A systematic review and meta-analysis of sarcopenia as a prognostic factor in gynecological malignancy

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ABSTRACT

Introduction

Sarcopenia is a condition described as the progressive, generalized loss of muscle mass and strength. While sarcopenia has been linked with poorer outcomes following a variety of malignancies, its relationship with all gynecological cancer clinical outcomes has to date, not been evaluated. This review interrogates the concept of sarcopenia as a prognostic tool for oncological outcomes and adverse effects of treatments in all primary gynecological malignancies.

Methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines, searching PubMed, Embase, and CINAHL without date or language restriction for studies reporting on sarcopenia and gynecological malignancies. Random effects meta-analysis models were used to determine the effects of sarcopenia on progression-free survival, overall survival and treatment-related adverse events.

Results

Data were analysed from 13 studies, including 2446 patients (range 60-323), including those with ovarian cancer (n= 1531), endometrial cancer (n=562) or cervical cancer (n=541). Sarcopenia was associated with lower progression free survival (HR: 1.69, 95% CI 1.03 to 2.76), OS (HR: 1.33 (95% CI 1.08 to 1.64) and no increase in adverse events (HR: 1.28, 95% CI 0.69 to 2.40). The risk of bias of the studies was mostly rated unclear, and Begg's and Egger's test revealed a potential publication bias for progression free survival and OS, although the hazard ratios remained significant when adjusting for it.

Discussion

Sarcopenia is associated with worse progression free survival and overall survival in gynecological oncology malignancies. Further research is warranted to validate those findings in larger and prospective samples, using standardized methodology and to examine if an intervention could reverse its effect in gynecologic oncology trials.

Precis

Sarcopenia is increasingly recognised as a pathology that contributes to oncological outcomes. We present a meta-analysis of sarcopenia in gynecological malignancies, showing worse progression free survival and overall survival. Future prospective trials are needed.

Highlights

1. The overall hazard of disease progression was increased by 69% for those with sarcopenia.
2. Sarcopenia potentially contributes to worse overall survival, with a pooled hazard ratio of 1.33
3. Sarcopenia should be a factor considered in future prospective trials

Introduction

Sarcopenia is a condition or syndrome described as the progressive and generalized loss of muscle mass and strength (1). The prevalence of sarcopenia increases with age, with up to 53% of individuals in their eighth decade considered sarcopenic and more than 40 million people affected worldwide (1). Sarcopenia can also be acquired as a consequence of several pathological processes, including malignancy (2). The diagnosis of sarcopenia is commonly based on assessment of low muscle mass, strength, and performance (3) or on quantifiable objective measures using various imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI) and dual energy x-ray absorptiometry (4). Measurement of the third lumbar vertebral area of skeletal muscle on CT imaging is the most frequently used test and has been shown to correlate well with whole body muscle mass (5). Sarcopenia is not reflective of an individual's nutritional status and as such, while it may be more readily diagnosed in normal or underweight individuals (5), body mass index generally correlates poorly with the diagnosis (6) and so sarcopenia can also occur concurrently with obesity, which may be associated with worse outcomes in the context of cancer treatments (7).

Sarcopenia has been shown to independently impact the course of several diseases, including gastrointestinal, renal, and lung malignancies (4). The relationship between sarcopenia and disease outcomes in oncological populations reflects an emerging area of research, and assessment of the impact of sarcopenia on morbidity and mortality in gynecological oncology is therefore a growing area of study (8). Traditionally, gynecologic oncologists have placed great emphasis on the detection and management of cachexia (weight loss), as its presence is associated with adverse malignancy-associated outcomes

(9). It is clear however that body mass index is not correlated with body composition and knowledge of muscle mass, or lack thereof, is an increasingly important consideration in the treatment of malignancy (10). This may be of particular relevance in gynecological oncology given the strong association between obesity and risk of endometrial and ovarian malignancies (11), where there will be a need for improved understanding of the less clinically apparent, sarcopenia in overweight and obese patients. Patient factors which allow clinicians to refine their treatment and prognostication are increasingly important in an era of personalized medicine. Sarcopenia may provide clinical information that allow treatment interventions not as readily apparent if one relies on more traditional assessments of nutrition (e.g. body mass index)(12), and further research is necessary to assess whether this process is of oncological benefit.

