Physical Therapy and Research in Patients with Cancer

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Editors
Shinichiro Morishita
Department of Physical Therapy
School of Health Sciences
Fukushima Medical University
Fukushima, Fukushima, Japan

Jiro Nakano
Department of Physical Therapy
Faculty of Rehabilitation
Kansai Medical University
Hirakata, Osaka, Japan

Junichiro Inoue
Division of Rehabilitation Medicine
Kobe University Hospital
Kobe, Hyogo, Japan

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Preface

It is known that cancer patients experience various physical and mental symptoms and a decline in both activities of daily living (ADL) and quality of life (QOL). These impairments are a result of both the cancer itself and the treatment process. Physical therapy in patients with cancer has recently come to be recognized as an important treatment modality in the recovery process after chemotherapy and radiotherapy. Physical therapy in patients with cancer not only improves physical functions such as muscle strength and exercise tolerance, as well as ADL and QOL, but also has the potential to contribute to survival and recurrence rates. Physical therapy in cancer patients targets a wide range of cancer types, including breast, gastrointestinal, lung, and hematologic cancers. In addition, physical therapy can be performed in cancer patients of all ages, from children to older adults, and physical therapists must have the proper knowledge to provide physical therapy to cancer patients. Although physical therapy has been reported to have a variety of benefits, it can also have negative effects on cancer patients if not properly applied. Therefore, risk management is also very important in the determination and application of physical therapy.

This book presents extensive knowledge and research findings of physical therapy researchers who are well experienced in the field of physical therapy for cancer. It is intended for a wide range of readers, including physical therapists and students who are interested in physical therapy in cancer patients, as well as clinicians and nurses who are seeking accurate information that can be immediately applied to their daily rehabilitation practice. In addition, the book presents cutting-edge cancer physical therapy research and evidence. We are pleased to share our knowledge with readers through this book, and we believe it will contribute to physical therapy in cancer patients.

Finally, we would like to express our deepest gratitude to our colleagues, who have contributed to each chapter, as well as Springer Publishers, all of whom have worked so hard in the preparation of this book.

Fukushima, Japan — Shinichiro Morishita
Kobe, Japan — Junichiro Inoue
Osaka, Japan — Jiro Nakano

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Part I

Physical Function and Health Related Quality of Life

Physical Function and Health-Related QOL in Cancer Survivors

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Shinichiro Morishita, Ryohei Jinbo, Atsuhiro Tsubaki, and Jack B. Fu

Abstract

Due to population growth and aging, as well as advances in early detection and treatment, the mortality rate from cancer is declining and the number of cancer survivors is on the rise. On the other hand, cancer treatment and aging impair physical function and health-related quality of life. Physical therapy is known to have the potential to maintain and improve both of these. This chapter describes reports on the actual physical function and quality of life of cancer survivors. Reports demonstrating the effectiveness of exercise therapy for cancer survivors will also be presented to serve as a reference for readers who provide survivors with this type of therapy.

Keywords

Cancer survivors · Physical function · Quality of life · Physical therapy Rehabilitation

S. Morishita (✉)
Department of Physical Therapy, School of Health Sciences, Fukushima Medical University, Fukushima, Japan
e-mail: morishit@fmu.ac.jp

R. Jinbo
Department of Rehabilitation, Kita-Fukushima Medical Center, Fukushima, Japan

A. Tsubaki
Department of Physical Therapy, Niigata University of Health and Welfare, Niigata, Japan

J. B. Fu
Department of Palliative, Rehabilitation & Integrative Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, USA

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1.1 Introduction

Advances in the early detection and treatment of cancer have reduced mortality rates, and the number of cancer survivors continues to rise. In the United States, on January 1, 2019, more than 16.9 million people with a history of cancer (8.1 million men and 8.8 million women) were still alive, and this number is projected to reach more than 22.1 million by 2030. More than half of cancer survivors have been diagnosed within the past 10 years, and about two-thirds are older than 65 years [1]. In addition, seven countries (Australia, Canada, Denmark, Ireland, New Zealand, Norway, and the United Kingdom) saw an increase in the 5-year survival rates for nearly all cancer types between 1995 and 2014. The improvement in survival rate is greater when the age at diagnosis of cancer is younger than 75 years and is particularly pronounced for cancers with poor prognoses (esophagus, stomach, pancreas, lung, etc.) [2]. Similarly, in Japan, the number of cancer survivors is increasing, and the long-term survival rates are improving for breast cancer survivors [3]. Thus, while the number of cancer survivors is increasing due to improved survival rates, a number of problems related to the effects of cancer treatment have been reported, including age-related physical functions and quality of life (QOL). Based on findings in previous literature, this chapter provides a comprehensive description of cancer survivors' QOL, weight, sarcopenia, exercise capacity, muscle strength (grip strength, knee extension strength), balance function, and peripheral neuropathy (Table 1.1). The second half of the chapter draws on a variety of literature to explain the effects of exercise therapies such as resistance training and aerobic exercise on cancer survivors, as well as the relationship between physical function and mortality.

Table 1.1 Physical function and quality of life assessment items

Physical function and quality of life	Evaluation battery
Quality of life	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)
	The Functional Assessment of Cancer Therapy (FACT) questionnaires
	The Short Form 36 Health Survey (SF-36)
Body weight	Body mass index (BMI)
Sarcopenia	Bioelectrical Impedance Analysis (BIA)
	Dual-energy X-ray absorptiometry (DXA)
Exercise capacity	Cardiopulmonary exercise stress test
	6-minute walking test (6MWT)
Muscle strength	Knee extensor strength
	Grip strength
Balance function	The modified Romberg test
	Timed up and go (TUG) test
	The short physical performance battery (SPPB)
Chemotherapy-induced peripheral neuropathy	Numerical rating scale
	EORTC QLQ-CIPN20

1.2 Quality of Life

The QOL of survivors of a variety of cancer tumors has been investigated. Zebrack et al. [4] compared the QOL of 1993 cancer survivors 5–10 years after cancer diagnosis and healthy controls. The study reported that the physical and mental health statuses of the cancer survivors were comparable to those of the healthy controls [4]. Similarly, Arndt V et al. [5] compared the QOL of 6952 long-term cancer survivors (breast, colorectal, or prostate) to 1878 age- and gender-matched healthy individuals reported that the overall QOL of the cancer survivors was comparable to that of the healthy individuals. However, they reported that social, role, emotional, cognitive, and physical function impairments, as well as items related to symptoms such as insomnia, fatigue, dyspnea, constipation, diarrhea, and financial difficulties, were worse in the cancer survivors [5].

We have also investigated QOL among cancer survivors and healthy controls in previous studies. QOL assessed using the Short Form 36 Health Survey (SF-36) and physical functions were compared between 36 cancer survivors, with an average duration of disease of 6 years, and 29 healthy subjects [6]. The physical function items of the SF-36 subscale were significantly lower in the cancer survivors compared to the healthy controls, and grip strength and knee extension muscle strength were both positively correlated with the physical function items of the SF-36 subscale [6]. Thus, physical function and QOL are related in cancer survivors, and the intervention of physical therapists may be highly significant.

The relationship between physical function and QOL in cancer survivors has been examined from various perspectives by cancer type. Among cancer survivors, there have been many reports on the QOL of breast cancer survivors. In a previous study, 190 breast cancer survivors 5 years after diagnosis were compared with age-matched healthy controls in terms of QOL (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)) by Schmidt ME et al. [7] They reported that QOL worsened during cancer treatment but improved to almost equal to that of the controls [7]. Klein D et al. [8] compared the long-term QOL of 652 breast cancer survivors at 5, 10, and 15 years after diagnosis with that of 1188 healthy individuals at the same time points. Physical function and role/physical scales on the SF-36 were each significantly lower compared to the healthy subjects, but the differences decreased over time, and the cancer survivors 15 years after diagnosis did not differ compared to the healthy subjects [8]. Kaur N et al. [9] divided 230 breast cancer survivors into three groups according to years since treatment: early-stage survivors (<2 years), moderate-stage survivors (2–5 years), and long-term survivors (>5 years), and compared their QOL (SF-36 and Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaires) with that of 112 age-matched healthy individuals. The long-term survivors scored higher than the early-stage survivors, in all categories, including physical QOL. However, their QOL scores remained lower than those of the healthy controls [9]. Breast cancer survivors may have better physical QOL the longer they survive. On the other hand, many breast cancer survivors suffer from physical anguish and

often experience adverse events such as fatigue (60%), restriction of shoulder movement (59.6%), and body and joint pain (63.5%) [9]. Breast cancer survivors are also reported to require treatment for physical ability (39%), joint pain (37%), weight problems (32%), and fatigue (31%) by Schmidt ME et al. [7]. In addition, in 2013, breast cancer survivors were studied at approximately 2 and 8 months post-diagnosis to determine the relationship between hours worked per week and changes in both employment and QOL by Timperi AW et al. [10] There was a significant association between hours worked per week and physical well-being at 8 months after diagnosis. Women who worked 20 or more hours per week had higher physical well-being than women who did not work. Continuing to work after a diagnosis of breast cancer may be beneficial for physical QOL [10]. In summary, while breast cancer survivors had a better physical QOL the longer they survived, they also ask about support for the physical aspects of the disease. It was suggested that continuing to work may be beneficial for physical QOL.

In gastrointestinal cancer survivors, the health-related quality of life (HRQOL) and esophageal cancer-specific QOL of 147 esophageal cancer survivors at an average of 39 months after esophagectomy were compared to those of healthy controls by Gutschow CA et al. [11] The results showed that overall health and QOL including physical function were significantly lower than values for healthy subjects [11]. However, the percentage of cancer survivors after esophagectomy whose overall health was comparable to that of healthy individuals was 53.4%, indicating that more than half of esophageal cancer survivors can achieve a QOL comparable to that of healthy individuals [11]. About half of gastrointestinal cancer survivors are able to maintain a high QOL.

There is also a growing body of research on the QOL of gynecologic cancer survivors. In a report of ovarian cancer survivors, 56 survivors, with an average survival of 14.0 years after start of treatment, were compared to those with 0–1 recurrences as well as those with multiple recurrences with respect to QOL by Lutgendorf SK et al. [12] The mean Functional Assessment of Cancer Therapy-General (FACT-G) scores of the ovarian cancer survivors were worse than those of the healthy subjects. In addition, those with multiple relapses reported worse QOL regarding physical and emotional health compared to those with 0–1 relapses [12]. In endometrial cancer survivors, Dobrzycka B et al. [13] investigated the QOL (EORTC QLQ-C30) of 328 endometrial cancer survivors who completed cancer treatment more than 3 years ago was compared with that of 284 healthy controls. They reported that the EORTC QLQ-C30 physical function items were comparable, with no differences between the groups [13]. Gynecologic cancer survivors may have a lower QOL in terms of physical function than healthy individuals, but this may improve over time.

In a report by Stolley MR et al. [14] on prostate cancer survivors, the QOL of 22 survivors who survived an average of 5.6 years after treatment was compared to the norm of the general healthy population. The prostate cancer survivors reported worse QOL regarding physical function compared to the general population [14]. Prostate cancer survivors may have a reduced QOL in terms of physical function.

In a report by Boşnak Güçlü M et al. [15] on hematopoietic malignancy survivors who underwent hematopoietic stem cell transplantation, QOL was compared in 80 patients more than 100 days after allogeneic hematopoietic stem cell transplantation (HSCT) and 60 age- and sex-matched healthy subjects. Functional and social function items on the EORTC QLQ-C30 have been reported to be significantly lower in survivors of allogeneic hematopoietic stem cell transplantation compared to healthy controls [15]. Alaloul F et al. [16] compared QOL (EORTC QLQ-C30) in 63 hematopoietic malignancy survivors and 63 age- and sex-matched healthy subjects more than 3 months after HSCT. Physical function items were significantly lower in post-HSCT survivors compared to healthy controls [16]. Hematopoietic malignancy survivors after hematopoietic stem cell transplantation may have reduced QOL related to physical function.

As described above, QOL related to physical function is likely to be lower than that of healthy subjects, although the extent of QOL decline varies by carcinoma. However, physical QOL can be expected to recover over time. Because physical function is associated with physical QOL, physical therapy may play a significant role.

1.3 Physical Function of Cancer Survivors

1.3.1 Body Weight

Weight trends in cancer survivors have also been reported. Jung SY et al. [17] reported female cancer survivors had a higher body mass index (BMI) than healthy individuals. Smith SA et al. [18] reported most of the breast cancer survivors (63%) had a BMI of ≥25 kg/m^2 or higher, which was significantly higher than that of women without a history of cancer. In addition, cancer survivors who received chemotherapy reported a greater likelihood of gaining weight compared to women without cancer [19]. Among stage I–III colorectal cancer survivors ($n = 459$), it was reported that 44% were overweight, and 31% were obese at diagnosis by Kenkhuis MF et al. [20] All anthropometric measurements showed a similar trend, decreasing from the time of diagnosis to 6 weeks after diagnosis and increasing for up to 24 months post-treatment. Increased adipose tissue and muscle function were associated with improved HRQOL and reduced fatigue in the long term [20]. Thus, cancer survivors may be more likely to be overweight. It may also be important to manage weight and body composition through physical therapy, as body composition may also be related to HRQOL and fatigue. Cancer type and gender may need to be considered when doing so.

1.3.2 Sarcopenia

Sarcopenia, which represents muscle atrophy, has also been investigated in cancer survivors. Marriott CJC et al. [21] found that, among 75 acute lymphoblastic leukemia (ALL) long-term survivors (10 or more years after diagnosis), sarcopenic

obesity was found in 32 (43%). They reported that there was a difference in overall HRQOL with and without sarcopenic obesity [21]. Villaseñor A et al. [22] reported 75 (15.9%) of 471 breast cancer survivors (median follow-up 9.2 years) were classified as sarcopenic. In a survey of 98 cancer survivors, the prevalence of sarcopenia was 23.1%, and that of metabolic syndrome was 30.0% by Lee SJ et al. [23] Those with sarcopenia tended to have higher waist circumference, BMI, triglyceride levels, and blood pressure, as well as lower high-density lipoprotein cholesterol levels than those without sarcopenia [23]. In another report, 259 adult cancer survivors without chronic disease and 1295 healthy individuals were screened for sarcopenia. Kim H et al. [24] reported the prevalence of sarcopenia was higher among nonobese male cancer survivors compared to healthy subjects (32.6% vs. 16.0%, $P = 0.034$). Conversely, obese female cancer survivors had more sarcopenia than healthy individuals (35.1% vs. 15.0%, $P = 0.005$) [24]. As described above, sarcopenia in cancer survivors is found in various carcinomas, although in different proportions. In addition, cancer survivors are at higher risk of sarcopenia than healthy individuals, and the type of sarcopenia appears to vary by gender.

1.3.3 Exercise Capacity

Exercise tolerance is also frequently assessed in cancer survivors, primarily through cardiopulmonary exercise testing and the 6-minute walk test (6MWT), a field test. Sanver MF[25] evaluated respiratory muscle strength and cardiopulmonary exercise test maximal oxygen consumption (VO_2peak), as well as fatigue in 20 colorectal cancer survivors, and compared them to 20 healthy subjects. VO_2peak (ml/min and %predicted) and VO_2peak/kg (%predicted) measured in the cardiopulmonary exercise test were significantly lower in colorectal cancer survivors [25]. Reding KW[26] compared the exercise tolerance of 14 cancer survivors at least 12 months after cancer treatment and 14 age-, gender-, and BMI-matched non-cancer survivors. The VO_2peak of the cardiopulmonary exercise test was 22% lower in the cancer survivors compared with the healthy controls (26.9 vs. 3.3 mL/kg/min, $p = 0.005$) [26]. The cancer survivors may have decreased oxygen intake compared to the healthy controls.

The 6MWT is also widely used as an indirect measure of exercise tolerance in various cancer patient populations. In a report by Ortiz A et al. [27], 89 breast cancer survivors, at least 3 months post-treatment, underwent fitness testing (6MWT, 30-s stand, grip strength, lower, upper extremity and hip strength, shoulder joint range of motion, and balance testing), physical activity (PA) assessment, and disability assessment. PA was assessed using the International Physical Activity Questionnaire (IPAQ). Breast cancer survivors exhibited low PA (76.5 ± 183.4 MET-min/week) and poor fitness (6MWT 436.4 ± 99.1 m, 30-s sit-stand 11.6 ± 3.1 stands) [27]. In another study, 62 lung cancer survivors reported an average 6-minute walk distance (6MWD) of 335 m and decreased EORTC-QLQ-C30 [28], and 6MWD was significantly associated with cancer-specific QOL [28]. 6MWT may also be associated with the degree of sensory impairment in cancer survivors. In

report by McCrary JM et al. [29], 100 cancer survivors (mean 17 ± 13 months post-treatment, mean age 59 ± 13 years) undergoing neurotoxic chemotherapy were asked about chemotherapy-induced peripheral neuropathy (CIPN) in addition to 6MWT. CIPN symptoms were reported by the majority of cancer survivors (87%) and were associated with decreased distance for the 6MWT [29]. As mentioned above, cancer survivors may have decreased exercise tolerance. Exercise tolerance is also associated with adverse events such as CIPN and may require consideration of how to involve physical therapy.

1.3.4 Hand Grip Strength

Grip strength measurement is a commonly used strength test in cancer survivors and can reflect whole-body muscle strength. In our previous study, grip strength was measured in 19 cancer survivors (mean time since disease onset 2116 ± 1566 days) and 14 healthy subjects. No significant difference in grip strength occurred in the cancer survivors compared to the healthy subjects [30]. Another study by Kim et al. [31] measured grip strength in 392 cancer survivors and 1176 healthy subjects. They reported no significant differences between the cancer survivors and the healthy subjects [31]. In our another study, when grip strength was compared between 15 breast cancer survivors and 13 age- and gender-matched healthy subjects, the breast cancer survivors' grip strength was significantly lower. However, they reported no significant differences in grip strength when comparing 11 survivors of other cancer types, excluding breast cancer, to 19 healthy subjects [32].

There are also scattered reports of an association between grip strength and QOL. One report found a significant association between QOL and grip strength among cancer survivors ($n = 392$). However, in the healthy controls ($n = 1176$), no significant relationship between low grip strength and QOL was observed [31]. Similarly, in our study, grip strength was correlated with physical function and physical pain items of QOL in cancer survivors [6]. In a report by Paek J et al. [33], 1037 cancer survivors with weak grip strength had increased dysfunction in the EuroQoL-5 dimension (EQ-5D) compared to those with normal grip strength. The association between grip strength and cognitive function was evaluated in cancer survivors aged 60 years and older. In 383 cancer survivors, women showed higher and better cognitive function scores for every 1 kg increase in grip strength by Yang L et al. [34] As described above, grip strength in cancer survivors may not differ from that of healthy subjects, but may be related to QOL and cognitive function. Physical therapists should actively assess grip strength in cancer survivors.

1.3.5 Knee Extension Strength

There are some studies measuring lower extremity muscle strength in cancer survivors. In our study, we evaluated knee extension muscle strength in 36 cancer survivors with an average disease duration of 2335 days, and 29 healthy subjects, and

reported no difference in muscle strength [6]. Another report compared knee extension muscle strength in 26 cancer survivors and 19 healthy subjects and found no significant differences [32]. On the other hand, our another study compared knee extensor strength in 19 cancer survivors (averaging 2116 days since diagnosis) and 14 healthy subjects and reported no significant differences in right knee extensor strength, but left knee extensor strength was significantly lower in the cancer survivors [30]. In report by Ihira H et al. [35], 37 older community-dwelling cancer women survivors aged 75 years or older had lower knee extension strength compared to older women without a history of cancer. In males, it was reported that there were no significant differences between those with and those without a history of cancer [35]. From the above, it is possible that the lower limb muscle strength of cancer survivors does not differ from that of healthy subjects, or that it is reduced. Furthermore, there may be gender differences. This may need to be considered when engaging in physical therapy.

1.3.6 Fall and Balance Function

Cancer survivors have reduced balance function and may be at higher risk for falls. Sulicka J et al. [36] compared the fall histories of cancer survivors and healthy non-cancer subjects with an average age of 79.4 years and average survival of 8.5 years from cancer diagnosis. Compared to non-cancer controls, cancer survivors were more likely to report a higher rate of falls (odds ratio (OR) = 1.38) and poorer health (OR = 1.49) [36]. In a study of the prevalence of falls among 421 cancer survivors by Gewandter JS et al. [37], 11.9% of cancer survivors had experienced a fall. Furthermore, they reported that these patients have motor neuropathy that is associated with falls [37]. Thus, cancer survivors may have more falls than those without cancer, which may be related to physical function. The timed up and go (TUG) test is a method of assessing performance, including balance function, and is used to assess cancer survivors. In our previous study, we performed TUG on 19 cancer survivors (average illness duration was 2116 days) and 14 healthy subjects and found that cancer survivors were significantly worse off [30]. In another study, 41 cancer survivors more than 1 year after diagnosis had significantly worse TUG compared with 33 healthy subjects [38]. Evans ES et al. [39] evaluated TUG in 20 breast cancer survivors and 23 women with no history of cancer; the survivors performed significantly worse than the controls [39]. Therefore, cancer survivors may have worse TUG performance than healthy individuals. The TUG test also assesses the agility and mobility of cancer survivors and may be a predictor of falls.

The short physical performance battery (SPPB) is also used worldwide as a physical assessment of the elderly. SPPB appears to be used in cancer survivors as well. Eighty-four breast cancer survivors aged 60 years or older (mean 7 years post-treatment) reported significantly lower SPPB scores compared to 40 non-cancer controls of the same age group (10.7 ± 0.1 vs. 11.7 ± 0.5, $p < 0.001$) by Winters-Stone KM et al. [40] In study by Blackwood J et al. [41], the reliability and validity of functional measures in older long-term cancer survivors were examined.

Forty-seven cancer survivors (mean age 73.70 ± 6.38 years, mean duration since cancer diagnosis 11.89 ± 8.81 years) were evaluated for SPPB twice, every 2 weeks. Test-retest reliability was good (ICC2, 1 = 0.85) and validity was reported in the SPPB [41]. Therefore, in older cancer survivors, SPPB may also be useful as an item to assess physical performance.

1.3.7 Sensory Disturbance Peripheral Neuropathy

Numbness of peripheral nerve origin is a common problem in cancer survivors. A better understanding of CIPNs may lead to improvements in how they are managed. Conventional chemotherapy is a well-known cause of peripheral neurotoxicity, often resulting in sensory deficits [42]. One of the most frequently reported symptoms among survivors of breast, gynecologic, colorectal, lung, and head and neck cancers was reportedly numbness in the hands and feet [43]. Mustafa Ali M et al. [44] examined the prevalence of peripheral neuropathy in 605 breast cancer survivors. All survivors underwent surgery and 62% received chemotherapy. Of these, 27% reported peripheral neuropathy [44]. In another study by Bao T et al. [45], of 296 postmenopausal survivors with a history of stage I–III breast cancer who had received taxane-based chemotherapy, 58.4% reported CIPN symptoms. Of these, 30.7% reported mild symptoms and 27.7% reported moderate to severe symptoms. Compared to subjects without, survivors with CIPN reported significantly higher insomnia severity, anxiety, and depression. CIPN severity was associated with higher fall rates, with 23.8, 31.9, and 41.5% of the "none," "mild," and "moderate-to-severe" groups experiencing falls, respectively (p = 0.028) [45]. Zanville NR et al. [46] examined the impact of CIPN on breast cancer survivors' perceptions of their ability to work after treatment. More than 50% of the 22 breast cancer survivors who received chemotherapy reported symptoms of discomfort, numbness, and weakness at 1 year after chemotherapy. The presence, number, and severity of these symptoms correlated with lower likelihood of being able to work in chemotherapy-treated patients at 1 month postchemotherapy [46]. In another study by Ezendam NP et al. [47], of 191 ovarian cancer survivors, the frequency of complaints of numbness in the hands, feet, and fingers was about 27% in survivors who had not received chemotherapy, but as high as 51% in the 129 who had [47]. As described above, cancer survivors who have undergone chemotherapy may complain of CIPN, which appears to have multifaceted effects, including falls and decreased employment and QOL. Physical therapists should keep in mind that cancer survivors are prone to numbness.

1.4 Physical Therapy

Physical therapy is generally safe for cancer survivors. Campbell KL et al. [48] stated that there is sufficient evidence to conclude that specific amounts of aerobic exercise, resistance training, and combinations of the two improve overall

cancer-related health outcomes, including anxiety, depressive symptoms, fatigue, physical function, and HRQOL. In this section, we describe the effects of resistance training and aerobic exercise alone, as well as their combined use, on cancer survivors. This article only introduces some of the reports on the effectiveness of exercise for cancer survivors.

1.4.1 Resistance Training

In study by Winters-Stone KM et al. [49], 106 breast cancer survivors (at least 1 year post chemotherapy or radiation therapy) aged 60 years or older were randomly assigned to a group that underwent a moderate-intensity resistance training program of three times a week for 1 year or a control group that underwent a low-intensity stretching program of similar frequency and duration. The resistance training group maintained bone density in the lumbar spine compared to the control group ($P = 0.001$). The exercise group also had a larger increase in lean body mass compared to the control group ($P = 0.01$) [49]. Madzima TA et al. [50] compared muscle strength, body composition, and muscle mass in breast cancer survivors (mean age 59 ± 8 years) between a 12-week resistance training-only group and a 12-week resistance-training-and-protein-supplementation group. Resistance training consisted of 2 sets of 10–12 repetitions of 10 different types of resistance exercises, 2 days per week. The protein supplementation group received 20 g of protein twice daily in addition to the same exercises. Both groups showed significant increases in upper and lower body muscle strength, lean body mass, fat mass, and body fat percentage [50]. In a study by Santagnello SB et al. [51], 20 breast cancer survivors were randomly divided into a resistance training group ($n = 11$) and a control group ($n = 9$) to investigate muscle strength, muscle power, lean body mass, and fatigue. The resistance training protocol consisted of three sets of each exercise (leg extensions, leg curls, 45° leg press, and calf raises), with 8–12 repetitions per set, and a standard load of 80% of the patient's one-repetition maximum (RM). The resistance training group performed these three times per week for 12 weeks. The control group performed stretching exercises only twice a week for the same period of time. After 12 weeks, the resistance training group had reduced fatigue and improved muscle power, maximal muscle strength, lean body mass, and performance on all tests (walking speed, sit-to-stand, TUG) compared to the control group [51]. Resistance training for the cancer survivors significantly improves muscle strength and muscle mass.

Serra MC et al. [52] examined fatigue (Piper fatigue scale; PFS), physical function, QOL (SF-36), glucose, lipid metabolism, skeletal muscle, and adipose tissue inflammation in 11 breast cancer survivors (average age 60) before and 16 weeks after moderate-intensity whole-body resistance training. After 16 weeks, muscle strength had improved from 25 to 30% ($P < 0.01$), QOL had increased by 10% ($P = 0.04$), chair stand time decreased by 15% ($P = 0.01$), 6MWD increased by 4% ($P = 0.03$), fatigue decreased by 58% ($P < 0.01$), fasting insulin decreased by 18%

($P = 0.04$), and diastolic and systolic blood pressure decreased by approximately 5% ($P = 0.04$) [52]. In addition, resistance training reduced inflammation-induced cytokines and tumor necrosis factor-α ($P < 0.05$). This study also reported that changes in muscle inflammation-induced cytokines were directly correlated with improvements in leg press strength ($r = 0.53$, $P = 0.04$) [52]. Thus, resistance training has been suggested to improve bone density, lean body mass, muscle strength, and QOL in cancer survivors and to reduce fatigue and anxiety. Furthermore, it may reduce inflammatory cytokines as a secondary effect.

Adherence to, and sustained effectiveness of, resistance training for cancer survivors have also been reported. In a randomized controlled trial of 106 breast cancer survivors aged 60 years or older, the subjects were randomly assigned to a 1-year resistance training group (exercise group) or a placebo program stretching group (control group) by Winters-Stone KM et al. [53] The exercise group showed significant gains in maximal leg press strength ($p < 0.04$) and bench press strength ($p < 0.01$) compared to the control group. Subjects who participated in more than 50% of the prescribed resistance training sessions had significantly better changes in maximal muscle strength measurements compared to those who were less adherent [53]. In a previous study, Dobek J et al. [54] reported that one year of supervised resistance training combined with impact training prevented bone loss and increased muscle strength in older breast cancer survivors. Whether these effects persisted for 1 year after the end of the intervention was examined. In 44 breast cancer survivors (mean age > 60 years, mean 6 years post-diagnosis) for whom follow-up evaluation was performed at 1 year, there was a significant group interaction for bone mineral density (BMD) of the spine and lower body muscle strength ($p < 0.01$), with a similar trend for upper body muscle strength ($p = 0.05$). Spine BMD decreased continuously over 2 years in the control group, whereas it remained stable in the exercise group throughout the intervention and follow-up periods. Lower body muscle strength, on the other hand, increased during the intervention period in the exercise group but decreased to near baseline levels during the follow-up period. In contrast, the control group showed no change during either period [54]. A study by Santos WDND et al. [55] randomly assigned 25 breast cancer survivors to a resistance training group ($n = 12$) and a control group ($n = 13$). In the resistance training group, one trainer per subject performed supervised resistance training once a week for 8 weeks. The resistance training group improved strength in the 10RM leg press and bench press. Participation in training in the resistance training group was more than 99% [55]. Adherence to resistance training is important for cancer survivors, and continued adherence may help maintain physical function. Continued exercise is more effective and may help cancer survivors maintain muscle strength and other benefits. We believe that resistance training is an effective approach to a variety of issues that cancer survivors face, including muscle mass and strength, physical performance, QOL, fatigue, and anxiety. Therefore, we believe that it is the role of physical therapists to actively introduce and encourage the continuation of this program.

1.4.2 Aerobic Exercise

Murtezani A et al. [56] conducted a study that randomly assigned 62 breast cancer survivors, average age of 52 years, to an exercise group (n = 30) or a control group (n = 32) to investigate the effects of moderate-intensity aerobic exercise on breast cancer survivors' QOL and the 12-minute walk test (12MWT). The exercise group trained at moderate intensity for 10 weeks. No training was performed in the control group. Significant improvements were evidenced in the exercise group compared to the control group on the FACT-B, FACT-G, functional well-being subscale, and emotional well-being subscale. The exercise group showed a significant increase in 12MWT [56]. In another study by Brdareski Z et al. [57], 18 female breast cancer survivors younger than 65 years were randomly assigned to an E1 group (n = 10), in which exercise load was determined based on measured VO_2max, or an E2 group (n = 8), in which exercise load was self-determined based on subjective fatigue, and the effect of 3 weeks of moderate-intensity aerobic exercise training on VO_2max of survivors was examined. Warm-up and cool-down sessions of 3 min each and a full training session of 15 min, for a total of 21 min, were performed twice a week. The E1 group had a load of 45–65% of the individual's VO_2max, while the E2 group had a load based on subjective exercise intensity at a level described as Borg scale 4–6. A statistically significant improvement in VO_2max was observed in both groups [57]. Thus, moderate-intensity aerobic exercise training may improve aerobic capacity and QOL in cancer survivors. The VO_2max 45–65% loading dose from the exercise stress test and the Borg scale 4–6 may be comparable. In addition, benefits may be seen even after a short exercise period.

There are also scattered reports examining the effects of different exercise intensities. In one study by Burnham TR et al. [58], 18 breast or colorectal cancer survivors (15 women, 3 men, ages 40–65) who were at least 2 months post-cancer treatment were randomly assigned to a control group (n = 6), a low-intensity (25–35% of heart rate reserve) group (n = 6), or a moderate-intensity (40–50% of heart rate reserve) group (n = 6) to examine the effects of aerobic exercise on the physiological and psychological function of cancer survivors. The exercise group showed statistically significant increases in aerobic capacity, lower body flexibility, QOL, and energy indices and a significant decrease in body fat compared to the control group [58]. In another study by Drum SN et al. [59], 14 cancer survivors, with an average of 4 months after completing cancer treatment, and 23 age-, height-, weight-, and BMI-matched healthy controls were given an 8-week low- to moderate-intensity aerobic exercise training program, and their physiological responses were compared. The cancer survivors had significantly lower VO_2peak, fatigue time, and maximal heart rate than the controls after baseline, as well as after 3 and 6 weeks of training, but not after 8 weeks. Cancer survivors significantly improved their exercise tolerance after 8 weeks of aerobic exercise training [59]. Thus, there may be little difference in the effects of low- and moderate-intensity aerobic exercise on cancer survivors' physiological and psychological function, and there may be benefits of exercise at lower intensities. In addition, long-term sustained aerobic

exercise may result in aerobic capacity and subjective fatigue comparable to that of healthy subjects.

Vardar Yağlı N et al. [60] randomly assigned 52 breast cancer survivors aged 20–60 years (at least 3 years post-treatment) to an aerobic exercise group ($n = 28$) or an aerobic exercise plus yoga group ($n = 24$) to determine the effects on exercise tolerance, peripheral muscle strength, QOL, and fatigue in breast cancer survivors. Both groups performed submaximal exercise for 30 min/day, 3 days/week for 6 weeks. Statistically significant increases in muscle strength, 6MWT distance, and QOL were observed in both groups. Furthermore, fatigue was significantly improved in the aerobic exercise plus yoga group compared to the aerobic exercise group [60]. Therefore, incorporating body-mind techniques such as yoga in addition to aerobic exercise may be useful in restoring physical function and improving psychosocial health.

Recent studies have shown efforts to maintain cardiopulmonary function at home using the latest methods, including the use of smartphones. Fifty women with breast cancer aged 20–59 years who had completed initial treatment other than hormonal therapy were randomly assigned to an exercise group ($n = 25$) or a control group ($n = 25$) to test whether 12 weeks of high-intensity interval training (HIIT) with body weight exercise would improve cardiorespiratory function in survivors of early-stage breast cancer by Ochi E et al. [61] VO_2peak and lower extremity muscle strength were significantly increased in the exercise group compared to the control group [61]. Thus, the use of modern technology has the potential to improve cardiopulmonary function and muscle strength at home and is expected to continue to develop in the future. As described above, aerobic exercise may be effective in improving cancer survivors' aerobic capacity, subjective fatigue, and QOL.

1.4.3 Combined Resistance Training and Aerobic Exercise

In addition to reports of resistance training or aerobic exercise alone, there are scattered reports of exercise programs that combine resistance training and aerobic exercise in regard to physical therapy for cancer survivors. In a study by Jones LM et al. [62], 51 breast cancer survivors aged 40–70 were randomly assigned to a 12-week exercise group ($n = 26$) or a control group ($n = 25$) that did not exercise. The exercise group performed 60 min of supervised resistance training, aerobic exercise, and functional exercise twice a week. After 12 weeks, a statistically significant effect was seen in aortic pulse wave velocity, a standard endpoint of arterial stiffness. VO_2 max and both upper and lower body muscle strength all showed significant improvement [62]. de Paulo TRS et al. [63] randomly assigned 36 elderly breast cancer survivors to an exercise group ($n = 18$) or a placebo control group ($n = 18$), in order to investigate the effects of a combination of aerobic exercise plus resistance training on body composition and metabolic markers. The exercise group performed 40 min of resistance training on a machine and 30 min of aerobic exercise on a treadmill three times a week. Evaluations were performed at baseline, 12, 24, and 36 weeks. Significant differences between group and time interactions were

found for total fat mass, trunk fat mass, and body fat percentage, with a slight increase in the control group, while fat mass decreased in the exercise group [63].

In a similar study by Thomas GA et al. [64], 121 breast cancer survivors (mean age 62.0 ± 7.0 years, 2.7 ± 3.1 years after cancer diagnosis) were randomly assigned to an exercise group (n = 61) or usual care group (n = 60) to examine the effects of 12 months of aerobic exercise and resistance training on body composition. The exercise group performed supervised resistance exercise training twice a week and aerobic exercise for 150 min/week for 12 months. After 12 months, the exercise group had significantly more lean body mass, lower body fat percentage, and lower body mass index, compared to the usual care group [64]. In a study by Marker RJ et al. [65], 170 cancer survivors with an average age of 57 ± 12 years participated in an exercise program combining resistance, aerobic, and flexibility exercises for 3 months, and after completion of the exercise program, cardiorespiratory function (VO_2peak), muscle strength (grip strength), fatigue (PFS), and depression (Beck Depression Inventory; BDI) were measured. All measures were significantly improved in participants who completed the exercise program [65]. In another study by Herrero F et al. [66], 16 breast cancer survivors aged 40–60 years (2–5 years after cancer treatment) were randomly assigned to exercise (n = 8) and non-exercise (n = 8) groups to participate in a short-term training program combining aerobic exercise and resistance training to improve cardiorespiratory function (VO_2peak) and muscle endurance. The effects on strength (maximum number of repetitions of chest and leg presses), a sit-stand test, body composition, and QOL (EORTC QLQ-C30) were evaluated. The exercise group underwent an 8-week exercise program consisting of 90-min sessions three times a week, under supervision. QOL, VO2peak, performance on the leg press, and a sit-stand test improved significantly after the exercise program, while no significant changes were observed in the control group [66]. As described above, an exercise program that combines resistance training with aerobic exercise may be effective for cardiorespiratory fitness, muscle strength, body composition, PA, fatigue, depression, and QOL. It is also possible that even a short period of time, such as 8 weeks, could reveal the benefits of exercise.

There are also studies on the durability of exercise effects. In a study by Møller T et al. [67], 153 breast cancer survivors who were physically inactive prior to diagnosis were randomly assigned to a supervised intervention group that included moderate- to high-intensity resistance training plus aerobic exercise or to an intervention group with a personal pedometer at home. Cardiopulmonary function in both groups declined significantly from baseline to week 12 during chemotherapy and recovered from week 12 to week 39. There were no significant differences between the groups. With regard to muscle strength, knee extension, lateral pull, and leg press showed an increasing trend in the supervised intervention group, with significant group differences at 12 weeks and persisting at 39 weeks [67]. Thus, a supervised exercise program that combines resistance training and aerobic exercise may maintain physical and other functions after the intervention period.

In a study by Kampshoff CS et al. [68], 227 cancer survivors (4–6 weeks after primary cancer treatment) were randomly assigned to a high-intensity group

($n = 91$), a low- to moderate-intensity group ($n = 95$), and a control group ($n = 91$), and then they exercised at different intensities to test cardiorespiratory function (VO_2peak), muscle strength (grip strength, 30-s chair stand up test), and fatigue. The exercise program was a combination of resistance training and aerobic exercise twice a week for 12 weeks. The high-intensity and low- to moderate-intensity groups showed significantly greater improvements in VO_2peak than the control group. No effect of exercise was observed on grip strength or the 30-s chair rise test. The high-intensity and low- to moderate-intensity groups significantly improved overall and physical fatigue, as well as reduced activity compared to the control group. The high-intensity and low- to moderate-intensity groups of cancer survivors were equally effective in reducing general and physical fatigue [68]. In a similar study by Kalter J et al. [69], 277 cancer survivors were assigned to an exercise group ($n = 186$) or a control group ($n = 91$) to perform high-intensity and low- to moderate-intensity resistance training and aerobic exercise to improve cardiorespiratory function (VO_2peak) and muscle strength (grip strength, 30-s chair stand test). They tested whether this would reduce fatigue (the multidimensional fatigue inventory; MFI) and improve QOL (EORTC QLQ-C30). The exercise group performed resistance training and aerobic exercise twice a week for 12 weeks. Compared to the control group, the exercise group improved cardiopulmonary function and reduced systemic and physical fatigue. Grip strength was significantly associated with lower physical fatigue, and lower body muscle function was significantly associated with lower physical and general fatigue [69].

Thus, the results suggest that exercise at any intensity can be safely implemented in exercise programs that combine resistance training and aerobic exercise and that it is beneficial to physical function, fatigue, and QOL. With respect to cardiorespiratory function, higher exercise intensities may be more effective. In addition, continued use may be effective even at lower intensities and for shorter periods of time. Since the effects of exercise are expected to be sustained, it may be necessary to actively introduce this system.

1.5 Relationship Between Physical Function and Mortality

Cancer survivors have been studied with respect to physical function and mortality and have reported that higher physical function may be associated with lower mortality. In our systematic review [70], grip strength was significantly associated with risk of death in cancer survivors (hazard ratio (HR) = 1.15, $P = 0.005$). Walking speed was also associated with risk of death (HR = 1.58, $P = 0.0004$). For grip strength and walking speed, the group of cancer survivors aged over 80 years had a higher risk ratio than the subgroup aged under 80 years. SPPB was significantly associated with mortality risk, with the greatest risk (HR = 2.37, $P < 0.00001$). The long distance in 6MWT was significantly associated with risk of death (HR = 1.55, $P = 0.001$). TUG was shown to be significantly associated with risk of death (HR = 2.66, $P < 0.00001$) [70]. Our other systematic review aimed at determining the effect of exercise on mortality and recurrence in cancer survivors reported that

exercise therapy significantly reduced the risk of death among cancer survivors (risk ratio (RR) = 0.76, $P = 0.009$) [71]. We also reported that exercise therapy significantly reduced the risk of recurrence in cancer survivors (RR = 0.52, $P = 0.030$) [71]. Hardee JP et al. [72] examined the independent association of PA and resistance training on all-cause mortality among cancer survivors. A total of 2863 male and female cancer survivors between the ages of 18 and 81 were included in the study. Resistance training was associated with a 33% reduction in risk of all-cause mortality [72]. As discussed above, physical function affects mortality in cancer survivors, and exercise therapy may improve recurrence and mortality rates.

1.6 Conclusions

Many cancer survivors appear to have reduced QOL after treatment. Physical QOL is often the same or lower than that of healthy subjects, although it varies by cancer type. In addition, cancer survivors often have poorer physical function compared to healthy individuals, which is associated with QOL, mortality, falls, and employment (Fig. 1.1). Furthermore, in light of the increase in the number of cancer survivors due to advances in early detection and treatment, and the aging of the population due to extended survival rates, we believe that physical therapy has a significant role to play (Fig. 1.2). Currently, resistance training, aerobic exercise, and combinations of the two are being implemented for survivors with each carcinoma, with good results (Table 1.2).

Further research is needed to investigate the physical function and QOL of cancer survivors, as well as the effects of physical therapy. For example, the number of reports varies by cancer type, with few reports for lung, esophageal, hepatocellular,

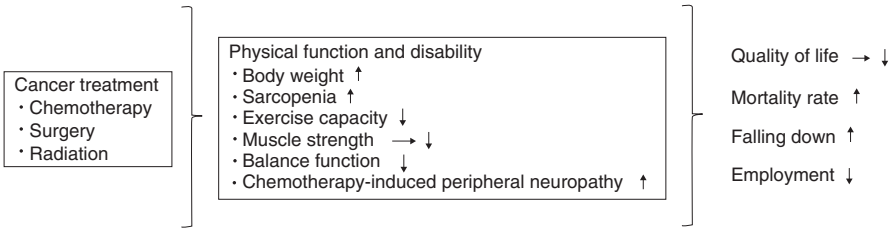

Fig. 1.1 Changes in physical function and disability in cancer survivors and their impact

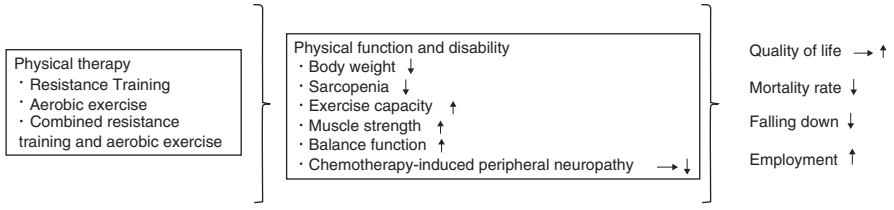

Fig. 1.2 Effects of physical therapy on cancer survivors

Table 1.2 Recommended physical therapy for cancer survivors

Type of exercise	Specifics of the exercise
Resistance training	Weight training using with dumbbells, weighted vests, and barbells
	Use of exercise machines for chest press, leg press, leg extensions, biceps curls, etc.
Aerobic exercise	Use of treadmills
	Use of stationary bicycles
	Use of stair climbers
Combination exercise	Combined resistance training and aerobic exercise

Table 1.3 Future recommended physical therapy research for cancer survivors

Research on physical function, QOL, and exercise effects in cancer survivors with lung, esophageal, hepatocellular, pancreatic, and other cancers
Research on the effect of exercise therapy on cancer recurrence and survival rates
Research on the effectiveness of physical therapy for elderly cancer survivors

and pancreatic cancers, which each have poor prognosis. Similarly, there are few reports of studies of late-stage cancer survivors. Many of the reports presented here were of survivors with relatively good life expectancy and cancer progression. Given its effectiveness for survivors with a relatively good prognosis for life and cancer progression, physiotherapy may also be expected to have a positive effect on the physical function and QOL of cancer survivors with a poor prognosis, as well as advanced cancer survivors. In addition, an increasing number of reports have investigated the effects of exercise therapy on cancer recurrence rates and survival rates, and further research is warranted (Table 1.3).

In addition to the actual status of physical function and QOL, it is currently not clear what disciplines and frequency are optimal with regard to exercise therapy. In the future, a large-scale, multicenter, collaborative survey and study may be needed.

It may also be necessary to consider how to approach providing physical therapy to older cancer survivors. Young to middle-aged cancer survivors may be able to get the latest information on exercise. Additionally, it may be possible to use modern devices, such as smartphone applications, to perform the exercises. However, regarding elderly cancer survivors, it is difficult for them to operate such devices. Therefore, it may be necessary to educate cancer survivors on the benefits of exercise, teach them how to exercise according to their cognitive functions, and provide exercise opportunities to encourage them to continue. We believe that future physical therapy and research for cancer survivors should be conducted based on the above.

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Physical Function and Health-Related Quality of Life After Breast Cancer Surgery

2

Yoshiteru Akezaki, Eiji Nakata, and Masato Kikuuchi

Abstract

We describe the methods of patient evaluation and rehabilitation after surgery for breast cancer, along with our research findings. Patient quality of life (QOL), depression or anxiety, functional ability of the upper limbs, muscle strength, axillary web syndrome (AWS), and pain need to be evaluated after breast cancer surgery. Both preoperative and postoperative rehabilitation is required for the most effective rehabilitation of breast cancer patients postoperatively. Our research has clarified the factors that affect the postoperative QOL in breast cancer patients: psychological problems, range of motion, AWS, lymphedema, return to work, and participation in leisure activities.

Keywords

Breast cancer · Rehabilitation · Assessment · Physical function · Quality of life

2.1 Introduction

Medical and technological advances have led to earlier detection and better treatment options for breast cancer, resulting in higher survival rates for women. However, surgery and other treatments for breast cancer may lead to upper

Y. Akezaki (✉)
Division of Physical Therapy, Kochi Professional University of Rehabilitation, Tosa, Japan
e-mail: akezaki@kochireha.ac.jp

E. Nakata
Department of Orthopaedic Surgery, Okayama University Hospital, Okayama, Japan

M. Kikuuchi
Department of Rehabilitation Medicine, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan

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extremity impairments, functional limitations, and disabilities such as pain, stiffness, lymphedema, axillary web syndrome (AWS), decreased muscle strength and range of motion (ROM), reduced tolerance to physical activity, decreased quality of life (QOL), and depressive symptoms [1–8].

Rehabilitation for breast cancer patients includes preoperative rehabilitation, early rehabilitation, resistance exercise, home-based multidimensional survivorship programs, water-based exercise, complex decongestive physical therapy, psychoeducational group interventions, and tai chi chuan. The positive effects of rehabilitation have been widely reported [9–16]. In this review, we describe the methods for patient evaluation and rehabilitation after surgery for breast cancer, along with our research findings.

2.2 Assessment

2.2.1 Quality of Life Assessments

There are a variety of tools for assessing QOL (Table 2.1). A brief description of the key QOL assessment tools is provided below.

Table 2.1 Target population and domains of QOL assessment tools

Assessment tool	Target population	Domains
SF-36	General	Physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health
WHOQOL-BREF	General	Assesses four domains of QOL (physical health, psychological health, social relationships, and environment). Two items measure overall QOL and general health
EORTC QLQ-C30	Cancer	Incorporates the Global Health Status/QOL scale, functional dimensions (physical, role, emotional, cognitive, and social), symptom items (fatigue, nausea or vomiting, and pain). Single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impacts)
FACT-G	Cancer	Physical well-being, emotional well-being, social/family well-being, functional well-being, and relationship with a doctor
EORTC QLQ-BR23	Breast cancer	Body image, sexual functioning, sexual enjoyment, future perspectives, systemic therapy side effects, breast symptoms, arm symptoms, and distress from hair loss
FACT-B	Breast cancer	Physical well-being, social/family well-being, emotional well-being, functional well-being, and a breast cancer subscale
Breast-Q	Breast cancer	Satisfaction with breasts, satisfaction with outcomes, psychosocial well-being, physical well-being, and sexual well-being

Abbreviations: *QOL* quality of life; *SF-36* short form with 36 questions; *WHOQOL-BREF* World Health Organization Quality of Life; *EORTC* European Organisation for Research and Treatment of Cancer; *FACT-G* Functional Assessment of Cancer Therapy-General; *FACT-B* Functional Assessment of Cancer Therapy-Breast

2.2.1.1 Short Form with 36 Questions

The SF-36 is a multidimensional QOL measure, consisting of 36 items and incorporating 8 different QOL indices. In each index, higher scores indicate better functioning in that domain [17].

2.2.1.2 European Organisation for Research and Treatment of Cancer QLQ-C30

The EORTC QLQ-C30 is a tool for assessing QOL in cancer patients, consisting of 30 questions subsequently transformed into 15 scales: 5 functional dimensions, 3 symptom items, 6 single items, and the Global Health Status/QOL scale [18]. Higher functioning and global health status scores indicate better health. In contrast, higher symptom scores indicate poorer health. Some studies use only the five functioning scales (i.e., physical, role, cognitive, emotional, and social functioning) and the Global Health Status/QOL scale rather than analyzing all items [19, 20].

2.2.1.3 European Organisation for Research and Treatment of Cancer QLQ-BR23

The EORTC QLQ-BR23 (QOL Questionnaire—Breast Cancer) comprises 23 questions for assessing QOL and is targeted specifically for breast cancer patients [21]. Similar to the QLQ-C30, higher scores on the functional and global QOL scales reflect higher levels of function and global QOL. Alternatively, higher symptom scores show greater impairments.

2.2.1.4 Functional Assessment of Cancer Therapy-Breast

The FACT-B consists of 36 items and 5 subscales [22]. Each item is rated on a scale from 0 (not at all) to 4 (very much). The scores of each domain are summed, with a maximum of 108 points. The higher the score, the higher the QOL.

2.2.1.5 Breast-Q

The Breast-Q was designed to meet the high standards of medical outcome assessment for patients undergoing breast surgery [23, 24]. All domain scores range from 0 to 100, with higher scores indicating better satisfaction or QOL.

2.2.1.6 World Health Organization Quality of Life

The WHOQOL-BREF is grouped into four QOL domains and two items that measure overall QOL and general health [25]. Higher scores indicate greater QOL and better perceptions of health conditions.

2.2.1.7 Lymphedema Functioning, Disability and Health Questionnaire for Upper Limb Lymphedema

The Lymph-ICF-UL scores the average disability in function, activity restriction, and participation restriction over the last 2 weeks [26]. Each of the 29 questions corresponds to a score between 0 and 100. The total score of the Lymph-ICF is

equal to the sum of the scores on the questions divided by the total number of answered questions. In addition, a score is determined for each of the five domains of the Lymph-ICF UL: (1) physical function, (2) mental function, (3) household activities, (4) mobility activities, and (5) life and social activities. Thus, the total score of the Lymph-ICF-UL and the scores on the five domains range between 0 and 100.

According to the World Health Organization taxonomy [27], impairments in function, activity limitations, and participation restrictions can be quantified with the following scale:

0–4%: No problem
5–24%: Small problem
25–49%: Moderate problem
50–95%: Severe problem
96–100%: Very severe problem

2.2.2 Depression and Anxiety Assessments

2.2.2.1 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) consists of two subscales with a total of 14 items (seven items for anxiety and seven for depression). The score of each subscale ranges from 0 to 21. A score of 11 or above is considered to indicate anxiety and depression [28, 29].

2.2.2.2 Distress and Impact Thermometer

The Distress and Impact Thermometer (DIT) is a self-report assessment tool for cancer patients [30]. The DIT uses a 0–10 scale, with 0 representing no distress and 10 indicating extreme distress. The DIT consists of two types of items: questions about the severity of the patient's distress (DIT-D) and its impact (DIT-I).

The standard DIT cutoff scores for screening psychological distress are as follows: a DIT-D score ≥4 and a DIT-I score ≥3 are indicative of adjustment disorders; a DIT-D score ≥5 and a DIT-I score ≥4 represent depression; major depression with suicidal ideation is indicated by a DIT-D score ≥5 and a DIT-I score ≥5.

2.2.2.3 Self-Rating Depression Scale

The Self-Rating Depression Scale (SDS) assesses subjective feelings of depression [31]. It consists of 20 items, each rated on a 4-point scale. Higher scores reflect greater levels of depression.

2.2.2.4 Self-Rating Anxiety Scale

The Self-Rating Anxiety Scale (SAS), designed by Zung, assesses subjective feelings of anxiety. It consists of 20 items that are rated on a 4-point scale [31]. Higher scores show elevated anxiety levels.

2.2.2.5 General Distress, Measured by the Symptom Checklist-90-Revised

The Symptom Checklist-90-Revised (SCL-90-R) measures general distress symptomatology in nine domains: somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism [32].

2.2.2.6 Centers for Epidemiological Studies-Depression

The Centers for Epidemiological Studies-Depression (CES-D) is a 20-item self-report questionnaire [33]. Total scores range from 0 to 60, with higher scores indicating more severe symptomatology.

2.2.3 Assessments of Upper Extremity Function

2.2.3.1 Disabilities of the Arm, Shoulder, and Hand

The Disabilities of the Arm, Shoulder, and Hand (DASH) self-report questionnaire measures upper extremity functional disability [34]. The questionnaire consists of 30 questions ranked on a scale from 1 (no difficulty in performing the activity) to 5 (unable to perform the activity) (Table 2.2). A scale score can be calculated if at

Table 2.2 All items of disabilities of the arm, shoulder, and hand

Item	
1. Open a tight or new jar	20. Manage transportation needs (getting from one place to another)
2. Write	21. Sexual activities
3. Turn a key	22. During the past week, to what extent has your arm, shoulder, or hand problem interfered with your normal social activities with family, friends, neighbors, or groups?
4. Prepare a meal	23. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder, or hand problem?
5. Prepare a meal	24. Arm, shoulder, or hand pain
6. Place an object on a shelf above your head	25. Arm, shoulder, or hand pain when you performed any specific activity
7. Do heavy household chores (e.g., wash walls, wash floors)	26. Tingling (pins and needles) in your arm, shoulder, or hand
8. Garden or do yard work	27. Weakness in your arm, shoulder, or hand
9. Make a bed	28. Stiffness in your arm, shoulder, or hand
10. Carry a shopping bag or briefcase	29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder, or hand?
11. Carry a heavy object (over 10 lbs)	30. I feel less capable, less confident, or less useful because of my arm, shoulder, or hand problem
12. Change a lightbulb overhead	
13. Wash or blow-dry your hair	
14. Wash your back	
15. Put on a pullover sweater	
16. Use a knife to cut food	
17. Recreational activities which require little effort (e.g., cardplaying, knitting)	
18. Recreational activities in which you take some force or impact through your arm, shoulder, or hand (e.g., golf, hammering, tennis)	
19. Recreational activities in which you move your arm freely (e.g., playing Frisbee, badminton, etc.)	

least 27 of the 30 items are completed. The score ranges from 0 to 100, with 0 indicating no disability or symptoms and higher scores reflecting an increased severity of impairment.

2.2.3.2 Shortened Disabilities of the Arm, Shoulder, and Hand Questionnaire

The Shortened Disabilities of the Arm, Shoulder, and Hand Questionnaire (Quick DASH) is a patient-reported questionnaire that includes 11 questions about upper limb function and severity of upper limb symptoms [35]. Each response is scored from 1 to 5, with a higher score suggesting a greater degree of disability or more severe symptoms. To calculate a Quick DASH score, at least 10 of the 11 items must be completed. The sum of all item scores is used to calculate a Quick DASH score from 0 to 100, with higher scores suggesting worse upper limb function.

2.2.4 Muscle Strength Assessments

2.2.4.1 Manual Muscle Testing

The manual muscle testing (MMT) scale categorizes muscle function into six grades [36]:

Grade 0: No perceptible muscle contraction
Grade 1: Muscle contraction palpable, but no motion
Grade 2: Motion of the part only with reduced gravity
Grade 3: Muscle holds the test position against the resistance of gravity but not with slight additional pressure
Grade 4: Muscle holds the test position against some pressure but breaks away
Grade 5: Muscle holds the test position against "full pressure"

Regarding points to consider when administering the MMT, the tester must be stronger than the subject [37]. In addition, the measurement results for Grades 4 and 5 require careful attention because the evaluator's subjectivity may influence the evaluation.

2.2.4.2 Handheld Dynamometer

An objective muscle strength evaluation can be made using a handheld dynamometer. Handheld dynamometry is limited by examiner strength and tends to underestimate strength when it is greater than 250 N (~56 lb) [38]. Therefore, the tester must be stronger than the subject [39]. Alternatively, a method using a belt has been reported here to improve measurement reliability.

The following methods for handheld dynamometry have been reported in previous research [39, 40]:

- Shoulder flexion: The shoulder is flexed at 90° with the elbow extended, and the dynamometer is placed just proximal to the epicondyle of the humerus.

- Shoulder extension: The shoulder is flexed at 90° with the elbow flexed; the dynamometer is placed just proximal to the epicondyle of the humerus.
- Shoulder abduction: The shoulder is abducted at 45° with the elbow extended, and the dynamometer is placed just proximal to the lateral epicondyle of the humerus.
- Shoulder lateral and medial rotation: The shoulder is abducted at 45° with the elbow at 90°, and the dynamometer is placed just proximal to the styloid processes.
- Elbow flexion: The elbow is flexed at 90° with the forearm supinated, and the dynamometer is placed just proximal to the styloid process.
- Hip abduction: Both lower limbs are in a neutral position, and the dynamometer is placed at the lateral femoral condyle.
- Knee extension: The hips and knees are flexed at 90° with hands resting in the lap, and the dynamometer is placed just proximal to the malleolus.

2.2.4.3 Grip Strength

Grip strength is measured using a digital hand dynamometer. Several measurement postures have been reported, including a seated position with the elbow flexed at 90° [41–44] and standing with the elbow and wrist fully extended [45, 46].

Higher grip strength has been reported when sitting with the elbow in 90° of flexion rather than fully extended [47]. Su et al. [48] evaluated grip strength with the elbow fully extended and 0°, 90°, and 180° of shoulder flexion, and also with the elbow flexed to 90° and 0° of shoulder flexion. The highest mean grip strength was found with the shoulder in 180° of flexion, and the lowest was found with the shoulder in 0° of flexion and the elbow flexed at 90°.

In another study, grip strength was compared in four positions: standing with the elbow fully extended, standing with arms raised, sitting with the elbow flexed at 90°, and sitting with the elbow extended [49]. The findings revealed that grip strength measured while standing with the elbow fully extended was greater than that measured while sitting, which is the posture currently recommended in clinical practice. Therefore, clinicians and researchers should choose the most appropriate and optimal postures to measure grip strength.

2.2.5 Assessment of Axillary Web Syndrome

The diagnostic criteria for AWS are described below:

- Visible or palpable cord of tissue in the axilla, upper extremity, or trunk region during maximal shoulder abduction [50].
- Pain and restriction of shoulder ROM, with associated visible or palpable taut cords of tissue in the axilla in maximal shoulder abduction [51].
- Presence of palpable and visible cords of tissue in the axilla in maximal shoulder abduction, with or without associated pain or shoulder ROM limitation [52].

2.2.6 Assessment of Lymphedema

Limb girth, water displacement, optoelectronic perometry, and bioelectrical impedance (only with pitting edema) are all valid and reliable methods for quantifying upper limb volume and identifying lymphedema [53, 54].

2.2.6.1 Circumference Measurements

Several methods for measuring limb circumference have been reported:

- Measuring circumference at the metacarpophalangeal joint and wrist and both 10 cm distal and 15 cm proximal to the lateral epicondyle: A ≥2 cm difference in circumference at any of these four points between the affected and non-affected arms is defined as lymphedema [55–57].
- Measuring circumference 10 cm above and 10 cm below the humeroradial joint: The presence of lymphedema is defined as a >10% difference between the involved and uninvolved sides, at least at one of the measurement sites, i.e., the relative difference in arm circumference between the involved and uninvolved arms [1].
- Arm circumference measured 10 cm above the wrist and 10 cm above the elbow using a leather measuring tape: Lymphedema is defined as a >2 cm difference in arm circumference between the treated and untreated sides at either of the two measurement locations [58].

2.2.6.2 Bioelectrical Impedance Analysis

Bioelectrical impedance analysis is a method of measuring body composition. Using a body composition analyzer (Inbody720, Biospace, Seoul, Korea), the ratio of extracellular water (ECW) to total body water (TBW), which represents the status of the extracellular fluid (ECF) and the presence of edema, can be obtained. The ECW/TBW ratio can be separated into three evaluation categories [59]: a constant hydration state (0.38), a mildly overhydrated state (0.390–0.399), or a moderately to severely overhydrated state (≥0.400).

Malnourished and elderly patients with chronic kidney disease may be susceptible to volume overload along with decreased intracellular water (ICW) and increased ECW [60]. Therefore, it is necessary to evaluate lymphedema not only with a body composition analyzer but also by other evaluation techniques, such as palpation and inspection.

Several body composition analyzers can perform measurements in the standing position as well as in supine and sitting positions (Fig. 2.1). Body composition analyzers can also measure body fat percentage, body fat mass, and muscle mass. When lymphedema occurs, the body composition analyzer suggests that there is high muscle mass at the site of edema. Therefore, an accurate measurement of muscle mass may not be possible with a body composition analyzer. For accurate measurements of muscle mass, it is necessary to confirm and evaluate the state of water balance.

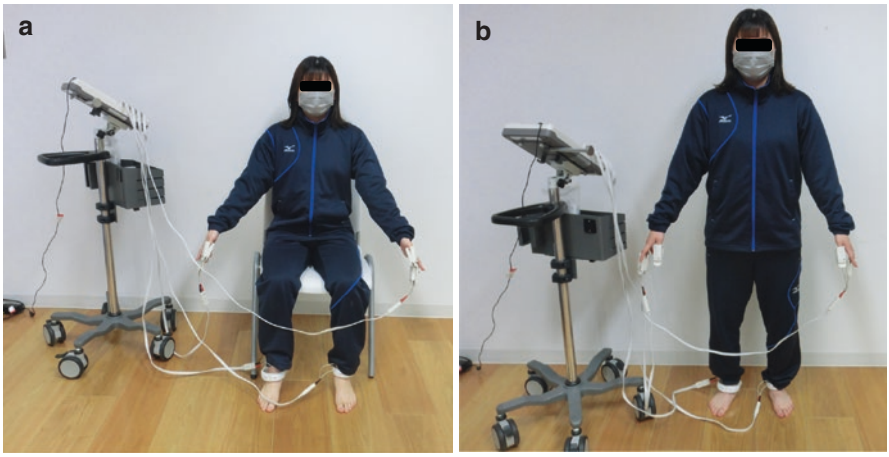

Fig. 2.1 Body composition analyzer method for measuring body water content. (**a**) Sitting, (**b**) standing

2.2.7 Pain Assessment

2.2.7.1 Visual Analog Pain Scale

The visual analog pain scale (VAS) provides quantifiable and reliable measurements of pain. Scores range from 0 to 100, with 0 reflecting no pain and 100 indicating the worst pain possible [61].

2.2.7.2 Numerical Rating Scale

The Numerical Rating Scale (NRS) assesses pain severity using a single 11-point (0 to 10) scale. A score of 0 indicates no pain, whereas a score of 10 indicates severe pain [62]. A systematic review of NRS cut points suggested that 0–4 be considered "mild pain," 5–6 "moderate pain," and 7–10 "severe pain" [63].

2.2.7.3 McGill Pain Questionnaire

The McGill Pain Questionnaire (MPQ) and its short form (MPQ-SF) are multidimensional pain questionnaires that can be used to assess cancer-related pain.

2.2.7.4 Brief Pain Inventory

The Brief Pain Inventory (BPI) [64] queries pain magnitude, interference, and location using a body diagram. Pain magnitude is considered through four items that ask about current pain, worst pain, least pain, and average pain. The items use a numeric rating scale anchored by 0 (no pain) and 10 (most severe pain). Pain interference consists of seven items that ask about how pain interferes with the aspects of daily living using a numeric rating scale anchored by 0 (no interference) to 10 (completely interferes). The BPI also has an abbreviated version (BPI-SF), often favored for its brevity and because it only relies on 24-h pain recall rather than a whole week, as required by the traditional BPI [65].

2.3 Rehabilitation

2.3.1 Preoperative Rehabilitation

A study compared an experimental group receiving preoperative education, prospective monitoring, and early physiotherapy to a comparison group. The experimental group maintained shoulder flexion ROM 7 months after surgery, but the comparison group showed a decrease in ROM [9]. Furthermore, preoperative rehabilitation program for breast cancer patients undergoing surgery is recommended based on the results of six studies included in a systematic review [9, 66–71].

2.3.2 Early Rehabilitation

Exercise programs initiated 4–6 weeks after breast cancer surgery are being investigated to reduce upper limb disability [10]. Patients were randomized to either an 8-week exercise program or a control group. The exercise program consisted of passive stretching of the shoulder muscles and a home-based program of progressive resistance training. Both groups reported few disorders, including swelling immediately following the intervention and 6 months thereafter. At the end of the exercise program, women in the exercise group had gained slightly greater ROM and abduction surface strength in both forward flexion and abduction directions compared to the control group.

In a systematic review of randomized controlled trials [72], a moderate level of evidence was exhibited regarding the effectiveness of protocols that used exercises to improve shoulder flexion, abduction, and external rotation ROM after a 3-month follow-up. The evidence was also moderate for protocols that associated ROM exercises with strengthening exercises to enhance shoulder flexion after 3- and 6-month follow-ups. A low level of evidence was found regarding the effectiveness of ROM exercises, muscle-strengthening exercises, and ROM exercises associated with muscle-strengthening exercise protocols to improve arm function.

In another study, a group receiving an early physical rehabilitation program was compared with a control group [73]. Starting from the second postoperative day, patients receiving early rehabilitation underwent assisted exercises favoring proper postural alignment of the head and neck. Starting from the third postoperative day and continuing five times a week for the duration of axillary drainage, passive exercises for arm flexion, abduction, adduction, and circumduction were performed. Additionally, the patients were invited to do active internal and external rotational movements of the arms. Once the drain was removed, patients in the early rehabilitation group underwent 20 physiotherapy sessions (five times a week) of 60 min each, adapted to the patient's power and gradually increasing the intensity of the exercises. The early physical rehabilitation program group showed statistically significant improvements in QOL.

2.3.3 Resistance Exercise

In patients with breast cancer-related lymphedema, resistance exercise for the upper body had positive effects during and shortly after intensive complex decongestive physical therapy [11]. Specifically, upper limb function and muscular strength improved without increasing arm volume.

In a systematic review [72], resistance exercise alone, or combined resistance and aerobic exercise, was reported to be a potentially effective procedure for reducing the risk and severity of breast cancer-related lymphedema. Another systematic review showed that resistance exercise did not reduce limb volume in patients with breast cancer-related lymphedema, nor did it increase the incidence of lymphedema. Furthermore, resistance exercise did not increase the risk of developing breast cancer-related lymphedema. Resistance exercise is a safe intervention for breast cancer survivors, and it does not increase the risk of lymphedema [74]. Only one study has reported the occurrence of adverse events with resistance exercise. This was the only study that showed an increase in arm volume after 4 weeks of resistance exercise [75]. However, lymphedema was evaluated with circumference measurements, and an analysis of tissue composition in the arm was not performed.

Ammitzbøll et al. showed that a program of early progressive resistance training after breast cancer surgery had significant effects on emotional and social functioning [76]. In the first 20 weeks, participants were offered twice-weekly supervised group exercise sessions and once-weekly self-administered exercise with dumbbells and resistance exercise bands. The training was self-administered in the following 30 weeks. Furthermore, in a subgroup of women who reported having a symptom cluster including pain, disturbed sleep, and fatigue at baseline, the intervention had an even greater impact on global health status and social functioning.

2.3.4 Home-Based Multidimensional Survivorship Programs

Home-based multidimensional survivorship programs (including symptom management, cognitive behavioral therapy, counseling, and exercise or wellness activities) following surgical treatment for breast cancer, with or without adjuvant chemotherapy or radiation therapy, effectively improve QOL—with effects persisting for 3 months [12]. Compared to controls, the home-based multidimensional survival program's effect on the QOL subscales showed improvements in the functional and emotional domains.

2.3.5 Water-Based Exercise

Fernández-Lao et al. compared the outcomes from breast cancer survivors in a water-based exercise group, a land exercise group, and a control group [13]. The

land exercise group exhibited a greater decrease in percentage body fat than those in the water-based exercise and control groups. Breast cancer survivors in the control group had greater waist circumference compared to those in the water-based and land exercise groups. Participants in the water-based exercise group experienced greater decreases in breast symptoms than those in the land exercise and control groups. The land exercise produced greater decreases in body fat and increases in lean body mass, whereas water-based exercise was better for improving breast symptoms.

Odynets et al. compared water-based exercise, Pilates, and yoga interventions [77]. Based on 12 months of monitoring, water-based exercise was more effective for improving QOL in the emotional well-being domain and decreasing the negative symptoms associated with breast cancer treatment compared with the Pilates and yoga interventions. The yoga intervention was more effective than the water-based exercise and Pilates interventions for improving QOL in the social and family well-being domain.

Important factors for continuing water-based exercise interventions include the convenience of easily modifiable and weightless exercises in water, social interaction, and access to a private dressing room. These factors are important to consider when encouraging the continuation of water-based exercise programs [78].

2.3.6 Complex Decongestive Physical Therapy

Complex decongestive physical therapy (CDT) is the gold standard for treating lymphedema [14]. It is a fourfold conservative treatment that includes two phases of manual lymph drainage, compression therapy (consisting of compression bandages, compression sleeves, or other types of compression garments), skin care, and lymph-reducing exercises [79] (Fig. 2.2). A meta-analysis concluded that additional manual lymphatic drainage is unlikely to significantly reduce the volume of the affected limb

Fig. 2.2 Complex decongestive physical therapy. (**a**) Compression therapy. (**b**) Lymph-reducing exercises

compared to treatments such as exercise, skin care, and compression therapy [80]. On the other hand, a subgroup analysis in a Cochrane systematic review demonstrated that manual lymph drainage was safe and, when used in combination with compression bandages, may provide additional benefits (including a reduced swelling in **breast cancer**-related lymphedema) compared with the use of compression bandages alone, particularly for patients with mild-to-moderate disease [81].

Elderly patients with Grade 1 or Grade 2 lymphedemas had significant improvements in all outcome measures (circumferential measurements, the Constant-Murley score, and the Lymphedema Functioning, Disability and Health questionnaire (Lymph-ICF)) after treatment [82]. Patients with Grade 1 breast cancer-related lymphedema also had a greater improvement in QOL scores, especially in terms of mobility, participation in daily living and social activities, and total QOL [82].

Kizil examined the effect of shoulder ROM exercise using continuous passive motion (CPM) for the treatment of breast cancer-related lymphedema [83]. Although CPM and CDT were effective in decreasing volumetric lymphedema or improving shoulder ROM, QOL, and functional recovery, the study was unable to show that the addition of CPM to CDT was more effective than CDT alone.

The multilayer bandaging used in CDT may increase tissue pressure, resulting in nerve entrapments. However, Phase 1 or the intensive phase of CDT has no effect on the size of the median nerve at the level of the carpal tunnel, neuropathic pain score, or arm disability [79].

2.3.7 Psychoeducational Group Interventions

Leclerc et al. examined the effects of a 3-month rehabilitation program that included physical training and psycho-education sessions [15]. After 3 months, flexibility, walking distance, and all parameters measured during a maximal incremental exercise test (except maximal heart rate) significantly improved in the experimental group. Body fat percentage decreased significantly, and significant improvements in QOL domains for health status, functional role, emotional state, physical functions, fatigue, pain, insomnia, and diarrhea were observed. In the control group, most of these improvements were not apparent, but significant increases in body mass index (BMI) and body fat percentage were observed.

2.3.8 Tai Chi Chuan

Tai chi chuan is a mild- to moderate-intensity whole-body exercise incorporating meditation and breathing control with slow, supple, graceful, curved, spiral, and sequential motions [84, 85]. A systematic review and meta-analysis revealed that, compared to non-exercise therapy, tai chi chuan has a positive effect on QOL, shoulder function, strength of the upper limb, pain, fatigue, and anxiety in breast cancer patients [16]. Tai chi chuan may be an effective intervention for improving QOL and physical function in breast cancer patients [16].

2.4 Factors Affecting Quality of Life

2.4.1 Factors Affecting the Quality of Life After Breast Cancer

Arm and shoulder problems and reduced QOL have been associated with breast cancer [57]. Arm and shoulder problems were associated with reductions in mental and physical QOL 8 years after breast cancer diagnosis [86]. Several studies have reported that breast cancer patients have a reduced QOL due to side effects from chemotherapy and radiation therapy [7, 87, 88]. Following adjuvant chemotherapy, breast cancer patients experienced a significant negative impact on QOL compared with patients treated with radiation therapy and adjuvant hormone therapy [89]. Radiation therapy is often associated with asthenia and skin disorders, mainly in the acute phase, which may affect physical and psychological functioning [90].

Risk factors for poor QOL in women with breast cancer include being divorced or living without a partner [91, 92]. Married or cohabiting patients had better QOL scores than patients living alone or who were divorced [93, 94]. Therefore, financial and emotional support from partners is important for enhancing QOL [91].

Women with depressive or anxious symptoms have poorer QOL [95]. Some studies found that depression was the main psychological factor associated with breast cancer patients' QOL during active cancer treatment, posttreatment, and through long-term survivorship stages [90, 95]. Higher depression and anxiety levels influence breast cancer patients to have more difficulty coping with cancer and affect their QOL at the disease-free survivor stage [95]. Anxiety and avoidant attachment styles were associated with poor QOL among women who have completed active breast cancer treatments within 2 years [96].

Among the physical functions, decreased aerobic capacity was significantly associated with a decrease in overall QOL [97]. Aerobic and resistance exercises reduce physical and psychosocial problems related to cancer and cancer treatment [98].

2.4.2 Our Study: Investigation of Factors Affecting Early Quality of Life of Patients After Breast Cancer Surgery [6]

2.4.2.1 Time Course of Quality of Life

Following breast cancer surgery, the physical, role, emotional, and social functions of the overall condition and functional scales of the QLQ-C30 were relatively improved in patients up to 3 months after surgery. However, on the symptom scale, nausea and vomiting, dyspnea, and loss of appetite tended to worsen 3 months after surgery.

2.4.2.2 Factor Affecting Quality of Life

Patient DASH scores affected improvements in all items of the global health scale and functional scale of QOL. The global health scale of patients following breast cancer surgery may be strongly influenced by improved upper limb function. On the

functional scale, physical functioning and role functioning require movements using the upper limbs, and thus DASH may have been influenced. Although emotional functioning, cognitive functioning, and social functioning are not aspects of QOL directly related to upper limb function, secondary effects were considered due to the reduction in upper limb function. As for the symptom items of the QLQ-C30, DASH affected all items.

The presence or absence of neoadjuvant chemotherapy affected improvements in physical functioning, role functioning, and symptoms of fatigue, pain, dyspnea, and appetite loss. Although neoadjuvant chemotherapy reduced physical functioning, role functioning, fatigue, pain, dyspnea, and appetite loss before surgery due to its side effects, these outcomes improved 3 months after surgery. Hence, patients who underwent neoadjuvant chemotherapy may have improved QOL.

Radiation therapy had a positive effect on emotional functioning in breast cancer patients. Patients who have not undergone radiation therapy include those who have undergone chemotherapy and hormonal therapy and those who have not received any adjuvant therapy. Patients who receive chemotherapy and hormonal therapy have psychological problems due to the side effects of the treatments, and patients without adjuvant therapy have psychological burdens due to the lack of treatment options. Therefore, the presence or absence of radiation therapy affects emotional functioning.

The recovery of pain in QLQ-C30 showed a lower degree of improvement among older patients. Older patients may feel less useful in life and may be affected by psychological aspects such as uncertainty about the future [49].

2.5 Factors Affecting Psychological Problems

2.5.1 Characteristics and Incidence of Psychological Problems

About half of all cancer patients have a psychiatric disorder. Among them, adjustment disorders and major depression are the most common [99]. Adjustment disorders have a prevalence of 7–35% among cancer patients, while major depression is reported by 5–26% [100–103].

Zabora et al. reported the prevalence of depression among breast cancer survivors to be 32.8% [104]. Although adjustment disorders and major depression are distinct conditions, they are often associated with anxiety and a depressed mood [105]. Symptoms of depression negatively influence a patient's QOL [106] and may affect compliance with medical treatment [107], as well as recurrence, recovery, and survival [108].

2.5.2 Factors Affecting Psychological Problems

Several studies have reported that the side effects of radiation therapy or chemotherapy, such as nausea and fatigue, are often associated with depressive symptoms

in patients with breast cancer [109, 110]. Factors influencing depression in patients with breast cancer include pain, being divorced, a history of depression, and stressful life events [111, 112]. Unmarried and widowed women with breast cancer are also at risk of psychological problems [94, 111, 113, 114]. Support from family and friends has been associated with less breast cancer-related distress [115].

2.5.3 Our Study: Risk Factors for Early Postoperative Psychological Problems in Breast Cancer Patients After Axillary Lymph Node Dissection [8]

2.5.3.1 Incidence of Psychological Problems

In this study, 37% of the patients had problems with psychological conditions 3 months after surgery, although there was a tendency for gradual improvements over this period. Psychological problems need to be managed effectively to facilitate patient treatment and appropriate clinical decision-making [116].

2.5.3.2 Factors Affecting Psychological Problems

Logistic regression analysis showed that only DASH was a critical factor related to psychological conditions. Therefore, although multiple factors affect psychological conditions in breast cancer patients with axillary lymph node dissection, upper limb function appears to have the strongest influence.

Analysis using receiver operating characteristic curves revealed that DASH scores of 18 or higher were found to predict psychological conditions with high specificity (84%). Patients with substantial disability from common hand problems might benefit from screening for clinical depression. The results also suggest that improving the upper limb function of breast cancer patients after surgery may alleviate problems with psychological conditions.

2.6 Factors Affecting Shoulder Range of Motion

2.6.1 Improvements in Range of Motion

Levy et al. reported that more than 60% of patients had limited shoulder flexion and abduction ROM 1 month after breast cancer surgery; after 1 year, the proportion reduced to 10.5% for flexion and 9.6% for abduction [117]. Observational studies reported that the incidence of shoulder ROM deterioration 1 year postoperatively ranged from 20 to 31% [1, 118–120]. Yang et al. reported that postoperative upper limb dysfunction among breast cancer patients had frequencies of 24.6%, 20.9%, and 26.8% when evaluated 3 months, 6 months, and 1 year after surgery, respectively [121].

2.6.2 Factors Affecting Range of Motion

Chemotherapy, BMI, and mastectomy are factors that influence postoperative ROM [117, 118]. Levy et al. reported that the side of involvement was a significant factor for impairments in abduction ROM when the involved side was contralateral to hand dominance [117]. Alternatively, Dantes de Oliveira et al. reported the opposite result [118]. Regarding symptoms, pain and numbness have been negatively correlated with upper limb function 12 months after surgery [117]. Yang et al. reported that upper limb dysfunction 12 months after surgery was associated with the type of surgery (mastectomy) and radiation therapy [121]. Breast cancer patients often suffer from reduced shoulder mobility after surgery that can substantially worsen during radiation therapy [122].

2.6.3 Our Study: Risk Factors of Shoulder Function Impairment After Axillary Dissection for Breast Cancer [123]

2.6.3.1 Improvements in Range of Motion

In breast cancer patients that underwent surgery with axillary lymph node dissection, both shoulder flexion and abduction ROM were lower 1 month postoperatively than preoperatively, but gradual improvements were demonstrated after 3 months. DASH scores had also decreased 1 month after surgery compared to preoperative scores, but after 3 months, gradual improvements were similar to those seen for shoulder flexion and abduction ROM. However, some patients' shoulder ROM and DASH scores had not improved enough even 3 months after surgery. Following breast cancer surgery, it is considered necessary for patients to have regular follow-up appointments after discharge from the hospital and interventions such as a proper rehabilitation program.

2.6.3.2 Factors Affecting Range of Motion

In our study, concordance between the dominant hand and the operated side negatively affected the recovery of shoulder ROM (flexion and abduction) 3 months after surgery. We recommended home exercises after leaving the hospital. Although we could not explain the cause of these different results, they might be due to differences in lifestyles between countries.

Our results showed that the absence of numbness 1 week postoperatively negatively affected the recovery of shoulder abduction 3 months after surgery. At the time of discharge from the hospital, patients were instructed about the importance of exercise from the early stages of recovery and encouraged to perform ROM exercises as much as possible, even if numbness was present. In patients with numbness, a lowering of their pain threshold might explain or lead to their motivation for improving shoulder ROM compared to patients without numbness.

Radiation therapy was also extracted as a cause of ROM limitation in our study. It may be possible that ROM loss was influenced by soft-tissue damage caused by radiation therapy.

