigation to confirm diagnosis. It may be performed by endometrial pipelle sampling or hysteroscopic biopsy. Patients with advanced disease may experience symptoms such as abdominal or pelvic pain and distension (119).

Endometrial cancer is broadly divided into 2 main sub-types: Type 1 endometrioid adenocarcinoma (80-90%) frequently arise from complex, atypical hyperplasia and is linked to excess oestrogen stimulation (124). Typically it has a good prognosis and low recurrence rate. Type 2 non-endometrioid carcinoma (10-20%) develops from an atrophic

endometrium (124) and is considered high grade by definition (122). High grade includes grade 3 endometrioid, the type 2 non-endometrioids - serous, clear-cell, undifferentiated carcinomas - and carcinosarcoma/malignant-mixed Müllerian tumour.

Staging and risk assessment

Endometrial cancer is a surgically staged disease (122). Staging is according to the FIGO system (Table 4) (125). Stage I can be further divided into the following three risk categories:

Low risk	Stage IA (Grade 1 and 2) with endometrioid type
Intermediate risk	Stage IA Grade 3 with endometrioid type Stage IB (Grade 1 and Grade 2) with endometrioid type
High risk	Stage IB Grade 3 with endometrioid type All stages with non-endometrioid

Histological sub-type, grade 3 histology, myometrial invasion ≥ 50%, lymphovascular space invasion, lymph node metastases and tumour diameter > 2cm are factors which confer a high risk of recurrence (123).

Management of Stage I and II

Surgery is the cornerstone of management for most patients. Standard treatment for stage I consists of total hysterectomy with bilateral salpingo-oophorectomy and lymph node assessment, with or without lymphadenectomy (123). A hysterectomy with bilateral salpingo-oophorectomy and systematic pelvic lymphadenectomy with or without para-aortic lymphadenectomy is the treatment for stage II disease (123).

Table 4. Staging of endometrial cancer by FIGO and TNM classification (125)

FIGO Stage	TNM	Description
I[a]	T1	Tumor confined to the corpus uteri
IA [a]	T1a	No or less than half myometrial invasion
IB [a]	T1b	Invasion equal to or more than half of the myometrium
II [a]	T2	Tumor invades cervical stroma, but does extend beyond the uterus[b]
III [a]	T3 or N1-2, or both	Local and/or regional spread of the tumor
IIIA [a]	T3a	Tumor invades the serosa of the corpus uteri and/or adnexae[c]
IIIB [a]	T3b	Vaginal involvement and/or parametrial involvement[c]
IIIC [a]		Metastases to pelvic and/or para-aortic lymph nodes[c]
IIICl [a]	N1	Positive pelvic nodes
IIIC2 [a]	N2	Positive para-aortic nodes with or without positive pelvic lymph nodes
IV [a]		Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA [a]	T4	Tumor invasion of bladder and/or bowel mucosa
IVB [a]	M1	Distant metastasis, including intra-abdominal metastases and/or inguinal nodes

[a] Either Grade 1, Grade 2 or Grade 3
[b] Endocervical glandular involvement only should be considered as Stage l and no longer as Stage ll
[c] Positive cytology has to be reported separately without changing the stage.

Minimally invasive surgery (laparoscopy or robotic) may be considered for staging of non-bulky endometrial cancer, as it is associated with reduced post-operative length of stay and fewer complications (119). Lymphadenectomy is a key part of the full surgical staging of endometrial cancer (118). Surgical pelvic and para aortic lymph node assessment is considered even when the disease appears to be confined to the uterus. The ASTEC trial showed no overall or recurrence-free survival benefit from lymphadenectomy (126). Histopathology lymph node status facilitates tailoring of adjuvant treatment and may reduce the risk of recurrence in those at high risk (127).

Full pelvic radiotherapy (external beam directed at the tumour) and brachytherapy (implanting a radioactive source within the body adjacent to the tumour) may be considered

for treatment of stage II disease if upfront surgery is not feasible due to tumour extension and/or medically inoperable patients (124).

Adjuvant treatment

The indication for adjuvant pelvic radiotherapy is determined by the presence of risk factors. Vaginal brachytherapy is the standard adjuvant treatment for patients with high/intermediate risk factors (124). It can be used alone if there is grade 1-2 tumour, myometrial invasion <50%, no lymphovascular space invasion, complete surgical staging and histopathological negative lymph nodes. Platinum-based chemotherapy and radiotherapy can be considered for stage 1 grade 3 and stage II disease with risks factors including patient > 60 years, deep myometrial invasion, grade 3 tumour, serous or clear cell histology, lymphovascular space invasion (123).

Management of Stage III-IV

In stage III disease, complete surgical resection of all pelvic and/or nodal disease is indicated for patients with resectable tumour and good performance status (123), followed by post-operative external beam radiation treatment and/or platinum-based chemotherapy (124). Optimal management of patients with Stage IV disease includes cytoreductive surgery, which is associated with better overall survival (128), followed by chemotherapy. Carboplatin and paclitaxel are recommended as standard for adjuvant treatment in Stage III and IV (124). Hormonal treatment e.g. progesterone has a limited role.

For unresectable, Stage III-IV disease, treatment can include pelvic irradiation with or without chemotherapy (129); surgery may be an option if disease is considered resectable

on completion of treatment (124). Combined treatments have demonstrated improved progression-free survival and a reduction in the risk of relapse in stage IIIC (130).

External radiation may be used to provide local tumour control and palliation of symptoms such as vaginal bleeding or pain (124).

Ovarian, Fallopian tube and Peritoneal Cancer

Incidence and Epidemiology

Ovarian cancer is the 6th most common cancer in women with over 411 news cases each year in Ireland (131). It is associated with the worst prognosis and highest mortality rate amongst the gynaecological cancers (132, 133) with a 5-year overall survival rate of 25-35% (134). Worldwide the incidence varies geographically, with North America (132) and northern European countries (135) having the highest incidence. The majority of cases are in women over 50 years. Although aetiology is unclear, risk factors include nulliparity/low parity, obesity, exogenous oestrogen and family history.

Pre-disposition to developing ovarian cancer doubles by having a first degree relative with breast or ovarian cancer. Inherited germline mutations in BRCA 1 or BRCA 2 genes increase the risk of ovarian cancer in carriers. BRCA 1 confers an overall risk of 16-39%, while carriers of the BRCA 2 germline mutation have an overall risk of 11-16% of ovarian cancer (136). Women with Lynch syndrome have a 12% lifetime risk of ovarian cancer (137). Identification of inherited genetic risk factors have treatment implications for the individual but also necessitate appropriate counselling, genetic testing and possible prophylactic surgical management of family members.

Pathology and Diagnosis

The majority of ovarian malignancies are epithelial, with stromal and germ cell accounting for approximately 10% of all ovarian cancers (138). Five major histological epithelial tumour sub-types are described by the WHO, namely high-grade serous, low-grade serous, endometrioid, clear cell and mucinous ovarian carcinoma (139).

High grade serous carcinoma is the most common histological subtype (135), in both ovary and fallopian tube (140) and accounts for more than 90% of all advanced ovarian cancer (135, 141). High-grade serous and low-grade serous are recognised as two distinct subtypes, with low-grade serous being relatively resistant to chemotherapy compared to high-grade serous. Endometrioid ovarian cancers are usually diagnosed early and are low grade (135). Clear-cell and mucinous ovarian cancers are rare, but most are diagnosed at an early stage, when surgery may be curative. Both, however, are challenging to treat in the adjuvant setting (142, 143).

Patients with disease confined to the ovary may have none or few symptoms. Patient-reported symptoms at all stages may include abdominal pain or discomfort, bloating, nausea, constipation, weight loss, diarrhoea, urinary frequency and fatigue (144). The broad and vague nature of the symptoms often results in delay in diagnosis. Seventy percent of patients with epithelial ovarian cancer are at an advanced stage of disease at diagnosis (145), when ascites, early satiety and anorexia are all commonly reported. Clinical and morphological findings including age, tumour fixation, ascites, radiological complexity with evidence of metastatic disease and elevated tumour makers (CA125) strongly support an ovarian cancer diagnosis (135).

Staging and Risk Assessment

In 2014, the Gynecologic Oncology Committee of FIGO revised the staging for ovarian cancer to incorporate ovarian, fallopian tube, and peritoneal cancer in the same system (140). FIGO staging is a strong indicator of prognosis (Table 5) (135). Histological subtype and maximum diameter of residual disease after cytoreductive surgery are also independent prognostic factors (140). Patients with epithelial ovarian cancers confined to the ovary or fallopian tube at initial diagnosis have a relatively good prognosis, however more than two-thirds of all epithelial ovarian cancers are Stage III or Stage IV at diagnosis.

In conjunction with pre-operative imaging for guidance, surgery is the standard approach to staging. Comprehensive surgical staging and volume of residual disease following cytoreductive surgery are independent prognostic factors for overall survival and disease-free survival in ovarian cancer. If surgical staging is not an option, a biopsy, whether image-guided or laparoscopic, should be taken (135).

Table 5. Cancer of the ovary, fallopian tube and peritoneal cancer staging system with corresponding TMN

Stage l. Tumor confined to ovaries or fallopian tube (s)
T1-N0-M0
1A: Tumor limited to 1 ovary (capsule intact) or fallopian tube surface; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
T1a-N0-M0
1B: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
T1b-N0-M0
1C: Tumor limited to 1 or both ovaries or fallopian tubes, with any of the following:
1C1: surgical spill
T1c1-N0-M0
1C2: capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
T1c2-N0-M0
1C3: malignant cells in the ascites or peritoneal washings
T1c3-N0-M0
Stage II. Tumor involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
T2-N0-M0
IIA: extension and/or implants on uterus and/or fallopian tubes and/or ovaries
T2a-N0-M0
IIB: extension to other pelvic intraperitoneal tissues
T2b-N0-M0
Stage III. Tumor involves 1 or both ovaries or fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
T1/T2-N2-M0
IIIA1: positive retroperitoneal lymph nodes only (cytologically or histologically proven): IIIA1(i) Metastasis up to 10mm in greatest dimension IIIA1(ii) Metastasis more than 10mm in greatest dimension IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
T3a2-N0/N1-M0
IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
T3b2-N0/N1-M0
IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)
T3c-N0/N1-M0
Stage IV. Distant metastasis excluding peritoneal metastases
Stage IVA: Pleural effusion with positive cytology Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)
Any T, any N, M1

Management of Early Stage Disease

The treatment for early stage ovarian cancer (I-IIA) is surgery, the goal of which is complete surgical resection and comprehensive staging of the tumour. This allows for appropriate adjuvant treatment planning and complete surgical staging improves disease-free and overall survival (146).

Non-fertility sparing surgery should include peritoneal washings, inspection and palpation of all peritoneal surfaces, bilateral salpingo-oophorectomy and total abdominal hysterectomy, infra-colic omentectomy, appendicectomy, biopsy of any lesion suspicious for metastasis, biopsy or resection of any adhesions in the abdominal field adjacent to the tumour and pelvic and para-aortic lymph node dissection up to the renal veins (135, 146)

Fertility-sparing surgery is possible but only following discussion with the patient in apparent stage I (unilateral) early-stage disease, where it is considered safe to leave the uterus and contralateral ovary in situ (147), and in conjunction with complete surgical staging (135, 146).

Adjuvant treatment

For patients with high-risk early-stage ovarian cancer or for sub-optimally staged patients, adjuvant chemotherapy – either single agent carboplatin or carboplatin and paclitaxel - should be part of the treatment plan.

Management of Advanced Disease

Surgery is also the cornerstone of treatment in advanced disease. The principal objective is complete cytoreduction or primary debulking i.e. zero residual macroscopic disease.

Complete cytoreduction increases overall survival and progression-free survival (148). Patients should be referred to specialist cancer centres where suitable surgical expertise is available to achieve the best outcomes (135). Surgical treatment for patients with advanced disease includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy in addition to bowel resection, peritoneal stripping, diaphragmatic resection, splenectomy and removal of bulky pelvic and para-aortic lymph nodes. Systematic pelvic and para-aortic lymphadenectomy of node negative lymph nodes is not associated with overall survival or progression-free survival (149). Adjuvant chemotherapy, the standard treatment being a combination of paclitaxel and carboplatin, is also appropriate for treatment of advanced disease following cytoreductive surgery (II-IV) (135).

Primary cytoreductive surgery may not be appropriate if the patient is frail or the disease is not fully resectable. Platinum-based neoadjuvant chemotherapy, usually 3–4 cycles, followed by surgery and then a further 2-3 cycles of chemotherapy is an alternative approach in advanced disease. Neoadjuvant chemotherapy decreases post-operative morbidity, while offering equivalent overall survival compared to primary cytoreductive surgery in patients with poor performance or nutritional status, higher tumour burden at presentation or co-morbidities with scope for improvement (150, 151).

Adjuvant treatment

Following neoadjuvant chemotherapy, if the tumour burden reduces sufficiently, patients may become eligible for interval cytoreductive surgery, the aim of which is optimal resection of residual disease, similar to primary cytoreduction.

Bevacizumab is used in the first-line setting with carboplatin and paclitaxel, after which it may be continued as single-agent maintenance therapy for stage III or IV disease following cytoreductive surgery (135).

1.3.4.6 Management of relapsed disease

More than two-thirds of patients will relapse in the first 3 years following completion of treatment (135). Surgery may be an option, particularly for those patients where complete cytoreduction had been achieved at their first surgery (152).

For those with platinum-sensitive disease, a re-challenge with further platinum-based chemotherapy in combination with non platinum-based chemotherapy may be considered. In addition to this, poly ADP ribose polymerase inhibitors (PARPi) may also be used as maintenance therapy for the patients with platinum-sensitive disease (153).

Bevacizumab has been found to improve progression-free survival when used in combination with standard chemotherapy for platinum-sensitive and platinum-resistant recurrent ovarian cancer (154, 155).

Vaginal Cancer

Incidence and Epidemiology

Primary vaginal cancer, defined as a cancer found in the vagina without clinical or histological evidence of cervical or vulval cancer or a history of these cancers in the previous five years (156), is very rare (157); it accounts for only 1–2% of gynaecological

cancers. Previously more common in elderly and post-menopausal women, incidence of vaginal cancer is rising in younger women, mainly due to the increase in persistent high-risk HPV infections, particularly with the HPV 16 subtype (158).

