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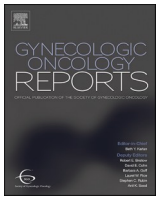

Impact of cachexia on disease recurrence and survival outcomes in endometrial cancer patients

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A B S T R A C T

Objective: Cancer cachexia is progressive weight loss due to muscle/adipose tissue wasting and inadequate intake that occurs in response to malignancy. It is an independent predictor of disease recurrence and reduced survival in several cancers. However, cachexia's relationship with gynecologic malignancy outcomes has only been examined in small studies with limited follow-up and inconsistent definitions of cachexia. This study investigated the impact of cachexia on disease recurrence and overall survival in high-risk endometrial carcinoma patients.

Methods: This retrospective cohort study examined data from patients with high-risk non-metastatic primary endometrial carcinoma treated at a single institution from 2015 to 2020. Treatment for all subjects included total hysterectomy, surgical staging, pelvic external beam radiotherapy with or without adjuvant chemotherapy. Radiation planning CT datasets were used to measure skeletal musculature at the L3 vertebral level. Skeletal muscle index (SMI) was defined as total L3 skeletal muscle cross sectional area (cm^2)/height2 (m^2), and cachexia was defined based on SMI.

Results: 55 patients were eligible for analysis. Several SMI thresholds were used to define cachexia, and analysis was performed for each definition. Kaplan-Meier and Cox-proportional hazards regression analysis yielded no significant reduction in overall survival (OS) or progression-free survival (PFS) in patients with cachexia, regardless of threshold chosen. However, 4 of 13 definitions of cachexia showed significantly improved OS in patients without cachexia, relative to those with cachexia. There were no significant differences in disease recurrence.

Conclusions: Cachexia as defined in this study was not associated with poor outcomes in endometrial carcinoma patients based on OS, PFS, or disease recurrence.

1. Introduction

Cachexia is progressive, involuntary weight loss due to host muscle and adipose tissue wasting and inadequate nutrient intake. It has been reported to a occur in a number of chronic disease states, most notably in patients diagnosed with cancer (Kern and Norton, 1988). In contrast to sarcopenia, which describes age-related loss of skeletal muscle tissue, cachexia is mediated predominantly by inflammation and can be frequently observed in the setting of an underlying malignancy (Marty et al., 2017). Along with the tumor microenvironment itself, metabolic, endocrine, and central nervous system changes are involved in mediating the muscle and adipose tissue catabolism that is seen in this condition (Baracos et al., 2018). It is thought that the prevalence of cachexia in cancer patients is approximately 50 %, with cachexia acting as a major contributor to cancer death in 20–50 % of these patients (Sadeghi et al., 2018; Peterson and Mozer, 2017). In addition to its direct impact on mortality, cachexia has also been established as an independent predictor of poor quality of life and reduced responsiveness and tolerance to treatment in those with cancer (Sadeghi et al., 2018). These associations have been explored in a number of disease sites, including lung, colorectal, and other gastrointestinal malignancies (Miyamoto et al., 2015; Prado et al., 2008; Martin et al., 2013).

Despite its strong association with poor cancer outcomes, consistently assessing and diagnosing cachexia has remained a challenge for clinicians. Traditionally, clinical factors such as patient-reported weight loss, low BMI, and certain biomarkers (e.g., hypoalbuminemia) have proven useful as screening tools for cachexia and are associated with poor outcomes and quality of life (Fearon et al., 2006; Fearon et al., 2011; Evans et al., 2008). However, sensitivity when using these methods remains limited.

In recent years, imaging-based methods have gained popularity as a more objective means of assessing cachexia independent of body

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habitus. A common method uses axial CT planes at the level of the L3 vertebral body to measure skeletal muscle mass and density (Gomez-Perez et al., 2016; Mourtzakis et al., 2008). This method has provided objective assessments of cachexia in a variety of malignancies, and CT-based definitions of cachexia have shown associations with poor survival outcomes even when traditional proxies such as weight loss fail to demonstrate a significant relationship (Prado et al., 2008; van Vledder et al., 2012).