2.7 Factors Affecting Axillary Web Syndrome

2.7.1 Period of Axillary Web Syndrome Occurrence

Following axillary lymph node dissection, AWS reportedly occurs in 5.2–72% of patients [52, 124]. Several studies have shown that AWS occurs 1–8 weeks after axillary surgery [4, 125] and resolves within 3 months of surgery [4]. Physiotherapy can shorten the natural course of AWS to 6–8 weeks [51].

2.7.2 Clinical Characteristics

Patients with AWS experience a statistically reduced ROM for shoulder abduction and flexion compared to patients without AWS [126]. Between 77% [127] and 100% [128] of patients with AWS have restricted shoulder ROM, of which 40 out of 47 (85.1%) patients with AWS have shoulder ROM restrictions following axillary lymph node dissection for breast cancer treatment [129].

Reduced function and lymphedema have also been associated with AWS [50, 130]. Several studies have shown that AWS caused patient anxiety and fear due to a poor understanding of the complication [131, 132].

2.7.3 Factors Affecting Axillary Web Syndrome After Breast Cancer

Risk factors for AWS may include extensive surgery [50, 63], younger age [52, 133], lower BMI [51, 52, 133], ethnicity, and healing complications [133, 134]. The risk factors for developing AWS include axillary lymph node dissection, lower BMI, and younger age [51, 52, 133, 134]. It is possible that the effect of age and BMI may be related since older people are more likely to have a higher BMI [51].

2.7.4 Our Study: Influence of and Risk Factors for Axillary Web Syndrome Following Surgery for Breast Cancer [7]

2.7.4.1 Occurrence of Axillary Web Syndrome

The rate of AWS was 23.1%, 19.7%, and 9.7% 1, 2, and 3 months after surgery, respectively, exhibiting a gradual decrease. After surgery, breast cancer patients were encouraged to perform self-training at home, but AWS occurred even 3 months after surgery.

2.7.4.2 Shoulder Joint Range of Motion Compared Between Patients with and Without Axillary Web Syndrome

In our study, AWS patients were instructed to raise the shoulder joint while flexing the elbow to extend the axilla if the upper limbs had a strong sense of tension or pain during the shoulder-raising movement (in the extended elbow position; Fig. 2.3).

Fig. 2.3 Exercise therapy for axillary web syndrome. (**a**) Active shoulder abduction exercise. (**b**) Active shoulder flexion exercise. (**c**) Passive shoulder abduction exercise. (**d**) Passive shoulder flexion exercise. (**e**) Shoulder abduction exercise using the wall. (**f**) Shoulder flexion exercise using the wall

Fig. 2.3 (continued)

There were no significant differences in active shoulder flexion ROM and abduction ROM between the AWS and non-AWS groups 1 month and 3 months after surgery. At 2 months after surgery, shoulder flexion and abduction ROM were significantly higher in the AWS group than in the non-AWS group. In other studies, rehabilitation interventions have been effective for improving AWS [24]. Patients with AWS tend to reduce the time they spend exercising due to a sense of tension or pain. In the present study, the patients were instructed to perform vigorous rehabilitation exercises at discharge and 1, 2, and 3 months after surgery. Also, patients who developed AWS 1, 2, and 3 months after surgery were given advice on exercise and activities of daily living (ADL) according to their condition. As a result, self-training time at home showed no significant differences between the AWS and non-AWS groups 1, 2, and 3 months after surgery. This means that the AWS group did not show a decrease in shoulder ROM compared to the non-AWS group 1 and 3 months after surgery. Furthermore, an increase in shoulder ROM was observed in the AWS group 2 months after surgery. Therefore, even patients who develop AWS can achieve good results by self-training at home.

2.7.4.3 Disabilities of the Arm, Shoulder, and Hand Compared Between Patients with and Without Axillary Web Syndrome

There was no significant difference in DASH scores between the AWS and non-AWS groups. Symptoms of AWS include a sense of tension or pain during shoulder flexion while extending the elbow and axilla. In raising the shoulder joint, elbow

joint flexion reduces AWS symptoms. In the DASH assessment, many of the items related to the degree of difficulty in performing different physical activities due to arm, shoulder, or hand problems can be performed with the elbow flexed. Thus, this may explain why the present study found no significant differences between the AWS and non-AWS groups.

2.7.4.4 Quality of Life Compared Between Patients with and Without Axillary Web Syndrome

There was no significant difference in QOL between the AWS and non-AWS groups 1–3 months postoperatively. Additionally, there were no significant differences in upper extremity function between the groups. Therefore, in the patients of the present study, the effect of AWS occurrence on QOL was low.

2.7.4.5 Factors Predicting Axillary Web Syndrome

After axillary lymph node dissection in breast cancer patients, age was the only risk factor for developing AWS 1 month postoperatively. No factors were observed to predict AWS after 2 months or 3 months. Since BMI was not identified as a risk factor, only age was, the reason why young age affects AWS remains unclear. However, younger age may be useful for predicting the development of AWS in the early postoperative period. Also, age was not seen to be a factor linked to AWS occurrence 2 or 3 months post-surgery in this study. There was a tendency for AWS to improve gradually over the 3 months following surgery. Therefore, age may affect the early occurrence of AWS but may not be linked with improving AWS.

2.8 Factors Affecting Lymphedema

2.8.1 Clinical Characteristics

Lymphedema causes pain, functional disability, deformity, and recurrent infections within the edematous limb [135–139]. Women with lymphedema also experience depression, anxiety, social isolation, and sexual problems [139, 140]. Ridner (2005) also reported that lymphedema lowers QOL by causing more upper extremity impairments [136].

2.8.2 Incidence of Lymphedema

The prevalence of lymphedema varies from 6 to 49% among patients undergoing lymphadenectomies [141–143]. Lymphedema may present immediately or years after treatment, although the majority of cases occur within 18 months [144, 145].

2.8.3 Risk Factors for Lymphedema

Lymphedema is associated with axillary lymph node dissection, a high number of positive lymph nodes (>8) [146], capsular invasion of the tumor [146], and cellulitis [147]. Younger breast cancer survivors are more likely to experience lymphedema [148] because they tend to have more aggressive tumors and receive more intensive therapy, but some studies have indicated that older age is a high-risk factor [149, 150]. However, other studies have shown that age is not associated with breast cancer-related lymphedema [151]. As such, the relationship between age and occurrence of lymphedema remains controversial [152].

Numerous reports show that lymphedema is associated with radiation therapy [9, 153] and chemotherapy [151, 154]. Using multivariate analysis, Jung et al. reported that taxane-based chemotherapy was an independent risk factor for lymphedema following axillary lymph node dissection [155]. A review comparing adjuvant chemotherapy with and without docetaxel for treating breast cancer patients showed that those receiving docetaxel consistently had increased edema rates [156]. Increased extracellular fluid is a common side effect of taxane-based chemotherapy (docetaxel), often presenting as fluid retention in the extremities [157–160]. In addition, docetaxel has relatively greater hematologic toxicity and is more commonly associated with edema than paclitaxel [161].

Radiation therapy can cause venous occlusion within the radiation field, lymphatic damage, and oppression of the venous and lymphatic circulation due to local muscle fibrosis [162]. A study has shown that a BMI $\geq$25 kg/m^2 was significantly associated with increased arm volume [146]. Ridner et al. [163] found that breast cancer survivors with a BMI $\geq$30 kg/m^2 at the time of treatment were approximately 3.6 times more likely to develop lymphedema than those with a BMI <30 kg/m^2.

Hypertension is a risk factor for breast cancer-related lymphedema [105]; however, further investigation is required [152].

2.8.4 Our Study: Risk Factors for Lymphedema in Breast Cancer Survivors Following Axillary Lymph Node Dissection [164]

2.8.4.1 Incidence of Lymphedema

Fifty-seven women (23.9%) developed lymphedema at the end of the follow-up period. On average, lymphedema occurred 10.5 months after surgery.

2.8.4.2 Risk Factors for Lymphedema

Neoadjuvant chemotherapy was a risk factor for lymphedema. Neoadjuvant chemotherapy is intended for patients with lymph node metastasis and large tumor diameters, so the wide range of surgical lymph node dissections may be related to the occurrence of lymphedema.

Adjuvant chemotherapy with docetaxel and cyclophosphamide was a risk factor for lymphedema. Since docetaxel and cyclophosphamide contained docetaxel, the docetaxel may have influenced lymphedema development.

Patients treated with neoadjuvant chemotherapy and adjuvant chemotherapy with **docetaxel** and **cyclophosphamide** should be observed closely after axillary lymph node dissection. Appropriate lymphedema interventions should be considered from an early stage.

2.9 Factors Affecting Return to Work

A prospective study of 227 breast cancer patients in Germany, diagnosed between 2002 and 2004, found that nearly three times as many breast cancer survivors dropped out of their job as compared to age-matched women from the general population [165]. Another study in Germany with 577 patients diagnosed with breast cancer in 2013 observed that 35.2% of the patients did not return to work within 40 weeks of surgery [166]. According to Hasset et al. [167], 93% of insured women return to their work within 12 months of diagnosis in the United States.

One year after the first surgery, a female breast cancer patient has almost three times as much risk of no longer working compared to a woman in the general population [165]. Fifty-six percent of breast cancer patients were reported to be on sick leave 4–6 weeks after surgery [168]. Johnsson et al. found that 59% of women had returned to work, whereas 41% were sick-listed part-time or full-time 10 months after surgery [169].

2.9.1 Incidence of Return to Work

Breast cancer survivors have indicated that upper limb problems make it difficult for them to resume normal activities associated with paid, as well as unpaid, work [169, 170]. Balak et al. showed that patients with impaired shoulder function resumed their work about 2 months later than those without any complaints [171]. Breast cancer survivors with upper limb ROM limitations and upper limb pain are more than two and a half times as likely to lose productivity than their counterparts with no upper limb morbidity [172]. Work-related physical workload, such as heavy lifting, has also been found to affect cancer survivors' employment negatively [173].

An accommodating workplace, as perceived by the employee, is a key factor increasing the likelihood of returning to work [174]. Manual work and lack of support from employers and colleagues were factors that discouraged survivors from reentering their jobs [175, 176]. A positive attitude from coworkers and discretion over work hours or the amount of work required of the employee were positively associated with returning to work [177].

A few studies have found that patients who received adjuvant therapies other than chemotherapy [178] or patients who did not receive any adjuvant therapy [179] returned to work earlier. Several studies reported that chemotherapy was associated with sick leave [180, 181] due to side effects such as nausea, vomiting, fatigue, and cognitive dysfunction [171, 176, 182].

Single, divorced, or widowed breast cancer survivors preferred to return to their work [179, 180]. A significant association has been reported between unemployment and childlessness [183]. In the results of these studies, financial insecurity may have also been a contributing factor. People of advanced age are less likely to return to work after completing their treatment [184].

2.9.2 Our Study: Factors Associated with Returning to Work for Breast Cancer Patients Following Axillary Lymph Node Dissection [185]

Return to work was examined up to 3 months after surgery. There was a tendency for the number of patients who returned to work to increase gradually up to 3 months after surgery. Forty-nine percent of patients had returned to work 3 months after surgery in this study.

2.9.2.1 Incidence of Return to Work

Logistic regression analysis showed that DASH and shoulder flexion ROM were the factors affecting return to work 3 months after surgery. The upper limbs are frequently used in ADL as well as in the workplace; as such, the appearance of upper limb disability and symptoms may be a factor limiting return to work. Furthermore, shoulder flexion ROM was found to affect return to work. Movements involving shoulder flexion, such as reaching overhead, are necessary for ADL and work.

Three months after surgery, 51% of patients had not returned to work. Two of the patients returned to work 1 month after surgery but retired 2 months after surgery. One patient returned to work 2 months after surgery. This individual continued to work for 2 months after surgery but retired 3 months after surgery. Active support from employers and colleagues encourages a return to work [186]. Therefore, support from the workplace that is appropriate for the patient's condition may increase the likelihood of returning to work.

2.10 Factors Affecting Participation in Leisure Activities

Positive experiences with hobbies after diagnosis reduce deaths from breast cancer [187]. Patients with hobbies lived longer than those without, with an increased number of hobbies reducing the risk of death and curability, depending on treatment [188].

2.10.1 Our Study: Factors Affecting Participation in Leisure Activities After Breast Cancer Surgery [189]

The proportion of patients involved in leisure activities significantly decreased from 34% before surgery to 23% 3 months after surgery. The global health, emotional function, and social function QOL domains were significantly higher in the leisure

activity group than in the non-leisure activity group. Also, severe stress was significantly associated with a decrease in health-related QOL scores; patients who participated in leisure activities may have had a higher QOL because their leisure activities reduced stress.

2.10.1.1 Factors Affecting Participation in Leisure Activities

Involvement in leisure activities before surgery was a critical factor that influenced participation in leisure activities 3 months after surgery. Participating in leisure activities before surgery had a positive effect on participation 3 months after surgery. Preoperative participation needs to be evaluated in order to encourage engagement in postoperative leisure activities. In particular, medical workers are required to pay attention to patients who do not participate in leisure activities before surgery.

2.11 Tai Chi Yuttari-Exercise

One of the most popular Chinese traditional martial arts is tai chi chuan [190]. Tai chi is a series of movements (positions) performed in a slow and flowing manner that is considered highly suitable for elderly individuals who tend to have limited balance and mobility [191]. Regularly practicing tai chi is associated with a delay in declining cardiorespiratory function [192, 193], flexibility [194], muscle strength, and balance [190].

Wu and Millon [195] reported that the tai chi gait exerts increased shear force and frontal plane torque on the joints of the lower extremity in comparison to a normal gait. This fact suggests that adapting to a tai chi gait may be difficult for elderly individuals with decreased physical function.

In Japan, a professional team (including a medical doctor, physical therapist, public health nurse, nurse, tai chi instructor, certified care worker, and physical education trainer) designed a tai chi exercise regimen that can be performed in a sitting or standing position, aiming to prevent the development of conditions that require long-term care [196]. Moreover, minor changes to this program were introduced following a preliminary survey of its effect on the elderly [197]. This program is now known as Tai Chi Yuttari-exercise.

Tai Chi Yuttari-exercise is a form of exercise developed to improve motor function in older people with reduced physical function [197]. In terms of its impact on physical function, we found that performing Tai Chi Yuttari-exercise for 3 months improves balance and functions of daily living in older people [198].

2.11.1 Our Study: Impact of Tai Chi Yuttari-Exercise on Arteriosclerosis and Physical Function in Older People: Subjects Without Cancer [199]

This non-randomized controlled study investigated the impact of practicing Tai Chi Yuttari-exercise for 1 year on arteriosclerosis and physical functioning among community-dwelling older adults. Vascular and physical functions were compared

between individuals who had (n = 45) or had not (n = 44) participated in Tai Chi Yuttari classes for 1 year.

Older adults deemed unsuitable for exercise by a physician were excluded from the study (e.g., unable to walk unaided, severely limited activities of daily living, serious circulatory or respiratory disease, undergoing treatment for an acute or chronic motor organ disease, seriously impaired motor function of the upper or lower limbs, a history of myocardial infarction or cerebral stroke within the previous 6 months, or previous serious infection). In the intervention group, the mean cardio-ankle vascular index improved significantly from 8.44 at baseline to 8.20 after 6 months; however, no significant difference was observed after 1 year. Conversely, compared with baseline, functional reach, gait speed, and timed up-and-go test results improved significantly after 6 months in the intervention group, and these improvements were maintained after 1 year. No significant changes in arteriosclerosis or physical function were observed in the control group. Therefore, Tai Chi Yuttari-exercise is effective for maintaining and improving arteriosclerosis status and physical function in older people. However, it should be performed at least three times per week to maintain or improve arteriosclerosis status.

2.11.2 Our Study: Investigating the Circulatory-Respiratory Response During Tai Chi Yuttari-Exercise Among Older Adults: Subjects Without Cancer [200]

The purpose of this study was to examine the circulatory-respiratory dynamics during Tai Chi Yuttari-exercise among older adults. The average metabolic equivalent (MET) of the exercise ranged from 1.34 to 1.87, and the average respiratory quotient (RQ) ranged from 0.82 to 0.90. The circulatory-respiratory dynamics observed in this study verified that older females with an average age of 70 years could safely perform Tai Chi Yuttari-exercise. A characteristic of this exercise is that it does not significantly increase blood pressure and does not involve Valsalva-type movements.

2.12 Future Research Topics

2.12.1 Evaluation of Breast Cancer Patients at Home

Early detection of the lymphedema that occurs after breast cancer surgery is important. It is vital to create a system that enables medical professionals to detect lymphedema and upper limb disorders at an early stage of development.

2.12.2 Rehabilitation to Motivate Patients

- Breast cancer patients are mainly rehabilitated at home because the length of their hospital stay is limited.

- For rehabilitation at home, it will be easier for patients to engage in programs that include exercises they enjoy. Training using virtual reality may also be effective.
- Tai Chi Yuttari-exercise is safe, so its effectiveness for cancer patients should be examined.

2.12.3 Rehabilitation for Elderly Breast Cancer Patients

The number of elderly breast cancer patients is increasing due to longer survival times. Elderly breast cancer patients also have complications such as the preoperative deterioration of physical function, hypertension, and heart disease. Therefore, it is necessary to examine the physical function of elderly breast cancer patients, the characteristics of their QOL, and the effects of rehabilitation.

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Physical Function and Health-Related Quality of Life in Patients with Gastrointestinal Cancer

3

Tsuyoshi Hara

Abstract

With progress in cancer medicine, the clinical outcomes of interest in patients with gastrointestinal cancer (GIC) not only include survival rate but also health-related quality of life (HRQoL). HRQoL in patients with GIC has been extensively investigated worldwide, and many influencing factors have been reported, one of which is walking capacity related to physical therapy. However, postoperative exercise therapy by physical therapists has not been reported to improve HRQoL in patients with GIC. We investigated the perioperative changes in HRQoL and factors affecting early postoperative HRQoL in patients with GIC. The results of our study showed that the early postoperative scores of HRQoL subscales, except for the general health and emotional well-being subscales, of patients with GIC were significantly lower than the average of the general population. Additionally, the walking capacity of patients with GIC was more strongly related to early postoperative HRQoL than other factors were. In the future, randomized control trials that address and overcome the challenges faced by previous studies should be designed to concretely determine whether postoperative exercise therapy improves early postoperative HRQoL in patients with GIC. Additionally, the mechanism behind the association between increase in physical function and improvement in HRQoL of patients with GIC should be elucidated.

Keywords

Postoperative health-related quality of life · Predictors · Walking capacity 6-minute walk test · Postoperative physical exercise

T. Hara (✉)
Department of Physical Therapy, School of Health Science, International University of Health and Welfare, Otawara, Japan
e-mail: hara@iuhw.ac.jp

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3.1 Introduction

The health-related quality of life (HRQoL) in patients with gastrointestinal cancer (GIC) may decline with cancer treatment [1, 2]. Despite successful treatment and uneventful hospital discharge, early postoperative HRQoL scores in patients with GIC were found to be lower than the average of the general population, except in certain subscales such as mental health [3]. Therefore, patients with GIC receiving cancer treatment (including radical surgery) require comprehensive care in the early postoperative period to improve survival and enhance HRQoL. Several studies worldwide have evaluated the HRQoL of patients with GIC using varying instruments that measure comprehensive outcomes or disease-specific outcomes [3–80], and many cross-sectional studies have focused on patients with colorectal cancer [5, 9–12, 14, 18, 21, 22, 24, 25, 27, 28, 30–33, 35–37, 41–47, 51–54, 57, 59–63, 65, 66, 68, 69]. These studies show that a variety of factors influence HRQoL in patients with GIC [4–70], and one of these factors is "walking capacity," an outcome directly related to physical therapy [3, 33, 63].

Based on these findings, randomized control trials were conducted to investigate the effect of pre- or post-surgery exercise interventions on several clinical outcomes including the HRQoL of patients with GIC [71–74]. However, no benefit of exercise intervention on HRQoL in patients with GIC could be elucidated [71–74]. The inconclusive findings of these trials could be a result of uncontrolled subject bias, insufficient sample size, and missing data on whether the exercise therapy after discharge was performed under active supervision of a physical therapist.

In this chapter, explanations of influencing factors of HRQoL and the effect of exercise intervention are discussed, and the findings of previous studies [4–74] and our reports [3, 75] are reviewed.

3.2 Influencing Factors of HRQoL in Patients with GIC

The factors influencing HRQoL in patients with GIC are shown in Fig. 3.1. In this chapter, factors influencing HRQoL, as reported in previous studies, were categorized based on the International Classification of Functioning, Disability, and Health (ICF). To observe the effect of physical therapy intervention on HRQoL in patients with GIC, the subject's health condition, personal factors, and environmental factors should be confirmed first. Previous studies reported that among the health condition factors, the clinical stage of the cancer, types of cancer treatment, and periods from diagnosis or after surgery affected the HRQoL. Therefore, when investigating the HRQoL of patients with GIC, all relevant clinical data of GIC including information on other comorbidities (e.g., heart disease, respiratory disease) that may affect the posttreatment prognosis should be collected at baseline. Such information may be difficult to acquire in studies that collect data from patients under home medical care. Nonetheless, the accuracy of this data should always be confirmed when reporting a study. In the posttreatment period, a variety of factors, such as postoperative complications, complications due to adjuvant therapy (including

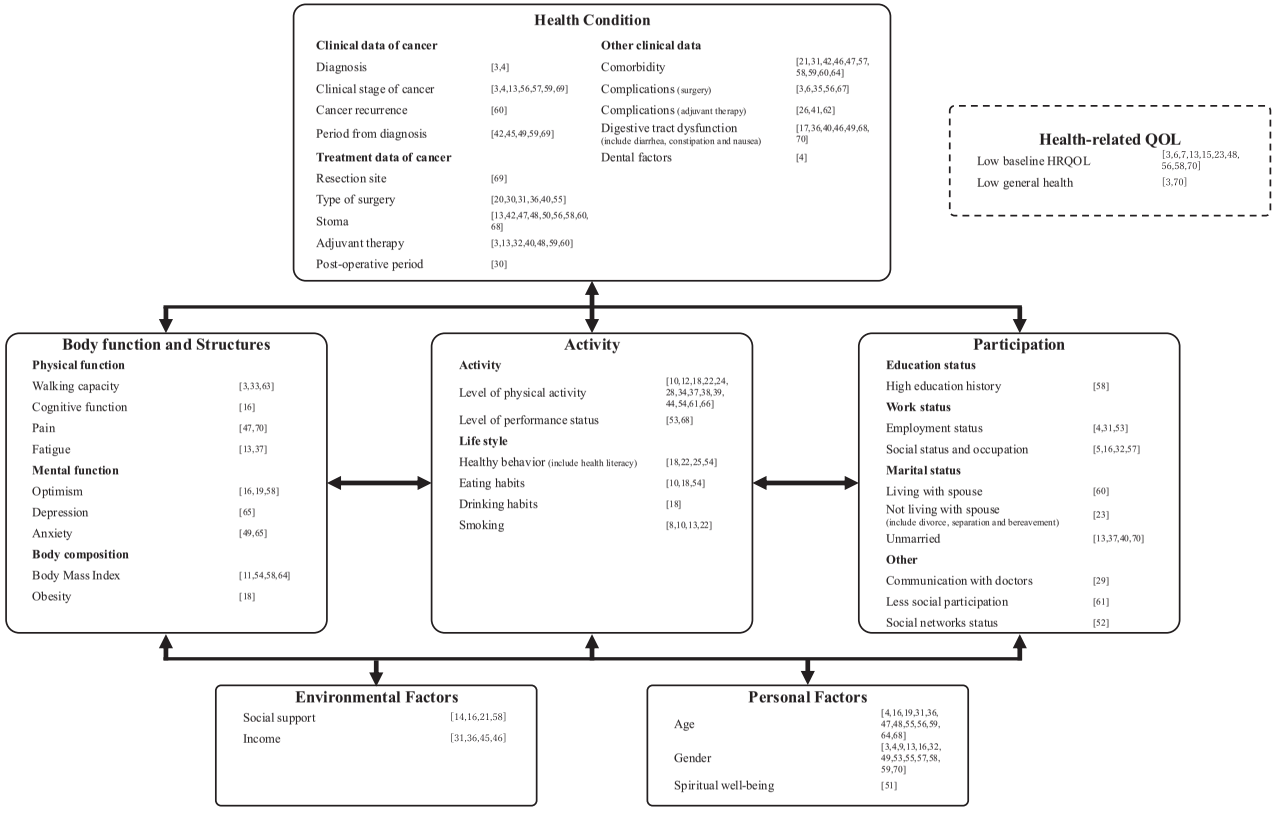

Fig. 3.1 Influencing factors of health-related QOL in patients with gastrointestinal cancer categorized based on the International Classification of Functioning, Disability, and Health

neoadjuvant therapy), and digestive tract dysfunction (including diarrhea, constipation, and nausea), were found to influence HRQoL. Thus, studies that assess the HRQoL in patients with GIC should also collect data on the sequelae of cancer treatment. Specifically, such studies should use indices that reflect disease-specific outcomes in addition to general health-related outcomes. When disease-specific outcomes, such as cognitive function, may not be available, it may also be good to consider assessing laboratory data (e.g., serum albumin and hemoglobin levels) that reflects disease-specific outcomes after GIC treatment. The ICF framework consists of two major components, namely, functioning and disability factors and contextual factors. The functioning and disability component of ICF further includes the following two categories: (1) body functions and structures and (2) activity and participation. The activity and participation domain of the ICF describes the patient's functional status in terms of their communication, mobility, interpersonal relations, and other social characteristics. In this domain, subcomponents such as education status (a history of high education), work status (employment status, social status, and occupation), and marital status (living with spouse or unmarried) were reportedly associated with the general QOL after treatment. Although numerous factors are found to influence the general quality of life, it is important to investigate factors that particularly influence the HRQoL in patients with GIC. In addition, even if certain participation factors cannot be adapted to patients with GIC (e.g., unemployed or living alone), the social participation status of the patient (e.g., older patients' connection with society) should be investigated because low social participation and social network conditions are important factors that influence HRQoL. Notably, personal and environmental factors, such as age, sex, social support, and income, that are associated with general QOL are also reportedly associated with HRQoL in patients with GIC. If the patient with GIC has a physical disability that limits their daily activities, they may be receiving some social support. In countries with well-developed insurance systems (e.g., Japan), data regarding use of social resources is reliable and therefore, should be evaluated to assess its impact on HRQoL in patients with GIC. In addition, the economic condition of patients with GIC should also be investigated because it is an important influential factor of HRQoL. It is, however, important to consider that data on economic condition may not be accurate when obtained from self-administered questionnaires. In countries with well-developed insurance systems, it is more efficient to collect such information from objectively classified indicators like "use of social support." Additionally, baseline HRQoL, which does not fall into the ICF category, has also been reported to influence post treatment HRQoL. Although several studies have examined HRQoL in patients with GIC, most of these studies are of low clinical significance because they have a cross-sectional design and do not reveal the change in HRQoL before and after GIC treatment. Therefore, a longitudinal study that considers the baseline HRQoL is desirable. To survey the HRQoL of patients with GIC more accurately, such longitudinal studies should not only limit the survey period for observation of the treatment course of physical therapy but also limit the target population by evaluating propensity score-matched cohorts.

Factors that are directly or indirectly related to physical therapy in the body function, structure, and activity domains of ICF are shown in Fig. 3.1. Notably, walking capacity in physical therapy is associated with HRQoL in patients with GIC. Previous studies have evaluated walking capacity using the 6-minute walk test (6MWT), and this test is recommended as the primary outcome to assess the effect of physical therapy in patients with GIC. However, factors that improve posttreatment walking capacity of patients with GIC remain unknown. To identify these influencing factors, future studies should examine the type of physical therapy (e.g., resistance training or aerobic exercise), amount and frequency of appropriate exercise therapy, and the timing of implementation.

Factors such as physical activity and performance status; lifestyle factors including eating habits, drinking habits, and smoking; and health behavior are related to activities of daily living in patients with GIC and reportedly influence HRQoL. The patient should be educated about the impact of these factors, and physical therapists should provide relevant guidance on these matter at discharge. Educating the patient about these factors is important because they not only affect the HRQoL but also influence cancer recurrence and survival rate. It is particularly important to inform patients with GIC to avoid habits that may lead to obesity and intake of carcinogens in daily life. By enabling the development of healthy habits like regular exercise, physical therapy may indirectly improve HRQoL in patients with GIC. Certain subjective symptoms, such as cognitive function, mental function, pain, and fatigue, are also reportedly associated with HRQoL. These symptoms are often evaluated when physical therapy is performed in clinical settings. Although the mechanism by which physical function improves HRQoL in patients with GIC remains unclear, studies show that fatigue acts as a mediator between physical fitness or exercise and QOL in cancer survivors [76, 77]. Therefore, to verify the effect of physical therapy on HRQoL in patients with GIC, it may be necessary to evaluate the role of subjective symptoms like fatigue.

The factors discussed above do not constitute an exhaustive list of variables that influence HRQoL in patients with GIC and should be considered as a starting point for further clinical research on how physical therapy impacts HRQoL of patients who have undergone GIC treatment.

3.3 Intervention Effect of Physical Therapy on Health-Related QOL of Patients with GIC

Recent studies have reported an improvement in the HRQoL of patients with GIC who underwent exercise therapy before or after surgery [71–74]. Providers of exercise therapy interventions for patients with GIC before and after surgery were kinesiologists [71, 72] and physical therapists [73, 74], respectively. In the exercise therapy programs performed in previous studies, many interventions were a combination of aerobic exercise and resistance training [71–73]. Additionally, the intensity of exercise therapy before surgery was set across a wide range from high

intensity (>90% oxygen uptake at peak) to moderate intensity (<40% maximum heart rate) [71, 72]. Contrastingly, no clear exercise intensity was set for the interventions performed after GIC surgery, and physical therapists determined the appropriate exercise intensity by adjusting to the postoperative course of the patient [73, 74]. Exercise therapy after surgery was also performed for patients with GIC as an intervention for certain postoperative symptoms, such as disorders of pulmonary function and upper extremity function [74]. Previous studies suggest that preoperatively, the general condition of patients with GIC is stable. Therefore, preoperative interventions can be performed using the unified exercise therapy program. However, most patients with GIC are unstable postoperatively and thus, cannot participate in a unified exercise therapy program. Additionally, exercise therapy after discharge was primarily an unsupervised program and required patients to perform the recommended exercises at home [73, 74]. As mentioned previously, intensive exercise therapy provided by physical therapists in medical institutions is difficult to continue after discharge, hence the switch to unsupervised therapy. Since only few studies have investigated the effects of exercise therapy among patients with GIC after hospital discharge, it is difficult to verify the benefits, if any, of supervised exercise therapy in the extended period. There are several reasons why it is challenging to provide a long-term supervised physical therapy program after discharge for patients with GIC. First, such long-term programs may not be covered by health insurance. In Japan, the medical insurance coverage of rehabilitation services is limited to the services availed during hospitalization and as palliative care after treatment of aggressive cancer or as terminal care at home. Long-term rehabilitation services, such as physical therapy, are not covered by the medical insurance in Japan, for patients with GIC who underwent aggressive cancer treatment at a medical institution and were then discharged. Second, the patient's knowledge regarding rehabilitation after GIC treatment is limited. Insurance coverage for certain rehabilitation services for patients with GIC has been available since 2010 in Japan. However, cancer rehabilitation has been a part of the Japanese medical system for a shorter period than it has in other advanced countries, and therefore, patients with GIC in Japan are not well aware of the clinical significance and effects of rehabilitation after cancer treatment. In the future, cancer rehabilitation should be made more commonplace in countries like Japan, where this concept is new, and provisions should be made for patients to continue exercise therapy under supervision of physical therapists, even after hospital discharge. This will enable further investigation on the effects of long-term supervised exercise therapy.

An improvement in the HRQoL of patients with colorectal cancer was reported when exercise therapy was performed preoperatively [71]. This preoperative exercise therapy consisted of 12 interval exercise sessions using a cycle ergometer over a 4-week period (including two recovery exercise sessions), and the intensity was set to 60 or 90% oxygen uptake at peak [71]. This study's results showed that to improve the preoperative HRQoL of patients with GIC, it is necessary to consider both the general stability of the patient and sufficient intensity of the exercise therapy. However, postoperative exercise therapy could not improve the HRQoL of patients with GIC [73, 74]. In patients with GIC who received postoperative

exercise therapy, the intervention period was 3 months, but the exercise program was mostly unsupervised, and active intervention by a physical therapist was limited only during hospital stay (average length of hospital stay was 10–20 days) [73, 74]. Additionally, the implementation status of the unsupervised program after discharge was assessed by a physical therapist at home once weekly [73] but was not objectively monitored and was based on the patient's own records [73, 74]. It is speculated that the HRQoL of patients with GIC did not improve by postoperative exercise therapy because (1) the quality and intensity of the intervention may have been insufficient during hospital stay owing to the patients' general condition being unstable and (2) the patient may not be performing the intervention with sufficient intensity at home because of the lack of active supervision by a physical therapist.

As mentioned previously, preoperative exercise therapy allows for high-intensity and high-frequency intervention and can improve HRQoL in patients with GIC. However, it is difficult to improve the HRQoL of patients with GIC because of individual differences in the postoperative course, thus making a unified (pre- and post surgery) physical therapy intervention impossible. It is also difficult to actively intervene after hospital discharge. Thus, methods to improve the HRQoL of patients with GIC after surgery need to be investigated, and to accomplish this goal, a fulfilling research environment is needed. Such environment can be created by strengthening the collaboration within and between medical institutions for research practice. Large-scale multicenter studies with well-controlled selection bias could help provide concrete evidence regarding the impact of postoperative exercise therapy on the HRQoL of patients with GIC. Additionally, it would help to create systems wherein the provision of exercise therapy supervised by physiotherapists is readily available for patients with GIC even after hospital discharge. Thus, upscaling of the organizational research practices and more comprehensive cancer rehabilitation systems are necessary to ensure sufficient quality and quantity of exercise therapy can be continued after discharge.

3.4 What Factors Are Needed to Improve HRQoL Early After Surgery Among Patients with GIC?

We investigated early postoperative HRQoL in patients with GIC. The present study aimed to observe the HRQoL from before surgery to 4 weeks after surgery and to analyze the influencing factors of HRQoL including walking capacity related to physical therapy and other factors reported in previous studies [3].

We found that the following subscales of the Short-Form 36-Item Health Survey (SF-36) were significantly lower in the cohort after surgery than before surgery: physical functioning, pain, vitality, social functioning, role physical, and role emotional. Additionally, the SF-36 subscale scores in the cohort after surgery were significantly lower than the average of the general population (Fig. 3.2). Therefore, in patients with GIC who underwent radical surgery and returned home with a good prognosis, early postoperative HRQoL scores were lower than that of the general population for most subscales. Of note, the mental health subscale of SF-36 in

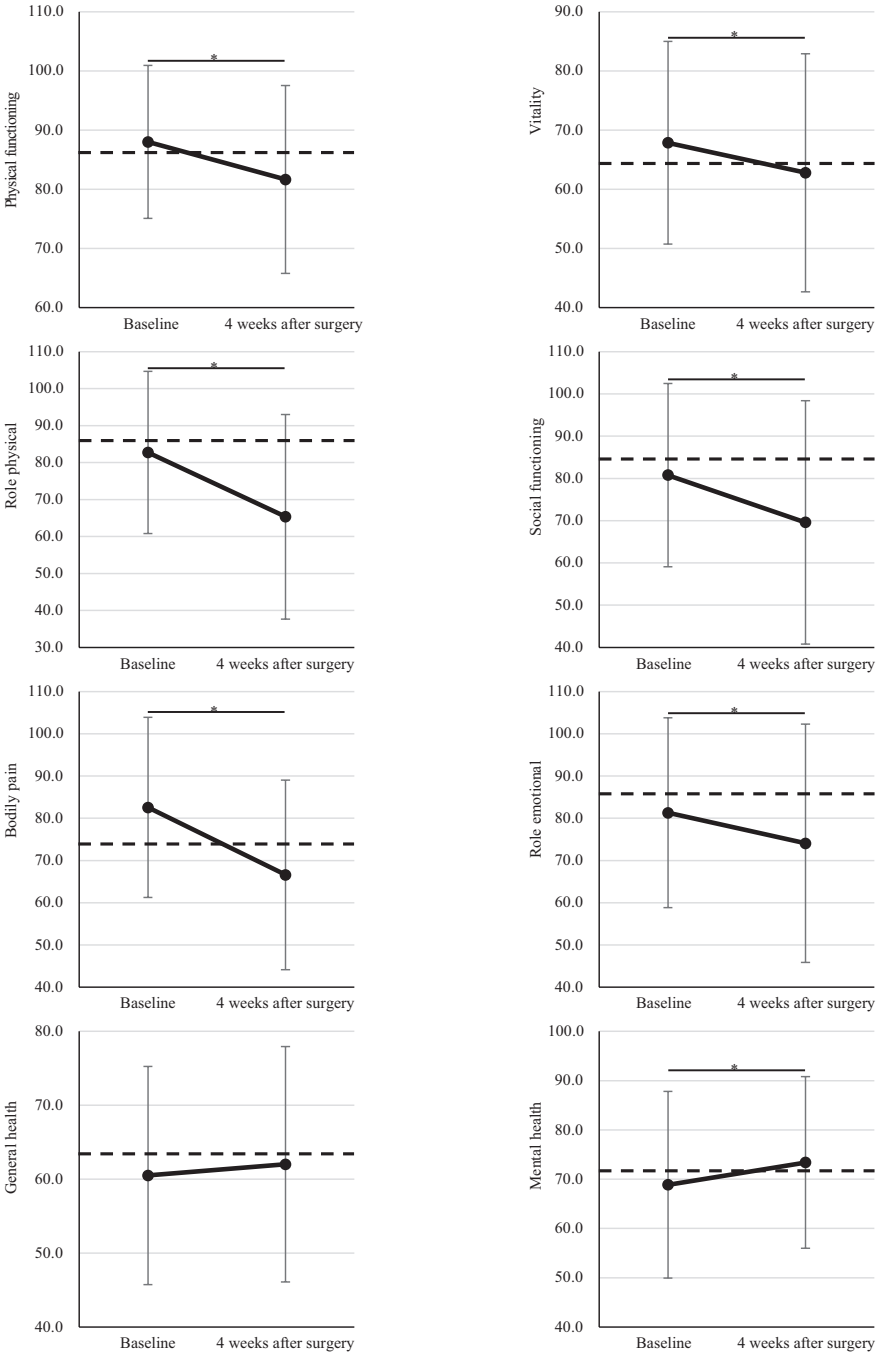

Fig. 3.2 Perioperative changes in the scores of Short-Form 36-Item Health Survey subscales from baseline to 4 weeks after surgery

patients with GIC early after surgery was significantly higher than that before surgery and higher than that of the average of the general population (Fig. 3.2). The reason for this increase in the mental health subscale of SF-36 in patients with GIC is unclear but may be due to a specific change in perioperative cancer management. Additionally, the general health subscale of SF-36 was not significantly different before and early after surgery and remained lower than the average of the general population (Fig. 3.2). The results of our study indicate that patients with GIC who undergo radical surgery and have a good prognosis may require more comprehensive cancer management than what is currently available under the rehabilitation programs in Japan because their early postoperative HRQoL, with the exception of emotional well-being, may be lower than the average of general Japanese population after hospital discharge. Additionally, a more comprehensive cancer health insurance coverage that extends beyond the short period of hospitalization is needed to efficiently improve early postoperative HRQoL of patients with GIC.

We analyzed the influencing factors of SF-36 subscales that significantly changed early after surgery based on the results of a longitudinal study [3]. The most frequent factor that influenced early postoperative HRQoL was the 6MWT score at 4 weeks after surgery. Therefore, improving walking capacity during the early postoperative period is important for improving the HRQoL in patients with GIC during this period. Accordingly, the recommended goal for physical therapy interventions during this period is to improve the patients' walking ability. Under the current cancer management plans, absolute rest after surgery is very rarely recommended for patients with GIC who have undergone radical surgery. Thus, the physical therapist plays an important role in actively improving the patients' walking ability by facilitating aggressive early ambulation in the early postoperative period after GIC treatment. Additionally, the preoperative HRQoL was the second most important factor (after 6MWT score at 4 weeks after surgery) influencing the SF-36 subscale scores. Preoperative exercise therapy of high intensity and frequency in patients with GIC has been proven to improve HRQoL before surgery [71]. Ideally, provision of preoperative physical therapy interventions such as resistance training or aerobic exercise could improve the HRQoL of patients with GIC; however, such provisions may not be possible because of the variations in the scope of cancer insurance plans in each country, for e.g., in Japan, the preoperative intervention period that can be covered by insurance is short. Although it is unclear whether physical therapy can improve HRQoL after radical surgery [71], such interventions may have good long-term effects. Future studies should investigate whether preoperative exercise interventions among patients with GIC improve the HRQoL in the long term by consistently tracking the patient's HRQoL scores after hospital discharge.

Apart from early postoperative walking capacity and preoperative HRQoL, factors that influence postoperative HRQoL include health status factors, such as the type of gastric cancer, clinical stage III of cancer, and receipt of neoadjuvant therapy and demographic factors such as sex. Postoperative complications were associated with early postoperative HRQoL in patients with GIC. Therefore, to improve early postoperative HRQoL of patients with GIC, it is also necessary to ensure good progress of preoperative treatment and perioperative care. Thus, physiotherapists

involved in cancer rehabilitation must provide interventions in consideration of the relevant clinical information, such as the surgical site and clinical stage of cancer, from before and after surgery and work in collaboration with other medical departments to improve the patient's walking capacity postoperatively.

To efficiently improve the early postoperative HRQoL in patients with GIC, we considered the optimal cutoff value of the 6MWT. The estimated minimal clinically important difference (MCID) of 6MWT scores was calculated using clinical data from a multicenter study [3] because our previous study had a single-center design and was thus susceptible to selection bias of patients with GIC [75]. The anchor of the MCID for the 6MWT in our study [75] was adopted as the average score of the general Japanese population in the physical functioning subscale of the SF-36. This score was used as an anchor because it is responsive to changes between pretreatment and cancer treatment periods [78, 79] and is related to the survival rate of cancer patients [80]. Based on the results of our study [75], the changes in 6MWT scores before and after surgery were significantly correlated with the change in the anchor, with a correlation coefficient of 0.398 (Fig. 3.3). The receiver operating curve indicated that the optimal cutoff value for clinically relevant change in the

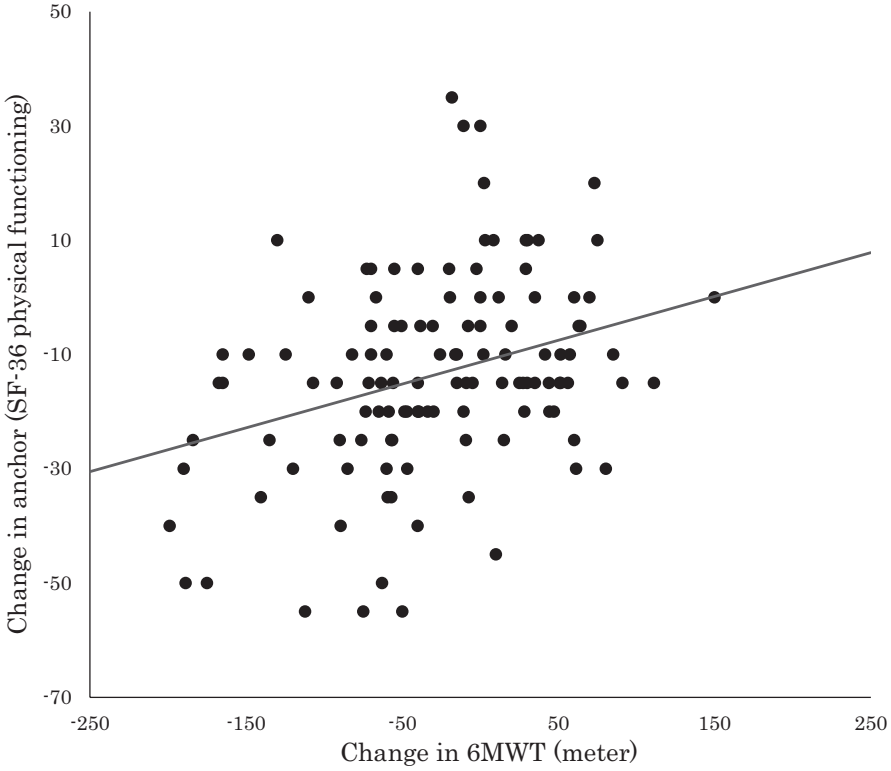

Fig. 3.3 Change in the 6MWT score and anchor from baseline to 4 weeks after surgery. *6MWT* 6-minute walk test; *SF-36* Short-Form 36-Item Health Survey

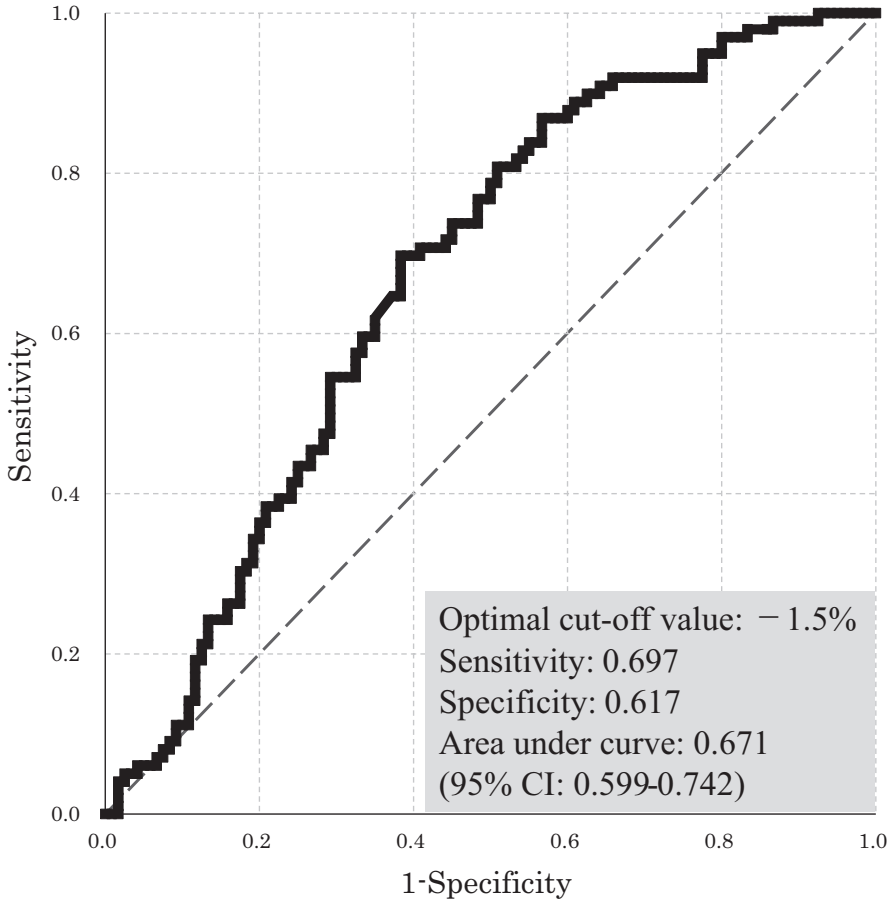

Fig. 3.4 Receiver operating curve of deterioration versus not-deterioration in the rate of change in the 6-minute walk test scores

6MWT score was −7.8 m (area under curve; AUC = 0.670, 95% CI = 0.599–0.741) or a −1.5% change (AUC = 0.671, 95% CI = 0.599–0.742) (Fig. 3.4). Therefore, to reach the average HRQoL of the general Japanese population, the postoperative 6MWT score of patients with GIC must be increased to the same level as that observed before surgery. The 6MWT score should be frequent evaluated if patients with GIC can walk safely after surgery. Additionally, when providing physical therapy interventions after surgery, it is recommended that the physical therapist and patients with GIC share the same target value for walking capacity. However, the optimal cutoff value for walking capacity was below AUC 0.7 [81] and did not have sufficient predictive ability. A previous study among patients with lung cancer reported that the optimal cutoff value for clinically relevant change in the 6MWT scores was −9.5%, which was below the AUC (0.66, 95% CI = 0.51–0.81) [82]. Thus, the cutoff value for indicating a clinically relevant change in 6MWT scores

pre- and post surgery among patients with GIC is accurate and similar to that observed among patients with lung cancer [82]. In the future, the validity of the MCID calculated in our study [75] should be investigated through clinical trials that focus on postoperative recovery in patients with GIC. Additionally, components of physical function other than walking capacity may also play a role in improving the HRQoL in patients with GIC. For example, physical therapists also assess muscle strength, balance ability, and flexibility when implementing the intervention in clinical settings. Improvement in these components after surgery may result in improved HRQoL of patients with GIC in the early postoperative period. Future studies should investigate the impact of these and other relevant components of physical therapy that are not reported previously and should their association with the HRQoL of patients with GIC.

3.5 Physical Therapy for Patients with GIC in the Future

Provision of exercise therapy among patients with GIC improved their HRQoL before surgery [71]; however, the effect of this intervention after surgery is unclear [73, 74]. This is because the general condition of patients with GIC is often unstable during hospitalization after surgery and after hospital discharge; it is challenging to provide active and supervised physical therapy intervention for the long term. Previous studies on this subject [73, 74] did not assess HRQoL as a primary outcome and did not have sufficient sample size to make a clinically relevant inference regarding this outcome. Therefore, to verify the effect of postoperative exercise therapy on HRQoL, an appropriate sample size should be calculated based on the effect size for the outcome. Moreover, in previous studies [73, 74], the postoperative exercise therapy after hospital discharge was implemented in clinical settings only once weekly under the supervision of a physical therapist [73], and the feedback on patient's adherence to the intervention at home was unclear. The augmented feedback for patients by physical therapists affects not only the motivation or energy to continue exercise but also the learning and performance variables [83]. Therefore, provision of exercise therapy by a physical therapist after hospital discharge and consistent augmented feedback regarding clinical data (e.g., cutoff value of 6MWT [75]) may help in improving the physical function and early postoperative HRQoL of patients with GIC.

The mechanism through which physical function improves the HRQoL of cancer survivors remains unclear. A possible explanation could be that fatigue acts as a mediator between physical fitness or exercise and QOL in cancer survivors [76, 77]. However, in previous studies, fatigue was self-reported subjectively by the cancer survivor according to how they felt after performing physical exercise [76, 77]. Thus, it is unclear whether the fatigue experienced by cancer survivors is attributable to physical or mental exhaustion. In the future, studies should clarify which type of fatigue (physical or mental) needs to be reduced to improve the impact of physical therapy on HRQoL of patients with GIC. Ideally, fatigue should be investigated as an objectively calculated variable that is directly associated with physical

therapy. For example, exploring specific mechanisms that improve muscle fatigue by increasing physical function of patients with GIC may lead to improved HRQoL. Once it is evident which type of fatigue needs to be treated in patients with GIC, physical therapy could by adjusted accordingly to better improve the patients' early postoperative HRQoL.

Future studies with a modified study design and more detailed intervention methods are needed to verify how the abovementioned factors involved in postoperative exercise therapy may improve the HRQoL of patients with GIC. Additionally, the mechanism through which an increase in physical function causes an improvement in the HRQoL of patients with GIC should be clarified to identify factors that cause or mitigate fatigue.

3.6 Conclusion

Previous studies report that a wide variety of factors related to physical therapy and cancer treatment including demographics and clinical findings influence the HRQoL of patients with GIC. Although physical therapy before surgery was reported to improve HRQoL preoperatively, the impact of postoperative physical therapy interventions remained inconclusive. Considering the limitations of existing research and the results of certain studies [3, 75], it may be concluded that provision of long-term and active postoperative exercise therapy by a physical therapist could lead to improvements in early postoperative HRQoL in patients with GIC. Future studies should verify these results with larger sample sizes and should assess the impact of postoperative exercise therapy that is consistently performed at home under the supervision of a physical therapist and after hospital discharge.

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4 Physical Function and Health-Related QOL in Surgically Treated Patients with Malignant Pleural Mesothelioma

Takashi Tanaka, Yuki Uchiyama, and Shinichiro Morishita

Abstract

Malignant pleural mesothelioma (MPM) is an extremely aggressive thoracic malignancy arising from the parietal pleura, with poor prognosis. In MPM, surgical resection includes either extrapleural pneumonectomy (EPP) or radical or extended pleurectomy/decortication (P/D). P/D is theoretically less radical than EPP and is associated with less perioperative mortality/morbidity and postoperative deterioration of cardiopulmonary function. According to reports, patients with lung cancer have decreased pulmonary function and exercise capacity after surgery. However, to date, physical function and health-related quality of life (HRQOL) after surgery for MPM have not been evaluated in detail in the convalescent phase. At present, there is no established rehabilitation approach for postoperative patients with MPM. In this chapter, we will introduce previous studies that investigated physical exercise function and HRQOL in postoperative patients with MPM, discuss our own research, and introduce the current rehabilitation approach for postoperative patients with MPM.

Keywords

Malignant pleural mesothelioma · Pleurectomy/decortication · Physical function
Health-related quality of life · Health utility

T. Tanaka (✉)
Department of Rehabilitation, Hyogo Medical University Hospital, Nishinomiya, Japan
e-mail: pt-tana@hyo-med.ac.jp

Y. Uchiyama
Department of Rehabilitation Medicine, Hyogo Medical University, Nishinomiya, Japan

S. Morishita
Department of Physical Therapy, School of Health Science, Fukushima Medical University, Fukushima, Japan

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4.1 Introduction

4.1.1 Surgical Treatment of Malignant Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) is an aggressive tumor arising from the mesothelial cells lining the pleura. MPM is a rare malignancy that is difficult to treat, with poor prognosis [1, 2], and its incidence is expected to increase in Asia and developing countries [3]. More than 80% of MPM cases are associated with occupational exposure to asbestos. The incidence has increased over the last 10 years, and this is mainly due to 30–50 years of latency between exposure to asbestos and clinical onset of the malignancy [4]. Because any type of planned surgery would be cytoreductive rather than radical, an optimal outcome via surgery alone is unlikely [3]. Treatment focuses on surgery combined with radiation and/or chemotherapy using a multimodality approach [3, 5]. Two types of curative intent surgery are currently offered: extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D) [6]. The essential objective of surgery is macroscopic complete resection (MCR); adjuvant therapy is required to treat microscopic residual disease [5]. Adjuvant therapy, including radiotherapy or chemotherapy, eliminates the residual microscopic disease at the surgical margins to prevent local recurrence and widespread dissemination. In this context, the surgical treatments for MPM are currently performed in combination with chemotherapy, with or without radiation therapy, as a part of a multimodality therapy. The standard strategies for multimodality therapies remain to be established, and no criteria are currently available to inform decisions on whether to choose EPP or P/D. EPP involves en bloc resection of the lung, pleura, pericardium, and diaphragm. P/D is a lung-sparing surgery that removes only the parietal/visceral pleura. EPP leaves fewer residual tumor cells compared with P/D; however, it often results in high mortality/morbidity, severe depression of cardiorespiratory function, and poor quality of life. To date, the risk–benefit ratios of P/D and EPP as part of multimodal therapy have not been clearly elucidated [3].

Theoretically, P/D is less radical than EPP, even though both are only cytoreductive procedures. However, most hospitals have reported equal or even better survival in patients who underwent P/D than in those who underwent EPP [5, 7–9]. In the context of multimodal therapy, Cao et al. [10], on the basis of their meta-analysis, concluded that selected patients who underwent extended P/D had lower perioperative morbidity and mortality with similar, if not superior, long-term survival, compared with those who underwent EPP. Furthermore, Luckraz and others reported that P/D combined with postoperative adjuvant therapy provided better survival compared with EPP, irrespective of factors such as advanced disease or surgically fewer fit patients [8].

4.1.2 Perioperative Rehabilitation of Malignant Pleural Mesothelioma

A previous study of the physical activity of lung cancer patients showed that individuals with non-small cell lung cancer were less physically active than healthy individuals [11]. In another previous study, at 5 days after lung resection, a significant deterioration in quadriceps strength was observed in a control group, while the strength was maintained in an intervention group that had undergone a training program following the procedure [12]. On the other hand, after lung resection, a significant worsening of effort tolerance and symptomatic status occurred [13]. Other studies showed worsened pulmonary function after lung resection for cancer [14–17]. For example, after lung resection, a significant loss of forced expiratory volume in 1 second (FEV1) and forced expiratory vital capacity (FVC) have been observed [14, 15]. Regarding quality of life (QOL) after lung resection, an average medium decline was observed in the physical domains [16, 17]. Thus, physical function, pulmonary function, and QOL decrease after lung resection for cancer. Likewise, after MPM, there is a possibility of decreases in physical function, pulmonary function, and QOL. We reported that, in patients undergoing P/D, postoperative exercise tolerance and pulmonary function were significantly lower than preoperative values in the acute phase [18]. Moreover, our previous study showed a decrease in health-related quality of life (HRQOL), particularly in the physical components, after P/D. A previous study demonstrated that the 6-minute walking distance (6MWD) improved from 2 weeks postoperatively and was comparable to preoperative values after 6 months. However, pulmonary function remained significantly decreased postoperatively [19].

In another previous study, at 12 months after EPP, significant deterioration was noted in pulmonary function, exercise tolerance, and HRQOL. For HRQOL, this deterioration was predominant in the physical components [20]. Quality-adjusted life-years (QALYs) is a measure of health status that incorporates both quantity and QOL. One QALY is equivalent to 1 year of life in perfect health. QALYs are fundamental for understanding the population burden of disease and the cost-effectiveness of disease treatment. They are estimated using health utility weights, where 1 is equivalent to perfect health and 0 is the worst possible state of health [21, 22]. Previous studies have recently reported that health utility has been used for analyzing various diseases [23–32]. As patients survive acute illness, long-term complications are more apparent. Weakness is a frequent complication and is associated with major disability and protracted rehabilitation [33]. Previous studies have shown the effectiveness of early postoperative rehabilitation [34]. However, there is currently no disease-specific program for postoperative rehabilitation of MPM. Therefore, a postoperative rehabilitation program is generally carried out as for conventional lobectomy. The postoperative rehabilitation of MPM is based on early exercise (mobilization).

Fig. 4.1 The postoperative rehabilitation of MPM is based on early exercise

4.1.3 Physiotherapy

Physiotherapy is promptly commenced the day after the surgery. In general, we instituted early rehabilitation with mobilization (such as sitting, standing, and walking) in the intensive care unit (ICU) or high-care unit five to six times a week (Fig. 4.1) [18].

4.2 Physical Function and Quality-of-Life Assessment

4.2.1 Demographic, Clinical, and Diagnostic Data

The following data are extracted from the medical records of each patient: age, sex, disease stage at surgery, affected side, duration of disease (from initial diagnosis to hospitalization), previous operation, and cycles of chemotherapy received prior to operation.

4.2.2 Handgrip Strength

A standard adjustable-handle dynamometer is used to measure handgrip strength as the index of upper-limb muscle strength and set at the second grip position for all subjects. Attention is paid to a possible Valsalva effect and the grip strength of both hands was measured. The measured data are used as the index of handgrip strength (kilogram-force (kgf)).

4.2.3 Knee Extensor Muscle Strength

Hand-held dynamometers (HHDs) are used to measure knee extensor muscle strength as an index of lower-limb muscle strength (Fig. 4.2). In all sessions, an HHD equipped with a stabilizing belt that the tester held when applying resistance is used.

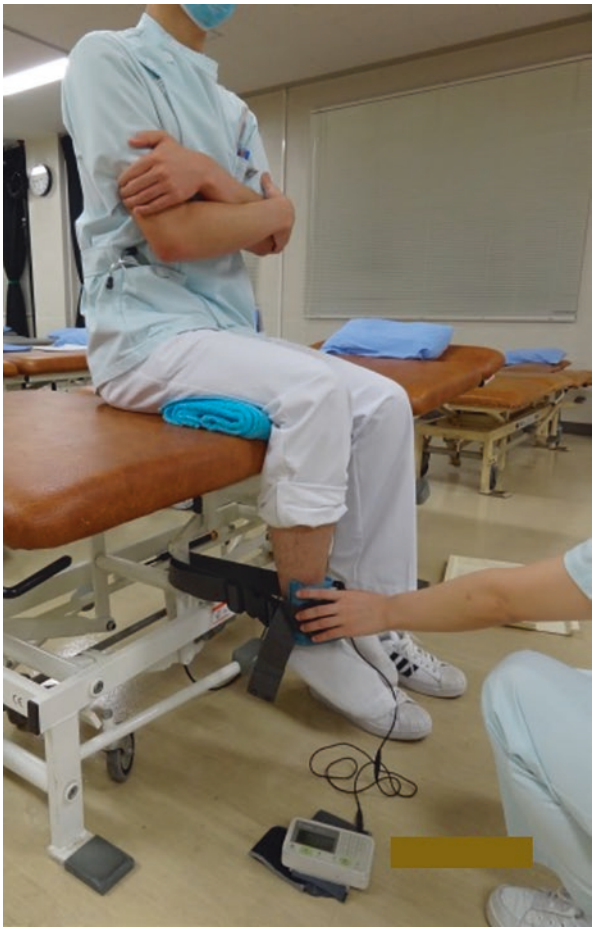

Fig. 4.2 Hand-held dynamometers (HHDs) are used to measure knee extensor muscle strength as an index of lower-limb muscle strength

The HHD is used in the manual mode using kgf units. A previous study showed that the intraclass correlation coefficient (ICC) was 0.98 with a belt and 0.04 without a belt [35]. In a reliability test-retest of the belt-restrained HHD, ICCs ranged from 0.94 to 0.96 [36]. Knee extension force is tested in a sitting position with the knee flexed at approximately 90°. The dynamometer is applied just proximal to the malleoli. The maximum force during 10 s of effort is recorded in kgf. The HHD is reset to kgf at the start of each measurement. Two measurements are conducted for each leg, and the higher value of the two measurements is selected for analysis.

4.2.4 Submaximal Exercise Capacity

Submaximal exercise capacity is assessed using the 6MWD measured in accordance with the American Thoracic Society guidelines. Patients walk up and down a 20-m corridor for 6 min at their own pace. They are encouraged to cover as much

distance as possible but are permitted to rest and continue walking as soon as they felt able or to stop if they experienced symptoms of dyspnea or leg pain. The following data were collected and analyzed: distance after 6 min (in meters), duration (in minutes), and heart rate at both initiation and at 6 min.

4.2.5 Pulmonary Function

Pulmonary function is assessed with spirometry and was measured in accordance with the American Thoracic Society guidelines. FVC and FEV1 are expressed in liters.

4.2.6 Health-Related Quality of Life

Early prediction of treatment response and survival is paramount for cancer patients, allowing clinicians and patients to make decisions according to the patient-specific prognosis. Along with demographic and clinical characteristics, patient-reported outcomes, mainly health-related quality of life (HRQOL), have emerged as prognostic factors [37]. There are various types of quality-of-life assessments for cancer patients, which are tailored to the characteristics of the patient. HRQOL is assessed with the SF-36 by the direct questioning of the subjects. Thus, those who were too confused or too dysphasic to answer were excluded. This self-administered questionnaire has been widely used and validated in the Japanese general population and in patients after P/D. The SF-36 assesses physical and mental health components in eight domains: physical functioning (PF), physical role functioning (RP), bodily pain (BP), general health perceptions, vitality (VT), social role functioning (SF), emotional role functioning, and mental health (MH). The SF-36 measures the multidimensional properties of HRQOL on a scale of 0 to 100, with higher scores indicating better HRQOL. Health utility assess using the Short Form Six-Dimension (SF-6D). The SF-6D measures the strength of preference for a particular health state, and results are represented as numbers between 0 and 1, with 0 being equivalent to death and 1 being equivalent to being alive for a year in perfect health. After the patients were assessed using the SF-36, the scores were converted to mean SF-6D utility scores.

4.3 Physiotherapy Research in the Surgical Field of Malignant Pleural Mesothelioma

As mentioned above, there is a paucity of research in the field of physiotherapy on MPM. Moreover, there are no disease-specific rehabilitation programs, and rehabilitation is carried out in accordance with conventional rehabilitation programs for respiratory diseases. Schwartz et al. performed a literature review on MPM patients to assess and compare QOL changes after P/D and EPP [38]. They reported that,

although the existing evidence is limited and of low quality, their results suggest that P/D patients have better QOL than EPP patients following surgery. QOL outcomes should be factored into the choice of surgical procedure for MPM patients, and the possible effects on lung function and QOL should be discussed with patients when presenting surgical treatment options [38]. Sauter [39] included 36 patients treated with partial pleurectomy who underwent different combinations of chemotherapy and radiation. Their symptoms were collected at baseline and during follow-up using the five grades (0–4) of pulmonary symptoms listed in the National Cancer Institute Common Toxicity Criteria. Dyspnea improved in 47% of patients after surgery, while pain only improved in 21%. Bolukbas [40] included 16 patients treated with radical pleurectomy followed by chemotherapy and radiation. Lung function was measured at baseline and at 2 months following treatment. All functional parameters improved between baseline and follow-up.

We studied 22 patients who underwent P/D and measured physical function (handgrip strength, knee extensor strength test, 6-minute walk distance), pulmonary function (FVC, FEV1), and QOL through the SF-36. The demographic and diagnostic data for the cohort are summarized in Table 4.1. At follow-up, handgrip strength, 6-minute walk distance, FVC, and FEV1 were all statistically significantly decreased, as well as physical functioning, body pain, and vitality as measured by the SF-36. Physiological variables, pulmonary function data, and HRQOL date are summarized in Tables 4.2 and 4.3 [18]. We reported statistically significant decreases in mean (± standard deviation) FVC1 (3.28 ± 0.85 liters to 1.92 ± 0.4 liters; $p < 0.0001$) and FEV1 (2.35 ± 0.59 liters to 1.57 ± 0.37 liters, $p < 0.001$) following P/D [18]. In another study [41], we assessed quality of life using health utility values (SF-6D). Health utility data are summarized in Table 4.4. Preoperative assessments were performed 1 day or 2 days before surgery, and postoperative assessments were performed approximately 3 weeks after surgery. Convalescent

Table 4.1 Patient baseline data ($n = 22$)

Characteristics	
Age (years)	64 (54–77)
Weight (kg)	64.4 (11.8)
Height (m)	1.64 (0.09)
Body mass index (kg/m^2)	23.8 (2.7)
Sex	
Men	20 (91%)
Women	2 (9%)
Disease stage at surgery	
I	12 (55%)
II	8 (36%)
III	2 (9%)
Affected side	
Right	12 (55%)
Left	10 (45%)
Duration of disease (month)	5 (3–8)
Number of chemotherapy cycles	3 (2–5)

Data are given as mean (SD), median (range) or *n* (percent)

Table 4.2 Body weight, strength, submaximal exercise capacity, and lung function

Physiological variables	Before P/D (n = 22)	After P/D (n = 22)	P
Body weight (kg)	64.4 (11.8)	61.4 (11.1)	<0.001
Hand grip (kgf)	34.5 (6.8)	32.6 (7.8)	<0.05
Knee extension (kgf)	38.5 (11.1)	37.2 (10.6)	0.256
6MWD (m)	470.6 (83.8)	399.7 (69.9)	<0.001
FVC (L)	3.28 (0.85)	1.92 (0.40)	<0.001
FEV1 (L)	2.35 (0.59)	1.57 (0.37)	<0.001

Data are given as mean (standard deviation). *P/D* pleurectomy/decortication; *6MWD* 6-minute walk distance; *FVC* forced vital capacity; *FEV1* forced expiratory volume in one second

Table 4.3 Health-related quality of life

SF-36 domain	Before P/D (n = 22)	After P/D (n = 22)	P
Physical functioning	83.6 (11.3)	66.1 (19.4)	<0.001
Role-physical	66.8 (25.7)	49.0 (27.7)	0.073
Bodily pain	67.2 (28.8)	45.1 (25.0)	0.002
General health	53.5 (15.7)	52.6 (14.0)	0.769
Vitality	62.0 (25.1)	47.2 (21.0)	0.005
Social functioning	65.9 (29.7)	56.8 (24.6)	0.084
Role-emotional	71.4 (26.2)	56.8 (28.9)	0.051
Mental health	62.5 (23.9)	56.8 (20.8)	0.121
Physical component summary	43.2 (8.8)	29.0 (15.0)	<0.001
Mental component summary	48.1 (12.8)	46.0 (10.9)	0.171

Data are given as mean (SD). *SF-36* short form 36; *P/D* pleurectomy/decortications. Higher scores indicate better quality of life; domain scores range from 0 to 100

Table 4.4 Health-related quality of life and health utility of patients

	Before P/D (n = 24)	After P/D (n = 24)	1 year after P/D (n = 24)	P (before vs. after)	P (after vs. 1 year after)	P (before vs. 1 year after)
SF-36 domain						
Physical functioning	84.0 (13.9)	62.5 (22.7)	79.4 (13.8)	< 0.001	< 0.001	0.470
Role-physical	67.2 (23.0)	47.9 (28.4)	60.2 (25.8)	0.667	0.903	0.407
Bodily pain	70.7 (22.7)	38.4 (27.1)	65.1 (19.7)	< 0.001	< 0.001	0.618
General health	58.1 (12.7)	47.3 (14.1)	56.0 (16.2)	< 0.001	0.001	0.632
Vitality	59.7 (18.3)	47.9 (15.7)	58.9 (18.4)	0.009	0.015	0.975
Social functioning	70.3 (25.5)	56.3 (27.6)	73.4 (24.0)	0.032	0.007	0.832
Role-emotional	68.7 (24.8)	55.6 (29.5)	68.4 (23.6)	0.059	0.068	0.998
Mental health	67.5 (18.3)	58.1 (17.4)	71.5 (15.1)	0.028	0.001	0.505
Physical component summary	43.4 (8.9)	25.6 (14.8)	39.5 (7.9)	< 0.001	0.001	0.283
Mental component summary	50.0 (8.9)	46.5 (8.0)	52.0 (9.3)	0.060	0.006	0.646
SF-6D	0.61 (0.12)	0.52 (0.10)	0.61 (0.11)	< 0.001	< 0.001	0.896

Data are provided as mean (SD). *P/D* pleurectomy/decortications; *SF-36* short form 36. Higher scores indicate better quality of life; domain scores range from 0 to 100, SF-6D, Short-Form Six-Dimension. Higher scores indicate better utility; domain scores range from 0 to 1

phase assessments were performed 1 year after surgery. After discharge, there was no rehabilitation intervention. Interestingly, 1 year after surgery, 6-minute walk distance, and health utility values were improved to the same levels as those before surgery.

4.4 Conclusion

MPM is a rare disease, and there is no disease-specific physical therapy approach at present. Further studies are needed to develop rehabilitation programs specific to patients with MPM. Although the existing evidence is limited and of low quality, QOL outcomes should be factored into the physical therapy approach of MPM patients, and the possible effects on lung function and QoL should be discussed with patients.

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5 Muscle Mass, Cachexia, and Health-Related Quality of Life in Patients with Hematologic Malignancies

Shun Ishii, Keisuke Hirota, and Jiro Nakano

Abstract

Treatment for hematologic malignancies may result in physical symptoms such as pancytopenia secondary to nutritional deficiencies and bone marrow suppression, nausea, vomiting, anorexia, cancer-induced fatigue, and mental symptoms including anxiety and depression and symptoms associated with the hematologic malignancy itself. These symptoms lead to decreased physical activity, particularly in patients who receive prolonged inpatient treatment. Patients with hematologic malignancies undergo unfavorable body composition changes during active treatment owing to physical inactivity, catabolic effects of cytotoxic, and immunosuppressive therapies, as well as metabolic changes and myopathy secondary to long-term glucocorticoid administration. Therefore, patients with hematologic malignancies are at a high risk of muscle dysfunction and reduced quality of life (QOL). Physical therapy is increasingly being recognized as an important intervention to improve muscle function and QOL. Rehabilitation to improve function and QOL of patients with malignancies usually involves mid- or high-intensity aerobic and resistance exercises. However, mid- or high-intensity exercise is often challenging in patients with hematologic malignancies owing to treatment-induced adverse effects. Fukushima et al. reported that high-frequency low-intensity exercise therapy was useful to maintain muscle function and improve physical function, mental and physical symptoms, and QOL in

S. Ishii (✉)
Department of Rehabilitation, Michinoo-Miyata Orthopaedic Clinic, Nagasaki, Japan

K. Hirota
Division of Rehabilitation, Kurume University Hospital, Fukuoka, Japan

J. Nakano
Faculty of Rehabilitation, Kansai Medical University, Osaka, Japan

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patients with hematologic malignancies, who underwent chemotherapy. We observed that a behavioral change intervention with feedback on physical function and physical activity may improve voluntary exercise and physical function in patients with hematologic malignancies, who receive chemotherapy. Reportedly, neuromuscular electrical stimulation and whole-body electromyostimulation (WB-EMS) during active oncological treatment safely and effectively improve muscle and physical function and QOL in patients with hematologic cancer. Therefore, this approach may effectively improve muscle function and QOL in patients with hematologic disorders, who are unable to perform mid- or high-intensity exercise as an alternative to low-intensity exercise therapy, behavioral change intervention, and WB-EMS.

Keywords

Low-intensity exercise therapy · Behavioral change interventions · Neuromuscular electrical stimulation

5.1 Introduction

Approximately 918,000 and 45,000 patients are annually diagnosed with hematologic malignancies worldwide and in Japan, respectively [1, 2]. Notably, 40,000 newly diagnosed cases of hematologic malignancies were recorded and accounted for approximately 19,000 deaths in Germany in 2013 [3]. Hematologic malignancies primarily include leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma. Treatment regimens used for these diseases are complex and include high-dose chemotherapy and total-body irradiation, probably pre- or post hematopoietic stem cell transplantation (HSCT). Although improved therapeutic modalities have increased patient survival over the past few years, therapy induced adverse effects are known to be associated with mortality in patients with hematologic malignancies [4–6]. Furthermore, chemotherapy for hematologic malignancies can induce physical symptoms such as pancytopenia secondary to nutritional deficiencies and bone marrow suppression [7–10], nausea, vomiting, anorexia [7, 11], cancer-induced fatigue [12], and mental symptoms including anxiety and depression [13, 14] and symptoms associated with the malignancy itself. These symptoms lead to decreased physical activity, particularly in patients who receive prolonged inpatient treatment [15–17]. Patients with hematologic malignancies undergo unfavorable body composition changes during active treatment owing to physical inactivity, catabolic effects of cytotoxic and immunosuppressive therapies, and metabolic changes and myopathy secondary to long-term glucocorticoid administration [18–20]. Therefore, patients with hematologic malignancies are predisposed to muscle dysfunction and poor quality of life (QOL). Physical therapy is increasingly being recognized as an important intervention to improve muscle function and QOL. In this chapter, we will discuss muscle mass, cachexia, and health-related QOL (HR-QOL) in patients with hematologic malignancies.

5.2 Muscle Mass and Cachexia

Muscle degradation is a particularly important concern among the negative effects of cancer on physical function. Treatment-associated muscle weakness also leads to functional decline that may be observed in cancer survivors [21, 22]. Vermaete et al. [23] reported that patients with hematologic malignancies show decreased muscle strength, including handgrip and quadriceps strength, which is observed during the pre-treatment period. Moreover, handgrip and isometric knee extensor strength were lower in these patients than in healthy controls [24].

In addition to decreased muscle strength, patients with hematologic malignancies tend to show loss of muscle mass. Fat mass increases during and after oncological therapy; however, muscle mass tends to decline. These alterations are usually irreversible, and muscle mass and strength are not restored to pre-illness and pre-treatment levels and may result in sarcopenic obesity, which may predispose patients to other metabolic diseases in the future [25–27]. Morishita et al. [25] observed that among 164 patients with hematologic malignancies in whom skeletal muscle mass (SMM) was measured using bioimpedance analysis, >50% of patients showed values below the cutoff value for sarcopenia. Xiao et al. [26] also reported that among 522 patients with lymphoma, who underwent computed tomography for skeletal muscle area measurement at the L3 vertebral level, 47% were diagnosed with sarcopenia. Hirota et al. [28] measured the visceral fat area (VFA), subcutaneous fat area (SFA), and psoas muscle area (PMA) at the L3 vertebral level in 25 patients with malignant lymphoma, pre- and post autologous HSCT (auto-HSCT). SMM was evaluated based on the psoas muscle index (PMI), and the PMI was calculated by normalization of the PMA (measured at the L3 level) by the square of the height (m^2) (Fig. 5.1). The PMI and VFA were significantly decreased after auto-HSCT. In fact, the total body and lower extremity SMM was lower in patients with hematologic malignancies than in healthy controls [24]. Fukushima et al. [29] measured the thickness of the vastus intermedius and rectus femoris muscles in patients with hematologic malignancies (Fig. 5.2) and observed that the lymphocyte count, geriatric nutritional risk index, and physical activity were significantly associated with

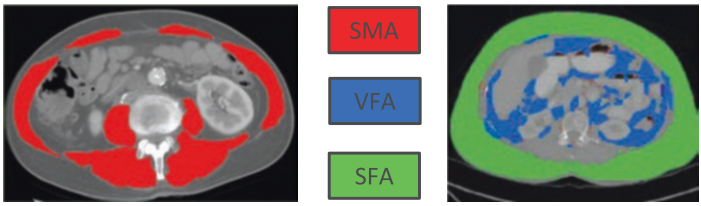


Fig. 5.1 Measurement of the skeletal muscle area, visceral fat area, and subcutaneous fat area. (1) SMA: Measurement of muscle mass using CT at the L3 vertebral level. Muscles in the L3 region consist of psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis. (2) VFA, SFA: Measurement of fat mass at the umbilical level. (3) SMI = The SMA value divided by the square of height. *CT* computed tomography; *SFA* subcutaneous fat area; *SMA* skeletal muscle area; *SMI* skeletal muscle mass index; *VFA* visceral fat area

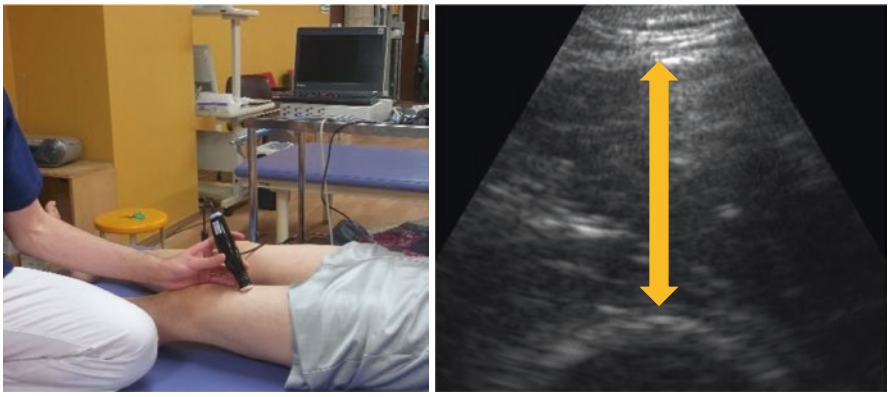


Fig. 5.2 Measurement of the thickness of the vastus intermedius plus rectus femoris muscles. Muscle thickness is measured using an ultrasound device with the patient placed in the supine position, with the legs flat and relaxed in extension. A straight line is drawn between the anterior superior iliac spine and the upper margin of the patella, and it is measured 10 cm proximal to the patella on this line

Table 5.1 Stages of cancer cachexia

Pre-cachexia	Cachexia	Refractory cachexia
• Weight loss ≤5% • Anorexia and metabolic change	• Weight loss >5% or BMI <20 and weight loss >2% or sarcopenia and weight loss >2% • Often reduced food intake/systemic inflammation	• Variable degree of cachexia • Cancer disease both procatabolic and not responsive to anticancer treatment • Low performance score • <3 months' expected survival

muscle thickness. Furthermore, muscle degradation in patients with hematologic malignancies may be affected not only by a decrease in the amount of physical activity but also by factors such as cancer cachexia, which is a characteristic of cancer. Cancer cachexia is defined as a multifactorial syndrome characterized by an ongoing loss of SMM (with or without loss of fat mass) that is not fully reversible with conventional nutritional support and invariably leads to progressive functional impairment (Table 5.1) [30]. A study has shown that 40% of patients with hematologic malignancies had cachexia [31]. The Glasgow prognostic score (GPS) is often used to classify cachexia in patients with hematologic malignancies and serves as an indicator of nutritional status and considers independent prognostic factors based on inflammatory markers, such as serum C-reactive protein (CRP) and albumin levels [32]. Patients were categorized into the following groups: patients with both elevated CRP (>10 mg/L) and hypoalbuminemia (<3.5 g/L) were defined as those with cachexia, patients with either biochemical abnormality were defined as those with pre-cachexia, and patients without either abnormality were defined as those without cachexia (Fig. 5.3). The association between low food intake, a systemic inflammatory response, and GPS has been reported previously [33]. Reportedly, the GPS objectively defines cachexia [34]. Based on the GPS, Fukushima et al. [24] observed

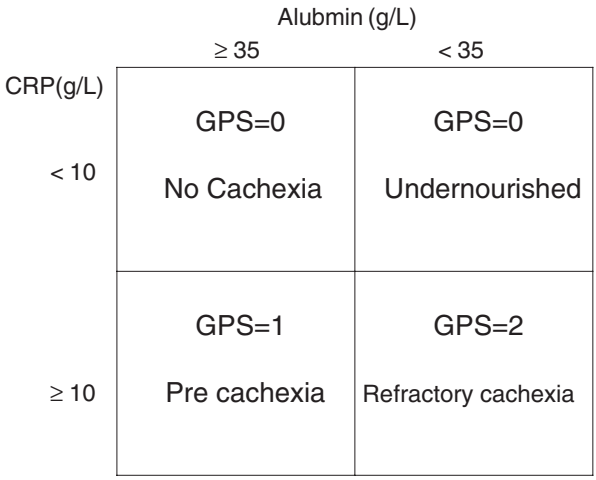


Fig. 5.3 The Glasgow Prognostic Score (GPS)

cachexia in 23.9% of patients with hematologic malignancies. Patients with hematologic malignancies may be better to evaluate cachexia, as it may be a cause of muscle loss.

