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Review Article

Sarcopenia: Clinical implications in ovarian cancer, diagnosis, etiology, and management

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ABSTRACT

Sarcopenia, loss of skeletal muscle and function, is a common condition among the elderly and is known to cause adverse health outcomes and increased risk of morbidity and mortality. This progressive and generalized disorder imposes a considerable socioeconomic burden. Sarcopenia is observed commonly in cancer patients. As Asia is one of the fastest aging regions in the world, it is clear that incidences of both sarcopenia and ovarian cancer will increase together in Asian countries. Ovarian cancer patients are vulnerable to develop sarcopenia during the treatment course and progress of disease, and a considerable number of patients with ovarian cancer seems to have physical inactivity and sarcopenia already at the time of diagnosis. Therefore, management of sarcopenia should be conducted together in parallel with ovarian cancer treatment and surveillance. Thus, in this article, we will review the clinical importance of sarcopenia in the aspect of ovarian cancer. Definition of sarcopenia, diagnosis, etiology, and intervention will be also introduced.

Introduction

Ovarian cancer, one of the most lethal gynecologic malignancies, is a global burden with estimation of 295,000 new cases and 185,000 deaths worldwide in 2018.[1] Ovarian cancer ranks the 8th most common cancer among women, and also 8th most common cause of female cancer deaths.[1] The incidence and mortality of ovarian cancer varies in different regions of the world, particularly according to level of development.[2] Due to atypical clinical symptoms and lack of effective early diagnosis measures, approximately a half of patients are diagnosed in the advanced-stage and shows high recurrence and mortality rates.[3] Despite recent advances in surgery and chemotherapy, finding new approaches to improve the prognosis of ovarian cancer is needed.

Sarcopenia, loss of skeletal muscle and function, is a common condition among the elderly and is known to cause adverse health outcomes and increased risk of morbidity and mortality.[4] This progressive and generalized disorder imposes a considerable socioeconomic burden.[5,6] People with sarcopenia have greater odds of hospitalization and on average more hospital stays. In the United States, the total annual cost of hospitalization for individuals with sarcopenia was reported as USD $40.4 billion.[6] As the elderly population is growing rapidly worldwide, health-care cost attributable to sarcopenia is estimated to increase significantly. Therefore, awareness about the consequences of developing sarcopenia, systematic screening and prevention of sarcopenia, and early and optimal intervention is necessary to support healthy aging.

Incidence of major cancers increases with age. Therefore, sarcopenia is commonly observed in cancer patients.[7] Most hospitalized patients with advanced cancer have muscle loss consistent with sarcopenia.[8]

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ASM, appendicular skeletal muscle mass; AWGS, Asian Working Group for Sarcopenia; BIA, bioelectrical impedance analysis; BMI, body mass index; CINV, chemotherapy-induced nausea and vomiting; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; EMT, epithelial-to-mesenchymal transition; EWGSOP, European Working Group on Sarcopenia in Older People; GH, growth hormone; HMB, β-hydroxy-β-methylbutyrate; HRT, hormone replacement therapy; IGF-1, insulin like growth factor-1; L3, the third lumbar vertebra; MRI, magnetic resonance imaging; NLR, neutrophil to lymphocyte ratio; OECD, Organisation for Economic Co-operation and Development; OS, overall survival the length of time from either the date of diagnosis or the start of treatment for a cancer that patients diagnosed with the disease are still alive; PFS, progression-free survival the length of time during and after the treatment of cancer that a patient lives with the disease but it does not get worse; RM, repetition maximum; SARM, selective androgen receptor modulator; SMM, skeletal muscle mass; SPPB, Short Physical Performance Battery; TUG, Timed-Up and Go.

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Sarcopenia is known to be related with increasing resistance and toxicity to chemotherapy in many malignancies.[9–13] In ovarian cancer, previous studies have reported adverse effects of sarcopenia on patients' progression-free survival (PFS) and overall survival (OS).[14,15] However, inconsistent results have also been reported. Our previous study and studies of other groups have failed to prove a significant relationship between sarcopenia and poor survival outcomes.[16–18] These inconsistencies are possibly caused by differences in study design, population, disease setting, and definition of sarcopenia among the studies.