Diagnosis and Pathology

Diagnosis is made through biopsy of the lesion and clinical assessment to ensure there is no evidence of cervical or vulval disease (157). Squamous cell carcinoma is the predominant histologic subtype (~ 90% of cases), followed by adenocarcinoma (~ 8–10% of cases). Other histological subtypes including small cell neuroendocrine, sarcomas, melanomas of the vagina are extremely rare.

Staging

Cancer of the vagina is primarily clinically staged, based on a physical exam, biopsy and pre-treatment imaging (157). The FIGO staging for primary vaginal cancer is shown in Table 6.

Table 6. Staging of vaginal cancer by FIGO and TNM classification (125, 157)

FIGO stage	TNM	Description
	T1a	The cancer is only in the vagina and is no larger than 2.0 cm (T1a)
I	N0	It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
	M0	
	T1b	The cancer is only in the vagina and is larger than 2.0 cm (T1b)
I	N0	It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
	M0	
	T2a	The cancer has grown through the vaginal wall, but not as far as the pelvic wall and is no larger than 2.0 cm (T2b)
II	N0	It had not spread to nearby lymph nodes (N0) or to distant sites (M0)
	M0	
	T2b	The cancer has grown through the vaginal wall, but not as far as the pelvic wall and is larger than 2.0 cm (T2b)
II	N0	It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
	M0	
	T1 to T3	The cancer can be any size and might be growing into the pelvic wall, and/or growing into the lower one-third of the vagina and/or has blocked the flow of urine (hydronephrosis), which is causing kidney problems (T1 to T3)
	N1	It has also spread to nearby lymph nodes in the pelvis or groin (inguinal) area (N1) but not distant sites (M0)
	M0	
III	or	
	T3	The cancer is growing into the pelvic wall, and/or growing into the lower one-third of the vagina and/or has blocked the flow of urine (hydronephrosis), which is causing kidney problems (T3)
	N0	It has not spread to nearby lymph nodes (N0) or to distant sites (M0)
	M0	
	T4	The cancer is growing into the bladder or rectum or is growing out of the pelvis (T4)
IVA	Any N	It might or might not have spread to lymph nodes in the pelvis or groin (inguinal area) (Any N). It has not spread to distant sites (M0)
	M0	
	Any T	The cancer has spread to distant organs such as the lungs or bone (M1). It can be any size and might or might not have grown into nearby structures or organs (Any T)
IVB	Any N	It might or might not have spread to nearby lymph nodes (Any N)
	M1	

Management of Early Stage Disease

The role of surgery is limited in primary vaginal cancer by the proximity to the bladder, urethra and rectum. It is used in the treatment of early (stage 1) disease and for small lesions confined to the vaginal mucosa (less than 2 cm) (157).

Management of upper vaginal disease is radical hysterectomy, vaginectomy (aiming for 1 cm disease-free margins) and pelvic lymphadenectomy. Radical vaginectomy with pelvic lymphadenectomy can be performed if the uterus has already been removed (157).

Lower third vaginal disease may be treated with radical wide local excision with 1 cm disease-free margins and bilateral groin node dissection.

Management of advanced disease

External beam radiation with or without a brachytherapy boost is the mainstay of treatment in advanced disease (157, 159). The optimal dose is 70 Grays (Gy) (160). Significant grade 3 and 4 toxicities have been reported with higher doses (161). External beam radiation to the pelvis incorporates the external iliac and obturator nodes and the inguinal nodes may be included if the tumour is in the distal vagina. Ovarian transposition prior to definitive radiation treatment may be offered to young women to prevent radiation-induced menopause.

Given the rarity of this disease, the numbers of patients available for research are usually small. However, there may be a role for concurrent cisplatin or fluorouracil (5FU)-based chemoradiation in the primary treatment of advanced vaginal cancer (162).

Pelvic exenteration is an option in recurrence if disease is central and isolated (157).

Vulval Cancer

Incidence and Epidemiology

Vulval cancer is uncommon, accounting for approximately 4% of all gynecological malignancies worldwide (163). Like vaginal cancer, vulval cancer was previously considered a disease of post-menopausal women, but an increase in incidence in younger women recently has been noted (164). The global rise in HPV infections has led to this shift in incidence and age of presentation (165).

Diagnosis and Pathology

Vulval cancer may be asymptomatic. However, most women present with vulval pruritus or pain; they may also have abnormal bleeding or discharge or may have noticed a lump or ulcer (165). For some, symptoms may be longstanding due to underlying lichen sclerosus. Diagnosis is confirmed by biopsy. It is recommended not to excise the entire lesion at the time of biopsy, as this may negatively impact subsequent definitive surgery (166).

Squamous cell carcinoma of the vulva is the most common (>80%) histological subtype (165). There are two main aetiological pathways which result in vulval carcinoma: keratinising squamous cell carcinoma and warty/basaloid squamous cell carcinoma. Keratinising squamous cell carcinoma usually occurs in older women. It is frequently associated with non-neoplastic epithelial conditions such as lichen sclerosus and/or differentiated vulval intraepithelial neoplasia (dVIN) (165). Warty/basaloid squamous cell carcinoma generally occurs in younger women. It is caused by persistent infections

with oncogenic HPV, particularly HPV 16, 18, 31, 33 subtypes. Basal cell carcinoma, verrucous carcinoma, Paget's disease of the vulva, adenocarcinoma and Bartholin gland carcinoma make up the remaining 20%, although these are all very rare histological sub-types.

Staging

Vulval cancer is surgically staged, according to the FIGO (Table 7). This staging system is not suitable for melanoma of the vulva. Final staging is based on histological evaluation of the vulval lesion and lymph nodes.

Management of Early Disease

Treatment for vulval cancer is predominantly surgical and this should be individualised so that the most conservative surgery that will result in cure is performed (167). Management of the vulval lesion and the groin lymph nodes are approached separately, as this can help maximize the chance of cure, while minimizing treatment-related morbidity (165).

Radical wide local excision of the tumour is the gold standard of treatment (165). If maximum depth of invasion is $\leq$ 1mm (stage 1A), lymphadenectomy is not necessary (165). The traditional approach to lymphadenectomy was full excision of femoral and inguinal lymph nodes through separate incisions.

Table 7. FIGO staging for cancer of the vulva

FIGO stage		Description
I		Tumor confined to the vulva
	IA	Lesions ≤ 2cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1.0mm[a], no nodal metastasis
	IB	Lesions > 2cm in size or with stromal invasion > 1.0mm[a], confined to the vulva or perineum, with negative nodes
II		Tumor of any size with extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with negative nodes
III		Tumor of any size with or without extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with positive inguinofemoral nodes
	IIIA	(i) With 1 lymph node metastasis (≥5mm), or **(ii)** With 1-2 lymph node metastasis(es) (<5mm), or
	IIIB	(i) With 2 or more lymph node metastasis(es) (≥5mm), or (ii) With 3 or more lymph node metastases (<5mm)
	IIIC	With positive nodes with extracapsular spread
IV		Tumor invades other regional (upper 2/3 urethra, upper 2/3 vagina), or distant structures
	IVA	Tumour invades any of the following: (i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa or fixed to pelvic bones or (ii) fixed or ulcerated inguinofemoral lymph nodes
	IVB	Any distant metastasis including pelvic lymph nodes

[a] The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion

For stage IB disease, sentinel lymphadenectomy is now the surgical staging modality of choice. This reduces morbidity and improves disease-specific survival.

Adjuvant treatment

Adjuvant pelvic and inguinal radiation may be used to treat patients who are node-positive (≥1) and who have extracapsular spread confirmed at inguinal lymph node dissection (168).

Management of Advanced Disease

Advanced vulval cancer includes tumours that extend beyond the vulva and/or where there are bulky positive groin nodes (165). Fine needle aspiration or biopsy and radiological imaging should be performed prior to treatment planning. Surgical excision of vulva has a role even in advanced disease to relieve symptoms such as pain and offensive discharge. Radiotherapy with or without prior surgery is indicated for grossly metastatic groin nodes.

Concurrent chemoradiation may be used to palliate large tumours, pelvic and groin metastases and if upfront surgery is likely to damage central structures (165).

Appendix II

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ORIGINAL ARTICLE

Clinical significance of weight changes at diagnosis in solid tumours

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Abstract

Purpose Weight changes occur throughout the cancer trajectory. Most research has focused on changes during or after treatment, so clinical significance of change at diagnosis remains unclear. This study aimed to determine prevalence, predictors and prognostic significance of weight changes at diagnosis in outpatients with solid tumours presenting to a tertiary academic medical centre.

Methods A retrospective study of the electronic medical record was conducted ($n = 6477$). Those with weight recorded within 6 months of cancer diagnosis (pre-diagnosis, T_0) and 2 subsequent weights (diagnosis, T_1; final visit, T_2) were identified ($n = 4258$). Percentage weight change was categorised into four bands (0.1–2.4%; 2.5–5%; 5.01–9.9%; ≥10%) for gain and loss. A stable category was also included.

Results Mean age is 61 ± 12.5 years. Common tumour sites: breast (17%; $n = 725$), prostate (16%; $n = 664$), lung (14%; $n = 599$). 15% ($n = 652$) had metastatic disease at T_1. 98% ($n = 4159$) had weight change at T_1. Head & neck and upper gastrointestinal cancers were significantly associated with weight loss ($p < 0.001$). Worst survival occurred with ≥10% weight gain or ≥10% weight loss. Overweight or obese body mass index with any percentage weight change band was associated with better overall survival.

Conclusions Most had evidence of clinically significant weight changes at diagnosis. Weight loss at diagnosis was associated with a higher risk of further weight loss. A detailed weight history at cancer diagnosis is essential to identify and intervene for those most at risk of weight change-related early mortality.

Keywords Cancer · Prognosis · Survival · Weight gain · Weight loss

Introduction

Weight changes (loss or gain) may occur throughout the cancer trajectory. Most research has examined weight changes after treatment [1–3] and in advanced cancer [2, 4]. A landmark study quantified weight loss at diagnosis and demonstrated an association with lower response to chemotherapy and shorter survival [5]. Recent evidence revealed that weight loss before treatment is associated with increased treatment side effects [6–8]. Despite this, weight loss is infrequently assessed or actively managed [9, 10] and the high prevalence of obesity is not considered. As a consequence, the clinical significance of weight change at diagnosis remains unclear.

Unintentional weight loss is common in people with cancer and a predictor of disease outcome [5, 11]. It is associated with increased morbidity and mortality. Weight loss is the predominant characteristic of cancer cachexia, a syndrome associated with ongoing loss of skeletal muscle mass (with or without fat), progressive functional impairment, and deranged metabolism [12]. Awareness and understanding of cancer cachexia amongst healthcare professionals vary [13, 14]. There is no consensus on the severity of weight loss considered clinically significant [15, 16].

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With the global trend towards overweight and obesity [17], it is increasingly difficult to clinically identify malnourished individuals. At diagnosis, some people with cancer present with a normal, overweight or obese body mass index (BMI). This may mask muscle wasting (sarcopenia) [18, 19]. Muscle wasting associated with simultaneous adiposity (sarcopenic obesity) has a negative survival impact [2, 3]. The effect of obesity is complex [20]. Although usually associated with greater all-cause mortality relative to normal BMI [21], it may confer a survival advantage in cancer [22]. Weight gain during treatment is a positive prognostic factor in ovarian cancer [1, 23]. However, obesity at breast cancer diagnosis [24, 25] and weight gain amongst breast cancer survivors [26, 27] are both associated with poorer outcomes. Obesity is associated with worse outcomes in colon cancer in the adjuvant setting [28].

A recent study investigated the survival impact of BMI and self-reported weight loss at presentation and subsequently proposed a cancer-associated weight loss grading system [22]. It supported the concept that weight loss severity be evaluated based on rate of weight loss and level of body reserve depletion. Previous work had demonstrated that weight gain was prognostic of reduced survival in advanced cancer [29]. That study focused on weight stable and weight loss groups, citing the difficulty associated with elucidating the true nature of weight gain as the reason for its exclusion. The same uncertainty exists with regard to how much weight loss is specifically tumour-driven. Although it is important to recognise the impact of weight loss, the consequences of weight gain should also be examined. Greater clarity on the clinical significance of a weight change spectrum at diagnosis would stimulate early recognition by oncologists of those most at risk and prompt intervention which may improve patient outcomes. To do this, we conducted a retrospective study of a large electronic medical record (EMR) data set of repeated weight measurements. We aimed to determine the prevalence, predictors, and prognostic significance of weight change at diagnosis in people with solid tumours.

Methods

Study design

This was a retrospective study of the EMR held at the Cleveland Clinic Taussig Cancer Institute (© Epic Systems Corporation, Verona, WI). Institutional Review Board approval was granted and the study met the criteria for waiver of informed consent as no protected health information was collected. Inclusion criteria were a primary diagnosis of solid tumour malignancy, age ≥ 18 years and a minimum of two consecutive outpatient weight measurements at the Cleveland Clinic Taussig Cancer Institute. Patients with a primary diagnosis of haematological malignancy, with a single recorded visit at the Cleveland Clinic Taussig Cancer Institute, who were reviewed at or were inpatients in other Cleveland Clinic facilities or those who attended for non-clinical encounters were excluded.

Data collection & handling

Data was extracted from the EMR by the Cleveland Clinic eResearch Team, a clinical informatics research technology group responsible for clinical data warehousing and electronic data extraction. It was downloaded to a Microsoft Excel spreadsheet (Microsoft Office Professional Plus 2013, Microsoft Corporation, Redmond, WA). Institutional regulations were followed for safe data storage and monitoring.

Those with a pre-diagnosis weight (T_0) recorded within 6 months of diagnosis date, a weight at diagnosis (T_1), and a final weight recorded ≥7 days after diagnosis date (T_2) were identified. 'Final weight' refers to the last encounter within the study period when weight was measured. At T_0, only weight data was extracted. At T_1 and T_2, age, gender, primary cancer site, metastatic disease, number of metastatic sites, treatment received, BMI, 'Abnormal Weight Loss' as per the International Classification of Diseases, 9th Revision (ICD-9) Code 783.21 and date of death data were extracted where available. 'Date of death' was obtained from the EMR; if unavailable, it was verified by Social Security Disability Insurance (SSDI) number. Patients were excluded if a secondary cancer was entered in 'Primary Cancer Site'; if 'Primary Cancer Site' was not specified as either primary or secondary; if BMI data was missing; if a discrepancy existed between EMR 'Date of Death' and SSDI 'Date of Death' or if recorded data was invalid.