5.3 Health-Related Quality of Life

Several studies have shown that hematologic disease negatively affects patients' overall QoL [35–38]. Compared with the general population, patients with advanced-stage hematologic malignancies typically show fatigue, pain, and decline in stamina, which are the prominent determinants of QoL [39, 40]. The QoL or HR-QoL is poorer in patients with hematologic malignancies than in the general population [41, 42]. Go et al. [43] reported that sarcopenia was associated with intolerance to chemotherapy and poor prognoses in patients with lymphoma. Muscle wasting and physical deconditioning not only enhance symptoms of fatigue but also significantly negatively affect patients' QoL, reduce therapy options, and worsen prognosis [15, 16, 25, 44–46]. Therefore, management of symptoms and declining physical function are crucial in patients with hematologic malignancies, who undergo chemotherapy.

Aerobic and resistance exercises are the common components of rehabilitation to improve QOL in patients with malignancies. Several clinical studies have investigated the effects of exercise in patients with hematologic malignancies [47, 48]. Streckmann et al. [47] showed that over 36-week aerobic, resistance, and balance exercises significantly improved QOL in patients with lymphoma. Similarly, Knols et al. [48] observed that walking exercises produced positive effects on the QOL in patients who underwent HSCT. Therefore, exercise is considered a useful intervention to improve physical function, symptomatology, and QOL in patients with hematologic malignancies. However, the use of mid- or high-intensity exercise is often challenging in patients with hematologic malignancies because of the

aforementioned effects of chemotherapy. Therefore, physical therapists need to devise novel methods to improve physical function and QOL without mid- or high-intensity exercise in this patient population.

5.4 Low-Intensity Exercise Therapy

The American Cancer Society guideline [49] provides the following pre- and post-treatment recommendations for patients with cancer: (a) Adults should engage in at least 150 min of moderate- or 75 min of vigorous-intensity activity each week or an equivalent combination, preferably spread throughout the week. (b) Children and adolescents should engage in at least 1 h of moderate- or vigorous-intensity activity each day, with vigorous-intensity activity performed at least 3 days/week. (c) Limit sedentary behavior such as sitting, lying down, watching television, or other forms of screen-based entertainment. (d) Some physical activity in addition to usual activities, regardless of the level of activity, should be performed for its many health benefits. However, it is often difficult to adopt these guidelines in patients with hematologic malignancies who undergo chemotherapy or HSCT because of physical and psychological issues. Therefore, low-intensity exercise focused on activities of daily living (ADLs) such as walking and standing is often encouraged in patients with hematologic malignancies in whom mid- or high-intensity exercise is difficult. Several recent studies have reported the effects of low-intensity exercise. Carballeira et al. [50] reported that 20 min of cycling training 3 days/week at low-to-moderate intensity improved body composition and increased walking and balance performance in only 6 weeks in older adults with multimorbidity. Furthermore, Tai Chi and resistance training at different intensities could alleviate cancer-related fatigue symptoms and improve the QoL of middle-aged and elderly patients with cancer [51]. Chang et al. [52] reported that 12 min of walking exercise performed over 3 weeks is clinically feasible for patients with acute myelogenous leukemia, who undergo chemotherapy and can effectively improve fatigue-induced symptoms. Studies have also reported that low-intensity exercise, such as walking reduces psychological distress [53]. Therefore, high-frequency low-intensity exercise therapy is expected to reduce anxiety and depression. Fukushima et al. [54] investigated the effects of low-intensity exercise on physical function and QOL in patients with hematologic malignancies, who underwent chemotherapy. Patients hospitalized for chemotherapy underwent low-intensity exercise therapy (Fig. 5.4) and were categorized into high- and low-frequency groups based on their exercise frequency. Muscle function was maintained, and physical function, ADLs, psychological distress, and QOL were significantly improved in the high-frequency group. However, lower extremity muscle function was significantly reduced without any other improvement in the low-frequency group (Fig. 5.5). Significant interactions were observed between the high- and low-frequency groups only with regard to cognitive function and insomnia symptoms on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. Global health, physical, role, emotional

Fig. 5.4 Examples of low-intensity exercise therapy. (**a**) Cycle ergometer exercise in the hospital room. (**b**) Walking in the hospital corridor. (**c**) Exercise in the hospital room using the resistance band

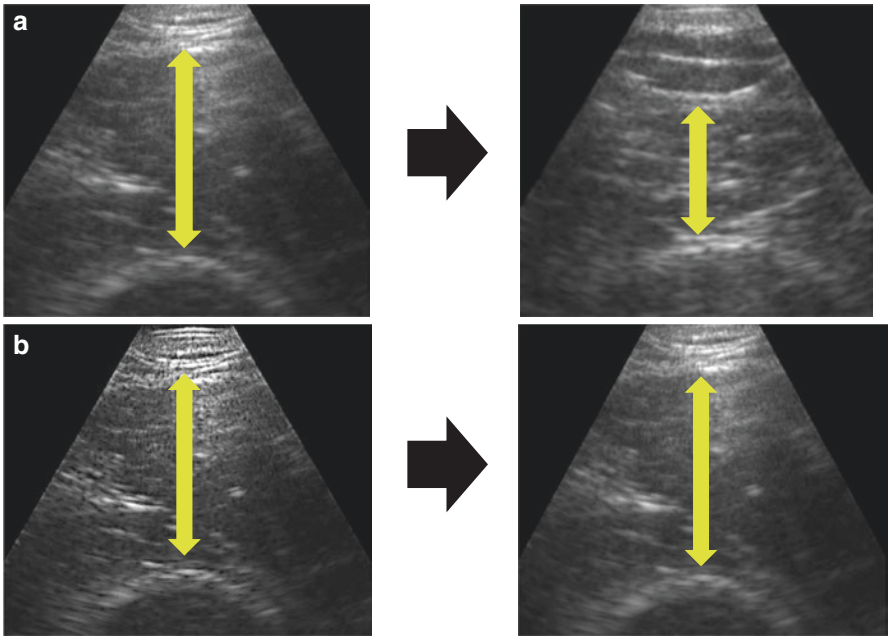


Fig. 5.5 Effect of high-frequency low-intensity exercise therapy. (**a**) Muscle thickness is reduced following low-frequency low-intensity exercise therapy. (**b**) Muscle thickness is maintained following high-frequency low-intensity exercise therapy

and cognitive functioning, fatigue, pain, and insomnia were significantly improved on the symptom scale in the high-frequency group. In contrast, we observed no improvement in the low-frequency group. Therefore, low-intensity exercise therapy could be a potentially useful treatment strategy for patients with hematologic malignancies, who undergo chemotherapy and are unable to perform mid- or high-intensity exercise.

5.5 Behavioral Change Interventions

Reportedly, increased physical activity is associated with improved QOL in patients with hematologic malignancies [55]. Therefore, based on the known association between QOL and the amount of physical activity, physical therapy is encouraged for improvement in the amount of physical activity in daily life. Patient education is viewed as a behavioral change intervention to improve the amount of physical activity in patients who have difficulty with mid- or high-intensity exercise [56]. Behavioral change intervention is a therapeutic practice that has evolved from psychotherapy to prevent maladaptive behaviors and establish new, more adaptive behaviors based on learning and behavioral theories. Recent studies have discussed the use of behavioral change in the medical field for prevention and treatment of chronic lifestyle-related diseases [57]. Behavioral change refers to an individual's progress through different stages to intentionally modify her/his behavior. This method consists of the following five stages of change, which in the context of physical activity refers to the readiness or propensity to engage in regular exercise (Fig. 5.6) [58]:

- *Precontemplation stage*: An individual in this stage is not engaged in regular exercise and has no intention of beginning an exercise plan in the future.
- *Contemplation stage*: A contemplator is an individual who is not currently exercising but is committed and plans to begin an exercise regimen.
- *Preparation stage*: An individual in this stage seriously considers beginning an exercise program and also initiates some action to achieve that objective, albeit unsuccessfully.
- *Action stage*: An individual in this stage is one who has been exercising consistently.
- *Maintenance stage*: An individual in this stage is one with an active lifestyle.

Knowledge of these stages and personalized feedback to users is often an effective strategy to ensure sustained behavioral change toward achieving a more active lifestyle. The following are the stage-specific intervention strategies to achieve consistent behavioral change toward a physically active lifestyle (Table 5.2):

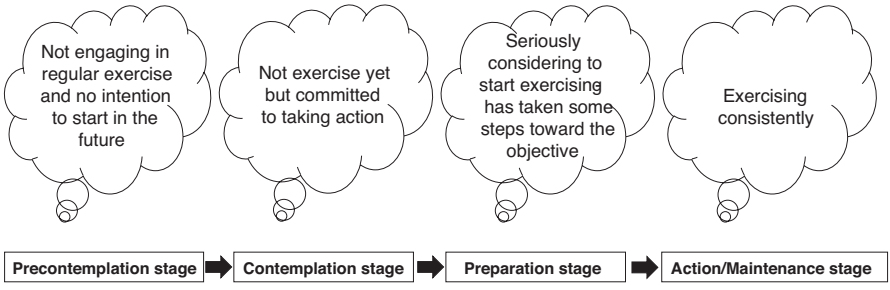


Fig. 5.6 Five stages of behavior change

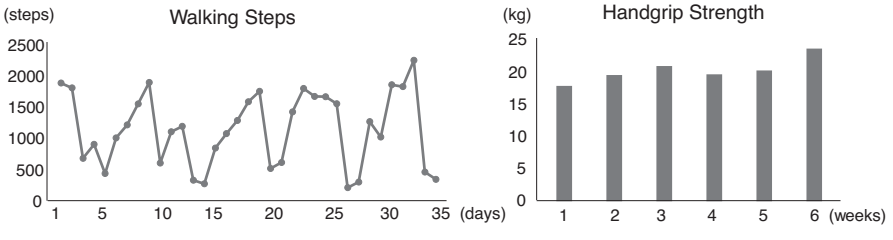
Table 5.2 Specific intervention strategies for each stage of behavior change

Stages of behavior change	Intervention strategies
Precontemplation stage Contemplation stage	• Education (nonbelievers in exercise) • Increase the importance of the cognitive dissonance (believers in exercise) • Increase users' awareness of their current behavioral patterns
Preparation stage	• Education • Increase the importance of the cognitive dissonance • Persistent visual feedback to increase users' awareness of their current behavioral patterns
Action stage	• Persistent visual feedback to monitor physical activity levels and to keep track of progress • Elements of social support
Maintenance stage	• Persistent visual feedback to increase the awareness of achieved results • Overcome problems arising • Stronger elements of social support

- *Precontemplation stage*: Actions targeted at precontemplators should be directed to motivate these individuals. For example, the detrimental effects of sedentary behavior and the benefits of adopting a healthy lifestyle should be highlighted. It is important to categorize nonbelievers and believers in exercise. The former do not typically have the intention to change their behavior and do not believe in the benefits of exercise. Therefore, patient education and improved awareness regarding the health benefits of regular exercise should be the focus in this stage [59]. Believers in exercise are expected to experience a psychologically uncomfortable cognitive dissonance between their positive attitude toward exercise and their actual sedentary behavior. These individuals try to reduce the dissonance based on their motivation to engage in regular exercise (a) by changing their attitude, (b) by changing their behavior, or (c) by reducing the importance of the dissonance. Educational strategies directed at these stagers should be focused on emphasizing the importance of this cognitive dissonance to encourage these individuals to take the first step toward physical activity.
- *Contemplation stage*: Contemplators consider changing their behavior but have not yet begun an exercise program. Similar to the previous stage, educational strategies and interventions aimed at emphasizing the importance of the cognitive dissonance may achieve a sustained initial behavioral change, albeit inconsistent. Persuasive visual feedback should be aimed at improving users' awareness of their current level of physical activity without making them uncomfortable [59].
- *Preparation stage*: Individuals in this stage are more motivated than precontemplators and contemplators to change their behavior and have begun exercise, although inconsistently. Education remains a useful tool to increase the cognitive dissonance in this stage. Persistent visual feedback that improves users' awareness of their behavioral patterns, and rewards for exercise should be provided [59]. Elements of social support and peer pressure should be provided optionally.

- *Action stage*: Individuals in this stage have been consistently exercising. Persuasive technologies help users monitor their exercise behavior and their progress toward their objectives to achieve consistency [59].
- *Maintenance stage*: Individuals in this stage have consistently performed the desired behavior. These individuals should receive interventions to improve awareness of their achieved results and to overcome potential issues [59]. Strong social support should be provided.

Interventions directed at behavioral change reportedly improve physical symptoms such as pain and fatigue in patients treated for cancer [60]. A systematic review and meta-analysis of physical activity and behavioral change interventions in recent post-treatment breast cancer survivors showed that the following behavioral change interventions effectively improved physical activity: the use of a pedometer or accelerometer to monitor physical activity, behavioral counseling via phone and e-mail, face-to-face interviews, counseling from a healthcare provider, supervised exercise sessions combined with cognitive behavioral therapy, tailored counseling sessions, and group discussions regarding perceived barriers and goals associated with physical activity [56]. We investigated the effects of a behavioral change intervention on patients with hematologic malignancies [61]; we measured physical activity using an accelerometer immediately after chemotherapy in these patients. Physical function was thereafter evaluated on a weekly basis with patient education through distribution of pamphlets showing the results of physical function and physical activity (Fig. 5.7). We explained the effectiveness and safety of exercise therapy and improvement in physical activity to patients with decreased physical



	Goal	Result	Comment
Walking Steps	3000steps	1307steps	The number of steps is a little low. Let's walk a little more according to your physical condition.
Handgrip Strength	20kg	23.7kg	You have achieved your goal. Let's maintain the physical function.
Knee Extensor Strength	30kgf	22.7kgf	You are almost to our goal. Let's exercise according to our physical condition.
10m Walking Time	10seconds	7.13seconds	You have achieved your goal. Let's maintain the physical function.

Fig. 5.7 Examples of pamphlets containing the results of physical function and physical activity

function and physical activity and advised avoiding excessive rest and sedentariness and motivated patients to establish specific goals and practice independently. Patients with improvement in physical function and physical activity were instructed to monitor their pulse rate and fatigue during exercise and modify their goals following discussion with the physical therapist to increase the amount of exercise. Patients with hematologic malignancies, who underwent chemotherapy, were categorized into those who underwent conventional rehabilitation (control group) and those who received a behavioral change intervention with feedback on motor function and physical activity (feedback group). We performed intergroup comparison of changes in motor function and physical activity from the commencement of rehabilitation until discharge. We observed a significant difference in walking speed between baseline and discharge. Changes in weekly steps were significantly higher in the feedback than in the control group.

Figure 5.8 shows the combination of exercise and behavioral change interventions adopted in these patients. The basic policy recommends mid- or high-intensity exercise in patients in whom the amount of physical activity is maintained. Mid- or high-intensity exercise with behavioral change intervention is recommended to improve physical function and QOL in patients with low physical activity but mild physical and mental symptoms. We aim to increase physical activity and improve QOL through a combination of low-intensity exercise and behavioral change intervention in patients with severe physical and mental symptoms.

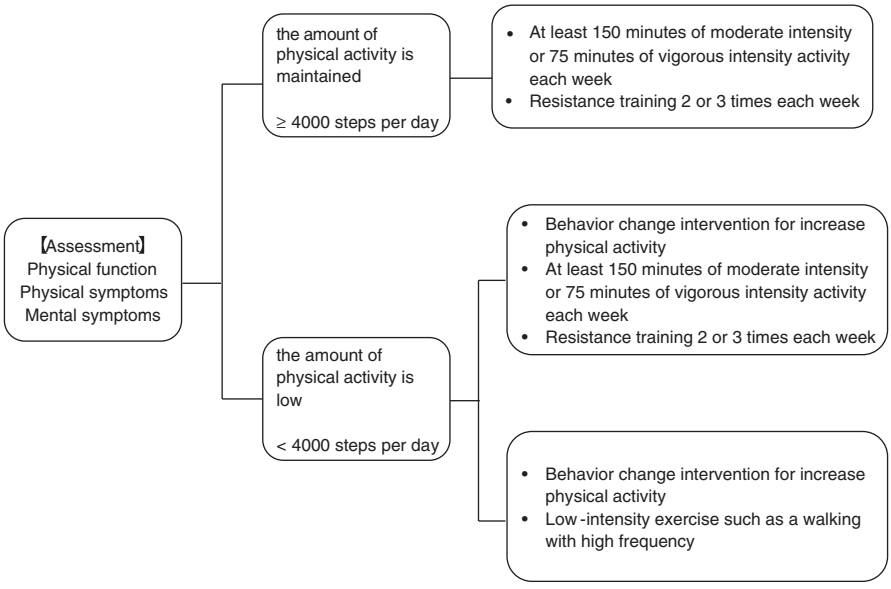


Fig. 5.8 Combination of exercise and behavioral change interventions

5.6 Neuromuscular Electrical Stimulation and Whole-Body Electromyostimulation

Even low-intensity exercise and behavioral change interventions are often difficult to perform in patients with hematologic malignancies, who present with severe fatigue. Patients with impaired functional status often experience exercise-limiting symptoms during treatment; in essence, as few as 5% of patients who undergo treatment are physically active [62]. Therefore, it is necessary to devise exercise protocols that can be used during cancer treatment to prevent the loss of muscle mass and physical function [63].

Neuromuscular electrical stimulation (NMES) and whole-body electromyostimulation (WB-EMS) are emerging fields in oncology rehabilitation (Fig. 5.9). High-frequency NMES has a proven muscle strengthening effect at frequencies ≥20 Hz in healthy individuals as well as in patients [64]. Emerging evidence suggests that low-frequency NMES (4 Hz) can elicit a comfortable and sustainable aerobic exercise response and enhance aerobic exercise capacity and exercise endurance in

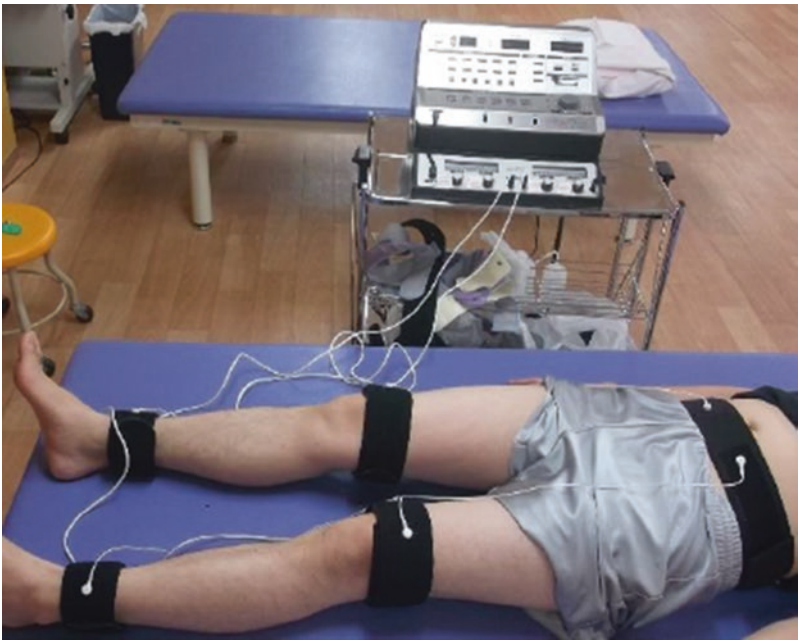


Fig. 5.9 Examples of neuromuscular electrical stimulation. Among various NMES devices available in clinical practice, B-SES uses a belt-shaped electrode placed around the lower trunk, thighs, and ankles. B-SES simultaneously induces muscle contraction in both the knee extensor and flexor muscles. *B-SES* belt electrode skeletal muscle stimulation; *NMES* neuromuscular electrical stimulation

healthy individuals as well as in patients [65, 66]. Recent studies have confirmed the safety, feasibility, and improvement in functional outcomes and QOL associated with NMES in patients with mixed cancer diagnoses [67]. WB-EMS serves as a novel, time-saving, and user-friendly option in patients with hematologic malignancies. WB-EMS includes mild physical exercises that enable the simultaneous activation of nearly all large muscle groups via electrodes incorporated into a vest and belt. Studies have confirmed the efficacy of WB-EMS in increasing muscle strength and mass in elderly and sedentary individuals and in patients with chronic heart failure [68–70]. Similar to its benefits in patients with advanced solid cancers [71], WB-EMS may also be useful in patients with hematologic malignancies and may be superior to exercise alone in stabilizing or even increasing SMM.

O'Connor et al. [72] investigated the effects of NMES in patients with advanced cancer and poor performance status. The NMES intervention was implemented over 4 weeks, and 10 of 18 participants completed the study. No adverse events were observed. Notably, seven of eight participants showed improved performance in the 6-min walk test, eight of ten participants showed improved performance in the 30-s sit-to-stand test, and eight of ten participants showed improved global QOL. The authors concluded that NMES appears to be safe and feasible in patients with advanced cancer and may improve physical outcomes and HR-QoL. Schink et al. [73] investigated the effects of combined supportive exercise and nutritional intervention using WB-EMS training and individualized nutritional support in patients who received active treatment for hematologic malignancies. In a controlled pilot trial, 31 patients with various hematologic malignancies were assigned to a control group (n = 9) that received nutritional support with standard care including a high-protein diet (>1.0 g/kg/day) and a physical exercise group (n = 22) in which participants additionally received WB-EMS training twice weekly for 12 weeks. No WB-EMS-induced adverse effects occurred in any participant. The SMM was higher in patients who performed the exercise program than in controls after 12 weeks. In contrast, the fat mass percentage was higher in the control group than in the WB-EMS group. Moreover, serum triglycerides were increased in the control group in contrast to a decrease in serum triglycerides in the WB-EMS group. Compared with the control group, the WB-EMS group showed significantly improved physical functioning, indicated by a greater increase in the 6-minute walking distance. Although we observed no significant intergroup differences, patients in the physical exercise group showed greater improvements in psychosocial functioning, indicative of improved social and role functioning. Patients in the exercise group also showed a definite increase in global health/overall QOL, following 12-week WB-EMS training. Intra-group analysis revealed significant amelioration of insomnia, a common symptom in patients with hematologic cancer. The authors concluded that WB-EMS may serve as a safe and effective therapeutic intervention during active oncological treatment in patients with hematologic cancer.

5.7 Conclusion

Treatment of hematologic malignancies can result in physical symptoms such as pancytopenia secondary to nutritional deficiencies and bone marrow suppression, nausea, vomiting, anorexia, cancer-induced fatigue, and mental symptoms including anxiety and depression and symptoms of the hematologic malignancy itself, all of which lead to decreased physical activity in this patient population. Patients with hematologic malignancies are at a high risk of muscle dysfunction and poor quality of life (QOL) owing to physical inactivity. Therefore, physical therapy is increasingly being recognized as a useful intervention to improve muscle function and QOL. Rehabilitation to improve muscle function and QOL in patients with malignancies usually includes mid- or high-intensity aerobic and resistance exercises. Low-intensity exercise therapy, behavioral change intervention, and WB-EMS may be effective to improve muscle function and QOL in patients with hematologic disorders, who are unable to perform mid- or high-intensity exercise. However, few studies have discussed these approaches in patients with hematologic malignancies. Further studies are warranted to conclusively establish the optimal physical therapy regimen for patients with hematologic malignancies.

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6 Exercise Capacity and Health-Related Quality of Life in Patients After Lung Resection for Non-small Cell Lung Cancer

Masato Oikawa, Masatoshi Hanada, and Ryo Kozu

Abstract

The number of lung cancer patients has been increasing worldwide. The most effective treatment for non-small cell lung cancer (NSCLC) is complete surgical resection with curative-intent treatment. In the perioperative period, physiotherapy may be administered. The aim of this approach is to prevent complications during the early postoperative period and to improve activities of daily living. This is in line with the common postoperative goals, such as recovery of physical function and enhanced recovery of health-related quality of life (HRQoL). Furthermore, the goals of physiotherapy are shifting from targeting short-term outcomes alone (such as reducing postoperative complications) to targeting long-term outcomes (such as functional exercise capacity and HRQoL) as well. In this chapter, we aimed to describe the clinical issues related to postoperative exercise capacity and HRQoL in patients who underwent lung resection based on previous studies. In addition, we aimed to present our clinical research based on limitations of previous studies.

Keywords

Non-small cell lung cancer · Surgery · Exercise capacity · Health-related QOL

Author's expertise was scientific research on exercise capacity and health-related QOL after lung resection for non-small cell lung cancer.

M. Oikawa (✉) · M. Hanada · R. Kozu
Cardiorespiratory Division, Department of Rehabilitation Medicine, Nagasaki University Hospital, Nagasaki, Japan

Department of Physical Therapy Science, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
e-mail: m-oikawa@nagasaki-u.ac.jp

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6.1 Introduction

Malignant neoplasm is the leading cause of death in Japan. In particular, lung cancer is the third most commonly diagnosed cancer and the leading cause of cancer-related deaths worldwide [1, 2]. In cases of early-stage lung cancer, surgical intervention is the best curative option [3]. Currently, more than 40,000 patients undergo surgery annually in Japan [4]. Multiple surgical techniques, such as wedge resection, segmentectomy, lobectomy, and pneumonectomy, have been developed for surgical intervention in lung cancer patients. Moreover, surgical techniques, such as thoracoscopic surgery, have been developed to reduce tissue damage. Although less often, surgical interventions may also be performed in high-risk patients, such as the elderly and those with comorbidities. Even if surgical techniques are available, the importance of postoperative management by medical staff, such as nurses and physiotherapists, does not change. In particular, physiotherapy involves not only hospitalization but also an increasing need to follow patients from preoperatively to long-term postoperatively. In this chapter, we describe exercise capacity and health-related quality of life (HRQoL), which are particularly important for the long-term postoperative outcomes of patients with lung cancer.

6.2 Physiotherapy in Patients for Non-small Cell Lung Cancer (NSCLC)

The aim of physiotherapy performed in the perioperative period is to prevent complications during the early postoperative period, to improve activities of daily living (ADL) and physical function postoperatively, and to enhance the recovery of HRQoL.

Programs and regimens of physiotherapeutic interventions during the perioperative period have changed over the past decade. In the past, perioperative physiotherapy for lung cancer patients was frequently limited to respiratory interventions, such as breathing exercises and postural drainage in the immediate postoperative setting. These measures aim to prevent postoperative pulmonary complications (PPCs), such as atelectasis, bronchospasm, and pneumonia [5]. In this decade, early mobilization has become more important than respiratory physiotherapy during the early postoperative period to prevent PPCs. Early mobilization, a perioperative management technique, is a typical intervention for enhancing recovery after surgery (ERAS). The ERAS program for patients undergoing lung cancer surgery has been shown to effectively accelerate postoperative recovery and save hospitalization costs without compromising patient safety [6]. Short-term postoperative outcomes have improved due to the development of surgical techniques and postoperative management, such as the ERAS program.

The timing of intervention in physiotherapy, which was limited to immediately after surgery, has expanded from the preoperative period to the long-term postoperative period.

In Japan, the hospital mortality of patients undergoing lung resection is less than 1%, and most patients have no complications with ADLs following their discharge from the hospital [7]. However, recently, the number of patients who are at a high risk of developing postoperative complications has been increasing. The following risk factors have been identified for acquiring postoperative complications: older age, poor general condition, coexistence of chronic heart failure and chronic obstructive pulmonary disease, weight loss, and malnutrition. In addition, high-risk patients may have problems after discharge even if they do not develop complications. Therefore, physiotherapy, which includes exercises, should be considered a part of the management during the pre- and postoperative periods for high-risk patients.

Preoperative physiotherapy (exercise training) performed as pre-rehabilitation may reduce the risk of developing PPCs, the duration of chest drain use, and the postoperative length of hospital stay and may improve both exercise capacity and pulmonary function in people undergoing lung resection for lung cancer [8]. Exercise training improves exercise capacity, peripheral muscle strength, HRQoL, and dyspnea following lung resection for lung cancer [9].

Thus, the purpose and interventions of perioperative physiotherapy are changing over time, and the outcomes of physiotherapy have changed from the incidence of postoperative complications to postoperative physical function and HRQoL.

6.3 Exercise Capacity in Patients with NSCLC

6.3.1 Exercise Capacity

Exercise capacity is defined as the maximum amount of physical exercise that a patient can sustain [10] and is associated with cardiovascular and respiratory functions. Most diseases affecting the cardiovascular or respiratory system cause progressive loss of physiological function and impair the reserve capacity of these systems. The decline in cardiac and respiratory reserves has only been tested during exercise in the early stages of the disease. By assessing the maximum capability of the patients, the medical staff evaluates the reserve capacity of each organ system that contributes to the exercise response.

In lung cancer, the reserve capacity of each organ system is related to postoperative complications, and exercise testing is most commonly used for assessing the operating risk [11]. In recent years, exercise testing has also been performed to clarify the postoperative exercise capacity of lung resection and nonsurgical patients, such as those with advanced lung cancer [9, 12]. Granger et al. recommended implementation of laboratory cardiopulmonary exercise testing (CPET), simple field testing with the 6-minute walk test (6-MWT), and incremental shuttle walk test (ISWT) as exercise tests for lung cancer patients [13].

6.3.2 Impact of Lung Resection on Exercise Capacity After Surgery

The authors have summarized findings from previous studies on lung resection (Table 6.1) [14–24]. CPET is most often used in postoperative exercise tests and preoperative evaluations. The peak oxygen uptake (VO_2) in CPET declines by 19–28% 14 days after surgery [15, 17].

Table 6.1 Summary if previous studies about postoperative functional exercise capacity of patients with lung cancer

Study	Postsurgical time point	Patient population	Exercise test/ instrument	Findings
Nomori H et al.	1 week	*n* = 112	6-MWT	PLT and AAT groups: 6MWD↓
Miyoshi S et al.	<2 weeks and 2 weeks	*n* = 16	CPET	<2 weeks: O_2 max↓73.1 ± 15.4% preop 2 weeks: O_2 max↑81.5 ± 19.7% preop
Brocki BC et al.	2 weeks and 6 months	*n* = 80	6-MWT	2 weeks: 6MWD↓37.6 ± 74.8 m 6 months: recovered
Nagamatsu Y et al.	1 month	*n* = 164	CPET	VO_2 max↑88% of preop
Brunelli A et al.	1–3 months	*n* = 200	CPET	Lobectomy 1 month: VO_2 peak 96% of preop 3 months: VO_2 peak 97% Pneumonectomy 1 month: VO_2 peak 87% of preop 3 months: VO_2 peak 89%
WinT et al.	1, 3, 6 months	*n* = 88	ISWT	6 months Lobectomy: lost 16% preop Pneumonectomy: lost 23%
Nugent AM et al.	3–6 months	*n* = 53	CPET	Pneumonectomy: VO_2 max 28%↓ Thoracotomy, wedge-resection, and lobectomy: unchanged
Bolliger CT et al.	3 and 6 months	*n* = 68	CPET	Lobectomy 3 months: VO_2 max↓preop 3–6 months: recovered Pneumonectomy 3 months: VO_2 max↓ 3–6 months: not recovered 6 mo: VO_2 max 20%↓preop
Nezu K et al.	3 and > 6 months	*n* = 82	CPET	Lobectomy 3 months: VO_2 max↓ >6 months: recovered, but did not reach the preoperative 13.3% preop Pneumonectomy 3 months: VO_2 max ↓ >6 months: not recovered, 28.1% preoperative

Table 6.1 (continued)

Study	Postsurgical time point	Patient population	Exercise test/ instrument	Findings
Burtin C et al.	<1 year	$n = 64$	CPET 6-MWT	Peak isometric quadriceps strength and DL_{CO} were significant predictors of VO_2 peak Quadriceps endurance and DL_{CO} were significant predictors of W peak. Quadriceps endurance capacity, but not DL_{CO}, significantly contributed to the 6MWD model
Wang JS et al.	1 year	$n = 28$	CPET	Pneumonectomy and lobectomy: VO_2 max↓(by 20% and 12%) Segmentectomy: no changed

AAT anteroaxillary thoracotomy; *CPET* cardiopulmonary exercise testing; *DLco* diffusing capacity of the lung carbon monoxide; *ISWT* incremental shuttle walk test; *6-MWT* 6-minute walk test; *PLT* posterolateral thoracotomy; *VO2* oxygen consumption

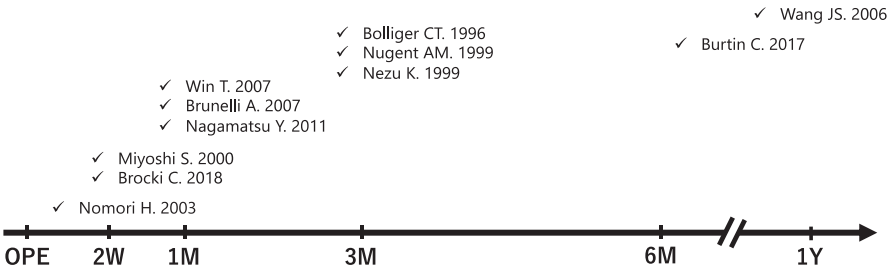


Fig. 6.1 Time point of exercise test in previous studies. The baseline for all studies was preoperative and the time points for postoperative evaluation varied, as shown in this figure

In addition, we focused on the time point of exercise testing in each study (Fig. 6.1). Many studies were conducted more than 1 month after the surgical procedures [17–24]. However, most patients have a short postoperative stay, and the early limitations of exercise capacity are unclear.

Assessment of exercise capacity during the early period after lung resection permits the detection of significant impairment and early intervention aimed at ameliorating the said impairment. Several studies using the 6-MWT have shown that the 6-minute walk distance (6-MWD) decreased significantly when measured within 14 days after the surgery [14, 16]. However, these studies had a small sample size ($n = 28$ patients following thoracoscopic surgery) [14] and a heterogenous population (including metastatic tumors and patients with nonmalignant tumors) [16]. Furthermore, the peripheral muscle force is strongly related to the 6-MWD in chronic obstructive pulmonary disease (COPD) [25, 26] and is an important factor in the exercise capacity of patients after lung resection in lung cancer [23]. However,

these factors has not been evaluated in previous studies [14, 16]. In addition, the associations between the change in the 6-MWD following surgery and factors, such as preoperative pulmonary function, surgical procedure, and postoperative progress, are unknown.

6.3.3 The Role of Exercise Capacity Tests in Lung Cancer

A review of the exercise capacity tests of patients with lung cancer summarizes the utility of exercise tests in four contexts: preoperative evaluation for lung cancer resection, postoperative evaluation after lung cancer resection, lung cancer prognosis, and assessment of the efficiency of exercise training programs [27]. This review investigated the number of previous studies in the context and on methods of exercise capacity tests using the Medical Subject Headings search terms "exercise testing" and "lung neoplasms" (Fig. 6.2). The four most frequently identified contexts were associated with preoperative evaluation for lung cancer resection. The method of testing was CPET.

The results of preoperative exercise tests may be used to decide whether surgery can be performed. This has been verified by many studies. The most recently published guidelines in 2013 showed preoperative risk stratification based on the results of the evaluation of pulmonary function and exercise capacity of patients undergoing lung resection [11]. The peak VO_2, as measured using CPET, is the most accurate physiological parameter and is recommended for high-risk patients with poor

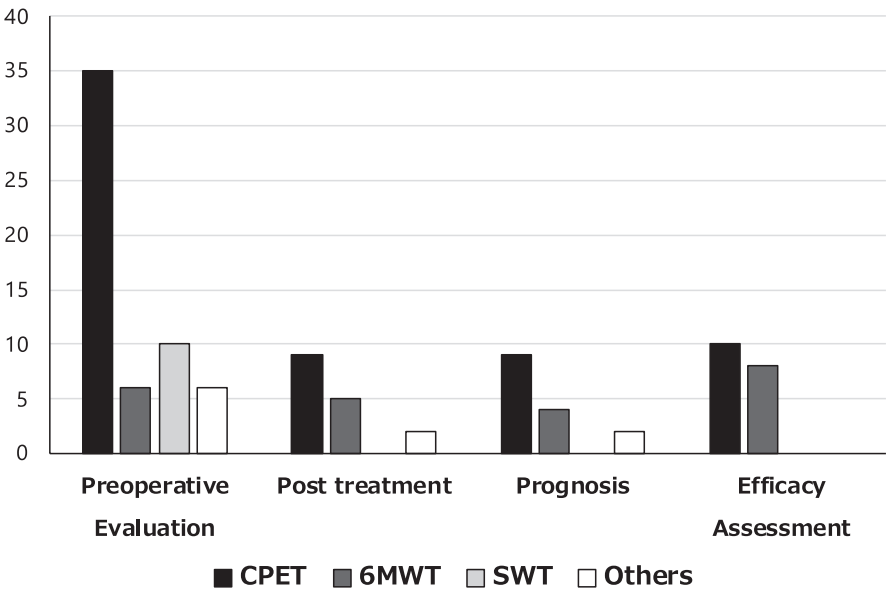


Fig. 6.2 The number of studies on exercise testing in lung cancer. *6-MWT* 6-minute walk test; *CPET* cardiopulmonary exercise testing; *SWT* shuttle walk test

pulmonary function. The ISWT and stair climbing associated with peak VO_2, instead of CPET, are recommended for moderate- or low-risk patients. In addition, the authors reported an association between specific problems (frailty and malnutrition) in older adults and postoperative complications [28, 29].

The main purpose of exercise testing for lung cancer patients is to assess the risk of postoperative complications. However, the outcomes of physiotherapy in patients who undergo surgery for lung cancer are changing from the incidence of postoperative complications to postoperative physical function and HRQoL. Therefore, the authors focused on "after lung resection" in patients who underwent surgery.

6.3.4 Methods of Exercise Capacity Tests

The authors hereby summarize the characteristics of CPET, 6-MWT, and ISWT, which are frequently performed in patients with lung cancer (Table 6.2). The details of each test are presented below:

6.3.4.1 Cardiopulmonary Exercise Test

CPET is the gold standard exercise stress and is a historical evaluation method (Fig. 6.3) [30]. CPET combines ventilation, VO_2, and exhaled carbon dioxide (VCO_2) with routine physiological and performance parameters measured during incremental exercise testing. These parameters include the heart rate, blood pressure, and work rate. Gas exchange measurements during exercise have been shown to enhance the decision-making process in several clinical settings, such as in deciding whether surgery or chemotherapy is possible.

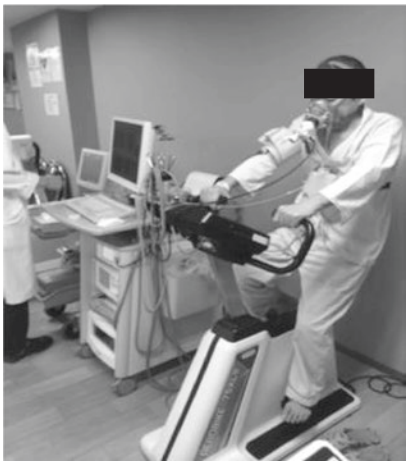
The indications for CPET include exercise capacity assessment, training prescription, treatment efficacy evaluation, diagnosis of the causes of unexplained reduced exercise tolerance, and evaluation of exercise pathophysiology in an extremely wide spectrum of clinical practice [31–34].

CPET can be performed using incremental or constant work rate protocols. Incremental protocols aim to optimize the O_2 transport and use system. As such,

Table 6.2 Characteristics of the exercise capacity tests

	CPET	6-MWT	ISWT
Reliability	●	▲	●
Standardization	●	▲	●
Generality	▲	●	■
Amount of parameters detected	●	▲	▲
Past reports for patients	●	●	▲
Implementation during oxygen therapy	▲	●	●
Cardiovascular monitoring	●	▲	▲
Intensity	●	■	■
Exercise induce hypoxemia on test	■	●	●

●: high and a lot, possible ■: moderate, ▲: low and a few, impossible
CPET cardiopulmonary exercise test; *ISWT* incremental shuttle walking test; *6-MWT* 6-minute walking test



Outcomes

- peak oxygen uptake (peak VO_2), ventilatory threshold, oxygen pulse, VE/VCO_2 slope, circulatory power, etc.

Fig. 6.3 Cardiopulmonary exercise test

they are routinely used in clinical settings. Among incremental protocols, ramp protocols are preferred and are characterized by a gradual increase in work rate, which is evenly distributed within each minute of the exercise phase [35].

CPET can be performed using a cycle ergometer or a treadmill. In most cases, a cycle ergometer is used because ramp incremental protocols are much easier to implement. Furthermore, it is easy to manage the risk of using a cycle ergometer in clinical setting.

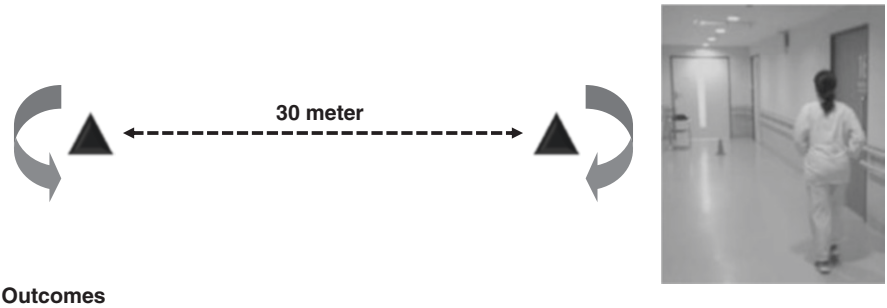
CPET systems contain flow meters and gas analyzers that allow breath-by-breath measurements of the ventilation, VO_2, and VCO_2. CPET can measure many physiological parameters, such as peak VO_2, ventilatory threshold, oxygen pulse, V_E/VCO_2 slope, and circulatory power [36]. The peak VO_2 is the principal parameter obtained from CPET.

Oxygen uptake is decreased in alveolar hypoventilation, pulmonary arterial flow limitation, cardiac dysfunction, peripheral vascular insufficiency, skeletal muscle dysfunction, and blood flow redistribution [37]. These parameters reflect the pulmonary, cardiac, skeletal muscle, pulmonary, and peripheral vascular and autonomic nerve functions.

6.3.4.2 6-MWT

The 6-MWT is commonly used for the objective assessment of functional exercise capacity in the management of patients with various pulmonary diseases (Fig. 6.4).

In the 6-MWT, patients are required to walk as fast as possible for 6 min. The primary outcome measure is the 6-MWD. A previous studies has evaluated the correlation between the 6-MWD and the physiological measures of exercise [38]. Furthermore, changes in the 6-MWD and other derived measurements can be used to determine the treatment response and predict morbidity and mortality in chronic respiratory diseases [39].



Outcomes

- 6 minute walking distance
- Response of each parameters
  pulse rate, oxygen saturation of peripheral artery, dyspnea, leg effort

Fig. 6.4 6-minute walking test

The American Thoracic Society (ATS) published guidelines for the 6-MWT in 2002, with a subsequent joint European Respiratory Society and ATS updated systematic review and technical standards in 2014 [39, 40]. According to these guidelines, the test should be performed in a minimally tracked area along a flat, straight corridor ideally for >30 m to be consistent with the established reference equations. Verbal encouragement is typically used to enhance participation. Careful attention should be paid to the language used to instruct patients and the frequency of encouragement. The guidelines provide standardized phrases for patient explanations and encouragement delivered at 1-min intervals. Two sets of tests should be performed, given the learning effect. A retrospective observational study showing the learning effect has reported that the 6-MWT was performed on patients with COPD and that the 6-MWD increased by an average of 26 m in subsequent retests, wherein most patients showed an improvement in the second walk [41].

The 6-MWT is safe, with rare complications. In a study of outpatients with chronic lung disease, the test was conducted in the pulmonary rehabilitation phase. In this test, the most common adverse event was oxygen desaturation of <80% in 5% of the patients. Patients who developed symptoms prematurely terminated the test in 1% of the patients [42].

6.3.4.3 Incremental Shuttle Walking Test

The ISWT was originally devised to assess the exercise capacity in patients with COPD [43]. It is an inexpensive tool that has been used to assess exercise capacity in pulmonary rehabilitation settings for various patients [44–47].

The protocol requires the patient to walk for a distance of 10 m, which is marked by two cones. The speed at which the patient was asked to walk was dictated by an audio signal played by a tape. The patient was required to turn around the cone by the time they heard the audio signal. Each minute, the walking speed was increased by a small increment. The first walking speed was referred to as level 1, the second

as level 2, and so on. Each level lasted for 1 min, and the tape was continued for ten levels. The test was symptom-limited. Thus, it ended when the patient was physically exhausted, too breathless to continue, or unable to complete a shuttle within the permitted timeframe.

The ISWT appears to be more productive and more closely associated with the peak VO_2, which is estimated more commonly by formal exercise testing than the 6-MWT [43, 48].

6.3.5 Research About Postoperative Functional Exercise Capacity

Based on limitations of previous studies, we investigated the functional exercise capacity of patients with lung cancer in the early postoperative period [49]. The aims of this study were to identify (i) the magnitude of decline in the 6-MWD during the early period after surgery and (ii) the associations between the changes in 6-MWD and factors, such as preoperative peripheral muscle force, pulmonary function, surgical procedure, and postoperative progress in patients following surgical resection for lung cancer.

6.3.5.1 Methods

Consecutive patients with preoperative clinical stage I–IIIA lung cancer who underwent lung resection at the Nagasaki University Hospital (Nagasaki, Japan) were enrolled. Patients in whom functional exercise capacity and skeletal muscle strength tests were performed preoperatively and postoperatively were eligible for this study.

The exclusion criteria were as follows: musculoskeletal and neurological disorders, cognitive impairment, and severe postoperative complications (POCs, Clavien-Dindo grade $\geq$ 3) [50] affecting the performance of exercise tests. Patients who underwent pneumonectomy or those with a history of thoracic surgery were excluded from the study.

The data we collected included the following: clinical stage of cancer, comorbidity, performance status (Eastern Cooperative Oncology Group Performance Status) [51], nutritional status (serum total protein and albumin), and pulmonary function (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, vital capacity (VC), and diffusing capacity of the lung for carbon monoxide (DLco)) prior to surgery. The pulmonary function tests were performed in accordance with the international guidelines [52].

6.3.5.2 Measurements

The following tests were performed within 2 days prior to surgery and on the first 7 postoperative days. Four physiotherapists were involved in data collection.

6.3.5.3 Functional Exercise Capacity

We assessed the functional exercise capacity using the 6-MWT. Previous studies [15, 17] have used CPET as a postoperative exercise capacity test. Cavalheri et al.

[53] reported that a CPET was a more maximal exercise test than the 6-MWT in patients with lung cancer; however, the 6-MWT was more suitable in the early postoperative period because some patients could not tolerate the CPET due to symptom burden, such as incisional pain, fatigue, and dyspnea. The test was performed according to previously published guidelines [39].

6.3.5.4 Skeletal Muscle Strength

The handgrip force (HF) and quadriceps force (QF) were measured as indices of the skeletal muscle strength. The HF was assessed using a dynamometer. HF was measured while standing, with the elbow extended and the arm fixed to the body. The highest values (kg) of the two attempts were recorded for both hands. QF was evaluated as the peak force developed by the dominant leg during a maximal isometric knee extension maneuver in the sitting position using a handheld dynamometer with a fixing belt in accordance with a standard protocol. The highest value of at least two maneuvers was recorded and expressed in kilograms of feet (kgf).

6.3.5.5 Surgical and Perioperative Management

Patients who were eligible to undergo thoracoscopic surgery or thoracotomy were selected based on the results of their chest radiographic studies, bronchoscopy, general condition, and comorbidities. Epidural or continuous intravenous analgesia was used to manage the postoperative incisional pain until the removal of chest drain. Afterward, oral analgesics were administered. The definition used for thoracotomy was defined as an incision of ≥6 cm and/or the use of a rib retractor.

POCs were defined as complications that occurred during the postoperative hospital stay. POCs were diagnosed by a surgeon and/or radiologist. Subsequently, we identified these POCs from the medical records based on the Clavien-Dindo classification [50].

Postoperative care included physiotherapy comprising early ambulation and airway clearance techniques. Physiotherapy was commenced on the first postoperative day and continued until the day before discharge.

6.3.5.6 Statistical Analysis

Comparisons between preoperative and postoperative 6-MWD and skeletal muscle strength were made using the paired t-tests.

The multiple regression analysis was used to determine the associations between changes in the 6-MWD after surgery and preoperative skeletal muscle strength and pulmonary function, surgical procedure, and postoperative progress. A multiple regression analysis adjusted for the preoperative 6-MWD was first performed to identify the potential predictor variables. Variables with a p-value <0.2 and those considered to be clinically relevant were included in the multivariate analysis to determine the independent predictors. When multicollinearity was present in the model, highly related variables were identified. Only the variable with the highest univariate relationship with the dependent variable was included in the model. The level of significance was set at 0.05 for all statistical tests.

6.3.5.7 Results

A total of 472 consecutive patients were screened for eligibility, of whom 297 (63%) were recruited for the study. Finally, the authors analyzed 218 patients who underwent surgery to resect NSCLC with a stage ranging from IA to IIIA (mean age, 69 years; 140 men (64%), 187 stage I (86%), 103 thoracoscopy (47%), 169 lobectomy (77%)). A total of 49 patients developed POCs: 14 cases of prolonged air leakage for 4 days, 13 cases of atrial fibrillation, 7 cases of chylothorax, 4 cases of delirium, 3 cases of pneumonia, 3 cases of atelectasis, 2 cases of hemothorax, 2 cases of recurrent nerve paralysis, 1 case of pyothorax, and 1 case of acute exacerbation of COPD. On average, chest drains and epidural catheters were removed on the third postoperative day. Most patients (65%) ambulated on the first postoperative day. Patients were able to walk around one floor (200 m) on the third postoperative day. In addition, they received advice from a physiotherapist about self-exercise and daily life in their home. The participants did not receive exercise training supervised by a physiotherapist.

The results of the preoperative and postoperative 6-MWD and skeletal muscle strength are shown in Fig. 6.5. The 6-MWD decreased markedly, whereas dyspnea in the post 6-MWT increased significantly during the early postoperative period, and the skeletal muscle strength decreased slightly.

The results of the multiple regression model showed that the duration of chest tube drainage ($P < 0.001$), presence of postoperative complications ($p = 0.014$), VC

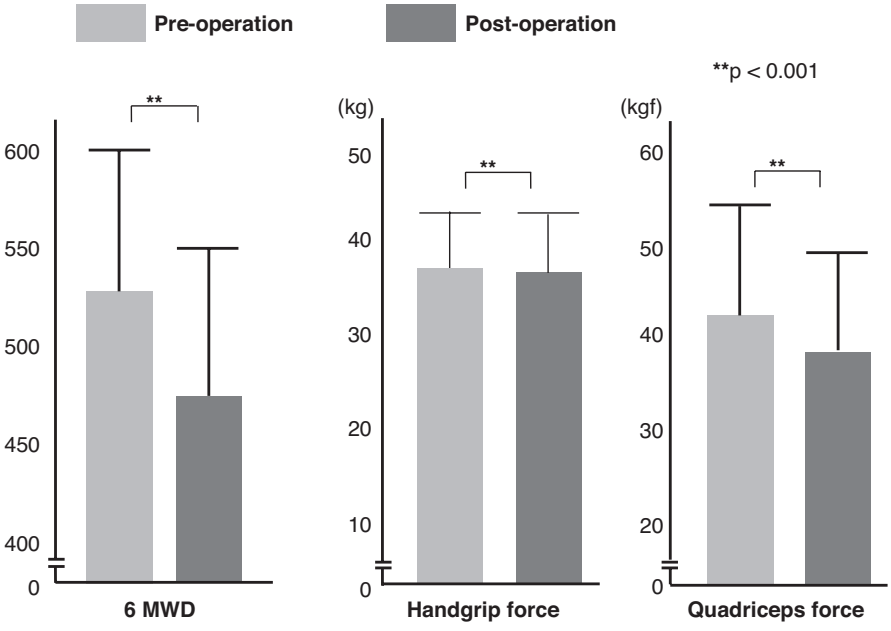


Fig. 6.5 Comparison of 6-minute walk distance (MWD) and skeletal muscle strength pre- and postoperatively

($P = 0.001$), and QF ($P = 0.034$) before surgery were significant predictors of change in 6-MWD. However, age, sex, and other variables related to surgery were not significant contributors to the model.

6.3.5.8 Conclusion

We found that impairment in functional exercise capacity, measured as the 6-MWD, during the early postoperative period significantly declined (45 m, 9%). We also found that the QF, VC, duration of chest tube drainage, and presence of POCs were independent predictors of the decline in 6-MWD. However, intraoperative factors, such as the surgical procedure and extent of lung resection, were not related to the decline.

Based on our findings, we recommend the 6-MWD as a routine evaluation before and after surgery, regardless of the type of surgery, to detect the initial decline in exercise capacity.

Future research should confirm whether improving postoperative exercise capacity by performing preoperative exercise training, early detection of the deterioration of exercise capacity, and performing exercise training enhance recovery in these subjects.

6.4 HRQoL in Patients with NSCLC

6.4.1 HRQoL

According to the World Health Organization (WHO), QoL is defined as the individuals' perceptions of their position in life in the context of their culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns [54].

Recently, optimizing QoL has been the target of therapeutic approaches, along with the assessment of efficacy and safety of treatment. In addition, self-assessed QoL is based on a subjective scale, which includes the severity of symptoms, clinical evaluation, limitations in daily activities due to illness or its treatment, and survival.

HRQoL is determined by the QoL and is affected by physical impairment, limitations of functional state, perceptions, and opportunities for social activity. This depends on the type of disease, treatment, and long-term follow-up.

The majority of researchers refer to the definition given by the WHO, where HRQoL denotes the complex self-assessment, including physical health, psychological state, level of independence, dependence on others, social relationships, religion, and personal beliefs [55].

HRQoL encompasses the physical dimension (pain and disability), psychological dimension (anxiety and depression), and social dimension (degree of isolation and ability to perform social roles) [56]. When conducting research, attention should also be given to functioning ability, perceptions of the situation, and disease symptoms [56].

The factors that negatively influence QoL include negative health behaviors, exposure to stressful situations, and strategies to overcome them.

6.4.2 Impact of Lung Resection on HRQoL After Surgery

A review of the impact of pulmonary resection on the QoL of cancer patients reported that surgery had a significant impact on HRQoL [57]. Additionally, many authors demonstrated that, independent of the instrument used, patients who underwent pulmonary resection due to lung cancer had the most consistent decline in their HRQoL during the first trimester after surgery.

The authors summarized the postoperative HRQoL in the domains of physical and mental components and symptoms.

6.4.2.1 Physical Component of HRQoL

The postoperative HRQoL, a physical component of NSCLC, had been consistently poor. Previous studies on physical components using the 36-Item Short Form Survey (SF-36) reported a significant decrease in physical HRQoL 6 months after surgery [58–63]. In addition, another study reported that at 6 months after surgery, 59% of the study subjects reported worse physical HRQoL, which was defined as a 10% reduction compared to the baseline [61]. Studies using the EORTC QLQ-C30 or LC-13 measured physical functioning 1 month after surgery and found that physical functioning dropped significantly below the preoperative values [64–68]. In some studies, physical functioning declined 6 months after surgery; one study reported an improvement in physical function [66, 69], while others reported no improvement [64, 65]. A study that measured the long-term physical functioning reported that even 2 years after surgery, patients experienced a diminished physical function compared to their preoperative levels [68].

Previous studies compared the postoperative physical HRQoL with physical HRQoL in the general population and found that patients had a lower physical HRQoL compared with the general population [59, 63, 70, 71].

6.4.2.2 Mental Health Component of HRQoL

Most studies measured the HRQoL 6 months after the patients' surgery using the SF-36. The 6-month time point was the most commonly used time point in assessments. Moreover, previous studies on the mental component that used the SF-36 have reported that the mean score for mental HRQoL at 6 months after surgery ranged from 37.8 to approximately 50 on a 0–100 scale [62, 70]. One study did not provide the score but reported that at 6 months, 33% of the subjects had worse mental components, whereas 67% remained stable or improved [61]. Studies measuring the mental component at 12 months or later reported that survivors who underwent lung resection had good mental HRQoL postoperatively and improved mental HRQoL over time [59, 71]. These findings suggest that the mental component improved over time after lung cancer surgery in most patients. In studies using the EORTC QLQ-C30/QLQ-LC13, the most common time points for measuring the HRQoL were prior to surgery and at 3, 4, 6, and 12 months after surgery. These studies have reported improvements in emotional functioning over time after surgery. Additionally, studies measuring long-term HRQoL (2–3 years) reported that survivors had good emotional functioning [68, 72, 73]. Thus, these findings suggest that mental HRQoL improves over time after lung cancer surgery in most patients.

6.4.2.3 Symptoms of the Disease

The most prevalent symptoms among patients were pain, fatigue, dyspnea, and coughing. During the first month after surgery, patients experienced increased pain, fatigue, cough, and dyspnea. Studies measuring symptoms at 3–4 months after surgery using the EORTC QLQ-C30/LC-13 reported that pain and dyspnea scores remained significantly worse than the patients' baseline values [64–66, 68, 69].

Dyspnea worsened significantly after surgery and did not improve over time. Kenny et al. prospectively examined the impact of surgery on HRQoL in 163 patients and found that even 2 years after surgery, approximately 53% of patients without disease recurrence still had increased levels of dyspnea, while 40% had worse fatigue than their baseline statuses [68]. A cross-sectional study reported that approximately 60% of subjects had dyspnea after surgery, with an average time since surgery of 3.5 years [74]. However, the significance of these symptoms varied according to the type of surgery and the patient's age. Ferguson et al. found that lung cancer survivors aged ≥70 years had more significant fatigue and dyspnea than those aged <70 years [72]. Patients who underwent more extensive surgery, such as pneumonectomy, experienced greater dyspnea and pain than those who underwent less extensive surgery, such as lobectomy [65].

6.4.2.4 Predictive Factors of Postoperative HRQoL

Patients who underwent lung resection inquired about permanent disability, loss of independence, and the impact of post-treatment HRQoL. For many patients, the risk of impaired HRQoL after surgery was an important consideration when deciding whether to proceed with the procedure. Many authors attempted to identify the factors associated with this decline in HRQoL.

A review of HRQoL after lung resection for lung cancer reported that predictive factors included the following: age, sex, type of surgery, extent of resection, smoking status, adjuvant treatment, comorbidity of COPD, and DLco level [75, 76].

The authors considered that perioperative impairment of functional exercise capacity may also be associated with impaired HRQoL, especially in the physical component. However, the extent to which these factors affected HRQoL remained unknown.

6.4.3 Measurement of HRQoL

The measurement of HRQoL has experienced significant growth in terms of the development and validation of different HRQoL assessment tools. In lung cancer, we can distinguish between three types of questionnaires: generic, cancer-specific, and lung cancer-specific (Table 6.3). Questionnaires for assessing HRQoL that are often used in the clinical setting are discussed hereby.

6.4.3.1 36-Items Short Form

The 36-Item Short Form Survey (SF-36) is a standardized, self-administered survey measuring the HRQoL [77]. The questionnaire comprises 36 items and measures health using eight subscales, with two to ten items per scale. The subscales and summary scores of the patients can be compared with those of the general population,

Table 6.3 Quality of life (QoL) questionnaires

Generic instruments
• Short-Form Health Survey (SF-36)
• The five-level (three-level) EuroQOL five-dimension (EQ-5D-5L, 3 L)
• Ferrans and Powers QoL Index (QLI)
• Nottingham Health Profile (NHP)
• WHO QoL instrument (WHOQOL-100)
Cancer-specific instruments
• EORTC QoL Questionnaire Core 30 (EORTC QLQ-C30)
• Functional Assessment of Cancer Therapy (FACT-G)
• Functional Living Index (FLIC)
Lung cancer-specific instruments
• EORTC Lung Module (LC-13)
• Functional Assessment of Cancer Therapy-Lung (FACT-L)
• Lung Cancer symptom scale (LCSS)

EORTC European Organization for Research and Treatment of Cancer; *QoL* quality of life

thus allowing norm-based interpretation. All scores were calculated according to the published scoring guidelines and were linearly transformed to a value ranging from 0 to 100, with higher scores indicating better functioning.

Several advantages of the PCS and MCS over the original eight scales of the SF-36 have been reported [78]. Very high PCS scores indicate lack of physical limitations, disabilities, decrements in well-being, or high energy levels. Very low scores indicate substantial limitations in self-care, physical, social, and role activities, severe bodily pain, or frequent tiredness. Very high MCS scores indicate frequent positive affect, absence of psychological distress, and limitations in usual social or role activities due to emotional problems. Very low scores indicate frequent psychological suffering and substantial social and role disabilities due to emotional problems.

6.4.3.2 EuroQOL

The five-level EuroQOL five-dimension (EQ-5D-5L) is an assessment tool used to estimate QoL and provide a QoL score, which can be used to calculate a quality-adjusted life year and to evaluate the incremental cost-effectiveness ratio [79].

The five dimensions assessed by the EQ-5D-5L were mobility (MO), self-care, usual activities, pain/discomfort, and anxiety/depression, each of which had five levels of severity. Level 1 corresponds to the ability to do activities without any difficulty or discomfort. Level 5 indicates difficulty in performing tasks or discomfort.

These health state parameters were transformed into utility values ranging from 0 to 1 using each national scoring function, where 0 represents death and 1 indicates full health.

6.4.3.3 European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30)

The EORTC-QLQ C30 is an internationally validated cancer-specific QoL questionnaire composed of 30 questions or items [80]. It comprises five multi-item functional scales (physical (PF), role (RF), cognitive (CF), emotional (EF), and social

(SF)), three multi-item symptom scales (fatigue (FA), nausea and vomiting (NV), and pain (PA)), six single-item symptom scales (dyspnea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhea (DI), and financial impact (FI)), and a two-item global quality-of-life scale (QL).

The questionnaire uses a four-point response format, with the exception of the QL scale, which was scored on a scale of 1–7. The scores ranged from 0 to 100, and a high score on a functional scale represented a high level of functioning, whereas a high score on the symptom scale represented a high level of symptoms. In addition, a summary score for the QLQ-C30 was introduced to supplement the 15-outcome profile [81].

The Lung Cancer Module (QLQ-LC13) comprises 13 items on a four-point Likert scale, translating into 10-symptom scales [82]. QLQ-LC13 has been useful for studying specific symptoms of patients with lung cancer, such as cough, hemoptysis, chest pain, and dyspnea [82].

6.4.3.4 Functional Assessment of Cancer Therapy General

The Functional Assessment of Cancer Therapy General (FACT-G) is a 27-item instrument that has four subscales: physical (e.g., I am forced to spend time in bed; seven items), functional (e.g., I am able to work, including work at home; seven items), social/family (e.g., I get emotional support from my family; 7 items), and emotional well-being (e.g., I worry about dying; six items) [83, 84].

This questionnaire uses a five-point Likert-type scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a bit; and 4 = Very much). The scale and subscale scores are summed to produce the total score and are calculated, so that a higher score indicates a better QoL.

There are approximately 20 additional versions of the FACT, each consisting of the core FACT-G items and a specific scale related to a particular type of cancer, treatment, and other QoL domains. The FACT-G and many of its disease-specific scales have also been translated and validated into several languages.

6.4.4 Our Research About Postoperative HRQoL

The aims of this study were to identify (1) the trajectories of HRQoL scores before and after lung resection in NSCLC patients and (2) associations between the changes in HRQoL score, operative factors, postoperative events, and impaired postoperative functional exercise capacity in patients following surgical resection for NSCLC [85].

6.4.4.1 Methods

The study methods were the same as those used in our previous study on postoperative functional exercise capacity (Sect. 6.3.5) except for the HRQoL measurements.

6.4.4.2 Measurements

HRQoL Assessment

The patients completed the EORTC QLQ-C30 (Japanese version 3.0) at each time point (1 preoperative day and 1 and 3 postoperative months). The authors focused on the PF domain in the EORTC QLQ-C30 because it had a strong test-retest reliability [86] and was responsive to changes during lung resection [74–78]. A change in the PF domain of five or more points is considered clinically relevant [87].

6.4.4.3 Statistical Analysis

The HRQoL scores were generally symmetrically distributed and summarized using the mean and standard deviation. Repeated measures of the analysis of variance were used to assess the significance of changes over time for each domain of the EORTC QLQ-C30 scores. For these analyses, simple contrast was used with each postoperative measure compared to the preoperative value. For each of the EORTC QLQ-C30 scores considered as a function of time, the global p-value was <0.05, and post hoc comparisons between preoperative and postoperative intervals were presented.

Patients were categorized into two groups, deteriorated and non-deteriorated, based on whether they had a change in the EORTC-QLQ-C30 PF domain between baseline and follow-up testing. Patients were classified as "deteriorated" if they had a decrease in the PF domain of 5 points or "unk" if they had a decrease in the PF domain of <5 points [87]. Logistic regression analysis was used to determine the factors contributing to PF at 1 and 3 months postoperatively. A stepwise selection procedure was used to identify variables with a p-value of <0.05. The level of significance was set at 0.05 for all statistical tests.

6.4.4.4 Results

We analyzed 95 patients who underwent surgery due to lung cancer at stages IA to IIIA (69 years, 59 men (62%), 84 stage I (88%), 61 thoracoscopy (64%), and 80 lobectomy (84%)).

Most of the EORTC QLQ-C30 scores decreased significantly 1 month after surgery and recovered to baseline at 3 months. However, PF and QL in the domain of functioning, DY and FA, and PA in the domain of symptoms were significantly lower than the baseline, even 3 months after surgery (Figs. 6.6 and 6.7). In particular, PF in the domain of functioning decreased in approximately 80% of patients 1 month after surgery, and the disorder persisted in 50% of patients even at 3 months.

This decline in PF was associated with incisional pain (numerical rating) as patients' symptoms at hospital discharge (OR 1.99, 95%CI 1.10–3.60) at 1 month after surgery and a decline in the 6-MWD (OR 1.01, 95% CI 1.00–1.02) at 3 months.

6.4.4.5 Conclusion

We found that (1) the postoperative decline in HRQoL, especially PF, significantly remained even 3 months after surgery, and (2) the postoperative pain and decline of the 6-MWD during hospitalization were related to the deterioration of the PF domain of postoperative HRQoL at 1 and 3 months.

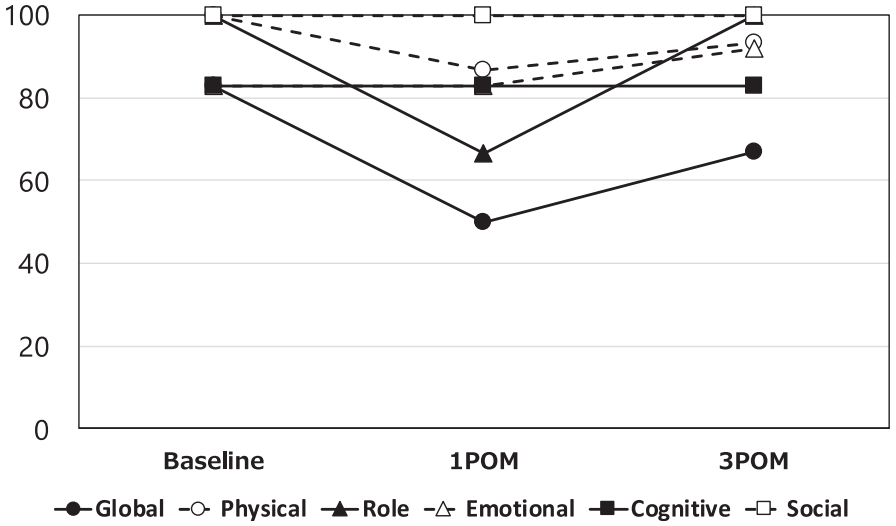


Fig. 6.6 The domain of functional scales and global QoL score at each time point

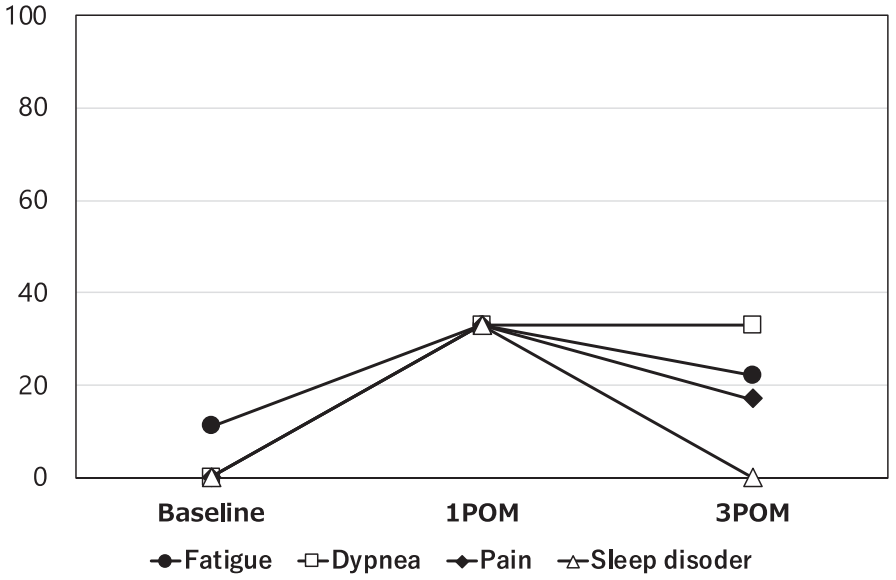


Fig. 6.7 The domain of symptom scale at each time points

These findings suggest that pain management and exercise training are necessary to enhance the recovery of HRQoL. Future research is needed to predict the delayed recovery of HRQoL and to perform exercise training to enhance the recovery in these patients.

6.5 Conclusions

Physiotherapy for lung cancer patients undergoing lung resection is an intervention performed immediately after surgery to prevent postoperative complications. This intervention has been improving due to the advances in surgical procedures and postoperative management. Therefore, the purpose and outcomes of perioperative physiotherapy have shifted to a new paradigm. Long-term outcomes, such as postoperative exercise capacity and HRQoL, are becoming more important factors due to the expansion of surgical indications for high-risk patients, including older people. Even if the surgery is successful, and survival is improved, if postoperative management is unsuccessful, the patient's life is restricted. To address this problem, it is necessary to identify patients whose functional recovery after surgery is likely to be delayed and to consider the early application of physiotherapy, such as exercise therapy. However, many unclear factors affect the dysfunction and long-term outcomes of surgery. As research in this field progresses, we hope that all patients who have undergone surgery would have better QoL.

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Part II

Physical Exercise

7 The Effect of Physical Exercise on Physical Function and Survival Rate in Cancer Patients

Takuya Fukushima

Abstract

Cancer treatment, while improving prognosis, frequently also results in impairment of daily physical activities and can seriously affect the quality of life of cancer patients. Cancer rehabilitation strategies, like physical therapy, to overcome such physical dysfunctions are thus very essential, subsequent to cancer treatment. In recent years, through various studies, it has become clearer that exercise therapy, and the resulting improvement in physical function can greatly reduce the recurrence of cancer and improve prognosis.

This chapter describes the various physical function assessments and exercise therapy procedures currently in use for the physical therapy of cancer patients in Japan, and through a systematic review and meta-analysis, we have summarized their positive effects on recovery and relapse in cancer patients.

Keywords

Physical function · Exercise therapy · Recurrence · Mortality · Cancer rehabilitation

7.1 Introduction

The most important outcome of cancer treatment is improved prognosis. Owing to advances in early detection and treatment, overall cancer mortality has been declining since 1991 [1], while cancer survivorship post treatment continues to steadily increase [2–5]. Cancer survivors can suffer from various physical function

T. Fukushima (✉)
Faculty of Rehabilitation, Kansai Medical University, Osaka, Japan
e-mail: fukustak@makino.kmu.ac.jp

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impairments and disabilities, either because of the treatments or the disease itself [6–8], which can lead to reduced abilities to perform activities of daily living (ADL) independently [8, 9] and/or a reduced quality of life (QoL) [10, 11]. Therefore, strategies to manage the decline in physical function in cancer patients are imperative, and cancer rehabilitation, including physical therapy, plays an important role in these situations.

Cancer rehabilitation, including physical therapy, was officially recognized as a new category of rehabilitation medicine by the healthcare insurance system of Japan in 2010 [12], and since then, has been implemented in many facilities [13]. Physical therapy interventions, especially exercise therapy, have been suggested to effectively improve physical function. In previous studies, undergoing exercise therapy before surgery, during chemotherapy and radiation therapy, and after treatment affected the muscle strength and aerobic fitness levels among patients [14–16]. Even cancer treatment plans include exercise therapy as a central part of the treatment strategies, which further enhances the role of physical therapy for cancer patients in Japan.

In recent years, exercise therapy for cancer patients has been effective not only for improving physical function but also for reducing physical and psychological symptoms [14, 15, 17] and QoL [18–20]. In addition, it is becoming clear that exercise therapy and the resulting improvement in physical function also affect recurrence and prognosis.

This section addresses the effect of exercise therapy and physical function on recurrence and prognosis in cancer patients.

7.2 Physical Function Outcome for Cancer Patients

Cancer patients have a wide range of unmet needs, which vary according to the disease, treatment, and clinical stage. Harrison et al. reported that although the prevalence of unmet needs differed according to the diagnosis, treatment, and post-treatment phases, the most frequently and widely reported unmet needs were in the ADL domain [21]. In addition, unmet needs were more prevalent in the physical aspects of ADL domains, and one unmet need most frequently rated as "moderate-to-high" was lack of energy/tiredness and not being able to do the things one usually did normally before getting affected by cancer [22]. These findings suggest a need for supportive care for improving the ADL functions of cancer patients. Cancer patients often experience a decline in physical function related to reduced ADLs. Specifically, cancer patients can develop various physical function impairments and disabilities, such as motor palsy, muscle dysfunction, contracture, decreased exercise capacity, balance dysfunction, edema, dysphagia, and excretory dysfunction, which can lead to reduced ADLs, including manifestations such as difficulty in walking as well as stair climbing and descending. This decline in physical function is affected by the disease itself, for example, decreased exercise capacity due to lung cancer, dysphagia due to head and neck cancer or esophageal cancer, and motor palsy due to brain or spinal cord tumors including metastases. Alternatively, the

decline in physical function may be caused by the treatment, such as decreased muscle strength and exercise capacity due to adverse events of chemoradiation therapy, decreased physical activity after hematopoietic stem cell transplantation, decreased muscle strength and walking ability after bone and soft tissue tumor surgery, lymphedema after breast cancer and gynecologic cancer surgery, and decreased muscle strength and exercise capacity after open-chest and abdominal surgery. Furthermore, sarcopenia, frailty, and cachexia due to the interaction between disease and treatment can also contribute to functional decline.

Among these, decreased muscle strength and exercise capacity are common physical dysfunctions in cancer patients. Muscle dysfunction is a prevalent phenomenon in the oncology setting, where patients across a wide range of conditions have impaired muscle function regardless of their tumor stage and nutritional status [7]. All cancer patients experience a wide range of cancer-specific and noncancer-specific degenerative factors, which are potential causes of muscle dysfunction, including aging [23, 24], malnutrition [23, 25], physical inactivity [23, 25], and factors directly related to disease pathophysiology and therapy toxicity [23]. Decreased exercise capacity is a physical dysfunction that applies to all cancer patients who are physically inactive. It is particularly common in patients with lung cancer [26], postoperative gastrointestinal cancer [27–29], and hematopoietic stem cell transplantation [30–32]. Therefore, the decline in physical function in these patients requires accurate evaluation.

Harrington et al. used a scoping review to systematically identify the literature related to the screening, assessment, and interventions associated with the physical function of cancer patients [33]. In this scoping review, it became clear that physical function in cancer research is predominantly measured using general health-related QoL tools such as the Medical Outcomes Study 36-Item Health Survey Questionnaire [34] and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Cancer 30 [35], rather than more precise functional assessment tools. However, no universally accepted operational definition of physical function has been established. Apart from patient-reported outcomes, objective measures of physical function are necessary in the future since they enable the quantification of various aspects of physical function, including muscle strength and exercise capacity. The common physical function assessments used by physical therapists in clinical practice are discussed in the next section.

7.2.1 Handgrip Strength

Handgrip strength (HGS) (Fig. 7.1a), a measure of muscle power or the maximum force/tension produced by the muscles of the forearm, reflects not only upper body strength but also overall muscle strength [36]. It is considered as an indicator of the whole-body muscle strength. Previous studies show that handgrip strength is a biomarker of current health status [37]. Sarcopenia, a progressive, generalized skeletal muscle disorder characterized by an accelerated loss of muscle mass and function [23], is one of the main geriatric syndromes among older people and often observed

in cancer patients. Although the appendicular skeletal muscle mass was the original basis for evaluation of sarcopenia [38], the current criteria for its evaluation vary. Currently, the diagnostic criteria of sarcopenia with a consensus in Asia and Europe includes loss of handgrip strength [23, 39]. Even physical frailty, which is characterized by weakness measured as a loss of HGS and considered as a high-risk factor for physical disability and hospitalization, is included in the definition of the diagnostic criteria [40]. Measurements vary widely, including maximum or mean values from one, two, or three attempts, with either hand or the dominant hand alone. Test-retest, inter-rater, and intra-rater reliabilities are established [41]. In Japan, the cut-off points of 28 kg in men and 18 kg in women that are suggested by the Asian Working Group for Sarcopenia are the most widely accepted [39]. This measurement is advantageous because it is simple and helps assess the general muscle strength easily and requires only a HGS meter.

7.2.2 Gait Speed

Another outcome measure used commonly to evaluate sarcopenia is the gait speed (Fig. 7.1b), which can be calculated by measuring the time taken to walk a specific distance and is included in the definitions of sarcopenia [39] and frailty [40]. It is a commonly used outcome measure across different studies, health-related disciplines, and patient populations. However, the methods of gait speed measurement and the descriptions of such methods vary greatly. A previous study revealed a wide range of variability in gait test methodologies, including pace (usual or fast), timing protocol (static or dynamic), and distance covered (varying from 2 to 400 m) [42].

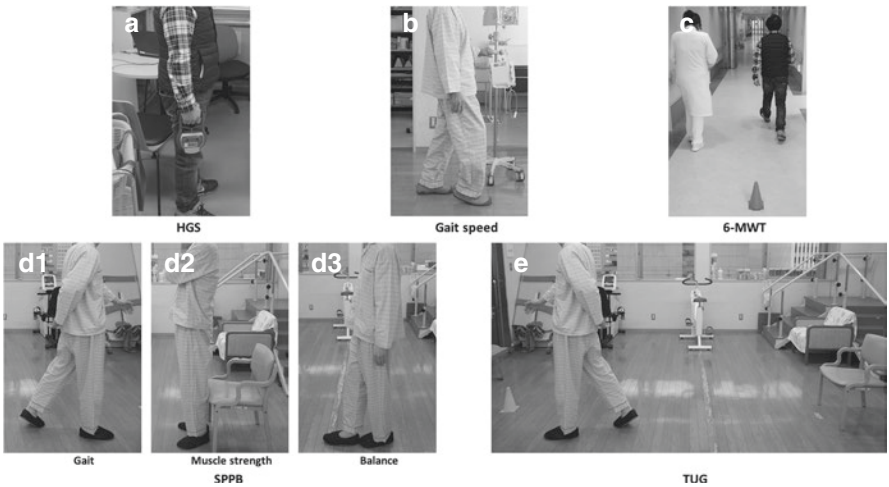

Fig. 7.1 Physical function outcome for cancer patients. (**a**) Handgrip strength (HGS), (**b**) gait speed, (**c**) 6-minute walking test (6-MWT), (**d**) short physical performance battery (SPPB), (**e**) timed up-and-go test (TUG)

Although almost all versions of these short, distance-based gait tests have demonstrated high (>0.90) test-retest and inter-rater reliabilities, previous study articulates the following tentative recommendations regarding the development of a standardized protocol to assess gait speed: adopt the 10-m straight line walk; use a static start with timing commencing at the start; use usual or comfortable pace as the standard; use fast pace as appropriate for specific research questions; and report gait protocol in detail, including pace instructions, verbal or other encouragement, and specific timing procedures [42]. It would be preferable to evaluate gait after proper conditioning according to the characteristics of the clinical situation and research. In Japan, the cutoff point of 1.0 m/s, as suggested by the Asian Working Group for Sarcopenia, may be the most widely accepted [39].

7.2.3 6-Minute Walking Test

The 6-minute walking test (6-MWT) (Fig. 7.1c) is a field walking test used for evaluating exercise capacity and was reported by Butland et al. in 1982 [43]. The primary outcome of the 6-MWT is walking distance that is recorded in meters or feet [44, 45]. It should be performed along a flat, straight course with a hard surface and little pedestrian traffic. A walking course of 30 m or more is recommended to be consistent with the courses on which the reference equations have been generated [44]. The ends of the course should be marked such that they are easily visible to patients, and they are encouraged every 60 s using standard phrases (1 min, "You are doing well. You have five minutes to go"; 2 min, "Keep up the good work. You have four minutes to go"; 3 min, "You are doing well. You are halfway there"; 4 min, "Keep up the good work. You have only two minutes left"; 5 min, "You are doing well. You have only one minute to go"; 6 min, "Please stop where you are"). Other words of encouragement and nonverbal prompts should not be used. If a patient stops walking during the test, the timer must not be stopped. The patient should be allowed to rest while sitting or standing, per their preference. While the patient is immobile, standardized encouragement should be provided every 30 s (if the patient stops during the test, arterial oxygen saturation should be measured every 30 s via pulse oximetry; once it has reached >85%, ask the patient to resume walking once they feel able). The time that the patient remained stationary and the time interval recommended for walking should be recorded. Although cardiopulmonary exercise testing using a treadmill or bicycle ergometer is used to evaluate exercise tolerance using a variety of equipment, the field walking test is essential and easy-to-use. Moreover, robust evidence supports the reliability, validity, and responsiveness of the 6-MWT. However, comparing the walking distances in the 6-MWT of individuals with different body sizes and diseases is challenging. Clinically, the changes in walking distance are commonly compared for the same individual. The minimum clinically significant difference in the 6-minute walking distance is 25–33 m (median; 30 m) in COPD patients [44].