It is clear that incidences of both sarcopenia and ovarian cancer will increase together in Asian countries, as Asia is one of the fastest aging regions in the world. Thus, in this article, we will review the clinical importance of sarcopenia in the aspect of ovarian cancer. Definition of sarcopenia, diagnosis, etiology, and intervention will be also introduced.

Definition and diagnosis

Definition of sarcopenia

In 1989, Dr. Irwin Rosenberg introduced the concept of age-related loss of muscle mass for the first time. He proposed the word, sarcopenia, derived from the Greek words *sarx* for "flesh" and *penia* for "loss".[19] Since the first Sarcopenia Workshop, held by the National Institute on Aging in 1994, the etiology, pathophysiology, risk factors, and consequences of sarcopenia have gradually been clarified.

Former definition of sarcopenia only considered low muscle mass. However, in 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) reached a consensus on definition of sarcopenia (EWGSOP1); a concept of muscle function was added to the former definition.[20] In parallel, the International Sarcopenia Consensus Conference Working Group defined sarcopenia as the age-associated loss of skeletal muscle mass and function.[21] In 2018, the EWGSOP met again and updated definition of sarcopenia (EWGSOP2) in order to reflect both scientific and clinical evidence.[7] Now, diagnosis of sarcopenia is confirmed by the presence of both low muscle strength and low muscle quantity or quality (Table 1). If an individual also has low physical performance, individual's sarcopenia is considered severe.

Clinical diagnosis

An individual who reports symptoms or sings of sarcopenia (i.e., falling, slow waking speed, difficulty rising from a chair or weight loss/muscle wasting) is recommended to undergo further testing for identifying sarcopenia. To screen for sarcopenia risk, a 5-item self-reported questionnaire, SARC-F, may be used.[22]

Muscle strength is measured by measuring grip strength or the chair stand test, defined as the amount of time needed for a patient to rise five times from a seated position without using his or her arms.[7] Physical performance can be objectively measured by gait speed, the Short Physical Performance Battery (SPPB), and the Timed-Up and Go test (TUG).[7]

Various techniques (e.g., magnetic resonance imaging (MRI), computed tomography (CT), and dual-energy x-ray absorptiometry (DXA)) are available to estimate muscle mass or quantity.[23] Muscle mass is reported in forms of total body skeletal muscle mass (SMM), appendicular skeletal muscle mass (ASM), or muscle cross-sectional area of specific muscle groups. However, cut-off points for low muscle mass has not yet been defined well. For estimation of total SMM or ASMM, bioelectrical impedance analysis (BIA) has been also suggested, however, validation study is necessary in specific populations.[24] In general, muscle mass is correlated with body size. To adjust body size, SMM or ASM is usually divided by height squared, weight, or body mass index (BMI).[25] Table 2 presents the specific cut-off values for each component of sarcopenia, postulated by the EWGSOP2 and the Asian Working Group for Sarcopenia (AWGS).[7,26] Interestingly, differences in the cut-off values are observed between the EWGSOP1 and EWGSOP2. For example, the cut-off values for hand grip strengths changed from <30 kg for males and <20 kg for females to <27 kg for males and <16 kg for females. Discrepancies between the prevalence of sarcopenia when applying the EWGSOP1 and EWGSOP2 definitions have been reported.[27–29] Van Ancum et al. concluded that the lower cut-off points for hand grip strength resulted in fewer adults being diagnosed with sarcopenia.[29]

In addition, one should recognize that cut-off values for sarcopenia depend on the measurement modalities and on the availability of reference studies and populations. The current EWGSOP2 recommendations focus on European populations, while the AWGS focus on Asian countries, such as Japan, Korea, and China. As body composition is different among the Organisation for Economic Co-operation and Development (OECD) member countries,[30] prevalence and clinical features of sarcopenia may vary by geographical regions and ethnicities. For example, proportions of overweight to obese populations are quite different among the countries, even different between Korea and Japan. Therefore, validation study determining the cut-off value for sarcopenia in each region or ethnicity are very required.