Thus this meta-analysis and systematic review of the literature aims to interrogate the concept of sarcopenia as a prognostic tool for oncological outcomes and for its association with treatment-related complications in the context of gynecological cancer.

Methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines. We searched PubMed, Embase, and CINAHL to identify all potentially relevant articles with no date limitation, without language restriction. Search strategies were customized to the subject heading and search structure of individual databases. Reference lists from review articles were also searched. The full search strategy can be found in Appendix 1. The search was

completed on the 25th of June, 2019. This study was registered with PROSPERO, registration number CRD42019139488.

Inclusion and exclusion criteria

All identified studies were assessed. Any study reporting on sarcopenia and outcomes in gynecologic cancer was considered, with participants in studies defined as women with uterine/endometrial, ovarian, cervical, vulvar, or vaginal cancer. Sarcopenia was defined using an accepted objective measure as determined by the study authors (see results). Cohort studies (prospective and retrospective) and randomized controlled trials were considered for inclusion. Conference abstracts, case reports and management recommendations or pharmaceutical treatment studies were excluded. Studies were excluded if they didn't report on the pre-determined outcome measures of interest and / or sarcopenia was not defined.

Outcome measures

Pre-determined outcomes of interest were progression-free survival, as defined as time from enrollment in the study until recurrence of disease; overall survival as defined as time from enrollment in the study until death from any cause; and adverse events associated with treatment, which were defined by the study authors and included intra-operative and post-operative complications, as well as complications of chemotherapy (Appendix 2). We also targeted tolerability of treatment as an outcome measure, however no study included in the final meta-analysis reported on this.

Selection of studies

Two authors (AC and YP) independently reviewed abstracts to identify all studies that potentially met the inclusion criteria and should be retrieved. The same two authors independently assessed each full text article to determine whether it met all of the selection criteria. Any disagreement and uncertainties were resolved by discussion, with involvement of a third author (EA).

Assessment of methodological and reporting quality

Methodological quality was assessed using the Cochrane Risk of Bias tool for randomized trials. For non-randomised studies, the Newcastle-Ottawa Scale was adapted and used for the cohort studies as it included three additional elements (all outcome measures reported, methods of assessment for outcome provided, authors discuss potential sources of bias) from the Strengthening the Reporting of Observational Studies in Epidemiology quality assessment tool when assessing cohort studies.

Statistical analysis

Study results were summarised in descriptive form, including number of patients involved, study design, year of study and main outcome measures. We conducted a meta-analysis of the combined data across all studies, regardless of cancer type first. Given the heterogeneity of the included studies, pooled hazard ratios were estimated using random-effects. To determine the effects of sarcopenia on progression free survival, overall survival, and adverse events we calculated the pooled hazard ratios (HR) and their corresponding 95% confidence intervals (CI). A two-tailed *P* value < 0.05 was considered statistically significant. Sarcopenia was defined according to the authors of individual studies. Given the range of accepted diagnostic modalities it was pragmatic to analyse studies together and

accept the limitations of this. We used Begg's and Egger's tests to evaluate the publication bias, with a two-tailed $P < 0.1$ indicating significant publication bias. All analyses were conducted using Stata software, version 15.1 (Stata Corp, College Station, TX, USA).

Results

Fig. 1 shows the Preferred Reporting Items for Systematic reviews and Meta-Analysis flow chart for the selection of studies. The search strategy returned 342 results after duplicates were removed. Of these, after exclusions were applied, 51 full texts were reviewed (14.9%), with 16 studies meeting the inclusion criteria.