7.2.4 Short Physical Performance Battery

The short physical performance battery (SPPB) (Fig. 7.1d) is a comprehensive measure of lower extremity function in terms of gait, lower extremity muscle strength, and standing balance [46]. For tests of 8 ft (2.4 m), individuals are timed walking at their normal pace and are scored according to quartiles for the length of time required. The faster time of two walks is used for scoring, as follows >5.7 s, a score of 1; 4.1–5.6 s, a score of 2; 3.2–4.0 s, a score of 3; and <3.1 s, a score of 4. For lower extremity muscle strength, individuals are asked to fold their arms across their chests and stand up from a sitting position once. If they successfully rise from the chair, they are asked to stand up and sit down five times as quickly as possible. Quartiles for the length of time required for this measure are used for scoring, as follows: >16.7 s, a score of 1; 13.7–16.6 s, a score of 2; 11.2–13.6 s, a score of 3; and <11.1 s, a score of 4. For standing balance, the individuals are asked to attempt to maintain their feet in side-by-side, semi-tandem (heel of one foot beside the big toe of the other foot), and tandem (heel of one foot directly in front of the other foot) positions for 10 s each. The individuals are given a score of one if they can hold a side-by-side standing position for 10 s, but are unable to hold a semi-tandem position for 10 s; two if they can hold a semi-tandem position for 10 s, but are unable to hold a full tandem position for more than 2 s; three if they can stand in the full tandem position for 3–9 s; and four if they can stand in the full tandem position for 10 s. A summary performance score is created by adding the scores for the walking, repeatedly rising from a chair, and standing balance tests [46, 47]. In a systematic review examining the reliability, validity, and feasibility of various clinically used measures in older adults, 78 articles compared 12 different measures of physical performance, with SPPB being the most recommended in terms of reliability, validity, and feasibility [48].

7.2.5 Timed Up-and-Go Test

The timed up-and-go (TUG) (Fig. 7.1e) test is an index of functional mobility, which consists of walking speed, strength, and static and dynamic balance. It uses the time required to rise from a chair of standardized height, walk a fixed 3-m distance, turn, return to the chair, and sit down again [49]. In the original method, the patient walks at a "comfortable speed" [49], but clinically, a "maximum speed" has been used to eliminate the effects of differences in the psychological state at the time of measurement or interpretation of the instructions. Intratester and intertester reliability and validity have been demonstrated in a previous study [50].

When assessing the physical function of cancer patients, it is necessary to assume that multiple functional impairments may occur due to adverse events associated with the disease and treatment. Therefore, it is necessary to adopt a multifaceted perspective and combine multiple evaluation indices to capture the image of disability rather than conducting only a single evaluation.

7.3 Exercise Therapy for Physical Dysfunction in Cancer Patients

Physical therapy with a focus on exercise therapy is considered an effective countermeasure for the decline in physical function of cancer patients, as described in the previous section. In principle, exercise therapy should be based on FITT (frequency, intensity, time, type). Previous studies have shown that moderate-intensity aerobic exercise, resistance exercise, or combined aerobic and resistance exercise performed three times weekly for 8–12 weeks can significantly improve self-reported physical function [51–53]. Specifically, it is recommended that aerobic exercise such as walking and ergometer be performed for 30–60 min, three times a week for 8–12 weeks at an exercise intensity of 60–85% of maximal heart rate, 60–85% of maximal oxygen consumption, and rating of perceived exertion (RPE) of 12–13. For resistance training, it is recommended to perform 2 sets of 8–12 repetitions, 2 to three times per week for 8–12 weeks at an exercise intensity of 60–75% of 1-repetition maximum (RM) and RPE of 13–15. In combined aerobic exercise and resistance training, aerobic exercise should be performed for 20–40 min, three times a week, at an exercise intensity of 60–85% of maximal heart rate, 60–85% of maximal oxygen consumption and rating of perceived exertion (RPE) of 12–13, and resistance training should be performed at 2 sets of 8–12 repetitions, two to three times per week for 8–12 weeks at an exercise intensity of 60–75% of 1-repetition maximum (RM) and RPE of 13–15. In general, supervised exercise appears to be more effective than unsupervised or home-based interventions [52], although unsupervised programs may be effective in older cancer survivors [53]. Community-based interventions that meet in groups and use behavior change strategies are recommended because they may produce greater effects in older adults.

Unlike the situation in Western countries, Japan has the characteristic of providing physical therapy to hospitalized patients undergoing treatment. In fact, it has been shown that the rate of cancer rehabilitation during hospitalization is high, whereas in the outpatient setting, the rate is lower [13, 54]. Recommended moderate- to high-intensity exercise is preferred, but is often difficult to apply to hospitalized patients due to treatment-related side effects. For this reason, low-intensity exercise therapy, set at 40% or less of the predicted maximum heart rate calculated by the Karvonen's formula [55], is often implemented in clinical practice. In our retrospective study [56], we included 44 patients with hematologic malignancies who underwent low-intensity exercise therapy during hospitalization for chemotherapy. Low-intensity exercise therapy consisted of aerobic and resistance training, which was carried out on weekdays. Patients were divided into high- and low-frequency groups according to their low-intensity exercise therapy frequency. In the high-frequency group, muscle function such as muscle mass, handgrip strength and isometric knee extensor strength was maintained, while physical function such as gait speed and TUG was significantly improved. However, in the low-frequency group, muscle function of the lower limb was significantly reduced and no other improvement was observed (Table 7.1). From these findings, it was inferred that even low-intensity interventions may lead to maintenance of muscle function and

Table 7.1 Changes in physical function with low-intensity exercise therapy

	HF group (n = 22)				LF group (n = 22)				Group × Time
Parameters	Baseline (mean ± SD)	Post-treatment (mean ± SD)	Change from baseline (mean ± SD)	Within-group P-value	Baseline (mean ± SD)	Post-treatment (mean ± SD)	Change from baseline (mean ± SD)	Within-group P-value	P-value
HGS, kgf	24.2 ± 11.4	25.0 ± 11.8	0.8 ± 2.1	0.240	21.5 ± 8.5	21.1 ± 7.8	−0.4 ± 4.0	0.619	0.238
IKES, kgf	27.2 ± 10.4	27.8 ± 10.2	0.7 ± 5.8	0.600	24.3 ± 13.7	21.5 ± 12.9	−2.9 ± 5.7	0.028	0.053
MT, mm	15.9 ± 6.0	15.3 ± 5.6	−0.6 ± 2.6	0.341	14.8 ± 5.2	13.4 ± 4.0	−1.4 ± 3.0	0.025	0.338
10MWT, s	8.2 ± 2.3	7.1 ± 1.7	−1.2 ± 1.4	0.003	8.8 ± 2.7	8.6 ± 2.7	−0.2 ± 1.7	0.531	0.067
TUGT, s	10.3 ± 3.4	8.0 ± 1.6	−2.2 ± 2.5	0.210	9.6 ± 3.5	8.9 ± 3.0	−1.2 ± 3.6	0.294	0.123

LF low-frequency; *HF* high-frequency; *Baseline* start date of rehabilitation; *Post-treatment* discharge; *HGS* handgrip strength; *IKES* isometric knee extensor strength; *MT* muscle thickness; *10MWT* 10-meter walk test; *TUGT* timed up and go test

improvement of physical function when given at a high frequency. Low-intensity exercise therapy could be a potential treatment strategy for inpatients with hematological malignancies undergoing chemotherapy who are unable to perform mid- or high-intensity exercise. While this data is helpful in clinical practice, it is only a retrospective study, so it is not possible to determine a causal relationship. Therefore, future prospective studies are expected.

7.4 Physical Function and Mortality

In recent years, an increasing number of reports have focused on the physical function and survival of cancer patients [57], which has made physical function a topic of increased scrutiny. We performed a systematic review to investigate whether HGS, gait speed, 6-MWT, SPPB, and TUG, which are used in clinical practice, affect the survival rate and discussed the results below.

In our systematic review [58], literature searches were conducted using the Web of Science, CINAHL, Cochrane Library, ProQuest, PEDro, and PubMed for articles published before September 2020. The search strategy was conducted on the aforementioned databases based on the following words: "cancer," "tumor," "neoplasm," "hematopoietic malignancy," "lymphoma," "sarcoma," "carcinosarcoma," "leukemia," "mortality," "survival," "predictor," "grip strength," "gait speed," "walking test," "short physical performance battery," "walking test," "activity," and "physical function," The phrase "disorder for cancer" was included in the search (such as lymphoma, hematopoietic malignancy, sarcoma, carcinosarcoma, and leukemia) as well. The inclusion criteria were observational studies that included cancer patients in any setting and assessed whether low physical function was a predictor of mortality in these patients. Studies that examined the future causes of death in healthy participants were excluded. The database searches retrieved 1370 references, which were reduced to 689 after excluding duplicate articles. The remaining 689 studies were screened by title and abstract, resulting in the exclusion of 589 studies due to irrelevant study designs or discrepancies regarding the population or intervention type. We performed full-text reviews of 100 articles and excluded 74 articles. Finally, 26 studies were identified that were deemed suitable for our meta-analysis. All the articles were observational studies. Detailed characteristics of the 26 studies are presented in Table 7.2 [58]. This meta-analysis included studies of cancers including hematological cancer [59–64], acute myeloid leukemia [65, 66], lung cancer [67–69], colorectal cancer [70], gynecological cancers [71], and brain tumors [72], as well as studies that included patients with a variety of cancers [73–84]. In the participants of the included studies, physical function outcome measures including HGS, gait speed, 6-MWT, SPPB, and TUG test results were analyzed. The types of physical assessments were different in each study. Five physical function outcomes (HGS, gait speed, 6-MWT, SPPB, and TUG score) from 26 studies were included in a random-effects meta-analysis. The effect of physical function on mortality risk was estimated using a forest plot of inverse hazard ratio (HR) and 95% confidence interval (CI). Subgroup analysis was used to identify the main possible

Table 7.2 Characteristics of studies included in the systematic review of physical function and mortality

Author, year, country	Participants (number, gender, age)	Cancer type	Functional outcomes	Follow up period	Confounders	Number of deaths
Bland et al., 2020, Australia	$n = 203$ Female, 37% Age: 68.6 ± 11.6 years	Mixed	Grip strength ≤tenth percentile	2.5 years	Adjusted results were not used because the results of a single variable analysis were used	$n = 133$
Brown et al., 2015, USA	$n = 413$ Female, 60% Age: 72.2 ± 0.47 (SE) years	Mixed	SPPB Fast walk test	18 years	Adjusted for age, sex, body mass index (continuous), type of cancer, time since cancer diagnosis (continuous), smoking status, healthy eating index, weekly drinking, hypertension, diabetes, asthma, arthritis, myocardial infarction, stroke, congestive heart failure, hospitalization in the prior year, self-reported health status, weekly walking (ordinal), hemoglobin, albumin, and C-reactive protein	$n = 315$
Burtin et al., 2020, Belgium	$n = 936$ Female, 36% Age: 68.0 ± 10.0 years	Lung	Grip strength	60 months (median)	Adjusted for age, gender, disease stage, and comorbidities	$n = 683$
Cesari et al., 2013, Italy	$n = 200$ Female, 100% Age: 73.5 ± 6.2 years	Gynecological	SPPB Gait speed Grip strength	1 year	Adjusted for age, body mass index, Mini-Mental State Examination, quality of life, and cancer stage	$n = 23$
Deschler et al., 2013, Germany	$n = 195$ Female, 32.3% Age: 71.0 (60–87) years	Hematological	TUGT	461 days	Adjusted results were not used because the results of a single variable analysis were used	Not reported
Deschler et al., 2018, Germany	$n = 106$ Female, 38.0% Age: 66.0 (60–78) years	Hematological	TUGT	43.5 months (median)	Adjusted results were not used because the results of a single variable analysis were used	$n = 68$

Ferrat et al., 2015, France	$n = 993$ Female, 48.8% Age: 80.2 ± 5.6 years	Mixed	TUGT	1 year	Adjusted for age, disease, and comorbidities, malnutrition	$n = 379$
Hamaker et al., 2014, Netherlands	$n = 108$ Female, 47.0% Age: 78.2 (67.1–98.9) years	Hematological	TUGT	2.8 years (median)	Adjusted for age, sex, comorbidity, hematological diagnosis, tumor characteristics, performance status, and treatment decision	Not reported
Jones et al., 2012, USA	$n = 118$ Female, 40% Age: 61.0 ± 10.0 years	Lung	6MD (<358.5, 358.5–450, >450)	3 years	Adjusted for age, gender, cohort, and performance status (ECOG)	$n = 77$
Jones et al., 2015, USA	$n = 407$ Female, 37.1% Age: 54.0 (18–75) years	Hematological	6MD (< 400, ≥ 400)	2 years	Adjustment for KPS alone and age alone and then after adjustment for clinical factors that had a significant univariate relationship ($p < 0.05$) with each outcome	$n = 172$
Kanesvaran et al., 2011, Singapore	$n = 249$ Female, 38.6% Age: 77.0 (70–94) years	Mixed	TUGT	11.9 months (median)	Adjusted results were not used because the results of a single variable analysis were used	$n = 172$
Klepin et al., 2010, USA	$n = 429$ Female, 36.1% Age: 77.2 ± 3.3 years Non-metastatic $n = 268$ Female, 32.8% Age: 77.1 ± 3.3 years Metastatic $n = 159$ Female, 41.5% Age: 77.5 ± 3.4 years	Mixed	Gait speed Grip strength 6MD	3.8 years (median)	The full models included demographics, smoking status, physical activity, major disability at baseline, cognitive screen (modified Mini-Mental State Examination score), diabetes mellitus, cardiovascular disease, obstructive pulmonary disease, and cancer type (breast, lung, prostate, colorectal)	Not reported

(continued)

Table 7.2 (continued)

Author, year, country	Participants (number, gender, age)	Cancer type	Functional outcomes	Follow up period	Confounders	Number of deaths
Klepin et al., 2013, USA	*n* = 74 Female, 45.9% Age: 68.8 (65.8–74.3) years	AML	SPPB	Not reported	Adjusted for age, gender, ECOG-PS, cytogenetic risk group, prior MDS, and hemoglobin	*n* = 39
Liu et al., 2019, USA	*n* = 448 Female, 34.8% Age: 79.7 ± 4.0 years	Hematological	Gait speed Grip strength	≥6 months	Adjusted for age, CCI, sex, intensive treatment, aggressive malignancy, five-word recall, executive function and PS	Not reported
Marjanski et al., 2019, Poland	*n* = 624 Female, 38% Age: 64.0 years	Lung	6MD (≤525, >525)	54 months (median) 92 months (maximum)	Adjusted for age, age-adjusted CCI, gender, pathological TNM, type of resection	*n* = 275
Pamoukdjian et al., 2017, France	*n* = 190 Female, 49.5% Age: 80.6 ± 5.6 years	Mixed	Gait speed <0.8 (m/s) SPPB <9/12	6 months	Adjusted for gender and ECOG-PS	*n* = 22
Pamoukdjian et al., 2020, France	*n* = 603 Female, 54% Age: 81.2 ± 6.1 years	Mixed	Gait speed SPPB Grip strength	6 months	Adjusted for sex, total CIRS(G) score, BMI, cancer site, cancer extension, and supportive care alone	*n* = 108
Puts et al., 2011, Canada	*n* = 112 Female, 69.6% Age: 74.1 (65–92) years	Mixed	Gait speed Grip strength	6 months	Adjusted for sex, age, number of comorbid conditions, extent of disease (early vs advanced), extensive treatment received (yes/no), and lung cancer diagnosis (yes/no)	*n* = 15
Ruden et al., 2011, USA	*n* = 243 Female, 32% Age: 49 ± 12 years	Brain	6MD (390 meters, 390–489 meters, 489 meters)	27.43 months (median)	Adjusted for age, sex, grade, the number of prior disease progressions, and KPS	*n* = 149

Salas et al., 2020, Canada	*n* = 168 Female, 48.8% Age: 58 (19–77) years	Hematological	Grip strength TUGT	1 year	Adjusted for disease-risk index and C-reactive protein	*n* = 32
Schmidt et al., 2018, Germany	*n* = 131 Female, 56.0% Age: 71 (68–75) years	Mixed	TUGT	1 year	Adjusted results were not used because the results of a single variable analysis were used	*n* = 37
Soubeyran et al., 2012, France	*n* = 348 Female, 40.5% Age: 77.45 (70–99.4) years	Mixed	TUGT	6 months	Adjusted for age, tumor site, activities of daily living, Mini-Mental State, platelet count, and performance status	*n* = 56
Timilshina et al., 2014, Canada	*n* = 239 Female, 43.3% Age: 57.5 years	AML	Grip strength	60 days	Adjusted results were not used because the results of a single variable analysis were used	*n* = 9
Ugolini et al., 2015, Italy	*n* = 46 Female, 47.8% Age: 80.5 ± 6.7 years	Colorectal	TUGT	4.6 years (median)	Adjusted results were not used because the results of a single variable analysis were used	*n* = 18
Versteeg et al., 2018, Netherlands	*n* = 103 Female, 34% Age: 70.0 ± 6.6 years	Mixed	Grip strength	436 days (median)	Adjusted for sex, cancer type, and treatment line	Not reported
Zhuang et al., 2020, China	*n* = 8257 Female, 47.3% Age: 58 (16) years	Mixed	Grip strength	1, 3 years	Adjusted for age, gender, body mass index, albumin, hemoglobin, weight loss, Karnofsky performance scores, nutritional risk screening 2002, patient-generated subjective global assessment scores, physical activity, intake status, mid-arm circumference, triceps skinfold thickness, maximum calf girth, smoking, alcohol drinking, tea drinking, previous treatments, types of chemotherapy, cancer stages, cancer types, quality of life, and comorbidities	Not reported

ADL activities of daily living; *AML* acute myeloid leukemia; *CCI* Charlson comorbidity index; *ECOG-PS* Eastern Cooperative Oncology Group-Performance Status; *SPPB* short physical performance battery; *TNM* tumor, lymph node, metastasis, *TUGT* timed up and go test; *USA* United States of America; *6MD* 6-minute distance

source of heterogeneity. Whenever possible, potential sources of heterogeneity for each outcome were examined based on age (mean: <80 or ≥80 years). Consequently, meta-analyses of five physical function outcomes from 26 observational studies showed that superior physical function was predominantly associated with the mortality risk in cancer patients. An analysis of 11 studies revealed that HGS was markedly associated with mortality risk (HR = 1.15, 95% CI = 1.04–1.28, $P = 0.005$, $n = 7182$), although high heterogeneity was observed ($I^2 = 71\%$). In the subgroup of patients aged ≥80 years, although heterogeneity decreased slightly ($I^2 = 60\%$), the effect size was high (HR = 2.90, 95% CI = 1.63–5.16, $P = 0.01$, $n = 603$) (Fig. 7.2). Six studies showed that gait speed was markedly associated with mortality risk, with a high effect size (HR = 1.58, 95% CI = 1.23–2.05, $P = 0.0004$, $n = 1912$), although high heterogeneity was found ($I^2 = 79\%$). High heterogeneity decreased slightly in the subgroup analysis, and the effect size of the subgroup of patients aged ≥80 years was higher than that of patients aged <80 years ($P = 0.009$, $I^2 = 85\%$) (Fig. 7.3). Five studies showed that the 6-MWT outcomes were markedly associated with mortality risk, showing low heterogeneity (HR = 1.55, 95% CI = 1.19–2.03, $P = 0.001$, $I^2 = 34\%$, $n = 1821$) (Fig. 7.4). SPPB results were the most characteristic, and in five studies the SPPB score was markedly associated with mortality risk with the largest effect size (HR = 2.37, 95% CI = 1.82–3.09, $P < 0.00001$, $I^2 = 4\%$, $n = 1270$). The effect sizes were large in both subgroups, and no significant differences were found between subgroups (Fig. 7.5). The TUG results were similar to those of SPPB, which was markedly associated with mortality risk with a high effect size and low heterogeneity (HR = 2.66, 95% CI = 2.22–3.18, $P < 0.00001$, $I^2 = 0\%$, $n = 2344$) (Fig. 7.6). All physical function outcomes were significantly

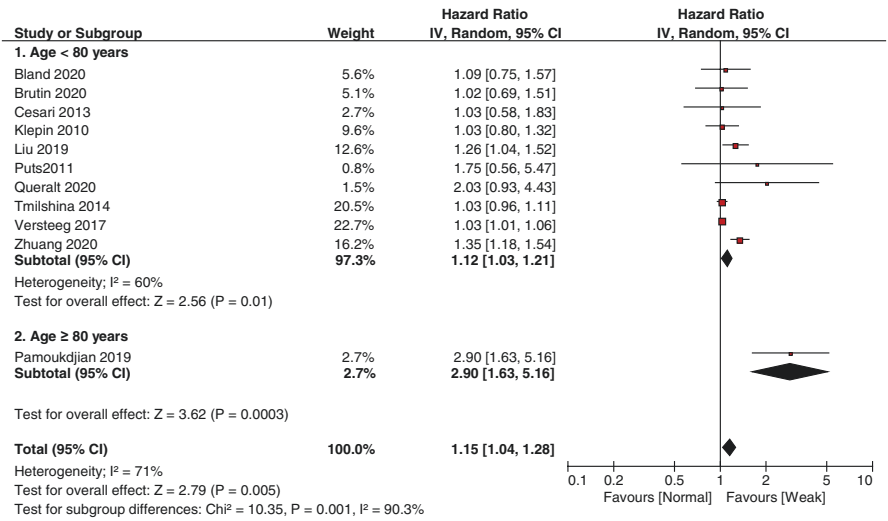

Fig. 7.2 Pooled estimate for mortality risk associated with handgrip strength in cancer patients. Subgroup was separated based on the mean age of patients of the study, whether older than 80 years or not. *IV* inverse variance; *CI* confidence interval

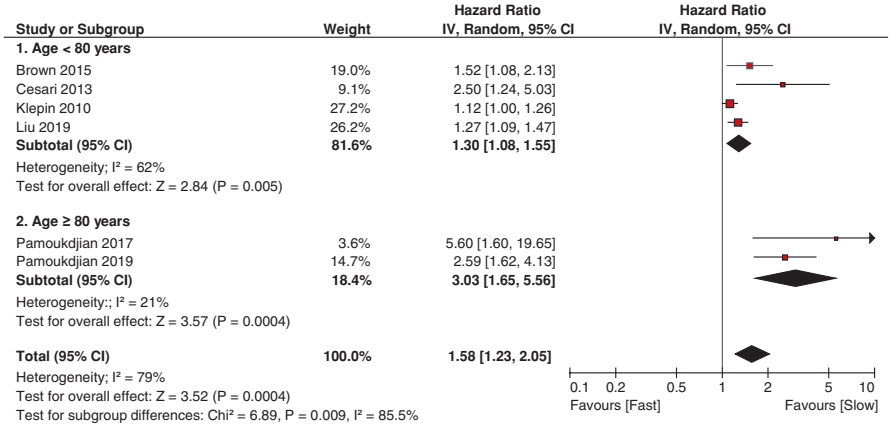

Fig. 7.3 Pooled estimate for mortality risk associated with gait speed in cancer patients. Subgroup was separated based on the mean age of patients of the study, whether older than 80 years or not. *IV* inverse variance; *CI* confidence interval

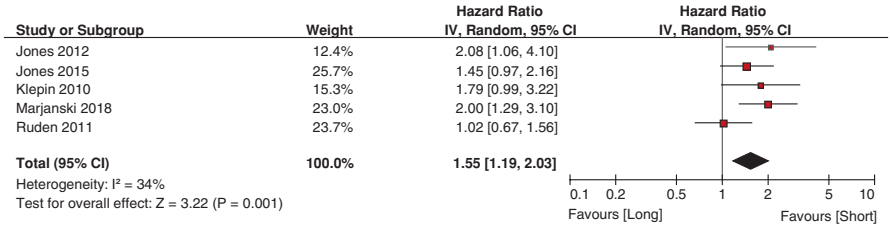

Fig. 7.4 Pooled estimate for mortality risk associated with 6-minute walking test in cancer patients. *IV* inverse variance; *CI* confidence interval

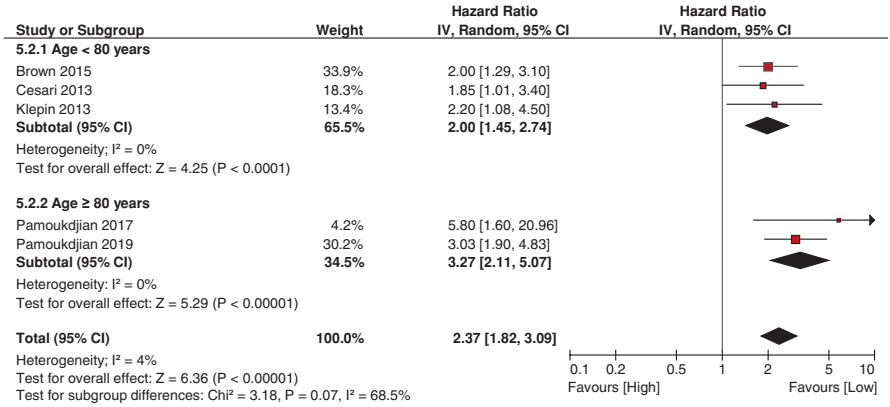

Fig. 7.5 Pooled estimate for mortality risk associated with short physical performance battery in cancer patients. Subgroup was separated based on the mean age of patients of the study, whether older than 80 years or not. *IV* inverse variance; *CI* confidence interval

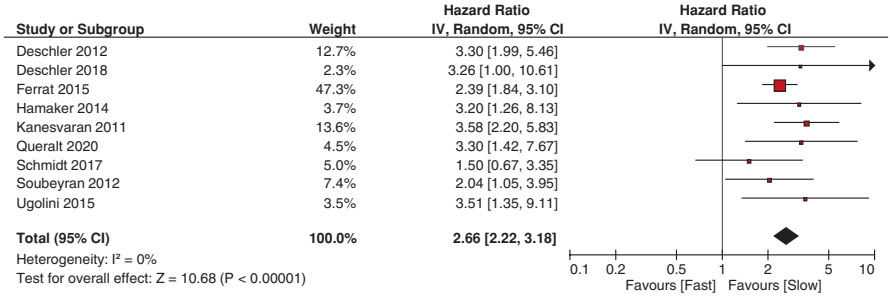

Fig. 7.6 Pooled estimate for mortality risk associated with timed up-and-go test in cancer patients. *IV* inverse variance; *CI* confidence interval

associated with mortality risk in cancer patients in our meta-analysis. The SPPB and TUG test showed an especially high HR, reflecting the mortality risk in cancer patients more accurately. Furthermore, for handgrip strength and gait speed, we divided the patients into two age groups: those aged ≥80 years and those aged <80 years. As a result, patients aged ≥80 years had a higher HR than those aged <80 years in both measurements.

The physical function outcomes may provide objective evidence of the reserve capacity, which is influenced by multiple factors, including chronic disease, physiological changes of aging, nutrition, fitness, psychosocial well-being, and motivation. However, the detailed mechanism by which physical function influences mortality remains unclear and further studies are warranted.

7.5 Exercise Therapy and Mortality

Exercise therapy is considered effective for not only the physical function of cancer patients but also the physical and psychological symptoms and QoL. Meanwhile, the understanding of the effects of exercise therapy on the recurrence and prognosis of cancer patients has improved. From the results of the systematic review by Ezzatvar et al. [57], the improvement in physical function can be attributed to the contribution of exercise therapy. However, we find it necessary to confirm that exercise therapy itself has an impact on relapse and prognosis as well, and, therefore, we conducted a meta-analysis to investigate this. We present the results in this section [85].

Literature searches were conducted using the MEDLINE, CINAHL, Cochrane Library, Scopus, ProQuest, and PEDro for articles published before May 2019. The search strategy was conducted on the aforementioned databases based on the following MeSH terms: “cancer,” “tumor,” “randomized controlled trial,” “exercise,” “rehabilitation,” and “physical therapy.” The phrase “disorder for cancer” was also

used for the search (e.g., lymphoma, hematopoietic malignancy, and carcinosarcoma). In addition, the words "mortality," "recurrence," and "prevalence" were added to the search terms. The inclusion criteria were randomized controlled clinical trials that included cancer patients and survivors in any setting; the intervention group performed physical exercise, and its effects on mortality were evaluated. Systematic reviews, editorials, cross-sectional studies, case reports, and case series were also excluded. Exercise guidance was excluded from the study. A control group that did not receive any (major) exercise intervention was used for comparisons. The database searches retrieved 2868 references, which were reduced to 2698 studies after excluding duplicate articles. The remaining 2698 studies were screened by the title and abstract; consequently, 2384 studies were excluding due to irrelevant study designs or discrepancies regarding the population or the intervention type. A full-text review was performed of 314 RCTs; 306 RCTs were excluded. Detailed characteristics of the eight RCTs are shown in Table 7.3 [85]. In two of the RCTs, the participants were patients with breast cancer who had undergone surgery [86, 87], in another RCT patients diagnosed with lung cancer [88] were included, who underwent allogeneic hematopoietic stem cell transplantation [89]. The rest of the RCTs included patients with other types of cancers [90–93]. Interventions in the RCTs were roughly categorized as a short-term intervention rehabilitation program (with a duration of 2 weeks) performed in a hospital setting [90, 91], and ambulatory treatment or home exercise (with a duration of 2–8 months) for long-term outpatients [86–88, 92, 93]. Regarding the content of the interventions, aerobic exercise and/or resistance training was conducted in all RCTs. Therefore, nine exercise groups from eight RCTs were included in the random-effects meta-analysis. This analysis included 656 patients in the exercise group and 579 patients in the control group. The efficacy of exercise therapy in terms of mortality risk and recurrence in cancer patients was estimated using a forest plot. A meta-analysis of nine exercise groups from eight RCTs showed that physical exercise significantly reduced the risk of mortality in cancer patients and survivors (risk ratio [RR] = 0.76, 95% CI = 0.40–0.93, I^2 = 0%, P = 0.009, n = 1235) (Fig. 7.7). Cancer recurrence data were available for only two RCTs, one of which included two exercise groups. Thus, a meta-analysis of three groups from two RCTs was performed, showing that exercise significantly reduced recurrence risk in cancer survivors (RR = 0.52, 95% CI = 0.29–0.92, I^2 = 25%, P = 0.030, n = 661) (Fig. 7.8). This meta-analysis also revealed that exercise interventions positively affected the mortality rates and recurrence in cancer patients. The increase in physical activity and activation of the immune system by exercise therapy were considered the reasons for this. We, as physical therapists, should remember that interventions aimed at improving physical function and ADLs may lead to continued treatment, which in turn may affect recurrence and prognosis. Elucidation of these detailed mechanisms may be a future challenge.

Table 7.3 Characteristics of studies included in the systematic review of exercise therapy and mortality

Author, year	Cancer type	Intervention	Participants (gender, number, age)	Intervention	Duration and timing of exercise	Observation period	Measure (outcome)
Courneya et al., 2014	Breast	Ex1 = aerobic exercise Ex2 = resistance training vs. Con = usual care	%female = 100% Ex = 160 <50 years = 90 >50 years = 70 Con = 82 <50 years = 42 >50 years = 40	Aerobic exercise: three times/week, beginning at 60% of their VO2max for 1–6 weeks and progressing to 70% during 7–12 weeks and 80% beyond 12 weeks. Exercise duration began at 15 min for 1–3 weeks and increased by 5 min every 3 weeks until 45 min at 18 weeks Resistance exercise (3 times/week): performing 2 sets of 8–12 repetitions of nine different exercises at 60–70% of their estimated 1-repetition maximum	Duration of chemotherapy, beginning 1–2 weeks after starting chemotherapy and ending 3 weeks after completing chemotherapy (at least 18 weeks)	8 years	DFS, mortality, DDFS, RFI
Dhillon et al., 2017	Lung	Ex = aerobic exercise vs. Con = usual care	%female = 45% Ex = 56 64 (38–80) years Con = 55 64 (34–76) years	Increasing recreational physical activity (PA) by>3 MET h/week. Sessions lasted 1 h; 45-min PA; 15-min behavior support. PA was predominantly aerobic, and home-based PA was encouraged	Ambulatory treatment 8 weeks	6 months	Mortality, physical activity, accelerometers (min/day)

Hayes et al., 2017	Breast	Ex = aerobic and resistance exercise vs. Con = usual care	%female = 100% Ex = 207 51.7 ± 8.8 years Con = 130 53.9 ± 8.3 years	Aerobic-based and resistance based: 180+ min, moderate-intensity exercise, to be accumulated on at least 4 days per week. Commencing at 6 weeks post-surgery	Post-surgery Home exercise 8 months	96 months	Mortality, DFS
Jones LW et al., 2014	Mix	Ex = aerobic training vs. Con = usual care	%female = 26% Ex = 47 64 ± 10 years Con = 43 66 ± 11 years Patients with heart failure	Supervised aerobic training (treadmill or stationary cycle ergometer) sessions per week lasting 20–45 min per session at 60–70% of heart rate reserve	Ambulatory treatment Home exercise 12 weeks	12 months	All-cause mortality
Licker et al., 2017	Mix	Ex = high-intensity interval training vs. Con = usual care	%female = 40% Ex = 74 64 ± 13 years Con = 77 64 ± 10 years	After a 5-min warm-up period at 50% at peak work rate (peakWR); two 10-min series of 15-s sprint intervals (at 80%–100% peakWR) interspersed by 15-s pauses and a 4-min rest between the two series; cooled down with a 5-min active recovery period at 30% peakWR	Pre-surgery Ambulatory treatment (2–3 times/week)	30 days	Postoperative morbidity

(continued)

Table 7.3 (continued)

Author, year	Cancer type	Intervention	Participants (gender, number, age)	Intervention	Duration and timing of exercise	Observation period	Measure (outcome)
Rief et al., 2014	Mix	Ex = resistance training vs. Con = control	%female = 45% Ex = 30 61.3 ± 10.1 years Con = 30 64.1 ± 10.9 years	Resistance training: 30 min	During hospitalization 2 weeks	12 weeks	Mortality, pain score
Rief et al., 2016	Mix	Ex = resistance training vs. Con = passive physical therapy	%female = 45% Ex = 30 61.3 ± 10.1 years Con = 30 64.1 ± 10.9 years	Resistance training: 30 min	During hospitalization 2 weeks	10 months (range, 2–35 months)	Mortality, PFS, bone survival
Wiskemann et al., 2015	Allogeneic hematopoietic stem cell transplant	Ex = endurance exercises and resistance exercises vs. Con = usual care	%female = 33% Ex = 50 48.2 ± 14.5 years Con = 53 50.0 ± 12.4 years	A combination of endurance exercises, three to five times weekly, and resistance exercises twice weekly, with each session lasting 20–40 min	After allogeneic stem cell transplantation Before and after hospital admission After discharge: 8 weeks	2 years	NRM, TM

Ex exercise group; *Con* control group; *DFS* disease-free survival; *DDFS* distant DFS; *RFI* recurrence-free interval; *PFS* progression free survival; *NRM* non-relapse mortality; *TM* total mortality

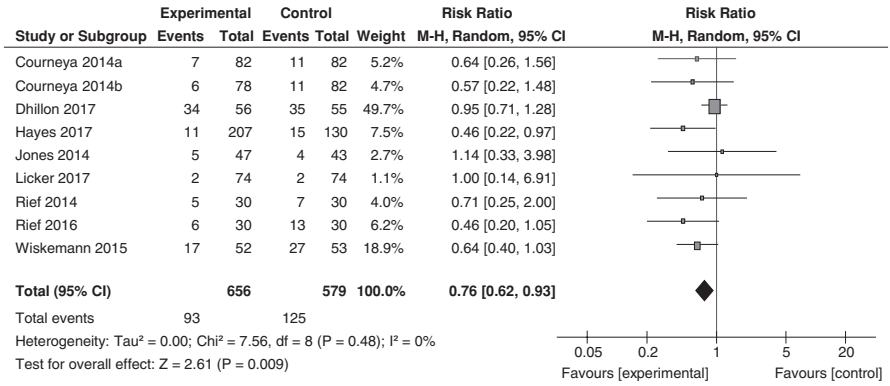

Fig. 7.7 Risk ratio for the effect of exercise on the mortality in cancer patients and survivors. *CI* confidence interval

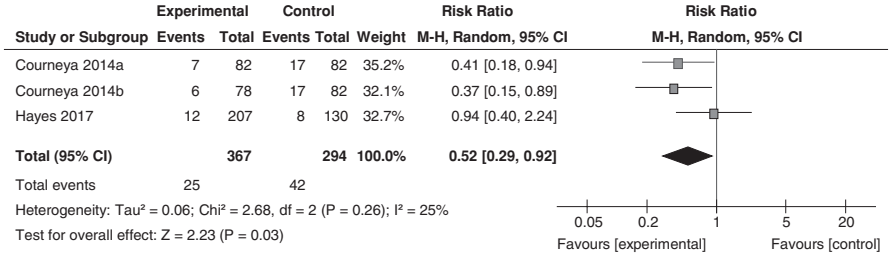

Fig. 7.8 Risk ratio for the effect of exercise on the recurrence in cancer survivors. *CI* confidence interval

7.6 Conclusions

In this chapter, the physical function assessments used in cancer physical therapy in Japan have been described. We explored the relationship between exercise therapy and improved physical functions in cancer patients and found that exercise therapy is effective not only for enhancing/improving the physical function but also for reducing the physical and psychological symptoms, which leads to improvement of the QoL. Moreover, there is an improved understanding of the effects of exercise therapy and the resulting physical function improvement on the recurrence and prognosis of cancer patients. Consequently, we inferred that exercise therapy is not just a supportive therapy but an active treatment. We hope that the mechanism underlying this positive effect will be elucidated in the future and the usefulness of exercise therapy will be widely recognized.

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8 Exercise Therapy on Muscle Mass and Physical Function in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Takahiro Takekiyo and Shinichiro Morishita

Abstract

Patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) tend to experience a significant decline in physical function after allo-HSCT due to decreased physical activity caused by adverse reactions such as high-dose chemotherapy for allo-HSCT and post-transplant complications. Therefore, rehabilitation during the transplant period is essential to prevent loss of physical function and/or muscle mass. Exercise therapy is recommended to be a combination of aerobic exercise and strength training. The exercise program should include daily stretching, strength training two to three times a week, and aerobic exercise for at least 150 min a week. It is also important to instruct patients to do self-directed exercise. The concept of inpatient allo-HSCT rehabilitation is to divide the exercise therapy into three periods: "admission to preconditioning," "allo-HSCT to engraftment," and "engraftment to discharge." Goals are set for each of these periods to help keep the patient as active as possible. Risk management is also important in the implementation of exercise therapy. In particular, it is necessary to consider the intensity and type of exercise therapy during the myelosuppressive phase, when there is a higher possibility of bleeding, and during complications such as graft-versus-host disease. It is important to maintain physical function to achieve early discharge from the hospital as well as early return to society.

T. Takekiyo (✉)
Department of Rehabilitation, Imamura General Hospital, Kagoshima, Japan
e-mail: ta.takekiyo@jiaikai.jp

S. Morishita
Department of Physical Therapy, School of Health Science, Fukushima Medical University, Fukushima, Japan
e-mail: morishit@fmu.ac.jp

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Keywords

Allogeneic hematopoietic stem cell transplantation · Exercise therapy · Muscle mass · Physical function

8.1 Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative treatment in hematopoietic malignancy [1]. After diagnosis, chemotherapy, including induction therapy and consolidation therapy, is administered. In general, it takes several months from diagnosis to transplantation. Therefore, patients often experience inactivity and anorexia for a long period of time; between being diagnosed and receiving allo-HSCT. As a result, it has been reported that muscle strength and endurance in such patients are already reduced compared to those in healthy people of the same age [2]. Factors contributing to the decline in physical function after transplantation include high-dose chemotherapy and radiation therapy (total-body irradiation: TBI) as pre-transplant treatment, fever, steroid administration, acute graft-versus host disease (GvHD), age, and decreased activity due to prolonged hospitalization [3–5]. Therefore, rehabilitation during the inpatient period is very important to prevent the decline of physical functions [5–7]. In recent years, pre-transplant rehabilitation has been investigated and reported to be safe and feasible [8, 9]. On the other hand, exercise therapy during the inpatient period is useful not only in preventing the decline of physical functions after transplantation but also in reducing fatigue and maintaining/improving quality of life (QOL) [10].

In this chapter, we focus on exercise therapy for maintaining physical function and muscle mass during the allo-HSCT inpatient period. In Japan, allo-HSCT rehabilitation is usually provided one-on-one by physiotherapist, and in this chapter we will introduce individualized rehabilitation.

8.2 Allo-HSCT Rehabilitation

Allo-HSCT rehabilitation can be divided into three main periods: pre-HSCT, inpatient, and outpatient (Fig. 8.1). During the inpatient period, it is helpful to divide it into three additional periods to facilitate the objectives of the interventions during that period (Fig. 8.2).

Fig. 8.1 Allo-HSCT physical therapy pathway

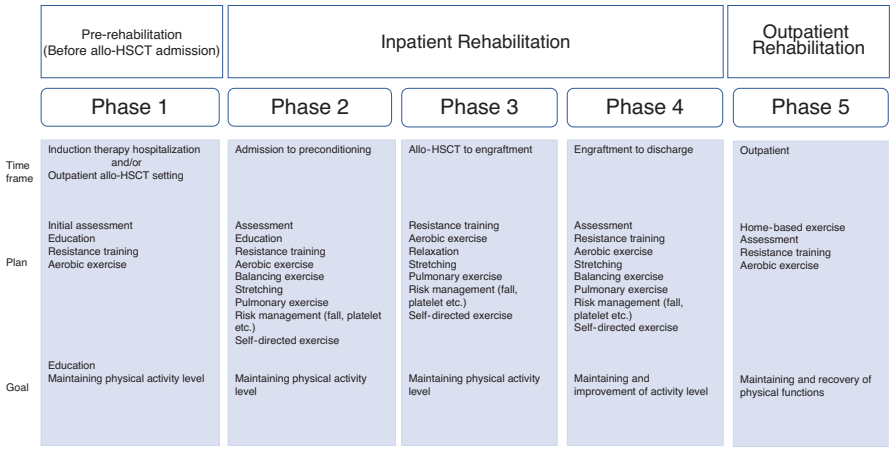

Fig. 8.2 Details of allo-HSCT physical therapy pathway

In particular, since various complications and symptom changes occur during hospitalization, it is expected that safe and effective rehabilitation can be carried out by changing the intervention according to the period.

8.3 Procedure

After diagnosis, induction therapy and consolidation therapy are administered. Once the decision to perform an allo-HSCT is made, a donor search is conducted. In general, it takes several months from diagnosis to allo-HSCT. Donors are determined from bone marrow donor registry and cord blood bank. In the case of banked donor transplantation, it takes several months from registration to transplantation.

In recent years, with the development of cord blood transplantation (CBT), early transplantation has become possible even without blood relatives or potential bone marrow donors.

Before transplantation, the patient undergoes a variety of evaluations, including general health condition (cardiovascular, respiratory, gastrointestinal, hepatic, renal, etc.), dental, and psychiatric, in addition to the condition of the primary disease. These assessments are performed at admission prior to allo-HSCT, or when the patient is an outpatient prior to hospitalization for HSCT.

8.4 Types of Allo-HSCT and Intensity of Preconditioning Treatment

The types of allo-HSCT can be divided into bone marrow transplantation (BMT), peripheral blood stem cell transplantation (PBSCT), and CBT based on the source of the transplanted cells [11]. The transplanted hematopoietic stem cells become

engrafted in the bone marrow and restore normal hematopoietic function, which is called engraftment. WBC (neutrophil) engraftment takes 2–3 weeks for BMT and PBSCT [12], and 3–4 weeks for CBT [13]. CBT has the advantage of finding a donor easily, but compared to other transplantation methods, the problems are that it takes longer to achieve engraftment (increased risk of infection) and that engraftment failure occurs when donor hematopoiesis does not recover.

The intensity of preconditioning treatment can be divided into myeloablative conditioning (MAC) with increased intensity of chemotherapy drugs and reduced intensity conditioning (RIC) [14]. MAC is generally used for younger patients, while RIC is used for older patients and for transplants in non-complete remission. Compared to RIC, transplants using MAC regimen have more severe side effects from the chemotherapy drug (stomatitis, myocardial damage, diarrhea, cystitis, abnormal liver and kidney function, and others).

8.5 After Hospitalization for Allo-HSCT

After hospitalization for allo-HSCT, high-dose chemotherapy and radiation therapy (TBI) are administered as pre-transplant treatments. Adverse reactions to these chemotherapies and radiation therapies usually begin to appear from the late stage of the preconditioning period to a few days after the transplant.

Pre-conditioning treatment causes a drop in blood counts. Hematopoietic agents (granulocyte colony stimulating factor; G-CSF) are used from around the fifth day of allo-HSCT to restore blood cells and promote an increase in donor-derived blood cells. In general, if more than 500 neutrophils appear three or more times in a row, white blood cell engraftment is considered to have been achieved [15]. If there are no donor-derived post-transplant complications (GvHD) or other infections, administration of immunosuppressive drugs can be changed from intravenous to oral, and the patient can be discharged. It takes approximately 1–3 months after allo-HSCT to be discharged from hospital.

8.6 Treatment Environment

In general, allo-HSCT is performed in a Class 100 clean room (International Organization for Standardization (ISO) Class 5) according to the US Federal Standards (US Fed. Std. 209E). After allo-HSCT, the patients stay in the same room until neutrophil recovery. After neutrophil engraftment, they move to a Class 1000–10,000 (ISO Class 6–7) environment.

In recent years, with the widespread use of bio-clean rooms (BCRs), allo-HSCT have been performed in private rooms rated Class 100–1000 (ISO class 5–6), as well as during inpatient care in a Class 10,000 (ISO class 7) clean ward environment. In cases where transplantation is being performed in a facility equipped with a BCR ward, restrictions on activity in the private room are relatively relaxed, and the patients are allowed to perform daily activities such as walking along the

Fig. 8.3 (**a**) Bio-clean room. (**b**) Bio-clean ward

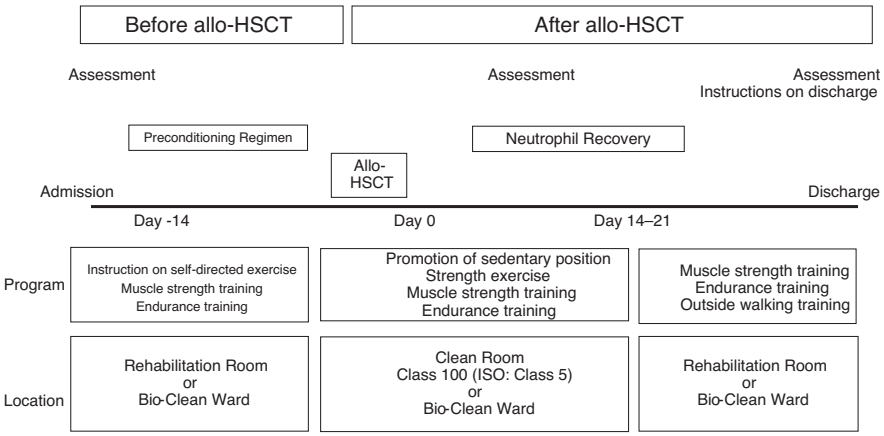

Fig. 8.4 Allo-HSCT rehabilitation protocol

corridors and showering. Our facility is equipped with a BCR, and allo-HSCT treatment and rehabilitation are performed in an ISO Class 6 private room (Class 7 in the ward) environment (Figs. 8.3 and 8.4).

8.7 Assessment

Various assessments are performed during allo-HSCT treatment. Pre-HSCT, post-HSCT, and discharge assessments are the most common.

Pre-HSCT evaluations may be performed early in the transplant admission process or may be done prior to admission (at the time of final consolidation therapy admission or as an outpatient).

Post-HSCT assessment is performed at the time of neutrophil recovery and again when the patient is first allowed to move to the rehabilitation room. Discharge assessment is performed approximately 1 week prior to the time of discharge (Fig. 8.4).

8.7.1 Assessment Items

Physical function assessment includes evaluation of muscular strength, endurance, walking ability, flexibility, and balance. Muscle mass is measured via body composition assessment. Muscle mass is measured using a bioelectrical impedance analysis (BIA), a noninvasive and safe measurement device. However, body composition assessment using magnetic resonance imaging (MRI), computed tomography (CT), and dual X-ray absorptiometry (DEXA) are more accurate than BIA. Other assessments such as activities of daily living (ADL), fatigue, anxiety, and QOL are also performed. Selecting assessments that can be performed in an isolated room (or BCRs) is useful for ongoing assessment. In recent years, many institutions have used muscle strength, endurance, and QOL assessments in HSCT patients, but they are not standardized or uniform. Typical assessment items are shown in Table 8.1.

Table 8.1 Assessment

Physical function	
Strength	Upper: handgrip strength
	Lower: knee extension strength (hand dynamometer) 30-S chair stand test, five times sit to stand test
Flexibility	Sit and reach test
Balance	Standing on one leg time, functional reach test
Endurance	6-minute walking test (6MWT)
Walking ability	Timed up and go (TUG) test
Physical activity	Steps (pedometer)
Body composition	
Muscle mass	Bioelectrical impedance analysis (BIA) Dual energy X-ray absorptiometry (DEXA) Magnetic resonance imaging (MRI) Computed tomography (CT)
Mentation	
Health-related QOL	SF-36, EORTC QLQ-C30
Depression	Self-depression scale (SDS), hospital anxiety depression scale (HADS)
Fatigue	Cancer fatigue scale (CFS), brief fatigue inventory (BFI)
Others	
ADL	Barthel index (BI)
	Functional independence measurement (FIM)
General condition	ECOG performance stace (PS)

Abbreviations: *QOL* quality of life; *SF-36* medical outcome study 36-item short form health survey; *EORTC QLQ-C30* the European Organization for Research and Treatment of Cancer QLQ-C30; *ADL* activities of daily living

8.8 Exercise Therapy

A combination of strength training and aerobic exercise is recommended as a component of exercise therapy [16]. In addition, stretching, balance exercises, and ADL exercises are also recommended. Exercise prescription should also be based on the frequency, intensity, time, and type (FITT) method.

It is important for therapists to keep in mind the need to continue strength training, maintain the patient's ability to perform ADLs, maintain a sitting time, and maintain walking opportunities throughout the hospital stay. Recent reports are summarized in Table 8.2.

Table 8.2 Exercise intervention characteristics

Study	Type	Exercise frequency	Exercise time	Intensity	Intervention
T Takekiyo et al., 2015 [4]	Aerobic	Five times a week 20–40 min/day	10–15 min	60% of the heart rate reserve	One-on-one
	Strength		10–15 min	10–13 (somewhat hard)	
S Morishita et al., 2017 [18]	Aerobic/strength	5 days/week	20–40 min		One-on-one
ED Hacker et al., 2017 [19]	Strength	Three times a week		Borg scale 13	Partly Supervised
A Ishikawa et al., 2019 [5]	Aerobic	5 days a week	Up to 30 min	60% of the heart rate reserve	One-on-one
	Strength	5 days a week			
A Pahl et al., 2020 [20]	Strength	daily	20 min	Borg Scale 14–16	One-on-one
DS Mina et al., 2020 [21]	Aerobic	Three times a week	10–30 min	60% of the heart rate reserve	One supervised session and two unsupervised sessions
	Strength		10–15 min	1–2 sets of 4–6 repetitions per exercise using the participant's exercise bands	
R Hamada et al., 2021 [17]	Aerobic	Five times a week	20–40 min/day	Borg scale "somewhat hard"	One-on-one
	Strength			Karvonen method 40–60% HR	

8.8.1 Strength Training

The target intensity for resistance training exercise is “somewhat hard” to “hard” based on the Borg scale (10–16) [22, 23]. The intensity of exercise therapy should be performed ranged from 13–16 (Borg scale) when before transplantation or near discharge and 10–13 during complications. It is important to choose a program that primarily uses large muscle groups, and it is important to do this for the upper extremities, lower extremities, and trunk. Performing exercises in the supine, sitting, and standing positions makes it easier for patients to perform them as a self-directed exercise. As lower extremity strength training, step climbing exercise using a 10–20-cm step is also useful, especially during the period of restricted activity leading up to the WBC (neutrophil) engraftment. During hospitalization for allo-HSCT, muscle mass loss due to disuse syndrome seems to be greater on the central side than on the peripheral side [4], so an enhanced approach to the central region is also desirable. It is recommended that strength training should be performed for two to three times per week [16, 24, 25]. At our institution, we have introduced 5–10 min of strength training (of a total of 40 min of exercise) into our daily program, and we practice training at moderate intensity (Borg 13) with breaks.

8.8.2 Endurance (Aerobic) Training

Endurance (aerobic) training is performed using the Karvonen method [26] with 60% of the maximum heart rate [4, 5, 21]. Endurance training should be performed using a bicycle ergometer or corridor walking. It is also useful to employ the Borg scale for endurance training [27], with a target score of 12–14. Maintenance of walking ability is essential for discharge to home, and patients should always be made aware of the need for walking exercise from the time of admission.

Aerobic exercise is recommended for at least 150 min per week, 3–5 days per week [16, 24, 25].

8.8.3 Stretching

Stretching serves as a warm-up in preparation for exercise or cool-down. It mainly involves stretching the large muscle groups of the upper and lower extremities, as well as those in the trunk. Stretching is also useful in preventing secondary pain such as back pain caused by lying in bed. Patients should be encouraged to do this as a voluntary activity. It is recommended that stretching should be performed daily [24].

8.8.4 Balance Exercise

Balance exercises may be performed in a sitting position using a balance disc or exercise ball. Standing exercises are also useful. Balance exercises are also useful in preventing falls and should be practiced throughout the hospital stay.

8.8.5 ADL Exercise

As discharge from the hospital approaches, it is necessary to make sure that the patient's ADL abilities are maintained according to their home environment. In Japanese houses, many people live using tatami mats, so the ability to stand up from a sitting position on the floor may be necessary. In addition, the ability to bathe, climb stairs, and perform other everyday physical tasks may be required.

8.8.6 Self-Directed Exercise

One-on-one or supervised exercise alone may be insufficient for the daily physical activity. It is useful to provide sufficient self-directed exercise instruction at the start of rehabilitation. Distributing leaflets is also helpful in order to visually understand the exercise. An exercise example is shown in Fig. 8.5a–c.

The exercise menu should include activities that can be performed in bed, in a sitting position, and in a standing position. Risk management (precautions) during exercise should also be explained. In particular, during the myelosuppression phase (anemia, thrombocytopenia), a thorough explanation should be added.

Exercise goals (exercise intensity) should be developed together with the patient, and if possible, a weekly plan should be made.

Physical activity of 1.6–2.9 metabolic equivalents (Mets) and 3.0 Mets or more have been reported to be positively correlated with the results of a 6-min walking test [18]. It is also useful to use the Mets index as a guide for the amount of physical activity that a patient should perform each day.

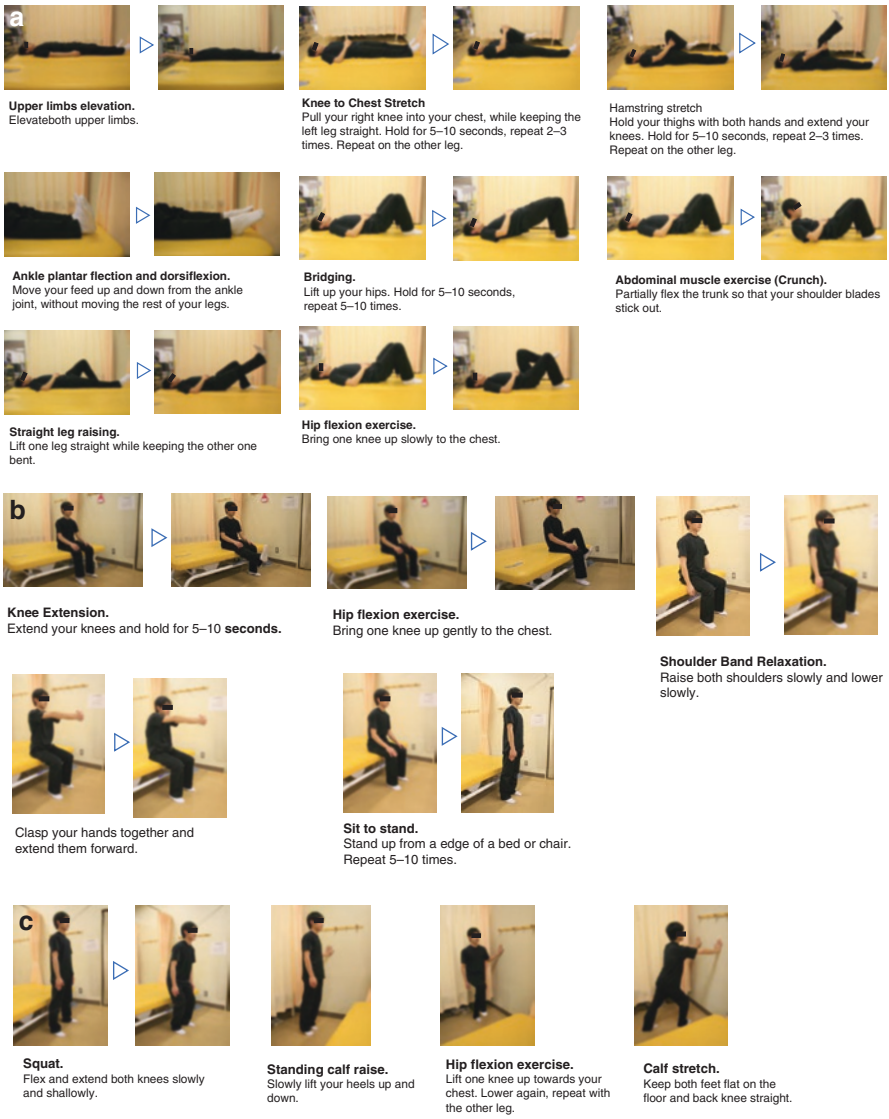

Fig. 8.5 (**a**) Self-directed Exercise (supine position). (**b**) Self-directed Exercise (seated position). (**c**) Self-directed Exercise (standing position)

8.9 Approach to Exercise Therapy

8.9.1 Pre-HSCT Treatment Period

When starting exercise therapy during the transplant period, it is necessary to fully explain the necessity of exercise therapy, an exercise program, self-directed exercise, and what to do in case of complications. In recent years, many HSCT patients have experienced rehabilitation during induction therapy or consolidation therapy, and many of them understand the necessity of exercise therapy. For patients who have not experienced rehabilitation, asking about their experience with adverse reactions, decreased activity, and muscle weakness, especially during induction therapy and consolidation therapy, can help them understand the need for exercise therapy. Regimen-related toxicity (RRT), such as nausea and diarrhea, often makes it difficult to implement rehabilitation. Therefore, when RRT occurs, if the patient's physical therapist explains the necessity of continuing to perform low intensity exercise (stretching and relaxation), complications are easier to deal with/treat, should they occur.

It is also important to explain to patients that only they can prevent the decline of their own physical functions, after making sure that a team approach will be fully implemented when the patients are unwell or have complications, and to plan their goals for the period of hospitalization together with them.

During the period between admission and the day of allo-HSCT, the patient's physical condition is usually relatively good, so the focus should be on whole body exercise. Since conditioning treatment for HSCT is usually administered in the morning and that for TBI is administered in the morning and evening, exercise therapy should be performed at times of the day other than these. Instructions regarding self-directed exercise are also important. In general, daily exercise therapy is about 40 min, which is insufficient for daily amount of physical activity, and self-directed exercise should be encouraged. Figure 8.6 shows the factors related to the decline in physical function after allo-HSCT.

Key Points

Explanation of the necessity and planning of rehabilitation

Establishment of self-directed exercise

8.9.2 Day of Allo-HSCT to Engraftment

Rehabilitation should be performed as normal on Day 0 (day of HSCT) if possible. In CBT, most transplants (infusion of hematopoietic stem cell) are performed in the morning; thus, if possible, intervention should be performed in the afternoon. In the case of banked transplantation, intervention can be done in the morning since the transplantation is performed in the afternoon. On the day of allo-HSCT, the RRT may be relatively mild, and light activity can be continued. However, after a few days of allo-HSCT, RRT is gradually observed and activity becomes difficult. This

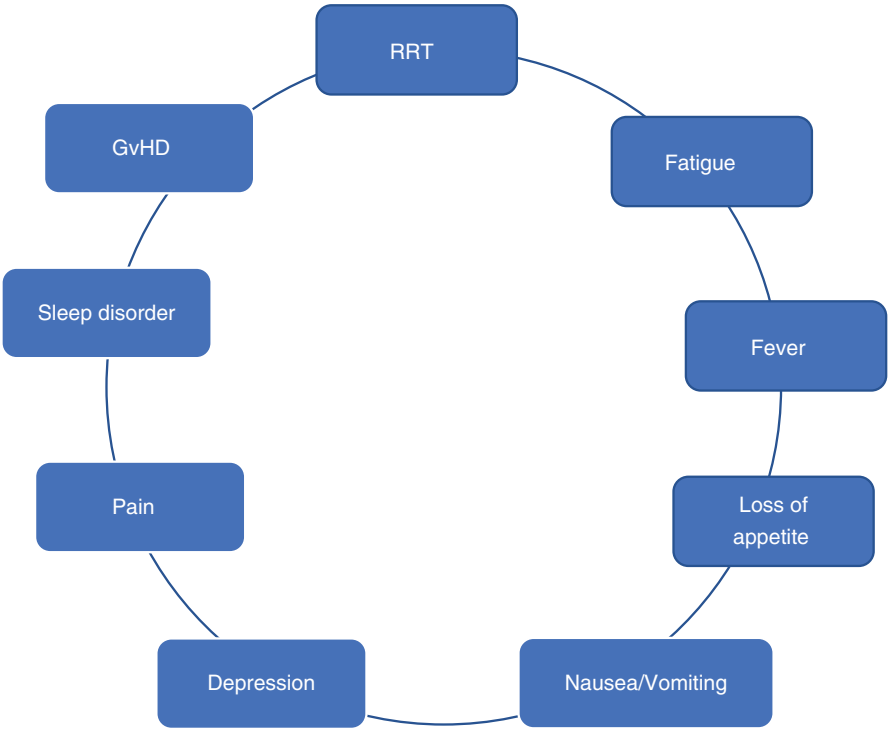

Fig. 8.6 Post-transplant-related factors associated with decreased physical function

is one of the most difficult times for exercise intervention. Therefore, it is important for the therapist to encourage exercises that the patient can perform. Even during nausea, diarrhea, and fever (except when the temperature exceeds 38 °C), it is important to encourage the patient to continue with stretching and promoting sitting alone, with sufficient explanation. If the therapist does not encourage the continuation of rehabilitation interventions, the patient will be expected to remain bedridden for some time afterward. This may result in progressive muscle weakness and increased risk of falling. Even if it is only stretching, continued low-intensity exercise can gradually lead to comfortable increase in intensity to the next level of exercise therapy, such as sitting/standing or walking exercise.

The goal during this period is to maintain ADLs and to continue exercise interventions such as relaxation only, even if they are brief. If the patient continues to have difficulty with intervention, it becomes impossible to ascertain the patient's abilities. Even if rehabilitation is not possible, it is important to continue to check (evaluate) the patient's movements, such as the getting−/standing-up motions, and walking to the toilet.

During the period before neutrophil recovery, the blood cell count is low, and it is necessary to thoroughly manage the risks when exercising (see below). It is also advisable to explain to the patient the precautions that should be taken in daily life

when anemia and/or low platelets are observed and to encourage the patient to manage the risk himself/herself, while at the same time striving to maintain ADL. In particular, when platelets are low, this is the time when extra care must be taken to prevent head bruises and falls.

Key Points

Continue with possible exercise therapy interventions (even in-bed exercises)

Assess the patient's ability to perform safe activities of daily living

8.9.3 Engraftment to Discharge

After WBC (neutrophil) engraftment, if there are no complications, early discharge from hospital is possible, but this is rarely the case, and a variety of symptoms can occur, such as inability to eat, persistent fatigue, and persistent diarrhea due to GvHD. Fatigue is also an important problem [28]. It is often observed that rehabilitation does not progress and ADLs do not improve due to decreased motivation and persistent fatigue.

If therapists immediately stop (cancel) rehabilitation or decrease the intensity of exercise in such cases, it is expected that the decline in activity will continue. It is important for the therapist to notice the timing of improvement in fatigue, nausea, etc. and to find the point of change, so that the patient can move from lying on their bed to sitting to standing to walking.

When patients are hospitalized for a long period of time, many of them lose their motivation to engage in physical activity. If low activity due to lack of motivation persists, patients may require supervision or assistance for their daily activities. It is important for therapists to keep an eye on daily changes in the patient's abilities and to provide positive feedback on improvements. Informing the patient that he or she is improving, even if it is only a small change, can reduce anxiety and help the patient to perceive specific changes in a positive way. In this way, showing the patient their specific improvements and setting goals for the week together with the patient can help them get through difficult times.

Falling also needs to be addressed. It has been reported that falls are more common before engraftment than after engraftment and are related to the use of opioids and lower limb muscle weakness [29]. Daily assessment and appropriate movement guidance are important because patients may have difficulty walking because they have been bedridden long-term due to GvHD (especially gastrointestinal GvHD) or viral infection after allo-HSCT. In particular, it is necessary to collaborate with the nursing staff to support the patients so that they can safely perform their daily activities.

As discharge from the hospital approaches, we should not focus only on physical functions such as simply being able to walk or improving endurance but also check whether the patient is able to perform the activities necessary for life at home. And if there is a problem, ADL exercise is also necessary. In particular, if the ability to climb up and down steps and stairs is necessary for the patient to return home, it is

necessary to begin exercise therapy as early and ensure that it is continued. At the time when immunosuppressive drugs are changed from intravenous to oral, discharge from the hospital is considered, and from this point, exercise plans that take home into consideration should be made. It is also desirable to understand the home environment at the time of admission and to continue the approach from the time of exercise intervention.

Key Points

Gradual increase in the amount of exercise and physical activity
- Support due to long-term hospitalization due to GvHD and infection
- Support due to decline in ADL
- Instruction regarding to ADLs after discharge

8.9.4 Important Considerations to Keep in Mind on a Given Day of Exercise Therapy

The first step in starting a given day's exercise is to perform an assessment. In addition to general vitals (body temperature, pulse, blood pressure), it is advisable to assess the patient's sleep status, food intake, and degree of fatigue before starting exercise. Regarding body temperature, if the patient has a slight (37.0–37.5 °C) but persistent fever, it may be necessary to adjust the amount of exercise due to fatigue. The same is true for sleep; if sleep deprivation continues for several days, the patient may become easily fatigued. In particular, once the pre-transplant treatment starts, a large amount of IV fluids are administered, which leads to increased nighttime urination and insufficient sleep in many patients, so it is necessary to check for fatigue.

In addition to managing the patient's physical condition through the above assessment, it is also important to convey a message to the patient that we, the medical staff, understand that there are always some symptoms. We often encounter patients who are apparently healthy but whose malaise worsens even with a little movement.

On the other hand, the progress from hospitalization (phase 2 (Fig. 8.2)) should be considered. If the patient is in the period from pre-conditioning to engraftment, it may be necessary to reduce the amount and intensity of exercise; however, if the patient is in the after engraftment period, it may be necessary to increase the amount of exercise therapy, so that the patient is ready for discharge, while simultaneously ensuring that they are still getting enough rest, even if fatigue is observed to some extent. Since an easy reduction in the amount (intensity) of exercise may delay the patient's recovery, it is necessary to encourage the patient to maintain and improve the amount of activity under sufficient assessment. For this reason, understanding the patient's fatigue from the previous day's exercise is also an important indicator when increasing the amount of exercise.

We therapists can listen to, praise, and encourage the patient's thoughts and feelings through many conversations as we perform 20–40 min of rehabilitation together. We can use such exercise sessions to help them overcome their activity difficulties.

8.10 Complications in Allo-HSCT Treatment

A variety of side effects and complications occur after allo-HSCT. In particular, RRT, GvHD, and infection can interfere with rehabilitation. The complications lead to a progressive decline in physical activity and physical functions (Fig. 8.6). Typical complications and their onset times are shown in Fig. 8.7. Exercise therapy for major complications is described below.

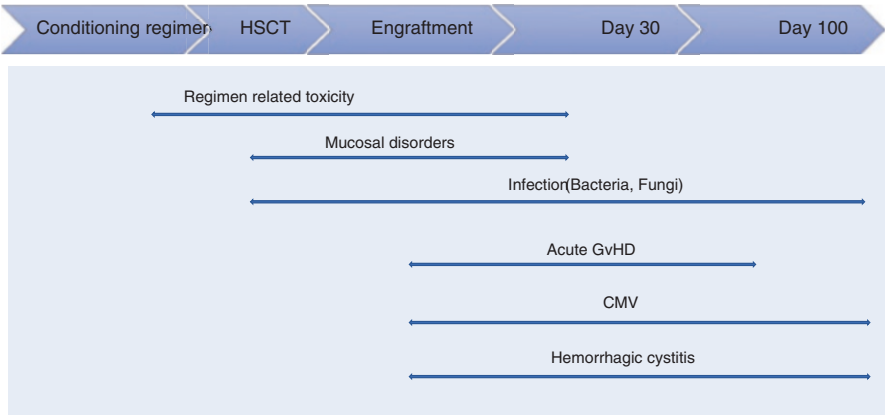

Fig. 8.7 Complications and infections that interfere with rehabilitation

8.11 Exercise During Complications

8.11.1 Influence of Pre-conditioning Treatment

The effects of RRT can occur before HSCT in some patients and during the preconditioning period, but often occurs after the day of allo-HSCT. The main symptoms are nausea/vomiting and diarrhea, followed by fever due to low WBC count. Regarding nausea/vomiting, they may be exacerbated by turning or rising movements alone. These patients will have low motivation regarding engaging in their exercises. In such cases, stretching interventions and relaxation should be used whenever possible to prevent secondary complications such as loss of flexibility and pain. Sitting is also helpful. In particular, exercises and activities that apply abdominal pressure are likely to lead to increased nausea, so it is also useful to choose activities in other body positions. Nausea and diarrhea are thought to be the most common RRT that interfere with the implementation of exercise therapy. However, nausea may not necessarily be exacerbated by leaving the bed. It is possible that nausea is enhanced by rising from supine position, but it is also common to find that it is reduced by remaining in a seated position for an extended period of time. Since RRT depends on the time of day, patients should be encouraged to perform activities according to their own schedules, for durations that they feel comfortable with, after having received adequate guidance on self-directed exercise.

The influence of RRT may persist long after neutrophil engraftment. The symptoms are often alleviated, but exercise therapy should be continued as much as possible based on thorough assessment.

8.12 GvHD

One of the problematic complications after allo-HSCT, GvHD develops mainly in the skin, gastrointestinal, and liver [30], and each of these areas has its own stage (stage 1–4), and the overall grade (grade I–IV) is used [31]. The higher the stage and grade, the more severe the symptoms. The first line of treatment for GvHD is steroids [32], but high doses of steroids increase the risk of steroid myopathy, and the risk of muscle weakness and falls must be considered. In cases of steroid resistance, treatment with TEMCELL™, a mesenchymal stem cell (MSC), may be an option [33]. This may require 4 or 8 weeks of treatment, which may result in prolonged hospitalization. In particular, gastrointestinal GvHD often requires long-term treatment; the onset of GvHD varies, but if it occurs when the patient is close to discharge from hospital, prolonged hospitalization is likely to reduce the patient's motivation to fight the disease and/or cause fatigue.

Before a patient undergoes, allo-HSCT, the risks and complications are fully explained by the attending physician and transplant coordinator; however, there have been many cases where patients have complained that the procedure was more painful than they had expected. For this reason, a team approach (interdisciplinary approach) is desirable.

8.12.1 Skin GvHD

Itching and pain may be localized or widespread. Blistering and pain on the same site may occur at stage 4. In general, it does not often interfere with ADL activities or movement unless it develops on the palms or soles. Itching may cause sleep disturbance, and depending on the sleep situation, it may lead to accumulation of fatigue, so, in cases with severe itching, it is necessary to check the patient's ability to fall asleep.

8.12.2 Gastrointestinal GvHD

The main symptom of lower gastrointestinal GvHD is diarrhea. In the upper gastrointestinal tract, it is accompanied by nausea and vomiting. In the early stages of diarrhea, the amount and frequency are not high; thus, bedside activities (exercise) can be continued. Walking exercise in the corridor may be possible in some cases. However, as the diarrhea becomes more severe, the activities that the patient can do become more limited. Frequent diarrhea cause exhaustion, and greatly reduces the patient's motivation to be active. Continuation of possible interventions, such as stretching and remaining in a sitting or standing position, is advisable when possible. In cases of severe gastrointestinal GvHD, fasting may be required, and nutritional management with total parenteral nutrition (TPN) is common. This often results in a low nutritional status, and the exercise intensity needs to be adjusted accordingly.

Among the types of GvHD, gastrointestinal GvHD is the one that is thought to restrict exercise the most. In the case of prolonged GvHD, it may take more than 1 month to improve, and in many cases, ADL decline is triggered by gastrointestinal GvHD. It is advisable to maintain activities as much as possible.

8.12.3 Liver GvHD

In the case of liver GvHD, the patients' situations vary. Some patients may be able to engage in light activity, but as liver function declines or jaundice develops, significant activity restriction may be necessary. The patient's general condition may also worsen, and the method of intervention, as well as the amount of activity, should be determined in collaboration with the attending physician.

8.13 Viral Infections

8.13.1 Cytomegalovirus Infection

Cytomegalovirus (CMV) infection is one of the most common infections after transplantation. If the intestinal tract is not affected, exercise therapy can be

continued. When CMV-induced enteritis occurs, it mainly results in diarrhea. The duration and severity of diarrhea in CMV are less severe than those in gastrointestinal GvHD, although the diarrhea may cause wasting. Exercise therapy should be continued according to the severity of the diarrhea.

8.13.2 Hemorrhagic Cystitis Caused by Adenovirus

Frequent urination and hematuria are symptoms of hemorrhagic cystitis caused by adenovirus. Pain occurs before, during, and after urination. Some patients may have very severe pain. Depending on the degree of pain and frequency of urination, a urinary catheter may be placed and opioid (narcotics) may be required. As a result, exercise therapy is often limited. Pain is often observed during urination, so rehabilitation may be possible at certain times. However, in most cases, frequent urination occurs, and severe pain may occur during rehabilitation. Since the treatment takes time, there is a concern that the patient's activity may also decrease. Therefore, if the pain is very severe, a rescue dose of opioids may be administered before the rehabilitation intervention. The timing of exercise therapy, the amount of exercise, and the use of medication need to be adjusted after consultation with both the patient and the attending physician.

8.13.3 Steroid Myopathy

The first line for treatment of acute GvHD is steroid therapy [32]; depending on the extent of GvHD, steroid pulse therapy may also be used. Steroid myopathy is one of the complications that can arise when undergoing steroid therapy, especially after high doses in GvHD patients. In addition to GvHD, steroid administration is also used in fevers caused by immune reactions due to pre-engraftment reactions.

Steroid myopathy is said to occur mainly in Type 2 fibers [34]. Therefore, patients with complications of steroid myopathy can walk, but the myopathy cases difficulty with activities such as standing up, climbing steps and stairs, and an increased risk of falling. There is a relationship between steroid use and muscle weakness, with high steroid use causing a decline in grip strength and lower limb muscle strength [3].

When high-dose steroids are used for long periods of time, it is important to continue to evaluate the patient during daily exercise therapy, especially for lower limb muscle strength and standing motions. It is important to perform regular, ongoing assessments in order to identify early changes in muscle weakness and movement difficulties and, if necessary, request supervised ambulation.

On the other hand, rehabilitation is important for improvement of steroid myopathy, and rehabilitation is expected to restore muscle strength [35].

8.14 Risk Management

8.14.1 Cytopenia

In addition to the usual risk management during HSCT rehabilitation, one item that requires attention is cytopenia. During the transplant period, blood is usually drawn three times a week, so it is necessary to check the laboratory data before starting exercise therapy. Even on days when blood is not drawn, physical therapists need to anticipate the possibility that a patient's platelet level may be low, and provide exercise therapy, especially during the thrombocytopenic phase.

8.14.2 Leukopenia

There are no specific contraindications to exercise therapy in patients with low WBC counts, but it should be performed with careful attention to infection control. The locations, including clean rooms, bio-clean rooms, and rehabilitation rooms, of exercise therapy in the myelosuppressive phase vary from institution to institution, and the exercise area should be determined after consultation with the attending physician.

8.14.3 Red Blood Cell Depletion

In red blood cells, hemoglobin levels are often used as an indicator of risk management. Hemoglobin <8 g/dL should not be used for hard exercise [36]. If a blood transfusion is required, exercise should be performed after the transfusion, if possible. However, even if Hb <8 g/dL, one-on-one moderate exercise is possible under patient risk management, with careful attention to clinical symptoms (anemia symptoms, fatigue, respiratory distress, etc.) [36]. In the absence of bleeding symptoms, such as hypovolemia, the decision to perform exercise should be based on the risks and benefits; some patients with aplastic anemia and myelodysplastic syndromes are accustomed to anemia. It is useful to collaborate with physicians and make individual adjustments using laboratory data as an indicator.

8.14.4 Thrombocytopenia

In low platelet levels, special attention should be paid in terms of bleeding prevention. If a platelet transfusion is necessary, exercise should be performed after the transfusion.

Historically, exercise has been contraindicated in patients with platelet counts <20,000, but recent reports have shown that exercise can be safely performed even in HSCT patients with platelet counts <10,000 [36, 37]. Low-intensity activities such as active assist range of motion (AAROM) and sitting/standing positions can be performed. In any case, when platelets are low, it is advisable to perform the procedure carefully and in a one-on-one/supervised situation, with full attention to falls, exercise intensity, and compressions on the skin. In addition to the laboratory data, if petechial bleeding is present, stretching and relaxation should be performed with extreme caution. It is also useful to check the skin condition after the intervention (check for subcutaneous bleeding). Medical staff must explain to the patient about the risk of bleeding and to perform daily activities with care to avoid falls and head bruising. In addition to platelet levels, coagulation factors (e.g., fibrinogen) should also be noted. During physical therapy sessions, bleeding events such as bruising, ecchymosis, and epitaxies have been reported to occur most frequently in patients with platelet counts <10,000. Even in these reports, the severity of bleeding events is low, and low-intensity activity to maintain physical function is possible [38, 39].

With references to two reviews on risk management of platelet counts or bleeding event during exercise therapy [36, 37], the intensity of exercise during low platelet levels is presented in Table 8.3.

Table 8.3 Exercise intensities

Platelet counts	Recommended exercise
5000/μL	AAROM/AROM. Therapeutic activity in bed Limited ADL activities (sitting at the edge of the bed or in the bed or chair) The patient may require a platelet transfusion before exercise
5000 < 10,000/μL	Static balance (sitting at the edge of the bed or in the bed or chair) ADL (standing at the edge of the bed or chair). Limited ambulation (in the room)
10,000–20,000/μL	Muscle motor training without resistance. Unlimited ambulation (out of the room) may be allowed
20,000–50,000/μL	Resistance training such as elastic tubing (TheraBand) may be used. The patients may be allowed to walk at a faster pace and practice step-ups or walking up stairs
> 50,000/μL	Intensive exercise may be allowed. Activities such as stationary cycling and Jumping are acceptable

AAROM active assisted range of motion; *AROM* active range of motion; *ADL* activity of daily living

8.14.5 Rehabilitation During Blood Transfusion

Exercise therapy during blood transfusion is considered to be contraindicated, but well-monitored physical therapy sessions may be safe during red blood cell transfusion [36].

Exercise therapy should preferably be performed after blood transfusion, but it may be possible to perform low-intensity exercise under close observation and monitoring of the patient's subjective symptoms and anemia symptoms.

On the other hand, to date there have been no reports on the safety of rehabilitation during platelet transfusion. If platelet transfusion is scheduled, exercise therapy should be performed afterward. During platelet transfusion, bedside care (e.g., stretching and relaxation) and sitting/standing may be possible in a well-monitored physical therapy session with the permission of the attending physician, with due attention paid to the risk of bleeding due to low platelet levels and adverse reactions associated with transfusion (e.g., allergic reactions). Sessions within the scope of activities of daily living (e.g., walking to the bathroom) may be possible.