BMI and weight history

BMI was calculated with the formula: current weight (kg)/height (m^2) and categorised into four groups as per the World Health Organisation (WHO) BMI Classification [30]: underweight (< 18.5), normal (18.5–24.9), overweight (25.0–29.9) and obese (≥30). Clinically significant weight loss or cancer cachexia was defined as weight loss > 5% in the previous 6 months [12].

Weight at each time point was recorded in kilogrammes (kg) to one decimal point. Percentage (%) weight change was calculated with the formula: [(current weight (kg) − previous weight (kg) / previous weight (kg)] × 100. This was categorised into four bands (0.1–2.4%; 2.5–5%; 5.01–9.9%; ≥10%) for both weight gain and weight loss; a

Table 1 Demographics and clinical characteristics at diagnosis and final visit ($N = 4258$)[a]

Characteristic	Diagnosis (T_1)		Final (T_2)	
	N	%	*N*	%
Gender				
Male	2315	54		
Female	1943	46		
Primary site				
Breast	725	17		
Prostate	664	16		
Lung	599	14		
Upper GI	470	11		
Head & neck	320	8		
Uterus	194	5		
Brain	191	4		
Kidney	165	4		
Colon	133	3		
Melanoma	104	2		
Other	693	16		
Treatment[b]				
Radiotherapy			2065	48
Chemotherapy			1868	44
Hormonal therapy			771	18
Biological modifier			762	18
Monoclonal antibodies			282	7
Age at diagnosis, years				
Mean	61		62	
SD	± 12.5		± 12.5	
Weight, kg				
Mean	82.7		81.2	
SD	± 21.2		± 21.4	
BMI, kg/m^2				
Mean	28.5		28.1	
SD	± 6.5		± 6.8	
BMI				
Underweight (< 18.5)	110	3	172	4
Normal (18.5–24.9)	1240	29	1319	31
Overweight (25.0–29.9)	1468	34	1374	32
Obese (≥ 30)	1440	34	1393	33
Weight change				
Weight gain	1705	40	1724	40
Weight stable	99	2	26	1
Weight loss	2454	58	2508	59
Weight change, %[c]				
Mean	− 0.7		− 1.6	
SD	± 3.7		±8.3	
Weight change, %[c]				
≥ 10% WL	65	1.5	673	15.8
5.01–9.9% WL	255	5.9	619	14.5
2.5–5.0% WL	542	12.7	497	11.7
0.1–2.4% WL	1592	37.4	719	16.9
0 (stable)	99	2.3	26	0.6
0.1–2.4% WG	1232	28.9	654	15.4
2.5–5.0% WG	335	7.9	456	10.7
5.01–9.9% WG	112	2.6	401	9.4
≥ 10% WG	26	0.6	213	5

Abbreviations: *BMI* body mass index, *SD* standard deviation, *WG* weight gain, *WL* weight loss

[a] Pre-diagnosis weight within 6 months of diagnosis; final visit ≥ 7 days after diagnosis

[b] > 1 treatment possible

[c] Percentage weight change based on weight recorded in previous 6 months

weight stable category was also documented. A categorical weight variable indicated weight loss, gain, or stability between time points.

Statistics

Demographic and clinical characteristics were analysed to establish if an association with weight change existed. All variables including age (< 65 years; ≥ 65 years) and weight change were analysed as categorical variables using Chi-square test. Overall survival was defined as the number of months from T_1 to date of death. All patients were observed to death or censored at T_2. Mean survival time was calculated as median survival time could not be used given the number censored. Survival analyses were calculated using Kaplan-Meier method (comparisons with Cox-Mantel log rank tests) and Cox proportional hazards model (estimated hazard ratios [HRs] and 95% confidence intervals [CIs]). Hazard ratios for combined BMI-%weight change categories at T_1 were also established. Analyses were completed using Microsoft Excel (Microsoft Office Professional Plus 2013, Microsoft Corporation, Redmond, WA), IBM SPSS Statistics for Windows Version 23 (SPSS, Chicago IL) and Stata Statistical Software: Release 14 (StataCorp. 2015. College Station, TX: StataCorp LP). Results were considered statistically significant if $p < 0.05$ (two-sided).

Results

A total of $n = 4258$ records were included in analysis. Demographic and clinical characteristics are in Table 1. Over half were male (54%) and mean age at diagnosis was

Table 2 Predictive value (survival) of categorical variables in a multivariable model at diagnosis (T_1)

Variable	B	SE	Wald	df	*p*	HR	95% CI for HR	
							Lower	Upper
Gender								
Male								
Female	0.06	0.07	0.67	1	.41	1.06	0.92	1.22
Primary site								
Breast			468.38	10	.00			
Lung	1.99	0.19	110.67	1	.00	7.36	5.07	10.67
Prostate	−0.02	0.26	0.01	1	.93	0.98	0.59	1.62
Upper GI	2.55	0.19	175.72	1	.00	12.83	8.80	18.72
Head & neck	0.86	0.23	13.53	1	.00	2.36	1.49	3.74
Kidney	1.62	0.23	49.00	1	.00	5.03	3.19	7.89
Brain	2.85	0.21	182.02	1	.00	17.29	11.43	26.17
Uterus	1.44	0.29	24.03	1	.00	4.21	2.37	7.48
Colon	1.33	0.26	27.24	1	.00	3.79	2.29	6.26
Malignant melanoma	1.48	0.29	27.08	1	.00	4.41	2.52	7.71
Other	1.74	0.19	81.56	1	.00	5.69	3.90	8.30
Metastatic disease								
Yes	0.80	0.07	119.49		.00	2.23	1.930	2.57
No								
Weight change, %								
≥ 10% WL			36.80	8	.00			
5.01–9.9% WL	−0.61	0.22	7.93	1	.01	0.55	0.36	0.83
2.5–5.0% WL	−0.59	0.20	8.59	1	.00	0.55	0.37	0.82
0.1–2.4% WL	−0.87	0.19	19.70	1	.00	0.42	0.28	0.61
Stable	−0.91	0.32	8.12	1	.00	0.40	0.21	0.75
0.1–2.4% WG	−0.93	0.20	21.27	1	.00	0.39	0.27	0.59
2.5–5.0% WG	−0.78	0.22	12.54	1	.00	0.46	0.29	0.71
5.01–9.9% WG	−0.59	0.29	4.21	1	.04	0.56	0.32	0.97
≥ 10% WG	−0.19	0.37	0.26	1	.61	0.83	0.40	1.70
BMI								
Underweight (< 18.5)			23.57	3	.00			
Normal (18.5–24.9)	−0.31	0.16	3.80	1	.05	0.73	0.54	1.00
Overweight (25–29.9)	−0.59	0.16	13.29	1	.00	0.55	0.40	0.76
Obese (≥ 30)	−0.55	0.17	11.17	1	.00	0.58	0.42	0.79
Age								
< 65								
≥ 65	0.44	0.07	43.24	1	.00	1.55	1.36	1.77

Abbreviations: *BMI* body mass index, *WG* weight gain, *WL*, weight loss

61 ± 12.5 years. The four most common primary sites (lung, breast, prostate and colorectal) accounted for 50% of all cases. Fifteen percent ($n = 652$) had metastatic disease. Twenty-three percent ($n = 981$) had died by T_2. Mean survival time was 24.4 ± 0.6 months.

Weight changes were nearly universal (98%) at T_1 (mean % weight change, −0.7 ± 3.7%). More than half had weight loss but only 3% were underweight and 8% cachectic. Most (69%) were either overweight (35%) or obese (34%) at T_1. Only 3% had 'Abnormal Weight Loss' recorded at T_1. Although weight change was also prevalent (99%) at T_2, mean % weight change was more than twice that at T_1 (mean % weight change, − 1.6 ± 8.3%). Most (59%) had weight loss at T_2. Of those who had weight loss at T_1, 71% continued to lose weight. Forty-two percent of those who had weight gain at T_1, had weight loss at T_2. Despite that most (65%) were still overweight or obese at T_2. Only 4% were underweight and 14% cachectic.

Table 3 Predictive value (survival) of categorical variables in a multivariable model (final visit)

Variable	B	SE	Wald	df	*p*	HR	95% CI for HR	
							Lower	Upper
Gender								
Male								
Female	0.05	0.07	0.46	1	0.49	1.05	0.91	1.21
Primary site								
Breast			445.18	10	0.00			
Lung	2.17	0.20	113.88	1	0.00	8.71	5.86	12.97
Prostate	−0.02	0.27	0.01	1	0.93	0.98	0.58	1.65
Upper GI	2.52	0.21	143.93	1	0.00	12.36	8.19	18.64
Head & neck	0.94	0.25	13.78	1	0.00	2.55	1.56	4.18
Kidney	1.75	0.25	49.64	1	0.00	5.77	3.54	9.39
Brain	3.11	0.23	183.05	1	0.00	22.49	14.33	35.31
Uterus	1.52	0.30	25.24	1	0.00	4.56	2.52	8.25
Colon	1.50	0.27	30.86	1	0.00	4.50	2.65	7.65
Malignant melanoma	1.59	0.29	28.47	1	0.00	4.91	2.74	8.81
Other	1.83	0.21	76.25	1	0.00	6.20	4.12	9.34
Metastatic disease								
Yes	0.73	0.08	86.66	1	0.00	2.07	1.78	2.41
No								
Biological therapy								
Yes								
No	0.01	0.09	0.01	1	0.92	1.01	0.85	1.21
Radiotherapy								
Yes								
No	−0.31	0.07	17.69	1	0.00	0.73	0.64	0.85
Monoclonal therapy								
Yes								
No	−0.15	0.13	1.49	1	0.22	0.86	0.67	1.09
Chemotherapy								
Yes								
No	−0.05	0.08	0.35	1	0.55	0.96	0.82	1.11
Hormonal therapy								
Yes								
No	0.24	0.10	5.41	1	0.02	1.27	1.04	1.56
Weight change, %								
≥ 10% WL			62.89	8	0.00			
5.01–9.9% WL	0.14	0.09	2.24	1	0.14	1.15	0.96	1.38
2.5–5.0% WL	−0.19	0.12	2.63	1	0.11	0.83	0.66	1.04
0.1–2.4% WL	−0.17	0.12	1.93	1	0.17	0.85	0.67	1.07
Stable	0.38	0.51	0.56	1	0.46	1.47	0.54	3.99
0.1–2.4% WG	−0.22	0.12	3.03	1	0.08	0.81	0.63	1.03
2.5–5.0% WG	−0.45	0.15	9.42	1	0.00	0.64	0.48	0.85
5.01–9.9% WG	−0.75	0.16	21.82	1	0.00	0.47	0.35	0.65
≥ 10% WG	−0.91	0.18	25.17	1	0.00	0.40	0.28	0.57
BMI								
Underweight (< 18.5)			29.76	3	0.00			
Normal (18.5–24.9)	−0.24	0.12	3.84	1	0.05	0.79	0.62	1.00
Overweight (25–29.9)	−0.54	0.13	16.93	1	0.00	0.58	0.45	0.75

Table 3 (continued)

Variable	B	SE	Wald	df	*p*	HR	95% CI for HR	
							Lower	Upper
Obese (≥30)	−0.58	0.14	17.77	1	0.00	0.56	0.42	0.73
Age								
< 65								
≥65	0.27	0.07	15.46	1	0.00	1.30	1.14	1.49

Abbreviations: *WL* weight loss, *WG* weight gain, *BMI* body mass index

BMI, metastatic disease and primary cancer diagnosis were significant predictors of % weight change ($p < 0.0001$) at T_1. At T_2, age, BMI, metastatic disease, primary cancer diagnosis ($p < 0.001$) and gender ($p < 0.005$) were significant predictors of % weight change. Treatment modality also predicted % weight change; chemotherapy, hormone therapy, radiotherapy, biological and monoclonal treatments were all significant predictors of % weight change ($p < 0.001$). Chemotherapy and radiotherapy were associated with weight loss ($p < 0.001$); hormone therapy with weight gain ($p < 0.001$).