Given its objectivity irrespective of patient BMI, CT as a tool to assess cachexia may be especially useful in endometrial cancer patients, in whom high rates of obesity have the potential to mask underlying muscle loss and obscure a diagnosis of cachexia. Because of this diagnostic challenge, the true prevalence of cachexia in this patient population and its effect on prognosis are not well understood at present, and there is a lack of high-quality studies that examine the relationship between cachexia and endometrial cancer outcomes. Given the robust relationships established at other disease sites, it is reasonable to hypothesize that utilizing an imaging-based definition of cachexia in endometrial cancer may provide useful prognostic information, possibly more so than commonly used metrics such as weight loss, BMI changes, or biochemical abnormalities. Our study set out to investigate the impact of cachexia (as defined on CT imaging) on disease recurrence and overall survival outcomes in women diagnosed with high-risk endometrial cancer.

2. Materials and methods

2.1. Patient selection

Patients eligible for this retrospective study were diagnosed with non-metastatic primary endometrial carcinoma and treated within the Department of Radiation Oncology at [Anonymized for Review] from January 1, 2015 to December 31, 2020. All patients during this time period were evaluated for potential inclusion. All patients selected were treated with curative intent with multi-modality treatments. Treatment for all subjects included total hysterectomy and surgical staging, followed by pelvic external beam radiotherapy, with or without adjuvant chemotherapy. Inclusion of patients receiving pelvic radiation enabled radiation planning CT scans to provide objective measurements at similar time points for all patients. All patients with high-risk disease based on surgical staging were eligible. FIGO 2009 surgical stage I–IVA endometrial carcinoma, clear cell or serous carcinoma were included. Eligible patients were required to be at least 18 years of age and could not have had a history of prior radiation therapy for other pelvic malignancies. Patients receiving neoadjuvant chemotherapy were excluded. All Eastern Cooperative Oncology Group (ECOG) performance statuses were allowed. Patients with medical comorbidities were not excluded. Patients on weight loss medication or who had prior weight loss surgery were excluded. Following institutional review board (IRB) approval, the electronic health record was used to identify eligible patients and gather baseline patient information, tumor characteristics, treatment information, and outcome data. Patients were classified as type I tumors or type II based on histology, grade and age. Patients with non-endometroid adenocarcinoma histology or high-grade adenocarcinoma in patients <60 were classified as type II.

2.2. Assessment of cachexia

Pre-radiation planning CT images were used for each patient to collect cachexia indices prior to adjuvant chemotherapy. Cachexia indices were assessed by measurements of skeletal muscles at the level of the L3 vertebral body. At the appropriate CT slice in the axial plane at the mid L3 level, both paraspinal (PS) and abdominal (ABD) musculature were identified. PS musculature contours included cross sections of the psoas, erector spinae, and quadratus lumborum muscles, while ABD contours encompassed the external oblique, internal oblique, transversus abdominus, and rectus abdominus muscles. A clinician utilized MIM Software tools to contour these two muscle groups, defining the lower limit of skeletal muscle radiation attenuation as −30 Hounsfield units (HU), with the upper limit set at 150 HU. Total L3 musculature was defined as the union of both the PS and ABD contours, resulting in three distinct contours (Fig. 1). Each of these contours was also manually repeated at two additional axial slices directly adjacent to the initial slice. For each contour, skeletal muscle area (SMA) was measured directly by the software and skeletal muscle index (SMI) was calculated as follows:

$$SMI = \frac{Total\ L3\ SMA\ (cm^2)}{Patient\ Height\ (m^2)} \quad (1)$$

SMI assessed in this same manner has been previously validated as a predictor of whole-body muscle mass (Ganju et al., 2020). Values for SMA and SMI were subsequently calculated as an average from these three slices.

The specific SMI and SMA thresholds used to define cachexia in endometrial cancer patients vary by study (Martin et al., 2013; Allanson et al., 2020). As a result, optimal stratification was utilized to establish definitions of cachexia. We divided the cohort into two cohorts based on average SMI and compared those above and below (bottom group) this threshold. We then divided the groups into bottom 10 % compared to upper 90 % and continued to increase the bottom percentage by 10 % up to a comparison of bottom 90 % to top 10 %. Based on the average SMI calculated, various techniques were also evaluated in an effort to simplify the assessment for future research: SMA, single-slice SMI/SMA, and SMI based on PS musculature or ABD musculature alone. These three calculations could simplify the process for future studies.