8.15 Nutritional Support

HSCT patients require nutritional management that takes into account intestinal complications, such as decreased appetite and diarrhea due to high-dose chemotherapy and intestinal damage due to GvHD [40]. Due to the susceptibility to infection during the cytopenia phase, there is a risk of various infections. These inflammatory findings promote protein catabolism and lead to a decrease in body composition. In most cases, it is difficult to maintain nutritional status by oral intake alone in allo-HSCT treatment [41]. Therefore, it is advisable to start nutritional therapy early [42]. Supplementation of inadequate oral intake with intravenous or enteral nutrition (EN) is the basic nutritional intervention [43]. During the allo-HSCT period, the ideal intake amount is 1.3–1.5 times the estimated basal energy expenditure (BEE), i.e., 30–50 kcal/kg/day. In recent years, the benefits of combining exercise therapy with nutritional support for maintaining physical function and body composition after HSCT have been reported [44]. The nutritional support in these reports is 30–35 kcal and 1.5 g of protein per kg adjusted weight [45], ingestion of 1.5 g/kg/day blended protein (50% whey, 50% soy) [46]. In a malnutrition state, physical function and performance are lower, and exercise therapy is less effective [47, 48]. Early nutritional support is desirable to improve the effectiveness of exercise therapy during allo-HSCT.

8.16 Elderly Patients

In recent years, there have been many allo-HSCTs for patients aged older than 70 years, and post-transplant survival and QOL have improved [49]. Rehabilitation of elderly allo-HSCT recipients is also safe and feasible [50]. It is conceivable that these recipients may experience a significant loss of abilities to move and perform functional activities due to inactivity during hospitalization. Compared to younger age groups, muscle weakness in elderly recipients is more likely to be directly related to decrease of ADL and walking ability. For this reason, it is desirable to start exercise therapy as early as possible after the HSCT decision is made. It is also important to instruct patients to exercise voluntarily from the early stage of the transplant decision. During hospitalization, patients should be supported to maintain independence in activities of daily living as much as possible. Decline in physical function at the time of discharge from hospital may have a significant impact on the patient's life after discharge. If possible, outpatient rehabilitation should be considered; continued support via long-term follow-up (LTFU) is necessary.

8.17 Long-Term Follow-Up; LTFU

In recent years, LTFU has become increasingly important in the support of long-term post-transplant survivors. LTFU is planned at 3 months, 6 months, 1 year, and then every other year after HSCT [51]. Factors that delay recovery of physical function after allo-HSCT are related to GvHD and glucocorticoid administration [52].

The role of the physical therapist in LTFU is to assess and interview the patient, as well as to design their exercise program. Based on the results of each evaluation, it is necessary to assess the current physical function and activity level and to update the patient's exercise program accordingly.

8.17.1 Medical Interview

The medical interview mainly focuses on the patient's living conditions, activity, pain, dietary intake and presence of complications such as chronic GvHD, history of falls, and return to work after discharge.

8.17.2 Physical Activity

As for the amount of physical activity, aerobic exercise of at least 150 min per week (at moderate intensity) on 3–5 days per week, daily stretching and strength training two to three times per week, is recommended [16, 24, 25].

8.17.3 Three-Month Follow-Up

At the 3-month LTFU, problems that arose during hospitalization (poor appetite, low physical activity, low muscle strength and endurance) are often still present, and some cases have residual low activity and muscle weakness. Problems with ADLs and ambulation may result in a significant decrease in outdoor activity. Current muscle strength and endurance should be assessed, and for cases showing functional decline, the goal should be to restructure the exercise program as deemed appropriate at the time. On the other hand, even in cases where physical function is maintained or is improving, the amount of activity appropriate for the case should be suggested, as many cases have not yet reached the pre-HSCT level.

8.17.4 Six-Month Follow-Up

At the 6-month post-HSCT assessment, many patients are experiencing a recovery of physical function and are able to engage in outdoor activities, with some even returning to work. In addition, at this point, some patients have recovered to pre-HSCT levels of physical function. Many patients have increased their activity and are encouraged to maintain their current level of activity. On the other hand, in some cases, patients with joint problems due to chronic GvHD need individual guidance. It is necessary to check if there are any difficulties with regard to daily activities.

8.17.5 One-Year Follow-Up

At 1 year after allo-HSCT, many patients with no or mild chronic GvHD have generally recovered to their pre-HSCT levels of both physical function and QOL [52, 53]. A slightly larger number of patients have returned to work and have reached their original level of living. It is also important to encourage continued exercise even in patients who have regained physical function [25].

Post-HSCT exercise therapy can lead to early recovery of physical function [19, 21, 54, 55]. In addition, patients with high physical function may be able to return to work earlier [53, 56]. In terms of the relationship between physical function and QOL in long-term survivors, patients with high physical function after discharge from hospital also have a good QOL [57]. Therefore, it is important to explain to patients that they should maintain their physical activity after HSCT.

Exercise therapy interventions during hospitalization are implemented in many facilities, but rehabilitation after discharge is often left to self-directed exercise. Since early recovery of physical functions is desired by maintaining the amount of activity after discharge [53], it is desirable to provide sufficient explanation and guidance on the necessity of continuing exercise after discharge from hospital during hospitalization.

8.18 Conclusion

Allo-HSCT treatment can lead to various complications and prolonged hospitalization. Rehabilitation interventions are very important to maintain physical functions and to facilitate early discharge from the hospital and early return to society. On the other hand, in order to carry out exercise therapy safely and effectively, an interdisciplinary approach is necessary. The HSCT team includes a wide range of staff, including hematologists, physiatrists, dentists, psychiatrists, nurses, pharmacists, dieticians, laboratories, and PT/OT/ST (Fig. 8.8). It is important that regular consultations are held to support the patient. The author hopes that physical, occupational, and speech therapists will become a part of these teams and continue to support patients as they work toward their own goals.

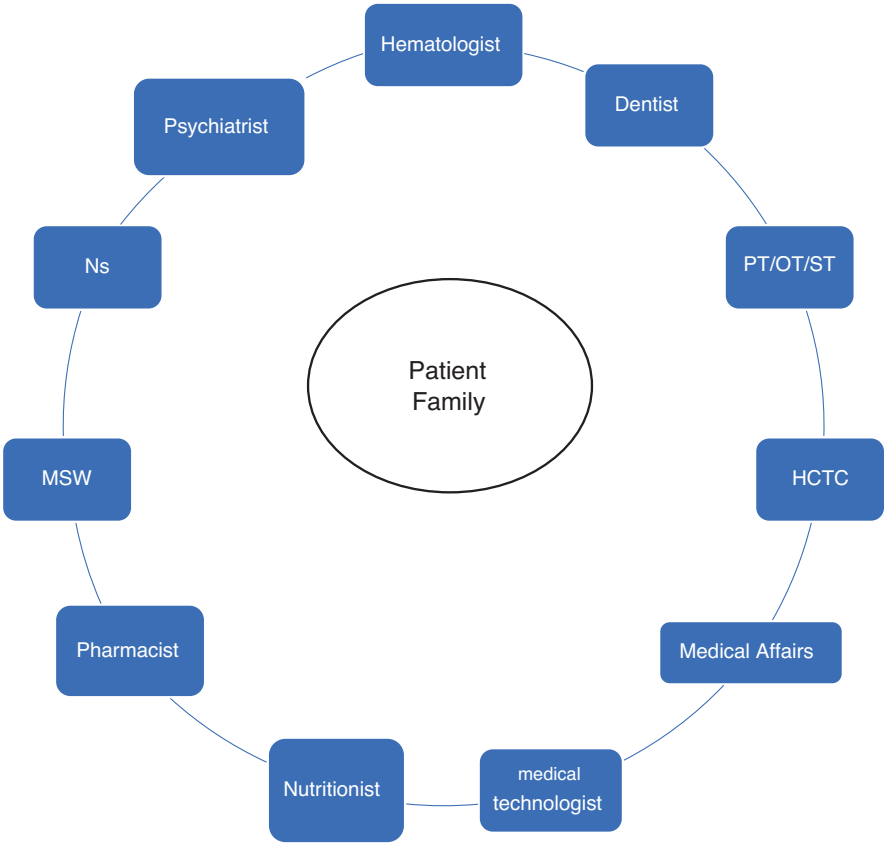

Fig. 8.8 Team approach

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9 Physical Exercise and Immune Function in Patients with Hematological Malignancies

Daiyu Kobayashi and Shinichiro Morishita

Abstracts

Patients with hematological malignancies have decreased immune function due to hematopoietic abnormalities and treatments such as high-dose chemotherapy and hematopoietic stem cell transplantation. Studies in healthy subjects have shown that exercise effectively improves immune function and may thus also benefit immune function in patients with hematological malignancies. However, sufficient evidence has not yet been established, since there are few studies on the association between immune function and exercise in patients with hematological malignancies. This chapter discusses the possible effects of exercise on immune function in patients with hematological malignancies and prospects, using references to healthy subjects and patients with hematological malignancies. In addition, we hope that this chapter will stimulate interest in immunity and exercise, contribute to the decision-making process for exercise prescription, and create theories for future research.

Keyword

Hematological malignancies · Immune function · Exercise · Neutrophils Lymphocyte · Cytokine

D. Kobayashi (✉)
Department of Rehabilitation, Saitama Medical Center, Saitama Medical University, Saitama, Japan
e-mail: k_daiyu@saitama-med.ac.jp

S. Morishita
Department of Physical Therapy, School of Health Sciences, Fukushima Medical University, Fukushima, Japan
e-mail: morishit@fmu.ac.jp

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9.1 Introduction: Patients with Hematological Malignancies and an Outline of the Immune System

Patients with hematological malignancies such as leukemia, malignant lymphoma, and multiple myeloma have reduced immune system function due to abnormalities in the hematopoietic system and treatment, and their recovery requires months to years after treatment. The 5-year relative survival rates for patients with hematological malignancies in Japan are 67.5% for malignant lymphoma, 44.0% for leukemia, and 42.8% for multiple myeloma, which are not as high as those for other types of cancer [1]. The causes of their deaths are infections involving the immune system, viral activity, and graft-versus-host disease (GVHD) [2–4].

Immune function in patients with hematological malignancies has been reported to be low in Cluster Designation (CD) 4^+ and $CD8^+$ cells and natural killer (NK) cells among immune cells in acute leukemia patients after chemotherapy [5], and immune cell recovery after HSCT took 7–12 months for $CD4^+$ cells, 10 months for $CD8^+$ cells, and 6 weeks for regulatory T cells [6]. In addition, steroids and immunosuppressive drugs administered for treatment after HSCT can also suppress immune cells. Thus, patients with hematological malignancies have compromised immune function and are at high risk for lethal infections such as sepsis, Pneumocystis carinii, toxoplasma encephalitis, cytomegalovirus, and bacterial infections caused by gram-negative or gram-positive bacteria [7, 8]. It is essential to improve the immune function of patients with hematological malignancies, as infections can interfere with the treatment of the disease and even cause death.

One method of improving immune function is physical exercise. It is known that exercise alters the nervous and endocrine systems and enhances the body's immune function. However, many studies on the effects of exercise on immune function have been conducted on healthy subjects and mice, and few studies have been conducted on patients undergoing intensive treatments such as high-dose chemotherapy and hematopoietic stem cell transplantation. Therefore, there is no evidence for exercise therapy that takes into account immune function in patients with hematological malignancies, and few physical therapists practice it in Japan clinical situations. This chapter will focus on the effects of exercise on immune function in patients with hematological malignancies, including representative immune cells and their effects that physical therapists should know, and data from healthy subjects. We hope that this chapter will lead to an interest in exercise therapy for immune function in patients with hematological malignancies and the development of future research.

9.1.1 Exercise in Healthy Subjects and Infection Epidemiology

It has been recognized that exercise is essential for health promotion, such as reducing the incidence of ischemic heart disease, diabetes, obesity and hypertension, preventing nursing care, and improving quality of life. Matthews et al. investigated the incidence of upper respiratory tract infections (URTI) in 547 healthy subjects over

12 months. They reported that the incidence was lower by 20–30% in cases where adult subjects engaged in moderate-vigorous physical activity (3.0–5.9 METs) compared to subjects who did not take part in such activities [9]. On the other hand, Nieman et al. investigated URTI episodes in runners who participated in the Los Angeles Marathon. They found that the incidence of upper respiratory infection symptoms before the marathon was twice as high in those who had trained heavily over the previous 2 months (>97 km/weeks) compared to those who had trained less (<32 km/weeks) [10]. Regarding the relationship between exercise intensity and URTI as described above, Nieman et al. proposed the J-curve model, since vigorous intensity exercise increases the risk of URTI, and moderate exercise decreases said risk [11]. Others have proposed the open window theory, in which vigorous intensity exercise transiently decreases immune function [12]. These studies indicate that the between exercise and immune function was attributed to immune cells changing depending on the intensity, duration, and type of exercise; therefore, in order to improve immune function, appropriate exercise prescriptions need to be tailored for each individual subject (Fig. 9.1).

Exercise intensity is often categorized into low intensity, moderate intensity, and vigorous intensity using % peak VO2, Karvonen value (k value), and RPE (Borg scale) for aerobic exercise [13]. Many studies have examined the relationship between exercise and immune function using this exercise intensity as a guide, and the same guide is often used in exercise prescription in clinical situations. In patients with early-stage or metastatic cancer, an exercise intensity of up to 70–80% maximal heart rate is safe, with fewer exercise-related adverse events. It is effective for

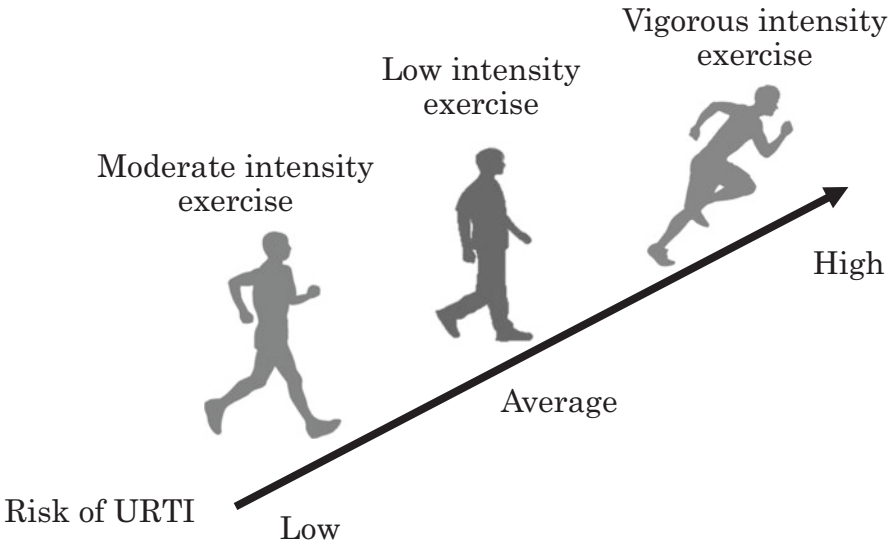

Fig. 9.1 The relationship between exercise intensity and the risk of developing upper respiratory tract infection (URTI). Moderate exercise decreases the risk of URTI, while vigorous intensity exercise increases the risk

physical function, quality of life, and early reintegration into society, and reports recommend vigorous intensity exercise [14]. This study excluded patients with severe comorbidities, bone metastases, neutropenia, thrombocytopenia, anemia (<8 g/dL), or ever, so it is questionable whether vigorous intensity exercise can be safely performed in patients with hematological malignancies and severe pancytopenia. However, patients with hematological malignancies also have many opportunities to receive exercise therapy, so it is important to understand exercise intensity and discuss its relationship with immune function.

9.1.2 Hematological Malignancy and Exercise

It is known that exercise reduces mortality in healthy subjects. A large cohort study in Japan examined the relationship between physical activity and mortality in men and women aged 45–74 years, and reported that the hazard ratio of total mortality was 0.73 (0.66–0.81) for men and 0.61 (0.54–0.88) for women in the group with the highest daily total physical activity level compared to the group with the lowest total physical activity level [15]. This is because moderate exercise improves physical function, quality of life, insulin sensitivity, obesity, blood pressure, triglycerides, and inflammation and thus reduces all-cause mortality. This suggests that a similar effect may be expected in patients with hematological malignancies. In addition, exercise for patients with hematological malignancies is cost-effective supportive care that can be performed before, during, or after treatment, and is easy for anyone to adopt. Wiskemann et al. studied the relationship between mortality and physical activity in hematopoietic stem cell transplant patients who underwent aerobic exercise during hospitalization (three to five times per week, walking and bicycle ergometer, mild subjective exercise intensity) and strength training (20–40 min, three to five times per week) and undertook a home exercise program both before and after hospitalization. The results showed that, after discharge from hospital, the exercise and non-exercise groups had total mortalities of 12.0 and 28.3%, respectively, as well as non-relapse mortalities of 4.0 and 13.5%, respectively. In addition, the exercise group experienced reduced incidence of total and non-relapse mortality of more than 50% each [16]. In summary, exercise for patients with hematological malignancies may improve survival by influencing immune cell rebuilding, such as anti-inflammatory effects, immune activity, and infection prevention.

The risks of incident hematological malignancies have been associated with obesity and the immune system. Exercise may reduce the risk of hematological malignancies because it prevents and improves obesity, increases insulin sensitivity, has anti-inflammatory effects, and activates an immune function in healthy individuals. Regarding physical activity and the incidence of hematological malignancies, a meta-analysis by Davies et al. compared high- and low-level groups of physical activity: lymphoma, RR 0.89 (95% CI 0.81–0.98); non-Hodgkin's lymphoma, RR 0.92 (95% CI 0.84–1.00); and Hodgkin's lymphoma, RR 0.72 (95% CI 0.50–1.04). This study shows that an increase of 3 MET h/week reduced the risk of occurrence (RR 0.99, 95% CI 0.98–1.00) [17]. Other studies have shown that the risk of

incident hematological malignancies is reduced by 10% with 26 MET h/week of physical activity (RR, 0.90; 95% CI, 0.83–0.97) and by 5% with each increase of 12 MET h/week of physical activity. (RR, 0.95; 95% CI, 0.91–0.99). However, the results of this meta-analysis showed that the risk of incident hematological malignancies compared to the high versus low physical activity levels were as follows: non-Hodgkin's lymphoma, RR 0.91 (95% CI, 0.82–1.00); Hodgkin's lymphoma, RR 0.86 (95% CI, 0.58–1.26); leukemia, RR 0.97 (95% CI, 0.84–1.13); multiple myeloma, RR 0.86 (95% CI, 0.68–1.09); and all hematological malignancies, RR 0.93 (95% CI, 0.88–0.99). This study found no association between the incidence of hematological malignancies and physical activity [18].

Thus, exercise may reduce the incidence of hematological malignancies, and one factor may be related to the immune system. However, there are reports that physical activity is not related to different types of hematological malignancies, and further research is needed.

9.2 Relationship Between the Function of Immune Cells and Exercise

We are constantly in contact with pathogens (bacteria, viruses, fungi, parasites). The human body has a defense mechanism to protect itself from these pathogens: the immune system. Immune systems can be broadly classified into two categories: innate immunity and acquired immunity. Innate immunity is the immune system in the early stage of infection that detects and eliminates pathogens that have invaded the human body through receptors. In addition, innate immunity can present antigenic peptides to acquired immunity to activate the immune system. These immune cells include neutrophils, macrophages, dendritic cells, and natural killer (NK) cells capable of phagocytosis. On the other hand, acquired immunity is a system that eliminates foreign substances by binding to antigen-specific receptors when pathogens invade the human body. The immune cells are largely divided into T cells and B cells, each with its antigen receptor. It is known that both innate immunity and acquired immunity can be altered by exercise. In this section, we will introduce the function of each immune cell and its effect of exercise on innate and acquired immunity.

9.2.1 Neutrophils

Neutrophils consist of 50–70% white blood cells, and they phagocytose bacteria and other organisms that invade the body, killing them with the enzymes myeloperoxidase and lysozyme. In addition, the enzyme NADPH oxidase produces potent reactive oxygen species that cause cell damage. The primary function of neutrophils is to defend the body against foreign substances, but the reactive oxygen species (ROS) produced by neutrophils can also damage normal tissues [19]. Therefore, it is essential to consider whether exercise-induced changes in neutrophils are beneficial or detrimental to the body.

Neutrophils are increased immediately after acute physical activity. Exercise mobilizes neutrophils from the bone marrow and other limbic pools into the peripheral circulation, increasing their blood concentration. This increase in neutrophils during exercise is transient between 1 and 5 h after exercise. To investigate the effect of exercise on neutrophil function, Syu et al. examined neutrophil chemotaxis, phagocytosis, citrate synthase activity, and $\Delta\Psi m$ in 13 healthy adult males classified into an exercise group ($n = 8$) and a control group ($n = 5$). The exercise group performed moderate-intensity exercise (bicycle ergometer, 60% HRmax, 30 min, five times a week) for 2 months and detraining for 2 months, while the non-exercise group performed detraining for 4 months. Both groups also performed a vigorous intensity exercise (bicycle ergometer, measured up to exhaustion) each month for the exercise group and about once every 2 months for the non-exercise group. As a result, the exercise group reported that maximal exercise promotes neutrophil apoptosis, but continuous moderate-intensity exercise delays neutrophil apoptosis and improves innate immunity [20]. Bartlett et al. examined the relationship between physical activity and neutrophil function and selected the most physically active elderly subjects ($n = 20$) and the least physically active elderly subjects ($n = 20$) from a sample of 211 subjects. As a result, they reported that the most active elderly had increased neutrophil chemotaxis and chemotactic index compared to the least active elderly. They concluded that migration of neutrophils declines with age and delays their mobilization to the site of infection, but that habitual physical activity improves neutrophil migration [21]. These reports indicate that neutrophil function is activated by moderate exercise and decreased by non-exercise or excessive exercise. Regarding associations between other neutrophils and exercise, Suzuki et al. had eight healthy male subjects perform vigorous intensity exercise (bicycle ergometer, 90 min, 90 W) and examined the relationship between neutrophils and muscle damage markers. The results indicated that neutrophil production of ROS increased from 60 min after exercise and continued to increase until 3 h after exercise. The increase in neutrophils correlated with myoglobin (Mb) levels and serum creatine kinase levels, which are markers of muscle damage. However, after 3 days of the same vigorous intensity exercise, increased catecholamines and no changes in neutrophils or serum Mb levels were observed. This suggests that an increase in neutrophils influences skeletal muscle inflammation after exercise and that there is a strong association between enhanced neutrophil responses and myocellular protein release. Furthermore, they consider that repeated vigorous intensity exercise attenuates exercise-related inflammation by neutrophils due to increased catecholamines [22]. According to the above reports, moderate exercise increases the number and strengthen the existing function of neutrophils, but an increase in neutrophils due to vigorous intensity exercise seems to induce inflammation due to muscle damage.

In summary, moderate exercise may increase the number and function of neutrophils. The increase in neutrophils from excessive exercise may promote apoptosis and induce inflammation due to muscle damage, but repeated exercise may attenuate the disadvantages of neutrophils to the body.

9.2.2 Lymphocytes (T Cell)

Lymphocytes are the general term for immune cells that possess antigen receptors for antigen-presenting cells and are the most critical in protecting the body against infection. The most important lymphocytes are T cells, for eliminating infected cells, and B cells, for antibody production and antigen-presenting cell functions. Understanding the function of and differentiation between T cells and B cells is essential to understanding the relationship between exercise and immune function. This subsection introduces the relationship between lymphocytes and exercise.

The major T cells are helper T cells ($CD4^+$ cells) that control the immune response, cytotoxic T cells ($CD8^+$ cells) that attack tumor cells and virus-infected cells, and regulatory T cells (Treg cells) that suppress the immune response. Helper T cells are divided into Th1, Th2, Th17, and Treg cells by cytokines and other inducers. Th1 cells produce cytokines such as interleukin (IL)-2 and interferon (IFN)-γ, which induce macrophages and increase killer T cells to cause an inflammatory response to eliminate intracellular parasitic bacteria and virus-infected cells. Th2 cells are produce cytokines such as IL-4, IL-5, and IL-13, which are highly associated with allergies. Th1 and Th2 cells have a relationship that inhibits the differentiation of each other's cells and maintains a balance by suppressing the onset of allergies caused by each other's overactivity. Th17 cells produce IL-17 cytokines and induce granulocytes to promote inflammatory responses. Treg cells produce cytokines such as IL-10 and are essential for suppressing autoimmune diseases, regulating transplantation immune responses, controlling infections, anti-inflammatory effects, and suppressing excessive immune responses. Th17 and Treg cells are able to maintain balance with each other. Both Th17 and Treg cells differentiate from naive T cells and differentiate into Treg cells in the presence of TGF-β only and Th17 cells in the presence of TGF-β and IL-6. This makes for an immune response system that induces Th17 cell differentiation to cause inflammation and induces Treg differentiation to suppress inflammation.

T cells mature under the influence of cytokines, and mature T cells produce cytokines to regulate each other's immune responses. The effects of exercise on T cells vary depending on the intensity, time, type, and duration of the exercise. Rhind et al. studied the effects of moderate-intensity exercise (bicycle ergometer, 60 min, 60% of maximal oxygen uptake) on immune cells in healthy subjects with no exercise habit. The results showed that immediately after moderate intensity exercise, the number of lymphocytes, $CD4^+$, $CD8^+$, and $CD56^+CD16^+$ cells increased, and the CD4/8 ratio decreased. Furthermore, they reported that 30 min after exercise, there was a decrease in the number of $CD4^+$, $CD8^+$, and $CD56^+CD16^+$ cells and that this decrease lasted for 2 h [23]. These findings indicate that the changes in immune cells after a single exercise session are biphasic, increasing immediately after exercise and decreasing gradually over time. Kobayashi et al. studied the effect of moderate intensity exercise (bicycle ergometer, 30 min, Karvonen value; $k = 40–60\%$) on immune cells in healthy subjects with no exercise habit. They reported that the lymphocyte fractions of $CD8^+$, $CD16^+CD56^+$, and Treg ($CD4^+CD25^+Foxp3^+$)

increased, and the fractions of $CD4^+$ and CD4/8 ratio decreased after moderate intensity exercise [24]. Clifford et al. studied 17 healthy subjects who participated in a marathon and reported that the Treg ratio ($CD3^+CD4^+Foxp3^+CD25^{++}CD127^-$) decreased immediately after the marathon and increased the next day. Vigorous intensity exercise produces inflammation by increasing neutrophils and pro-inflammatory cytokines, and the sustained increase can cause excessive tissue damage. This suggests that the change in Treg cells caused by prolonged vigorous intensity exercise was a suppressive immune response against excessive tissue damage by switching from a pro-inflammatory environment to an anti-inflammatory environment [25]. In summary, moderate exercise maintains immune tolerance by increasing NK cells according to the increase in cytotoxic cells and provides an anti-inflammatory environment by Treg cells. On the other hand, overexercise may result in a decrease in immune function due to a transient increase in cytotoxic cells and a pro-inflammatory environment due to a decrease in Treg cells. Thus, it can be seen that moderate-intensity exercise produces an immune response that results in immune tolerance. In contrast, vigorous exercise produces an immune response that induces inflammation in the body.

For helper T-cell subsets, Kostrzewa-Nowak et al. performed a maximal exercise stress test (mechanical treadmill, measured up to exhaustion) on 14 soccer players and examined the changes in T cells pre- and post-exercise. The results showed an increase in Th1 cells but no changes in Th2, Th17, or Treg cells after exercise. Furthermore, 17 h after exercise showed an increase in Th1, Th17, and Treg cells and no change in Th2 cells. This study examined changes in cytokines, suggesting that the increase in inflammatory cytokines (IL-12p70 and IL-6) immediately after exercise promoted the differentiation of Th1 and Th17 cells and that the increase in Treg cells was an immune response to suppress inflammation by Th17 cells [26]. In addition, they performed a maximal exercise stress test (shuttle run with 10 s of active recovery between each shuttle (a Jogtrot) and exercise stress to exhaustion) on 31 soccer players and examined the changes in T cells before and immediately after exercise, as well as 17 h after exercise. The results showed that Th1 and Th17 increased immediately after exercise. In addition, after 17 h, Th1 and Th17 had increased, Treg had decreased, and Th2 remained unchanged [27]. These results show that the changes in immune cells differ depending on the mode of exercise: continuous running on a mechanical treadmill versus intermittent running back and forth on a shuttle run.

Regarding long-term exercise, Koizumi et al. studied T-cell changes in 27 middle-aged and elderly people with no exercise habits after 12 months of a combined exercise program (bicycle ergometer, Karvonen value; $k = 50–60\%$, 30 min, 10RM × 10 strength training sessions). As a result, they reported that the number of T cells, $CD4^+$ cells, and $CD4^+CD45RO^+$ cells increased and that immune function improved [28]. Shimizu et al. studied the changes in T cells in healthy elderly subjects classified into a 12-week combined exercise program (bicycle ergometer; 10 min, strength training; 40% of 1RM, 15 times × 2 sets) group ($n = 12$) and a non-exercise group ($n = 12$). The results showed that the number of $CD4^+$ cells and $CD8^+$ cells did not change, but the number of $CD28^+CD8^+$ cells, which promote

cytokine synthesis and T cell activation increased in the exercise group. This study showed that regular exercise may improve immune function through T-cell proliferation and differentiation in the elderly, because it ameliorates the age-related impairment of $CD28^+CD8^+$ expression [29]. On the other hand, Woods et al. studied T-cell changes in elderly subjects after 6 months of exercise (brisk walking, increased from 50% VO2 to 60–65% VO2, 10–15 min to 40 min, three times a week). They reported no changes in $CD4^+$%, $CD8^+$%, $CD45RA^+$%, $CD4^+CD45RO^+$%, or $CD8^+CD45RO^+$% in lymphocyte fractions before and after the 6-month period [30]. Cosgrove et al. investigated T cell changes in ten triathletes before and after 6 months of training. They reported that there were no differences in $CD3^+CD4^+$, $CD3^+CD8^+$, or CD4/8 ratio before and after training [31]. Thus, the effect of long-term exercise on T cells is still unclear, with some studies reporting improvement and others reporting no change. However, these reports differ regarding subject characteristics, as well as exercise duration and intensity. Therefore, it is necessary to clarify the effects of various exercise intensities that are tailored to individual subjects on T cells in the future.

9.2.3 Lymphocytes (B Cell)

B cells produce antibodies (immunoglobulins) against specific antigens. Immunoglobulins are classified into IgG, IgA, IgM, IgD, and IgE, which bind to and neutralize pathogen and toxin molecules. Secretory IgA (SIgA) in the saliva is important in protection against upper respiratory tract infections, its association with exercise has been investigated. Akimoto et al. studied changes in salivary SIgA after a 12-month combined exercise program (60 min on a bicycle ergometer; Karvonen value, $k = 0.6$; 8–15 strength training sessions) in 45 healthy elderly subjects with no exercise habit. As a result, they reported that the concentration of salivary SIgA and the rate of SIgA secretion increased and that moderate long-term exercise improved mucosal immune function [32]. On the other hand, Jia et al. studied changes in immunoglobulins in 60 military personnel before and after 3 months of military training against vigorous intensity exercise. As a result, they reported that IgG, IgA, and IgM decreased. This suggests that humoral immunity may be decreased due to excessive training [33]. Pacque et al. also studied the changes in SIgA pre- and post-running race in 17 marathon runners. The results showed that SIgA decreased immediately post-race and did not return to baseline until the following day, indicating that vigorous intensity exercise decreased mucosal immunity. This study, however, examined the incidence of upper respiratory tract infections before and after the race and reported the same in the two 2-week periods before and after the race [34].

These reports indicate that moderate exercise increases antibody production capacity is increased by moderate exercise and decreased by overexercise. However, there is a report that there was no relationship between changes in immunoglobulins due to exercise and upper respiratory tract infections [34]; therefore, further investigation is needed.

9.2.4 Lymphocytes (Natural Killer Cell)

NK cells have no antigen receptors that differ from T cells and B cells and thus directly attack and destroy both tumor cells and virus-infected cells in a nonspecific manner. NK cells secrete IFN-γ, which is responsible for activating macrophages of infected cells to eliminate bacteria and promote the differentiation of helper T cells. It has also been reported that high NK cell activity is associated with a lower incidence of cancer and upper respiratory tract infection [35] and that NK cell activity was low in patients with severe COVID-19, which has been a hot topic in recent years [36]. This indicates that NK cells and NK cell activity enhance the biological defense response. The important cytokines associated with these NK cells are IL-2 and IL-15, which enhance differentiation, proliferation, and cytotoxic activity.

Regarding the relationship between NK cells and exercise, Rhind et al. studied the changes in NK cells after moderate-intensity exercise (bicycle ergometer, 60 min, 60% of maximal oxygen uptake) in healthy subjects with no exercise habit. The results showed that the CD4/8 ratio decreased, but NK cells ($CD56^{+}CD16^{+}$) increased, indicating that homeostasis of the defense mechanism against infection was maintained [23]. Moyna et al. studied the effects of exercise on NK cells and NK cell activity in 64 healthy adults. In this study, they examined changes in NK cells ($CD3^{-}CD16^{+}CD56^{+}$) and NK cell activity in the exercise group (bicycle ergometer, gradual increase in load of 55%, 70%, and 80% of VO2max) and non-exercise group by taking blood samples before, as well as 6 min, 12 min, 18 min, and 2 h after exercise. As a result, they reported that the number and ratio of NK cells increased with the gradual increase in exercise intensity and that NK cell activity increased at 6 min after 55% VO2max but remained unchanged thereafter [37]. This indicates that the number of NK cells and NK cell activity increases after a short period of moderate-intensity exercise or more. This mechanism is thought to be that NK cells and T cells have adrenergic receptors, and the increase in catecholamines due to exercise causes cells in the spleen and lymph nodes to mobilize to the peripheral blood [38, 39]. Furthermore, NK cells have a higher adrenergic receptor density (NK cell > CD8 > CD4) and are more likely than T cells to increase after exercise. On the other hand, Nieman et al. studied the effects of vigorous intensity exercise (treadmill, 45 min, 80% VO2max) and moderate-intensity exercise (treadmill, 45 min, 50% VO2max) on NK cells ($CD3^{-}CD16^{+}CD56^{+}$) and NK cell activity in ten healthy young subjects. As a result, they reported that NK cells and NK cell activity increased immediately after both vigorous and moderate-intensity exercise and decreased from baseline at 1 h after exercise [40]. Thus, NK cells and NK cell activity increase immediately after exercise but decrease with sustained and excessive exercise. The increase in glucocorticoids caused by excessive exercise downregulates IL-1 and IL-2, thereby suppressing NK cells and NK cell activity. In summary, moderate exercise transiently increases NK cells and NK cell activity, but prolonged and overintense exercise causes an immune response that suppresses the body's defense against viral infection, because NK cells and NK cell activity are reduced several hours after exercise.

9.3 Relationship Between the Function of the Endocrine System and Movement

Immune cells have receptors for hormones of the endocrine system and try to maintain homeostasis from neuroendocrine-immune interactions. Stress from exercise is known to alter the blood levels of hormones such as adrenaline, noradrenaline, and glucocorticoids, which alter the immune response. This subsection will introduce the effects of exercise on the endocrine system and immune cells.

9.3.1 Catecholamines

When the body is stressed by exercise, catecholamines (dopamine, adrenaline, and noradrenaline) are secreted from the adrenal medulla via the hypothalamic-pituitary-adrenocortical system (HPA axis). Catecholamines act through α-receptors and β-receptors. Adrenaline acts on α-receptors and β-receptors and is involved in cardiac stimulation and metabolism of sugar and lipids. Noradrenaline acts mainly on α-receptors and is involved in blood pressure elevation.

These effects of catecholamines increase with increasing exercise intensity and decrease after the end of the exercise. The increase in catecholamines due to exercise releases immune cells with high adrenergic receptor density (NK cells > CD8 > CD4) from the spleen and lymph nodes into the peripheral blood [38, 39]. Regarding the relationship between exercise intensity and catecholamines, Davies et al. studied changes in catecholamines in cyclists and non-exercisers by performing bicycle ergometry at 30%, 45%, 60%, and 75% maximal exercise intensity. The results showed that both groups had increases in noradrenaline and adrenaline in proportion to increased exercise intensity. However, the cyclists showed a minor increase, and the non-exercisers showed a significant increase in adrenaline concentration ≥60% maximal exercise intensity. In both groups, catecholamine concentrations decreased rapidly after exercise. Furthermore, adrenaline and noradrenaline concentrations were reported to be significantly higher in the non-exercisers than in the cyclists [41]. This suggests that adrenaline and noradrenaline increase along with exercise intensity, but the size of the increase varies depending on the subjects' physical function and exercise habits.

9.3.2 Carbohydrate Corticoids

Glucocorticoids are steroid hormones produced by the adrenal cortex that increase blood glucose levels and have anti-inflammatory effects. Cortisol affects metabolism by maintaining blood glucose levels during exercise and is involved in supplying energy to increase amino acids and lipids. However, during long periods of vigorous intensity exercise, cortisol is excessively increased to produce immunosuppression by promoting inflammation in response to muscle

damage, downregulating IL-1 and IL-2 cytokines, and suppressing lymphocyte migration as well as T and NK cells [42, 43]. In addition, cortisol is known to suppress immune cells; there are reports that cortisol correlates with apoptosis of lymphocytes [44] and that mice treated with dexamethasone in a dose-dependent manner have reduced T cells ($CD3^+$, $CD4^+$, $CD8^+$) in a dose-dependent manner and increased Treg cells ($CD4^+CD25^+$) [45].

Exercise-induced changes in immune cells are influenced by catecholamines at the start of exercise, but are influenced by cortisol for a longer duration. In general, serum cortisol levels increase with exercise duration and remarkably increase when exercise intensity exceeds 60% VO2max [46, 47]. Bloom et al. studied changes in catecholamines in cyclists and non-exercisers by performing bicycle ergometry at 30%, 45%, 60%, and 75% maximal exercise intensity. Their results indicated that both groups showed a decrease in cortisol below 45% maximal exercise intensity and an increase at 60%. In addition, the study reported that the increase in cortisol was greater in cyclists [41]. Cortisol was remarkably increased by vigorous intensity exercise, suggesting that such exercise leads to immunosuppression by inducing cytokines and lymphocyte apoptosis.

On the other hand, Adachi et al. investigated the relationship between antiviral immunity and glucocorticoids by subjecting virus-infected mice to vigorous intensity exercise. This study showed that vigorous intensity exercise worsened the infection because it transiently decreased plasmacytoid dendritic cells (pDCs). However, pDCs were transiently elevated 6–12 h after exercise, indicating improved immune function [48]. Previously, vigorous intensity exercise was thought to decrease immune function by increasing cortisol. However, this report concludes that depending on the timing of the vigorous intensity exercise, it may effectively enhance antiviral immunity. This suggests that vigorous intensity exercise may improve immune function, although further research is expected.

9.4 Relationship Between Cytokine Function and Exercise

Cytokines are proteins secreted by immune cells that signal transduction between cells. They are involved in inflammatory responses, immune responses, hematopoiesis, wound healing, and regulate the proliferation, differentiation, and function of immune cells. Cytokines are substances that have potent effects in small amounts and regulate the immune system through complex interactions. The most relevant cytokines to exercise are IL, IFN, growth colony stimulating factor, and tumor necrosis factor (TNF).

IL-6 is highly associated with exercise and has attracted attention as a myokine produced by skeletal muscle during muscle contraction. IL-6 starts to increase at 30 min after the start of exercise and continues to increase for several hours thereafter. Initially, the function of IL-6 was thought to be an inflammatory cytokine caused by excessive exercise. In recent years, IL-6 has been thought to regulate insulin secretion from the pancreas [49], promote myogenesis [50], and have anti-inflammatory effects [51]. Pedersen et al. reported that exercise increased IL-6,

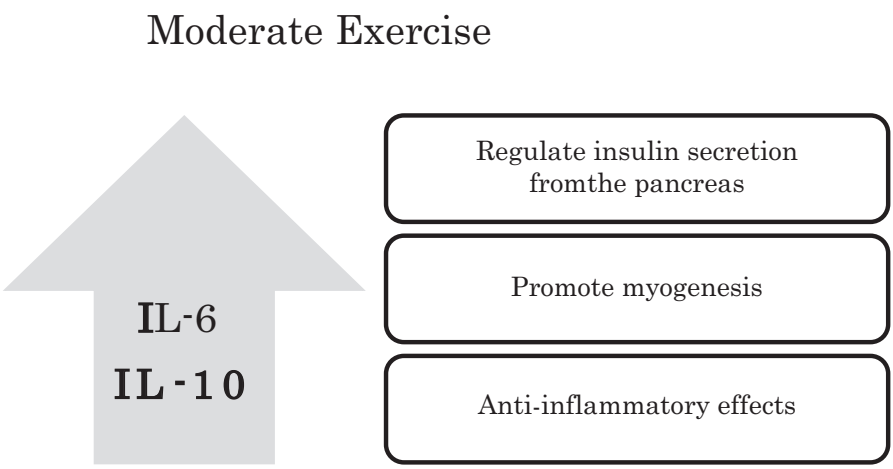

Fig. 9.2 Cytokine changes in moderate exercise. Moderate exercise leads to various benefits for the body due to increased IL-6 and IL-10, with little or no change in TNF associated with muscle damage

IL-1RA, and IL-10, but not the inflammatory cytokine TNF-α that is elevated in sepsis. This suggests that exercise-induced increase in IL-6 is not related to muscle damage but may be associated with anti-inflammatory cytokines (Fig. 9.2) [52].

Among other cytokines, IL-10 is an anti-inflammatory cytokine that protects the body from excessive immune responses and has been studied in relation to exercise. Svendsen et al. studied a healthy male subject who performed 120 min of bicycle ergometer at 60% VO2max and reported an increase in IL-10 [53]. On the other hand, reports in healthy subjects showed that IL-10 decreased before and after maximal exercise load on a bicycle ergometer [54] and that IL-10 did not change after 75 min of bicycle ergometry at 75% VO2max [55]. In addition, Smits et al. showed that endurance-trained athletes had higher IL-10 and Treg cell counts than sedentary and recreationally active groups [56]. This indicates that prolonged moderate-intensity exercise increases IL-10, which has anti-inflammatory effects, while vigorous intensity exercise either decreases or has no effect on IL-10.

9.5 Effect of Exercise on Immune Function in Patients with Hematological Malignancies

In recent years, patients with hematological malignancies have been reported to experience prolonged survival due to therapies such as high-dose chemotherapy, immunotherapy, and allogeneic hematopoietic stem cell transplantation. However, patients with hematological malignancies have decreased immune cells due to intense therapy, and reconstruction takes time. Patients with acute myeloid leukemia (AML) have decreased T cells and NK cells at the time of diagnosis and after chemotherapy [5], and the recovery of immune cells such as T cells and NK cells

after hematopoietic stem cell transplantation has been reported to be 6 months to 1 year [6]. Therefore, patients with hematological malignancies are susceptible to severe infections due to the potentially prolonged rebuilding of immune function and decreased immune function caused by disease and treatment. Therefore, it is essential to improve the immune function of patients with hematological malignancies, and one approach for this is exercise. Exercise has the potential to enhance immune function in patients with hematological malignancies because it alters immune cells, cytokines, and hormones.

Regarding immune function and exercise in patients with hematological malignancies, Kim et al. examined the effect of bed exercise on lymphocytes in allogeneic bone marrow transplant patients. In their study, HSCT patients were categorized into exercising group ($n = 18$) and non-exercising groups ($n = 17$), and bed exercises (stretching, relaxation breathing, and upper and lower extremity automatic movements, 30 min daily) were performed for 6 weeks. The results showed that the exercise group had slightly increased lymphocytes after the 6-week period, while the non-exercise group had decreased lymphocytes. However, the percentage of $CD3^+$, $CD4^+$ and $CD8^+$, and CD4/8 ratio did not differ significantly between the two groups [57]. Battaglini et al. studied cytokine changes in ten patients with acute leukemia undergoing chemotherapy during aerobic exercise (heart rate reserve 40–50%, 5–10 min, bicycle ergometer) and strength training (5–15 min) three to four times a week during hospitalization and aerobic exercise (walking, at least three times a week, 10–30 min) as a home program during discharge. As a result, they reported that IL-6 tended to decrease after exercise, whereas IL-10 and IFN-γ tended to increase [58]. Therefore, Battaglini et al. suggest that continuous combined training can provide anti-inflammatory cytokines and improve immune function by increasing lymphocytes for patients with hematological malignancies during chemotherapy. On the other hand, Kobayashi et al. studied the effect of moderate-intensity exercise (bicycle ergometer, 30 min, Karvonen value; $k = 40–60\%$) on immune cells in 20 patients with hematological malignancies who had previously undergone chemotherapy or hematopoietic stem cell transplantation. The results showed that, after moderate intensity exercise, the lymph fractions of $CD4^-CD8^+$ were increased; the lymph fractions of $CD4^+CD8^-$ ratio, CD4/8 ratio, and Treg ($CD4^+CD25^+Foxp3^+$) ratio were decreased; and the lymph fractions of $CD56^+CD16^+$ ratio were not changed. Therefore, Kobayashi et al. concluded that moderate-intensity exercise might reduce immune function and induce exercise-induced inflammation in patients with hematological malignancies after treatment [24]. In summary, low-intensity exercise may enhance immune function in patients with hematological malignancies, while moderate-intensity exercise may transiently decrease immune function. However, moderate-intensity exercise may enhance immune function if it becomes a habit. It is known that continued exercise of the same intensity attenuates increases in serum myoglobin levels and neutrophils, which are markers of muscle damage, and increase anti-inflammatory cytokines [22]. Patients with hematological malignancies have not been studied, but it has been suggested that repeated moderate-intensity exercise may benefit immune function in the same way as in healthy subjects.

Regarding vigorous intensity exercise, Shore et al. studied changes in immune cells before and after 12 weeks of training (aerobic exercise, 70–85% MaxHR aerobic exercise, 30 min) in 6 pediatric patients with acute lymphoblastic leukemia (ALL) and 11 healthy children. The results showed that the ALL patients had lower baseline $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD25^+$, and PHA-induced lymphocyte prolife ratios than the healthy children. In addition, the ALL patients reported decreased $CD3^+$ and $CD4^+$ and $CD8^+$ and CD4/8 ratio, decreased $CD25^+$ and $CD56^+$, and increased spontaneous and IL-2 induction after 12 weeks of training [59]. Inbar et al. reported that rats with leukemia were subjected to forced swimming stress, which resulted in decreased survival, increased survival with β-adrenoceptor antagonists and COX inhibitors and decreased survival and NK cell activity with epinephrine and PGE2 [60]. Thus, vigorous intensity exercise may have negative effects on patients with hematological malignancies by transiently decreasing their immune function. On the other hand, Ladha et al. studied the relationship between neutrophils and exercise in four children with ALL undergoing chemotherapy and six age-matched healthy subjects. The exercise consisted of 10 min of running (85% HR of VO2peak), then 10 min of walking (70% HR of VO2peak), and another 10 min of running (85% HR of VO2peak), totaling 30 min. The results showed that neutrophils increased from pre- to post-exercise were decreased at 1-h post-exercise and increased from 1 to 2 h post-exercise in both the ALL patients and the control group. Furthermore, they reported that the oxidative capacity of neutrophils remained lower in the ALL group, but improved with exercise [61]. Perry et al. studied changes in immune cells pre- and post-vigorous intensity exercise (treadmill, 45–60 min, target heart rate 70% of Karvonen value) in four untreated CLL patients. The results showed that CLL patients had no change in the lymphocyte number of $CD4^+$ cells or the lymphocyte fractions pre- and post-exercise. Furthermore, after 60 min of exercise showed a decrease in Treg, an increases in Thl7 cells as well as IL-6 and TGF-β were observed, although there was no change in IL-2 [62]. TGF-β and IL-2 induce Treg cell differentiation, but the combination of TGF-β and IL-6 does not induce Thl7 cells. TGF-β and IL-2 induce Treg cell differentiation, while the combination of TGF-β and IL-6 induces Thl7 cell differentiation. CLL patients have increased Treg cells, and Thl7 cells have been shown to have anti-tumor immune-surveillance effects. Thus, vigorous intensity exercise may restructure immune function in CLL patients. In summary, vigorous intensity exercise in patients with hematological malignancies seems to reduce immune cells and produce an open window similar to healthy subjects. However, it is expected that further studies on vigorous intensity exercise and immune function will be conducted because vigorous intensity exercise improves neutrophil function and the disease-specific immune system. In addition, these reports examined exercise-induced changes in immune cells, hormones, and cytokines and did not examine the endpoints of morbidity or survival of infection in patients with hematological malignancies. Future long-term studies are expected to examine the effects of exercise-induced changes in immune cells on said endpoints.

9.6 Effects and Challenges of Exercise on the Treatment of Patients with Hematological Malignancies

Exercise has been shown to have an anti-tumor effect on certain cancers because of its positive effects on immune cells, cytokines, and hormones. Exercise may also be expected to improve the tumor microenvironment and have anti-tumor effects in patients with hematological malignancies, but there is no evidence that exercise is effective as a treatment. This subsection will present the potential and prospects of exercise on the immune system to treat hematological malignancies.

9.6.1 Is Exercise a Treatment Tool for Hematological Malignancies?

Exercise may promote apoptosis and delay the growth of hematological tumor cells. Singh et al. studied the effect of exercise on tumor cells in mice implanted with Dalton's lymphoma of T-cell lymphoma. The mice were divided into three groups: those who underwent 90 min of exercise per day for 10 days (treadmill, 17 m min^{-1}), those who underwent 120 min of exercise (treadmill, 17 m/min^{-1}), and those who did no exercise. The results showed that the 90- and 120-min exercise groups had prolonged survival, increased DL cell apoptosis, and decreased DL cell numbers compared to the no-exercise group. Furthermore, macrophage-mediated tumor cytotoxicity and IL-1, TNF, and NO were increased. These results indicate that treadmill exercise may enhance the production of IL-1, TNF, and NO and the tumoricidal activity of macrophages, inhibit tumor cell proliferation, and induce tumor cell apoptosis [63]. Zielinski et al. studied the changes in the tumor cells of mice with allogeneic lymphoid tumors (EL-4 tumor cells) by classifying the mice into a vigorous intensity exercise group (treadmill, 5% grade, 20–40 m/min, 3 h or until exhaustion) and a non-exercise group, and monitoring them for 5–14 days. The results showed no difference in tumor volume between the exercise and non-exercise groups, but the exercise group had a delay in peak tumor volume and greater tumor regression. Furthermore, the exercise group had lower inflammatory cells (macrophages and neutrophils), blood vessel density, and fewer apoptotic bodies than the non-exercise group. This indicates that prolonged and excessive exercise may affect the tumor microenvironment, causing delayed tumor growth and regression [64]. Bigley et al. studied the relationship between changes in exercise (bicycle ergometer, 5%, +5%, +15% of LT, which is the lactate work rate, for 30 min) on NK cell subsets and NKCA against HLA-expressing tumor cell lines (U266, RPMI-8226, 721.221, 221 AEH, K562) in 16 healthy subjects. As a result, NK cell subsets were increased at all exercise intensities (highly differentiated ($CD158b^+$/$NKG2A^-$) > moderately differentiated ($CD158b^+$/$NKG2A^+$) > poorly differentiated ($CD158b^-$/$NKG2A^+$), and NKCA per cell against multiple myeloma (U266) and malignant lymphoma (221 AEH) cell lines were 1.6-fold higher after exercise. It was concluded that the cytotoxicity against target cells was enhanced [65]. Zimmer

et al. studied changes in serum macrophage migration inhibitory factor (MIF) and interleukin 6 (IL-6) in 30 post-chemotherapy non-Hodgkin's lymphoma patients and 10 healthy subjects divided into four groups: exercise group (bicycle ergometer, RPE scale: 13–14, 30 min) and a non-exercise group. They reported that the patients had higher pre-exercise serum MIF and IL-6, as well as lower NK-cell H3K9 histone acetylation than the healthy subjects, and a negative correlation between pre-exercise IL-6 and endurance. In addition, the patients in the exercise group had higher IL-6 after exercise, increased CD8H4K5 1 h after exercise, and advanced acetylation, but no changes in MIF pre- and post-exercise. These results indicate that moderate exercise may decrease inflammatory biomarkers, induce acetylation of H4K5 in $CD8^+$ T lymphocytes, and affect tumor-competitive lymphocytes [66].

These results indicate that exercise effectively induces apoptosis in hematopoietic tumor cells, improves the tumor microenvironment, and increases cytotoxic immune cells, giving hope that exercise can be a treatment with anti-tumor effects. However, the evidence is insufficient, and we hope that further research will be conducted in the future to clarify the specific type, intensity, frequency, and duration of exercise that can have anti-tumor effects.

9.6.2 Does Exercise Promote the Treatment of Hematological Malignancies?

In recent years, the treatment of patients with hematological malignancies has focused on the development of immune checkpoint inhibitors that use inhibitory antibodies to block signaling to the T-cell inhibitory receptor cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death (PD-1). CTLA-4 on T cells ligates to CD28 and B7 molecules on T cells and suppresses T cell activation [67]. Cancer cells regulate CTLA-4 to inhibit T-cell activation and proliferation, thereby reducing anti-tumor immunity. In addition, PD-1 is expressed on activated T cells, and when it binds to the ligand PD-L1, which is expressed on the surface of tumor cells, T cell activation and proliferation are inhibited, resulting in a state of exhaustion and reduced anti-tumor immunity. Immune checkpoint inhibitors bind to such molecules and ligands to inhibit the transmission of immunosuppressive signals. In addition, patients with hematological malignancies are also developing immunotherapies other than immune checkpoint inhibitors. In this subsection, we discuss exercise as a means to promote the therapeutic use of immunotherapy.

Schenk et al. investigated the effects of exercise on aryl hydrocarbon receptor (AhR) and PD-1 of $CD8^+$ T cells, as exercise affects kynurenine (KYN) metabolism. The subjects were 24 healthy subjects who performed endurance exercise (bicycle ergometry, Peak power 60%, 45 min) and resistance exercise (five exercise machines, 1RM 70%, 8–10 times × 4 sets) once each. The results showed that the number of $PD\text{-}1^+$ $CD8^+$ T cells increased immediately after endurance exercise and that the mean fluorescence intensity of PD-1 of $CD8^+$ cells and cytoplasmic AhR decreased after 1 h. On the other hand, resistance training had no effect on the

PD-1 levels of the $CD8^+$ T cells. This suggests that endurance exercise affects AhR levels and PD-1 expression and suggests the importance of exercise as a therapeutic strategy [68].

Immuno-cell therapy to reduce the risk of recurrence in hematopoietic stem cell transplant (HSCT) patients is effective with adoptive transfer immunotherapy, which involves culturing and transferring tumor-associated-antigen (TAA)-specific cytotoxic T-cells (CTLs). LaVoy et al. investigated whether sufficient numbers of functional TAA-specific CTLs could be obtained from healthy donors through exercise. They also examined the effects of the fast ascent of 260 stairs and the Bruce Maximal Exercise Test (treadmill, maximal exercise) on changes in melanoma-associated antigen 4 (MAGE-A4), antigen preferentially expressed in melanoma (PRAME), and Wilms tumor protein (WT-1) pre- and post-exercise in healthy adults. As a result, 84% of participants (16 out of 19) reported an increase in TAA-specific CTLs after exercise (MAGE-A4-specific CTLs, 70% of participants; PRAME-specific CTLs, 61%; and WT-1-specific CTLs, 38%). Furthermore, increased CTLs were shown to be functional cells capable of secreting IFN-γ and killing target cells. This raises the possibility that exercise may be an effective means of adoptive transfer immunotherapy [69].

These studies reported the possibility that exercise may promote immunotherapy treatment in patients with hematological malignancies. However, to the best of our knowledge, there have been no reports of improved mortality due to the addition of exercise to immunotherapy, so this may be a subject for further study.

9.6.3 Effects of Exercise on Immune Cells in Patients with Hematopoietic Stem Cell Transplantation

Exercise for HSCT patients has been recommended to improve physical functions such as endurance, muscle strength, fatigue, and quality of life. In addition, there are reports that exercise can benefit HSCT patients by altering immune cells; some of these findings are discussed in this subsection.

Autologous HSCT harvests stem cells from the patients themselves and reintroduce the harvested stem cells into the patients after high-dose chemotherapy. Stem cell engraftment and remission in autologous HSCT are better with higher numbers of CD34 and MNC cells than with lower numbers. Kasravi et al. hypothesized that exercise would increase CD34 and MNC cells and studied CD34 and MNC cell counts in a continuous aerobic exercise group (7 days, two times/day, 30 min, RPE12-14), a discontinuous aerobic exercise group (7 days, two times/day, 15 min, RPE12-14), and a control group without aerobic exercise. They reported that continuous aerobic exercise increased the numbers of CD34 and MNC cells more than noncontinuous aerobic exercise and the control group. This suggests that exercise mobilizes hematopoietic stem cells from bone marrow to peripheral blood and may contribute to the outcome of autologous hematopoietic stem cell transplantation [70]. Transfer of donor-derived virus-specific T-cells (VSTs) has been shown to effectively treat viral infections after allogeneic hematopoietic stem cell

transplantation. Kunz et al. investigated whether exercise could increase VSTs specific to nonpersistent viral antigens (AdV). They enrolled 14 healthy subjects who performed 30 min on a bicycle ergometer at an exercise intensity 10–15% higher than the point at which their blood lactate levels were curvilinearly elevated. As a result, post-exercise increases in the number of hexon-specific, penton-specific total AdV-specific T-cells by 2.0-fold, 1.9-fold, and 1.33-fold, respectively, were observed. These results suggest that exercise is effective in the multiplication of VSTs specific to latent herpesviruses (i.e., cytomegalovirus and Epstein-Barr virus) as well as non-latent viruses (i.e., AdV) [71]. These studies suggest that exercise may have a positive effect on the treatment outcome of HSCT.

Patients with HSCT develop GVHD caused by donor-derived lymphocytes attacking normal cells. GVHD occurs when cellular tissues are damaged by pre-transplant therapies such as systemic radiation and chemotherapy, triggering the release of inflammatory cytokines such as TNF-α, IL-1, and IL-6. The damage of each organ in GVHD is associated with both the increase and loss of helper T-cell subsets (Th1, Th2, Th17, and Treg cells) and cytokines, and the balance between them is important for the control of GVHD [72]. Exercise may regulate GVHD because it modulates helper T-cell subsets. In a study of mouse models, Fiuza-Luces et al. performed 11 weeks of moderate intensity exercise (treadmill, five times per week, beginning with duration 25 min, speed 35% of the Vmax, and inclination 0% grade, and ending with duration 60 min, speed 70% of the Vmax, and inclination 25% grade) in mice with acute and chronic GVHD who underwent HSCT and examined the effects of exercise on GVHD severity and immune function. As a result, they reported that the mice's cytokines (IL-2, IL-4, IL-6, IL-17, IFN-γ, TNF-α) did not change after moderate intensity exercise, indicating that such exercise does not exacerbate acute and chronic GVHD [73]. Fiuza-Luces et al. also evaluated the effect of exercise on chronic GVHD in mice with chronic GVHD treated with cyclosporine A after HSCT, by performing 11 weeks of moderate-intensity exercise (treadmill, 5 days a week, 60 min at 70% Vmax and 25% gradient). As a result, they reported that post-exercise decreases in TNF-α and IL-4 and improved the total GVHD score. Regarding this mechanism, the results considered that anti-inflammatory cytokines such as myokine IL-6 and adipokine IL-10, which inhibit TNF-α, may be increased by exercise and may prevent the severe effects of GVHD [74]. This study reported that exercise effectively alters cytokines and regulates GVHD, but it should be noted that the study used a mouse model, and their results may not be the same as those found in humans. In other studies, the administration of low-dose IL-2 to patients with GVHD has been found to increase Treg cells and control GVHD [75]; thus Treg cells have been the focus of recent study. Regarding Treg cells and exercise, Kobayashi et al. reported on 20 patients with hematological malignancies who had undergone chemotherapy or HSCT and who underwent moderate-intensity exercise (bicycle ergometer, 30 min, Karvonen value; k = 40–60%). They found that Treg cells ($CD4^+CD25^+Foxp3^+$) were decreased [24]. Therefore, it is possible that, in patients with hematological malignancies who are immunocompromised or immunosuppressed, decreased Treg cells during moderate-intensity exercise may exacerbate GVHD. These reports did not include patients with GVHD, so it is unclear

whether similar results can be obtained in a clinical situation. It can be difficult to conduct research on exercise for patients with GVHD, because it is difficult to standardize the safety, compliance, duration, frequency, and intensity of the exercise, as well as illness severity. However, exercise in healthy subjects and mice may modulate helper T-cell subsets and cytokines to control GVHD. In the future, it will be necessary to understand the pathophysiology and mechanisms of action of exercise on GVHD from basic research, and to conduct randomized controlled trials on humans.

9.7 Conclusion

In this chapter, we discussed the possibility that appropriate exercise for patients with hematological malignancies may restructure immune function leading to prevention of infections, therapeutic measures against tumor cells, promotion of treatment, and improved survival. In addition, excessive exercise may be disadvantageous to the body by suppressing the immune system. Therefore, we believe that it is important to consider immune function when prescribing exercise, because exercise can positively or negatively affect the immune function of patients with hematological malignancies, depending on the exercise intensity.

However, the relationship between immune function and exercise in patients with hematological malignancies has not been established by evidence, and there are still many unclear areas. Therefore, some readers may think that our conclusions are exaggerated, but we hope this chapter will trigger your interest in the relationship between immune function and exercise in patients with hematological malignancies. In the future, we hope to identify a clear prescription for exercise to improve immune function in patients with hematological malignancies.

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10 Exercise Protocols for Counteracting Cancer Cachexia-Related Declines in Muscle Mass and Strength and the Clinical Assessment of Skeletal Muscle

Daisuke Tatebayashi and Rei Ono

Abstract

Cancer cachexia causes significant declines in skeletal muscle mass and strength and is associated with a poor prognosis and impaired activities of daily living and quality of life. Therefore, treating cachexia is an important aim in physical therapy in patients with cancer. Although many studies have reported that training exercises can reduce cancer-related declines in muscle mass and strength, there is still no consensus on the most effective exercise protocol. The first part of this paper reviews the effectiveness of various exercise protocols in animal models of cancer cachexia and in patients with advanced cancer. The review includes resistance training, aerobic training, and combined training performed at least twice per week at an intensity of at least 60% of the maximal strength or heart rate. Protocols that included resistance training appeared to yield the greatest improvements in muscle strength. However, improvements in muscle mass are rarely reported, and the methods used to measure muscle mass are inconsistent. Therefore, the latter half of this paper describes clinically relevant methods for assessing muscle mass and quality. To develop the field of cancer rehabilitation, further studies should examine in detail how physical activity affects muscle mass and muscle quality, in addition to muscle strength.

D. Tatebayashi (✉)
Division of Rehabilitation, Kobe University Hospital, Kobe, Japan
e-mail: ttbys411@med.kobe-u.ac.jp

R. Ono
Department of Health Promotion and Exercise, National Institutes of Biomedical Innovation, Health and Nutrition, National Institute of Health and Nutrition, Tokyo, Japan

Department of Public Health, Kobe University Graduate School of Health Sciences, Kobe, Japan

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Exercise protocols · Cancer cachexia · Advanced cancer · Muscle mass Muscle strength · Muscle quality · Clinical assessment

10.1 Introduction

Cancer cachexia (CCX) is a complex multifactorial syndrome characterized by progressive loss of skeletal muscle mass with or without loss of fat mass [1], which cannot be fully reversed by conventional nutritional supplementation [2]. Low skeletal muscle mass is associated with higher overall mortality in patients with various types of cancer [3–6]. Recently, a meta-analysis by Shachar et al. [7] including 7843 patients reported that cancer patients with sarcopenia had shorter overall and disease-free survival compared with non-sarcopenic patients. Similarly, a recent systematic review by Pamoukdjian et al. [8] of 6894 adults diagnosed with cancer showed that sarcopenia is associated with chemotherapy-induced toxicity, postoperative complications, and a poor prognosis.

On the other hand, CCX causes not only loss of skeletal muscle mass but also muscle dysfunction [9, 10]. The combination of loss of muscle mass and muscle dysfunction causes a marked reduction in skeletal muscle strength, impairing activities of daily living and quality of life (QOL). Thus, maintaining or improving muscle condition is an important aim in cancer rehabilitation.

Although many studies have shown that physical exercise attenuates CCX-related skeletal muscle atrophy, optimal training protocols have yet to be established. Herein, we reviewed the effects of various exercise training programs on muscle mass and strength in patients with advanced cancer (ACP) and rodent models of CCX. Additionally, we present assessment methods for skeletal muscle (strength, mass, and quality) in clinical practice.

10.2 Physiology

10.2.1 Cancer Cachexia

Overall, up to 80% of ACP suffer from cachexia [11, 12], which is implicated in up to 20% of cancer deaths [1]. The severity and prevalence of cachexia are related to the type of cancer, with gastrointestinal and pancreatic cancers accounting for 85% of cases [12]. Low skeletal muscle mass leads to higher postoperative complication rates [8, 13], increased chemotherapy toxicity, and lower chemotherapy efficacy, resulting in more frequent treatment discontinuation [8, 13, 14] and decreased survival [7].

CCX is a systemic chronic inflammatory syndrome induced by the immune response triggered by tumor-host interactions. Strikingly, in a murine model of CCX, Zhou et al. [15] demonstrated that maintaining skeletal muscle mass prolongs

survival, even though there was no change in tumor growth, fat loss, or serum inflammatory cytokines. Therefore, although the underlying mechanisms are not completely understood, skeletal muscle mass is regarded as an independent predictor of prognosis in cachexia.

The mechanism of skeletal muscle atrophy associated with CCX is multifactorial and highly complex. The release of inflammatory mediators such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 promotes an imbalance between muscle protein synthesis and degradation, leading to decreased muscle mass and increased fatigue [16, 17]. On the other hand, Braun et al. [18, 19] demonstrated that central nervous system inflammation causes activation of the hypothalamic-pituitary-adrenal axis, and the resulting release of glucocorticoids is a key factor in skeletal muscle atrophy.

10.2.2 Physical Exercise in Cancer Patients

Treatment of cachexia is critical for improving the overall mortality and QOL of patients with cancer. Nevertheless, owing to the complexity of the disease, the development of treatments has shown poor progress, and an international standard of therapy remains to be established. Various nonpharmacological strategies have been investigated to counteract CCX. Among these, exercise training is well known for its anti-inflammatory effects, which have been observed in healthy subjects [20] and cancer hosts [21]. Consistently, various exercise modalities such as resistance training (RT), aerobic training (AT), and combined training (CBT) have been shown to induce increased secretion of anti-inflammatory cytokines by adipose tissue, followed by a significant decrease in C-reactive protein (CRP) levels [22–24].

Myokines released by skeletal muscle contraction, such as oncostatin M and secreted protein acidic and rich in cysteine (SPARC), have been found to inhibit the progression of breast and colorectal cancer, respectively [25]. Muscle-derived IL-6 is another myokine that induces tumor apoptosis via the activation of natural killer cells. Intriguingly, Starkie et al. [26] demonstrated that the administration of IL-6 at levels similar to those observed in the plasma of subjects undergoing long-term, high-intensity exercise can promote a significant reduction in TNF-α levels.

Many researchers have shown that the physical exercise inhibits tumor growth, as illustrated by a review by Spiliopoulou et al. [27]. In line with this, guideline by the American College of Sports Medicine [28] recommended exercise for all patients with cancer, regardless of cancer stage. Systematic reviews by Heywood et al. [29] have consistently shown that exercise interventions, including RT, are safe and feasible, even in the setting of advanced cancer.

RT induces the expression of genes associated with muscle damage [30], suggesting that caution is required when implementing this type of intervention in cancer patients. Additionally, given that very high-intensity exercise causes temporary suppression of specific immune factors [31], it should be avoided in patients with myelosuppression or compromised immunity. Moreover, Argiles et al. [32] reported that patients with cancer concurrent anemia should avoid strenuous physical

exertion. Thus, in order to avoid adverse events, it is important to assess the patient's general condition to determine an exercise intensity that is safe and tolerable.

With the progression of cachexia, exercise tolerance decreases owing to cancer-related fatigue and various treatment-related adverse events [33]. In addition, muscle mass acquisition is affected by a depressed protein synthetic response, a phenomenon termed anabolic resistance [34], likely accelerated by multidisciplinary therapies, including chemotherapy and radiotherapy. Therefore, physical therapy should be initiated prophylactically or early in the course of disease.

10.2.3 Chemotherapy-Induced Toxicity in Skeletal Muscle

In many cases, the first option for antitumor treatment is systemic chemotherapy, which targets rapidly and abnormally mitotic cells and induces autologous cell death pathways by DNA damage [33]. However, this effect is not specific to malignant cells. Recently, the toxicity of anticancer drugs to skeletal muscle has been increasingly studied. Several anticancer agents, particularly doxorubicin, cisplatin, and 5-fluorouracil, have been shown to cause muscle wasting and dysfunction, either directly or indirectly, through systemic cachexia induction, including inflammation, neutropenia, and anorexia [34]. In addition, chemotherapy induces muscle mitochondrial dysfunction and the subsequent release of reactive oxygen species [35], likely contributing to anabolic resistance [34]. Mitochondrial dysfunction has been reported to play a crucial role in the development and progression of cachexia [36]. Researchers have suggested that cancer and chemotherapy cause muscle loss via the same pathway [18, 37]. Consequently, exercise could have an attenuating effect on cancer- and chemotherapy-induced cachexia [38].

10.3 Effects of Training Protocols on Muscle Strength and Mass in Cancer Cachexia

10.3.1 Resistance Training

RT is a form of physical activity designed to improve muscular strength by exercising a muscle group against external resistance, which has been shown to improve HbA1c, insulin resistance, cardiovascular markers, sleep quality, and cognitive function as well as body composition, bone mineral density, and exercise tolerance [39]. It is widely accepted that the effect of RT is dependent on load intensity and that the load intensity positively correlated with the magnitude of the effect obtained. Traditionally, muscle strength gains observed in the initial phase of training are due to the adaptation of the nervous system (mainly an increase in the number of motor units recruited), and the increase in muscle strength up to 20 days after the start of training occurs without an increase in muscle cross-sectional area [40–42]. Subsequently, muscle hypertrophy is thought to become the main mechanism of strength gain only after 8–12 weeks [43–46].

A meta-analysis by Borde et al. [47] showed that the following protocol is recommended for RT to improve muscle strength in healthy older adults: training intensity should be at 70–79% of the one repetition maximum (1RM), 7–9 repetitions per set, a training volume of 2–3 sets per exercise, a time under tension of 6 s, a frequency of 2 sessions per week, a rest of 4 s between repetitions, and a rest between sets of 60 s. On the other hand, the recommended parameters for RT to improve muscle morphology are as follows: training intensity should be at 51–69% of the 1RM, with 7–9 repetitions per set, a training volume of 2–3 sets per exercise, a time under tension of 6 s, an interset rest of 120 s, and a training frequency of 3 sessions per week. Notably, in both cases, their meta-analysis recommended a training period of 50–53 weeks. Therefore, further research is needed to determine which training protocols are more effective for short-term improvements in muscle function and mass, such as during hospitalization.

CCX causes a significant decrease in muscle mass not only in slow-twitch muscles but also in fast-twitch muscles that are typically less affected by inactivity [12]. Given that many fast-twitch muscles have a large volume, maintaining or increasing the fast-twitch muscle mass is key to increasing whole-body skeletal muscle mass. According to the size principle, an exertion of 80% or more of the maximal muscle strength is required to recruit most fast-twitch muscle fibers [48]. However, measuring maximal muscle strength and accurately adjusting the load to 80% of that strength are challenging in clinical practice because of the need for specialized and expensive equipment such as isokinetic machines. To solve this problem, a previous study reported that it is possible to recruit most fast-twitch muscle fibers at a 6–10 RM [49]. This means that the load should be adjusted to reach failure in the range of six to ten repetitions. On the other hand, the rating of perceived exertion (RPE) method, mainly using the Borg Scale, has recently become mainstream to determine the intensity of RT. An 8–10 RM converts to 15–17 Borg Scale and a Borg category-ratio scale (CR-10) of seven to eight in elderly subjects [50]. It is noteworthy that the training effect obtained using the RPE method is very similar to that obtained by the RM method [51].

Most of reports on RT in rodent models of CCX have investigated the effects of ladder climbing (Table 10.1). Studies by Donatto et al. [52] and Padilha et al. [53] showed an increase in gastrocnemius muscle mass in Walker 256 tumor-bearing rats. Conversely, in the same animal model, Neves et al. [54] found that squat-like RT did not improve extensor digitorum longus and plantaris muscle mass or forelimb grip strength. Because the load intensity and training period employed were 65% of the 1RM and 2 weeks, respectively, which were lower and shorter than those used in other reports, this may not have been sufficient to improve muscle mass and strength. Moreover, Khamoui et al. [30] demonstrated that ladder climbing did not sufficiently increase gastrocnemius muscle mass or forelimb grip strength in colon 26 (C-26) tumor-bearing mice. The intervention period in their study was sufficient, but there were presumed differences in the animal species.

Table 10.2 shows previous studies examining the effect of RT on ACP. Jensen et al. [55] reported that RT at 60–80% of the 1RM improved muscle strength in patients with advanced gastrocnemius cancer. In agreement with this, Grote et al. [56] demonstrated that muscle strength measured by leg and chest press was

Table 10.1 Effects of resistance training on skeletal muscle mass and/or strength in rodent models of cancer cachexia

Author	Species	Model	Type	Exercise parameters				Results
				Intensity	Repetition	Frequency/ week	Periods	
Donatto et al. 2013	Rat	Walker 256	Ladder climbing	75%, 90% and 100% of the rat's previous maximal carrying capacity	3–5 climbs	2 days	8 weeks	• Gas muscle weight was higher than control group
Neves et al. 2016	Rat	Walker 256	Squat-like	65% 1RM	10 repetitions × 3 sets	4 days	2 weeks	• No effects on muscle weight and forelimb grip strength
Padilha et al. 2021	Rat	Walker 256	Ladder climbing	progressively increased loading weight according to their daily performance	4–8 climbs	3 days	4 weeks	• The sum of Gas, SOL, and FHL muscle weight was higher than non-exercise group (+14%)
Khamoui et al. 2016	mouse	C-26	Ladder climbing	50% of body weight followed by 10% increases biweekly	3 climbs × 5 sets	3 days	8 weeks before and 3 weeks after tumor implantation	• No effects on Gas muscle, lean body mass, and forelimb grip strength

RM repetition maximum; *Gas* gastrocnemius; *SOL* soleus; *FHL* flexor hallucis longus

Table 10.2 Effects of resistance training on skeletal muscle mass and/or strength in patients with advanced cancer

Author	Subjects	Stage	Treatment	Type	Exercise parameters				Results
					Intensity	Duration/ repetition	Frequency/ week	Period	
Jensen et al. 2014	Advanced gastrointestinal cancer	N/A	5-Fluorouracil + oxaliplatin ($n = 6$) 5-Fluorouracil + other ($n = 7$) Capecitabine + other ($n = 7$) Cisplatin + gemcitabine ($n = 2$)	Resistance training of large muscle groups	60–80% of 1RM	15–25 repetitions × 2–3 sets	2 days	12 weeks	• Muscular strength increased in biceps (+46%), back (+41%), and knee flexors (+17%), but not in the triceps or knee extensor
Solheim et al. 2017	NSCLC or inoperable pancreatic cancer	III-IV	Surgery ($n = 6$) Chemotherapy ($n = 5$) Radiotherapy ($n = 7$)	Resistance training consisted of 6 individualized exercises + EPA intake	N/A	20 min	3 days	6 weeks	• Percent decrease in muscle mass was lower than control group but no effect on grip strength
Grote et al. 2018	Cachectic patients with head and neck cancer receiving radiation therapy	I-IV	Chemotherapy + radiotherapy ($n = 13$) Neck dissection ($n = 11$)	Three exercise for major muscle groupes for 30 min	The weight loading was increased at the next workout if RPE < 7 (0–10)	8–12 repetitions × 3 sets	3 days	13 training sessions	• Weight loading for leg press (+19.0%), chest press (+29.8%) and latissimus pull-down (+22.8%) were improved • Lean body mass form BIA was unchanged
Tatematsu et al. 2021	Advanced cancer	N/A	N/A	Resistance training consisted of three to five exercise components	Modified Borg Scale 3–5	10 repetitions × 3 sets	7 days	8 weeks	• Skeletal muscle index (cm^2/m^2) in compliant group was higher than noncompliant group • Physical function (hand grip, 6-min walking, gait speed, 5-time-sit-to-stand) was unchanged

NSCLC non-small cell lung cancer; *EPA* eicosapentaenoic acid; *N/A* no available; *RPE* ratings of perceived exertion; *RM* repetition maximum; *BIA* bioelectrical impedance analysis

increased by RT at an RPE of 7 or more (from 0 to 10), whereas lean body mass measured by bioelectrical impedance analysis (BIA) was unchanged. In contrast, Tatematsu et al. [57] recently reported that daily training set to Modified Borg Scale of three (moderate) to five (hard) increased the skeletal muscle index (cm^2/m^2), while physical function remained unchanged. The few reports, incorporating sufficient exercise intensity, have proven that RT improves muscle strength even in ACP. In contrast, the effects of exercise of insufficient intensity on muscle strength and physical function may reportedly be poor. With the inconsistency of methods used, reported measurements of muscle mass are unreliable and difficult to compare. Nevertheless, even if it cannot definitively be said that RT increases muscle mass in ACP, it can reduce the rate of muscle mass loss, as demonstrated in many fundamental experiments. Solheim et al. [58] reported that the rate of muscle mass loss was lower in a RT group (supplemented with eicosapentaenoic acid) than in a control group.

In conclusion, it appears that an appropriate exercise protocol includes three sets of RT with a hard load intensity using the RM or RPE method, adjusted to avoid the occurrence of adverse events. In accordance with the finding of previous studies, training should be performed at least 2 days a week, and the protocol recommended by Borde et al. should be followed [47]. However, the effect of exercise on improved muscle mass is controversial, and considering anabolic resistance, the use of higher loads may be warranted.

10.3.2 Aerobic Training

AT is a well-established approach for improving aerobic capacity and skeletal muscle function characterized by low- or moderate-intensity exercises with high repetition. It has been suggested that low-intensity AT attenuates muscle mass loss via anti-inflammatory effects [59, 60]. AT is less effective than RT in increasing muscle mass and strength, but it effectively decreases intramuscular adipose tissue and total body fat mass [61]. Moreover, AT improves muscle antioxidant capacity, insulin sensitivity, and endurance [62–64]. Since skeletal muscle endurance is significantly reduced during cancer progression [62–65], AT is an effective countermeasure.

In 1985, Deuster et al. [66] reported that AT prevented atrophy of the gastrocnemius muscle in Walker 256 tumor-bearing rats, and as shown in Table 10.3, even relatively low-intensity AT maintains muscle mass in fast-twitch muscles such as the gastrocnemius and tibialis anterior and improves forelimb grip strength in animal models [67–71]. Conversely, some researchers have shown that similar AT protocols did not improve muscle mass in murine models of CCX [30, 60, 72]. Thus, the impact of AT on skeletal muscle mass and function in cachexia is still under debated.