Those with head & neck (OR = 5.54, $p < 0.001$) or upper gastrointestinal (GI) malignancy (OR = 4.46, $p < 0.001$) were

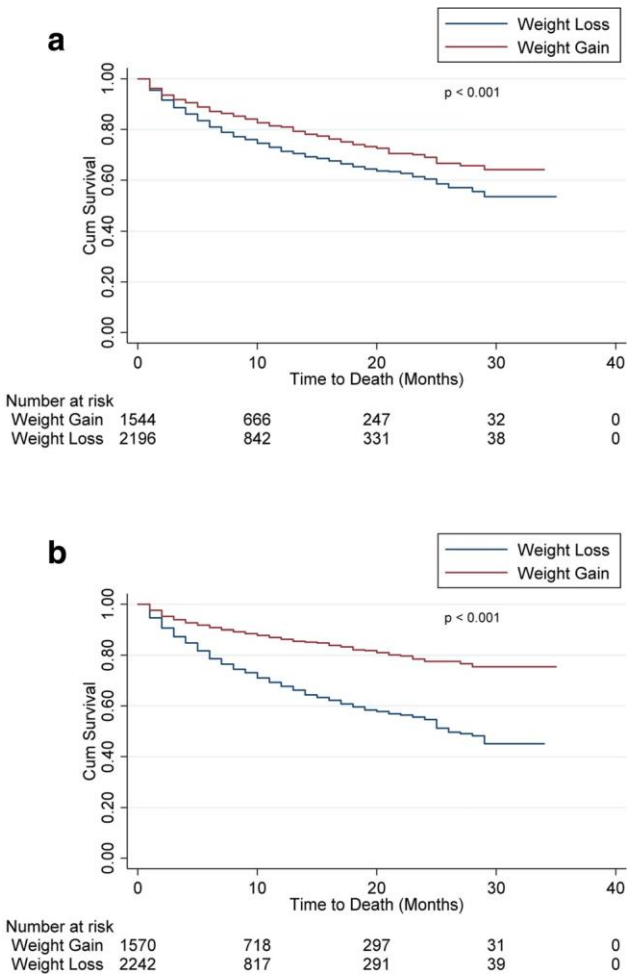

Fig. 1 Kaplan-Meier plot of overall survival by weight change category at (a) diagnosis (T_1) and (b) final visit (T_2)

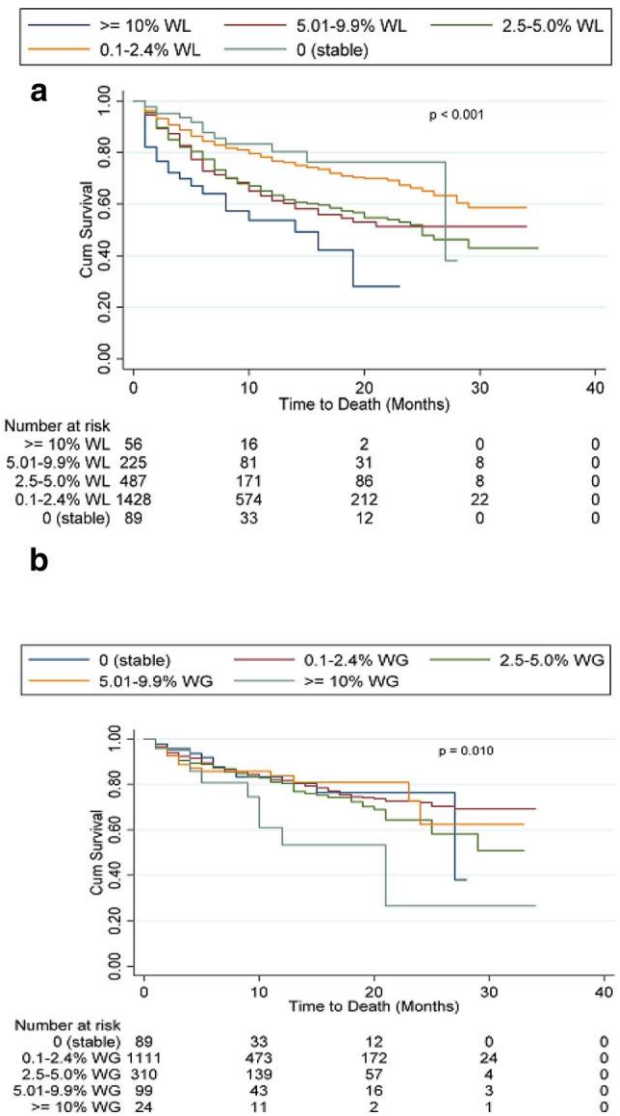

Fig. 2 Kaplan-Meier plot of overall survival by (a) percentage weight loss category and (b) percentage weight gain category at diagnosis (T_1)

Table 4 Combined BMI-percentage weight change categories at diagnosis: number of cases, median survival (months) and hazard ratio

BMI category	Underweight (< 18.5)			Normal (18.5–24.9)			Overweight (25–29.9)			Obese (≥30)			
	N	Median survival	HR	*N*	Median survival	HR	*N*	Median survival	HR	*N*	Median survival	HR	*N*
% Weight change ≥ 10% WL	8	16	2.8	26	8	3.6	17	19	2.0	14	9	3.0	65
5.01–9.9% WL	14	31	1.4	104	11	2.3	80	34	1.1	57	15	2.0	255
2.5–5.0% WL	16	8	3.3	204	14	1.9	198	22	1.5	124	26	1.3	542
0.1–2.4% WL	38	17	2.4	428	29	1.4	545	33	1.1	581	34	0.7	1592
Stable	2	5	4.8	22	21	0.5	35	23	1.0	40	28	0.7	99
0.1–2.4% WG	23	9	2.6	310	34	REF	436	34	0.8	463	34	0.7	1232
2.5–5.0% WG	6	25	2.2	111	27	1.2	116	29	1.2	102	32	0.8	335
5.01–9.9% WG	1	2	14.9	28	23	1.0	36	33	0.7	47	25	1.1	112
≥ 10% WG	2	13	3.2	7	10	3.4	5	15	0.0	12	21	1.6	26
	110			1240			1468			1440			Overall *N*

Abbreviations: *BMI* body mass index, *WL* weight loss, *WG* weight gain

most at risk of weight loss. Patients with metastatic disease were also more likely to have weight loss (OR = 1.68, $p < 0.001$) or be cachectic (OR = 1.36, $p < 0.05$) at T_1.

Cox multivariate analysis identified independent predictors of survival at T_1 (Table 2) and T_2 (Table 3) after controlling for known risk factors. Age (< 65 years), gender (male), primary site (breast, prostate) and loco-regional disease independently predicted better survival at T_1 and T_2. A weight gain of 0.1–2.4% at T_1 and > 5% at T_2 were also predictive of better overall survival. Brain, lung and upper GI malignancies had the shortest survival.

Survival analysis based on weight change (gain or loss) alone showed that those with weight gain at T_1 or T_2 (Fig. 1) had a better overall outcome compared to those who had WL. When individual % weight change bands were analysed, the worst survival was associated with ≥ 10% weight loss and ≥ 10% weight gain (Fig. 2). On analysis of combined BMI-%weight change (Table 4), there was considerable variation across categories but improved survival was associated with those who were overweight or obese at all % weight change bands. With normal BMI/0.1–2.4% weight gain considered best, worst outcomes were mostly associated with increased deviation from this category.

Discussion

Weight change at T_1 was highly prevalent. Weight loss was nearly universally undiagnosed or under-documented, despite an option to record Abnormal Weight Loss in the EMR. Those who had weight loss at T_1 continued to have further weight loss by T_2, but most were still overweight or obese. When weight change was considered in isolation, those who had weight gain were more likely to have longer survival compared to weight loss with one exception: ≥10% weight gain at T_1. More than two thirds of adults in the United States are overweight or obese [31] and both are increasingly seen in the cancer population [18, 32], a trend also evident in this study.

Head & neck and upper GI cancers were most likely to be associated with any weight loss. Nutritional deficits are common with these tumours: their location can cause dysphagia and metabolic changes which may alter appetite and chemosensation. In this study, those with head & neck and upper GI cancers were also more likely to be cachectic at both T_1 and T_2. Cachexia is associated with increased treatment toxicity, reduced quality of life and poorer survival. However, as weight history is not routinely assessed at diagnosis, it is likely that this would go undetected before treatment particularly in those with a high BMI. Given that treatment modality can further impact weight change, it again emphasises the critical need for early recognition of those most at risk to ensure delivery of appropriate supportive care and ongoing surveillance.

This study supports previous evidence of weight loss as a predictor of survival [5, 11]. It also highlights the role weight gain (which may mask sarcopenia) plays in sub-optimal identification of undernourished patients which may impair their survival. Weight gain and loss have both been linked with disease progression. In this study, those with metastatic disease were less likely to have weight gain at T_1 and significantly more likely to be cachectic at T_1 and T_2 than those with loco-regional disease. Although there was minimal change in the number who were overweight or obese from T_1 to T_2, those who were cachectic almost doubled. Cancer treatment and disease

progression may both account for this. It seems weight loss alone is an insufficient marker based on the proposed cancer-associated weight loss grading system [22]. We observed median survival based on combined BMI-%weight change at T_1 was greatest for those overweight at all % weight change bands (Table 4). Weight gain in the underweight group appeared to have a variable impact on survival, making it difficult to draw any definitive conclusions. The small numbers in these groups may have contributed to this variability.

Clinicians may be lured into a false sense of security in those with lesser degrees of weight loss or weight gain. This study shows that any weight loss at diagnosis (including those traditionally considered weight stable i.e. ± 2.5%) are at high risk of further weight loss. ESPEN Guidelines [33] recommend identification of 'nutritional disturbances' through reg- ular evaluation of weight change and BMI beginning at cancer diagnosis. Although the clinician's instinct may be to prioritise those with weight loss, based on our results weight gain also warrants attention.

Perhaps in reality it is the early identification of any weight change which is important for identification of those most at risk. The optimal time is at diagnosis if the opportunity to intervene with timely, targeted interventions is to be taken. Given the negative relationship between survival and ≥10% weight gain observed (Fig. 2b), perhaps a spectrum of cancer-associated weight change should be established with stages of weight gain (i.e. pre-obese, obese, refractory obesity) like the proposed weight loss spectrum [12]. The proposed diagnostic criteria for cachexia [12] provided an initial framework and expanded beyond simple weight loss with the inclusion of muscle mass measurement. More recent research has built on this with the proposed BMI-weight loss matrix [33]. Further refinement of this concept may lead to the inclusion of other factors like inflammatory markers. Based on this research, further insight may be gained from the study of individual primary cancer sites and disease stages. Age and gender may also require further examination.

This study had several strengths. The data was representative of the most common primary cancer sites. It focused on the significance of weight change at diagnosis. This is important given the increased risk of additional weight loss for those with it at diagnosis, further increasing the risk of cachexia. Also, uniquely, it included a true weight stable category i.e. no weight gain or loss.

There were also limitations to this study. Performance status and tumour stage are recognised prognostic factors [1, 5, 29]. Additional data on these could have enabled greater stratification at diagnosis of those most at risk of weight change, potentially further improving patient selection for intervention. Weight change may be disproportionately associated with poorer performance status and more advanced disease stage. Refractory cachexia is associated with a low performance status score, which negatively impacts response to systemic treatment and survival [5], while tumour stage frequently dictates treatment options. However due to the retrospective nature of this study, this data was unavailable as neither performance status nor tumour stage were reliably recorded in the EMR. The generalisability of the results is also limited by this.

Given the important role cachexia and sarcopenic obesity play in treatment tolerability and survival, body composition at diagnosis should be established. To help identify those most at risk, greater emphasis should be placed on the evaluation of more individualised outcomes by diagnosis and disease stage. This will support the recognition of cancer-associated weight change early in the disease trajectory and allow the effectiveness of targeted treatments to be determined. Future studies should include comprehensive information not just on weight change but also performance status and stage of disease.

Conclusions

Many newly diagnosed patients with solid tumours had evidence of clinically significant, yet frequently undiagnosed, weight changes. Worst survival was seen with ≥ 10% weight gain or ≥ 10% weight loss. Survival analysis based on weight change alone showed that those who had weight gain at diagnosis or later had a better overall survival compared to weight loss. Any weight loss at diagnosis increased the chance of further weight loss with the additional risk of treatment toxicities and worse survival. For combined BMI-%weight change data, improved survival was associated with overweight or obese at all % weight change bands. Consideration should be given to the use of a weight change spectrum, which would reflect risk associated with various weight loss and weight gain bands. A detailed weight history at diagnosis and at each subsequent visit for every cancer patient is essential to promptly identify and intervene for those most at risk. Such research would be enhanced by in-depth analysis of the interplay between disease stage, performance status, nutritional status including BMI, and inflammatory markers such as C-reactive protein.

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Compliance with ethical standards

Ethical approval Institutional Review Board approval was granted for this study.

Informed consent This study met the criteria for waiver of informed consent.

Conflict of interest The authors declare that they have no conflicts of interest.

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Appendix III

Odds Ratio Tables

Weight loss x metastatic disease

	OR	95% CI	*p*
No Metastatic Disease	Reference Category		
Metastatic Disease	1.68	1.40-2.00	<0.001

Weight loss x primary cancer site

	OR	95% CI	*p*
Breast Cancer	Reference Category		
Lung	2.13	1.70-2.65	<0.01
Prostate	1.10	0.89-1.36	0.365
Upper GI	4.46	3.43-5.80	<0.001
Head and Neck	5.54	4.03-7.61	<0.001
Kidney	1.54	1.10-2.16	0.013
Brain	1.09	0.79-1.50	0.589
Endometrial	2.12	1.53-2.94	<0.001
Colon	1.78	1.22-2.58	0.003
Malignant Melanoma	1.71	1.13-2.59	0.012
Other	2.05	1.66-2.53	<0.001

Cachexia x metastatic disease

	OR	95% CI	*p*
No Metastatic Disease	Reference Category		
Metastatic Disease	1.36	1.020-1.824	=0.037

Appendix IV

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

Dr Niamh O'Donoghue
15 Hainault Park
Foxrock
Dublin 18

15th September 2016

Ref: 20160608

Title of Study: Nutritional status of patients with Cancer: A survey of healthcare providers' knowledge and practice.

Dear Dr O'Donoghue,

Further to a meeting of the School of Medicine Research Ethics Committee held in June 2016, we are pleased to inform you that the above project has been approved.

Yours sincerely,

Professor Thomas Rogers
Chairperson
School of Medicine Research Ethics Committee

An tOllamh Paul Browne
Ms. Orla Bannon
Scoil an Leighis
An Institiúid Eolaíochtai Bitheolaíochta
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Appendix V

Trinity College Dublin
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The University of Dublin

NUTRITIONAL STATUS OF PATIENTS WITH CANCER

A SURVEY OF HEALTHCARE PROVIDERS' KNOWLEDGE & PRACTICE

Dear Colleague,

Malnutrition is common in the cancer population and can adversely affect clinical outcomes, including treatment toxicity, quality of life and survival. However, it often goes unrecognised. Proactive screening and intervention are the cornerstones of success in preventing symptoms of malnutrition. A number of screening tools to identify those at nutritional risk exist but in the absence of professional guidelines for screening, assessment and management of people with cancer, it is unclear which tools are routinely being used and by whom.

We are conducting a study to establish healthcare providers' knowledge and practice in relation to nutritional status in people with cancer. You are being invited to participate as you are a pertinent specialist working within the discipline of medicine, surgery, dietetics or nursing. Participation is voluntary and you may withdraw at any time.

We would be very grateful if you would take a few minutes to complete this short, anonymous survey. The anonymous responses collected will be used for research purposes. Once the results have been analysed, we will distribute them through your professional representative body.

Thank you for your participation.