The characteristics of the 16 included studies, of which all were retrospective cohort studies, are shown in **Table 1**. Nine studies (56.25%) reported on sarcopenia in ovarian cancer, 3 (18.75%) on endometrial cancer, 1 (6.35%) on both endometrial and ovarian cancer (with data combined), and 3 (18.75%) on cervical cancer. Sample sizes ranged from 60 to 323 patients. Three studies(13-15) had crossover periods and potential crossover patients with other included papers and so were excluded from any further analysis. 2466 patients from 13 studies were included in the final meta-analysis. All included studies were published from 2015 onwards. Sarcopenia was defined in a variety of ways including muscle attenuation (16), skeletal muscle index (9, 14, 17-25), muscle mass measurement (26), skeletal muscle loss during treatment (13, 15), and the psoas index (27), all of which were defined in the included papers. Ten (77%) studies reported on overall survival, 4 (31%) reported on progression free survival, and 5 (38%) studies reported on adverse events (Appendix 2).

Progression free survival

Overall, 4 studies (2 ovarian and 1 each for endometrial and cervical cancer) contributed data towards analysis exploring the relationship between sarcopenia and disease progression. The progression free survival by cancer type and overall is shown in **Fig. 2**. Findings indicate that overall the hazard of disease progression was increased by 69% for those with sarcopenia (HR: 1.69, 95% CI 1.03 to 2.76, I^2 54.6%, P = 0.085; low to moderate heterogeneity in the included studies). The relationship between progression free survival and sarcopenia is inverse, which means that the presence of sarcopenia has a negative impact on progression free survival.

Overall survival

Ten studies reported on the relationship between sarcopenia and overall survival. The overall pooled hazard ratio was 1.33 (95% CI 1.08 to 1.64, I^2 40.8%, P = 0.086) with low to moderate heterogeneity in the included studies. Subgroup analyses showed the magnitude of effect is accentuated for women with endometrial cancer (**Fig. 3**). The relationship between overall survival and sarcopenia is inverse, with the presence of sarcopenia associated with a negative impact on overall survival.

Adverse events

Data from 5 studies (with high heterogeneity) suggest no significant increase in adverse events in those with sarcopenia (HR: 1.28, 95% CI 0.69 to 2.40, I^2 = 69.4%, P = 0.011) (**Fig. 4**).

Assessment of methodological quality

Supplemental Fig. 1 summarises the assessment of methodological quality of the included studies. The majority of studies had an unclear risk of bias in seven of eight domains. Six of 13 studies (46%) had a high risk of bias in the domain of representativeness of the exposed cohort. Six studies were also at low risk of bias in the domain of comparability of the cohorts.

Publication bias

Publication bias was assessed using both Begg's and Egger's tests. For OVERALL SURVIVAL potential publication bias was identified (Begg's test p-value = 0.049, Egger's test p-value = 0.014), however the HR remained significant after applying the trim and fill method (HR = 1.21, 95% CI 1.03-1.42). This was similar in progression free survival (Begg's test p-value = 0.089, Egger's test p-value = 0.063), with a HR after applying the trim and fill method of 1.54 (95% CI 1.07-2.18). There was no apparent publication bias for the outcome of adverse events (Begg's test p-value = 0.324, Egger's test p-value = 0.115, HR= 1.30, 95% CI 0.72-2.37)

Discussion

This systematic review and meta-analysis explored the relationship between sarcopenia and gynecologic oncology outcomes. We found evidence from 13 studies that sarcopenia was significantly associated with impaired overall survival and progression free survival with a trend towards an increased risk of adverse events. The impact of sarcopenia on overall survival was pronounced for patients treated for endometrial cancer. Sarcopenia was also associated with a trend towards higher adverse events risk related to cancer treatment (variably defined), although these results should be interpreted with caution as only few

studies reported on this outcome, and there was marked heterogeneity of the included studies as indicated by the high I-index (69.4%).