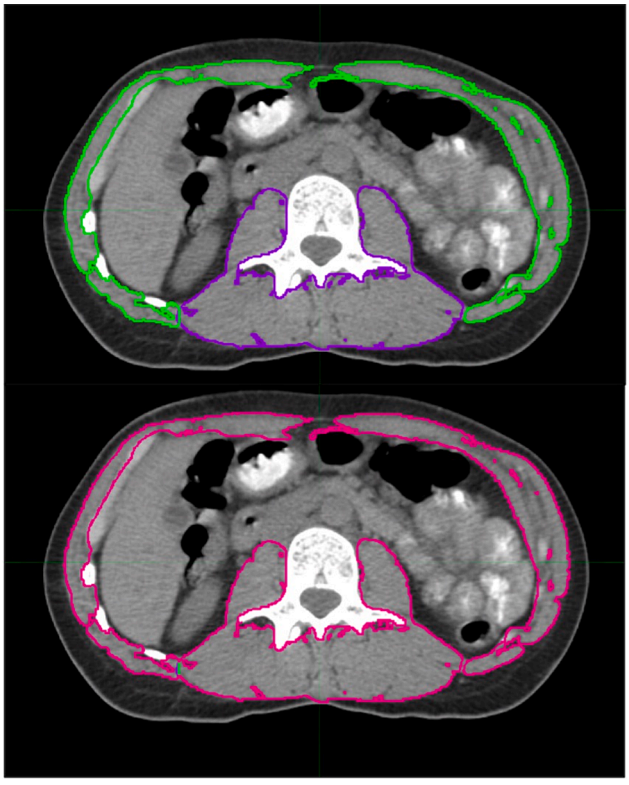

Fig. 1. Manual contours of paraspinal (purple), abdominal wall (green), and total (pink) musculature on a single axial slice at the L3 vertebral level. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3. Statistical analysis

Overall survival in cachectic vs. non-cachectic patients was estimated using the Kaplan-Meier method. Univariate and multivariate Cox proportional hazards regression models were also used to identify variables associated with overall survival rates. The relationship between cachexia and disease recurrence, a binary outcome, was analyzed using logistic regression models.

3. Results

A total of 55 patients were eligible for analysis, with baseline clinical characteristics summarized in Table 1. On average, patients were 65 years of age at diagnosis, with an average baseline BMI of 31 (BMI > 30 considered obese) at the time of initial radiation oncology consult. The majority of patients ($n = 28$, 51 %) had stage III disease, and most ($n = 39$, 71 %) had an ECOG performance status of 0 at the initial consultation. The majority of patients received adjuvant chemotherapy (92.7 %). The average modified frailty index was 9.7 % for the entire cohort, with the majority having zero or one risk factors (72.7 %). Lymphovascular invasion was present in 35 patients (64 %). Classification of patients at type I or II identified 32 patients within the type I classification, of which 9 had a recurrence (28.1 %), compared to the 23 patients with type II, of which 8 had a recurrence (34.7 %).

Using measurements from paraspinal and abdominal musculature contoured at the L3 level, cachexia was defined in a number of possible ways in an attempt to identify which definition achieved the best separation between patients with favorable vs. adverse outcomes (Table 2). Using the Kaplan-Meier method and Cox-proportional hazards regression, none of the 13 definitions of cachexia showed a significant reduction in overall survival (OS), reduction in progression-free survival (PFS), or increase in disease recurrence in patients in the cachexia group.

The only significant differences observed were *improved* OS in the groups labeled as having cachexia as defined by SMI in the bottom 40th, 50th, 60th, and 70th percentiles, respectively (Table 2 **Rows 8–11**). For example, with cachexia defined as SMI in the bottom 50 % of the study group, Cox multiple regression (accounting for patient age, FIGO stage, tumor grade, and lymphovascular space invasion) for OS resulted in a hazard ratio of 0.33 ($p = 0.007$) in the cachexia group relative to the non-cachexia group. Using the same definition, Kaplan-Meier analysis also yielded increased OS in this group ($p = 0.0026$; Fig. 2).

Cox-proportional hazards regression showed no significant differences in OS or PFS based on FIGO stage of disease, tumor grade, presence of lymphovascular space invasion (LVSI), Eastern Cooperative Oncology Group (ECOG) performance status or tumor type (I vs. II). Logistic regression also showed no significant differences in disease recurrence based on these variables.

Table 1
Baseline clinical characteristics.