Dr Niamh O'Donoghue, MSc, MB BCh BAO
Dr Suzanne Doyle, PhD

Trinity College Dublin

Coláiste na Tríonóide, Baile Átha Cliath

The University of Dublin

NUTRITIONAL STATUS OF PATIENTS WITH CANCER

Professional Profile: Education, Qualifications & Work Status

1. Are you a:

- ◯ Oncology Liaison Nurse Specialist
- ◯ Medical Doctor
- ◯ Surgeon
- ◯ Other (please specify e.g. Oncology Clinical Trials Nurse)

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NUTRITIONAL STATUS OF PATIENTS WITH CANCER

Professional Profile: Education, Qualifications & Work Status

2. Please choose one of the following:

- ◯ Consultant
- ◯ Specialist Registrar
- ◯ Other

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Professional Profile: Education, Qualifications & Work Status

3. Does your practice primarily involve working with people with cancer?

- ◯ Yes
- ◯ No

4. What speciality do you work in? (tick all that apply)

- ☐ Haematology
- ☐ Medical Oncology
- ☐ Palliative Medicine
- ☐ Radiation Oncology
- ☐ Surgical Oncology
- ☐ None of the above

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Professional Profile: Education, Qualifications & Work Status

5. What is your highest healthcare qualification?

- ◯ Diploma
- ◯ Bachelor's degree
- ◯ Post graduate diploma
- ◯ Master's degree
- ◯ Doctorate
- ◯ Other (please specify)

6. How many years have you been practicing (select the most appropriate range of years since qualification)?

- ◯ <5
- ◯ 5-10
- ◯ 11-15
- ◯ 16-20
- ◯ >20

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NUTRITIONAL STATUS OF PATIENTS WITH CANCER

Professional Profile: Education,Qualifications & Work Status

7. Have you ever had any formal education in nutrition as part of your training programme/healthcare qualification?

- ◯ Yes
- ◯ No

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Professional Profile: Education, Qualifications & Work Status

8. Do you think education in nutrition would be helpful to you in your current practice?

- ◯ Yes
- ◯ No

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NUTRITIONAL STATUS OF PATIENTS WITH CANCER

Professional Profile: Education, Qualifications & Work Status

9. Has this been helpful to you in your current practice?

- ◯ Yes
- ◯ No

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Professional Profile: Education, Qualifications & Work Status

10. In the past 12 months, have you attended any professional training or continuing professional development (CPD) related to the nutritional status of people with cancer?

- ◯ Yes
- ◯ No

Professional Profile: Education, Qualifications & Work Status

11. What type of training was it? (e.g. workshop, study day)

12. Who delivered the course?

13. Was it mandatory (required by employer or governing body) or optional?

- ◯ Mandatory
- ◯ Optional

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Section 2: Workplace Profile

14. What is your primary clinical practice setting (tick all that apply)?

- [ ] Public hospital
- [ ] Private hospital
- [ ] Palliative Medicine centre/hospice
- [ ] Other (please specify)

15. Do you work in one of the eight designated cancer centres in Ireland?

- ◯ Yes
- ◯ No
- ◯ I don't know

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Section 2: Workplace Profile

16. The Department of Health & Children published guidelines in 2009 on food and nutritional care in hospitals. Are these guidelines implemented in your work place?

- ◯ Yes, always
- ◯ Yes, sometimes
- ◯ No
- ◯ Don’t know
- ◯ I’m not familiar with the guidelines

17. Is there a local nutritional screening policy in place in your workplace?

- ◯ Yes
- ◯ No
- ◯ I don't know

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Section 2: Workplace Profile

18. Do all cancer patients have access to a full-time dietitian in your workplace?

- ◯ Yes - full time dietitian access for both inpatients and outpatients
- ◯ No - full time dietitian access for inpatients only
- ◯ No - full time dietitian access for outpatients only
- ◯ No – part time dietitian only
- ◯ No dietitian at all
- ◯ Don’t know

Other (please specify)

Section 2: Workplace Profile

19. Does the dietitian routinely attend multidisciplinary team meetings?

- Yes
- No
- I don't know

Section 3: Cancer Cachexia

20. What do you understand by the word ‘cachexia’?

21. In 2011, an international group of experts (Fearon and Strasser, 2011) defined cancer cachexia and identified criteria for diagnosing it. Please rate your level of familiarity with this definition:

- ◯ Not familiar at all
- ◯ Somewhat familiar
- ◯ Moderately familiar
- ◯ Very familiar

Section 3: Cancer Cachexia

22. What percentage (%) of unintentional weight loss over a 3-6 month period do you consider significant (choose one option for 'Pre-treatment' and one for 'During Treatment')?

	PRE-TREATMENT	DURING TREATMENT
> 2%	☐	☐
> 5%	☐	☐
> 10%	☐	☐

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Section 4: Nutritional Screening & Assessment

23. Is a nutritional screening tool routinely completed in your setting?

- ◯ Yes
- ◯ No
- ◯ I don't know

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Section 4: Nutritional Screening & Assessment

24. Which tool is used?

- ○ Malnutrition Screening Tool (MST)
- ○ Malnutrition Universal Screening Tool (MUST)
- ○ Abridged Scored Patient Generated-Subjective Global Assessment (abPG-SGA)
- ○ Other (please specify)

25. Who completes it? (tick all that apply)

- ☐ Consultant
- ☐ NCHD
- ☐ Oncology Liaison Nurse Specialist
- ☐ Oncology Day Ward Nurse
- ☐ Oncology Ward Nurse
- ☐ Dietitian

26. When is it completed (tick all that apply)?

- [ ] At diagnosis
- [ ] At each visit while on treatment
- [ ] If weight loss occurs during treatment
- [ ] On completion of treatment
- [ ] On admission to hospital
- [ ] Patient request
- [ ] Don’t know
- [ ] Other (please specify)

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Section 4: Nutritional Screening & Assessment

27. Do you routinely refer cancer patients to a dietetic colleague for assessment at diagnosis?

- ◯ Never
- ◯ Occasionally
- ◯ Often
- ◯ Always
- ◯ Other (please specify)

28. Please read the following scenario and choose which treatment plan you would recommend for the patient.

65 year old male with colorectal cancer admitted for surgical resection. Current weight 55kg, BMI 18 kg/m^2, no reported weight loss or recent change in appetite and intake.

- ◯ Low risk – routine clinical care
- ◯ Medium risk – observe dietary intake over next three days and determine if adequate
- ◯ High risk – refer to dietitian

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NUTRITIONAL STATUS OF PATIENTS WITH CANCER

Section 5: Management

29. In your opininon, at what point should the dietitian be part of the treatment plan (tick all that apply)?

- [ ] At diagnosis for all cancer types
- [ ] At diagnosis for those most at risk of cachexia
- [ ] When the patient has lost > 5% body weight
- [ ] When the patient has lost > 10% body weight
- [ ] Other (please specify)

30. How confident do you feel to give nutritional advice to cancer patients?

- ( ) Very confident
- ( ) Quite confident
- ( ) Somewhat confident
- ( ) Not at all confident

31. In your opinion, how often should a patient's nutritional status be reviewed during treatment? (tick all that apply)

- [ ] Weekly
- [ ] At each clinic visit
- [ ] At each treatment visit
- [ ] When the patient requests a review
- [ ] Other (please specify)

32. Which of these do you consider important barriers to providing optimal nutrition care to cancer patients? (tick all that apply)

- [ ] Difficulty in correctly identifying patients at nutritional risk
- [ ] Inadequate/insufficient training on the identification and treatment of cancer cachexia
- [ ] Inadequate/insufficient training on how to use nutrition screening tools
- [ ] Time constraints limiting ability to carry out nutrition screening
- [ ] Lack of sufficient dietetic services
- [ ] Lack of a clear guidelines on the identification and management of malnutrition and cachexia in cancer patients
- [ ] Other (please specify)

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NUTRITIONAL STATUS OF PATIENTS WITH CANCER

Thank you for taking the time to complete this survey

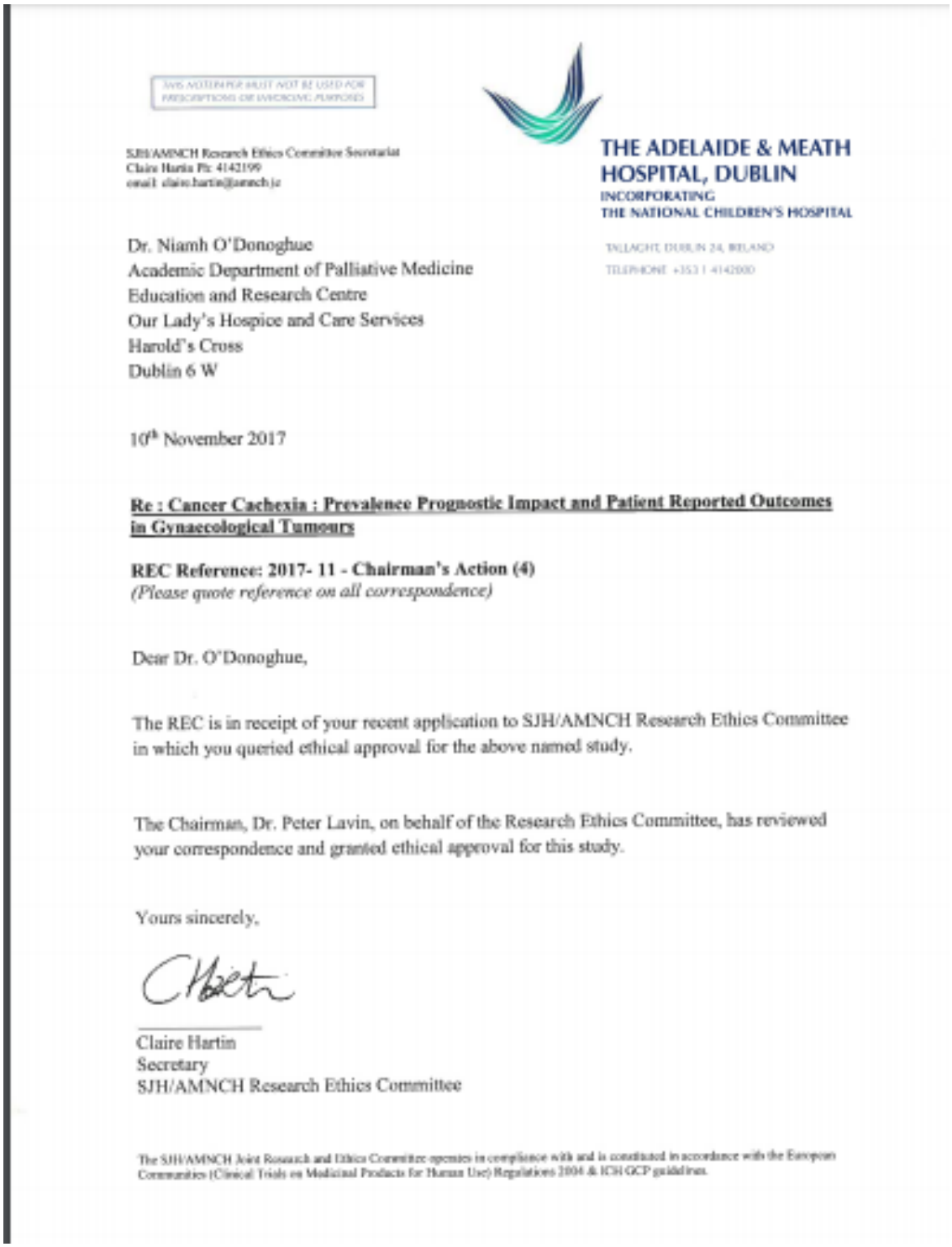
Your contribution is very valuable and will help us establish the current knowledge and practice regarding nutritional status in people with cancer. Once the results have been analysed, we will distribute them through your professional representative body.

Thank you for participating.

Dr Niamh O'Donoghue, MSc, MB BCh BAO
Dr Suzanne Doyle, PhD

Appendix VI

Ethical Approval for Cancer Cachexia Gynaecological Oncology Study



THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR MEDICINAL PURPOSES

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

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Dr. Niamh O'Donoghue
Academic Department of Palliative Medicine
Education and Research Centre
Our Lady's Hospice and Care Services
Harold's Cross
Dublin 6 W

10th November 2017

Re : Cancer Cachexia : Prevalence Prognostic Impact and Patient Reported Outcomes in Gynaecological Tumours

REC Reference: 2017- 11 - Chairman's Action (4)
(Please quote reference on all correspondence)

Dear Dr. O'Donoghue,

The REC is in receipt of your recent application to SJH/AMNCH Research Ethics Committee in which you queried ethical approval for the above named study.

The Chairman, Dr. Peter Lavin, on behalf of the Research Ethics Committee, has reviewed your correspondence and granted ethical approval for this study.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH 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.

Appendix VII

PARTICIPANT INFORMATION LEAFLET

STUDY TITLE: Cancer Cachexia: Prevalence, Prognostic Impact & Patient Reported Outcomes in Gynaecological Tumours

NAME OF PRINCIPAL INVESTIGATOR: Dr Noreen Gleeson

You are invited to participate in a research study. Please read this document and ask any questions you may have before agreeing to participate.

WHAT IS THE PURPOSE OF THIS STUDY?

Cancer and cancer treatments can cause malnutrition. Identifying nutritional problems early in the disease e.g. at diagnosis may allow treatments to be started to prevent malnutrition and/or further deterioration in nutrition levels.

The aims of this study are to:

- look at how common nutritional problems are in people with gynaecological tumours;
- determine the impact nutritional status has on outcomes and quality of life;

WHY HAVE I BEEN CHOSEN?

You have been invited to participate in this study because you are at risk of a change in weight as a result of your illness. It is hoped that your participation in the study will inform our understanding of when and how weight change should be assessed.

WHAT WILL HAPPEN IF I VOLUNTEER?

Taking part is entirely voluntary. If you initially decide to take part, you can change your mind later. This will not affect your future treatment in any way. Your doctor may decide to withdraw you from this study if he/she feels it is not in your best interest. Participation in this study does not affect your chances of being included in another study should your doctor deem it appropriate. If you agree to participate, the study will take place over 4 different days and will take approximately 60 minutes in total.

STUDY DAY 1 (Maximum 30 minutes)

You will be asked to complete 2 questionnaires. The first will ask about your regular diet, any recent weight change and symptoms you may be experiencing. The second asks about your quality of life. The researcher will also perform a short clinical examination. She will review your medical notes to confirm details like your diagnosis and what medications you are on and she will also look at your recent CT scan to calculate how much muscle you have.