Recently, researchers have suggested CT scans as useful clinical tools to determine sarcopenia. A cross-sectional image of CT scans at the level of the third lumbar vertebra (L3) is known to represent an individual's body composition (e.g., total body skeletal muscle and adipose tissues and fat distribution).[31,32] Identification of sarcopenia using CT scans in cancer patients is very feasible because CT scans are taken routinely as part of cancer patients' care. However, CT-based evaluation of sarcopenia in cancer patients has significant limitations. First, well-agreed and acceptable cut-off values for sarcopenia is not established; each study groups have used their own cut-off values.[18,33,34] In Korea, the

Table 1
Definition of sarcopenia from the EWGSOP2.

Probable sarcopenia is identified by Criterion 1.
Diagnosis is confirmed by additional documentation of Criterion 2.
If Criteria 1, 2 and 3 are all met, sarcopenia is considered severe.

[1] Low muscle strength
[2] Low muscle quantity or quality
[3] Low physical performance
Reproduced from Cruz-Jentoft et al. Age Ageing 2019; 48:16–31.[7]

Abbreviation: EWGSOP, European Working Group on Sarcopenia in Older People.

Table 2
Sarcopenia cut-off values from EWGSOP2 and AWGS.

Test	EWGSOP2		AWGS	
	Men	Women	Men	Women
Muscle strength				
Hand grip strength	<27 kg	<16 kg	<28 kg	<18 kg
Chair stand	>15 s for five rises	>15 s for five rises		
Muscle mass/quantity				
DXA ASM/height^2	<7.0 kg/m^2	<5.5 kg/m^2	<7.0 kg/m^2	<5.4 kg/m^2
BIA ASM/height^2			<7.0 kg/m^2	<5.7 kg/m^2
Performance				
Gait speed	≤0.8 m/s	≤0.8 m/s	≤0.8 m/s	≤0.8 m/s
SPPB	≤8 point	≤8 point	≤9 point	≤9 point
TUG	≥20 s	≥20 s	Not recommended	Not recommended

Abbreviations: ASM, appendicular skeletal muscle mass; AWGS, Asian Working Group for Sarcopenia; BIA, bioelectrical impedance analysis; DXA, dual-energy x-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People. SPPB, Short Physical Performance Battery; TUG, Timed-Up and Go test.

sex-specific cut-off values for sarcopenia have not been validated yet. Second, if abdominal distension is present due to the presence of ascites or intra-abdominal mass, it is possible that the skeletal muscle area or fat area would be measured inaccurately, producing exaggerated or reduced values. Lastly, most studies on CT-based evaluation of sarcopenia have conducted using data from healthy adult men/women without any disease. Thus, more validation studies are warranted for the moment.

Etiology and pathogenesis

The pathophysiology of sarcopenia is complex and multifactorial. The main cause of sarcopenia is aging, however, other factors also contribute to development of sarcopenia.[35] Physical inactivity, low nutritional intake or malnutrition, reductions of anabolic hormones, such as testosterone, estrogens, growth hormone (GH), and insulin like growth factor-1 (IGF-1), and increases of pro-inflammatory cytokines, such as IL-6 and TNF-α, are considered as underlying mechanisms for the loss of muscle strength and quantity.[36,37] Remodeling in skeletal muscle, alterations in muscle protein turnover, accumulated mutations in muscle tissue mitochondrial DNA, mitochondria dysfunction, loss of α-motor neurons, and accelerated muscle cell apoptosis were also reported to be associated with loss of muscle mass.[38]

Physical inactivity

Physical activity refers to any movement that uses skeletal muscles, and can include waking, running, swimming, and etc. Physical inactivity causes decrease of muscle strength first, then decrease of muscle mass, and in turn, it results in reduced activity levels.[39] Protective role of physical activity against sarcopenia development has been documented well: previous studies concluded that physical activity reduces the odds of acquiring sarcopenia in later life.[40–42]

Aerobic exercise (e.g., walking, running, cycling or swimming) is known to improve muscle strength, quantity, and/or quality, leading to decreased morbidity and mortality. Aerobic exercise reduces body fatness, while stimulates muscle protein synthesis.[37,43] Meanwhile, resistance training, such as weight lifting, significantly improves muscle strength, quantity, and/or quality in older people.[20] Resistance training is known to increase muscle protein synthesis and neuronal adaptation.[44,45]