In ACP, Courneya et al. [73] reported that AT improved lean body mass, while a study by Solheim et al. [58] showed no improvement (Table 10.4). Courneya et al. included patients with less severe stage I–II cancer and treated them with more frequent and longer exercise sessions, which may have contributed to the improvement

Table 10.3 Effects of aerobic exercise on skeletal muscle mass and/or strength in rodent models of cancer cachexia

Author	Species	Model	Type	Exercise parameters					Results
				Speed	Distance/day	Duration	Frequency/ week	Periods	
Deuster et al. 1985	Rat	Walker 256	Treadmill	20.0 m/min on incline 13%	N/A	100 min	3 days	7 weeks	• Gas muscle weight to body weight ratio in exercise group was higher than that of the sedentary group
Salomao et al. 2010	Rat	Walker 256	Swimming	N/A	N/A	5–45 min	5 days	8 weeks	• Gas muscle weight to body weight ratio in exercise group was higher than that of the sedentary group
Tanaka et al. 2019	Rat	AH-130	Treadmill	15.0 m/min	N/A	30 min	Everyday	8 days	• SOL muscle wet weight and forelimb muscle strength were higher than that of the sedentary group
Ballaro et al. 2019	Mouse	C-26 + OXFU	Treadmill	11.0 m/min	N/A	45 min	5 days	4 weeks	• Gas and TA muscle weights and forelimb grip strength were higher than that of the non-exercise group
Pin et al. 2015	Mouse	C-26 and LLC	Treadmill	14.0 m/min	N/A	45 min	5 days	2 or 4 weeks	• No effect on muscle weight • Grip strength was higher than that of the sedentary group

(continued)

Table 10.3 (continued)

Author	Species	Model	Type	Exercise parameters					Results
				Speed	Distance/day	Duration	Frequency/ week	Periods	
Ballaro et al. 2019	Mouse	C-26 + OXFU	Treadmill	11.0 m/min	N/A	45 min	5 days	4 weeks	• Gas and TA muscle weights and forelimb grip strength were higher than that of the non-exercise group
Morinaga et al. 2021	Mouse	C-26	Treadmill	12.0 m/min	N/A	20 min	5 days	4 weeks	• Gas and TA muscle weights in exercise group were higher than that of the sedentary group
Khamoui et al. 2016	Mouse	C-26	Wheel running	5.0–6.5 m/min	N/A	60 min	5 days	8 weeks before and 3 weeks after tumor implantation	• No effects on Gas mass/body weight, lean body mass, and forelimb grip strength
Pigna et al. 2016	Mouse	C-26	Voluntary running	1.9 ± 0.1 km/h (31.7 m/min)	N/A	N/A	Everyday	19 days	• TA muscle weight was higer than that of the sedentary group
Hiroux et al. 2021	Mouse	C-26	Voluntary running	N/A	6.7 ± 1.0 km	N/A	Everyday	17 days	• No effect on muscle wet weight, forelimb grip strength, twitch and tetanus tension
Kitaoka et al. 2021	Mouse	C-26	Voluntary running	N/A	13.1 ± 1.0 km	N/A	Everyday	4 weeks	• Gas and Pla muscle wet weights and forelimb grip strength were higher than that of the sedentary group

N/A no available; *OXFU* oxaliplatin and 5-fluorouracil; *LLC* Lewis lung carcinoma; *Gas* gastrocnemius; *SOL* soleus; *TA* tibialis anterior; *Pla* plantaris

Table 10.4 Effects of aerobic training on skeletal muscle mass and/or strength in patients with advanced cancer

					Exercise parameters				Results	
Author	Subjects	Stage	Treatment	Type	Intensity	Duration	Frequency/ week	Period	Endurance capacity improved?	Muscle strength and mass
Courncya et al. 2009	Lymphoma	I–IV	Chemotherapy ($n = 53$)	Aerobic exercise	60–75%VO2 peak	15–20 min increased by 5 min weekly to 45 min	3 days	9 weeks	Yes	• Lean body mass in post-test (+0.9 kg) was higher than at baseline
Hwang et al. 2012	NSCLC	IIIA-IV	Iresa ($n = 8$) Afatinib ($n = 5$) Tarceva ($n = 11$) Previous chemotherapy ($n = 15$) Previous radiotherapy ($n = 13$)	Treadmill or cycling ergometer	Alternating with high (80% VO2 peak or RPE 15–17), and active recovery of moderate intensity (60% VO2 peak or RPE 11–13)	2–5 min (total 30–40 min including 10-min warm-up and 5 min cool-down)	3 days	8 weeks	Yes	• Isometric knee extension strength was increased in both control(+9%) and exercise group(+10%)

(continued)

Table 10.4 (continued)

Author	Subjects	Stage	Treatment	Type	Exercise parameters				Results	
					Intensity	Duration	Frequency/ week	Period	Endurance capacity improved?	Muscle strength and mass
Jesnsen et al. 2014	Advanced gastrointestinal cancer	N/A	5-Fluorouracil + oxaliplatin ($n = 6$) 5-Fluorouracil + other ($n = 7$) Capecitabine + other ($n = 7$) Cisplatin + gemcitabine ($n = 2$)	Aerobic exercise	60% PR in week 1–4, 70–80% PR in week 5–12	45 min	2 days	12 weeks	Yes	• The median watt capacity increased from 1.1 W/kg body weight to 1.2 W/kg
Solheim et al. 2017	NSCLC or inoperable pancreatic cancer	III-IV	Surgery ($n = 6$) Chemotherapy ($n = 5$) Radiotherapy ($n = 7$)	Aerobic exercise+EPA	N/A	30 min	2 days	6 weeks	No	• No effect on physical activity or muscle mass from CT

NSCLC non-small cell lung cancer; *EPA* eicosapentaenoic acid; *CT* computed tomography; *RPE* ratings of perceived exertion; *PR* pulse rate; *N/A* no available

in lean body mass. Therefore, AT three times a week rather than twice a week, and of a longer duration, may be more effective in improving muscle mass. This being said, few studies measured changes in muscle mass, and the measurement methods used were inconsistent.

It has been reported that the use of treadmills and ergometers improves knee extensor strength [74]. However, rate of increase is low, probably because AT places a smaller load on the muscles than dose RT. In most cases, the primary purpose of AT is conditioning, such as improving maximal oxygen uptake (VO_{2max}) and anti-inflammatory effects, whereas RT is more effective in improving muscle mass and function. Therefore, exercise protocols including RT should be performed.

10.3.3 Combined Training

Combined RT and AT is often used in the field of rehabilitation. However, there is no literature that fully demonstrates that CBT has the best effect compared with RT or AT alone. Stewart et al. [75] reported increased muscle strength and decreased CRP levels in physically inactive young and elderly subjects who engaged in CBT. Furthermore, CBT has been reported to downregulate the inflammatory response more than aerobic-only training [76].

Only one animal-model study by Ranjbar et al. [77] examined the effects of CBT (ladder climbing + wheel running) and reported improvements in both muscle mass and forelimb grip strength. On the other hand, in ACP, CBT has been the most widely studied exercise modality (Table 10.5). The load intensity of RT used in the CBT was set to 60–80% of the 1RM or an RPE of 12–16, which is consistent with the recommendations described in Sect. 10.3. The number of repetitions was most frequently 3–4 sets of 5–12 repetitions. AT was most frequently at around 80% of maximum heart rate (HR) or an RPE 12–16 (moderate-high intensity). The session duration varied from 10 to 60 min, at a frequency of 2 days per week, and the training period was often 6 weeks or more. A study by van dan Dungen et al. (2014) showed improved muscle strength over the shortest period (3 weeks). Many other studies have reported improvements in muscle strength. Two reports by Cormie et al. [78, 79] have shown that CBT caused an increase in lean body mass measured by dual-energy X-ray absorptiometry (DXA). However, evidence regarding the effects of CBT on muscle mass remains insufficient.

Comparing the effects of RT alone and CBT on ACP, CBT is not more effective for muscle strength and mass. However, since the combination of AT also improves endurance capacity, CBT is presumed to be recommended.

10.3.4 High-Intensity Interval Training

In recent years, high-intensity interval training (HIIT) has been one of the most remarkable training protocols, and the number of reports examining its effectiveness has increased dramatically over the past decade [80]. HIIT is a training

Table 10.5 Effects of combined exercise training on skeletal muscle mass and/or strength in patients with advanced cancer

Author	Subjects	Stage	Treatment	Type	Exercise parameters				Results	
					Intensity	Duration or repetition	Frequency/ week	Period	Endurance capacity improved?	Muscle mass and mass
Temel et al. 2009	NSCLC	IIIB with effusion or IV	Chemotherapy (n = 18) Radiation (n = 5) Chemotherapy and radiotherapy (n = 2)	Resistance training + treadmill and upright bicycle	60–80% of 1 RM for resistance, 70–85% HR peak for endurance	10 repetition × 3 sets for resistance, 30 min for endurance	2 days	2 months	No	• Muscle strength of elbow extension increased (+21%) but not of shoulder flexion, elbow flexion, hip extention and abduction and knee extension
Oldervoll et al. 2011	Various cancer	Life span ≤2 years	Chemotherapy (n = 126) Radiotherapy (n = 13) Hormonal therapy (n = 44) Targeted therapy (n = 9)	Circuit (resistance + aerobic) training	N/A	50–60 min circuit training	2 days	8 weeks	N/A	• Hand grip strength increased in exercise goup (+5%), but not in control group

Quist et al. 2012	NSCLC and SCLC with extensive disease	IIIB-IV	First-line carboplatin + vinorelbine ($n = 16$) Second- and third-line erlotinib ($n = 2$) Second-line pemetrexed ($n = 1$) First-line cisplatin + etoposide + thoracic radiotherapy ($n = 2$) First-line carboplatin + etoposide ($n = 2$)	Resistance + aerobic training + home training (walking and relaxation)	70–90% of 1RM for resistance and 85–95% HRmax for endurance	5 repetition × 3 sets for resistance and 10–15 min for endurance	2 days	6 weeks	Yes	• Muscle strength in leg press (+16.5 kg), chest press (+9.5 kg), lat machine (+3.4 kg), abdminal crunch (+4.6 kg), lower back (+7.8 kg) and leg extension (+6.5 kg) increased in post intervention
Cormie et al. 2013	Prostate cancer with bone metastasis	N/A	Previous ADT ($n = 20$) Previous radiotherapy ($n = 11$) Previous surgery ($n = 4$)	Resistance training + walking and/or stationary cycling	RPE 12–16 for resistance and moderate for endurance	8–12 repetition × 4 sets for resistance and 60 min for endurance	2 days	3 months	Yes	• Whole body lean mass by DXA increased (+0.6 kg) in post intervention

Table 10.5 (continued)

Author	Subjects	Stage	Treatment	Type	Exercise parameters				Results	
					Intensity	Duration or repetition	Frequency/ week	Period	Endurance capacity improved?	Muscle mass and mass
Henke et al. 2014	Lung cancer	IIIA-IV	Platinum-based chemotherapy ($n = 29$)	Resistance training + hallway and stair walking	Moderate	6 min	5 days for endurance, every other day for resistance	N/A	Yes	• Muscle strength in intervention group increased in biceps curl (+8%), triceps extention (+6%), bridging (+18%), and abdominal exercise (+14%), but not in control group
van den Dungen et al. 2014	Advanced cancer	N/A	Surgery ($n = 1$) Chemotherapy ($n = 10$) Hormone therapy ($n = 6$) Other ($n = 3$) None ($n = 6$)	Resistance training + cycling	60–80% 1RM for resistance, 3 min at 50–70% HR peak alternating 4 min at 80–90% HR peak for endurance	12 repetition × 3 sets for resistance, 30 min for endurance	2 days	3 and 6 weeks	Yes	• Hand grip and 1 RM of leg press, lunge, ventical row, lat pull down, abdminal crunch, pull over and bench press increased at week 3 and 6 compared to baseline

Cormie et al. 2014	Prostate cancer with bone metastasis	Gleason score 8.0 ± 0.9	Previous ADT ($n = 20$) Radiotherapy ($n = 11$) Surgery ($n = 4$)	Resistance training + walking and/or stationary cycling	RPE 12–16 for resistance and moderate for endurance	8–12 repetition × 2–4 sets+60 min walking and/or ergometer	2 days	3 months	Yes	• Whole body lean mass by DXA increased (+1.5 kg) in post exercise
Kuehr et al. 2014	NSCLC	IIA-IV	Chemotherapy ($n = 33$) Chemotherapy + radiotherapy ($n = 7$)	Resistance training + treadmill/ ergometer	RPE 12–14 for endurance and RPE 12–16 for resistance	N/A	5 days	2 months	Yes	• Muscle strength in elbow flexion (+7 N), extension (+14 N), hip abduction (+12 N), knee flexion (+32 N), and extention (+72 N) increased by end of intervention

(continued)

Table 10.5 (continued)

Author	Subjects	Stage	Treatment	Type	Exercise parameters				Results	
					Intensity	Duration or repetition	Frequency/ week	Period	Endurance capacity improved?	Muscle mass and mass
Quist et al. 2015	NSCLC and SCLC with extensive disease	IIIB-IV	Carboplatin/ cisplatin + vinorelbine +/− bevacizumab ($n = 73$) Carboplatin/ cisplatin + docetaxel/ paclitexel ($n = 4$) Cisplatin + pemetrexed + bevacizumab Pemetrexed ($n = 7$) Carboplatin/ cisplatin + etoposide ($n = 19$) Carboplatin/ cisplatin + topotecan ($n = 1$)	Resistance + aerobic training + home training (walking and relaxation)	70–90% of 1RM for resistance and 85–95% HRmax for endurance	5 repetition × 3 sets for resistance and 10–15 min for endurance	2 days	6 weeks	Yes	• Muscle strength in leg press (+14.5 kg), chest press (+5.2 kg), lat machine (+1.9 kg), abdominal crunch (+6.7 kg), lower back (+5.9 kg), and leg extension (+3.4 kg) increased in post intervention

NSCLC non-small cell lung cancer; *SCLC* small cell lung cancer; *N/A* no available; *RPE* ratings of perceived exertion; *RM* repetition maximum; *DXA* dual-energy X-ray absorptiometry; *HR* heart rate

regimen that consists of short to long repetitions of relatively high-intensity exercise at 85–95% of the peak HR or 70–80% of VO_{2max}, alternating with low-intensity exercise or rest. Conventionally, HIIT is performed on a stationary bicycle or treadmill, and its main advantage is that it can maximize exercise capacity in a short time to achieve improvements in cardiorespiratory fitness [81, 82].

HIIT has been shown to be safe and feasible for the prehabilitation of patients with cancer [83] and for cancer survivors [84]. However, there is no evidence that it can be safely performed in ACP. A systematic review by Mugele et al. [85] showed that short-term HIIT has a positive effect on physical fitness and health-related outcomes, similar to that achieved by moderate-intensity training in patients with cancer. They posited that HIIT might be a time-efficient intervention for patients with cancer across all stages of therapy and aftercare. However, they showed that HIIT does not offer an advantage in the gain of lean muscle mass compared to moderate-intensity AT. Several studies have reported that HIIT results in improvements in muscle strength [86, 87]; however, none have reported improvements in muscle mass.

Twelve weeks of HIIT was reported to suppress serum TNF-α and IL-6 levels in patients with breast cancer [88], and Moghadam et al. [89] showed that HIIT reduced serum TNF-α concentrations more than moderate-intensity continuous training. Notably, HIIT has been shown to inhibit tumor growth and increase survival rates in tumor-bearing mice [90]. Therefore, further research is needed to evaluate the efficacy of HIIT in patients with CCX, as well as its safety.

10.3.5 Neuromuscular Electrical Stimulation

Neuromuscular electrical stimulation (NMES) involves attaching electrodes to the body surface and triggering involuntary muscle contractions via electrical stimulation, producing an effect similar to that of exercise. For example, NMES activates the mammalian target of rapamycin complex 1 (mTORC1), a key regulator of muscle protein synthesis, and peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), the master regulator of mitochondrial biogenesis [91]. In addition, it has been shown that various types of myokines such as ILs and growth hormone are produced as a result of NMES-induced muscle contraction [92].

In contrast with voluntary exercise, NMES induces the activation of all muscle fiber types independent of the size principle [93], which is beneficial for the recruitment of fast-twitch muscle fibers. The greatest advantage of this approach is that it can be performed in a supine resting position, rendering it suitable for patients with limited mobility and/or prolonged bed rest, including those with cancer.

NMES is often regarded as a type of RT. NMES-induced muscle hypertrophy and the activation of mTORC1 signaling are modulated by mechanical loading during contraction [94]. Eccentric (ECC)-mode training provides a greater mechanical load on the contracting muscle than concentric (CON)-mode or isometric (ISO)-mode training, resulting in higher muscle hypertrophy [94]. In previous reports examining the effects of NMES on experimental animal models of CCX (Table 10.6),

Table 10.6 Effects of neuromuscular electrical stimulation training on skeletal muscle mass in rodent models of cancer cachexia

Author	Species	Model	Electrode	Stimulation parameters													Results
				Contraction mode	Intensity	Duration	On	Off	Frequency	Total volume	Total time/day	Total time/ period	Frequency	Period	Angle of foot joint	Angular velocity	
Al-Majid and McCarthy 2001	Mouse	C-26	Needle	Eccentric (TA, EDL) Concentric (Gas, SOL)	4–16 V	1.0 ms	3 s	10 s	100 Hz	10 contractions × 6 sets	180 s	1440 s	Every other day	16 days	Full	Rapidity	• EDL muscle weight was higher in ES group (+62%) than in CNT group • No effects on SOL, Gas, and TA muscle weights
Tatebayashi et al. 2016	Mouse	C-26	Surface	Isometric (TA, EDL, Gas, SOL)	60% of MIT	0.5 ms	2 s	4 s	50 Hz	~30 contractions	~60 s	840 s	Every other day	28 days	20° of DF	0°/s	• SOL muscle weight was higher in ES group (+28%) than in CNT group • No effects on Gas, EDL, and TA muscle weights
Tatebayashi et al. 2018	Mouse	C-26	Surface	Eccentric (Gas)	Supramaximal (45 V)	0.5 ms	2 s	4 s	100 Hz	5 contractions × 4 sets	40 s	280 s	Every other day	28 days	From 0° to 40°	20°/s	• Gas muscle weight was higher in ES group (+6%) than in CNT group
Hardee et al. 2016	Mouse	$Apc^{Min/+}$	Needle	Eccentric (TA) Concentric (Gas)	Supramaximal (6–12 V)	1.0 ms	3 s	10 s	100 Hz	10 contractions × 6 sets	180 s	1260 s	Every other day	14 days	Full	Rapidity	• TA muscle weight was higher in ES group (+3%) than in CNT group • No effects on Gas muscle weights
Hardee et al. 2020	Mouse	$Apc^{Min/+}$	Needle	Eccentric (TA)	Supramaximal (6–12 V)	1.0 ms	3 s	10 s	100 Hz	10 contractions × 6 sets	180 s	1260 s	Every other day	17 days	Full	Rapidity	• TA muscle weight was higher in ES group (+9%) than in CNT group

TA tibialis anterior; *EDL* extensor digitorum longus; *Gas* gastrocnemius; *SOL* soleus; *MIT* maximum isometric tension; *CNT* control; *DF* dorsal flexion

we and other researchers have demonstrated that NMES with ECC-mode training attenuates CCX-induced muscle wasting [95–97]. In contrast, it has been shown that CCX-induced muscle wasting is not prevented by NMES with CON-mode training or ISO-mode training [98, 99].

Although many researchers have reported that NMES maintains or improves muscle mass and function in many diseases, few studies have examined the effects of NMES on muscle mass and strength patients with cancer. Among them, a study by Maddocks et al. [100] showed that NMES did not prevent decreased muscle strength and thigh lean mass in patients with lung cancer. However, since the current intensity in their study was set within the range of endurance from the degree to which muscle contraction was visible, it is possible that the amount of physical load on the muscle was insufficient to prevent muscle atrophy. Conversely, O'Connor's group [101] applied a protocol that started with a current intensity of 14 mA and increased it by 14 mA every 3 min (≥70 mA over 15 min) to the quadriceps muscles of 10 ACP and poor performance status (Eastern Cooperative Oncology Group score of ≥2), resulting in improved repetition of a 30 s sit-to-stand test and physical function. Therefore, as with exercise training, the key to improving muscle function when applying NMES is most likely the load intensity, hence, the important to increase the current intensity. Accordingly, it is necessary to study in detail how the muscle responds to the amount of current applied.

In patients undergoing hematopoietic stem cell transplantation or intensified chemotherapy, NMES has been shown to be safe, even when platelets are less than 20,000/μL [102]. Moreover, there were no serious adverse events in the protocols of O'Connor et al. [101], suggesting that it is safe and feasible for patients at all stages of cancer. However, since pain and discomfort intensity when the current intensity is increased, strategies to reduce these effects should be considered.

10.4 Assessment of Skeletal Muscle in Clinical Practice

Assessments of skeletal muscles, at least in the field of rehabilitation in Japan, are usually performed using only muscle strength tests. However, while many previous studies have measured changes in muscle strength in relation to exercise training, there is insufficient evidence for changes in the quantity and quality of muscle. Muscle strength correlates with muscle mass, but the correlation with muscle cross-sectional area, muscle thickness, and muscle strength is moderate [103, 104]. Therefore, not all changes in muscle strength can be explained by muscle mass changes alone [105]. With the recent development of technology, quantitative and qualitative changes in muscles can be measured partially but noninvasively (Table 10.7). Hence, for the development of rehabilitation, it is possible and necessary to evaluate the effect of training not only on muscle strength but also on muscle quantity and quality.

Table 10.7 Pros and cons of skeletal muscle assessment methods. (Modified from Aleixo et al. 2019)

Method	Pros	Cons
MRI	• No radiation exposure • Can be used at multiple sites of the body to assess sarcopenia • Sensitive to changes in muscle structure • European and Asian guidelines recommended method • Can estimate muscle and fat measures • Qualitative evaluation is partially possible	• Non-portable • Requires expensive equipment • Requires long examination time • High level of technical expertise required • Needs special software for evaluation • Opportunistic use of routine imaging for muscle assessment is not possible • Not for use in patients with implantable devices
CT	• Provides highly accurate and reproducible results • Can be used in many different muscles to assess sarcopenia • Gold standard method for European and Asian guidelines • Can estimate muscle and fat measures • Qualitative evaluation is partially possible	• Non-portable • Requires expensive equipment • High amount of radiation exposure • High level of technical expertise required • Needs special software for evaluation
DXA	• Results are immediately available • Sufficient sensitivity and specificity • Can indirectly estimate lean body mass • European and Asian guidelines recommended method	• Radiation exposure • Non-portable • Requires expensive equipment • Requires high level of technical expertise • Requires special calibration knowledge • Qualitative evaluation is impossible
BIA	• No radiation exposure and noninvasive • Portable • Not expensive • Little or no training is required to operate it • Results are immediately available • Accepted by Asian guidelines • Qualitative evaluation is partially possible	• Lower sensitivity and specificity than the gold standard method • Requires pre-test protocol for hydration and exercise • Not for use in patients with implantable devices
US	• No radiation exposure • Not expensive • Portable • Results are immediately available • Qualitative evaluation is partially possible	• Results are highly influenced by variations in operator technique • Measurement technology has not been standardized

MRI magnetic resonance imaging; *CT* computed tomography; *DXA* dual-energy X-ray absorptiometry; *BIA* bioelectrical impedance; *US* ultrasound diagnostic analysis

10.4.1 Skeletal Muscle Strength

In Japan, manual muscle testing, requiring no equipment and little skill, has been frequently used both in the past and present for muscle strength measurement. It is a six-point test ranging from 0 (no evidence of muscle contraction) to 5 (full range of motion against maximal manual resistance). However, given that the maximum manual resistance depends on the muscle strength of the evaluator, this test is neither objective nor scientifically sound. Furthermore, it has the disadvantage of not being able to assess muscle strength above that of the evaluator.

Unless the purpose is to determine paralysis or local functional impairment, grip strength or knee extension muscle strength measurements show good reproducibility and accuracy and are often used in physical therapy for patients with cancer. Those are correlated with whole-body muscle strength, and the measurement devices are relatively inexpensive. Grip strength is one of the criteria for the diagnosis of sarcopenia in recent years, and the cutoff values for Asians are less than 28 kg and 18 kg for men and women, respectively [106]. For lower-limb muscle strength, isometric knee extension muscle strength at 90° of knee joint flexion is often used as a representative value [107]. When measuring with a handheld dynamometer, it is desirable to use a fixed belt for higher reproducibility and reliability.

In contrast, an isokinetic machine is a medical rehabilitation exercise device designed to measure, evaluate, and increase muscle strength and is superior in terms of accuracy and objectivity of measurement. However, owing to the high cost of the necessary equipment and the complexity of the process, it may be difficult to implement this technology in the field of rehabilitation of patients with cancer.

10.4.2 Skeletal Muscle Mass

10.4.2.1 Imaging-Based Muscle Mass Assessment

There is no noninvasive method to quantify skeletal muscle mass in humans, and all assessment methods are indirect. Recently, the measurement of muscle cross-sectional area by magnetic resonance imaging (MRI) and computed tomography (CT) images has emerged as the gold standard and has been applied to many diseases [108]. These methods use software to calculate the muscle mass, visceral fat, and subcutaneous fat from cross-sectional images. In particular, CT is commonly used to estimate total body muscle mass from the muscle area of the psoas muscle at the level of the third lumbar vertebra (L3) [109–112], which objectively reflects the total body composition and can capture muscle loss relatively accurately [113]. CT scans are frequently used in clinical diagnostic studies, especially in cancer patients, and it has been reported that a level of 5 cm cephalad from the L4-L5 intervertebral space provides the most accurate measurement [114]. Additionally, this method is useful for evaluating patients with CCX [115, 116]. Most patients with gastrointestinal cancer undergo periodic abdominal CT scans, which provide the advantage of easy follow-up. However, the disadvantages of these methods are that they involve exposure to radiation and require large, expensive, and non-portable equipment.

Quantification of the lumbar L3 cross-sectional area has been performed using MRI [117]. Additionally, median thigh images from MRI and CT have also been used in many studies because they are good predictors of whole-body skeletal muscle mass and are very sensitive to changes in muscle mass [118–121]. Central thigh muscle area correlates more strongly with total body muscle mass than the lumbar muscle area at L1-L5 [117]. Narici et al. [122] described the advantages of MRI over CT in that the orientation of the image plane can be changed, different tissue types can be distinguished, and the subject is not exposed to X-rays. However, MRI requires large, nonmobile, and expensive equipment, and the procedure has a long duration. Therefore, it has not been widely used for muscle assessment in rehabilitation.

10.4.2.2 Dual-Energy X-Ray Absorptiometry

DXA is a muscle mass measurement method that involves low radiation exposure. DXA measures lean body mass but is not a method to formally measure skeletal muscle mass and has low sensitivity for evaluating muscle mass changes [123]. The skeletal muscle index (SMI) is calculated as the volume of lean mass in the limbs divided by the square of height (kg/m^2). The diagnostic criteria for sarcopenia in Asians for SMI as measured by DXA are 7.0 kg/m^2 and 5.4 kg/m^2 for men and women, respectively. DXA also requires a large, non-portable instrument and involves radiation exposure, which is a serious obstacle to its use in the routine clinical practice of rehabilitation.

10.4.2.3 Bioelectric Impedance Analysis

BIA is a method for estimating body composition based on the difference in the inherent electrical conductivity of body issues [124]. Recently, the development of multifrequency BIA and impedance spectroscopy has made it possible to estimate muscle mass more accurately [125]. This procedure is noninvasive, takes less than a few minutes, does not require advanced measurement techniques, and can provide immediate results. Furthermore, this equipment is less expensive than CT, MRI, and DXA. Depending on the measurement device, the skeletal muscle mass of the whole body, limbs, and trunk can be measured, and the SMI calculated by BIA can also be used for the diagnosis of sarcopenia. According to the Asian Working Group of Sarcopenia (AWGS), the diagnostic criteria for sarcopenia in Asians are an SMI of less than 7.0 kg/m^2 and 5.7 kg/m^2 for men and women, respectively [126]. In a systematic review, BIA was shown to be an accurate method for detecting sarcopenia in cancer patients and a valid alternative to CT, MRI, and DXA in the field of clinical oncology [127]. However, the disadvantage of this assessment is that it is affected by edema (extracellular water to total body water ratio). During chemotherapy, patients with cancer often undergo hydration, and the time point of BIA measurement should be carefully considered. Moreover, because the algorithm differs depending on the measuring device, it is difficult to compare the results when different devices are used [128, 129].

10.4.2.4 Ultrasound Diagnostic Imaging

The ultrasound (US) imaging system emits US waves from a probe to a subject, and the reflected waves from the subject are received by the probe again to create an image of the internal tissues. The greatest advantage of this device is that it can be used to evaluate individual muscles. For example, it may be possible to evaluate differences in training responses between fast- and slow-twitch muscles, since it is possible to separately evaluate muscles that contain a large amount of fast-twitch fibers and those that are composed mainly of slow-twitch fibers. Importantly, US imaging correlates strongly with assessment of muscle mass using MRI [130–132], CT [133], and DXA [134–137]. However, until recently, the measurement technique has not been standardized [138].

Muscle thickness is generally measured in transverse images with the probe in contact perpendicular to the running of the muscle fiber in brightness (B)-mode. A probe pressure of less than 100 gf results in low inter-rater reliability [139]. The thickness of the quadriceps femoris muscle, especially the rectus femoris and vastus intermedius, has been the most studied in healthy and ill subjects. Measuring changes in quadriceps thickness is appealing because it allows for comparison with knee extensor strength measured using a handheld dynamometer as described above. The biceps brachii muscle and medial head of the gastrocnemius muscle are also representative areas that are close to the body surface and can be easily measured and compared with muscle strength (Fig. 10.1). Yuguchi et al. [140] found that medial gastrocnemius muscle thickness measured by US was independently associated with low skeletal muscle mass measured by BIA in healthy Japanese individuals aged ≥65 years. Furthermore, they showed that the cutoff value of medial gastrocnemius thickness to indicate the low skeletal muscle mass was 11.6 mm regardless of sex. To our knowledge, there are no reports on US measurement of muscle thickness in patients with cancer; thus, future studies could refine and apply this technique.

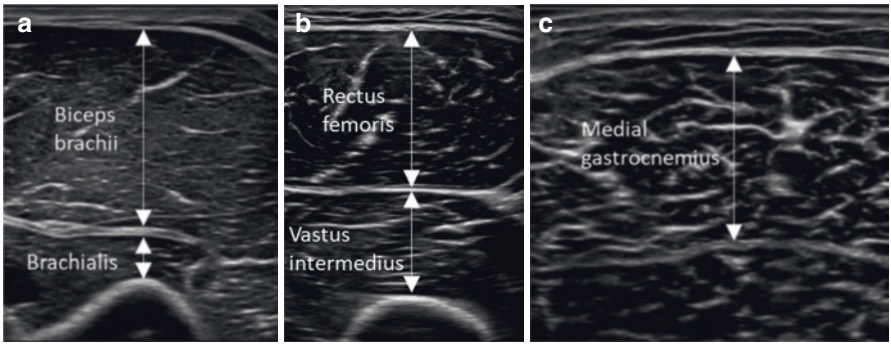

Fig. 10.1 Ultrasound images of biceps brachii and brachialis (**a**), rectus femoris and vastus intermedius (**b**), and medial gastrocnemius (**c**) in a healthy subject. The imaging site was determined in accordance with previous studies [140, 167, 168]

10.4.3 Methods for Qualitative Assessment of Skeletal Muscles

Data on aging over a 5-year period by Delmonico et al. [141] showed that the rate of decrease in muscle strength was two to five times greater than the degree of reduction in muscle cross-sectional area (CSA), suggesting that reduced muscle quality (increased adipose tissue in muscle cells) is a contributing factor. Therefore, muscle quality has been suggested as a critical determinant of skeletal muscle function [142]. Skeletal muscle tissue contains not only contractile tissue but also noncontractile components such as extracellular fluid, adipose tissue, and fibrous tissue in the intercellular spaces. These noncontractile tissues are included in the CSA and muscle thickness in imaging evaluation, which inevitably leads to overestimation. Hence, it is worthwhile to assess the density of contractile tissue and the proportion of noncontractile tissue within skeletal muscle. In addition to quantitative assessment, BIA and US imaging devices can partially evaluate the quality of skeletal muscle.

10.4.3.1 Measurement of Intramuscular Noncontractile Tissue in CT Imaging

The Hounsfield unit (HU), a measurement of the signal intensity of X-rays, is used for the evaluation of muscle mass on CT. In a recent study, water was defined as 0 HU, air as 1000 HU, adipose tissue as −30~190 HU, muscle as 0~100 HU, and bone as >200 HU, and the area of each was calculated [143]. In the elderly [144] and in wasting diseases [145, 146], noncontractile tissue in muscles including lipids increases, resulting in a decrease in HU. However, it is important to note that this method is unable to assess whether the lipids in the muscle are intracellular or extracellular. Because of the high cost and radiation exposure mentioned above, CT imaging is implausible solely for muscle mass evaluation and has not been widely used in rehabilitation.

10.4.3.2 Phase Angle

In BIA, the phase angle (PA) is calculated as a qualitative evaluation of muscle tissue. The PA is the phase difference between the overall current and voltage [147] and is considered to reflect the amount and integrity of the body cells [148, 149]. It has been reported that the PA decreases with age and correlates with muscle strength in community-dwelling elderly people [150]. Elderly people with reduced PA are at higher risk of sarcopenia, frailty, and mortality [151, 152]. Furthermore, PA in ACP was revealed to be associated with survival independent of conventional prognostic indicators such as serum albumin [153]. In addition, a recent study demonstrated that the PA derived from BIA positively correlates with CT-derived muscle density in critically ill patients [154]. Therefore, PA is an alternative indicator of myocyte density and is worthy of further investigation and utilization in the field of cancer research.

10.4.3.3 Muscle Echo Intensity

Muscle echo intensity (EI) has recently been used to evaluate muscle quality using US imaging [155]. Muscle EI is thought to reflect the increase or decrease in adipose and fibrous tissues in the extracellular matrix of skeletal muscle [156]. Indeed, muscle EI has been reported to be strongly correlated with intramuscular fat and

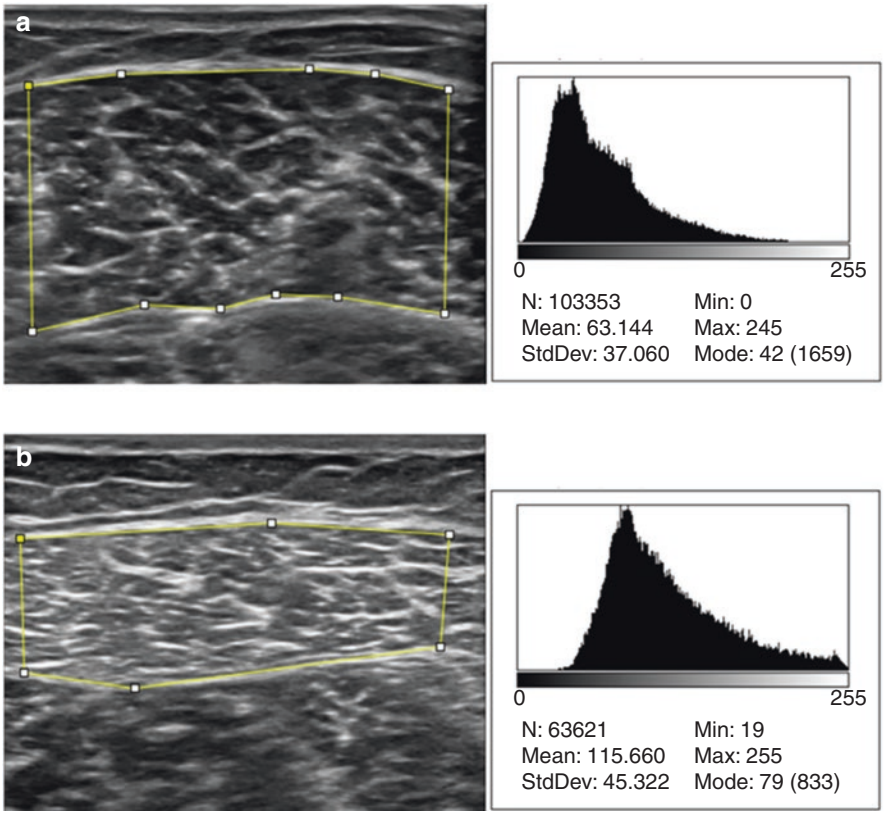

Fig. 10.2 Echo intensity (EI) in medial gastrocnemius muscles. Images show the 8-bit grayscale analysis of the ultrasound image in a healthy subject (**a**) and patient after bone-marrow transplantation (**b**). The EI within regions of interest using image j software is represented by the mean value of the histogram shown on the right

fibrous tissue on muscle biopsy [157, 158]. Normally, healthy muscle tissue is depicted with low intensity (i.e., it appears black), whereas increased extracellular fat and fibrous tissue in muscle increases the intensity (i.e., it appears white). Muscle EI is generally quantified and compared using an 8-bit grayscale method (Fig. 10.2). This approach quantifies the brightness of the region of interest in 256 shades from 0 (black) to 255 (white) and then calculates the average value. The measurement of EI with 8-bit grayscale can be easily performed using various image analysis tools, including freely available software.

Over the past decade, several studies have reported that RT decreases muscle EI in young [159] and elderly people [160–162], suggesting an improvement in the muscle composition. Fukumoto et al. [163] showed that EI was significantly correlated with quadriceps muscle strength independent of age or muscle thickness, and stepwise regression analysis revealed that muscle thickness and EI were independently related to quadriceps muscle strength. These data highlight the importance of measuring muscle EI in clinical practice.

Dankel et al. [164] showed that even a slight probe tilt caused significant changes in EI, but not in muscle thickness. Furthermore, they found that probe tilt had a significant effect on the test-retest reliability of EI. Therefore, consistency between examiners and the standardization of image acquisition protocols in research studies are essential. In addition, this method is only suitable for observation of muscles close to the body surface because the echo beam attenuates in deeper layers. To solve this problem, a method for correcting the EI of muscles according to the thickness of adjacent subcutaneous fat has recently been proposed [165, 166]. Advances in science and technology are expected to improve the accuracy of deep muscle evaluation.

10.5 Conclusions and Future Perspectives

It is noteworthy that most of the studies have focused on preventive interventions for muscle atrophy in patients with cancer. This indicates that recovery from muscle atrophy after progression is presumably difficult. Therefore, the key is to delay the progression of atrophy by initiating countermeasures at an early stage. Many previous studies of exercise intervention in ACP have shown improvements in muscle strength, although it should be noted that dropout rates due to adverse events are high. However, evidence regarding the effect of exercise training on quantitative and qualitative measurement of muscle tissue is insufficient. It is important to evaluate and examine the strength, mass, and quality of skeletal muscles from multiple perspectives, without depending on a single evaluation measure. Otherwise, the establishment of effective training methods would be impeded, retarding the development of the field of physical rehabilitation. A future challenge is to evaluate the effects of training on skeletal muscles from various perspectives and to establish evidence for physiotherapy for patients with cancer to prevent muscle function decline induced by CCX.

Currently, we are investigating the changes in skeletal muscle during multidisciplinary treatment using a combination of the evaluation methods described in this paper. Further research will reveal in more details the characteristics of skeletal muscle changes associated with different types of cancer and anticancer drugs and identify the effects of training on these changes. As a further development, combination effects of various drug therapies, nutritional therapies (e.g., intake of leucine for muscle hypertrophy), and NMES should be examined to enhance the effects of exercise therapy.

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Physical Exercise and Skeletal Muscle Adaptation in Cancer Cachexia

11

Mitsunori Miyazaki

Abstract

Cancer cachexia is a muscle wasting syndrome observed in cancer and other chronic wasting diseases and is a highly challenging disorder to manage due to the complexity of its clinical symptoms. Successful management of cachexia, including the maintenance of muscle mass, body weight, and locomotive physical function, is highly important for patients because it leads to the maintenance/improvement of life outcomes and survival rates, as well as tolerance and successful response to anticancer treatment. Despite the substantial need for cachexia treatment, there are no clinical therapies that are currently approved for the prevention of cachexia. This lack of effective preventative treatment may be due to the absence of a molecular mechanism for the onset and progression of cancer cachexia. The lack of animal experimental models that can accurately reproduce complex cachexia symptoms may also be a contributing factor. Therefore, this chapter aims to outline the characteristics of the experimental animal models used for researching cachexia. Molecular mechanisms underlying the onset and progression of cancer cachexia will also be discussed, with a particular focus on the regulatory mechanisms of energy and muscle protein metabolism. In addition, emphasis is placed on physical exercise as a promising treatment to prevent the progression of cancer cachexia. The impact of exercise therapy on the regulation of protein metabolism is a particularly promising option for treatment.

M. Miyazaki (✉)
Department of Integrative Physiology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

Department of Physical Therapy, School of Rehabilitation Sciences, Health Sciences University of Hokkaido, Hokkaido, Japan
e-mail: mmiya4@hiroshima-u.ac.jp

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Keywords

Cancer cachexia · Animal model · Protein synthesis · Mechanistic target of rapamycin · Protein degradation

11.1 Introduction

The skeletal muscle is one of the most essential organs for controlling the functioning of humans, as it not only provides the force output necessary for daily activities such as standing and walking but is also involved in the control of energy metabolism and heat production and works as an endocrine organ. In recent years, a wasting syndrome called cachexia, which refers to the secondary loss of body weight, skeletal muscle, and adipose tissue in chronic primary diseases such as cancer, has been recognized as a serious clinical problem [1]. Cancer cachexia is characterized by a systemic and multifactorial metabolic abnormality that occurs in association with a primary disease and is distinct from irreversible skeletal muscle degenerative diseases such as muscular dystrophy or age-associated muscle loss/weakness like sarcopenia. It is often characterized by a marked loss of body weight and skeletal muscle mass (with or without fat mass loss) that leads to a drastic decline in the quality of life and poor rates of morbidity and mortality in cachexia patients [2–4]. In addition, patients may experience more frequent and severe toxicity reactions to anticancer therapies, resulting in lower levels of tolerance to treatment and a further negative impact on the chance of survival [5].

The frequency of cachexia in cancer patients varies widely. For example, prostate and breast cancer patients have an approximate frequency of 15–30% and a relatively low risk of cachexia development, while gastrointestinal, pancreatic, and lung cancer patients have a high frequency of cachexia (some reports show over 70%) and a risk for cachexia development, and the frequency of cachexia increases with the advancement of the disease [6–10]. At present, there are no established effective anti-cachexia therapies for the treatment of this complex, intractable syndrome [11, 12]. This may be due in part to the lack of proper experimental animal models that allow us to understand the exact molecular mechanisms of the complex nature of cachexia syndrome. In this regard, there is a growing recognition of the need for animal models to represent the pathology of cancer cachexia. In practice, many animal models have been developed and are being used in the field of basic research [13–16]. The following is an overview of experimental animal models of cancer cachexia including the characteristics and application of each approach and the developmental pattern of cachexia.

11.2 Animal Model of Cancer Cachexia

Experimental research on cancer cachexia has historically been conducted using allografts of tumor cells (such as colon 26 carcinoma, Lewis lung carcinoma, Walker 256 carcinoma, and Yoshida ascites hepatoma AH-130) that are capable of inducing symptoms of cachexia in animal models. Indeed, these allograft models have been employed by many researchers to date, and a large body of experimental data has been accumulated.

11.3 Colon 26 Adenocarcinoma Model

One of the most extensively employed animal models of cancer cachexia is the experimental system that uses colon 26 (C26) carcinoma. The detailed experimental method is described in a previous article elsewhere [17, 18]. Briefly, this model mimics cachexia by subcutaneously transplanting C26 tumor cells derived from mice, which are a colorectal cancer cell line, into mice dorsal or flank regions, thereby inducing rapid reduction of body weight, muscle mass, and adipose weight as the C26 tumor grows [19–25]. Cell numbers for inoculation vary widely, ranging from 0.5×10^5 to 1×10^6 or more cells. Most studies have reported that body weight loss occurs in about 2 weeks, and cachexia progresses for about 3–4 weeks following cancer cell grafting, although reporting on this varies among the previous studies [18, 22, 26, 27]. The progression of cachexia associated with C26 tumor growth is largely caused by excessive catabolism of lipids and skeletal muscle proteins. It also causes hepatic and spleen enlargement [25], loss of cardiac muscle weight [28], and a drastic increase in the production of pro-inflammatory cytokines [21, 29, 30]. C26-induced muscle loss is largely caused by a decrease in muscle protein content with a smaller incidence of cell death and loss of muscle fiber number as seen in other experimental models of muscle atrophy [31]. Since the C26 cell line was originally derived from the colon carcinoma in BALB/c mice and usually grows well in mouse strains of the BALB/c or CD2F1 (BALB/c × DBA/2 F_1), these two lines are commonly employed as tumor hosts [18]. Typical experimental results of subcutaneous transplantation of C26 cells into CD2F1 mice are shown in Fig. 11.1.

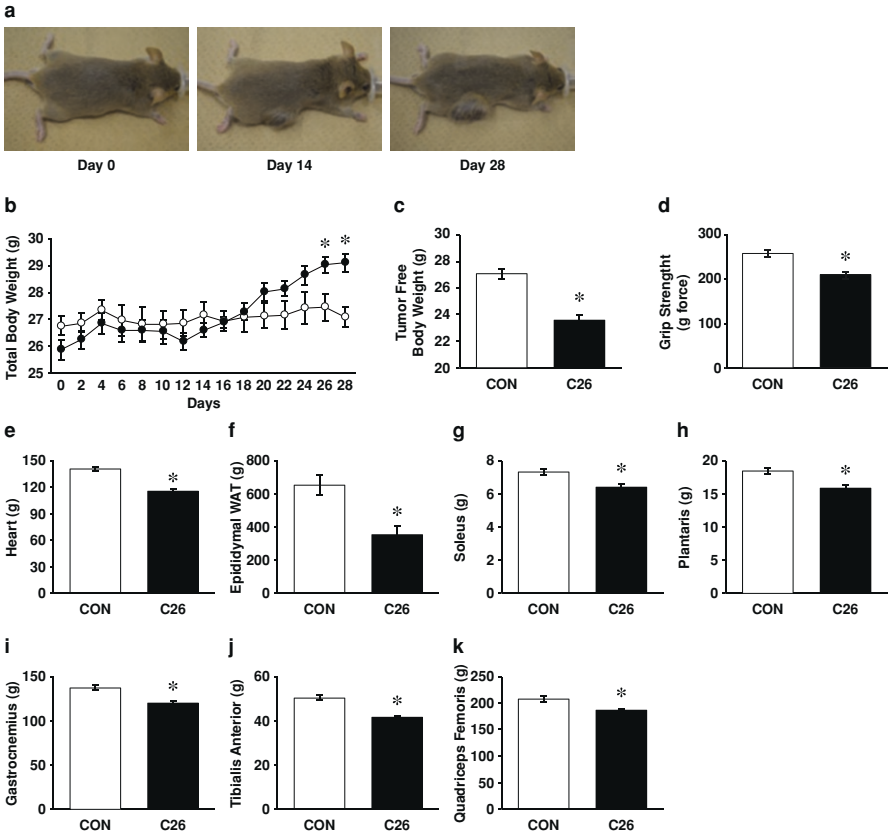

Fig. 11.1 Progression of cancer cachexia associated with transplantation of C26 carcinoma. Male CD2F1/Slc mice (Japan SLC, Japan) aged 7–8 weeks were used. The C26 carcinoma cell line (RCB2657) was provided by RIKEN BRC through the National Bio-Resource Project of MEXT, Japan. The C26 cells were grown in RPMI-1640 medium supplemented with 10% FBS and penicillin–streptomycin. After trypsinization and neutralization, 1×10^6 C26 cells per individual were suspended in 100 μL of PBS and subcutaneously implanted into the flank region of the abdominal wall unilaterally using a 26-guage syringe. Body weight and muscle strength were measured over time from 0 to 28 days following C26 cell transplantation while confirming tumor tissue formation. Typical images of a mouse model of cachexia (**a**). Although the total body weight was gradually increased with C26 tumor growth (**b**), the tumor-free body weight was significantly decreased after 4 weeks of C26 tumor-bearing (CON, 27.07 ± 0.38 g; C26, 23.50 ± 0.41 g; **c**). Tumor-bearing mice exhibited a wasting physiological status at the end of the experimental period, with decreased muscle strength (**d**) and a loss of tissue weight (heart, epididymal white adipose tissue, and skeletal muscles, (**e**–**k**). These results confirm that the C26 tumor-bearing model is adequate for mimicking cancer cachexia similar to that of previous studies. All results are expressed as mean ± standard error. Significant differences: *, between CON and C26 mice for each experimental condition ($p < 0.05$)

11.4 Lewis Lung Carcinoma Model

Along with C26 cells, another popular model of cancer cachexia is the subcutaneous allograft of Lewis lung carcinoma (LLC) in mice. Similar to the C26 model, the cultured LLC tumor cells are grafted to mice dorsal or flank regions subcutaneously (~1×10^6 cells) to induce cachexia [32, 33]. Cachexia develops approximately 3–4 weeks following the transplantation of LLC cells. Grafting of LLC tumors can also be done via intramuscular injection which results in a larger loss of muscle mass compared to the process of implantation in the flank region [34, 35]. It is important to note that the LLC lineage is known to metastasize and the efficiency of cachexia development and extent of muscle atrophy may vary depending on the location of the grafts [34, 36]. LLC cells were originally isolated from spontaneous tumors of C57BL/6 mice and are now available from the American Type Culture Collection (https://www.atcc.org). One of the most significant advantages of using the LLC model of cancer cachexia is that it is readily available for application in experiments that use genetically engineered mice [33, 37, 38]. The background of the mice most frequently used to generate genetically engineered animals is the C57BL/6 line, as this is the same line from which LLC cells are derived. To use the aforementioned C26 model of cachexia in genetically engineered mice, it is essential to backcross the target animal to the BALB/c strain, and this requires a great amount of effort.

11.5 Walker 256 Carcinoma Model

The Walker 256 carcinoma model is a well-known experimental model of cancer cachexia and is particularly used with rats [39–42]. Walker 256 tumor cells were originally isolated from carcinomas that spontaneously developed in the region of the mammary glands of a pregnant albino rat. The experimental method is described in detail in a previous article [43]. This experimental model is similar to the C26 and LLC models described above in which tumor cells are subcutaneously transplanted mainly into the flank region of the abdominal wall to allow for a solid formation of the tumor. A wide variety of cell numbers preparing to be implanted ranged from 1×10^5 to 8×10^7 cells and are characterized by the rapid development of cachexia [42–45]. Food consumption and body weight loss are observed within 7 days, and muscle mass loss rapidly develops after 14 days of the implantation of cancer cells [42, 45, 46]. It is also known for its high capacity to proliferate and metastasize and is sometimes used as a bone metastasis model when it is injected into the tibia or femur [47, 48].

11.6 Yoshida Ascites Hepatoma AH-130 Model

The Yoshida ascites hepatoma AH-130 model frequently uses rats for a model of cancer cachexia [49–51]. This cell line was established by converting the aminoazo-dye-induced hepatoma of the rat into the ascetic form [52]. This experimental model is based on the intraperitoneal injection of the AH-130 Yoshida ascites hepatoma into rats. The tumor cells that will be used for transplantation are harvested from the exponential tumors grown in the peritoneal cavity of another rat and are allografted. This cancer cachexia model is characterized by a very aggressive, rapid, and progressive loss of body weight and reduced food intake, along with protein and lipid hypercatabolism in host animals [53]. Rapid body weight loss with the implantation of tumor cells is accompanied by wasting of both skeletal muscle and fat tissue and a large increase in the production of inflammatory cytokines including interleukin-1 (IL-1), IL-6, and Tumor Necrosis Factor alpha (TNFα) [53–55].

11.7 Other Tumor Transplantation Models

Other often-used experimental models, in which the transplantation of tumor cells induced cachexia, include allografting of murine tumors (e.g., MAC16, murine adenocarcinoma 16 cells; RXF, RXF393 kidney cancer cell line) into syngeneic/allogeneic animals [56–58] or xenografting of patient-derived tumor cells into immunosuppressed animals [59, 60]. Animal models based on allografting transplantation of tumor cells have been widely used because of the simplicity of the research design, and a great deal of experimental evidence has been accumulated. However, the extensive use of the allografting model in various fields has raised concerns about the reproducibility of experimental results. It has been suggested that the experimental methods should be standardized [17], but the existence of various cell lineage variants is another factor that makes the problem difficult. Current animal models of cancer cachexia using ectopic allografting into subcutaneous implantation fail to represent the actual clinical situation of cachexia patients in many respects, including (1) primarily employing flank subcutaneous transplantation in the abdominal wall, (2) a very rapid onset of body weight/muscle mass wasting and a short survival period, and (3) allografting implantation is typically performed on young mice. Recent reports also indicated that gene expression changes in skeletal muscle following the transplantation of the two most commonly used cachexia models, C26 and LLC, do not reflect the characteristics of cachexia patients [16]. A possible approach to address these concerns is to use a cancer cachexia model with genetically modified mice that can provide highly reproducible results and reflect the pathology of cachexia patients more accurately.

11.8 Genetic Model of Cancer Cachexia

A commonly used genetically modified model of cancer cachexia is $Apc^{Min/+}$ mice [61, 62]. $Apc^{Min/+}$ mice are a spontaneous colon cancer model that exhibits cachexia that has a heterologous mutation in the tumor suppressor gene *Apc*, resulting in the development of intestinal and colon tumors. This mouse model develops intestinal polyps at about 4 weeks of age and progressively develops cachexia symptoms from between 12 and 20 weeks of age [63, 64]. $Apc^{Min/+}$ mice also exhibit a variety of characteristics related to cancer cachexia, including an impaired gut barrier function [64], lower circulating testosterone levels/smaller gonad size [65], impaired glucose metabolism in the liver [66], and muscle mitochondrial dysfunction [67].

More recently, a genetically modified model reflecting the pathophysiology of cachexia caused by pancreatic ductal adenocarcinoma (PDA), which has a higher frequency of cachexia in human subjects, has been proposed. Talbert et al. [16] developed and proposed a KPP mouse model with a genetically modified model that can induce the expression of a constitutively active mutant of Kras ($Kras^{G12D}$), a proto-oncogene, and a conditional knockout of Pten (floxed-Pten) which is a tumor suppressor gene in a pancreas-specific manner (tamoxifen-inducible Cre recombinase driven by the Ptf1a promoter). The KPP model appears to be a model that can reproduce the typical features of cachexia and gene expression in skeletal muscle in PDA patients very closely. Other models that reflect cachexia induced in PDA like the KPC model have also been reported. This KPC model is characterized by the conditional activation of mutant endogenous alleles of the proto-oncogene Kras and tumor suppressor gene Trp53 [68]. Particularly, an active form of Kras ($Kras^{G12D}$) and a dominant-negative mutation in Trp53 ($Trp53^{R172H}$) are conditionally activated in a mouse pancreas-specific manner (expression of Cre recombinase was driven by the pancreas-specific Pdx-1 promoter) (Fig. 11.2). This KPC model

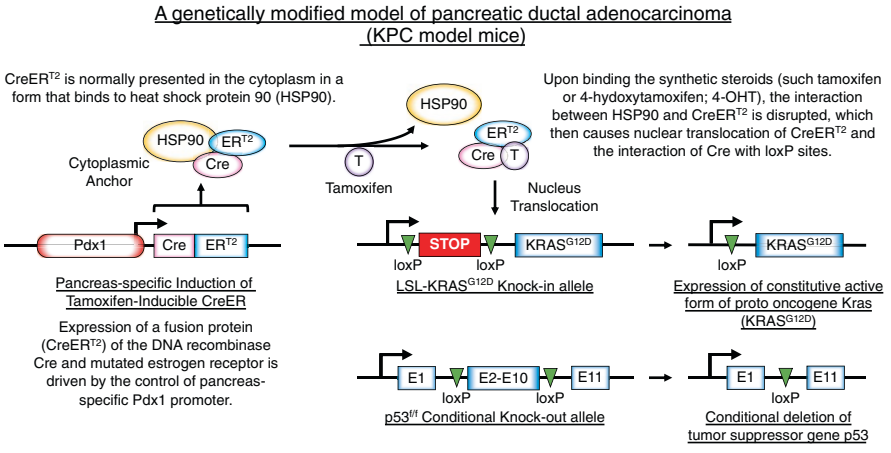

Fig. 11.2 A genetically modified model of pancreatic ductal adenocarcinoma

also recapitulates the critical features of cancer cachexia including loss of muscle mass and fat weight and abnormalities in the exocrine function that is associated with pancreatic cancer [15, 69, 70]. However, it should be noted that it may not completely reproduce the skeletal muscle pathology of PDA patients [16]. The use of genetically engineered models of cancer cachexia in alignment with clinical cachexia pathology should offer a new avenue for preclinical investigations.

11.9 Regulatory Mechanism of Muscle Mass During Cancer Cachexia

Although the exact mechanism of muscle loss during the progression of cachexia remains unclear, skeletal muscle undergoes hypercatabolism because of increased production of inflammatory cytokines and the effects of proteolysis-inducing factors that are derived from the primary disease [71, 72]. Skeletal muscle tissue is a cluster of terminally differentiated multinucleated muscle fibers, and the total numbers of mature muscle fibers remain essentially unchanged. The quantitative alterations in the overall skeletal muscle tissue such as an increase (hypertrophy) or decrease (atrophy) in skeletal muscle mass indicate a change in the size of individual muscle fibers [73, 74]. This means that a loss of muscle mass is defined as a status that protein degradation is exceeding protein synthesis in skeletal muscle. The overall imbalance of protein metabolism is a hallmark feature of cancer cachexia. While the loss of muscle mass with cancer cachexia is driven by a multifactorial process, clear evidence suggests that muscle proteolytic systems are excessively activated. The following section provides an overview of the underlying mechanisms of impaired skeletal muscle protein metabolism in cancer cachexia with a particular emphasis on the excessive enhancement of the proteolytic system and dysfunction of the protein synthesis system.

11.10 Proteolysis System During Cancer Cachexia

As molecular mechanisms that induce muscle protein breakdown, the ubiquitin-proteasome system (UPS), which is considered to be a selective proteolysis system, and the autophagy-lysosome system (ALS), also referred to as a nonselective bulk degradation system, have been indicated as major proteolysis pathways that contribute to the development of muscle wasting [75–79]. These proteolytic systems are involved in different cellular processes. In skeletal muscle cells, the proteasome system is especially involved in the degradation of contractile proteins and short-lived regulatory proteins, whereas the lysosome system is implicated in the clearance of damaged organelles and removal of abnormal structural/regulatory proteins [27, 80].

The UPS involves the polyubiquitination of target proteins via enzymes including E1 (ubiquitin-activating enzymes), E2 (ubiquitin-conjugating enzymes), and E3 (ubiquitin ligases), and the ubiquitinated proteins are subsequently recognized and

degraded by the 26S proteasome. E3 ubiquitin ligases are responsible for determining the substrate specificity, and some E3 ligases are specifically expressed in skeletal muscle and involved in the degradation of muscle proteins [81]. The most widely explored are atrogin1 (also known as MAFbx: muscle atrophy F-box, official name and symbol; Fbxo32: F-box protein 32) and MuRF1 (muscle ring finger-1, official name, and symbol; TRIM63: tripartite motif-containing 63), which are muscle-specific E3 ubiquitin ligases that have been demonstrated to be involved in skeletal muscle atrophy [82]. Skeletal muscle loss associated with cancer cachexia has also been reported to be caused by the enhanced proteolysis via the UPS including the marked induction of gene and protein expression of atrogin1 and MuRF1 which are both in several animal models and cachexia patients [6, 80, 83–87]. Other muscle-specific E3 ubiquitin ligases, including the neural precursor cell-expressed developmentally downregulated gene 4.1 (Nedd4.1), TNF receptor-associated factor 6 (TRAF6), muscle ubiquitin ligase of SCF complex in atrophy-1 (MUSA1), and ligases specific of muscle atrophy and regulated by transcription (SMART) have also been implicated in the proteasome-dependent proteolytic system associated with cancer cachexia [80, 87–91]. Just as in other studies with human patients, enhanced proteasome-dependent proteolysis in skeletal muscle was demonstrated in many types of cancer cachexia [92]. A recent report in gastric cancer patients with cachexia indicated that enhanced proteasome-dependent proteolysis is involved in the progression and severity of cachexia [93]. However, some studies have reported no change in the biochemical and molecular biological markers of UPS despite the progression of cancer cachexia in human subjects [94, 95]. It is also important to note that some reports indicated that treatment with proteasome-specific inhibitors (e.g., bortezomib) did not prevent muscle wasting in cancer cachexia patients [96, 97].

ALS has also been involved in the regulation of skeletal muscle homeostasis by modulating the muscle proteolysis system [98]. ALS was first thought to be a non-selective bulk degradation system that processes aggregates of abnormal proteins and damaged organelles such as mitochondria, whereas the molecular mechanisms that control target selectivity are now becoming evident [99]. The molecular mechanisms of ALS regulation have been described in detail elsewhere in review articles [99–103]. As for the cancer cachexia, it is still controversial whether ALS is involved in muscle protein degradation and wasting. Initially, excessive activation of ALS was thought to be involved in muscle wasting associated with cachexia, as the animal models of cancer cachexia [104, 105] and skeletal muscles of human patients with gastrointestinal or esophageal cancer [93, 95, 106, 107] showed an increase in autophagic flux. In contrast, some reports have found no increase in autophagy flux but rather that pharmacological (AICAR; activator of AMPK, or rapamycin; inhibitor of mTOR) or exercise-induced activation of autophagic flux ameliorates the muscle wasting and counteracts the development of cachexia [84, 98]. Indeed, recent studies evaluating the impact of either autophagy inhibition (knocking down beclin-1) or promotion (overexpressing TP53INP2/DOR) on cancer cachexia have indicated that muscle wasting in tumor-bearing mice did not improve regardless of autophagy inhibition or promotion. Furthermore, hyperactivation of autophagy

leads to the exacerbation of muscle loss and impaired mitochondrial function [27]. Since ALS is essential for maintaining cellular homeostasis by eliminating abnormal proteins and damaged organelles, it seems that preserving an adequate autophagic flux within the proper range without becoming excessive is important for maintaining muscle mass.

11.11 Alteration of Protein Synthesis During Cancer Cachexia

The molecular mechanism that activates skeletal muscle protein synthesis has been shown to be involved in the mechanistic target of rapamycin (mTOR)-dependent signaling. mTOR is found in two distinct multi-protein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), with mTORC1 playing a particularly important role in promoting intracellular protein synthesis. The most well-characterized upstream regulator of mTORC1 signaling in skeletal muscle occurs through the growth factor (e.g., insulin/insulin-like growth factor-1 (IGF-1))-dependent activation of the phosphoinositide 3-kinase (PI3K) Akt pathway [108–110]. The ligand binding of insulin/IGF-1 to its receptor activates the receptor tyrosine kinase which initiates a cascade reaction of downstream signaling, leading to the activation of the PI3K/Akt/mTORC1 pathway. The activation of mTORC1 signaling results in enhanced protein translational machinery through the phosphorylation of the ribosomal protein s6 kinase and the translational repressor eukaryotic initiation factor 4E-binding protein 1 [111, 112].

In studies using skeletal muscle from several animal models of cancer cachexia, the suppression of IGF-1 expression and reduced activity of mTORC1 signaling were observed with the onset and progression of cancer cachexia, and a decreased level of skeletal muscle protein synthesis associated with cachexia was also reported [55, 113–116]. In addition to a reduced expression of growth factors, it has also been suggested that abnormal oxidative metabolism is involved in the impairment of mTORC1 signaling and decreased protein synthesis due to cancer cachexia, possibly through insufficient ATP production. This induces AMPK phosphorylation which in turn negatively regulates mTORC1 activity [117, 118]. Although the majority of previous studies have shown that protein synthesis is suppressed during cancer cachexia in animal experimental models, the exact extent of its involvement in muscle wasting is still controversial [80, 89, 119]. Indeed, it has been noted that muscle protein synthesis rates remained unchanged despite the muscle wasting and elevated inflammatory cytokine levels that were observed following the implantation of Yoshida AH-130 sarcomas [54]. The situation is more complex with respect to the alteration of muscle protein synthesis in human cachexia patients, with some reporting a decreased level [120, 121] and others reporting unchanged [122] or even higher levels [123] of muscle protein synthesis than what was recorded in controls or cancer patients with non-cachexia. Also, there have been attempts to improve cancer cachexia by promoting muscle protein synthesis through several reagents (nutritional supplementation, growth factors, or genetic tools), but many of them have not yielded favorable results [31, 80, 124, 125]. This may be explained by the

characteristics of the skeletal muscle in cancer cachexia, primarily anabolic resistance, which is a blunted stimulation of muscle protein synthesis. Skeletal muscle in cancer cachexia is generally less responsive to anabolic factors including mechanical, nutritional, or humoral stimuli [114, 126, 127]. Indeed, our study using a mouse model of cancer cachexia indicated that skeletal muscle with cancer cachexia has a diminished rate of muscle protein synthesis to the increased mechanical load and that retardation of muscle growth is associated with a reduced expression of the IGF-1 gene (unpublished observation). However, this anabolic resistance in the skeletal muscle of cancer cachexia remains open to therapeutic intervention, as it has been suggested that it could be improved by a combination of appropriate inflammation management, exercise, and nutritional intervention [122, 124, 126, 128–130].

11.12 Abnormal Oxidative Metabolism and Muscle Wasting During Cancer Cachexia

It has been demonstrated that mitochondrial dysfunction in skeletal muscle contributes to reduced muscle weight in various animal models including physical inactivity, denervation, and aging [131, 132]. Evidence has also been reported concerning mitochondrial impairments in cancer cachexia [133, 134]. Previous studies using a genetic model of colon cancer [135] or elderly patients with gastric cancer [136] have demonstrated that the abnormal expression of proteins regulating mitochondrial dynamics in skeletal muscle was induced with the progression of cachexia. Our laboratory recently demonstrated that in the C26 model of cancer cachexia, decreased muscle mitochondrial content (decreased level of OXPHOS subunit proteins and mitochondrial content) and dysregulation of mitochondrial dynamics (decreased expression of Drp1 and Mfn2, regulatory proteins of mitochondrial dynamics) occurred and that they increase mitochondrial oxidative stress, leading to abnormal mitochondrial morphology and functioning [22]. Similar findings have also been reported from other works using other animal models of cancer cachexia [135, 137–139]. Importantly, the muscle wasting and mitochondrial dysregulation that are associated with cancer cachexia can be corrected by running exercise [22]. The other reports of physical exercise correcting mitochondrial dysfunction and cachexia progression [25, 140] strongly suggest that exercise therapy may be a very effective intervention for cancer cachexia (discussed later).

While mitochondrial dysfunction is evident in the skeletal muscle of cancer cachexia, understanding is still lacking concerning the process that leads to muscle wasting. A potential mechanism involves regulation through PGC-1α which is a master regulator of mitochondrial biogenesis. An increased expression of PGC-1α has a protective effect against muscle atrophy induced by aging, inactivity, and the administration of inflammatory cytokines [141, 142]. Indeed, the expression level of PGC-1α was suppressed in the skeletal muscle of cancer cachexia, while the overexpression of PGC-1α prevented LLC-induced muscle wasting [143]. However, there is a conflicting report regarding the protective role of PGC-1α for cancer

cachexia [144]. Another candidate mechanism could be through the energy sensor AMPK. Mitochondrial dysfunction induces oxidative stress including the increased production of the reactive oxygen species which leads to decreased ATP production and the activation of AMPK [134]. Increased circulating IL-6 with cancer cachexia has also been associated with muscle AMPK activation [118]. Activation of AMPK negatively regulates the mTORC1 signaling and consequently decreases protein synthesis and muscle wasting in cancer cachexia [117, 118].

11.13 Exercise Intervention for Cancer Cachexia

Therapeutic strategies for cancer cachexia require a comprehensive approach that includes pharmacological interventions (e.g., anti-inflammatory and anti-cytokine therapies) for chronic inflammation from the underlying primary disease, as well as nutritional and exercise therapies [145, 146]. Previous epidemiological studies have reported the effectiveness of physical exercise in preserving and improving the life span and quality of life for cancer patients [147, 148]. Depending on the tumor type, physical activity composed of 9–18 METs (metabolic equivalents) per week is associated with a significant decrease in cancer-specific mortality and/or overall mortality after a diagnosis of cancer [148–151]. Nine METs/week is equivalent to a total of 3–5 h of walking per week [149] which is considered to be a relatively low level of intensity for physical exercise. The relationship between physical exercise and an increased survival rate depends on the amount of exercise engaged in after the diagnosis of cancer rather than pre-diagnostic exercise habits [148, 150], which strongly suggests the importance of the use of physical exercise interventions in maintaining the life outcome and quality of life for cancer patients.

Many patients with cancer cachexia suffer from chronic fatigue and muscle weakness caused by the disease or its treatment, thus leading to continued inactivity, and a reduced level of physical exercise that further accelerates the loss of muscle mass [152]. Decreased physical activity in patients and animal models of cancer cachexia is clearly evident [152, 153], suggesting the significance of ensuring that physical activity is used in preventing the development of cancer cachexia. Exercise therapy for cancer cachexia includes relatively low-intensity resistance and aerobic exercises which can reduce the loss of weight and skeletal muscle and have anti-inflammatory effects, although it is important to note that randomized controlled trials in human patients have not been reported in large numbers to date [154, 155]. In experimental animals, it has been reported that aerobic exercise including running on a treadmill or voluntary wheel exercise is effective in suppressing skeletal muscle wasting associated with cancer cachexia [22, 25, 84, 156–158]. Indeed, exercise with running on a treadmill has been shown to activate the mTORC1 signaling pathway which improves muscle protein synthesis and prevents muscle wasting in a mouse model of cancer cachexia [25, 118, 140, 159, 160]. Our laboratory demonstrated that in the C26 model of cancer cachexia, both suppression of protein synthesis and enhancement of proteolysis are induced simultaneously. We have also

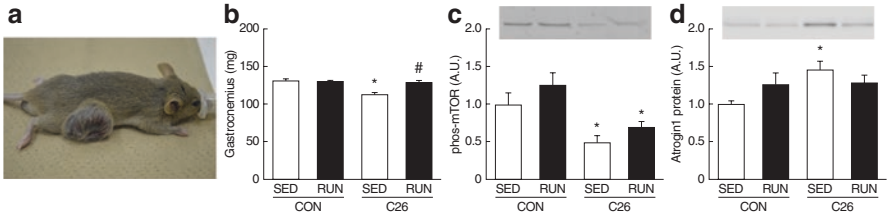

Fig. 11.3 Altered regulation of protein metabolism by cancer cachexia and the preventive effects of voluntary exercise. C26 carcinoma were subcutaneously transplanted into male CD2F1/Slc mice, followed by 4 weeks of sedentary or voluntary wheel running (**a**). Body weight and skeletal muscle mass were significantly decreased with the development of cancer cachexia but were maintained comparable to the control group following 4 weeks of running exercise (**b**). Decreased phosphorylation of mTOR, a hallmark of the protein synthesis system (**c**), and increased protein expression of the muscle-specific E3 ubiquitination ligase atrogin1 were induced with cachexia, whereas atrogin1 expression was suppressed by voluntary running exercise (**d**). All results are expressed as mean ± standard error. Significant differences: *, between CON and C26, #, between sedentary and running for each experimental condition ($p < 0.05$). Data are partially extracted and modified from the previous paper by Kakuta et al. (2019) [160]

revealed that defects in protein metabolism during cancer cachexia are corrected by intervention with aerobic exercise using voluntary wheel running (Fig. 11.3) [160].

Aerobic exercise has also been shown to improve the oxidative stress and mitochondrial dysfunction that is associated with cachexia to prevent muscle wasting from occurring [22, 157, 161]. Our laboratory recently demonstrated that in the C26 model of cancer cachexia, increased mitochondrial oxidative stress, mitochondrial dysfunction, and abnormal morphology caused by cancer cachexia were significantly improved by voluntary running exercise (Fig. 11.4) [22].

The resistance-type exercise which is generally considered to be effective in increasing muscle mass also appeared to be beneficial in preventing the progression of cancer cachexia. Increased mechanical loading or electrical stimulation appears to promote protein synthesis through the activation of mTORC1 signaling and reduces oxidative stress, thereby contributing to the maintenance of muscle mass in patients with cancer cachexia [116, 162, 163]. In contrast, an earlier report indicated that resistance-type exercise in tumor-bearing mice was not effective in preventing the progression of cachexia because excessive stress led to muscle damage [25]. A recent study from our group has also confirmed that anabolic resistance occurs in skeletal muscles with cancer cachexia in which the protein synthesis response to the mechanical load is blunted (unpublished observation). It is also important to note that patients with cancer cachexia usually have a lower tolerance for exercise, making high-intensity exercise difficult for them to perform. Physical exercise therapy is undoubtedly effective in improving cancer cachexia, though further basic research is necessary to optimize the selection of the type and intensity of exercise, as well as for deciding how to combine it with nutritional and pharmacological interventions.

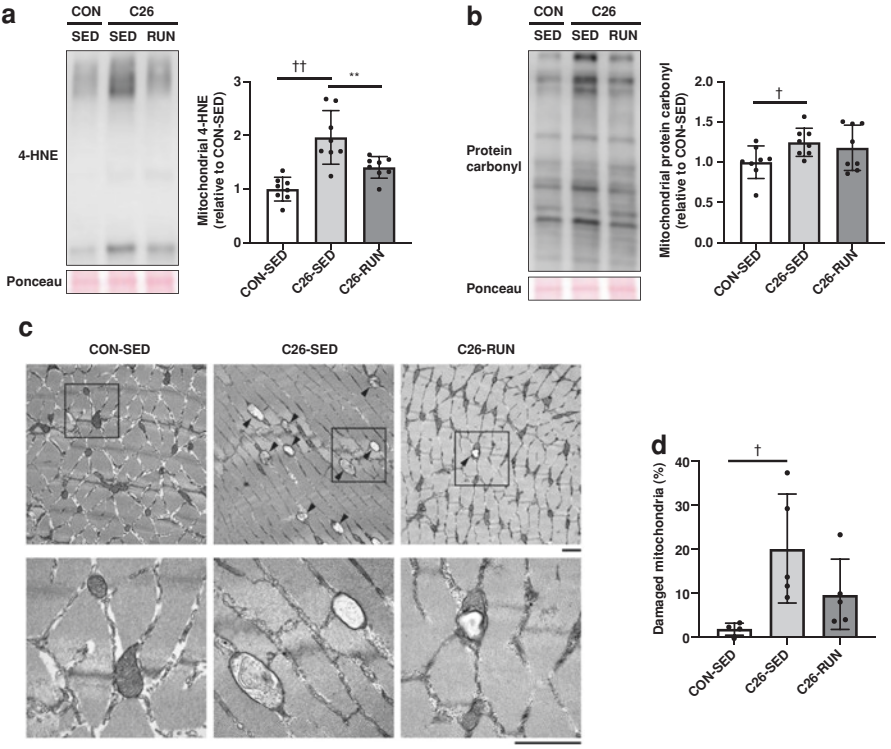

Fig. 11.4 Increased mitochondrial oxidative stress, mitochondrial dysfunction, and abnormal morphology caused by cancer cachexia are improved by voluntary running exercise. C26 carcinoma were subcutaneously transplanted into male CD2F1/Slc mice, followed by 4 weeks of sedentary or voluntary wheel running. Hallmarks of oxidative stress in skeletal muscle including 4-HNE (**a**) and protein carbonyls (**b**) were markedly elevated in isolated mitochondria, suggesting that mitochondrial abnormality in skeletal muscle is accompanied by cancer cachexia. The observations showing abnormal regulation of mitochondrial quantity were rescued with the intervention of voluntary exercise. We also examined the morphological alterations of mitochondria in skeletal muscle using electron microscopy and found that physical exercise could alleviate an increased appearance of damaged mitochondria with disrupted cristae structure in cancer cachexia mice. (**c**) Representative images (Scale bars: 1 μm). Arrowheads indicate damaged mitochondria with disrupted cristae. (**d**) Percentage of damaged mitochondria. All results are expressed as mean ± standard error. Significant differences: †, between CON-SED and C26-SED, *, between C26-SED and C26-RUN ($p < 0.05$). Data are partially extracted and modified from the previous paper by Kitaoka et al. (2021) [22]

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Physical Function and Physical Activity in Patients with Advanced Lung Cancer

12

Taro Okayama

Abstract

Most advanced lung cancers are accompanied by bone metastases, brain metastases, lung damage, or cachexia, which brings the different physical conditions to each patient and consequently requires different physical therapies for each patient.

This article presents the points that therapists should consider when providing physical therapy to patients with advanced lung cancer. In addition, it presents some published studies on the physical function before and after diagnosis and the relationships between survival and both the exercise capacities and physical activities of advanced lung cancer patients.

Cancer treatment, while improving prognosis, frequently also results in impairment of daily physical activities and can seriously affect the quality of life of cancer patients. Cancer rehabilitation strategies, like physiotherapy, to overcome such physical dysfunctions are thus very essential, subsequent to cancer treatment. In recent years, through various studies, it has become clearer that exercise therapy and the resulting improvement in physical function can greatly reduce the recurrence of cancer and improve prognosis.

This chapter describes the various physical function assessments and exercise therapy procedures currently in use for the physiotherapy of cancer patients in Japan, and through a systematic review and meta-analysis, we have summarized their positive effects on recovery and relapse in cancer patients.

T. Okayama (✉)
Division of Rehabilitation Medicine, Shizuoka Cancer Center, Shizuoka, Japan
e-mail: ta.okayama@scchr.jp

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Keywords

Advanced lung cancer · Bone metastasis · Brain metastasis · Cancer cachexia · Exercise capacity · Physical activity · Physical function · Exercise therapy · Recurrence · Mortality · Cancer rehabilitation

12.1 Introduction

The number of patients with advanced lung cancer is increasing due to the aging of the global population and the advance in cancer treatments in recent years. The yearly worldwide incidents are approximately 2.2 million with 1.8 million deaths (18% of all sites) [1], which is significantly higher the second-place cause of death due to cancer, colorectal cancer, which results in 930,000 deaths annually (9.2% of all sites).

Lung cancer is often diagnosed with distant metastasis [2] (Fig. 12.1). The postoperative recurrence rate is higher than those of other cancers, which results in a higher number of advanced cancer patients. The survival time of advanced lung cancer patients has been steadily prolonged with the development of targeted therapies and immune checkpoint inhibitors [3, 4]. Consequently, it is becoming increasingly important to maintain physical function through physical therapy while controlling treatment-related side effects and administering appropriate treatment for new lesions such as bone and brain metastases.

However, since advanced cancer patients mostly have good performance status (PS) at the time of diagnosis and are treated on an outpatient basis thereafter, physical therapy is not introduced as easily as with inpatients. A Cochrane review published in 2019 includes information on physical therapy for advanced lung cancer patients that showed the exercise capacity and the disease-specific global health-related quality of life (HRQoL) were meaningfully improved in the intervention

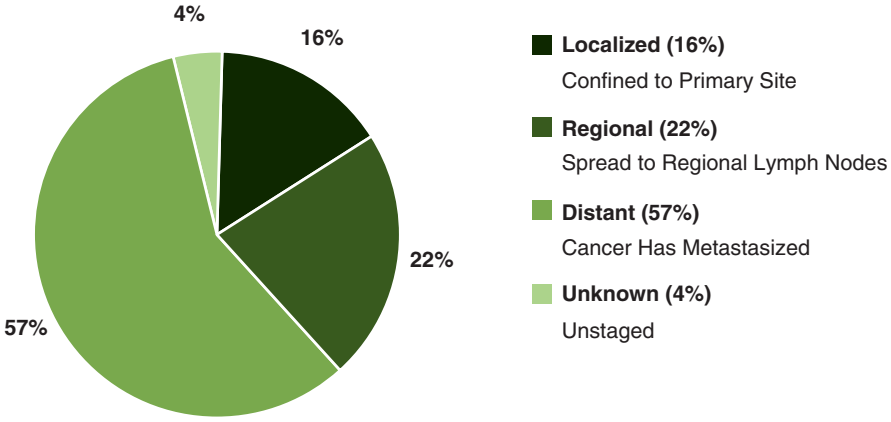


Fig. 12.1 Percentages of lung and bronchus cancer cases by stage at diagnosis

group compared to the control group [5]. However, this was the result for patients with enough physical function to undergo assessment via the 6-minute walk test (6MWT) and cardiopulmonary exercise, not for advanced lung cancer patients with poor physical function who often consult for physical therapy. That is, little has been reported about the effectiveness of physical therapy for those frail patients as well as the goal of their therapy. In current clinical practice, the goal for an individual patient is mostly set by the therapist based on their own knowledge and experience.

This article describes the practice of physical therapy for advanced lung cancer patients and includes published studies on exercise interventions, their effects on physical function and activity, and other research on physical therapy.

12.2 Clinical Practice in Physical Therapy for Advanced Lung Cancer Patients

12.2.1 Bone Metastasis

Bone metastasis occurs in 30–40% of advanced lung cancer patients [6], and the most common sites are (1) spine, (2) pelvis, (3) extremities, and (4) scapula [7]. Physical therapy for patients with bone metastasis focuses on movement guidance to prevent a pathological fracture (Fig. 12.2), as well as maintenance and improvement of muscle strength, walking ability, and physical activity. If metastases exist in the lower extremities and pelvis, appropriate load-relieving measures need to be taken and, if necessary, walking aids should be used to promote gait practice.

For spinal metastases with the spinal instability neoplastic score (SINS) score of 7 or higher (possible spinal instability), a cervical collar from the first cervical to

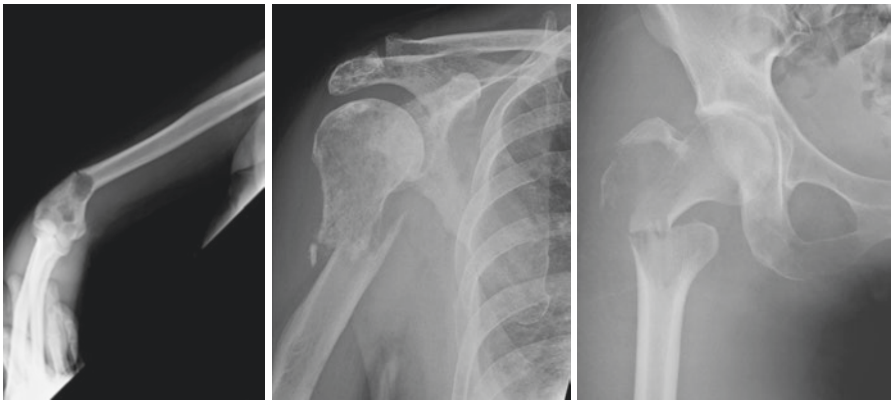


Fig. 12.2 Pathological fractures. Pathological fractures can lead to interruption or discontinuation of systemic treatment, decreased physical function, and decreased quality of life

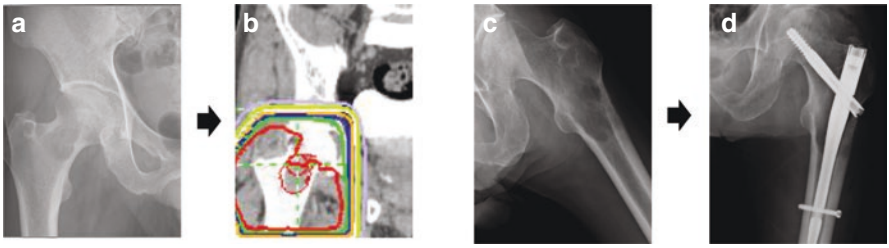


Fig. 12.3 Remedial examples of femoral bone metastasis. (**a**) Right femoral bone metastasis. (**b**) Radiotherapy for femur metastasis (3Gy × 10Fr). Exercise load: toe-touch weight-bearing. (**c**) Left femoral bone metastasis. (**d**) Intramedullary nailing for femoral bone metastasis. Exercise load: permitting full weight-bearing in accordance with the degree of pain

second thoracic spine and a corset from the tenth thoracic to fifth lumbar spine are recommended to prevent spinal instability.