Prior to this review, the relevant body of evidence for gynecologic malignancies consisted of only one meta-analysis, including data from 8 studies, suggesting a significant association of low skeletal muscle index with overall survival in ovarian cancer (HR 1.11). However, the authors concluded that the quality of the evidence was low in all contributing publications (28). In our meta-analyses, there is a trend towards worse overall survival in sarcopenia in ovarian cancer (6 studies) and a significant association between sarcopenia and overall survival endometrial cancer (2 publications). Further, although lacking statistical significance, findings relevant to women with cervical cancer were in the same direction as those for women with endometrial and ovarian cancer. The magnitude of effect reported from this review was consistent with those from a variety of other solid malignancies, including gastric (29), renal and colorectal malignancies (30).

In our analysis of progression free survival, there were small numbers of included studies but overall a significant association of sarcopenia with progression free survival. In other oncological studies, there are conflicting results with regards to the impact of sarcopenia on this outcome (30). Given the small number of studies, the role of sarcopenia in specific gynecological malignancies is difficult to interrogate. It is however apparent that sarcopenia has the potential to be of significance in the progression of both ovarian and endometrial malignancies and it will be important to explore the mechanisms driving this effect in future prospective studies.

Although less well studied, in a variety of solid malignancies such as gastric and hepatopancreatobiliary tumors, sarcopenia has been associated with increased treatment-related complications (31, 32). We did not find a significant relationship between sarcopenia and adverse events in this analysis, although included studies and numbers of patients were limited.

Of particular note are the findings of this meta-analysis pertaining to women with endometrial cancer. Specifically, compared with the overall HR across all gynaecological malignancies, HR relating to subgroup analysis for overall survival following endometrial cancer was the most pronounced. Over 60% of women diagnosed with endometrial cancer are obese (33), and the diagnosis of sarcopenia in obese patients may be challenging. Assessment of sarcopenia prior to treatment could assist with identification of patients at high risk of poor outcomes. Those patients could be targeted for future intervention trials.

This systematic review and meta-analysis had broad inclusion criteria and followed rigorous quality protocols. All papers included were published from 2015 onwards, highlighting these findings as likely reflective of current patients and practice. Nonetheless, key limitations of this review include the heterogeneous methods of sarcopenic assessment and retrospective data collection of included studies, with the latter limitation likely contributing to unclear risk of bias and the publication bias identified. The accepted definitions and specific measurement of sarcopenia varied widely between studies, which limits the interpretation of the analysis and the capacity to rigorously compare included studies. We were unable to interrogate the impact of sarcopenia diagnosed at different time points in the course of cancer treatment, and are aware that this may impact the magnitude of the effect of

sarcopenia on patient outcomes(34). A standardized approach to the diagnosis will be necessary if we are to consider further the role it may play in trials and assessment of oncological outcomes. Furthermore, while sarcopenia may be acquired as a consequence of cancer treatment, for example as a side-effect of chemotherapy(35), it is also clear that it may associated with age, previous comorbidities and declines in physical activity(1). Retrospective studies, such as those included in this meta-analysis, lack the methodological robustness to provide sufficient detail regarding the direction of the relationship being assessed.

There is also clear scope for rigorous and comprehensive assessment the potential relationship between adverse events and sarcopenia in gynecological malignancies. It was beyond the scope of this review to evaluate the timing of sarcopenia development and its impact on survival outcomes and adverse events; this represents a clear area in need of future research with high translational potential. The lack of prospective studies in this field remains a significant limitation in being able to comprehensively consider the role of sarcopenia in clinical gynecological oncology, particularly with respect to both its capacity to be modified as well as its potential to guide prognosis at various stages of an oncological diagnosis. Therefore, future prospective research with a uniform definition of sarcopenia and with consideration to the relationship between sarcopenia and other prognostic factors in malignancy is required to obtain high-level evidence on the impact of sarcopenia on treatment-related complications and survival outcomes.

In conclusion, sarcopenia is associated with worse oncological outcomes in gynecological malignancies in this systematic review of retrospective cohort studies. Given that sarcopenia

is a potentially modifiable risk factor, prospective research using predefined criteria is warranted to explore the potential of interventions to reverse it.