STUDY DAY 2 & STUDY DAY 3

You will be asked to complete 3 further brief assessments at 6 weeks and 3 months after your surgery. Each will take approximately 10 minutes to complete. This will involve 2 questionnaires as before and you will also be asked some short questions on how well you have been since your last appointment. This can be done in person when you come to St James Hospital for your usual appointment or it can be done over the phone, at a time that suits you – whichever you prefer.

ARE THERE ANY BENEFITS FROM MY PARTICIPATION?

You will not benefit directly from taking part in this study. However, your participation in this research will help to improve our understanding of how weight change and nutritional status at diagnosis may be related to outcomes and quality of life. This may help improve how we care for cancer patients in the future.

ARE THERE ANY RISKS INVOLVED IN PARTICIPATING?

There is a risk that study participation may reveal a nutritional issue of which you were not previously aware. Should this occur, the researcher will inform your doctor within 24 hours. A copy of the study records will be provided to your doctor who will advise you if further investigation or treatment is required.

WHAT HAPPENS IF I DO NOT AGREE TO PARTICIPATE?

Participation is entirely voluntary. You have the right to decline or withdraw participation at any time. This would not affect your current or future treatment.

CONFIDENTIALITY

A study number will identify you and ensure confidentiality is maintained at all times. Your identity will not be disclosed to anyone outside of the research team. In the final report of the study, no identifiable details will be published or disclosed. All the information collected in this study will be kept securely in a password protected file until December 2023 and then destroyed.

COMPENSATION

You will not be paid for taking part in this study.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?

This study is organised by Trinity College Dublin, in collaboration with researchers from St James Hospital and Our Lady's Hospice & Care Services.

HAS THIS STUDY BEEN REVIEWED BY AN ETHICS COMMITTEE?

Tallaght Hospital / St. James's Hospital Joint Research Ethics Committee (REC) has reviewed and approved this study.

CONTACT DETAILS

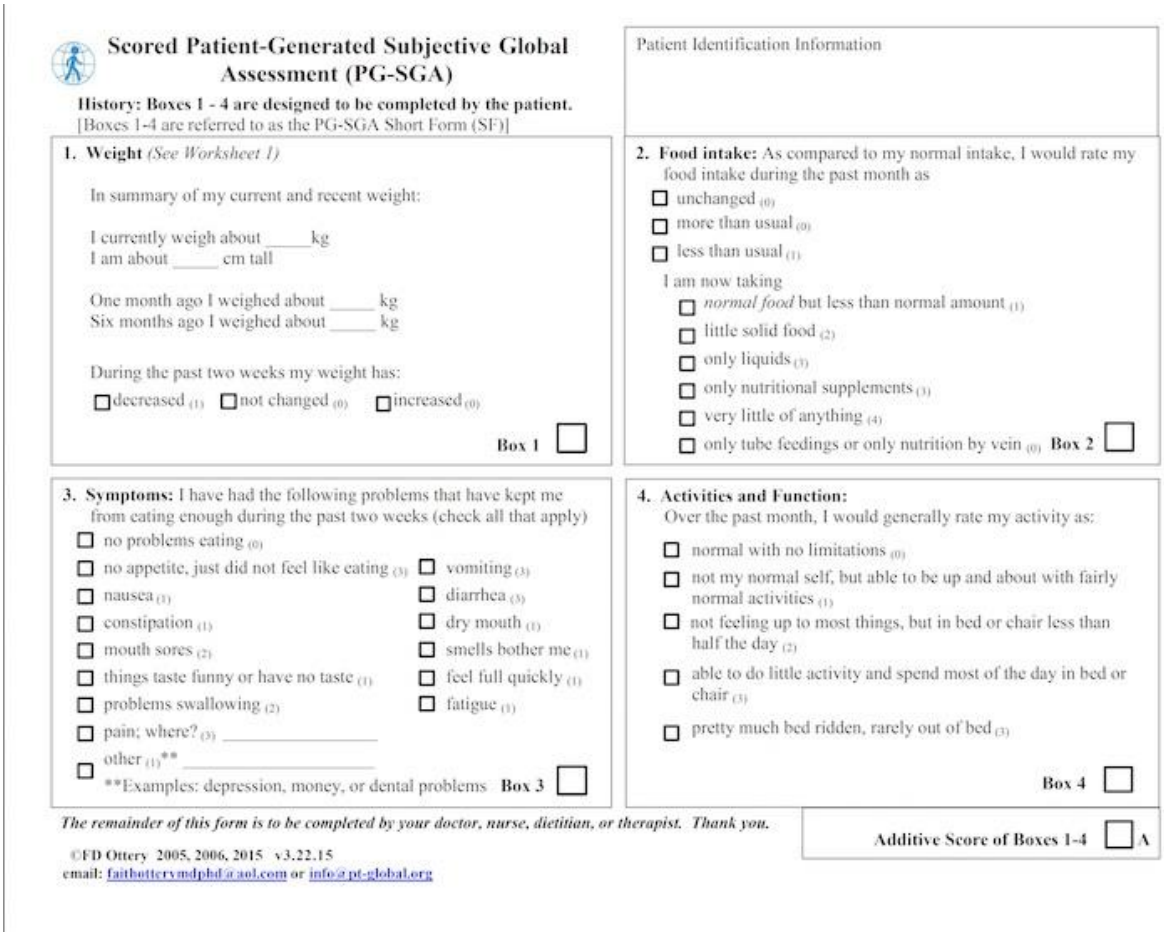
Dr Niamh O'Donoghue

Tel: 087 714 7104

Email: **odonogn2@tcd.ie**

Thank you for taking the time to consider participating in this study

Appendix VIII



Scored Patient-Generated Subjective Global Assessment (PG-SGA)

History: Boxes 1 - 4 are designed to be completed by the patient.
[Boxes 1-4 are referred to as the PG-SGA Short Form (SF)]

Patient Identification Information

1. Weight *(See Worksheet 1)*

In summary of my current and recent weight:

I currently weigh about _____kg
I am about _____ cm tall

One month ago I weighed about _____ kg
Six months ago I weighed about _____ kg

During the past two weeks my weight has:

☐ decreased (1) ☐ not changed (0) ☐ increased (0)

Box 1 ☐

2. Food intake: As compared to my normal intake, I would rate my food intake during the past month as

- ☐ unchanged (0)
- ☐ more than usual (0)
- ☐ less than usual (1)

I am now taking

- ☐ *normal food* but less than normal amount (1)
- ☐ little solid food (2)
- ☐ only liquids (3)
- ☐ only nutritional supplements (3)
- ☐ very little of anything (4)
- ☐ only tube feedings or only nutrition by vein (0)

Box 2 ☐

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply)

- ☐ no problems eating (0)
- ☐ no appetite, just did not feel like eating (3)
- ☐ nausea (1)
- ☐ constipation (1)
- ☐ mouth sores (2)
- ☐ things taste funny or have no taste (1)
- ☐ problems swallowing (2)
- ☐ pain; where? (3) _____
- ☐ other (1)** _____
- ☐ vomiting (3)
- ☐ diarrhea (3)
- ☐ dry mouth (1)
- ☐ smells bother me (1)
- ☐ feel full quickly (1)
- ☐ fatigue (1)

**Examples: depression, money, or dental problems

Box 3 ☐

4. Activities and Function:
Over the past month, I would generally rate my activity as:

- ☐ normal with no limitations (0)
- ☐ not my normal self, but able to be up and about with fairly normal activities (1)
- ☐ not feeling up to most things, but in bed or chair less than half the day (2)
- ☐ able to do little activity and spend most of the day in bed or chair (3)
- ☐ pretty much bed ridden, rarely out of bed (3)

Box 4 ☐

The remainder of this form is to be completed by your doctor, nurse, dietitian, or therapist. Thank you.

Additive Score of Boxes 1-4 ☐ A

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Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Worksheet 1 – Scoring Weight Loss

To determine score, use 1-month weight data if available. Use 6-month data only if there is no 1-month weight data. Use points below to score weight change and add one extra point if patient has lost weight during the past 2 weeks. Enter total point score in Box 1 of PG-SGA.

Weight loss in 1 month	Points	Weight loss in 6 months
10% or greater	4	20% or greater
5-9.9%	3	10- 19.9%
3-4.9%	2	6- 9.9%
2-2.9%	1	2- 5.9%
0-1.9%	0	0- 1.9%

Numerical score from Worksheet 1 ☐

Additive Score of Boxes 1-4 (See Side 1) ☐ A

5. Worksheet 2 – Disease and its relation to nutritional requirements:

Score is derived by adding 1 point for each of the following conditions:

- ☐ Cancer
- ☐ AIDS
- ☐ Pulmonary or cardiac cachexia
- ☐ Chronic renal insufficiency
- ☐ Presence of decubitus, open wound or fistula
- ☐ Presence of trauma
- ☐ Age greater than 65

Other relevant diagnoses (specify) _____

Primary disease staging (circle if known or appropriate) I II III IV Other _____

Numerical score from Worksheet 2 ☐ B

6. Worksheet 3 – Metabolic Demand

Score for metabolic stress is determined by a number of variables known to increase protein & caloric needs. **Note:** Score fever intensity or duration, whichever is greater. The score is additive so that a patient who has a fever of 38.8 °C (3 points) for < 72 hrs (1 point) and who is on 10 mg of prednisone chronically (2 points) would have an additive score for this section of 5 points.

Stress	none (0)	low (1)	moderate (2)	high (3)
Fever	no fever	> 37.2 and < 38.3	≥ 38.3 and < 38.8	≥ 38.8 °C
Fever duration	no fever	< 72 hours	72 hours	> 72 hours
Corticosteroids	no corticosteroids	low dose (< 10 mg prednisone equivalents/day)	moderate dose (≥ 10 and < 30 mg prednisone equivalents/day)	high dose (≥ 30 mg prednisone equivalents/day)

Numerical score from Worksheet 3 ☐ C

7. Worksheet 4 – Physical Exam

Exam includes a subjective evaluation of 3 aspects of body composition: fat, muscle, & fluid. Since this is subjective, each aspect of the exam is rated for degree. Muscle deficit/loss impacts point score more than fat deficit/loss. Definition of categories: 0 = no abnormality, 1+ = mild, 2+ = moderate, 3+ = severe. Rating in these categories is not additive but are used to clinically assess the degree of deficit (or presence of excess fluid).

Muscle Status		Fat Stores	
temples (temporalis muscle)	0 1+ 2+ 3+	orbital fat pads	0 1+ 2+ 3+
clavicles (pectoralis & deltoids)	0 1+ 2+ 3+	triceps skin fold	0 1+ 2+ 3+
shoulders (deltoids)	0 1+ 2+ 3+	fat overlying lower ribs	0 1+ 2+ 3+
interosseous muscles	0 1+ 2+ 3+	**Global fat deficit rating**	**0 1+ 2+ 3+**
scapula (latissimus dorsi, trapezius, deltoids)	0 1+ 2+ 3+	**Fluid status**	
thigh (quadriceps)	0 1+ 2+ 3+	ankle edema	0 1+ 2+ 3+
calf (gastrocnemius)	0 1+ 2+ 3+	sacral edema	0 1+ 2+ 3+
Global muscle status rating	**0 1+ 2+ 3+**	ascites	0 1+ 2+ 3+
		Global fluid status rating	**0 1+ 2+ 3+**

Point score for the physical exam is determined by the overall subjective rating of the total body deficit.

No deficit	score = 0 points
Mild deficit	score = 1 point
Moderate deficit	score = 2 points
Severe deficit	score = 3 points

Again, muscle deficit/loss takes precedence over fat loss or fluid excess.

Numerical Score for Worksheet 4 ☐ D

Total PG-SGA Score (Total numerical score of A+B+C+D) ☐

Clinician Signature _____ RD RN PA MD DO Other _____ Date _____

Global PG-SGA Category Rating (Stage A, Stage B or Stage C) ☐

Worksheet 5 – PG-SGA Global Assessment Categories

	Stage A	Stage B	Stage C
Category	**Well-nourished**	**Moderate/suspected malnutrition**	**Severely malnourished**
Weight	No weight loss **OR** recent non-fluid wt gain	< 5% loss in 1 month (<10% in 6 months) **OR** Progressive weight loss	> 5% loss in 1 month (>10% in 6 months) **OR** Progressive weight loss
Nutrient intake	No deficit **OR** Significant recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms (NIS)	None **OR** significant recent improvement allowing adequate intake	Presence of NIS (Box 3 of PG-SGA)	Presence of NIS (Box 3 of PG-SGA)
Functioning	No deficit **OR** Significant recent improvement	Moderate functional deficit **OR** Recent deterioration	Severe functional deficit **OR** Recent significant deterioration
Physical Exam	No deficit **OR** chronic deficit but with recent clinical improvement	Evidence of mild to moderate loss of muscle mass &/or muscle tone on palpation &/or loss of SQ fat	Obvious signs of malnutrition (e.g., severe loss muscle, fat, possible edema)

Nutritional Triage Recommendations:

Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage).

First line nutrition intervention includes optimal symptom management.

Triage based on PG-SGA point score

- **0-1** No intervention required at this time. Re-assessment on routine and regular basis during treatment.
- **2-3** Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and lab values as appropriate.
- **4-8** Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms (Box 3).
- **≥ 9** Indicates a critical need for improved symptom management and/or nutrient intervention options.

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Appendix IX

The ASA Score is used to assess the physical status of patients before surgery to provide a global measure of pre-operative health (Table 4.3). The ASA score was assigned to each participant prior to induction of anaesthesia by the consultant anaesthetist. This was subsequently recorded in the operative note by a member of the surgical team on completion of surgery.

Table 4.3 Description of ASA Physical Status Classification System (44)

Class 1	A normal healthy patient.
Class 2	A patient with a mild systemic disease.
Class 3	A patient with a severe systemic disease that is not life-threatening.
Class 4	A patient with a severe systemic disease that is a constant threat to life.
Class 5	A moribund patient who is not expected to survive without the operation.
Class 6	A brain-dead patient whose organs are being removed with the intention of transplanting them into another patient.