	Total *n* (%)
T Stage	
T1	25 (45 %)
T2	17 (31 %)
T3	12 (22 %)
T4	1 (2 %)
N Stage	
N0	34 (62 %)
N1	19 (35 %)
N2	2 (4 %)
FIGO Overall Stage	
I	12 (22 %)
II	12 (22 %)
III	28 (51 %)
IV	3 (5 %)
ECOG Performance Status	
0	39 (71 %)
1	13 (24 %)
2	1 (2 %)
3	2 (4 %)
Grade	
1	21 (38 %)
2	10 (18 %)
3	24 (44 %)
Type	
I	23 (42 %)
II	32 (58 %)
Lymphovascular Invasion Present	35 (64 %)
Recurrence	17 (27 %)
	Average Value (Range)
Age at Diagnosis	65 years (58–73 years)
Weight	180 lbs. (149–216 lbs.)
Height	65 in. (61.8–67.0 in.)
BMI	31 (25–35)
Modified Frailty Index	9.7 % (0–45.5)
Tumor Size	4.0 in. (2.60–6.05 in.)

4. Discussion

Cancer cachexia is widely prevalent among those with various malignancies, and it is thought to be a major driver of reduced survival, quality of life, and response and/or tolerance to treatment (Sadeghi et al., 2018; Peterson and Mozer, 2017). These associations have been consistent across numerous disease sites. For instance, Miyamoto et al. described a 5-year recurrence-free survival of 56 % in cachectic colorectal cancer patients, compared to 79 % in those who were not cachectic (Miyamoto et al., 2015). Prado et al. found that overall survival was shortened by 10 months in obese patients with lung and gastrointestinal malignancies who were found to have cachexia compared with those without cachexia (Prado et al., 2008). Martin et al. similarly found reduced survival in lung and gastrointestinal cancer patients with cachexia, regardless of baseline BMI (Martin et al., 2013). Other solid tumors in which associations between cachexia and decreased survival have been demonstrated include pancreatic cancer, head and neck cancers, renal cell carcinoma, esophageal cancer, and hepatocellular carcinoma (Shachar et al., 2016; Okumura et al., 2015; Chargi et al., 2019). These studies overwhelmingly use lumbar musculature contoured on CT to define cachexia, though the precise criteria for these definitions remain highly heterogeneous.

To date, the relationship between cachexia and endometrial cancer outcomes has not been well studied, a knowledge gap that is of particular concern given that obesity is highly prevalent among endometrial cancer patients. As a result, disease-related loss of muscle mass may not be readily appreciated in this clinical setting. Even so, 40 % of endometrial cancer patients are thought to be at risk of developing cachexia, so the potential for under-recognition of this condition is substantial (Anker et al., 2019). Some prior studies have attempted to investigate the relationship between cachexia and gynecologic malignancies, but they have been limited to small retrospective cohort studies with short-term follow-up and mixed results (Ganju et al., 2020; Allanson et al., 2020; Silva de Paula et al., 2018; de Paula et al., 2019; Rodrigues and Chaves, 2018; Kuroki et al., 2015; Seebacher et al., 2022). Moreover, the CT-based criteria for cachexia vary, as with studies performed in other disease sites. Authors use SMI, SMA, and/or average radiation attenuation to varying extents, and all studies identify their own respective thresholds to separate cachectic and non-cachectic patients.

In the present study, no significant survival advantage (as assessed by OS or PFS) or reduced rates of disease recurrence were observed in primary endometrial carcinoma patients without cachexia, as compared

Table 2
Definitions used for cachexia and association with overall survival (OS), progression-free survival (PFS), and/or disease recurrence.

	Measurement Used	Threshold for Cachexia	Muscle Group(s) Included	CT Slices Used	Significant OS Difference? ($P < 0.05$)	Significant PFS Difference? ($P < 0.05$)	Significant Recurrence Difference? ($P < 0.05$)
1	SMA	Bottom 50 %	Total	Average of 3 slices	No	No	No
2	SMI	Bottom 50 %	Total	Single slice only	No	No	No
3	SMI	Bottom 50 %	PS only	Average of 3 slices	No	No	No
4	SMI	Bottom 50 %	ABD only	Average of 3 slices	No	No	No
5	SMI	Bottom 10 %	Total	Average of 3 slices	No	No	–
6	SMI	Bottom 20 %	Total	Average of 3 slices	No	No	–
7	SMI	Bottom 30 %	Total	Average of 3 slices	No	No	–
8	SMI	Bottom 40 %	Total	Average of 3 slices	**Yes**	No	–
9	SMI	Bottom 50 %	Total	Average of 3 slices	**Yes**	No	No
10	SMI	Bottom 60 %	Total	Average of 3 slices	**Yes**	No	–
11	SMI	Bottom 70 %	Total	Average of 3 slices	**Yes**	No	–
12	SMI	Bottom 80 %	Total	Average of 3 slices	No	No	–
13	SMI	Bottom 90 %	Total	Average of 3 slices	No	No	–