Interestingly, there is strong evidence that physical inactivity increases risk of several types of cancer.[46,47] Physical inactivity is also associated with an increased risk of ovarian cancer.[48,49] Considering the incidence of ovarian cancer increases with advanced age and high prevalence of ovarian cancer in the elderly, a considerable number of patients with ovarian cancer seems to have physical inactivity and sarcopenia already at the time of diagnosis. During the course of treatment consisting of extensive surgery and several cycles of chemotherapy, physical inactivity and sarcopenia of the patients may worsen further. Therefore, there is a need to provide them adequate physical interventions to improve sarcopenia and get survival benefits.[50]

Low nutritional intake and malnutrition

Elders frequently have an impaired energy regulation, which is associated with progressive loss of body weigh including muscle.[51] A previous study reported imbalance between energy intake and resting metabolic rate response in older subjects.[51] Muscle protein synthesis, especially mitochondrial protein synthesis, is also decreased in elderly.[52] Because muscle protein synthesis is directly stimulated by intake of amino acids,[53,54] a deficient intake of energy and protein contributes to loss of muscle and function. Reduced intake of vitamin D is also known to be associated with low functionality in the elderly.

In ovarian cancer patients, poor dietary intake is frequently observed owing to the following reasons: In advanced-stage or recurrent disease, patients may complain of dyspepsia or abdominal distention due to the large amount of ascites. During debulking or palliative surgery, bowel resection is often conducted. If peritoneal carcinomatosis develops, bowel movement is decreased and hinders subject's nutrient absorption. Patients might suffer from long persistent seeding ileus caused by postoperative adhesion formation or bowel infiltrating tumors. All these points may lead patients to experience low nutritional intake and malnutrition, limiting the delivery of dietary amino acids to the peripheral skeletal muscle.

During ovarian cancer treatment, chemotherapy-induced nausea and vomiting (CINV) are very common side effects and also cause poor dietary intake. A recent meta-analysis study reported that CINV was associated with worse PFS and OS in patients with recurrent ovarian cancer.[55] Although we could not know exactly whether such deteriorated survival outcomes originated from development of sarcopenia or not, this study raises awareness about the importance of supportive care during chemotherapy. Once again, ovarian cancer patients are vulnerable to develop sarcopenia along with cancer progression and treatment courses.

High level of cytokines and inflammation

Aging is associated with increased inflammatory cytokines, particularly IL-6, IL-1, TNF-α and *C*-reactive protein[56–58]. It is well known that these cytokines cause excessive protein breakdown and activate apoptosis pathway in muscle tissues, resulting in loss of muscle mass. Cytokine-related aging process or chronic state of inflammation in the elderly is considered one of underlying mechanisms for sarcopenia, and associated with poor outcomes.[59,60] Younger adults with chronic medical conditions such as heart failure and cancer also show an increased serum level of pro-inflammatory cytokines and loss of muscle strength and mass.[61]

Like the relationship between sarcopenia and systemic inflammation, the relationship between cancer and systemic inflammation has been also reported. To date, inflammation is known to play a key role in the tumor growth, progression, invasion and metastasis. In patients with ovarian cancer, elevation of pro-inflammatory cytokines and systemic inflammatory indices, such as neutrophil to lymphocyte ratio (NLR), is frequently observed. In detail, IL-6 has been known to activate signaling pathways, such as JAK and STAT3 pathway, and promote tumor proliferation. IL-6-induced JAK/STAT activation leads to constitutive activation of STAT3, resulting in tumor cell growth and resistance to chemotherapy. IL-6 has also been shown to act as a trigger of the epithelial-to-mesenchymal transition (EMT), the first step of metastasis.[62] Systemic inflammation is also associated with patients' survival outcome. Previously, our research team reported that high NLR was related with decreased PFS in ovarian cancer.[63] In a recent meta-analysis study, ovarian cancer patients with increased NLR had significantly worse PFS and OS.[64]

In this aspect, the inflammatory state, sarcopenia and ovarian cancer seems to share many common parts, and they are difficult to be considered separately. In one individual, sarcopenia may exist first, and ovarian cancer may progress or worsen through sarcopenia-related increased systemic inflammation. Or on the contrary, ovarian cancer itself may increase systemic inflammation, causing or aggravating sarcopenia. It is hard to know which of the two comes first and is principal, but it is certain that they together result in poor prognosis, consequently. Therefore, in ovarian cancer patients, it is imperative to consider preventing and improving sarcopenia, not just treating ovarian cancer.