Appendix X

Clavien-Dindo Classification System (46)

Grade l	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimes are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complication. Blood transfusions and total parental nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication including CNS complications including brain haemorrhage, ischaemic stroke, sub-arachnoidal bleeding requiring critical care management
Grade Iva	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

Appendix XI

Normative Grip Strength Data

		Males		Females		Males		Females	
Age	Hand	Mean (lbs)	SD	Mean (lbs)	SD	Mean (kg)	SD	Mean (kg)	SD
6-7	R	32.5	4.8	28.6	4.4	14.7	2.2	13.0	2.0
	L	30.7	5.4	27.1	4.4	13.9	2.4	12.3	2.0
8-9	R	41.9	7.4	35.3	8.3	19.0	3.4	16.0	3.8
	L	39	9.3	33	6.9	17.7	4.2	15.0	3.1
10-11	R	53.9	9.7	49.7	8.1	24.4	4.4	22.5	3.7
	L	48.4	10.8	45.2	6.8	22.0	4.9	20.5	3.1
12-13	R	58.7	15.5	56.8	10.6	26.6	7.0	25.8	4.8
	L	55.4	16.9	50.9	11.9	25.1	7.7	23.1	5.4
14-15	R	77.3	15.4	58.1	12.3	35.1	7.0	26.4	5.6
	L	64.4	14.9	49.3	11.9	29.2	6.8	22.4	5.4
16-17	R	94	19.4	67.3	16.5	42.6	8.8	30.5	7.5
	L	78.5	19.1	56.9	14	35.6	8.7	25.8	6.4
18-19	R	108	24.6	71.6	12.3	49.0	11.2	32.5	5.6
	L	93	27.8	61.7	12.5	42.2	12.6	28.0	5.7
20-24	R	121	20.6	70.4	14.5	54.9	9.3	31.9	6.6
	L	104.5	21.8	61	13.1	47.4	9.9	27.7	5.9
25-29	R	120.8	23	74.5	13.9	54.8	10.4	33.8	6.3
	L	110.5	16.2	63.5	12.2	50.1	7.3	28.8	5.5
30-34	R	121.8	22.4	78.7	19.2	55.2	10.2	35.7	8.7
	L	110.4	21.7	68	17.7	50.1	9.8	30.8	8.0
35-39	R	119.7	24	74.1	10.8	54.3	10.9	33.6	4.9
	L	112.9	21.7	66.3	11.7	51.2	9.8	30.1	5.3
40-44	R	116.8	20.7	70.4	13.5	53.0	9.4	31.9	6.1
	L	112.8	18.7	62.3	13.8	51.2	8.5	28.3	6.3
45-49	R	109.9	23	62.2	15.1	49.8	10.4	28.2	6.8
	L	100.8	22.8	56	12.7	45.7	10.3	25.4	5.8
50-54	R	113.6	18.1	65.8	11.6	51.5	8.2	29.8	5.3
	L	101.9	17	57.3	10.7	46.2	7.7	26.0	4.9
55-59	R	101.1	26.7	57.3	12.5	45.9	12.1	26.0	5.7
	L	83.2	23.4	47.3	11.9	37.7	10.6	21.5	5.4
60-64	R	89.7	20.4	55.1	10.1	40.7	9.3	25.0	4.6
	L	76.8	20.3	45.7	10.1	34.8	9.2	20.7	4.6
65-69	R	91.1	20.6	49.6	9.7	41.3	9.3	22.5	4.4
	L	76.8	19.8	41	8.2	34.8	9.0	18.6	3.7
70-74	R	75.3	21.5	49.6	11.7	34.2	9.8	22.5	5.3
	L	64.8	18.1	41.5	10.2	29.4	8.2	18.8	4.6
75+	R	65.7	21	42.6	11	29.8	9.5	19.3	5.0
	L	55	17	37.6	8.9	24.9	7.7	17.1	4.0

CALIBRATION

The unit should be returned to Sammons Preston after 12 months of use for recalibration. Contact Sammons Preston at 800-228-3693 to arrange for service.

Appendix XII

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 the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	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, washing yourself 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 other leisure 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 that best 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

Appendix XIII

ENGLISH

EORTC QLQ – CX24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems, please answer by circling the number that best applies to you.

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
31.	Have you had cramps in your abdomen?	1	2	3	4
32.	Have you had difficulty in controlling your bowels?	1	2	3	4
33.	Have you had blood in your stools (motions)?	1	2	3	4
34.	Did you pass water/urine frequently?	1	2	3	4
35.	Have you had pain or a burning feeling when passing water/urinating?	1	2	3	4
36.	Have you had leaking of urine?	1	2	3	4
37.	Have you had difficulty emptying your bladder?	1	2	3	4
38.	Have you had swelling in one or both legs?	1	2	3	4
39.	Have you had pain in your lower back?	1	2	3	4
40.	Have you had tingling or numbness in your hands or feet?	1	2	3	4
41.	Have you had irritation or soreness in your vagina or vulva?	1	2	3	4
42.	Have you had discharge from your vagina?	1	2	3	4
43.	Have you had abnormal bleeding from your vagina?	1	2	3	4
44.	Have you had hot flushes and/or sweats?	1	2	3	4
45.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46.	Have you felt less feminine as a result of your disease or treatment?	1	2	3	4
47.	Have you felt dissatisfied with your body?	1	2	3	4

Please go on to the next page

During the past 4 weeks:	Not at all	A little	Quite a bit	Very much
48. Have you worried that sex would be painful?	1	2	3	4
49. Have you been sexually active?	1	2	3	4

Answer these questions only if you have been sexually active during the past 4 weeks:	Not at all	A little	Quite a bit	Very much
50. Has your vagina felt dry during sexual activity?	1	2	3	4
51. Has your vagina felt short?	1	2	3	4
52. Has your vagina felt tight?	1	2	3	4
53. Have you had pain during sexual intercourse or other sexual activity?	1	2	3	4
54. Was sexual activity enjoyable for you?	1	2	3	4

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Appendix XIV

EORTC QLQ – EN24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems.

	During the past week:	Not at all	A little	Quite a bit	Very much
31.	Have you had swelling in one or both legs?	1	2	3	4
32.	Have you felt heaviness in one or both legs?	1	2	3	4
33.	Have you had pain in your lower back and / or pelvis?	1	2	3	4
34.	When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
35.	Have you passed urine frequently?	1	2	3	4
36.	Have you had leaking of urine?	1	2	3	4
37.	Have you had pain or a burning feeling when passing urine?	1	2	3	4
38.	When you felt the urge to move your bowels, did you have to hurry to get to the toilet?	1	2	3	4
39.	Have you had any leakage of stools?	1	2	3	4
40.	Have you been troubled by passing wind?	1	2	3	4
41.	Have you had cramps in your abdomen?	1	2	3	4
42.	Have you had a bloated feeling in your abdomen?	1	2	3	4
43.	Have you had tingling or numbness in your hands or feet?	1	2	3	4
44.	Have you had aches or pains in your muscles or joints?	1	2	3	4
45.	Have you lost hair?	1	2	3	4
46.	Has food and drink tasted differently from usual?	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
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you felt less feminine as a result of your disease or treatment?	1	2	3	4

During the past 4 weeks:	Not at all	A little	Quite a bit	Very much
49. To what extent were you interested in sex?	1	2	3	4
50. To what extent were you sexually active?	1	2	3	4
Answer these questions only if you have been sexually active during the past 4 weeks:				
51. Has your vagina felt dry during sexual activity?	1	2	3	4
52. Has your vagina felt short and / or tight?	1	2	3	4
53. Have you had pain during sexual intercourse or other sexual activity?	1	2	3	4
54. Was sexual activity enjoyable for you?	1	2	3	4

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Appendix XV

EORTC QLQ - OV28

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have abdominal pain?	1	2	3	4
32. Did you have a bloated feeling in your abdomen / stomach?	1	2	3	4
33. Did you have problems with your clothes feeling too tight?	1	2	3	4
34. Did you experience change in bowel habit as a result of your disease or treatment?	1	2	3	4
35. Were you troubled by passing wind / gas / flatulence?	1	2	3	4
36. Have you felt full up too quickly after beginning to eat?	1	2	3	4
37. Have you had indigestion or heartburn?	1	2	3	4
38. Have you lost any hair?	1	2	3	4
39. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
40. Did food and drink taste different from usual?	1	2	3	4
41. Have you had tingling hands or feet?	1	2	3	4
42. Have you had numbness in your fingers or toes?	1	2	3	4
43. Have you felt weak in your arms or legs?	1	2	3	4
44. Did you have aches or pains in your muscles or joints?	1	2	3	4
45. Did you have problems with hearing?	1	2	3	4
46. Did you urinate frequently?	1	2	3	4
47. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
48. Did you have hot flushes?	1	2	3	4
49. Did you have night sweats?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
50. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
51. Have you been dissatisfied with your body?	1	2	3	4
52. How much has your disease been a burden to you?	1	2	3	4
53. How much has your treatment been a burden to you?	1	2	3	4
54. Were you worried about your future health?	1	2	3	4

During the past 4 weeks:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
55. To what extent were you interested in sex?	1	2	3	4
56. To what extent were you sexually active?	1	2	3	4
Answer the following two questions only if you were sexually active:				
57. To what extent was sex enjoyable for you?	1	2	3	4
58. Did you have a dry vagina during sexual activity?	1	2	3	4

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Appendix XVI

EORTC QLQ – VU34

Patients sometimes report that they have the following symptoms or problems. Some of these relate to the genital area. Whether or not you have had surgery in your genital area, please indicate the extent to which you have experienced these symptoms or problems.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Have you had pain in your genital area?	1	2	3	4
32.	Have you had itchy or irritated skin in your genital area?	1	2	3	4
33.	Have you had sore skin in your genital area?	1	2	3	4
34.	Have you had tearing or splitting of the skin in your genital area?	1	2	3	4
35.	Have you had narrowing/tightness of your vaginal entrance?	1	2	3	4
36.	Has scarring in your genital area caused you problems?	1	2	3	4
37.	Have you had difficulties sitting due to problems in your genital area?	1	2	3	4
38.	Have you had unpleasant discharge from your vagina or genital area?	1	2	3	4
39.	Have you had swelling in the genital area?	1	2	3	4
40.	Has the skin felt tight in your genital area?	1	2	3	4
41.	Have you had swelling in your groin?	1	2	3	4
42.	Have you had sore skin in your groin?	1	2	3	4
43.	Have you had pain in your groin?	1	2	3	4
44.	Have you had swelling in one or both legs?	1	2	3	4
45.	Have you felt heaviness in one or both legs?	1	2	3	4
46.	Has the skin felt tight in your leg(s)?	1	2	3	4
47.	Have you had pain in your leg(s)?	1	2	3	4

Please continue on the next page

During the past week:		Not at all	A little	Quite a bit	Very much
48.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
49.	Have you felt less feminine as a result of your disease or treatment?	1	2	3	4
50.	Have you been dissatisfied with your body?	1	2	3	4

51. Do you have a urine catheter or a urine stoma bag (artificial bladder)? No Yes

Please answer these questions ONLY IF YOU DO NOT HAVE A URINE CATHETER OR A URINE STOMA BAG:

During the past week:		Not at all	A Little	Quite a bit	Very much
52.	Have you passed urine frequently?	1	2	3	4
53.	Have you had pain or a burning feeling when passing urine?	1	2	3	4
54.	Have you had leaking of urine?	1	2	3	4
55.	When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4

56. Do you have a bowel stoma bag? No Yes

Please answer these questions ONLY IF YOU DO NOT HAVE A BOWEL STOMA BAG:

During the past week:		Not at all	A Little	Quite a bit	Very much
57.	Have you had leaking of stools?	1	2	3	4
58.	When you felt the urge to move your bowels, did you have to hurry to get to the toilet?	1	2	3	4

Please continue on the next page

During the past 4 weeks:

59. Have you been sexually active? No Yes

Answer these questions only if you have been **SEXUALLY ACTIVE DURING THE PAST 4 WEEKS:**

During the past 4 weeks:		Not at all	A little	Quite a bit	Very much
60.	Have you worried that sex would be painful?	1	2	3	4
61.	Have you had pain during sexual intercourse or other sexual activity?	1	2	3	4
62.	Has your vagina felt narrow and/or tight during sexual intercourse or other sexual activity?	1	2	3	4
63.	Has your vagina felt dry during sexual intercourse or other sexual activity?	1	2	3	4
64.	Has sexual activity been enjoyable for you?	1	2	3	4

Appendix XVII

	At T_0	From T_0 - T_1	From T_1 - T_2
Nutritional supplements	2	0	0
TPN	1	0	0
Oral nutritional supplements (prescribed)	1	4	1
Oral nutritional supplements (self-prescribed)	0	1	0
Appetite stimulant	0	0	0
Dietetic review	2	14	3
Steroids as part of chemotherapy regimen	-	7	10
Admission to hospital		6	9
- scheduled procedures related to disease management		0	2
- syncopal episode		1	1
- pulmonary embolus		2	0
- post-operative per vagina bleed		2	0
- respiratory tract infection		0	1
- urinary tract infection with related nausea/vomiting		1	0
- urinary tract infection		0	1
- nausea/vomiting		0	1
- vomiting/diarrhoea		0	1
- investigation of pain		0	1
- other (non-disease related)		0	1
Dose interruption [a]		0	5[b]
Dose reduction		0	0

[a] Patients receiving primary chemoradiation, neoadjuvant chemotherapy or radiotherapy (n=18)
[b] Delay in treatment due to (i) hospital admission (n=3); (ii) inclement weather (n=1); (iii) did not complete radiotherapy course (n=1).