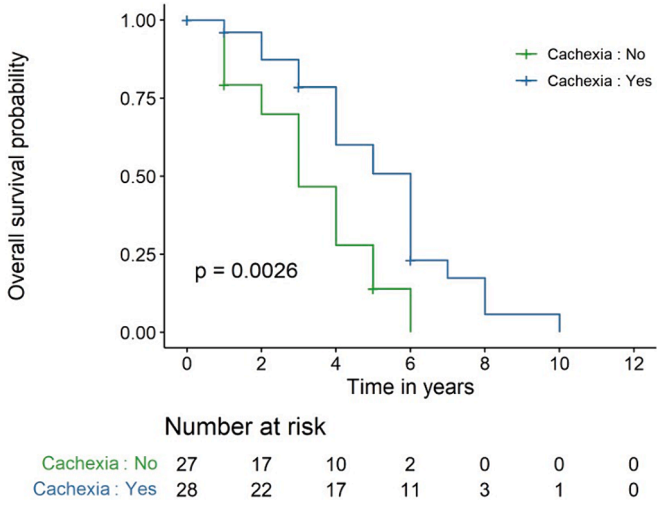

Fig. 2. Overall survival curve for cachectic and non-cachectic endometrial cancer patients (cachexia defined as SMI in the bottom 50% among all subjects).

to those who had cachexia based on definitions selected. Rather, Kaplan-Meier analysis demonstrated an unexpected OS advantage in the cachexia group when cachexia was defined as SMI in the bottom 40–70 % of the cohort. These results are in opposition to trends observed in other solid tumors, which have predominantly demonstrated poor outcomes in cases complicated by cancer cachexia. The diagnostic methods used in this study (namely, defining cachexia by quantifying paraspinal and abdominal musculature at the lumbar level on CT) were analogous to studies at other disease sites. Moreover, in an attempt to account for the variable thresholds for cachexia used in prior studies and to identify the criteria with the greatest prognostic value, a number of definitions of cachexia (13 in total) were investigated in this study. None of the definitions showed a positive association between cachexia and poor outcomes.

Cancer patients are by no means a uniform population, and the prognostic factors that are considered most predictive are in general dependent on disease site and tumor type. The results of this study are a reminder of this. Cachexia, which has been robustly associated with poor outcomes across a number of solid tumors, does not appear to be a major driver of OS, PFS, or disease recurrence in endometrial cancer patients. Patients with primary endometrial carcinoma constitute a unique population, with younger median age at diagnosis and higher rates of obesity than many other malignancies. Obesity in this patient population may be a competing risk factor against cachexia with both ends (overweight and cachexic) of the population having worse outcomes. This explains why the middle group subsets had better outcomes than either end of the spectrum. This study supports the conclusion that other indicators may be more prognostically useful in this population than a CT-based diagnosis of cachexia.

Limitations of this study include a small sample size ($n = 55$) and short interval follow-up. That even widely accepted prognostic factors such as stage, grade, LVSI, and performance status showed no association with OS or PFS could indicate insufficient power or number of recurrences needed to detect prognostic differences among subgroups. In addition, the study group consisted of patients treated at a single tertiary care institution, which may limit generalizability of the conclusions. A better understanding of the relationship between cachexia and endometrial cancer may benefit from larger, multicenter investigations with more extended follow-up.

In addition, the unique role of obesity in endometrial cancer and its potential confounding relationship with a clinical diagnosis of cachexia warrants additional investigation. Obesity, which itself has been linked to decreased endometrial cancer survival and increased disease recurrence, may be more prognostically significant in this population (Kokts-Porietis et al., 2021). The multidirectional relationship among obesity, cachexia, and endometrial cancer may be explored further in future studies.

CRediT authorship contribution statement

Paul Kinkopf: Investigation, Writing – original draft, Writing – reviewing & editing. **Hyunwoo June Choo:** Writing – review & editing, Methodology, Conceptualization. **Ishan Roy:** Writing – review &

editing, Methodology, Conceptualization. **Jonathan Strauss:** Writing – review & editing, Methodology, Conceptualization. **Zequn Sun:** Writing – review & editing, Formal analysis. **Eric Donnelly:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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