Cancer cachexia

Cancer cachexia is a syndrome defined by a progressive loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support. Similar to sarcopenia, cancer cachexia shows systemic inflammation and leads to progressive functional impairment.[65] Considerable over-laps are observed between cancer cachexia and sarcopenia, however, technically, they are different terms; while sarcopenia

is a gradual and progressive, long term age-related process, cancer cachexia is related with acute metabolic change towards hyper-catabolism.[37] Nevertheless, cancer cachexia is one of the main reasons for secondary sarcopenia in cancer patients; sarcopenia is a feature commonly observed in patients with cancer cachexia. Cancer patients who are underweight are at high risk of having both sarcopenia and cancer cachexia.

Sarcopenic obesity

Obesity, especially the visceral obesity, is associated with a chronic inflammatory state, which leads to adverse metabolic consequences and development of sarcopenia.[66,67] In the elderly, loss of muscle mass tends to cause physical inactivity that leads to obesity. Then, an obesity-related inflammatory state could lead to accelerated loss of muscle mass. Such vicious cycles are known as "sarcopenic obesity", the term referring to the coexistence of sarcopenia and obesity.[68,69] Characteristically, patients with sarcopenic obesity have increased fatty infiltration in their skeletal muscle, which is associated with reduced muscle strength and function.[70]

Previous studies have reported that the presence of sarcopenic obesity increased disease recurrence and mortality in patients with colorectal cancer.[71,72] In ovarian cancer, our research team revealed that sarcopenic patients with a relatively large amount of fat compared to muscle mass showed a poor OS.[73] The possible explanation for these results would be that adipose stem cells from visceral and subcutaneous fat may facilitate the growth and migration of cancer cells.[74] Therefore, in ovarian cancer patients, it is important not to become obese and to maintain proper body compositions. Such efforts are believed to be helpful in preventing sarcopenia.

Management

Physical exercise, nutrition, and pharmacological approaches have been proposed as key factors in managing sarcopenia. Not only muscle strength, but also muscle mass should be improved. While physical exercise increases both muscle strength and mass, pharmacologic treatment, such as growth hormone, increases muscle mass without a significant change in strength.[75]

In the elderly, preventing gradual loss of skeletal muscle strength, function, and mass is more important than gaining muscle mass. Prevention should be accompanied by treatment, and treatment should be conducted as early as possible.[76] Exercise is the single most effective intervention for sarcopenia.[77] However, combination of physical intervention and nutritional support is more effective management of sarcopenia.[78] Pharmacological treatment has not yet reached consensus because there is no clear evidence.

Physical exercise

Physical exercise is effective in preventing and treating sarcopenia. Aerobic exercise helps regulate metabolism, reduces oxidative stress and improves athletic performance.[79] For the elderly, it is recommended to exercise for at least 30 min on 5 days per week or vigorous-intensity aerobic exercise for at least 20 min on 3 days per week.[79] Herein, vigorous-intensity aerobic exercise refers to activities performed at six or more times the intensity of rest on an absolute scale. On a scale relative to an individual's personal capacity, it is usually a 7 or 8 on a scale of 0–10.[80]

Other training intervention is resistance exercise. Resistance exercise is effective in increasing muscle strength and mass, and it should be started as soon as possible to ensure its effectiveness. To increase muscle mass and improve muscle strength in the elderly, the use of both single- and multiple-joint exercises with slow-to-moderate lifting velocity, for 1–3 sets per exercise with, 60–80% of one-repetition maximum (1 RM) for 8–12 repetitions with 1–3 min of rest between sets is recommended for 2–3 days per week.[81] In terms of power training, the use of single- and multiple-joint exercises for 1–3 sets per exercise using light to moderate loading (30–60% of 1 RM) for 6–10 repetitions with high repetition velocity is recommended to the elderly.[81] Details of the intensity and methods of exercise therapy are described in Table 3.