When administering physical therapy to a patient with bone metastasis, it is important to understand where the patient is in their cancer journey, because the therapy will depend on how much physical stress the patient is ready to take. For a patient whose bone metastasis is detected along with the primary diagnosis for lung cancer stage IV, the goal for therapy should be high in preparation for coming long systemic treatments. On the other hand, for a patient with bone metastasis having experienced various treatments, or currently taking best supportive care with no other treatment options, the goal shouldn't be so high. In addition, the physical therapy for each patient should be planned taking into consideration the treatment process for bone metastasis, such as radiotherapy or surgery (Fig. 12.3). For example, when a patient has severe paralysis of the lower limbs due to spinal metastasis, the best possible quality of life (QOL) should be aimed at the level of wheelchair activities of daily living (ADL) by practicing physical therapy such as basic movements and transfer exercise for wheelchair.

12.2.2 Brain Metastasis

Brain metastasis occurs in 10–30% of cancer patients [8], and for nearly half of the cases, the primary tumors are lung cancer [9]. Particularly, in small cell lung cancer, which accounts for about 15% of lung cancers, brain metastasis is said to occur in about half of the total cases [10].

Brain metastasis has three major differences from cerebrovascular disease.

1. The patient is susceptible to compression and edema caused by the tumor.
2. The symptoms are affected by bone metastasis, cachexia, and/or pulmonary dysfunction.
3. The patient's general condition can get deteriorated in accordance with the progression of lung cancer.

Physical therapy for patients with brain metastasis is performed from low to high level of the function (sitting, standing, and walking) while keeping the trunk function stable. For patients who can walk stably, further physical ability and activity should be the aim. It is important to set the goal of physical therapy taking the expected survival time into consideration, as in the case of bone metastasis. The median survival from brain metastasis is 15 months (IQR 6–32 months) for adenocarcinoma and 9 months (IQR 4–19 months) for nonadenocarcinoma [11]. The median survival for adenocarcinoma largely depends on genetic mutations and is 23 or 15 months with or without epidermal growth factor receptor (EGFR) mutations, and 44 or 17 months with or without ALK mutations, respectively. Therefore, it is important to take into consideration not only the patient's physical condition but also the process of given systemic treatment when planning physical therapy. The goals of physical therapy should be high if long-term survival is expected.

12.2.3 Pulmonary Dysfunction

Lung cancer is a smoking-related disease, and the patients often (20–50% of all sites) have chronic obstructive pulmonary diseases (COPD) (Fig. 12.4) [12–14]. It is known that advanced lung cancer patients with COPD often suffer from symptoms such as coughing, sputum, and dyspnea. Their QOL is lower than patients without COPD, and their survival time is shorter than the same [13, 15, 16]. The physical therapy for each patient with COPD is determined depending on the degree of the patient's COPD (particularly dyspnea and exercise capacity). Patients with severe COPD should begin with conditioning to reduce dyspnea and low-load training for endurance and muscle strength. However, patients with mild COPD should undergo aggressive training for endurance and muscle strength.

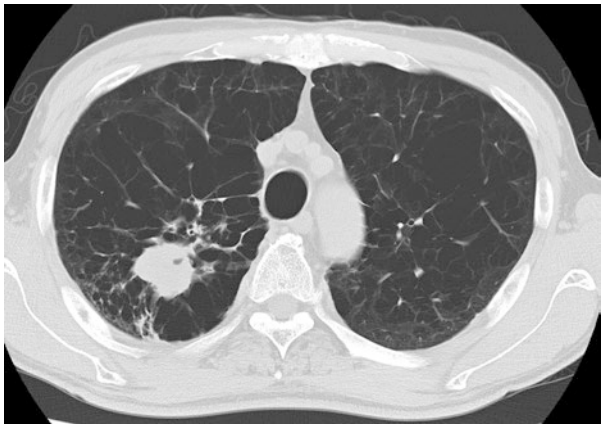
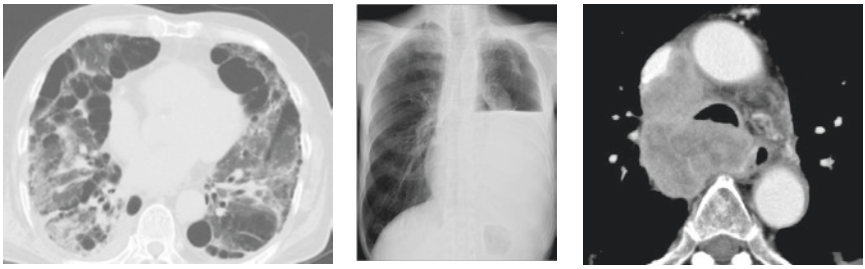


Fig. 12.4 Lung cancer complications with COPD. Chest CT scan revealed a substantial mass in the right upper lobe. In addition, the existing lungs showed severe emphysematous changes



Drug-induced interstitial pneumonia | Pleural effusion associated with pleural dissemination | Stenosis of the airway due to enlarged mediastinal lymph nodes

Fig. 12.5 Various lung disturbances in patients with advanced lung cancer

Drug-induced lung injury, pleural effusion due to cancer progression, and atelectasis due to tumor-induced obstruction of the trachea or bronchus tend to induce more severe respiratory disturbances (Fig. 12.5). The main symptom for drug-induced interstitial pneumonia is dyspnea on exertion. Hypoxemia during exertion reduces the frequency and the distance of walking, which, often with decline of skeletal muscle due to steroid therapy, promotes a vicious cycle of muscle-strength decline, inactivity, and a lowering of ADL. For preventing this cycle and maintaining physical function, it is important to increase oxygen inhalation dose temporarily before executing low-load muscle strength exercise and short-distance walking.

12.2.4 Cancer Cachexia

It has been reported that approximately 40–70% of patients with advanced lung cancer at the time of diagnosis have cachexia [17, 18]. Since cancer cachexia brings persistent skeletal muscle loss, which induces a decline of physical function [19] (Fig. 12.6), muscle-strengthening exercises are a fundamental part of physical therapy treatment for cachexia. Such exercises should be performed for the lower extremities as a priority, for the following two reasons.

1. In advanced cancer patients, the decline in muscle mass compared to healthy controls has been found to be more remarkable in the lower extremities than in the upper extremities or the trunk [20].
2. Frail lower extremities impaired the ability to stand up and walk and the ability to live independently later [21].

The anti-inflammatory effect of aerobic exercise is considered to work effectively against chronic inflammation, which is one of the main pathophysiologies of cancer cachexia [22]. According to a previously reported meta-analysis on the effect of exercise on immunity in cancer survivors, aerobic exercise meaningfully reduced pro-inflammatory markers such as C-reactive protein (CRP) and

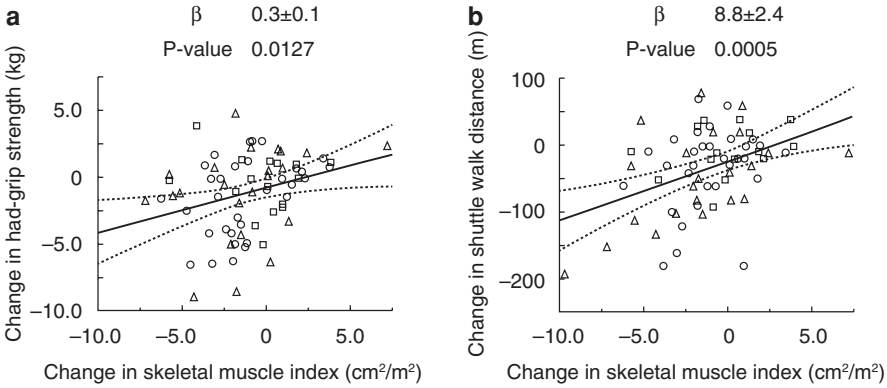


Fig. 12.6 Association between changes in skeletal muscle mass and physical function. A prospective study of elderly patients with advanced lung cancer performed a shuttle walking test, grip strength test, and skeletal muscle mass measurement at 3 points, before (T1), 6 weeks after (T2), and 12 weeks after (T3) initial treatment. The association between changes in muscle mass, hand-grip strength (**a**), and shuttle walking distance (**b**) at all points are plotted. The dotted lines indicate the 95% confidence intervals. The circles, triangles, and squares represent changes at T2 from baseline, T3 from baseline, and T3 from T2, respectively

interleukin-9, and the combination of aerobic exercise and resistance training was further effective [23].

However, in a randomized feasibility study of nutrition and exercise in advanced pancreatic and lung cancer patients with cachexia conducted in Norway, 40% of patients were unable to perform 30 min of aerobic exercise twice a week [24]. In a study on combined nutrition and exercise conducted in Japan, advanced pancreatic and lung cancer patients were able to perform moderate or vigorous physical activity for only 5 min in the post-diagnostic period [17]. These studies revealed that advanced cancer patients are often unable to perform aerobic exercise recommended by nutrition and physical activity guidelines for cancer survivors.

It is important to individually adjust the intensity and duration of each aerobic exercise to the current physical ability of the patient. Patients with good PS or good physical ability should continuously perform necessary exercise for anti-inflammatory effects, but patients with poor physical ability should perform milder aerobic exercise for shorter durations.

12.2.5 Physical Therapy to Improve Quality of Life

The quality of life (QOL) of patients with advanced lung cancer has become more important as its survival rate has improved. It is an essential criterion in the efficacy evaluation of clinical trials and supportive care [25, 26]. Physical therapy should contribute not only to physical function but also to the total QOL of each patient.

It is known that the QOL remains low when the goals are too high for the patient to achieve, while it can be improved and kept high when the goals meet the reality

[27]. Therefore, physical therapists should be aware of the reality including the patient's physical conditions and the broad course of prognosis all the time. In case they realize the goals are too high or not really achievable, it will be their critical responsibility to adjust them flexibly through dialogue with the patient.

12.3 Previous Studies on Physical Function, Exercise Capacity, Physical Activity, and Exercise Intervention in Patients with Advanced Lung Cancer

12.3.1 Physical Function at the Time of Diagnosis

In most advanced lung cancer patients, their muscle strength and exercise capacity are already declined at the time of diagnosis. Simone Hummlera et al. [20] compared the muscle strength and 6MWD (6-minute walk distance) of patients under first-line chemotherapy to those of age-matched healthy controls. The results showed that muscle strength was at least 20% lower than the references in most cases, especially in the lower extremities, and the 6MWDs were also lower in both men and women (434/411 m vs. 597/514 m).

Christina Titz et al. [28] also reported that muscle strength and 6MWDs in patients with advanced lung cancer shortly after diagnosis were significantly lower than those of age-matched healthy controls and that patients who met the guideline recommendations, i.e., 150 min aerobic activity per week, had significantly better 6MWDs than those who did not.

Naito et al. [19] also reported that the body mass index (BMI), skeletal muscle mass, and exercise capacity of elderly patients with advanced lung cancer significantly declined during their first cycle of treatment and 3 months thereafter (Fig. 12.7).

The decline of the physical function, described above, of patients with advanced lung cancer at the time of diagnosis was most likely because they were already affected by COPD and/or cachexia and because they often refrained from exercise or physical activity during the stressful period with many clinical examinations prior to diagnosis.

12.3.2 Relationship Between Exercise Capacity and Survival

Jones et al. [29] conducted 6MWTs for patients with advanced lung cancer after the median period of 13.4 ± 16.7 months from diagnosis. They divided the patients into three groups according to their 6MWD results, <358.5 m, 358.5–450 m, and >450 m, and analyzed the survival of each group. The results show that the adjusted hazard ratio (HR) for all-cause mortality of the mid-group (358.5–450 m) and the top group (>450 m) to the bottom group (<358.5 m) were, respectively, 0.61 (95% confidence interval [CI], 0.34–1.07) and 0.48 (95% CI, 0.24–0.93).

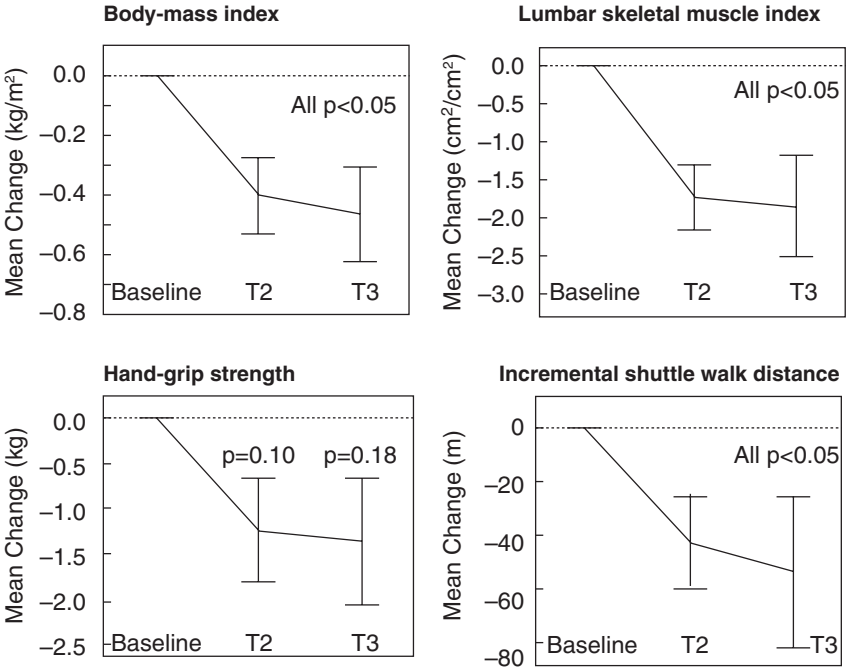


Fig. 12.7 Longitudinal changes in body-mass, muscle mass, and physical function at 3 points, before (T1), 6 weeks after (T2), and 12 weeks after (T3) initial treatment. Mean changes ± standard error of physical parameters from baseline value are shown. P-values of the Wilcoxon signed-rank test are shown

Kasymjanova et al. [30] conducted 6MWT for patients with advanced non-small-cell lung cancer three times: at diagnosis, before first chemotherapy, and after two courses of chemotherapy. Sixty-four patients enrolled, 45 of whom completed all tests. In the initial test, the average 6MWD by the 45 patients was 445 m ($p = 0.004$), while that by the 19 patients who dropped out was 363 m. When comparing patients who walked ≤400 m in the initial test to those who walked >400 m, the former had a significantly higher dropout rate ($p = 0.02$), more significant progression of disease ($p = 0.03$), and significantly shorter median survival (6.7 months vs. 13.9 months, $p = 0.01$) than the latter.

The authors [31] conducted ISWT (incremental shuttle walking test) in 60 elderly patients (aged ≥70 years) with advanced lung cancer prior to initial treatment for investigating the relationships among exercise capacity, healthcare resources used in the whole year after starting treatment, and survival period. The results showed that the mobile group (ISWD ≥290 m) had shorter total hospital stay (41.3 vs. 72.9 days/person, $p < 0.05$), lower inpatient medical costs (1.9 vs. 2.9 million yen/person, $p < 0.05$), and longer overall survival time (25.9 months vs. 11.2 months, $p < 0.05$) than the less mobile group (ISWD <290 m) (Fig. 12.8).

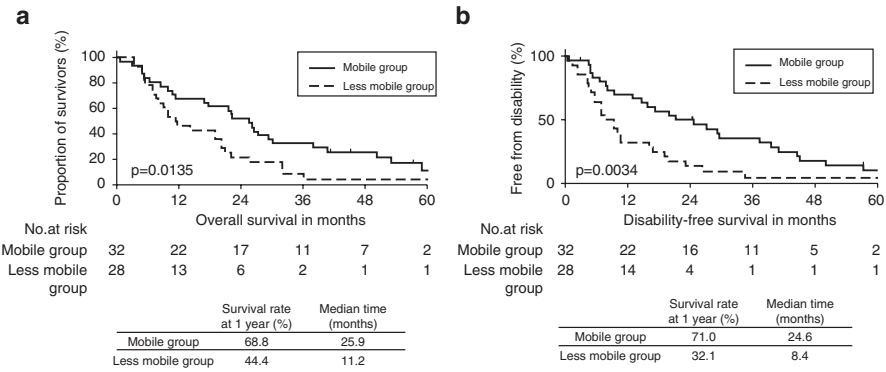


Fig. 12.8 Overall and disability-free survival curves. (**a**) Kaplan-Meier curve of overall survival. (**b**) Kaplan-Meier curve of disability-free survival. *p*-values were calculated using log-rank tests. Disabling events were defined as a reduction in the Barthel index from the baseline value by >10 points. For patients whose disabling events were not confirmed, they were censored at the date of their last visit

Generally, patients with PS 0–1 are considered to have good physical function, but the result of the three studies above indicates that the patient's exercise capacity is another factor predicting the prognosis and the survival. Therefore, it is important to ensure that the patient and their family understand the importance of maintaining and improving physical function, even if the PS is good at the time of diagnosis.

12.3.3 Relationship Between Physical Activity and Survival

Friedenreich et al. [32] published a systematic review and meta-analysis of 136 articles studying patients with various cancers that met the eligibility criteria. They reported that HRs (hazard ratios) of the highest to the lowest of pre-diagnosis physical activity level were 0.47 (95% confidence interval [Cl] = 0.29–0.75) for all-cause mortality and 0.82 (95% CI = 0.79–0.86) for cancer-specific mortality. HRs obtained in a similar manner for the post-diagnosis physical activity level were 0.61 (95% Cl = 0.51–0.73) for all-cause mortality and 0.63 (95% Cl = 0.53–0.75) for cancer-specific mortality.

According to two articles among the 136 that focused on lung cancer patients, the HR of the highest post-diagnosis physical activity level to the lowest was 0.76 (95% Cl = 0.6–0.97) for all-cause mortality.

In one of the two articles, Sloan et al. [33] surveyed the physical activity levels of 1466 lung cancer patients, half of who had advanced cancer, by questionnaire and divided them into 2 (physically active and physically inactive) groups. The estimated survival of the active group was 4 years longer, on average, than that of the inactive group, although the disease recurrence rates did not differ from each other.

According to the estimated survival of each group by the Cox regression model with several covariates (age at diagnosis, sex, race, stage, treatment, smoking status, and pack-years), the estimated HR of the inactive group to the active group was 1.29 (95% CI = 1.00–1.67, $p = 0.05$).

Those findings are especially important for patients with advanced lung cancer who have significantly extended survivals. That is, it is crucial for medical professionals to understand the importance of physical practice from the point of diagnosis and share it with the patients.

12.3.4 Exercise Intervention

Two systematic reviews on the safety and feasibility of exercise interventions in patients with advanced cancer reported 6 (0.55%) and 9 (1.8%) exercise-related adverse events, respectively; none of which were serious [34, 35]. Those good results are considered because the exercise intervention was performed under a high level of supervision by qualified exercise professionals, and high-risk patients were excluded.

Peddle et al. [5] reported their study on the effectivity of exercise intervention in advanced lung cancer in the Cochrane Database. In this study, based on the total of six randomized trials, the physical capacity (6MWD) after intervention and disease-specific global HRQoL of the intervention group were significantly better than those of the control group (respective mean differences of 63.33 m and 0.51 and 95% Cis of 3.70–122.96 and 0.08–0.93). On the other hand, there were no meaningful differences between the two groups in physical functioning HRQoL, dyspnea, or fatigue. Finally, it was concluded that the confidence of the study findings is insufficient as a whole due to the risk of bias in the trials.

Recently, clinical trials have been conducted to investigate the efficacy of exercise intervention combined with nutritional intervention and lifestyle counseling [17, 24, 36, 37]. The authors conducted a feasibility study of combined intervention consisting of home-based lower extremity training, lifestyle counseling to improve physical activity, and nutritional advice including oral branched-chain amino acids (BCAA)-rich supplements in patients aged >70 years undergoing first-line treatment for advanced pancreatic or non-small cell lung cancer [17]. A total of 30 participants were scheduled to take the supplements and perform the home strength training every day for a period of 8 weeks. Both the supplementation and training were feasible and performed by most patients, in which the median rates of performance were 99% and 91%, respectively. At the end of the period, several criteria, including five-time-sit-to-stand time and moderate or vigorous physical activity, significantly improved the level before the trials. The Phase II study of the larger scale, in which the primary criterion is a disability-free survival time, is currently ongoing. The data obtained from randomized trials completed by 130 selected patients at multiple medical facilities are currently under final analysis.

12.4 Physical Therapy Research for Patients with Advanced Lung Cancer

12.4.1 Study Design

A single case report is achievable from recorded clinical practice without a large amount of time and effort. However, it is a valuable guide for PTs (physical therapists) who work with patients that are similar to the patient from the case report. It enables the PT to estimate the effect and the risk of treatment and physical therapy for individually unique patients with bone metastases, brain metastases, lung disorders, and other disorders. In physical therapy for patients with advanced lung cancer, however, retrospective studies seldom get high-level evidence since those patients have uniquely different backgrounds and physical therapy contents, which often bring strong selection bias, unlike patients undergoing perioperative physical therapy.

In contrast, prospective studies define the eligibility and exclusion criteria for enrolling enough patients suitable to the study as well as the items to be evaluated, such as exercise capacity, nutritional status, skeletal muscle mass, QOL, and intervention programs. A prospective study includes an observational study (basically without intervention), a pilot study, and a randomized controlled study. An observational study is divided into a cross-sectional study and a longitudinal study. The former compares the evaluation items of the patient with those of age-matched healthy controls, and the latter investigates the temporal changes of the items. The patients are often classified into several groups according to certain items, in order to compare the backgrounds and/or the survival of the groups. It should be noted that participants in the longitudinal study gradually drop out from the study so the longer the study period becomes, the more likely it is that only the "superior" patients are observed.

A pilot trial is useful study for testing the safety, feasibility, and effectiveness of exercise interventions.

In the randomized controlled study, it is important to set endpoints that are suitable to the study and the protocol of intervention to achieve them. Table 12.1 shows several results of recent randomized controlled studies on physical therapy for patients with advanced lung cancer.

Those studies had some difficulties, as shown below, with possible countermeasures (CMs).

1. How to confirm intervention exercises performed voluntarily at home.
   CM = Confirm through patient diaries and pedometer data.
2. How to motivate patients to exercise when they are experiencing side effects of treatment or cancer progression.
   CM = Motivate the patient through frequent face-to-face talks and telephone calls.
3. Number of patients who obliged to refrain from the evaluation by the side effects or cancer progression possibly deteriorates the statistical significance.
   CM = Enroll enough patients to ignore the absence of those patients.

Table 12.1 A randomized controlled trial on physical therapy for patients with advanced lung cancer

Reference	Primary endpoint	Intervention to IG and CG	Result
H.M. Dhillon, 2017 [38]	A difference in mean fatigue scores between IG and CG at 2 months	IG: 8 weeks of individual instruction for 1 h per session (45 min of aerobic exercise and 15 min of behavioral support) CG: General health education by materials	No significant differences in fatigue among the groups at 2, 4, or 6 months
Lara Ebrooke, 2019 [37]	Changes in functional exercise capacity (6MWD) at 9 weeks from the baseline	IG: 8-week home rehabilitation program (aerobic exercise + resistance training) plus support for behavior change and symptoms CG: Instruction by phone calls once a month	No significant 6MWD differences among the groups at 9 weeks
Chueh-Lung Hwang, 2012 [39]	Impacts of 8-week exercise training on exercise capacity (VO2peak) of patients with NSCLC under targeted therapy	IG: 24 sessions of moderate-to-high intensity aerobic interval training on treadmills and ergometers for 30 to 40 min, three times a week for 8 weeks in an outpatient clinic CG: General patient education and social phone calls every 2–3 weeks	VO2peak and %predVO2peak increased by 1.6 mL/kg/min and 5.3% ($p < 0.005$), respectively, which were associated with improvements in circulatory, respiratory, and muscular functions at peak exercise Dyspnea and fatigue were also lowered
B. L. Vanderbyl, 2017 [40]	Changes in anxiety, depression, and quality of life at 6 weeks from the baseline	IG: Medical Qigong (QG) in 45-min group sessions plus QG at home for up to 1 h every day CG: standard endurance and strength training (SET)	No significant difference in changes of anxiety and depression scores and QOL between QG and SET SET advantageously improved perceived strength ($P = 0.05$) and walking distance ($P = 0.02$)
C. C. Henke, 2014 [41]	Changes in independence in activities of daily living (Barthel Index [BI]) after three cycles of chemotherapy from the baseline	IG: Endurance training and breathing exercises 5 days a week and strength training every other week during the three cycles of chemotherapy CG: Conventional physical therapy	IG presented significantly better BI than CG (IG = 92.08; CG = 81.67; $p = 0.041$). IG also presented several QOL subdomains significantly better than CG

(continued)

Table 12.1 (continued)

Reference	Primary endpoint	Intervention to IG and CG	Result
Brett C. Bade, 2021 [42]	Changes in enrollment rates, physical activities, QOL dyspnea, depression, and biomarkers at 3 months from the baseline	IG: 15 min in-person teaching session on the benefits of physical activity in lung cancer and individual advice for walking goals based on the daily average step count UC: Advice to remain physically active	IG increased PA more than UC (mean change [min/week]: IG = 123 [SD 212] vs. UC = 35 [SD 103]; $p = 0.051$)

IG intervention group; *CG* control group; *UC* usual care; *6MWD* 6-minute walk distance; *VO2peak* peak oxygen uptake; *%predVO2peak* percentage of predicted VO2peak

12.4.2 Protocol Design

The protocol of a prospective study should be designed keeping the patient's burden in mind.

The number of evaluation items built into the protocol, such as exercise capacity, physical activity, muscle strength, balance, body composition, QOL, fatigue, and nutritional assessment, tends to increase because having various items allow for various analyses, which, however, increase the patient's burden. The patients are required not only to be subject to the evaluations for the items in the protocol but also to understand intervention methods and to keep a patient diary. In addition, some interventions are not single practices, but combinations of several practices such as aerobic exercise, resistance training, nutritional interventions, and the guidance thereof, further increase the burden. The burden must be within an acceptable range for patients undergoing treatment for the duration of the study. It is worth considering, for example, that in some cases, the 6-minute walk test is replaceable by the 30-s chair stand test, which is less of a burden for the patient.

12.5 Conclusion

Previous studies show that maintaining higher physical activity and exercise capacity contributes to longer and better survival of patients with advanced lung cancer. In this respect, it is definitely important to start physical therapy from the beginning of treatment unlike actual cases today in which it mostly starts after PS has declined significantly.

In terms of clinical research, we need to examine the effects of physical therapy interventions starting from early diagnosis on the patient's long-term physical function and survival as well as the effects of physical activity and physical therapy in patients with bone or brain metastases, who have been excluded from clinical trials so far.

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Physical Activity in Patients with Breast Cancer

13

Takashi Saito and Rei Ono

Abstract

Physical activity is an important lifestyle habit in patients with breast cancer. Engaging in high levels of physical activity can help prevent the development of breast cancer and improve life expectancy after the disease. Physical therapists must help their patients acquire these benefits of physical activity. To do so, it is necessary to understand the evidence of physical activity benefits among patients with breast cancer and the different methods and characteristics of assessing physical activity and how to apply them clinically.

In addition, maintaining physical activity is beneficial for breast cancer treatments, such as surgery, chemotherapy, and hormone therapy. Although its development has greatly prolonged life expectancy, breast cancer treatment leads to various adverse events, such as lymphedema, neuropathy, joint pain, and bone loss. It is now known that physical activity plays an important role in reducing these conditions. In addition, research on exercise therapy for cardiotoxicity caused by molecular targeted drugs and myokines produced by muscles is being conducted; these areas are expected to develop in the future.

T. Saito (✉)
Division of Rehabilitation Medicine, Department of Rehabilitation, Tokushima University Hospital, Tokushima, Japan

Department of Public Health, Kobe University Graduate School of Health Sciences, Kobe, Japan
e-mail: t.saito@tokushima-u.ac.jp

R. Ono
Department of Public Health, Kobe University Graduate School of Health Sciences, Kobe, Japan

Department of Physical Activity Research, National Institutes of Biomedical Innovation, Health and Nutrition, National Institute of Health and Nutrition, Tokyo, Japan

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Keywords

Physical activity · Occupational activity · Leisure-time activity · Walking Sedentary behavior · Breast cancer patients · Prevention

13.1 Introduction

Physical activity is an important lifestyle habit in patients with breast cancer. Engaging in high levels of physical activity can help prevent the development of breast cancer and improve life expectancy. In addition, it has various benefits, such as the reduction of adverse events during treatment. In this chapter, we introduce the impact of physical activity and outline how it can be applied to clinical practice. Each piece of information is accompanied by a bibliography for those who wish to understand the topic in more detail. In addition to the benefits of existing physical activities, this book also introduces the latest findings in areas that are desirable for future development. It is my hope that this information will be meaningful for physical therapists worldwide.

13.2 Traditional Physical Therapy Regarding Physical Activity in Patients with Breast Cancer

Breast Cancer Epidemiology. An overview of physical activity-related issues that physical therapists caring for patients with breast cancer should be aware of; clinical applications will also be described.

13.2.1 The Effect of Physical Activity on Patients with Breast Cancer

Many studies have shown that physical activity affects the risk of breast cancer development, prevention of recurrence, and survival. This section outlines the impact of physical activity on each event and introduces the types of physical activity described in previous studies.

13.2.1.1 Physical Activity and Breast Cancer Risk

Evidence of the association between physical activity and cancer development has been accumulating since the 1990s. NHANES I showed that the risk of developing cancer is increased in groups with low levels of physical activity compared to those with high levels, and site-specific analyses showed that the risk of developing breast and cervical cancers is more associated with physical activity levels in women [1]. Since then, a number of papers have been published focusing on physical activity and the risk of developing breast cancer. The World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) publication “Diet, nutrition physical activity and breast cancer” contains the latest expert report and

recommends engaging in physical activity to prevent the development of breast cancer [2]. Several other reviews and meta-analyses have also been published. In a meta-analysis published in 2013, 31 articles demonstrated that a group with a high level of physical activity had a relative risk (RR) of developing breast cancer of 0.88 (95% confidence interval (CI): 0.85–0.91) compared to a group with a low level of physical activity [3]. This meta-analysis concluded that a high level of physical activity, both occupational and nonoccupational, reduced the RR. In addition, a dose-response analysis showed that every 25 metabolic equivalent (MET)-h/week increase in nonoccupational activity was associated with a 2% reduction in the risk of developing breast cancer, every 10 MET-h/week increase in leisure time activity was associated with a 3% reduction in risk, and every 2 h/week increase in moderate- and high-intensity leisure time activities was associated with a 5% reduction in risk. As shown above, the preventive effect varied depending on the type and intensity of physical activity. According to the WCRF expert report, most physical activities are effective in preventing the risk of developing breast cancer in postmenopausal women, whereas only high-intensity physical activities contribute to the prevention of breast cancer risk in premenopausal women [2]. Thus, it is almost certain that physical activity can reduce the risk of developing breast cancer. However, it is important to note that there are differences in the preventive effect depending on the type and intensity of physical activity, and the appropriate type and intensity of physical activity differ according to menopausal status.

The mechanism by which physical activity affects the risk of breast cancer development remains unclear. It is generally believed that the mechanism by which physical activity suppresses the risk of developing all cancers is that physical activity reduces the number of fat cells, which in turn suppresses the production of endogenous hormones and growth factors for tumor cells. Physical activity improves insulin resistance and decreases fasting insulin and C-peptide levels, which are factors in cancer development [2]. The key to breast cancer-specific mechanisms is female hormones. Women who are obese, postmenopausal, or hormone receptor positive (HR+) have been shown to be more sensitive to physical activity [4, 5]. Based on these findings, female hormones have been identified as a factor associated with the relationship between physical activity and risk of developing breast cancer. Factors that contribute to the development of breast cancer include early menarche, late menopause, and first childbirth after the age of 30 years, all of which increase exposure to the female hormone estrogen [2]. In postmenopausal women, high levels of physical activity have been shown to lower female hormone levels. Future research should be conducted on the mediating factors between physical activity and risk of developing breast cancer.

13.2.1.2 Physical Activity and Recurrence

According to the Breast Cancer Treatment Guidelines published by the Japanese Breast Cancer Society, physical activity has no effect on breast cancer recurrence. A meta-analysis was conducted separately for two periods, before or at diagnosis and after diagnosis of breast cancer, and physical activity did not reduce the risk of breast cancer recurrence in either period (RR before or at diagnosis: 0.93 (95% CI:

0.60–1.45); RR after diagnosis: 0.81 (95% CI 0.64–1.04)) [6]. However, only three studies were included in each period, and there were differences in subject characteristics due to differences in age, menopause information, and postoperative treatment. In addition, the type and intensity of physical activity have not been sufficiently examined, and evidence is insufficient to conclude that physical activity does not affect breast cancer recurrence.

13.2.1.3 Physical Activity and Survival

Many studies and review articles have evaluated the relationship between physical activity and breast cancer mortality risk [7, 8]. As a result, physical activity is effective for breast cancer death, and a physical therapist, the director of promoting physical activity among breast cancer patients, should be aware of this. In the WCRF/AICR expert report, physical activity before, at, and after the diagnosis of breast cancer was associated with a reduced risk of all-cause mortality [2]. A meta-analysis of physical activity and risk of breast cancer mortality was also conducted in the Japanese Breast Cancer Treatment Guidelines, which reported an RR of 0.86 (95% CI 0.78–0.95) before or at diagnosis and an RR of 0.77 (95% CI 0.72–0.83) for all-cause mortality. Physical activity after diagnosis led to an RR of 0.57 (95% CI 0.46–0.71) for breast cancer mortality and RR of 0.56 (95% CI 0.46–0.69) for all-cause mortality [6]. It is clear from the results of many studies and meta-analyses that physical activity has a protective effect on the risk of death from breast cancer and all-cause mortality.

13.2.2 Promoting Physical Activity Among Patients

13.2.2.1 Promote Physical Activity Before Diagnosis of Breast Cancer

The goal is to reduce the risk of developing breast cancer. The target population is not patients with the disease, but people who have not yet developed breast cancer, that is, residents of the community. Physical therapists, who are mainly in charge of post-disability rehabilitation, may not have many opportunities to intervene directly in this population. In addition, while there are various lifestyle-related diseases such as stroke, heart disease, diabetes, and obesity, it is rare for physical therapists to be involved in preventive approaches, specifically for breast cancer. However, in recent years, there have been an increasing number of opportunities for citizens to think about breast cancer through breast cancer awareness events such as the Pink Ribbon Movement and the promotion of cancer screening [9]. If physical therapists can be involved in such situations, it would be meaningful to promote physical activity among citizens with the aim of reducing the risk of developing breast cancer.

In practice, the main intervention should be to provide information on physical activity that reduces the risk of developing breast cancer through the media and leaflets. The following points should be noted. The assessment of physical activity conducted in previous studies was diverse, and it was difficult to present a uniform amount of physical activity. In addition, the response to the amount of activity

Table 13.1 Physical activity guidelines from three major cohort studies

Study name, age (years)	Physical activity	Follow-up years	Sample size
The JPHC study, 40–69 [4]	Leisure-time activities other than work should be conducted more than **three times once a week**	14.5	53,578
The WHI observational study, 50–79 [10]	Engage physical activity more than **40 MET-h/week**	4.7	74,171
The Japan collaborative cohort study, 40–69 [11]	Walking for at least **1 h per day** and exercising for at least **1 h per a week**	12.4	30,157

changes depends on the presence or absence of factors, such as obesity and menopause. It is advisable to understand the characteristics of the target subject and set the amount of physical activity by referring to studies conducted on similar subjects. The following table presents some guidelines for physical activity (Table 13.1).

All these findings are based on the results of large-scale cohort studies and have a high level of evidence, making them easy to refer to. In addition, the number of times, duration, and intensity of physical activity have been set in concrete terms, making it easy to image. Therefore, it is recommended to refer the abovementioned guidelines for the amount of physical activity needed.

13.2.2.2 Promoting Physical Activity During and After Breast Cancer Treatment

The goal is to reduce the risk of breast cancer recurrence and improve life expectancy. Current evidence shows that the effect of physical activity on life expectancy is more beneficial than its effect on the risk of recurrence [6]. Therefore, it is appropriate to refer to the physical activity intensity in life prognosis studies when conducting physical therapy. In addition, physical activity during breast cancer treatment has the effect of reducing the adverse events caused by the treatment, and it is also meaningful to perform physical activity to improve these events. The effects of physical activity on adverse events will be discussed in Sect. 13.3.

Physical therapists can provide information about physical activity in patients with breast cancer undergoing rehabilitation during or after surgery, chemotherapy, or radiation therapy. The WCRF/AICR expert report concluded that the impact of physical activity on life expectancy at diagnosis and beyond is beneficial [2]. Some guidelines for physical activity are presented below:

Engage in physical activity more than 10 MET-h/week [12].

> Moderate intensity exercise for 2.5 h/week or high-intensity exercise for 1.25 h/week

For every 10 MET-h/week increase in physical activity, the RR decreases to 0.8–0.9 [2].

Let us note that whether changes in physical activity levels affect life expectancy. Bertram et al. reported that in a cohort of patients who did not achieve 10 MET-h/week prior to diagnosis, but improved physical activity levels to 10 MET-h/week or

more during the first year after diagnosis, subsequent life expectancy did not change compared with the group that did not improve [13]. This article suggests that annual changes in physical activity are not sufficient to reduce the risk of death in patients with breast cancer and that longer exposure to physical activity is needed. We need to pay attention to these points when teaching our patients and provide them with information on how to develop the habit of engaging in physical activity for as long as possible.

13.2.3 The Determinants of Physical Activity Among Cancer Patients with Breast Cancer

Promoting physical activity is important for improving life expectancy for patients with breast cancer, and there are many studies around the world that aim to promote physical activity. However, the same approach may result in increased physical activity levels in some individuals but not in others. For an effective approach, it is necessary to understand the determinants of physical activity. A systematic review of exercise adherence in patients with cancer showed that those with a previous exercise habit had better adherence to exercise interventions. However, they found inconsistent results for age, sex, treatment status, physical function, and psychological, social, and environmental factors related to physical activity [14]. Furthermore, few studies have comprehensively analyzed these factors using multivariate analysis, which is a subject for future research. Therefore, we comprehensively evaluated and analyzed these factors to investigate the determinants of habitual physical activity in patients with cancer receiving chemotherapy. Physical activity was assessed using a triaxial accelerometer to measure the number of steps, and potentially determinant variables, such as patient characteristics, medical data about cancer treatment, adverse events according to chemotherapy, physical function (handgrip strength and gait speed), psychological factors (self-efficacy and the decision balance for exercise), social factors (social support scale and lodgers), and environmental factors, were collected. We recruited 37 outpatients receiving chemotherapy. They walked approximately 4200 step counts per day during the treatment. This number was higher than expected. We conducted linear regression analyses and found that positive feelings toward exercise increased habitual physical activity during cancer treatment (Table 13.2) [15]. However, medical data and adverse events, such as fatigue, vomiting, pain, and dyspnea; physical function; social factors; and environmental factors showed no significant association with habitual physical

Table 13.2 Determinants of the mean number of steps per day from multiple regression analysis ($n = 37$)

Variables	Standard beta	p
Grip strength	0.19	0.22
Gait speed	0.15	0.35
Self-efficacy for exercise	0.06	0.74
Pros	0.35	0.04
Drinking habit	0.30	0.05
Adjusted R^2	0.32	

activity. Therefore, we should pay attention to this result. Positive feelings toward exercise is one of the transtheoretical models and a commonly used among community-dwelling elderly people. In recent years, these models have been suggested to be important for patients with cancer [16]. While it is difficult to modify the progression of the disease and the contents of the treatment, as well as its side effects, it is highly possible to change the patient's own knowledge and motivation for physical activity through our approach. It is important to provide accurate and clear information so that patients can understand the importance of exercise and spontaneously change their behavior.

13.2.4 Assessment Tools of Physical Activity and Clinical Applications

13.2.4.1 Assessment of Physical Activity Using Questionnaires

Most large cohort studies have used questionnaires to investigate physical activity [4, 17]. In patients with breast cancer, physical activity has been quantified using METs-h/week and associated with the risk of disease and life expectancy. Although other assessments of activity may be based on subjective judgment of the patient [1], it is more useful to calculate METs-h/week using questionnaires. Each large cohort study used a specific questionnaire: the Japan Public Health Center (JPHC) cohort study used the JPHC prospective study-based physical activity questionnaire (JPHC-PAQ) [18] and the Women's Healthy Eating and Living (WHEL) study used the Women's Health Initiative (WHI) [10]. We introduce the JPHC-PAQ to calculate METs-h/day in Fig. 13.1. It is necessary to check each study for specific assessment methods.

Question:
How long on average do you engage in the following activities each day?

Activity	Answer		
Heavy physical work or strenuous exercise	None	<1 h	≥1 h
Sitting	<3 h	3 - <8 h	≥8 h
Standing or walking	<1 h	1 - <3 h	≥3 h

MET-hours/day	Time scores		
4.5	0	0.5	3
1.5	1.5	5.5	7.5
2.0	0.5	2	8.5

Calculated
total METs/day score
= (MET-h/day) * (Time scores)

Fig. 13.1 Questionnaire estimating METs/day from JPHC cohort

13.2.4.2 Assessment of Physical Activity Using Pedometers and Accelerometers

The questionnaire-based evaluation method was introduced in the previous section. There is a high possibility of recall bias and discrepancy between the actual physical activity and amount of activity in the questionnaire responses. To correct these measurement errors, it is essential to evaluate physical activity using objective indicators. Pedometers and accelerometers are evaluation methods that have been in use for a long time and can objectively assess the amount of physical activity. Particularly for accelerometers, new devices are being developed, which are becoming increasingly accessible to the general public. For some devices, correlation coefficients with actual movements have been calculated [19, 20], and it can be said that they are good tools for accurately assessing physical activity in clinical settings. Recently, the use of smartphones to assess physical activity has been shown to be valid [21].

13.2.4.3 Clinical Indications

When assessing physical activity among a large group of people, such as in a community-based intervention, a questionnaire-based assessment method such as that introduced in Sect. 13.2.4.1 is appropriate. If one has the opportunity to care for patients in a hospital or clinic-based setting, and they encounter situations that need promoting physical activity in patients, the use of a pedometer or accelerometer is preferable for a more accurate assessment. There are many criteria for using data from an accelerometer [22], such as wearing season, wearing days (including weekend or not), available day (how many hours do they wear the device), and situation (walking time only or all day). The number of seconds required to measure counts varies depending on the type of accelerometer and how the non-wear time is determined varies from study to study (e.g., how long does the zero last). For example, in a study using ActiGraph to assess physical activity, patients were asked to wear the device at the waist on the right side for 21 consecutive days. The non-wear time was defined as 60 consecutive zero counts/min. Sedentary behavior was defined as 0–50 counts/min. Light physical activity was defined as 51–759 counts/min, moderate lifestyle physical activity was defined as 760–1951 counts/min, and moderate- to vigorous-intensity physical activity as ≥1952 counts/min [23]. It is advisable to decide which study to refer to, depending on the method and timing of the study and the accelerometer used. The amount of physical activity calculated using accelerometers is often difficult for patients to interpret. Therefore, it is important to obtain understandable information from the accelerometer, such as step counts/day and the amount of time the patient has been walking. These devices also allow patients to monitor their own activities for easy self-care, as many can check the number of steps taken by looking at device's monitor.

13.3 Research Trend for Physical Activity for Patients with Breast Cancer

In this section, we will discuss the research trends in the field of physical activity in patients with breast cancer. As discussed in Sect. 13.2, numerous studies have shown the impact of physical activity on breast cancer incidence and prognosis.

With the development of breast cancer treatment, the 5-year survival rate for early stage breast cancer has been improving and the number of breast cancer survivors is increasing [6]. While long-term survival has been achieved through continuous treatment, the number of patients suffering from the side effects of treatment is expected to increase. In recent years, physical activity has been shown to be an effective treatment for these side effects, and we will discuss it, along with our research.

13.3.1 Lymphedema After Breast Cancer Surgery

Although surgery is one of the major treatments for breast cancer, lymphedema may occur in the upper extremities when the lymph nodes are damaged by axillary lymph node dissection. The incidence of lymphedema is 20%, and the risk factors include axillary lymph node dissection, number of lymph node dissection areas, and mastectomy [24]. Lymphedema can cause pain, heaviness in the arms, limited range of motion and limitation of movement, and decreased quality of life [25]. To prevent lymphedema, surgical treatment and combined physical therapy (such as compression therapy, manual lymphatic drainage, skin care, and exercise therapy) are used, and evidence supporting these is slowly accumulating. These treatments require hospital visits, and it is expected that some patients will not be able to receive the treatments because of the number of facilities, accessibility issues, and financial problems. After surgical treatment, patients are given self-care guidance such as skin care, circumference measurement, and massage. At that time, they should also be provided with guidelines for physical activity. In this subsection, we introduce the effects of physical activity on lymphedema after breast cancer surgery.

Recently, there has been a paradigm shift regarding whether exercise should be administered to patients with lymphedema. In the past, care for lymphedema often involved teaching patients to refrain from the active use of the surgical side of the upper extremity. This tends to lead to a negative cycle of inactivity due to the anxiety of worsening edema, which in turn leads to obesity, a condition that can exacerbate edema. However, it has been shown that resistance training including the surgical side upper extremity is effective in reducing the circumference of the upper limb without worsening edema [26]. Based on the results of these studies, it is now recommended that patients with lymphedema should be actively encouraged to exercise. In addition to these exercise interventions, it is becoming clear that habitual physical activity can also affect lymphedema. Vrieze et al. reported that the lower the level of physical activity, as assessed using the International Physical Activity Questionnaire (IPAQ), the lower the level of lymphedema-related symptoms and life function [27]. Breast cancer patients with lymphedema have been found to have low levels of physical activity [28]; therefore, promoting their activity levels is a necessary issue. In a more practical report, a study investigating risk factors for lymphedema exacerbation showed that postoperative employment and household activities do not lead to lymphedema exacerbation and concluded that there is no need to change the content of work activities before and after surgery [29]. Some studies examined the relationship between physical activity and lymphedema by dividing them into different areas. Although the contribution of physical

activity is still unclear due to the small number of studies, the current evidence suggests that it is important to maintain the same level of activity after surgery as before, without becoming inactive.

13.3.2 Hormone Therapy

13.3.2.1 Bone-Related Events: Physical Activity

Postoperative hormone therapy is widely used for postmenopausal patients with HR+ breast cancer, and aromatase inhibitors have shown great efficacy in improving overall survival (OS) and disease-free survival (DFS) compared to tamoxifen, a conventional hormone therapy [30]. However, they have also been found to cause skeletal-related events (SRE) such as osteoporosis and fractures as side effects. It has been reported that 5-year administration of Arimidex reduces bone mineral density (BMD) of the lumbar spine and femoral neck by −6% and −7%, respectively [31]. Moreover, fracture events occur in as many as 7% of patients after exemestane treatment [32]. In addition to primary therapies such as bisphosphonates and denosumab, exercise therapy has been regarded as a non-pharmacological treatment [33]. There is scattered evidence of supervised exercise interventions for SRE, and exercise therapy has been recommended in the Joint Position Statement by multiple societies [34]. However, some meta-analyses have shown that exercise has no effect on BMD [35]. Since there are not enough high-quality studies, further accumulation and review of evidence are desirable.

For SRE, the role of habitual physical activity may be more important than that of exercise therapy because hormone therapy lasts for about a year, while exercise interventions last for a month at most, which is much shorter than the duration of therapy. Brooke-Wavell et al. reported that brisk walking can improve bone mineral density for up to 5 years, indicating that the response of bone metabolism to exercise requires a certain period of time. From this perspective, it is important to understand that the response of bone metabolism to exercise requires a certain period of time [36]. It is important to promote habitual physical activity and prevent SRE throughout the treatment period of hormone therapy rather than short-term exercise interventions. However, few studies have examined the relationship between habitual physical activity and SRE. Against this background, we investigated the association between habitual physical activity and bone mineral density, as well as and bone metabolism, in patients with breast cancer receiving postoperative aromatase inhibitor therapy [37]. We found that the level of light physical activity (LPA) and work activities, such as employment and housework, was negatively correlated with the bone metabolism markers P1NP and TRACP-5d. This suggests that even mild physical activity may inhibit the increase in bone metabolism. As patients with breast cancer undergo prolonged treatment, it is difficult for them to engage in high-intensity physical activity and maintain the amount of physical activity; therefore, it is reasonable to conclude that even repetitive walking and occupational activity in daily life can contribute to SRE. However, there are some limitations of the study, such as the fact that it was a cross-sectional study and causality cannot be

mentioned, and there was no effect on BMD. It is hoped that more high-quality studies will be conducted in the future.

13.3.2.2 Joint Pain: Physical Activity

Aromatase inhibitors are widely used in the postoperative period of breast cancer, and SREs have been described in the previous subsection as a side effect. Moreover, aromatase inhibitors induce musculoskeletal symptoms such as joint pain. This is called aromatase inhibitor-induced musculoskeletal symptoms (AIMSS), and it has been reported that arthralgia occurs in as many as 47% of patients and joint stiffness in 44% of patients [38]. It is symmetrically located in the joints of the extremities, and the degree of pain is often severe. It is not caused by joint inflammation, as in orthopedic surgery, but by depletion of the female hormone, estrogen [39]. Therefore, AIMSS occur during hormone therapy. AIMSS not only reduce quality of life but may also cause interruption of hormone therapy [40], affecting the rate of treatment completion. Exercise therapy is important, even for AIMSS. A meta-analysis concluded that exercise therapy can reduce pain and stiffness caused by AIMSS [41]; however, a Cochrane review did not show the effectiveness of exercise [42], and no consensus has been reached. Interventions tend to include high-intensity resistance training and home-based aerobic exercise (>150 min/week), and some studies have reported that interventions increase physical activity levels [33]. At present, no studies have examined the relationship between habitual physical activity and AIMSS, and it is unclear whether physical activity is effective against AIMSS. In contrast, in a cross-sectional study, 60% of patients with AIMSS showed decreased activity after the start of treatment, suggesting a relationship between AIMSS and physical activity [43]. Further studies are needed to confirm this hypothesis.

13.3.3 Chemotherapy

The use of taxanes, such as paclitaxel, in addition to AC therapy during postoperative chemotherapy improves DFS and OS in patients with breast cancer with positive lymph nodes [44]. Taxanes are plant alkaloids classified as microtubule inhibitors. As such, they can cause peripheral neuropathy. This is known as chemotherapy-induced peripheral neuropathy (CIPN) and includes symptoms such as paresthesia and pain which appear in a symmetrical globe-sock pattern [45]. Taxane-induced peripheral neuropathy (PN) affects the completion rate of chemotherapy in patients with breast cancer. Approximately 17% of patients with breast cancer have their prescription reduced because of taxane-induced PN, particularly paclitaxel [46]. In addition, CIPN has been shown to reduce physical activity and predispose patients to falls [47, 48]. There is no standard treatment for CIPN, and the main approach is to reduce or discontinue drugs that induce PN. Exercise therapy has been shown to contribute to the improvement of balance disorders caused by CIPN, including taxanes. Therefore, exercise therapy may alleviate CIPN symptoms and prevent falls [49]. Exercise includes aerobic exercise and resistance

training, which can be performed with self-care. As outpatient chemotherapy has become the mainstream treatment in recent years, it is expected that more research will be conducted to determine whether habitual physical activity and exercise therapy can contribute to the alleviation of CIPN symptoms.

Physical therapists also need to take a preventive perspective on issues such as decreased physical activity and occurrence of falls. With regard to physical inactivity, physical therapists need to understand the risk factors for the development and exacerbation of CIPN, and when working with patients undergoing anticancer therapy, interventions should focus on high-risk patients. Although factors such as age, creatinine clearance, and pack-year have been extracted, the results have been inconsistent across studies [50]. However, in recent years, studies on anemia and CIPN have begun to be published. We also reported that vincristine-induced CIPN, a plant alkaloid system similar to taxanes, was exacerbated by baseline anemia [51]. Similarly, anemia was recently reported to be a risk factor for paclitaxel-induced PN [52]. Therefore, patients with anemia should be carefully monitored for CIPN development and exacerbation. For monitoring, we must assess CIPN, and the evaluation of CIPN is often subjective by medical personnel or is based patient-reported outcomes (PRO). However, these assessments lack an objective. Therefore, we quantitatively assessed CIPN using SWMs (Semmes-Weinstein Monofilament SOT-DM06A, Sakai Med, Tokyo, Japan) and a 128 Hz tuning fork (Luze c128 Hz 01–008, NITI-ON, Chiba, Japan) (Fig. 13.2). We recruited patients with various types of cancers receiving chemotherapy which was inducing peripheral neuropathy. We assessed CIPN at the lower extremity using the SWMs and 128 Hz tuning

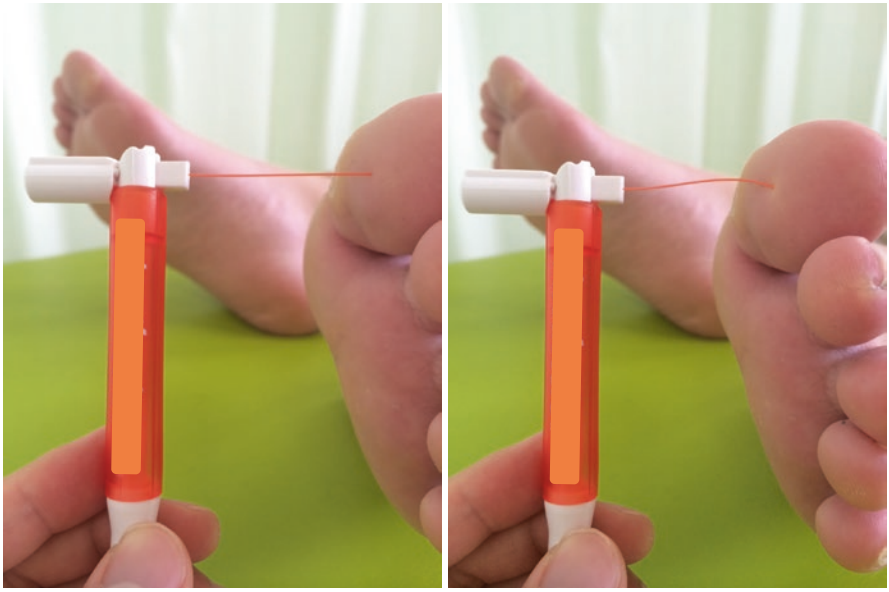

Fig. 13.2 Monofilament testing

fork at baseline (first day of treatment regimen in arbitrary course) and follow-up (3 months after baseline). These assessment tools can be used to evaluate the tough detection threshold and vibration sensation, respectively. Both sensations are classified as superficial and are related to balance disorders and falling. We defined patients who had a tough detection threshold, higher than 10 g at any measuring site, or who had no vibration sensation as having an abnormal sensation. The results showed that 37% of the patients had sensory abnormalities associated with fall risk during follow-up [53]. We also found that there was a discrepancy between subjective and quantitative assessments, making it difficult to accurately assess symptoms by interviews alone. To screen for the risk of falls, CIPN should be assessed objectively as well as subjectively. The prevention of physical inactivity and falls is an area in which physical therapists must play a role. Therefore, it is necessary to understand the aggravating factors of CIPN and know how to accurately assess the risk of falling.

13.3.4 Herceptin for HER2-Positive Molecular Target Drugs

HER2-positive breast cancer accounts for approximately 20% of all breast cancers and has poor prognosis [54]. Recently, trastuzumab, a monoclonal antibody, has been developed. The addition of trastuzumab to anthracycline chemotherapy, which is the standard of care, has led to favorable treatment outcomes [55]. However, cardiotoxicity is a major side effect of trastuzumab. Trastuzumab inhibits the production of HER2 protein by acting on ErbB2, a gene that expresses not only HER2 protein, but also neuglerin, an epidermal growth factor that plays an important role in ventricular formation. Therefore, bilateral heart failure is known to occur in patients treated with trastuzumab [56]. Cardiac decompensation has been reported in 27% of patients treated with anthracycline chemotherapy [57], and 5% of patients treated with trastuzumab give up treatment due to heart failure [58]. For patients with breast cancer, cardiotoxicity is an important side effect that leads to discontinued treatment. The most important risk factor for cardiotoxicity is anthracycline use, and similar risk factors for common cardiac events have been reported, including older age, coronary artery disease, diabetes, hypertension, smoking history, poor cardiac function at baseline, and obesity [56]. Drugs such as ACE inhibitors and B blockers are administered. In recent years, the concept of cardio-oncology has been proposed to address the decline in cardiac function caused by cancer treatments.

Evidence of the effect of exercise therapy on trastuzumab-induced cardiotoxicity has not yet been established. However, regular exercise, smoking cessation, and appropriate dietary habits can reduce the mortality of cardiovascular events; therefore, promoting physical activity could also contribute to the reduction of symptoms due to trastuzumab-induced cardiotoxicity. The ASCO guidelines also emphasize the importance of a healthy lifestyle including physical activity [59]. In addition, the American Heart Association's Scientific Statement states that cardiac rehabilitation is useful in cardio-oncology and has proposed Cardio-Oncology

Rehabilitation (CORE) and presents an algorithm for patients with cancer [60]. Although specific interventions have not yet been developed, cardiac rehabilitation often involves supervised aerobic exercise for at least 40 min, two to three times a week, as in regular cardiac rehabilitation. There is little evidence on the amount of physical activity required; however, considering the contents of cardiac rehabilitation, habitual activity may be useful in reducing the cardiotoxicity of trastuzumab.

13.4 Further Research

In this section, we will discuss the theme of this chapter and the amount of physical activity in patients with breast cancer. We will also discuss what kind of evidence is expected to further confirm the effects of different levels of physical activity.

13.4.1 Assessment of Physical Activity

As mentioned in Sect. 13.2, physical activity can be assessed in various ways. The MET is calculated, and LPA, moderate physical activity (MPA), and vigorous physical activity (VPA) are often classified. However, this is insufficient to obtain a more accurate picture of daily physical activity. In recent years, the concept of sedentary behavior, bouts, which indicate the continuity of physical activity; breaks, which indicate the interruption of activity; and domain-specific physical activity, such as leisure activities, transportation, work, and housework; as well as the amount of physical activity have been introduced. The intention is to evaluate the amount of physical activity in greater detail.

Sedentary behavior is defined as "all waking behaviors that consume less than 1.5 METs of energy in the sitting, semi-supine, or supine position [61]." An increase in sedentary behavior results in a high risk of cancer-related death [62]. The key question is how to reduce sedentary behavior, which accounts for approximately 60% of the waking time. The number of papers on this subject has been increasing rapidly in recent years, and it is a field that is attracting much attention. Bouts and breaks have also received attention in recent years. Most conventional studies on the amount of physical activity have assessed the total amount of daily activity. Bouts and breaks, on the other hand, show the continuity and interruption of physical activity and provide clinically important information on how physical activity should be performed. Regarding the amount of physical activity by domain, research has been conducted to provide an indicator of the importance of the amount of physical activity in situations such as leisure activities, transportation, such as commuting to and from work and school, work, and housework.

As described above, there are various concepts or scales regarding the amount of physical activity, apart from intensity and time, and it is becoming possible to grasp physical activity in detail [63].

13.4.2 Myokine

In recent years, it has become clear that myokines produced from muscles play an important role in the mechanism of regular exercise, which reduces morbidity and improves prognosis in various diseases, including breast cancer. Myokines are hormones expressed, produced, and secreted by skeletal muscles, and are widely known as IL-6 [64]. Evidence for the importance of myokines in patients with breast cancer is beginning to emerge. In vivo studies have shown that oncostatin M and irisin, a type of myokine, inhibit the proliferation of breast cancer cells and induce apoptosis [65, 66]. Although there are no clinical studies so far, it is expected that the impact of these myokines on life expectancy and other outcomes will soon be investigated in clinical studies. We hope that more research on myokines will be conducted in the field of physical therapy. It is necessary to investigate the physical activities that contribute to the production of myokines in detail.

In this section, we described the future perspectives on physical activity in patients with breast cancer. It is important to evaluate physical activity in detail. Myokines can be developed from the in vivo level to the clinical level to show the etiology of physical activity and health outcomes. Through these studies, we will be able to provide evidence-based guidance regarding the amount of activity.

13.5 Conclusion

This chapter outlines the effects of physical activity on patients with breast cancer. Previous studies have shown that physical activity provides significant benefits to these patients, and physical therapists should take the lead in encouraging the amount of physical activity in patients with breast cancer. We also hope that further research will be conducted on the mechanisms between physical activity and breast cancer development, life expectancy, and the reduction of side effects.

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Part III

Physical Function and Other Symptom

Multiple Frailty in Elderly Patients with Cancer

14

Mayu Mizuta and Rei Ono

Abstract

Frailty is one of the notable health problems of the elderly. Frailty has been proposed as a multidimensional concept with multiple domains, including physical frailty, cognitive frailty, and social frailty. Previous studies have shown that frailty in elderly cancer patients affects treatment efficacy, prognosis, and quality of life (QOL). Therefore, frailty is also considered important in the field of oncology. However, at present, there is no internationally unified concept and evaluation method for frailty and the domains that comprise it.

Cancer has become a disease for which long-term survival is expected due to widespread screening and improved treatment techniques. Physical therapists involved in the treatment of elderly cancer patients need an understanding of the multidimensional concept of frailty and the viewpoint of a long-term perspective that focuses on the life course. We hope that further research and discussion will lead to the realization of a seamless and comprehensive physical therapy intervention focusing on multiple frailty in elderly cancer patients.

Keywords

Frailty · Physical frailty · Cognitive frailty · Social frailty · Elderly cancer patients
Perioperative period · Physical therapy

M. Mizuta
Kobe University Graduate School of Health Sciences, Kobe, Japan

R. Ono (✉)
Kobe University Graduate School of Health Sciences, Kobe, Japan

Department of Physical Activity Research, National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health and Nutrition, Tokyo, Japan
e-mail: ono@phoenix.kobe-u.ac.jp

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14.1 Introduction

Aging is a major risk factor for the development of cancer [1, 2]. In Japan's super-aged society, the number of elderly people suffering from cancer is increasing. Frailty has recently attracted attention as an age-related state among the elderly. Although there have been several studies on frailty in elderly cancer patients, the concept of frailty has not been consensually defined yet.

In this chapter, we will review the concept of frailty and its different assessment methods. We will also discuss the current status and impact of frailty in elderly cancer patients, highlighting the importance of the physical therapist's involvement in the care of elderly cancer patients and alluding to future perspectives.

14.2 Section 1

This section describes the current status of cancer in the elderly and discusses frailty, a health problem of the elderly, in the context of both geriatrics and oncology.

14.2.1 Epidemiology of Older Cancers

According to the Ministry of Health, Labour and Welfare Vital Statistics, malignant tumors have been the leading cause of death in Japan since 1981, accounting for approximately 30% of all deaths, with this percentage consistently increasing throughout the years [3]. Approximately 70% of all cancer cases in Japan occur in elderly patients aged 65 years and above [4]. The percentage of the elderly among cancer cases worldwide has also been increasing in recent years [5, 6]. This suggests that cancer in the elderly is an area of focus in Japan and other countries with aging populations. Recent advances in cancer screening and surgical treatment with minimally invasive techniques such as robotic, thoracoscopic, and laparoscopic surgery have increased the survival rate of cancer patients [7, 8]. Consequently, standard treatments such as surgery are now being offered to the elderly, who were previously not eligible for treatment. Heidi et al. [9] identified the aging phenomena that impact cancer progress, treatment tolerability, and treatment efficacy in the elderly, discussing processes related to disrupted homeostasis, heterogeneity, reduced adaptability, and changes in pharmacokinetics. With respect to heterogeneity, they cite the ability to tolerate toxicity associated with cancer-specific therapies and reserve capacity in organ systems within an individual. In particular, these aging processes may increase the vulnerability of elderly cancer patients, making them more susceptible to the adverse effects of cancer and its treatment than young cancer patients. Furthermore, age-related functional decline is influenced by genetic, lifestyle, and environmental factors, which results in individual differences in the rate and extent of progression and areas of the age-related functional decline.

Therefore, physiological reserves cannot be predicted solely based on chronologic age [10]. Moreover, there are life events and experiences that are unique to the elderly, such as bereavement of friends and relatives, experiences of loss such as retirement, onset of illness, changes in social and living environment due to hospitalization, and awareness of decline in physical functions in daily life. These experiences impose change in the environment and relationships surrounding the elderly and might thus cause psychological stress. In light of the above, the role of physical therapists becomes important in participating in the treatment of elderly cancer patients by not only individually considering the pathology of cancer as a disease but also assessing and integrating the physiological, functional, and psychosocial aspects that are unique to the elderly.

14.2.2 Frailty in Geriatrics

Frailty is a clinical syndrome that is common in the elderly. It is defined as an age-related decline in reserve and function of multiple multifaceted physiological systems resulting in increased clinically recognizable vulnerability and decreased ability to cope with daily or acute stressors [11]. Frailty is also defined as a state in which the individual is able to move dynamically between different levels of severity [12]. In other words, it is a reversible state in which the individual is able to move back to a healthy state with appropriate intervention. Frailty is a multidimensional concept that includes cognitive and psychosocial components [13, 14]. An assessment based on this concept is the Comprehensive Geriatric Assessment (CGA), which is a multi-subject assessment tool that identifies, describes, and explains the multiple difficulties faced by elderly people. This assessment also catalogs the resources and strengths of the elderly, assesses their need to services, and develops a coordinated care plan that provides problem-focused solutions and interventions [15]. Specifically, CGA has items on functional status, comorbidities, cognitive function, nutritional status, psychological status, social support, and pharmacotherapy of the elderly [16]. Frailty is also included in the International Statistical Classification of Diseases and Related Health Problems (ICD-10) developed by the WHO [17], and it is considered one of the most important clinical conditions internationally. Frailty has been associated with various adverse outcomes such as falls, disability, hospitalization, and death [18–20]. It has also been associated with reduction of healthy life expectancy in the elderly [21]. Frailty is a multidimensional concept that encompasses multiple domains such as physical frailty, cognitive frailty, and social frailty. Definitions and assessment methods focusing on each domain have been proposed; however, the concepts and definitions are not yet unified. The domains are considered to influence each other, leading to negative health outcomes [22]. Some studies have focused on specific domains in relation to specific outcome, and some of them have been conducted on elderly cancer patients.

14.2.3 Frailty in Oncology

The concept of frailty in the context of oncology is particularly important for considering treatment options. A major problem that arises when considering treatment options for elderly cancer patients is individual differences in treatment efficacy due to heterogeneity of aging. Some elderly cancer patients can tolerate standard doses of chemotherapy as well as younger patients, while others show severe toxicity, forcing the decision to reduce, delay, or discontinue treatment [23]. Therefore, oncologists treating elderly cancer patients are faced with the challenge of appropriately selecting patients who can be treated with standard therapy and those who should be given reduced-dose therapy. The National Comprehensive Cancer Network (NCCN) guidelines on elderly cancer and the International Society of Geriatric Oncology (SIOG) have recommended a CGA-based approach to decide on treatment for elderly cancer patients [24, 25]. This CGA approach allows for better tailoring of treatment plans at the individual level and permits the classification of elderly cancer patients into the following three categories [26–28]:

1. Fit: A condition in which a person can receive the same standard of care as a healthy non-elderly person.
2. Vulnerable: A condition in which a person cannot receive the same standard treatment as healthy non-elderly people but can receive some treatment.
3. Frail: A condition in which a person is not considered eligible for aggressive treatment (indication for best supportive care or palliative medicine).

The above concept of frailty in the context of oncology conforms to that proposed by the European Organization for Research and Treatment of Cancer (EORTC) elderly task force [23], while it is not synonymous with frailty in the field of geriatrics. Frailty is "a state of increased vulnerability due to aging that is reversible with appropriate intervention," as defined in geriatrics has the equivalent of "vulnerable" in the field of oncology.

14.2.4 Assessment Tools of Frailty (Table 14.1)

Used as an evaluation method, CGA is comprised of a large number of items; thus, its use demands a lot of time and effort. In addition, because it is not reinforced by the healthcare system, it is rarely used in daily clinical practice. Therefore, other screening tools that can be easily performed in a shorter time have been developed for elderly cancer patients as shortened versions of the CGA, and the sensitivity and specificity of these screening tools have been verified [29]. The following are some of these tools that are most frequently used in research and clinical practice owing to their relatively high sensitivity and specificity: Geriatric 8 (G8) [30], Vulnerable Elders Survey (VES-13) [31], and Groningen Frailty Indicator (GFI) [32].

1. Geriatric 8 (G8)

   It is a simple screening tool comprising seven items from the Mini Nutritional Assessment (food intake, weight, ability to walk, presence of mental

Table 14.1 Screening tools for geriatric assessment in older cancer patients [12, 29]

	G8	VES-13	GFI
Physical function	△	◯	◯
Comorbidity	—	—	—
Drugs	△	—	△
Nutrition	◯	—	△
Cognitive function	—	—	△
Mood	△	—	◯
Social support	—	—	—
Geriatric syndrome	—	—	—
Sensitivity (%)	65–92%	39–88%	39–66%
Specificity (%)	3–75%	62–100%	86–87%

G8 Geriatric 8; *VES-13* Vulnerable Elders Survey; *GFI* Groningen Frailty Indicator
◯ = assessable; △ = insufficient assessment; — = unassessable

or emotional problems, BMI, polypharmacy, subjective health status) and age. A score of ≤14 is considered abnormal [33]. It takes less than 5 min to complete.

2. Vulnerable Elders Survey (VES-13)

   It is a self-administered questionnaire consisting of 12 functional assessment items (subjective health status, physical activity, activities of daily living (ADL), instrumental activities of daily living (IADL) and age. A total score of ≥3 indicates vulnerability. It takes approximately 5 min to complete.

3. Groningen Frailty Indicator (GFI)

   It is a questionnaire comprising 15 questions covering three areas: daily activities, health problems, and psychological functions. If four or more items are applicable, the patient is considered to be in a frailty state. It takes approximately 15 min to complete [12].

14.2.5 Frailty in Elderly Cancer Patients

The concept of frailty in the field of oncology is largely utilized as a reference for guiding treatment [12, 29, 30]. The condition of elderly cancer patients before and during treatment is assessed individually through a multidimensional evaluation, so that appropriate treatment selection and modification can be made. The concept of frailty in oncology is hardly a concept that focuses on the life and prognosis of elderly cancer patients from before to after treatment. From the viewpoint of a long-term perspective that focuses on the life course from immediately after the diagnosis of cancer to after the patient returns to the community after treatment, it is important to consider frailty in elderly cancer patients from the perspective of the geriatric field as well. The concept of frailty in the field of geriatrics is defined as "a state of increased vulnerability and decreased ability to cope with daily and acute stressors due to aging" [11]. Applying this concept to elderly cancer patients, cancer and its treatment are considered major stressors, and elderly cancer patients in the state of frailty are at increased risk of adverse events due to their inability to cope with these stressors. Furthermore, in cancer patients of older age, cancer symptoms, treatment side effects, inactivity during hospitalization, and psychological stress

may contribute to the decline in physiological reserve due to aging [34]. Based on the above, we believe that the perception of "vulnerable cancer patients" in the field of geriatrics, rather than "at-risk elderly" in the field of oncology, is more appropriate for the current and future society, where cancer patients are aging and having long-term prognosis after cancer due to improved treatment outcomes.

For clinical application, it is desirable to identify individuals in a frailty state using indicators based on multidimensional concepts as to allow intervention at earlier stages of reversibility. In the elderly, the degree of functional decline in physiological, cognitive, and psychosocial aspects may differ among individuals. Therefore, when intervening, it is important to consider which domains of frailty are the most affected by the decline and whether the intervention is expected to have a variable effect on different individuals, based on the assessment. This is important for offering individualized interventions both when considering treatment by an oncologist and planning rehabilitation by a physical therapist. It is thus important to plan and implement intervention programs. In the treatment of elderly cancer patients, it is also meaningful to focus on each domain that constitutes frailty. The existence of interactions between the various domains has also been proposed [35]. Social frailty is a risk factor for the later development of physical frailty [36], and physical frailty is a component in the definition of cognitive frailty [37], as will be discussed in later sections, which suggests the existence of interaction between the various domains of frailty. The existence of interactions means that factors in one domain can affect factors in another domain, contributing to or inhibiting the progression of frailty. The "Frailty Cycle" [38] as proposed by Fried is a well-known mechanism of frailty progression, in which all factors are interrelated, forming a vicious cycle. As an approach to improving frailty, it is important to break this vicious cycle. The factors that form this vicious cycle are a mixture of those that are variable through individual awareness and intervention, such as the amount of food, activity, and social activity participation, and those that are not variable, such as living alone and economic status. Considering the interaction between the domains described above, it is thus possible for the influence of non-variable factors belonging to one domain to be corrected by intervening with variable factors belonging to another domain. From the physiotherapist's perspective, the intervention in the physical domain is expected to be mostly significant.

14.3 Section 2

In Sect. 14.2, we discussed the importance of considering frailty in elderly cancer patients not only in the field of oncology but also in the field of geriatrics and of focusing on each of the domains that comprise frailty. This section summarizes the definitions and assessment methods currently proposed for each of the domains that comprise frailty, as well as the prevalence rates of frailty domains reported in previous studies.

14.3.1 Multiple Frailty

14.3.1.1 Physical Frailty

Physical frailty is defined as a medical condition characterized by a decline in strength, endurance, and physiological function due to multiple factors, leading to receiving nursing care and later death [39]. Physical frailty has been shown to be a strong predictor of adverse health outcomes such as falls, fractures, disability, hospitalization, institutionalization, and death [40–42]. Although many methods have been proposed for the assessment of physical frailty, the most commonly used is the Cardiovascular Health Study (CHS) criteria proposed by Fried et al. [42]. These criteria are based on the concept that five phenotypes, namely, shrinking, exhaustion, low physical activity, slowness, and weakness, are manifested when a person enters a state of frailty, and each phenotype is assessed using an alternative index that can be easily measured (Table 14.2). A state of frailty is defined by three or more applicable phenotypes, whereas one or two phenotypes define the state of pre-frailty which is the stage before frailty [11, 40]. Satake et al. [43, 49] have developed a Japanese version of the original CHS criteria (J-CHS) which is simpler and more suited to the characteristics of the elderly in Japan, and this is the version that is used in clinical practice in Japan.

Table 14.2 Phenotype, alternative indicator, and criteria of CHS, J-CHS [47, 48]

Phenotype	Alternative indicator	CHS criteria	J-CHS criteria
Shrinking	Weight loss	Self-reported weight loss of >4.5 kg or recorded weight loss of ≧ 5% per year	Self-reported unintentional weight loss of ≧2 kg in the past 6 months?
Exhaustion	Self-reported exhaustion	Self-report of either of: 1. Felt that everything I did was an effort in the last week 2. Could not get going in the last week	Self-report of: In the past 2 weeks, have you felt tired without a reason?
Low physical activity	Low energy expenditure	Energy expenditure Men: <383 kcal/week Women: <270 kcal/week	No to both questions: 1. Do you engage in moderate levels of physical exercise or sports aimed at health? 2. Do you engage in low levels of physical exercise aimed at health?
Slowness	Slow gait speed	Walking 15 feet (4.57 m) at the usual pace Standardized cutoff times to walk 4.57 m, stratified by sex and height	Gait speed <1.0 m/s
Weakness	Weak grip strength	Lowest 20% (grip strength, stratified by sex and body mass index)	Grip strength Men: <28 kg Women: <18 kg

In a study of breast cancer survivors aged 50 years or older, the prevalence of frailty and pre-frailty was 12.5% and 50.0%, respectively, and frailty was reported in 18.2% of aged 70–79 years [44]. In a study of elderly cancer survivors aged 50 years or older, the prevalence of frailty was 16.1% and that of pre-frailty was 59.8%, using a modified version of the index proposed by Fried et al. [45]. Although no studies mentioned above have specified the stage of the perioperative period at which the patients were at the time of the study, it is likely that many of them were living in the community after treatment. A study of outpatient elderly patients by Panuwat et al. [46] found that the proportion of cancer survivors among those with physical frailty was significantly higher than that of those with non-frailty.

14.3.1.2 Cognitive Frailty

The concept and operative definition of cognitive frailty were first proposed in 2013 by an International Consensus Group of the International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics [37]. Cognitive frailty is defined as a condition which has clinical symptoms characterized by the simultaneous presence of physical frailty and cognitive dysfunction [37] and in which the following two conditions are met:

- The presence of physical frailty and cognitive impairment (Clinical Dementia Rating score = 0.5)
- Exclusion of concurrent Alzheimer's disease dementia or other dementias.

The above definitions indicate that cognitive dysfunction in cognitive frailty is primarily caused by the physical dysfunction rather than physiological neurodegenerative processes in the brain [50]. However, there is insufficient evidence for a causal relationship between physical frailty and cognitive impairment [37], and in clinical practice and research, it remains difficult to distinguish between cognitive impairment caused by neurodegenerative disease and physical impairment. Previous studies have shown that people with cognitive frailty have an increased risk of ADL impairment, decreased quality of life (QOL), and increased mortality compared to people with physical frailty alone [51–53]. People with cognitive frailty also had a higher hazard ratio for developing dementia compared to people with physical frailty alone or cognitive impairment alone [54].

The evaluation method of cognitive frailty involves a combination of a tool for determining physical impairment and a tool for determining cognitive impairment. For the former, the use of inflammatory markers (e.g., CRP, IL-6), gait speed, grip strength, weight loss, and actigraphy is recommended. For the latter, it is recommended to conduct a comprehensive cognitive function assessment that investigates not only memory but also other cognitive functions (e.g., executive function) [37].

The low prevalence of cognitive frailty based on the original operative definition limited the clinical utility of this concept and showed that the criteria are needed to be modified. Subsequently, new criteria were proposed to add pre-physical frailty and pre-clinical stages of subjective cognitive impairment or dementia (asymptomatic but positive for biomarkers such as Aβ and tau) to the International Consensus

Group criteria [55]. The concept of motoric cognitive risk syndrome, which focuses on the risk of developing dementia due to the coexistence of reduced walking speed and cognitive impairment, has also been proposed [56]. However, no consensus has been reached on a definition of cognitive frailty for clinical or community use, and the best index for detecting cognitive impairment has also not been settled yet [57].

A review article reported that the prevalence of cognitive frailty in the community was 1.0–12.1% [10], with some studies showing a prevalence of less than 5.0%, while others in people with certain comorbidities such as heart disease reporting a higher prevalence of 10.7–39.7%, an increase compared to the community. Although no studies have assessed the prevalence of cognitive frailty among elderly cancer patients, it is assumed that the prevalence is higher than the regional prevalence in terms of having a specific disease. However, it is also necessary to distinguish cancer patients with cognitive frailty from patients with cancer-related cognitive impairment, which is a cognitive impairment caused by cancer or its treatment [58].

14.3.1.3 Social Frailty

Social frailty is the most under-explored domain of frailty. It is a multidimensional concept that takes into consideration the individual's various general and/or social resources (including spouse and children), social behaviors and activities (such as maintaining relationships, or social participation), and self-management skills (such as the ability to make important decisions), which contribute to meeting social needs. From this perspective, social frailty can be defined as a continuum of being at risk of losing, or having lost, social and general resources, activities, or abilities that are important for fulfilling one or more basic social needs during the life span [36, 59].

As an evaluation method for social frailty proposed by Makizako et al. [60], five simple questions are used: going out less frequently than last year (yes), visiting friends occasionally (no), feeling useful to friends and family (no), living alone (yes), and talking to someone everyday (no). Cases wherein two or more of the above conditions apply indicate social frailty, and those in which one of the above conditions applies indicate pre-social frailty.

On exploring the concept of social frailty by Bunt et al. [59], general resources, social resources, and social behavior/activities are listed as the elements needed to satisfy basic social needs. Factors included in these elements of social frailty were lifestyle, basic activities of daily living, size of social network, marital status, maintenance of intimate relationships, occupation, and social participation, and so on. These factors change for the elderly due to inevitable life events and phenomena such as retirement, bereavement of a spouse or friend, or physical decline. Therefore, the elderly are a group of individuals at a high risk for social frailty, and in an aging society, social frailty is expected to become a serious problem in the future.

In two studies on preoperative elderly patients with gastrointestinal cancer, the prevalence of social frailty was 27.0% [61] and 46.8% [62], respectively. These studies were conducted in Japan, and there are few other studies that explore the prevalence of social frailty in elderly cancer patients.

Table 14.3 Prevalence of each frailty domain in community-dwelling older adults and older cancer patients

	Community-dwelling older adults			Older cancer patients		
	Reference	Index	Prevalence	Reference	Index	Prevalence
Physical frailty	Montero-Odasso et al. [50]	CHS	Frailty 13.9% Pre-frailty 52.0%	Jill et al. [44]	CHS	frailty 12.5% Pre-frailty 50.0%
				Thuy et al. [45]	CHS (four items)	Frailty 16.1% Pre-frailty 59.8%
Cognitive frailty	Shimada et al. [64]	CHS MoCA	Frailty 1.2%	—	—	—
Social frailty	Makizako et al. [60]	Five questions [60]	Frailty 10.2% Pre-frailty 24.9%	Okumura et al. [61]	Five questions [60]	Frailty 27.0%
				Ono et al. [62]		Frailty 46.8%

In this section, we describe the definitions of each of the domains that comprise frailty, reviewed the methods of assessment of frailty, and discussed the prevalence of frailty in elderly cancer patients (Table 14.3). There is no consensus on the concept of frailty in any of the domains, and the assessment methods that were described are only a subset of those proposed by many researchers. The Asia Pacific Guidelines for Frailty Care [63] recommend the selection of a validated method that is appropriate and accessible for the purpose, number of subjects, and site of implementation. In particular, when targeting the elderly, it would be desirable to select an assessment instrument that has questions that are easy to ask and implement, does not take too long, and does not require excessive effort to implement, taking into consideration physical and cognitive functions.