Conflict of interest

The authors declare no conflict of interest.

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Author contributions

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All authors approved the final version of the manuscript.

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251 **Table 1.** General characteristics of included studies, all of which were retrospective cohort studies.

First author	Publication year	Country	Study period (year)	Cancer type	Sample size	Median follow-up (months)	Age (years)	Sarcopenia criteria	Outcome
Ataseven B (16)	2018	Germany	2011-2016	Ovarian	323	40	Median 60, range 21-89	Muscle attenuation < 32 HU	Overall survival
Aust S (17)	2015	Austria	2004-2012	Ovarian	140	56	Mean 60	Skeletal muscle index < 41 cm2/m2	Progression free survival; Overall survival
Bronger H (9)	2017	Germany	2003-2013	Ovarian	105	27	Median 65, range 33-85	Skeletal muscle index ≤ 38.5 cm2/m2	Progression free survival; Overall survival
Conrad LB (18)	2017	US	2007-2015	Ovarian	102	26	Mean 55	Skeletal muscle index < 38.5 cm2/m2	Adverse events
de Paula NS (36)	2018	Brazil	2008-2015	Endometrial Ovarian	250	1	Not available	Skeletal muscle index < 38.9	Adverse events
de Paula NS (20)	2019	Brazil	2008-2015	Endometrial	232	12	Median 64.3	Skeletal muscle index < 38.9 cm2/m2	Overall survival
Kiyotoki T (13)	2018	Japan	2004-2014	Cervical	60	33.5	Median 56.1, range 25-74	Skeletal muscle ≥ 15% loss during treatment	Progression free survival; Overall survival
Kumar A (21)	2016	US	2006-2012	Ovarian	296	33.2	Mean 64.6	Skeletal muscle index < 39 cm2/m2	Overall survival
Kuroki LM (26)	2015	US	2005-2009	Endometrial	122	32.8	Mean 65.9	Muscle mass < 4.33 cm2	Progression free survival; Overall survival; Adverse events

Lee J (22)	2018	Taiwan	2004-2015	Cervical	245	62.7	Mean 63	Skeletal muscle index < 41 cm2/m2	Overall survival
Matsuoka H (23)	2019	Japan	2004-2018	Cervical	236	34.5	Median 61, range 25-88	Skeletal muscle index < 36.55 cm2/m2	Progression free survival; Overall survival
Rodrigues CS (14)	2018	Brazil	2008-2014	Endometrial	208	12	Mean 64.2	Skeletal muscle index < 42.4 cm2/m2 Average muscle radiation attenuation < 30 HU	Overall survival
Rutten IJG (25)	2016	Netherlands	2000-2014	Ovarian	123	23	Mean 66.5, range 39-86	Skeletal muscle index < 41.5 cm2/m2	Overall survival
Rutten IJG (24)	2017	Netherlands	2000-2015	Ovarian	216	57	Mean 63.1, range 16-85	Skeletal muscle index ≤ 38.73 cm2/m2	Overall survival; Adverse events
Rutten IJG (15)	2017	Netherlands	2000-2015	Ovarian	150	23	Median 67, range 39-86	Skeletal muscle attenuation loss during treatment	Overall survival
Yoshikawa T (27)	2017	Japan	2010-2015	Ovarian	76	NA	Median 62, range 33-81	Psoas index < 58 mm2/m2	Adverse events

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254 **Table/Figure legends**

255 **Table 1.** General characteristics of included studies, all of which were retrospective cohort

256 studies.

257 **Fig.1.** Preferred Reporting Items for Systematic reviews and Meta-Analysis checklist of

258 included studies.

259 **Fig.2.** The forest plot for association between sarcopenia and progression-free survival. HR,

260 hazard ratio; CI, confidence interval.

261 **Fig.3.** The forest plot for association between sarcopenia and overall survival. HR, hazard

262 ratio; CI, confidence interval.

263 **Fig.4.** The forest plot for association between sarcopenia and adverse events. HR, hazard

264 ratio; CI, confidence interval.

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