Several studies have suggested that physical exercise has a benefit for patients with certain cancers, such as breast cancer[82–86] and colorectal cancer.[87–90] Exercise is known to improve fatigue, physical functioning, cardiorespiratory fitness, and quality of life in cancer patients and survivors. Moreover, physical exercise after a diagnosis of cancer appears to reduce the risk of recurrence and mortality in both breast and colorectal cancer survivors.[85–91] However, few studies discussed to date the beneficial effects of exercise after a diagnosis of ovarian cancer. In particular, associations between post-diagnosis physical activity and survival outcomes, chemoresistance, or prevention and management of sarcopenia in patients with ovarian cancer have not elucidated yet. Therefore, further researches to explore such topics are needed in near future.

Nutritional intervention

Nutritional supplementation is essential for the prevention and treatment of sarcopenia because malnutrition contributes to the poor muscle function in the elderly.[78,92] Providing sufficient energy and supplementing certain nutrients is important to prevent and treat sarcopenia.[93] For elderly people, daily consuming 1.0–1.2 g of protein per kilograms of body weight is recommended to maintain and recover lean body mass and function. Elderly people with severe kidney disease (i.e., estimated GFR <30 mL/min/1.73 m^2) may reduce dietary protein94.

Supplementation of vitamin D is also one of the nutritional interventions because serum vitamin D levels below 50–100 nmol/L are associated with muscle weakness.[95] Therefore, it is most important to replace depleted serum vitamin D levels and maintain adequate intake according to the current recommendations (i.e., 700–1000 IU/day cholecalciferol).[76] Supplementing creatine monohydrate increases the available phosphocreatine which is a form of energy storage needed for high-power exercise. In a previous study of male and female subjects between the ages of 65 and 86, consuming creatine for 14 days improved the maximum grip strength and physical working ability.[96]

Oxidative stress is one of the pathogenesis of sarcopenia.[97] For this reason, administration of antioxidants has been proposed for the management of sarcopenia.[97] In a study of older people with high plasma levels of antioxidants, there was a low risk of developing disorders and reducing muscle strength.[98] However, prescribed antioxidants can paradoxically act as pro-oxidants, increasing the risk of death.[98] A meta-analysis study including 68 randomized trials with 232,606

Table 3
Physical exercise for sarcopenic elderly people.

Type of training	Frequency	Intensity	Duration/set
Aerobic exercise	Minimum 5 days/week for moderate intensity or 3 days/week for vigorous intensity	Moderate intensity at 5–6 on a 10-point scale; Vigorous intensity at 7–8 on a 10-poiont scale	At least 30 min/day of moderate intensity activity, in bouts of at least 10 min each; continuous vigorous activity for at least 20 min/day
Resistance exercise	2–3 days/week	Slow-to-moderate velocity 60–80% of 1 RM	8–10 exercises 1–3 sets per exercise 8–12 repetitions 1–3 min of rest between sets
Power training	2 days/week	High repetition velocity 30–60% of 1 RM	1–3 sets per exercise 6–10 repetitions

Abbreviation: 1 RM, 1-repetition maximum.

participants have reported that treatment with beta carotene, vitamin A, and vitamin E alone or combined with other antioxidants significantly increased mortality.[99] Essential amino acids, β-hydroxy-β-methylbutyrate (HMB), and omega-3 fatty acids can also be nutritional strategies for sarcopenia when combined with resistance exercise.[97] The nutritional strategies are summarized in Table 4.

Patients with ovarian cancer need nutritional help indeed. However, no specific nutritional intervention method to prevent and treat sarcopenia has been established in ovarian cancer patients. Individualized consultation with a nutritional expert is very necessary. Nutritional state should be evaluated at first day of hospitalization before starting cancer treatment.[100]

Pharmacological treatment

Many pharmacological agents have been studied to treat sarcopenia, but there is not enough evidence to make them a mainstream sarcopenia treatment.[101] Table 5 displays currently available pharmacological treatment for sacropenia.