Appendix XVIII

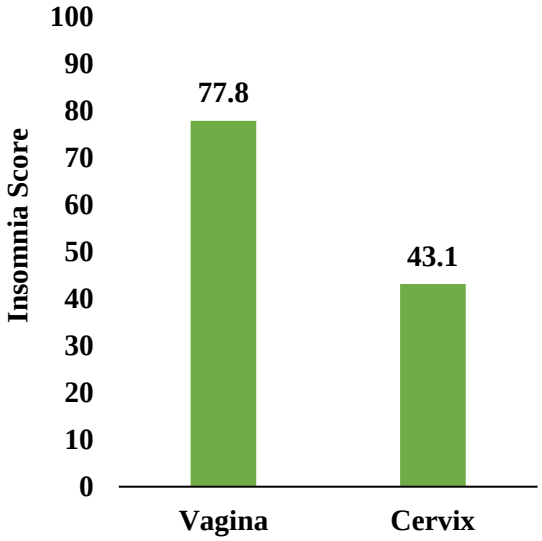
Distribution of mean QoL scores measured by the EORTC Core 30 at T_0, T_1 and T_2

QoL variable	T_0 (n=94)	T_1 (n=65)	T_2 (n=60)
	Mean ± SD	**Mean ± SD**	**Mean ± SD**
Global health status/QoL	58.3 ± 28.04	61.41 ± 20.18	61.81 ± 24.21
Functional scales			
Physical functioning	83.83 ± 21.82	73.13 ± 18.67	76 ± 21.26
Role functioning	70.21 ± 33.23	57.18 ± 33.20	64.17 ± 30.25
Emotional functioning	66.22 ± 28.80	77.18 ± 23.63	77.36 ± 25.19
Cognitive functioning	79.26 ± 24.03	83.33 ± 20.67	82.22 ± 21.70
Social functioning	74.11 ± 29.34	67.18 ± 28.64	69.44 ± 27.41
Symptom scales	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Fatigue	33.92 ± 26.65	36.58 ± 23.28	37.04 ± 26.27
Nausea / vomiting	10.11 ± 19.78	7.69 ± 12.77	12.5 ± 21.86
Pain	23.23 ± 29.90	20.77 ± 24.81	23.89 ± 31.97
Dyspnoea	12.41 ± 25.26	13.33 ± 23.97	11.67 ± 20.02
Insomnia	36.88 ± 35.22	40 ± 33.69	33.89 ± 33.05
Appetite loss	31.56 ± 34.85	16.41 ± 27.50	22.22 ± 30.23
Constipation	14.89 ± 26.46	15.90 ± 27.49	20 ± 30.55
Diarrhoea	14.89 ± 25.55	8.21 ± 23.41	15 ± 24.66
Financial difficulties	13.12 ± 26.28	21.03 ± 29.57	20 ± 31.74

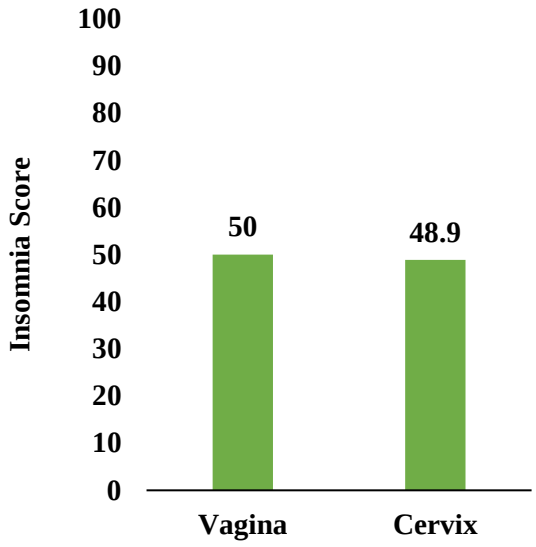
Appendix XIX

Gynaecological cancer sites with highest insomnia score at T_0 and T_2

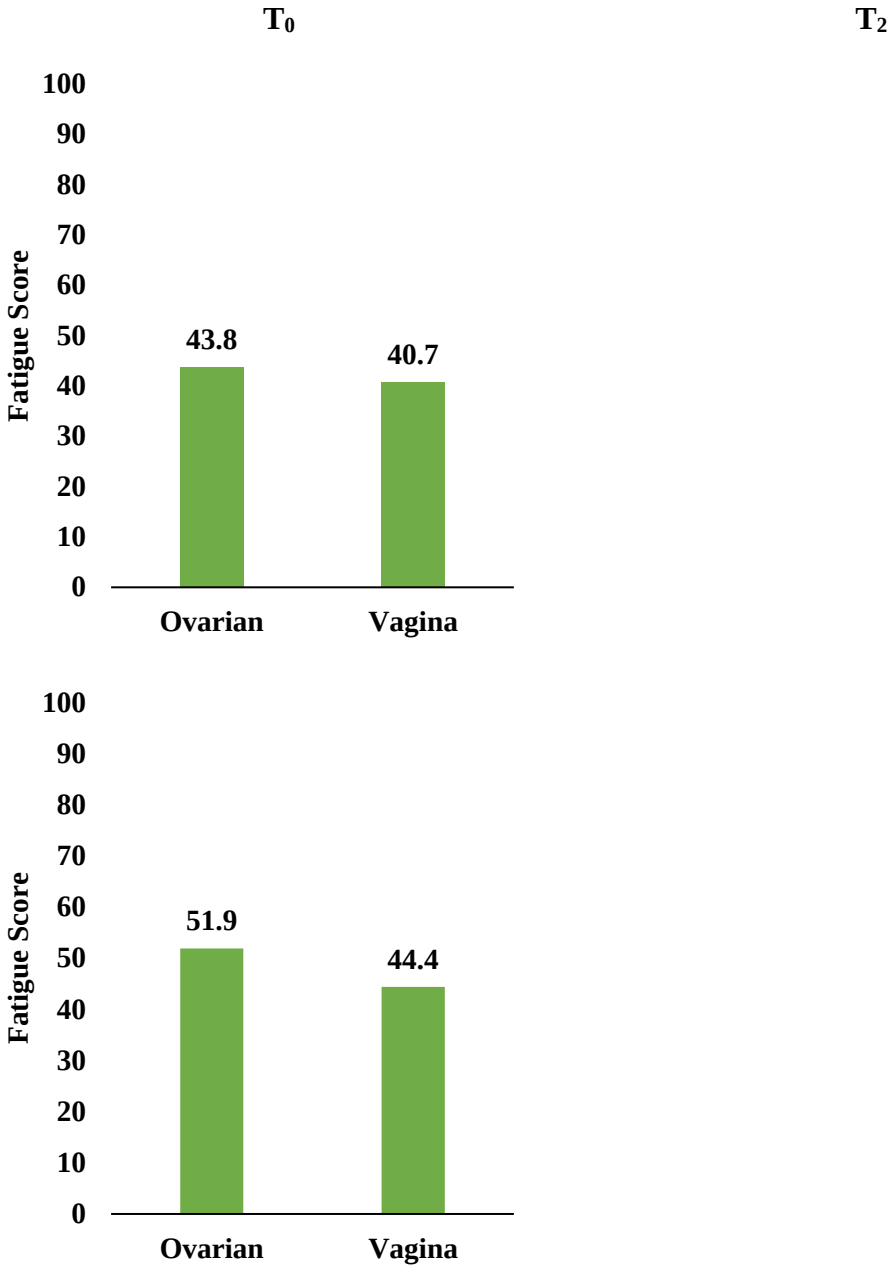
T_0



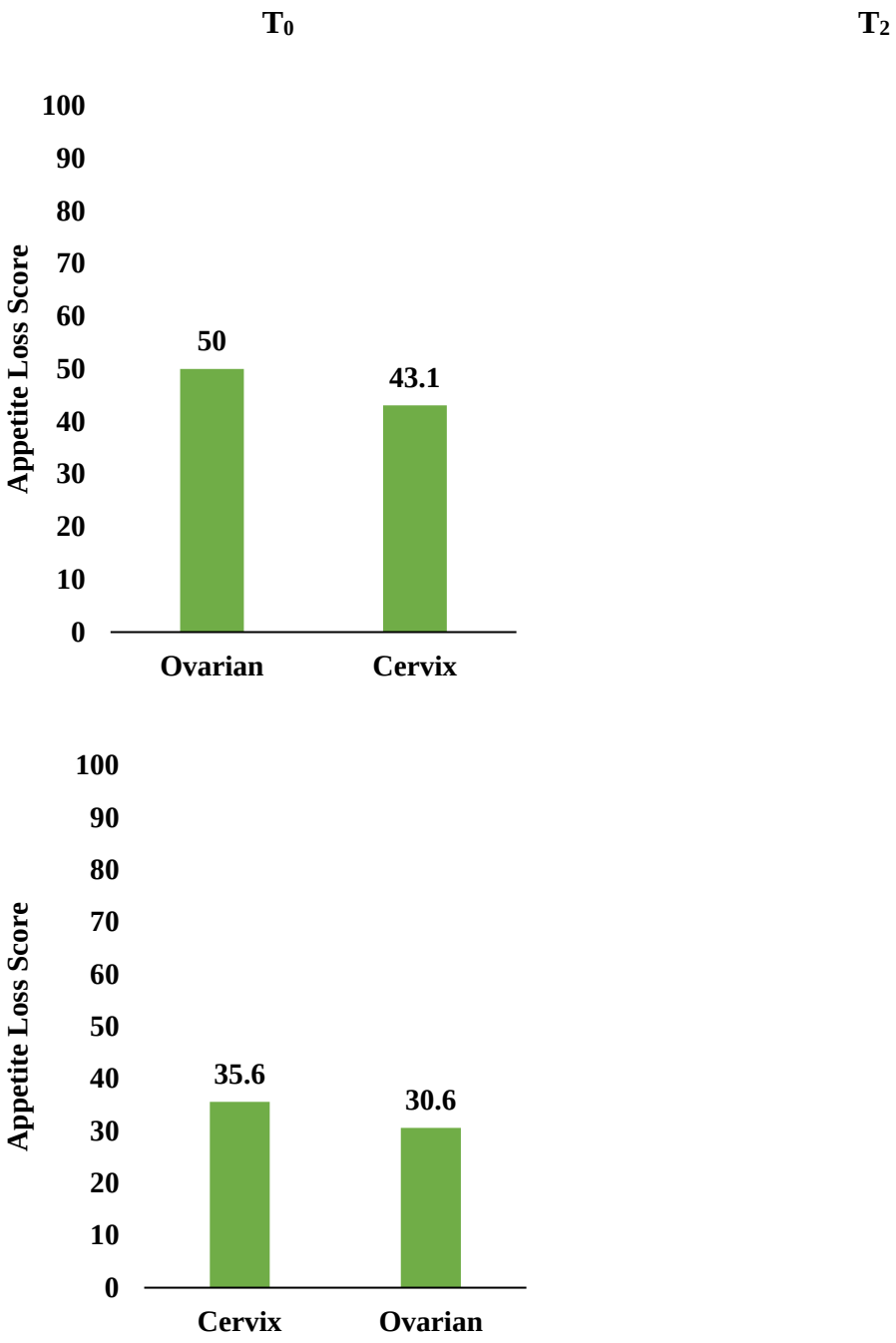
T_2



Gynaecological cancer sites with highest fatigue score at T_0 and T_2

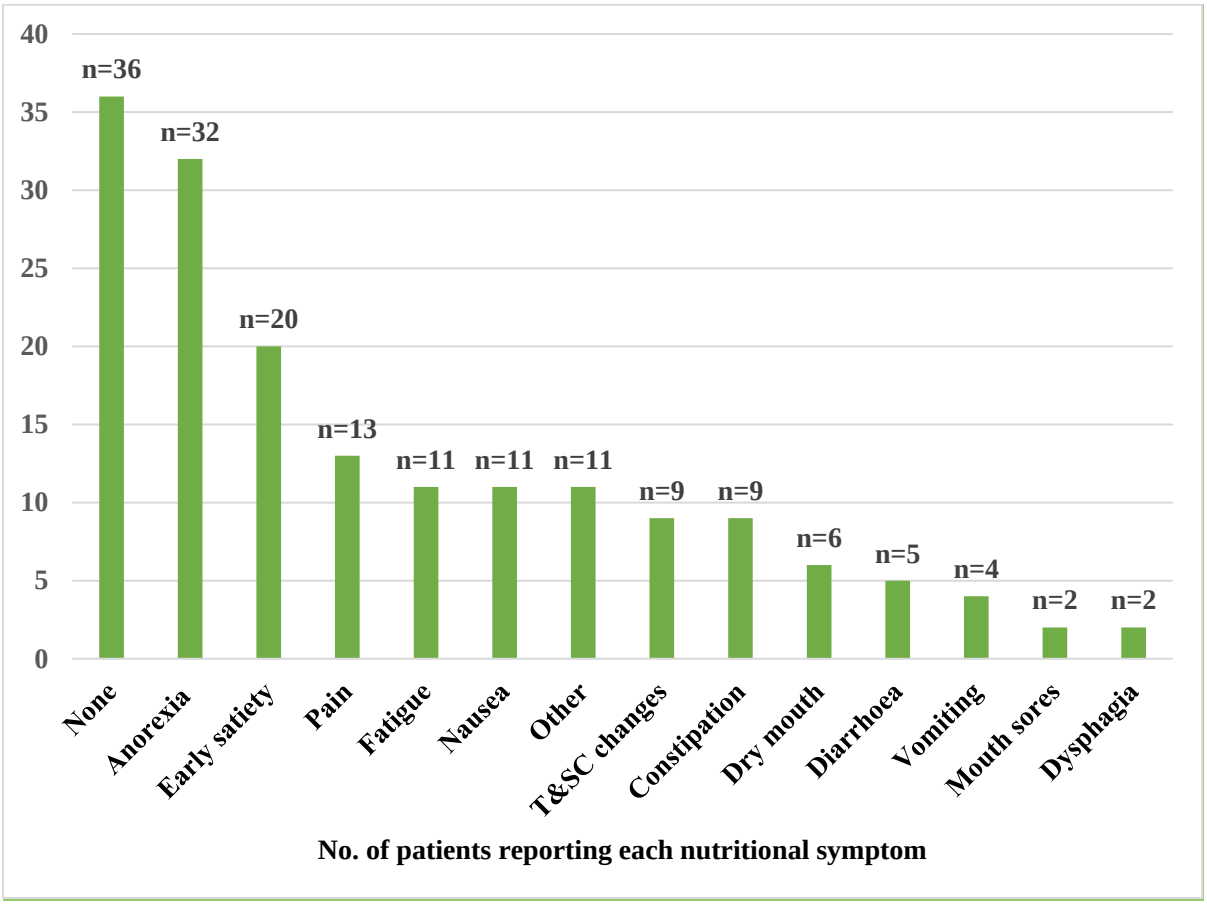


Gynaecological cancer sites with highest appetite loss score at T_0 and T_2



Appendix XX

Nutritional impact symptoms at baseline



Abbreviations: T&SC taste and smell changes combined