In elderly men, decline of testosterone is associated with loss of muscle mass and strength. Thus, testosterone replacement therapy is recommended in elderly men: previous studies have reported that testosterone supplementation increased muscle mass and strength, whereas it decreased fat mass.[102–105] However, high doses of testosterone in the elderly is also associated with several side effects, such as cardiovascular diseases, gynecomastia, and prostatic disease.[106] Selective androgen receptor modulators (SARMs) are considered safe, and have been reported to effectively improve lean body mass and physical function.[107]

In elderly women, decline of estrogen results in decrease of muscle mass and function. Skeletal muscle is an estrogen-responsive tissue, therefore, a significant decrease in muscle strength occurs in postmenopausal women. Estradiol acts through estrogen receptors in the skeletal muscle and improves the function of myosin, consequently increasing muscle strength.[108] Therefore, hormone replacement therapy (HRT) can be considered in postmenopausal women to improve sarcopenia.[109]

In patients with ovarian cancer, there are concerns that HRT may increase the risk of recurrence and mortality and increase the risk of breast cancer. Therefore, physicians have been reluctant to prescribe HRT to ovarian cancer survivors. However, a randomized trial including 150 patients who had been diagnosed with ovarian cancer showed that HRT did not deteriorate patients' survival outcomes; rather it improved PFS and OS.[110] A recent meta-analysis concluded that HRT might improve OS in patients with ovarian cancer, but the certainty of the evidence was low.[111] Further studies investigating associations between HRT and ovarian cancer patients' survival outcomes and effectiveness of HRT on prevention and management of sarcopenia are warranted.

Table 4
Nutritional interventions.

Nutritional strategies	Recommendations
Protein supplement[94,120]	At least 1.0–1.2 g/kg/day in old age An increase in protein intake above 0.8 g/kg/day for maintaining muscle mass GFR 30–60, 0.8 g/kg/day GFR <30, 0.6–0.8 g/kg/day
Vitamin D[92,121]	Vitamin D should be supplemented in all persons which values less than 100 nmol/L Maintain adequate intake at 700–1000 IU/day of cholecalciferol
Creatine monohydrate[92]	Short-term creatine monohydrate supplementation 5–20 g/day of creatine monohydrate for 2 weeks
Antioxidants[98,99]	Selenium, vitamin A, vitamin C, and vitamin E, and β-carotene However, antioxidants may exhibit pro-oxidant activity depending on the specific set of conditions.
Essential amino acid supplementation[122]	Daily leucine 2.5 g or 2.8 g with combination of resistance exercise
β-hydroxy-β-methylbutyrate (HMB)[123]	HMB alone, or with arginine and lysine or with resistance exercise
Omega-3 fatty acids[124]	A possible effective nutrient for muscle loss.

Table 5
Agents for pharmacological interventions.

Pharmacologic strategies	Recommendations
Testosterone[104,105]	In lower doses, testosterone increases protein synthesis Testosterone is the most effective and safest if not at high doses of 300 and 600 mg/week
Selective androgen receptor modulators (SARMs)[107]	SARMs appear to be safe and effective in increasing lean body mass Clinical trials of long-term follow-ups are needed to demonstrate long-term safety and efficacy of selective SARMs
GH/IGF-1[125]	Side effects such as orthostatic hypotension, gynecomastia, myositis, and edema in single small study
Ghrelin and Ghrelin receptor agonist[113]	Studies about ghrelin or ghrelin receptor agonists had positive effects on food intake and increased muscle mass and function.
Angiotensin-converting enzyme inhibitor[105,115]	Perindopril has shown to increase physical performance and to reduce the incidence of hip fractures in the elderly

Abbreviations: GH, growth hormone; IGF-1 insulin like growth factor-1.

GH and IGF-1 are reported to increase lean body mass, but no advantage of muscle strength in the elderly, and are related to various side effects.[112] However, evidences supporting effectiveness of GH and IGF-1 on prevention and management of sarcopenia and their safety regarding to survival outcomes are still insufficient in patients with ovarian cancer. Ghrelin and ghrelin receptor agonist improved food intake and muscle mass and function, but were not significant. For this reason, more clinical trials are needed to demonstrate the effectiveness of these agents in long-term treatment.[113] Most cost effective pharmacologic intervention would be angiotensin converting enzyme inhibitor (ACEi). Perindopril, one type of the ACEi, has been reported to improve physical performance, especially the 6-min walking distance, and to reduce the rate of hip fractures in the elderly.[114] The ongoing LACE study, a clinical trial on the effects of leucine and perindopril, will conclude the new cost-effective treatment to the older patients with sarcopenia.[115]

Special considerations in ovarian cancer patients

Management of sarcopenia in ovarian cancer patients and general sarcopenic elderly people is bound to show different properties. In ovarian cancer patients, the disease-specific factors that make sarcopenia worse should be addressed first. If patients' poor dietary intake originates from abdominal distention due to large amount of ascites, drainage of ascitic fluid should precede other interventions. If patients suffer from long persistent seeding ileus, palliative procedures such as stoma formation should be provided. Oral intake can be inhibited by CINV, therefore, adequate anti-emetics should be prescribed to patients during chemotherapy. Sometimes, parenteral nutrition can improve patients' nutritional status. If patients suffer from depressive disorder, which leads to a decreased physical activity, additional psychiatric treatment, as well as psychosocial support from care givers and familial members, should precede exercise treatment. Severe cancer pain may leave bedridden patients. In that case, adequate pain control is necessary to help patients maintaining daily living and physical activity. Thus, best supportive care or palliative care reliving pain and other symptoms should be offered to patients with ovarian cancer during the whole treatment course and progress of disease.[116]

Sarcopenia can develop secondarily due to preexisting cancer cachexia.[117] In such cases, management of cancer cachexia should be also conducted. In brief, nutrition experts recommend high-protein,

high-calorie, nutrient-dense food. Enteral tube feeding or parenteral nutrition can be also considered to manage cachexia in patients with advanced cancer. In terms of pharmacological treatment, scientific evidences are insufficient to recommend any agents to improve cancer cachexia outcomes. Nevertheless, short-term (weeks) use of progesterone analogs is currently available to improve appetite and/or weight gain117. In terms of exercise prescription, scientific evidences are still insufficient: for patients with cancer cachexia, the safety and effectiveness of exercise has not been determined yet.[117–119]

As mentioned above, management of sarcopenia should be conducted together in parallel with ovarian cancer treatment and surveillance. However, the most appropriate management has not yet been established for ovarian cancer patients with both sarcopenia and cancer cachexia. Further prospective studies are warranted.

Conclusion

In this study, we reviewed definition of sarcopenia, diagnosis, etiology, and intervention in the aspect of ovarian cancer. To date, management of ovarian cancer has focused only on chemotherapy and surgery. Ovarian cancer patients are vulnerable to develop sarcopenia during the treatment course and progress of disease. As ovarian cancer is more prevalent in the elderly women, and tends to be diagnosed at advanced stage, patients with ovarian cancer might already have sarcopenia at the time of diagnosis. Therefore, more active screening and prevention of sarcopenia is necessary in patients with ovarian cancer. Management of sarcopenia should be conducted together in parallel with ovarian cancer treatment and surveillance.

The exact prevalence of sarcopenia in ovarian cancer patients has not yet been clearly reported. However, as the elderly population is growing rapidly worldwide, patients with both sarcopenia and ovarian cancer will increase together. Clinicians should provide patients adequate sarcopenia management with a multi-dimensional therapeutic approach, consist of physical exercise, nutritional intervention, and pharmacolgical treatment is necessary.

Submission statement

We confirm that we have given due consideration to the protection of intellectual property associated with this work and there are no impediments to publication, including the timing of publication, with respect to intellectual property.In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Authors' contributions

Conceptualization: YS Song; Writing - original draft: A Seol, SI Kim; Writing - review & editing: all authors; Supervision: YS Song.

Conflict of interest

No conflicts of interest, relevant to this article, exist.

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