14.4 Section 3

In this section, we will discuss what is currently known about the relationship between cancer incidence/treatment and frailty in the elderly and the impact of frailty on elderly cancer patients.

14.4.1 Relationship Between Cancer Incidence and Frailty

Previous studies have shown a high prevalence of frailty in older adults with a history of cancer [46, 65]. Studies examining risk factors for physical frailty in elderly cancer patients have identified age, self-rated physical health, depressive symptoms, ability to perform activities of daily living, and mobility as risk factors [45]. It is unclear whether cancer causes new frailty or frailty is a risk factor for the development of cancer [47]. However, cancer patients are at a higher risk of having depressive symptoms [66], and cancer symptoms and the side effects of treatment drive the

decline in ADL and IADL [67]. It is thus possible to speculate that cancer may cause or enhance the risk factors that lead to the progress of frailty indirectly contributing to the development of frailty.

14.4.2 Impact of Frailty in the Perioperative Period

14.4.2.1 Before Treatment

Studies have investigated the prevalence of frailty and its negative effects in the period from cancer diagnosis to the start of treatment. Preoperative physical frailty in elderly cancer patients prior to surgical treatment reportedly predicts the development of postoperative complications [68, 69]. Similarly, preoperative social frailty was shown to predict the development of depressive symptoms and impact the postoperative overall survival and cancer-specific survival in the first year after surgery [61, 62]. Using a multidimensional index, Miao et al. [70] reported that elderly gastric cancer patients with preoperative frailty had a significantly longer hospital stay and a significantly higher incidence of postoperative complications. Additionally, the same study reported that patients with both preoperative physical and social frailty had lower QOL 1 month after discharge from the hospital.

Assessment of pretreatment frailty in elderly cancer patients prior to chemotherapy using CGA or VES-13 has been described as a predictor of mortality, chemotherapy-related toxicities, and poor treatment tolerance [71], and studies focusing on physical frailty have shown similar results [72]. In addition to surgery and chemotherapy, radiotherapy is a typical cancer treatment, but the prognostic value of frailty and radiotherapy has not been well-studied yet and is still an underexplored area.

14.4.2.2 During Treatment

A greater rate of neutrophil depletion has been reported in elderly non-Hodgkin's lymphoma patients characterized by reduced bone marrow reserve, as a result of treatment with high-dose chemotherapeutic agents [73]. However, this study did not include an assessment based on frailty, and the decreased bone marrow reserve was discussed in terms of pathophysiology of disease, not in relation aging. However, the of concept "decreased reserve" parallels that of frailty, suggesting that frailty, which is characterized by age-related loss of physiologic reserve, may also affect the efficacy of treatment and other outcomes. With treatment, patients are expected to experience side effects of treatment, decreased activity due to periods of rest, isolation from the social environment during hospitalization, and reduced opportunities for social interaction. This situation may affect all physical, cognitive, and psychosocial aspects of frailty and increase vulnerability to symptoms caused by cancer and its treatment.

14.4.2.3 After Treatment

Some studies have been conducted on the prevalence of frailty and its effects on the physical and mental functions in community-dwelling older persons [74, 75]. However, few studies in this regard have been conducted on older people with a

history of cancer. Cancer symptoms and side effects of cancer treatment may persist for several years to decades after the onset of the disease, or they may newly occur [76–78]. This may affect the progression of frailty, especially in the elderly.

14.4.3 Summary of the Section

This section presents reports on the impact of frailty during the different phases of the perioperative period in elderly cancer patients. Based on these results, two points are important to consider when intervening with elderly cancer patients. The first is the timing of assessment and intervention. There is a "waiting period" in the course of treatment for cancer patients from the time a treatment plan is determined based on diagnosis and test results until treatment is initiated [79]. The length of this period varies depending on several factors among which is the type of cancer and ranges from approximately 1 week to approximately 1.5 months. Since previous studies have shown that the presence of frailty prior to the start of treatment influences subsequent prognosis, it is important to assess frailty during the waiting period after diagnosis and to start the intervention based on the current status of frailty. The second is frailty assessment from a multidimensional perspective. Approximately half of the hospitalized elderly patients experience a decline in physical function. Additionally, many of these patients also have psychological and social problems such as anxiety, depression, and limited social support [80, 81]. Studies on elderly patients with heart disease have shown that there is a significant overlap between the different frailty domains and that this overlap becomes more pronounced with increasing age. Furthermore, the higher the number of overlapping frailty domains is, the higher the mortality and rehospitalization rates are [70]. In other words, elderly patients may have more frailty domains as they age, leading to a risk of poor prognosis. This can be applied to elderly cancer patients as well. By focusing on each domain and the overlap between different the domains, more individualized and specific interventions could be implemented.

14.5 Section 4

There have been many studies on frailty in healthy older adults with and without cancer. On the other hand, studies on frailty in elderly cancer patients have been more limited. This section discusses areas for further research and discussion regarding multiple frailty in elderly patients with cancer (Fig. 14.1).

14.5.1 Prehabilitation

In general, there is a certain waiting period in the treatment process for cancer patients from the time of diagnosis and determination of the treatment plan until the start of treatment. In recent years, the preoperative waiting period has been

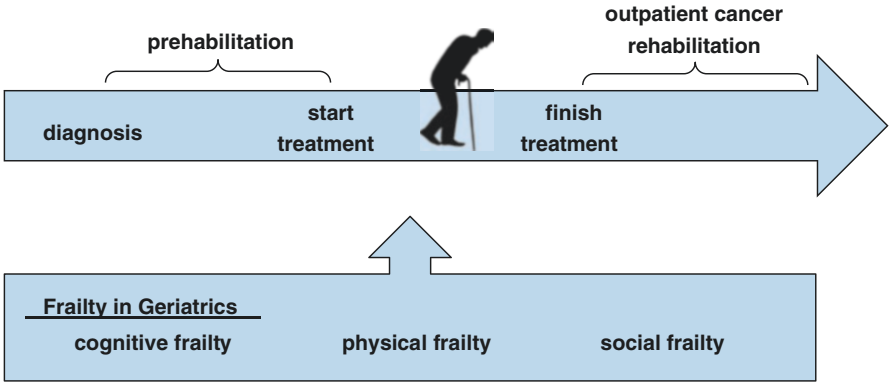

Fig. 14.1 Rehabilitation and frailty in geriatrics for cancer patient in the perioperative period

recognized as an opportunity for prehabilitation to modify risk factors and improve patients' prognosis [82–84].

Early prehabilitation studies focused on the effects of interventions at the level of a single domain such as exercise and nutrition [85]. In recent years, however, there has been an increase in studies of multimodal prehabilitation programs that include exercise, nutrition, and psychological interventions [86, 87]. Studies have been conducted on prehabilitation in elderly cancer patients and have shown effects on outcomes such as lower mortality, fewer complications, and shorter hospital stays [88–90]. The need for prehabilitation to improve frailty in elderly cancer patients has also been suggested, and individualized rehabilitation interventions based on individual needs and problems in specific frailty domains identified by preoperative assessment was shown to be more effective [91]. Although there have been studies investigating the association between preoperative frailty and adverse outcomes after various surgical procedures, few studies have evaluated the role of prehabilitation in improving posttreatment outcomes in elderly cancer patients with frailty status [70, 92]. Recently, a protocol on prehabilitation for elderly cancer patients in frailty has been proposed [93]. It is expected that more clinical studies will be developed to further study and promote prehabilitation of elderly cancer patients in clinical practice.

14.5.2 Outpatient Cancer Rehabilitation

After the elderly cancer patients complete hospital treatment and are discharged, the interplay of domains that comprise frailty can lead to a series of vicious cycles. For example, postoperative elderly gastric cancer patients often suffer from postoperative fatigue (postoperative fatigue; POF), decreased tolerance of oral intake, intra-abdominal abscess, delayed gastric emptying, and other physical problems specific to the postoperative period, resulting in a significant decrease in physical and social activity [94, 95]. In parallel, restriction of social activities may lead to a decrease in

skeletal muscle metabolism due to reduced activity, resulting in muscle atrophy, decreased physical capacity, and decreased independence [96]. This suggests that attention should be paid to each domain of frailty continuously after treatment as a way to improve the prognosis of elderly cancer patients from a long-term perspective. Although there is growing recognition of the importance of outpatient cancer rehabilitation, the current lack of evidence leaves it up to each hospital to decide whether or not to provide such services. In other words, opportunities for cancer patients to receive outpatient rehabilitation are still uneven and inadequate. If outpatient cancer rehabilitation becomes a common practice, it will not only provide long-term care for many elderly cancer patients under the care of specialists for side effects and late symptoms but also provide opportunities to maintain activity levels and social interactions after discharge. It is thus expected that outpatient cancer rehabilitation would be effective not only in improving frailty but also in preventing it. This sheds the light on the importance of developing more studies and strategies focusing on continued intervention and rehabilitation post cancer treatment in the elderly.

14.5.3 The Multidimensional Concept of Frailty

Sacha et al. [97] stated that each of the domains that comprise frailty can be combined to form subgroups with multiple frailty domains, which may allow for more accurate prediction of adverse outcomes by understanding the specific condition of individual patients. Few studies have investigated the relationship between subgroups and outcomes in elderly cancer patients [62, 70]. As the number of elderly cancer patients increases, interventions focusing on frailty will become more important.

More evidence based on the multidimensional concept of frailty, including the effects of each domain and their overlapping subgroups, will thus be required.

14.6 Conclusion

What is described here is the author's summary of various proposals, and there is currently no unified concept of frailty or method of its assessment. We hope that further research and discussion will lead to the realization of a seamless and comprehensive physical therapy intervention focusing on multiple frailty in elderly cancer patients.

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Postoperative Complications in Patients with Esophageal Cancer

15

Junichiro Inoue and Rei Ono

Abstract

Esophagectomy is a complex procedure that is associated with postoperative complications, morbidity, and mortality. In recent years, several reports have shown the efficacy of a multimodal approach, termed the enhanced recovery after surgery (ERAS), in the preoperative, intraoperative, and postoperative periods of esophagectomy. The ERAS protocol is composed of preoperative nutrition, prehabilitation, counseling, smoking and alcohol cessation, cardiopulmonary evaluation, surgical technique, anesthetic management, intra- and postoperative fluid management and pain relief, mobilization and physiotherapy, enteral and oral feeding, removal of drains, and several other components. Prehabilitation and early mobilization are the core components of the ERAS. This multimodal approach, including prehabilitation and early mobilization, cannot only improve physical function and performance and activities of daily living (ADL) but also reduce postoperative complications, morbidity and mortality, shorten the length of hospital stay, and prevent unplanned readmissions following esophagectomy.

Keywords

Esophageal cancer · Esophagectomy · Postoperative complications · Morbidity Mortality · Prehabilitation · Early mobilization · ERAS protocol

J. Inoue (✉)
Division of Rehabilitation Medicine, Kobe University Hospital, Kobe, Japan
e-mail: jinoue@panda.kobe-u.ac.jp

R. Ono
Department of Physical Activity Research, National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health and Nutrition, Tokyo, Japan

Kobe University Graduate School of Health Sciences, Kobe, Japan

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15.1 Introduction

Esophageal cancer is the eighth most common cancer and the fourth most common cause of mortality worldwide [1]. Esophageal cancer is a debilitating disease, which is frequently diagnosed in the advanced stages, and is associated with poor surgical outcomes. Despite considerable advances in the treatment of esophageal cancer, surgical resection remains the primary treatment. Procedures for thoracic and abdominal surgery for esophageal cancer are associated with a high risk of postoperative complications, including respiratory complications, such as pneumonia and atelectasis, deep vein thrombosis, delirium, and intensive care unit-acquired weakness (ICU-AW); therefore, strategies to reduce postoperative complications are of considerable importance [2].

Rehabilitation plays a key role in managing postoperative complications and enhancing the recovery of patients' physical function and activities of daily living (ADL) from the preoperative to postoperative periods, as well as facilitating their early return to society and higher quality of life (QOL).

In this section, we describe the pathogenesis mechanism underlying the risk of developing postoperative complications, the clinical practice of rehabilitation, and the role of the multidisciplinary medical team in managing postoperative complications from the preoperative to postoperative periods in patients with esophageal cancer undergoing esophageal cancer surgery.

15.2 Problems Following Esophagectomy

15.2.1 Risk Factors of Postoperative Complications in Esophagectomy

Endoscopic resection and esophagectomy are common surgeries performed for resectable esophageal cancer. The therapeutic intervention is chosen depending on the physical health of the patients and the clinical stage of the tumor. In the early stages of cancer, endoscopy or surgery is performed, whereas, in advanced stages, surgery with or without chemotherapy or chemoradiotherapy is performed [3].

Esophageal cancer surgery usually involves lymph node dissection and esophageal reconstruction, representing an extremely invasive procedure, with many complications associated with its outcomes. Recently, thoracoscopic methods have been integrated with minimally invasive laparoscopic approaches to achieve better outcomes. Integration of three-dimensional cameras has also allowed surgeons to view histological and microanatomical organizations during surgery [4]. Single-port mediastinoscopy using transmediastinal and cervical approaches has been performed in recent years, which can reduce perioperative complications [5, 6]. Surgical techniques are likely to reduce the frequency of postoperative mortality and morbidity [7]. Esophageal cancer surgery is considered one of the most invasive cancer surgeries and is associated with 60–80% rate of postoperative adverse events and a corresponding reduced overall survival rate [8].

Postoperative (including intraoperative) complications and morbidities are associated with common risk factors, such as smoking and alcohol consumption, advanced age, increasing body mass index (BMI), malnutrition, and preoperative heart problems [9]. Table 15.1 shows the major preoperative and intraoperative risk factors that can lead to intraoperative and postoperative complications.

Table 15.1 Intra–/postoperative complication and risk factors

Intraoperative and postoperative complications	Risk factors
Pneumonia	Poor oral hygiene
	Hyperbilirubinemia
	Reduced skeletal muscle mass
	Perioperative increase in mean arterial pressure
	Increased pH of esophagus
	Drinking consumption
Pulmonary complications	Smoking consumption
	Dysphagia
	Reduced perioperative expiratory flow
	Inflammation
	Prolonged surgery
Cardiovascular complications	Hypotension
	Blood loss
	Preoperative calcium channel blockers
	Preoperative angiotensin enzyme inhibitor and receptor blockers
	Increased preoperative brain natriuretic peptide
Renal complications	Intraoperative administration of colloids
	Increased creatinine levels
	Emergency surgery
Recurrent laryngeal nerve injury	Serial pleural amylase
	C-reactive protein
	3 lymph node dissection
	Thin diameter of recurrent laryngeal nerve
	Female sex
	Increased body mass index (BMI)
Anastomotic leak and stricture	Postoperative arrhythmias
	Ivor Lewis approach
	Advanced cancer stage
	Lower preoperative prealbumin
	Increased amylase drain
Gastroesophageal reflux	Malnutrition
	Advanced age
	Amount of unresected tumor
	Diabetes mellitus
	Compromised cardiopulmonary function
	Surgical trauma
	Use of antibiotics
	Use of antacids
	Open surgery
	Adenocarcinoma patients

In recent years, along with the increase in the number of older patients with cancer, as a consequence of the aging of the population, and the advances in surgical techniques and perioperative management, the treatment indications for positive surgery in older patients with esophageal cancer have been expanding. In addition to age-related decline in physical function, exercise tolerance, and respiratory function, older patients often have comorbidities, such as chronic obstructive pulmonary disease (COPD), heart failure, and diabetes mellitus. In such cases, the patients' reserve capacities for respiratory, circulatory, hepatic, and renal functions are already low prior to surgery; therefore, the risk of postoperative complications following esophagectomy, including pulmonary complications, deep vein thrombosis, delirium, and ICU-AW is increased, accompanied by difficulty with oral intake and poor nutritional status before surgery.

15.2.2 Postoperative Pulmonary Complications in Esophagectomy

15.2.2.1 Incidence Rate

In thoracoabdominal surgery for gastrointestinal cancers, such as esophageal, gastric, and colorectal cancers, the incidence rate of postoperative pulmonary complications (PPCs), including atelectasis and pneumonia, has been reported to be 5–30% [10, 11]. Contrarily, the incidence rate of PPCs has been reported to be 20%, even in minimally invasive esophagectomy reconstruction procedures [12]. PPCs, especially pneumonia, represent some of the most fatal and severe complications of esophagectomy. Indeed, 45.5–55.0% of in-hospital deaths after thoracoabdominal surgery occur due to PPCs, and they have a significant impact on postoperative outcomes, such as prolonged postoperative duration of hospitalization [13]. Although thoracoscopic esophagectomy reconstruction has been reported to be advantageous in improving postoperative pulmonary function and suppressing inflammatory responses, it has not yet been shown to reduce the incidence of postoperative complications [14]. Therefore, it is important to understand the pathogenesis mechanism underlying the risk of developing postoperative complications and to introduce rehabilitation as early as possible to prevent PPCs, with the aim to facilitate early discharge from the hospital, early return to society, and improvement in QOL.

15.2.2.2 Pathogenesis Mechanism

Respiratory System and Esophagectomy

In esophagectomy, general anesthesia, intraoperative mechanical ventilation, recumbent positioning during surgery, neuromuscular blockade, and the surgical approach all directly contribute to the pathophysiological effects on the respiratory system [15, 16]. These deleterious side effects can increase the susceptibility of patients to develop PPCs. The most significant factor in the development of PPCs is reduced lung volume, particularly functional residual capacity (FRC).

Lung Volumes and Atelectasis

The volume of air at the end of a normal tidal breath, the FRC, is dependent on the complex dynamic relationship between respiratory muscle tone, lung compliance, chest wall compliance, position of the thorax relative to gravity, and the pressure differential between the abdominal and thoracic cavities [17]. General anesthesia and neuromuscular blockade during surgery cause almost complete paralysis of the respiratory muscles, which alters the chest wall compliance and subsequently lowers the FRC [16]. A supine body position during surgery shifts the abdominal contents in a cephalad direction, further lowering the FRC [17].

Lung volumes are significantly reduced in the first week after abdominal and cardiothoracic surgery [18, 19], which is attributed to the large influence of these specific surgical procedures on respiratory mechanics, respiratory muscle dysfunction, and changes in intra-abdominal and thoracic pressures [20]. Although other surgical- and anesthetic-related factors, including impaired surfactant production, slowed mucociliary clearance [21], reduced central drive to breathe [20], and mechanical ventilation settings, can directly cause atelectasis [22], FRC reduction is considered to be the most important factor for atelectasis genesis and gas exchange deficiencies [23, 24].

Atelectasis resolves rapidly and without clinical consequences in almost all patients following peripheral surgery [18, 22]. Contrarily, half of all patients exhibit significant degrees of atelectasis 24 h after major abdominal or cardiac surgery, despite modern perioperative practices [19, 25, 26].

Pulmonary shunts, impaired gas exchange, and airway infection are direct consequences of extensive atelectasis [24]. In addition, severe atelectasis leads to increased load on the respiratory muscles, following which greater physical work is required by the respiratory muscles to generate the pleural pressure required to expand the less compliant lung tissue. Following major surgery, this problem is exacerbated by concurrent respiratory muscle weakness.

Respiratory Muscle Dysfunction

Following major abdominal and cardiothoracic surgery, the respiratory muscles demonstrate significantly diminished capacity to generate force with maximal inspiratory pressure, and peak cough flows are reduced 20–50% from preoperative measures [27–29]. Muscle weakness worsens on the first postoperative day and improves slowly with small daily incremental strength gains [30]. Even so, respiratory muscle weakness remains significantly less than the preoperative levels on hospital discharge and only normalizes within a month of major surgery [27].

The causes of postoperative respiratory muscle weakness are multifactorial and include the residual effects of intraoperative neuromuscular blockade [31], choice of reversal agent [32], inhibition of muscles via pain modulated motor neuron pathways, direct surgical insult, reduced consciousness affecting resting muscle tone and volitional use, and systemic inflammatory response to surgery [18].

The inevitable pathophysiological effects of major surgery on the respiratory system, including low FRC, atelectasis, and weakened respiratory muscles, can be attenuated by patient-related comorbidities (e.g., age, smoking history, existing

respiratory disease, obesity, malnutrition, and frailty) and surgery-related factors (e.g., length of anesthesia and blood transfusions). In susceptible patients, the deleterious effects of surgery on the respiratory system produce an environment conductive to reduced minute volume, impaired gas exchange [33], and microbial infection, which are the primary precursors to the development of PPCs [15, 16, 24].

Pneumonia and Its Causes

Pneumonia is one of the most severe postoperative complications of esophagectomy. Aspiration of oropharyngeal fluid with bacterial agents that attach to the mucosa of the lower respiratory tract can lead to pneumonia [34]. The most commonly reported pathogenic microbes involved in pneumonia are *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Xanthomas maltophilia* [35].

Prolonged operation time, dysphagia, drinking and smoking, and oral bacteria are significantly associated with the incidence of pneumonia. Some studies have shown that maintenance of oral hygiene before and after surgery by brushing the teeth and tongue, breathing training, and halting smoking can reduce the incidence of pneumonia [36, 37].

Additionally, perioperative increases in mean arterial pressure, pH, and low preoperative peak expiratory flow can predict postoperative pneumonia [38, 39].

Asala et al. reported a relationship between systemic inflammatory response syndrome (SIRS) and pneumonia in patients undergoing esophagectomy [37]. The overproduction of inflammatory cytokines is likely to activate adhesion molecules that assist the attachment of bacteria to the mucosa. These cytokines impair the integrity of the epithelium and assist bacterial colonization [37]. Interestingly, single-nucleotide polymorphism in IL-10 (-819 T/T) is associated with a greater incidence of postoperative pneumonia and decreased levels of postoperative IL-10 [40].

Older patients with malnutrition and reduced skeletal muscle mass (sarcopenia) have a high risk of developing postoperative pneumonia, which would reduce the overall survival rate following esophagectomy [41].

Pneumonia is associated with a decreased overall survival rate after esophagectomy. A therapeutic method known as “bundle therapy” has been suggested to treat pneumonia after esophagectomy [42]. Tracheostomy with ventricular assistance, hemodynamic support, enteral administration of food via a tube, and the use of antibiotics and expectorants can effectively treat complicated pneumonia and reduce the risk of other complications.

15.2.3 Sarcopenia and Esophagectomy Outcomes

Loss of weight and muscle mass can be recognized at diagnosis and progress during neoadjuvant therapy in patients at risk of sarcopenia and cancer cachexia [43]. Weight loss during neoadjuvant therapy and poor performance status predict postoperative complications and survival rate [44, 45]. Several algorithms are available for diagnosing sarcopenia. The 2019 Consensus Update on Sarcopenia Diagnosis

and Treatment by Asian Working Group for Sarcopenia state that sarcopenia can be diagnosed by walking speeds <0.8 m/s and/or handgrip strength <26 kg in men and <18 kg in women, in addition to muscle mass < 7.0 kg/m^2 (bioelectrical impedance analysis [BIA] and dual-energy X-ray absorptiometry [DXA]) in men and <5.7 kg/m^2 [BIA] or <5.4 kg/m^2 [DXA] in women [46]. Other performance measures for sarcopenia include the Short Physical Performance Battery (SPPB), which evaluates balance, gait speed, and lower limb strength; the Timed-Up and Go test (TUG); and the Stairs Climb test [47].

Handgrip strength <25 kg and sarcopenia are both associated with greater mortality, morbidity, prolonged length of hospital stay, and slower progression to oral intake following esophagectomy [48, 49]. Moreover, muscle wasting during neoadjuvant chemoradiotherapy is associated with chemotherapy-induced toxicity and postoperative mortality [50]. The median survivals of patients with a SPPB score of 7–9 and ≥10 points were 10.5 and 13.4 years, respectively, compared with 5.0 years in patients with SPPB ≤6 points [51].

15.2.4 Cardiopulmonary Function and Esophagectomy Outcomes

Several previous studies have reported an association between cardiopulmonary function and esophagectomy outcomes. Liedman et al. reported that a working capacity <80 W was associated with high postoperative mortality in patients aged >65 years undergoing surgery for gastroesophageal cancer [52]. In a report by Nagamatsu et al., preoperative VO_{2max} correlated with cardiopulmonary complications, and a VO_{2max} > 800 mL/min/m^2 cut-off point to determine surgical candidacy was proposed in patients undergoing esophagectomy [53]. However, some studies have reported no association between the VO_2 peak and postoperative outcomes. In a cohort study of 78 patients who underwent esophagectomy, the preoperative VO_2 peak was low in patients developing PPCs, but anaerobic threshold (AT) <11 mL/min/kg could not predict morbidity, and no other predictive value could be clarified [54]. A previous study showed that AT <9 mL/min/kg might predict cardiopulmonary complications, although its clinical application was limited due to a weak sensitivity of 74% and specificity of 57% [55]. Moreover, a preoperative shuttle walking test >340 m was associated with postoperative survival at day 30 in patients undergoing esophagectomy [56].

15.2.5 Clinical Practice of Rehabilitation in Esophagectomy

In the perioperative and postoperative periods of esophagectomy, it is important to prevent PPCs, disuse syndrome, and other postoperative complications to improve ADL and QOL by providing seamless rehabilitation. Rehabilitation should be provided under the intervention of a multidisciplinary medical team from the time of preoperative outpatient visit to postoperative recuperation at home after discharge from the hospital. A conceptual diagram of the clinical rehabilitation protocol for esophagectomy is shown in Fig. 15.1.

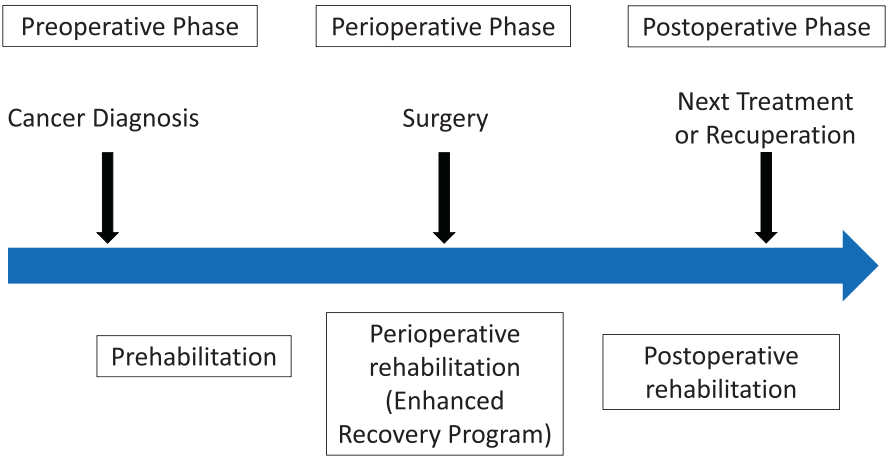

Fig. 15.1 Conceptual diagram of clinical rehabilitation protocol in esophagectomy

15.2.5.1 Preoperative Rehabilitation (Prehabilitation)

Definition and Components of Prehabilitation

Patients with esophageal cancer have a high preoperative risk of developing PPCs, with risk factors including advanced age, smoking and alcohol consumption, low respiratory function, malnutrition, dyspepsia, and low immune function due to preoperative chemotherapy and radiotherapy. In particular, older patients are more likely to have sarcopenia and frailty preoperatively than younger patients. It has been reported that older patients with esophageal cancer with preoperative sarcopenia and frailty not only have an increased incidence of postoperative complications but also have adverse effects on postoperative outcomes, such as increased unplanned hospital readmission rate and shortened overall and disease-free survival [57, 58]. Moreover, it has been reported that preoperative frailty (physical and social frailty) is associated with overall survival and cancer-specific survival among older patients with gastrointestinal cancer [59].

Recently, prehabilitation has been proposed for surgical settings and has emerged as a promising component of oncology care. Prehabilitation has the potential to improve rehabilitation outcomes and be cost-effective by helping patients with cancer avoid increased hospital stays and unplanned readmissions as well as prevent postoperative complications, improve survival rate, shorten length of hospital stay, reduce readmission rate, and reduce medical costs by improving physical and psychological functions, ADL, and QOL.

Prehabilitation is defined as follows:

> "A process on the cancer continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment and includes physical and psychological assessments that establish a baseline functional level, identify impairments, and provide interventions that promote physical and psychological health to reduce the incidence and/or severity of future impairments" [60].

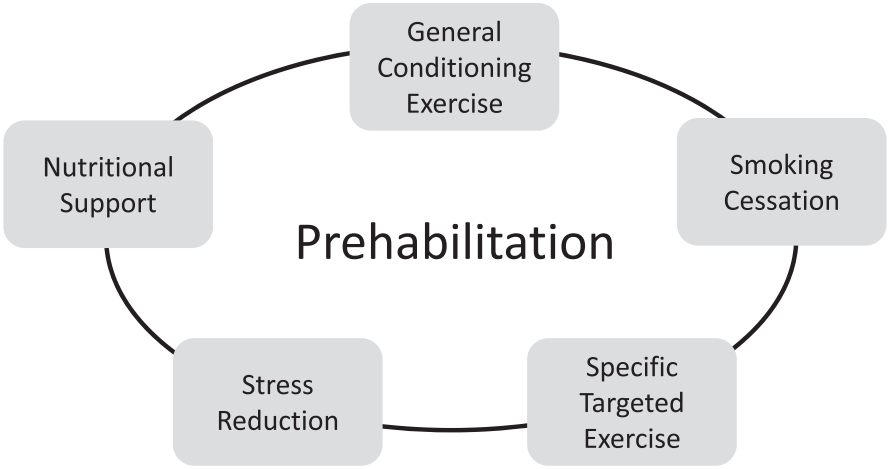

Fig. 15.2 Multimodal components of prehabilitation

Prehabilitation studies and clinical practices have tended to focus mainly on exercise as the primary modality. However, in 2016, a panel of U.S. and Canadian subject matter experts evaluated both unimodal and multimodal approaches [61]. The panel identified four other prehabilitation components in addition to general conditioning exercise, including nutritional support, smoking cessation, stress reduction, and specific targeted exercise (Fig. 15.2). The previous studies targeted for patients with colorectal cancer showed that the unimodal exercise prehabilitation protocol was not effective in increasing functional capacity prior to surgery, whereas the multimodal prehabilitation protocol was [62, 63].

Exercise is considered the primary component of cancer prehabilitation. In the prescription of exercise, recommendations by the American Cancer Society are referred to [64]. In the guidelines, exercise of at least 75 min/week of vigorous intensity or at least 150 min/week of moderate intensity is recommended [64], with many clinicians using this recommendation. However, there are no other guidelines that focus on individual patient factors, functional impairments, comorbidities, treatment side effects, and sequelae. More targeted exercise programs should be considered for each cancer treatment setting and phase. Further research on the level of exercise intensity and its effectiveness is needed.

Nutrition is a multimodal prehabilitation component that leads to successful surgical outcomes. The expert consensus of the North American Surgical Nutrition Summit recommended that nutrition therapy should be provided not only in the setting of malnutrition but also in the preventive preoperative setting for at-risk patients [65]. Nutritional support, especially protein supplementation, in the prehabilitation phase is essential to prepare for high-stress surgery [66].

Smoking cessation is another component of multimodal prehabilitation to improve surgical outcomes. Smoking cessation in the preoperative phase reduces the risk of postoperative complications and improves functional conditions and QOL. Contrarily, smoking during cancer treatment results in an increased risk of

postoperative complications, impaired surgical wound healing, increased risk of adverse events of adjuvant chemotherapy and radiotherapy, and increased incidence of cancer recurrence and second primaries [67].

The strategy of stress reduction prior to surgery is another important component that has been associated with better surgical outcomes. Psychological factors such as anxiety and depression have been associated with prolonged hospitalization and poor compliance with cancer treatment [68, 69]. Bradt et al. reported that music therapy may reduce anxiety, pain, and sympathetic arousal in patients undergoing surgery [70].

Efficacy of Prehabilitation in Esophagectomy

It has been reported that the incidence of PPCs is lower in patients who could maintain higher preoperative physical activity levels and better respiratory function than in those who could not [45]. Therefore, it is thought that prevention of PPCs will also promote physical activity and improve respiratory function by prehabilitation prior to esophagectomy; however, there are limited data on the efficacy of prehabilitation for reducing postoperative complications in esophagectomy.

With regard to the effect of prehabilitation on the prevention of PPCs in esophagectomy, Halliday et al. reported that a preoperative personalized and home-based exercise program, consisting of muscle strength training and aerobic exercise, prevented PPCs, and the participation in prehabilitation was associated with a 77% reduction in cases of postoperative pneumonia [71]. In an article by Inoue et al., comprehensive respiratory rehabilitation (muscle strength training, respiratory training, aerobic exercise, etc.) for >7 days preoperatively was also shown to prevent PPCs [72]. Similarly, Yamana et al. showed the efficacy of preoperative respiratory rehabilitation for >7 days in reducing PPCs [73]. A recent study by Zylstra et al. documented that structured prehabilitation exercise during neoadjuvant chemotherapy improved tumor regression and downstaging, highlighting a new possibility of prehabilitation [74].

These reports support the efficacy of prehabilitation on reducing PPCs in esophagectomy, but further research is necessary to clarify these findings.

15.2.5.2 Perioperative Rehabilitation

The main purpose of perioperative rehabilitation after esophagectomy is to prevent postoperative complications, such as PPCs, disuse syndrome, delirium, and ICU-AW, and to recover patients' postoperative physical function, ADL, and QOL. In particular, prevention of delirium and ICU-AW is essential because they not only cause a temporary decline in physical and psychological functions but also have long-term adverse events such as prolonged length of hospital stay and increased mortality. An overview of delirium and ICU-AW is presented below.

Notable Postoperative Complications in Esophagectomy

Delirium

Delirium is defined as an acute decline in cognitive function, which tends to occur in older patients during hospitalization and is particularly prevalent in surgical and ICU settings [75]. Among patients with gastrointestinal cancer, 15–24% develop postoperative delirium [76, 77]. While a single factor may lead to delirium, delirium is more commonly multifactorial in older persons. The multifactorial model for the etiology of delirium has been well validated and widely accepted. The development of delirium involves a complex interrelationship between a vulnerable patient with multiple predisposing factors and exposure to precipitating factors. The predisposing factors predispose patients to delirium, and the precipitating factors induce, worsen, and prolong delirium [75] (Table 15.2). It is important to recognize preoperatively that patients with predisposing factors are at high risk for delirium, so as to remove triggering factors such as physical restraints and indwelling bladder catheters from the early perioperative period, and to promote early mobilization.

As delirium is a fluctuating brain dysfunction, it is essential to continuously assess and monitor it after surgery for early detection and treatment. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [78] and Intensive Care Delirium Screening Checklist (ICDSC) [79] are available screening tools for delirium.

Table 15.2 Predisposing factors and precipitating factors of delirium

Predisposing factors	Precipitating factors
Dementia	Medications
Cognitive impairment	Multiple medications add
History of delirium	Psychoactive medication use
Functional impairment	Sedative-hypnotics
Vision impairment	Use of physical restraints
Hearing impairment	Use of bladder catheter
Comorbidity/severity of illness	Physiologic
Depression	Elevated serum urea
History of transient ischemia/stroke	Elevated BUN/creatinine ratio
Alcohol abuse	Abnormal serum albumin
Older age	Abnormal sodium, glucose, or potassium
	Metabolic acidosis
	Infection
	Any iatrogenic event
	Surgery
	Aortic aneurysm
	Noncardiac thoracic
	Neurosurgery
	Trauma admission
	Urgent admission
	Coma

Table 15.3 ABCDE bundle

A: Awaken the Patient Daily: Sedation Cessation
B: Breathing: Daily Interruptions of Mechanical Ventilation
C: Coordination: Daily Awakening and Daily Breathing Choice of Sedation or Analgesic Exposure
D: Delirium Monitoring and Management
E: Early Mobility and Exercise

ICU-Acquired Weakness (ICU-AW)

The term "ICU-AW" designates clinically detected weakness in critically ill patients in whom there is no plausible etiology other than a critical illness [80]. It is diagnosed according to the diagnostic criteria for ICU-AW [81]. The incidence rate of ICU-AW is approximately 50% in patients with sepsis, multiple organ failure, and long-term ventilation [82]. The development of ICU-AW affects short- and long-term outcomes, including delayed weaning from the ventilator, increased mortality, long-term functional decline, and decreased health-related QOL [83, 84]. As the risk of developing ICU-AW increases in patients with postoperative complications after esophagectomy, a multidisciplinary medical team should take an approach based on the ABCDE bundle to prevent ICU-AW [85] (Table 15.3).

Postoperative Symptom Management

Early mobilization is a key strategy to prevent postoperative complications; however, there are barriers to mobilization following esophagectomy, including pain, hypotension, painful or restrictive attachments, and subconsciousness. Timely removal of drains and attachments and early discharge from the critical care environment are necessary for mobility progression. The most common barriers following esophagectomy are inadequate pain control, cardiac instability, and multiple attachments, such as nasogastric tubes and chest drains. Cardiovascular issues include arrhythmias, particularly atrial fibrillation, and peak in incidence at POD3. Rehabilitation staff should carefully plan mobility practice after esophagectomy to ensure adequate staff support, access portable monitoring equipment, and careful handling of medical attachments [87]. Assessment of the cardiac reserve, epidural sequelae, and motor block should be recorded at baseline. The outcomes recorded during mobilization included pain, exercise intensity, and mobilized distance.

Early mobilization

Postoperative rest is necessary for postoperative healing, including conservation of metabolic resources used for the recovery of organ functions impaired by surgical invasion and increased oxygen delivery to the impaired organ due to decreased muscle oxygen consumption. However, excessive bed rest not only decreases physical and respiratory functions but also causes various postoperative complications, such as decreased bowel movement, development of delirium and deep vein thrombosis, making the patient's condition more severe; therefore, mobilization should be started as early as possible after esophagectomy.

Early mobilization is defined as any low intensity of movement that aims to optimize cardiopulmonary function, including moving in bed, sitting out of bed, standing, and ambulating on the spot or in a hallway [86]. Mobilization involving an upright position utilizing the effect of gravity increases respiratory function to the greatest extent, so extended periods of sitting out of bed are encouraged after esophagectomy [87]. High sitting or a Fowler position, in which the head of the bed is elevated to 45°, is recommended to reduce post-esophagectomy gastroesophageal reflux [88]. Gastroesophageal reflux is described in up to 80% of patients after esophagectomy, is often worse in the supine than in the standing position, and can compromise the integrity of the anastomosis [89]. High sitting, particularly sitting out of bed, optimizes basal ventilation/perfusion matching [90] and is applied prophylactically after esophagectomy to prevent postoperative complications such as atelectasis. A structured postoperative mobilization program is recommended; however, studies examining the benefits of early mobilization after esophagectomy are lacking, and recommendations are based on the best clinical practice. Recommendations for POD1 range from sitting out of bed for ≥2 h to short-distance walks (10 m). Generally, on POD7, patients should be mobilized independently and suitable for discharge, but clinician judgment should be used to alter and progress therapy based on the individual [91].

Delayed mobilization increases postoperative morbidity and complications [92]. In Haines's report, the risk of PPCs increased threefold for each day patients did not mobilize >10 m from the bed [92].

15.2.6 Multidisciplinary Medical Team Approach in Esophagectomy

Esophagectomy has been associated with unacceptable morbidity and mortality rates. A multidisciplinary medical team approach is essential to prevent postoperative complications and promote early recovery. The enhanced recovery after surgery (ERAS) protocol, also called Fast track, is one of the most beneficial strategies [93]. The ERAS protocol aims to improve perioperative care, minimize complications, and accelerate recovery; it shows promise for achieving better perioperative outcomes. The ERAS is a multidisciplinary team approach involving surgeons, anesthesiologists, critical care physicians, physiotherapists, nutritionists, nurses, medical/clinical engineers, and so forth, in the perioperative care of the patient and integrating evidence-based protocols into clinical practice. This multimodal approach has been shown to reduce the surgical stress response, shorten the length of hospital stay, decrease morbidity, and expedite recovery [94]. Moreover, the implementation of the ERAS protocol has decreased the medical cost of the overall treatment without compromising outcomes [95].

The ERAS components straddle the preoperative, intraoperative, and postoperative periods, and they need to be seen in continuum and not as isolated elements.

Table 15.4 Components of ERAS protocol

Phase	Preoperative	Intraoperative	Postoperative
Intervention	Preadmission counseling	Use of short-acting anesthetic agents	Continued use of epidural anesthesia
	Fluid and carbohydrate loading	Use of epidural anesthesia	Avoidance of nasogastric tubes
	Avoiding prolonged fasting	Avoidance of drains and indwelling catheters, if possible	Appropriate management of postoperative nausea/vomiting
	Selective use of bowel preparation	Minimizing intravenous fluid administration	Minimizing intravenous fluid administration
	Appropriate antibiotic prophylaxis	Maintenance of normothermia	Early removal of drains and indwelling catheters, if possible
	Thromboprophylaxis		Early enteral nutrition
			Use of non-opioid analgesics
			Early mobilization
			Audit and feedback of processes of care

The components of the protocol in esophagectomy include preoperative nutrition, prehabilitation, counseling, smoking and alcohol cessation, cardiopulmonary evaluation, surgical technique, anesthetic management, intra- and postoperative fluid management and pain relief, mobilization and physiotherapy, enteral and oral feeding, removal of drains, and several other components [96] (Table 15.4).

Evidence regarding the ERAS protocol for esophagectomy is limited. As there were no standardized guidelines until 2018, previous studies addressing the feasibility of the ERAS in esophagectomy have examined various protocols with different ERAS components.

Despite being a multidisciplinary medical team approach, the ERAS protocol prevented PPCs in esophagectomy [97]. A systematic review by Findlay et al. reported favorable morbidity, mortality, and length of hospital stay but concluded that the evidence was weak and incomplete [98]. A meta-analysis by Pisarska et al. showed that the ERAS protocol shortened the duration of hospital stay and reduced postoperative nonsurgical and pulmonary complications but did not decrease overall morbidity, mortality, and unplanned readmission rates [99]. As ERAS protocol guidelines in esophagectomy have been published by the ERAS society, it is possible to easily refer to the details of integrating evidence-based protocols and multimodal clinical practice [100].

15.3 Conclusion

To prevent postoperative complications, maintain and improve physical function, ADL and QOL, and reduce morbidity and mortality following esophagectomy, integrating evidence-based and multimodal clinical practice including adequate

assessment and seamless management and care by the multidisciplinary team approach are important in all phases, including the preoperative, intraoperative, and postoperative phases. However, evidence on the efficacy of interventions in patients undergoing esophagectomy is limited, and further research should be performed.

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Cancer-Related Lymphedema and Obesity

16

Akinori Sato and Masaya Kawada

Abstract

Edema is an abnormally increased volume of interstitial fluid, and there are various causes of it. In particular, lymphedema due to lymphatic obstruction, which is closely related to cancer, will be reported, and the role of physical therapists in its treatment will be discussed. Some reports indicate that lymphedema occurs 15–20% of the time after breast cancer surgery and about 25% of the time after gynecologic cancer surgery. However details on the cause and duration of lymphedema are unknown. Treatment of lymphedema can be broadly classified into surgical and conservative treatments, and the effectiveness of each treatment method has been reported. Obesity has been widely reported to be involved in the development and exacerbation of lymphedema and may be a risk factor associated with the development of upper extremity lymphedema after breast cancer surgery. Clinically, it is known that fat cells proliferated and enlarged by obesity compress capillary lymph vessels and blood vessels, stagnating lymphatic movement and causing edema, but there are many causes for the development of edema. Adipocytokines, a group of protein factors secreted by white fat cells, have been reported to perform various functions. Among them, this time we focused on leptin. Comparison of leptin concentration between nonobese (10 ng/mL) and obese (100 ng/mL) subjects has shown that leptin concentration-dependent lymphatic vessel structure cannot be demonstrated and that tube formation is reduced. The suggestion that obesity may be involved in the development

A. Sato (✉)
Department of Physical Therapy, Faculty of Human Science, Hokkaido Bunkyo University, Eniwa, Japan
e-mail: a-sato@do-bunkyodai.ac.jp

M. Kawada
Division of Breast Surgery, KKR Sapporo Medical Center Tonan Hospital, Sapporo, Japan
e-mail: kawada@tonan.gr.jp

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and exacerbation of lymphedema in vivo and in vitro indicates that physical therapists are experts in managing this disease by providing appropriate and effective physical therapy based on adequate evidence of exercise therapy for obesity.

Keywords

Lymphedema · Obesity · Leptin · Combined treatment

16.1 Edema

Edema is an abnormally increased amount of interstitial fluid in spaces between supporting tissues, including the cellular tissue components, venous system (capillaries and lymphatic vessels), and collagen fibers. When generalized edema is recognized in clinical situations, the increase in interstitial fluid is 2–3 L, with increased interstitial pressure.

16.2 Causes and Characteristics of Edema

There are various causes of edema, and the mechanisms underlying the causes can be broadly classified into the following categories: (1) increased hydrostatic capillary pressure, (2) hypoalbuminemia, (3) increased capillary permeability, and (4) increased subcutaneous and interstitial osmotic pressure and lymphatic obstruction [1].

Edema is classified into local and systemic edema; a list of typical diseases is presented in Table 16.1. Recognizing the underlying disease that causes edema and reducing or eliminating it via context-specific treatment are essential. Therefore, treating the cause is the first step. Exercise therapy and lifestyle guidance provided

Table 16.1 Mechanisms underlying causes of edema and typical diseases

Increase in capillary hydrostatic pressure	Systemic edema	Cardiac failure, disuse, renal failure, venous obstruction, drug-induced edema, pregnancy and premenstrual edema, idiopathic edema, etc.
	Localized edema	Venous obstruction
Hypoalbuminemia	Systemic edema	Cirrhosis (decreased production), hypovolemia (decreased production), nephrotic syndrome (increased excretion), malignant edema (increased consumption), infection (increased consumption), etc.
Increased vascular permeability	Systemic edema/ localized edema	Vasculitis, inflammation, allergy, angioedema, burns
Increased subcutaneous and interstitial osmotic pressure and lymphatic obstruction	Systemic edema	Hypothyroidism, malignant lymphoma, and lymph node metastasis of malignant tumors
	Localized edema	Postoperative lymph node dissection, filarial infection

by physical therapists are not always the first treatment choice; however, they play a very important role in treating edema.

We report about lymphedema caused by lymphatic vessel obstruction because of its close association with cancer and assess physical therapists' role in treating this condition.

16.3 Lymphedema

Lymphedema affects more than 200–300 million people worldwide; however, its causes are unknown. Lymphedema can be broadly divided into primary and secondary lymphedema [2]. Primary lymphedema refers to cases in which no specific causative disease can be identified; however, it has been reported that a congenital disease owing to a genetic abnormality or other causes may be involved (cases in patients aged <35 years are called early onset, and those in patients >35 years are called late onset). In contrast, secondary lymphedema is caused by trauma, filarial infection, deep vein thrombosis, or malignant tumor exacerbation.

Lymphedema caused by filarial infection is transmitted via mosquito sucking and affects approximately 51 million people in tropical and subtropical developing countries, with 863 million people at risk [3]. There have been no such cases in Japan since 1978. The most common cause of lymphedema in Japan is postoperative cancer in patients with secondary edema. In addition, lymphedema is associated with cancer treatments such as lymph node dissection, postoperative irradiation, and taxane drugs, accounting for 80% of all lymphedema cases. However, the causes of lymphedema are unknown. Some reports revealed that there is a 15–20% probability of lymphedema occurring after breast cancer surgery and approximately 25% after gynecological cancer surgery. Furthermore, lymphedema develops within 5 years postoperatively; however, several patients have developed lymphedema ≥20 years postoperatively and had to report for treatment. Lymphedema diagnosis and evaluation are not well documented and therefore underestimated.

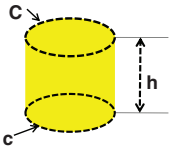
16.4 Diagnosis and Evaluation of Lymphedema

Lymphoscintigraphy is used for the definitive diagnosis of lymphedema and is recommended by the International Society of Lymphology (ISL). In Japan, reimbursement applications have been available since 2018. Furthermore, fluorescent lymphangiography with indocyanine green dye (ICG) can be used with a photodynamic eye to observe the running and functional dynamics of superficial lymphatic vessels. Dermal backflow associated with valve regurgitation in the ductus deferens can be identified as a finding specific to lymphedema (not covered by insurance). However, at present, only a few facilities have the capability to perform any of the imaging tests listed here. Therefore, measurement of limb circumference is used in routine practice in no small numbers for diagnosis and therapeutic evaluation of lymphedema, and it is essential to ensure that patients learn self-measurement as part of their preoperative self-care during lymphedema guidance and management. It is essential to ensure that patients learn self-measurement as part of their preoperative

self-care during lymphedema guidance and management. Circumferential measurements of the extremity, which are generally performed by physical therapists, can only confirm an increase or decrease in edema at the evaluation site but can also assess the left-right difference in edema and the rate of improvement. Furthermore, the increase or decrease in edema can be determined from the approximate value of volume. The Casty-Smith method for calculating the approximate volume (mL) is shown in Fig. 16.1a. In addition, Fig. 16.1b shows how to calculate the improvement rate (%) of unilateral edema. Although neither of these figures is precise, they provide a rough indication of the approximate improvement. These evaluations are not limited to lymphedema evaluation but can be used for general edema improvement status. Lymphedema staging and unilateral lymphedema severity classification are shown in Table 16.2. This severity classification was used to compare patients with healthy side before and after surgery or owing to changes in the condition.

Estimated Volume and Percentage Improvement of Edema

a Estimated Volume (ml)



$$\text{Volume (ml)} = \frac{h\,(C^2 + Cc + c^2)}{12\,\pi}$$

C: Circumferential value (Central)
c: Circumferential value (peripheral)
h: height (length)

b Improvement rate (%)

$$= \frac{\text{Volume before treatment (affected side) - Volume after treatment (affected side)}}{\text{Volume before treatment (affected side) - Volume of healthy side}} \times 100$$

Fig. 16.1 (**a**) Estimated volume and (**b**) percentage improvement of edema

Table 16.2 Lymphedema staging and unilateral lymphedema severity classification

(a) Lymphedema staging	
Stage 0	A latent or asymptomatic condition in which lymphatic fluid transport is injured but edema is not evident.
Stage I	Interstitial fluid with a relatively high protein content is present, but it is still in the early stages and subsides with the elevation of the extremity. Indentations may be observed.
Stage II	Early stage: Tissue swelling rarely improves with the elevation of the extremity alone, and indentations are evident. Late stage: Tissue fibrosis is observed, and no indentation is noted.
Stage III	In addition to lymphatic stasis elephantiasis in which no indentation is noted, skin changes such as skin thickening and fatty deposits may be observed.
(b) Unilateral lymphedema severity classification	
Mild	<20% edema
Moderate	20–39% edema
Severe	>40% edema

Modified from ISL

16.5 Lymphedema Treatment

Lymphedema treatment can be broadly classified into surgical and conservative treatments. The representative conservative treatment is complex decongestive physiotherapy (CDP) or complex physical therapy (CPT). This therapy's effectiveness has been reported, and CPT is recommended by the ISL [4]. CPT's importance has been reported in Japan and is the first treatment choice. CPT refers to the following four treatment methods: (1) "skin care" to manage skin conditions, (2) "manual lymph drainage" to induce lymphatic flow, (3) "compression therapy" using elastic bandages and special clothing, and (4) "exercise therapy under compression" using a muscle pump to promote lymphatic fluid flow. These four treatment methods were used in this study. Although these therapies remain the mainstay of treatment, it does not mean that the best conservative treatment is provided only when CPT is used. Therefore, considering the prevalence of treatment and various circumstances, the Lymphedema Training Committee of the MHLW's Lymphedema Project decided that the current standard treatment for lymphedema is "complex therapy" comprising conservative treatment centered on CPT, daily life guidance, and other measures. This includes avoiding prolonged standing and housework, elevating the affected limb as necessary, maintaining normal body weight, and providing nutritional guidance because obesity is a cause of the onset and aggravation of lymphedema.

Treatment effects and evidence for each CD item have not been discussed in this report because they are specifically related to obesity; however, the evidence for the upper limb is currently better established than that for the lower limb.

16.6 Lymphedema and Weight Gain (Obesity)

Fatty lymphedema is a cause of secondary lymphedema [5, 6]. In Japan, there are few reports of such cases; however, in other countries, the incidence of fatty lymphedema is approximately 50% of all edema cases. Fatty lymphedema is caused by excessive weight gain. It has been widely reported that weight gain (obesity) is involved in developing and aggravating lymphedema. Brorson and Svensson reported that there is sufficient evidence that tissue swelling in lymphedema occurs because of fat deposition and fluid accumulation. They further reported that excess adipose tissue in the affected limb might develop in chronic lymphedema after breast cancer surgery [7].

Although the data are a bit old, among 28 women hospitalized for breast cancer surgery who underwent axillary lymph node dissection in 2012, 5 developed upper extremity lymphedema from the postoperative period to March 2016 and 23 had no lymphedema. In this study, five factors associated with developing upper extremity lymphedema (age, body mass index [BMI], estrogen receptor [ER], progesterone receptor [PgR], and low-density lipoprotein cholesterol [LDL-C]) were analyzed as risk factors for developing upper extremity lymphedema. Although there were no significant differences in age, ER, PgR, and LDL-C between patients with and

Table 16.3 Factors associated with the development of lymphedema

	Total number of patients with axillary lymphedema ($n = 28$)	No lymphedema ($n = 23$)	Objective lymphedema ($n = 5$)	P-value
Age (years)	63.4 ± 12.8	62.8 ± 11.1	63.6 ± 13.4	n.s.
BMI ≥25 kg/m^2	9 (32%)	5 (22%)	4 (80%)	$P = 0.047$
ER	15 (60%)	12 (52.2%)	3 (60%)	n.s.
PgR	14 (50%)	8 (35%)	3 (60%)	n.s.
LDL-C ≥140 mg/dL	6 (21.4%)	4 (17%)	2 (40%)	n.s.

Data for age are presented as mean ± SD
Body mass index (BMI) and number of participants with BMI >25 kg/m^2 are shown; estrogen receptor (ER) and progesterone receptor (PgR) are shown as the number of positive participants
Low-density lipoprotein cholesterol (LDL-C) is reported for people having levels over 140 mg/dL

without lymphedema, four of five (80%) patients with upper extremity lymphedema had significantly higher BMI than those without lymphedema (Table 16.3). In this study, height was self-reported at admission, and weight was measured to calculate BMI. The World Health Organization defines BMI of ≥30 kg/m^2 as obese [8]; however, a BMI of ≥25 kg/m^2 in Japan is classified as obese considering the percentage of the obese population.

Accordingly, overweight (obesity) is considered a risk factor associated with developing upper extremity lymphedema after breast cancer surgery. Therefore, the Guidelines for Lymphedema Treatment (2018) was created in Japan, and it was mentioned that obesity is "almost certain" to be a risk factor for secondary lymphedema in the upper limbs. However, there was no evidence of this in the lower extremities. Moreover, there is little evidence regarding the lower extremities, and further research is needed [9]. Contrary to the reported involvement of obesity in upper extremity lymphedema, the manner in which this disease is exacerbated in patients who have already developed it and subsequently become obese remains unclear.

16.7 Mechanisms of Obesity and Lymphedema Development

We summarized the relationship between obesity and lymphedema development, especially in the upper extremities. There are reports overseas that >50% of edema is fatty. First, from a clinical point of view, it is known that fat cells that proliferate and increase in size because of obesity compress capillary lymph vessels and blood vessels, stagnate lymph vessel movement (blood vessels), and prevent body fluid and lipid transport, leading to a more vicious circulatory function and causing edema [10]. This knowledge can be obtained by studying lymphedema causes in Japan.

Figure 16.2 shows lymphatic vessels collected from the peribreast area of a patient who underwent total mastectomy and lymph node dissection. Figure 16.2a shows a preoperative computed tomography image of a patient with left breast

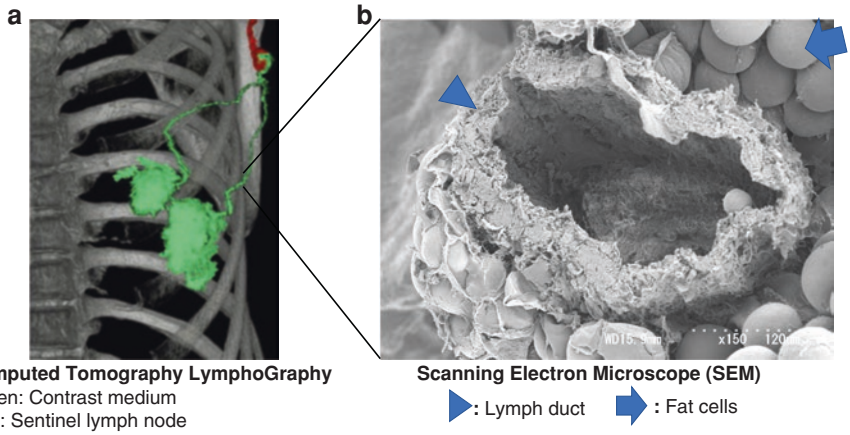


Fig. 16.2 Cross-sectional view of lymph vessels and the surrounding area. (**a**) Computed tomography lymphography. (**b**) Scanning electron microscope (SEM)

cancer used to identify the sentinel node. Green indicates the area around the contrast medium injection, with the image showing the contrast medium movement into the small ducts. Red indicates that the first lymph node was reached, and the examination showed a sentinel node. Figure 16.2b shows a cross-sectional image of the lymphatic vessels obtained using a scanning electron microscope (SEM) after trimming the sampled lymphatic vessels' surrounding tissues. Large lymphatic vessels are surrounded by smooth muscles that perform the vessels' automatic movements and other functions. Smooth muscle is unique because it does not exist in capillary lymph vessels. The arrows in the image indicate adipocytes, and it has been reported that obesity causes adipocyte proliferation and enlargement and lymphatic vessel compression. In addition, it has been reported that obesity causes inflammation, thus preventing lymphedema improvement [11]. Kataru et al. reported that macrophages regulate lymphatic vessels and perform various functions such as inflammation, immunity, and tissue repair [12]. There are two types of macrophages: classically activated macrophages (M1), which highly express inflammatory cytokines and are involved in T-cell activation and participate in stress production, and alternatively activated macrophages (M2), which highly express anti-inflammatory cytokines and suppress inflammatory cytokines and participate in stress production by M1 macrophages. In addition, M2 macrophages inhibit T-cell proliferation and tissue repair. However, it acts in angiogenesis and immunosuppression and promotes tumor growth. Most macrophages infiltrating the tumor tissue are M2 macrophages. It has been reported that the degree of infiltration correlates with malignancy in many tumors. M2 macrophages are generally predominant in healthy adipose tissue, whereas obese adipose tissue has fewer M2 macrophages and more M1 macrophages. This is often reported in patients with diabetes and other patients who report that fat reduces M2 macrophage expression and explosively increases M1 macrophages. It was also reported that M1

Table 16.4 Characteristics of macrophages in adipose tissue (M1/M2)

	Classically activated macrophage (M1)	Alternatively activated macrophage (M2)
Distribution in adipose tissue	Clustering hypoxic area and forming crown-like structures	Distributed ubiquitously
Changes in obesity	Dramatically increase	Slight increase
Role in adipose tissue microenvironment	Enhancing inflammation inhibiting angiogenesis	Regulation of adipocyte progenitors

macrophages surround necrotic adipocytes, creating crown-like structures, and M2 macrophages are reduced for macrophages residing in the stroma. Conversely, in lymphedema, the crown-like structures in which macrophages in the interstitium surround necrotic adipocytes are believed to be due to excessive lymph fluid accumulation in the interstitial fluid, thereby inhibiting M1 migration capacity. Table 16.4 describes the general M1/M2 macrophage characteristics in obesity.

Other reports of increased fat deposition and fat thickness owing to surgery, increased lymphedema volume owing to inadequate drainage, and skin tissue fibrosis in lymphedema indicate that lymphedema is not merely an effect of lymphatic compression by fat cells, particularly in chronic lymphedema; it has been reported that lymphatic flow stagnation causes chronic inflammation, resulting in protein accumulation and tissue fibrosis [13].

16.8 Role of Fat

Actual fat cells can be broadly classified into white fat cells, which store fat, and brown fat cells, which burn fat [14, 15]. White fat cells are problematic in obesity, and their number is reported to be as high as approximately 80 billion, although it varies depending on the degree of obesity. White fat cells store and break down fat, supplying it to the entire body when energy is needed. They also play various other roles such as insulating the body to maintain temperature and internal organs. Adipocytokines, a group of protein factors secreted by white fat cells, have been reported to perform various functions [16]. Adiponectin inhibits diabetes, atherosclerosis, and inflammation. Leptin regulates feeding and heat production; visfatin has antidiabetic effects; and adipose tissue provides good bodily functions. Conversely, when white fat cells proliferate and increase because of obesity, adipose tissue deteriorates, and angiotensin II, which originally had the good function of supplying oxygen to the cell ends, is secreted in increased amounts, increasing blood pressure and causing hypertension. In addition, increased tumor necrosis factor-α secretion impairs insulin function and is associated with diabetes onset, whereas monocyte chemoattractant protein-1 and free fatty acids increase in fat cells and blood and are involved in arteriosclerosis onset and worsening. The functions of adipocytokines secreted by white adipocytes are shown in Fig. 16.3. We focused on leptin among adipocytokines in this study because in addition to its previously reported actions such as appetite suppression, energy metabolism renewal, and blood pressure elevation, there is a new report that it is involved in

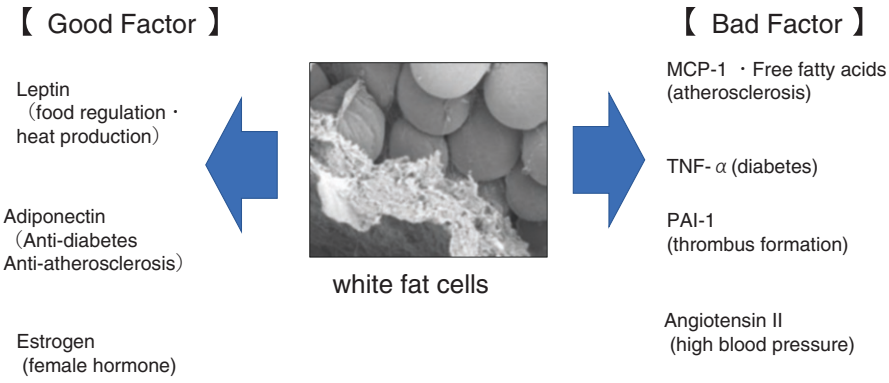


Fig. 16.3 Main function of white fat cells

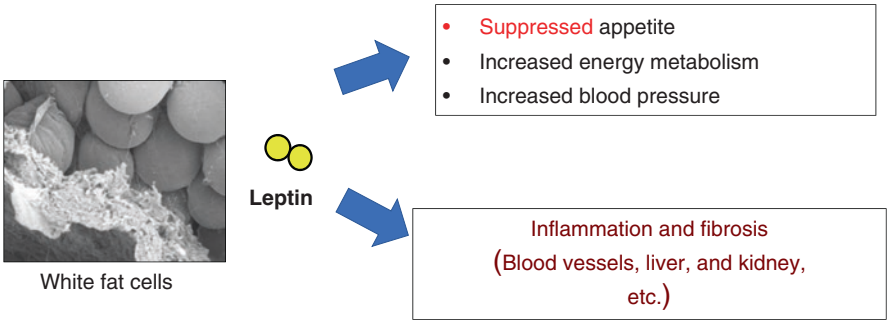
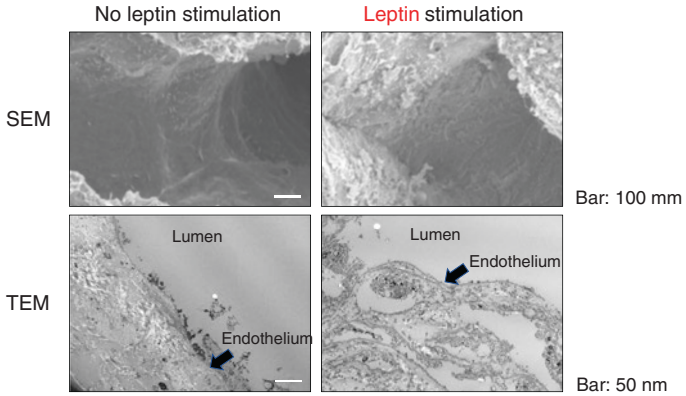


Fig. 16.4 Role of leptin

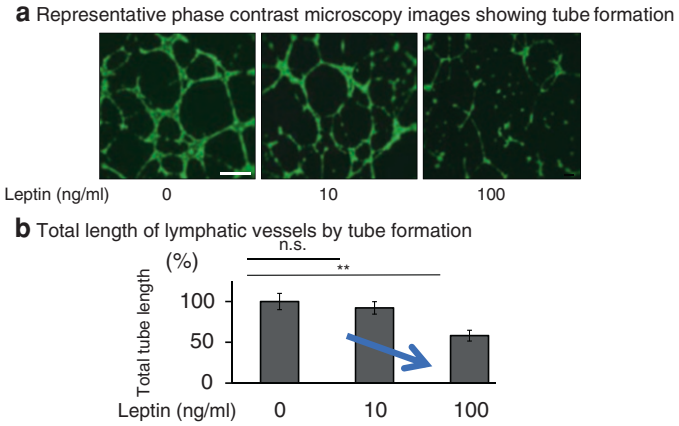
blood vessel, liver, and kidney inflammation and fibrosis (Fig. 16.4) [17–19]. In addition, although studies on blood vessels have been conducted, there have been few studies on lymphatic vessels.

First, human mammary lymphatic tissue was collected and stimulated with leptin; the lymphatic endothelial cell condition using SEM is shown in Fig. 16.5. The lumenal condition was confirmed using transmission electron microscopy. Leptin stimulation showed an abnormal duct structure in the lymphatic vessels' lumen. The different structures from the control group indicated that leptin had some effect on the lymphatic vessels. Because it is generally reported that the leptin levels in human serum are approximately 10 ng/mL in nonobese individuals and higher (approximately 100 ng/mL) in obese individuals, we performed a lumenal morphogenesis test. We found that leptin concentration-dependently induced lymphatic lumen formation in human dermal lymphatic endothelial cells could not exhibit lymphatic vessel architecture in a leptin concentration-dependent manner [20]. We examined the tube formation assay that forms these lymphatic vessels and found leptin concentration-dependently altered lumen formation of the lymphatic vessels and leptin concentration-dependently decreased tube formation of the lymphatic vessels (Fig. 16.6a) [20]. Figure 16.6b shows the results of calculating the



(Sato A, et al. Novel Mechanisms of Compromised Lymphatic Endothelial Cell Homeostasis in Obesity: The Role of Leptin in Lymphatic Endothelial Cell Tube Formation and Proliferation, PLOS ONE, 2016)

Fig. 16.5 Lumen of mammary lymphatic tissue. (Sato A, et al. Novel Mechanisms of Compromised Lymphatic Endothelial Cell Homeostasis in Obesity: The Role of Leptin in Lymphatic Endothelial Cell Tube Formation and Proliferation, PLOS ONE, 2016)



(Sato A, et al. Novel Mechanisms of Compromised Lymphatic Endothelial Cell Homeostasis in Obesity: The Role of Leptin in Lymphatic Endothelial Cell Tube Formation and Proliferation, PLOS ONE, 2016)

Fig. 16.6 Tube formation assay. (**a**) Representative phase contrast microscopy images showing tube formation. (**b**) Total length of lymphatic vessels by tube formation. (Sato A, et al. Novel Mechanisms of Compromised Lymphatic Endothelial Cell Homeostasis in Obesity: The Role of Leptin in Lymphatic Endothelial Cell Tube Formation and Proliferation, PLOS ONE, 2016)

total length of lymphatic vessels using a tube formation assay. Although it is impossible to make a judgment based on this study alone, since various substances' expression changes, besides leptin, an imbalance in "adipocytokines" secreted by adipocytes can cause vascular disorders such as myocardial infarction, cerebral infarction, and kidney disease. The study also suggested the possibility of damage to lymphatic vessels.

16.9 Case Study

A 36-year-old man was diagnosed as having lymphedema with lymphangitis and lymphatic leakage and underwent CPT. Patient information and improvement rates in weight change and edema after 30 days of in-hospital treatment are shown in Table 16.5. In addition, a subjective assessment of edema was performed. Motor and sensory impairment due to edema as well as appearance (cosmetic) and psychological aspects were evaluated using a visual analog scale. The evaluation criteria were described by the patients themselves, with 0 being the worst condition and 100 being the best condition. Further results are shown in Fig. 16.7. Compression therapy was performed only on the left lower extremity; however, an approximately 800-mL reduction in edema was also observed in the right lower extremity. Although sufficient evidence has not yet been obtained in Japan regarding the effectiveness of lymphedema treatment for obesity, with few reports, we are experts in providing

Table 16.5 Case characteristics

	Day 0	Day 30
Body weight (kg)	123	109
BMI	44.1	39.4
Range of motion (left knee flexion) (°)	125	135
Volume of lower extremity (right/left) (mL)	7672.7/16,406.0	6875.1/9170.5
Motor impairment (per 100)	29	81
Sensory impairment (per 100)	47	94
Appearance (cosmetic) (per 100)	0	93
Psychological (per 100)	0	97

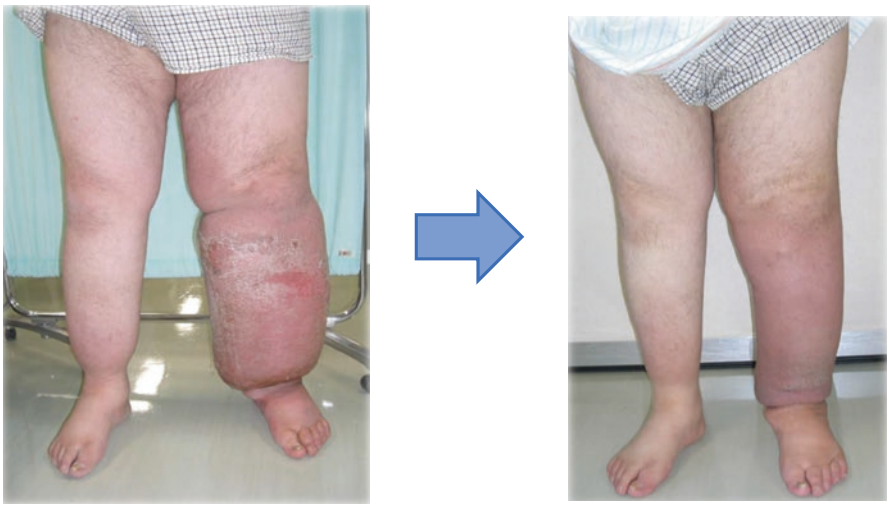


Fig. 16.7 Comparison of edema before and after treatment

physiotherapy based on sufficient evidence for exercise therapy for obesity. Since it has been suggested that obesity may be involved in lymphedema development and exacerbation both in vivo and in vitro, as physical therapists, we must establish evidence for combined treatments, including obesity management, with a focus on CDP.

16.10 Future Policy

The pathophysiological events that may be responsible for lymphedema onset and progression are characterized by obesity; however, the details may not be completely explained, and further research is needed.

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Cancer-Related Pain and Effects of Non-pharmacologic Intervention

17

Jiro Nakano

Abstract

Pain derived from a tumor or cancer treatment is categorized as cancer-related pain. It is important that physical therapists and other physicians understand the nature and characteristics of this kind of pain in order to better the management and treatment in the rehabilitation of cancer patients. This chapter provides basic information on cancer-related pain. The treatments which physical therapists can implement include non-pharmacologic interventions such as physical exercise, thermal therapy, massage therapy, and transcutaneous electrical nerve stimulation (TENS). Non-pharmacologic interventions are important for cancer-related pain that has not been completely resolved with pharmacotherapy. Because the efficacy of TENS for cancer pain is still uncertain, studies examining the safety and efficacy were presented. Research results showed that TENS for cancer-related pain was safe and provided limited pain relief. Additionally, nausea and appetite were also improved by TENS in cancer patients. These results indicated that TENS may be an effective tool for the treatment of cancer pain.

Keywords

Cancer-related pain · Non-pharmacologic interventions · TENS · Exercise Thermal therapy · Massage

J. Nakano (✉)
Department of Physical Therapy, Faculty of Rehabilitation, Kansai Medical University, Hirakata-shi, Osaka, Japan
e-mail: nakanoj@hirakata.kmu.ac.jp

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17.1 Introduction

Pain is one of the most common, burdensome, and feared symptoms experienced by cancer patients [1]. A meta-analysis by Sheinfeld et al. of 122 studies ($N = 4199$) showed that about 55% of patients experience pain during cancer treatment, and about 40% experience pain after curative treatment [1]. Pain in cancer patients is classified into: (1) pain caused by the cancer itself; (2) pain associated with cancer treatment (surgical treatment, chemotherapy, radiotherapy, and other treatments); (3) pain in cancer patients caused by diseases other than cancer; and (4) 70% of the patients in the Sheinfeld's study said that their pain was caused by the cancer itself, and the remaining 30% said that their pain was a result of the treatment or other diseases [2–4].

Pain is classified into acute pain and chronic pain. Acute pain is pain that occurs when nociceptors are excited by tissue damage or physiological pain stimuli. Acute cancer pain is often a combination of nociceptive and neuropathic pain. Cancer-related pain is mainly nociceptive pain because the size of causative lesion (tumor) increases over time, but with time the size of tumor increases, and neuropathic pain occurs due to nerve compression. Cancer-related pain is often characterized by both acute and chronic pain. The condition causing cancer-related pain worsens over time. Then, as the pathological condition worsens or new lesions appear, new pain is added, and it is accompanied by breakthrough pain, which is transient and intense pain with a short time lapse. Cancer-related pain is associated with an acute pain that gradually intensifies, resulting in a decrease in active daily living (ADL) and reduction in quality of life (QOL). Thus, cancer-related pain is considered to be chronic pain that gradually increases with the occurrence of acute pain.

For many cancer survivors, pain may become chronic as a long-term sequela of cancer treatment. In particular, taxanes, platins, vincristine, and bortezomib can cause chemotherapy-induced peripheral neuropathy that manifests as pain in some patients [5]. Surgery can lead to phantom limb pain [6] or pain from scar tissue contraction [7], and aromatase inhibitors can cause diffuse joint pain [8]. If the pain is left untreated, it can cause a variety of problems. In addition to limiting ADL and decreasing QOL, a "vicious cycle of pain" may occur as a physical problem, and as a psychological problem, the persistence of the unpleasant experience of rash pain may cause loss of individuality and depression. Furthermore, if performance status (PS) decreases due to pain, it may be difficult to continue cancer treatment for patients who are undergoing aggressive cancer treatment. Therefore, prompt analgesia is necessary in cancer patients. The principal approach to cancer pain management has been based on the World Health Organization's (WHO) method for cancer pain relief [9]. Not only doctors, nurses, and pharmacists but also physical therapists and occupational therapists can participate in the treatment of cancer-related pain. Physical therapists need to consider their approaches based on a thorough understanding of the mechanisms and treatments of cancer-related pain.

17.2 Classification of Pain by Pathology

17.2.1 Nociceptive Pain

Nociceptive pain is an acute pain caused by the excitation of pain receptors by nociceptive stimuli such as necrosis of surrounding tissues caused by tumors or infection. Pain associated with inflammation is also a type of nociceptive pain because it is induced by inflammatory substances that excite nociceptors [10].

Somatic pain: Pain that is relatively localized and sharp. One of the characteristics of somatic pain is that it increases with physical movement, as in bone metastasis. Nonnarcotic analgesics, analgesics, and nerve blocks are indicated for the treatment of somatic pain. Active maintenance of rest is also an effective treatment method.

Visceral pain: This is constrictive pain that is nonlocalized and vague, sometimes accompanied by autonomic symptoms and iatrogenic associated pain. It is caused by contraction, dilation, and extension of ductal organs; swelling of parenchymal organs; and extension of the capsule. Opioids are effective for this type of pain, as are abdominal plexus blocks (recommended by WHO).

17.2.2 Neuropathic Pain

Neuropathic pain is a syndrome that develops due to nerve tissue damage. It is characterized by persistent or electrifying spontaneous pain and abnormal sensations such as allodynia and hyperalgesia, which are caused by damage to peripheral and central nerves as a result of treatment such as surgery, chemotherapy, and radiation, in addition to tumor invasion and compression. Neurogenic pain tends to progress from acute pain to chronic pain. Multiple causes of neuropathic pain have been described, and its incidence is likely to increase due to the aging global population, increased incidence of diabetes mellitus, and improved survival from cancer after chemotherapy. Imbalances between excitatory and inhibitory somatosensory signaling, alterations in ion channels, and variability in the way that pain messages are modulated in the central nervous system have all been reported to contribute to neuropathic pain. The burden of neuropathic pain seems to be related to the complexity of neuropathic symptoms, poor outcomes, and difficult treatment decisions [11].

17.2.3 Psychogenic Pain

Pain is sometimes difficult to resolve by anatomical and neurological approaches alone, and psychological factors are involved in the appearance and exacerbation of pain. Depression, anxiety, anger, and distrust are factors that can enhance pain, and

personality and relationships with family and medical staff are factors that can modify pain [12]. However, even if there are no physical findings corresponding to the patient's complaint, a diagnosis of psychogenic healing pain should not be made easily. It is advisable to seek consultation from a psychiatrist regarding the use of antipsychotic drugs.

17.2.4 Immobilization-Induced Pain

After tissue injury, the injured area is exposed to inactivity for therapeutic purposes. Even in the absence of medical treatment, pain can cause a patient to avoid exercise, including at the site of the pain, resulting in inactivity. In such cases, motor unit dysfunction, such as contractures and muscle atrophy, is induced secondarily. Recently, it has become clear that inactivity itself is a risk factor for the occurrence and exacerbation of pain, which is called "immobilization-induced pain" [13].

The mechanism of immobilization-induced pain is thought to be influenced by the sensitization and plastic changes that occur in the nervous system, including the spinal cord and brain, as well as primary nociceptive neurons, due to the weakening or loss of sensory stimulus input caused by inactivity [14]. In addition, these changes in the nervous system become more pronounced after prolonged periods of inactivity, which may lead to chronic pain.

17.3 Classification of Cancer-Related Pain

Cancer-related pain differs from orthopedic pain with regard to its characteristics, as well as the sites and organs where it occurs (Table 17.1).

17.3.1 Visceral Pain

Tumor-induced visceral pain is caused by pancreatitis, retroperitoneal lymphadenopathy, or mesenteric invasion of the luminal organs of the liver. These types of pain are often described as a heavy pushing pain or a deep squeezing pain. Unlike somatic pain, which has a well-defined localization of pain, visceral pain is widespread and poorly localized. This is because the innervation of viscera is more extensive than that of somatic tissues, with afferent projections spanning several segments within the spinal cord. Visceral afferents, which transmit visceral perception, have cell bodies in the dorsal root ganglia of the spinal cord in the thoracolumbar region and project into the spinal cord. Most of these nerves are either high-threshold mechanoreceptors that respond only to strong mechanical stimuli or silent receptors that respond only when tissue damage such as inflammation is observed. The pain-producing substances (hydrogen ions, prostaglandin, anti-inflammatory cytokines, bradykinin, and other substances) released by stretching of luminal organs and inflammation of internal organs bind to their respective

Table 17.1 Classification of cancer-related pain

Classification	Nociceptive pain		Neuropathic pain	Immobilization-induced pain Psychogenic pain
	Somatic pain	Visceral pain		
Stimuli that cause pain	• Mechanical stimulation body movement compression progress	• Increased internal pressure in luminal organs • Rapid development of organ capsules • Local organ tissue inflammation	• Nerve compression, tear	• Equivalent to nociceptive and neuropathic pain
Example	• Bone pain • Muscle gagging associated with inflammation	• Abdominal pain associated with increased internal pressure, development, and inflammation of organs • Gastrointestinal obstruction	• Brachial plexus invasion of cancer • Epidural invasion of spinal metastases	• Immobile due to nociceptive and neuropathic pain • Bedridden • Living in a small area
Characteristics of pain	• Well-defined localization • Aggravated with body movement	• Deep, squeezing, pushing pain • Localization unclear	• Pain with numbness • Pain that feels like an electric shock	• Increased nociceptive and neuropathic pain
Treatment	• Rescue dose is important	• Opioids are important	• Requires analgesic assistance	• Non-pharmacological therapy are important • Exercise

receptors on the nerve and induce action potentials [15]. These action potentials induce pain, and axonal reflexes promote the release of calcitonin gene-related protein (CGRP) and substance P at the lesion site, resulting in blood flow regulation, intestinal motor reflexes, and neurogenic inflammation [16].

In recent years, the molecular mechanisms of visceral pain associated with inflammatory bowel disease have been elucidated, but there are few reports on the pathogenesis of visceral pain caused by tumors. This is because it is difficult to evaluate visceral pain in cancer patients due to the pain's unclear location.

17.3.2 Bone Pain

The incidence of bone metastasis varies widely depending on the primary disease. Among solid cancers, bone metastasis occurs more frequently in prostate cancer, breast cancer, lung cancer, kidney cancer, thyroid cancer, and malignant melanoma. Bone is the most abundant tissue in the body that contains growth factors, and it is considered to be a favorable environment for cancer cells to colonize and proliferate

in. The bones that are most prone to metastasis are the spine, but it is also common in the ribs, sternum, pelvis, and other trunk bones with abundant blood flow.

The pain associated with bone metastasis is often mild and numbness in the early stage, and changes to persistent tingling pain or sharp pain with physical movement as the cancer condition worsens. Pathological analysis has shown that bone pain is caused by (1) an increase in osteoclasts and their activation; (2) a decrease in pH around the tumor tissue; or (3) a decrease in the number of osteoclasts in the cancer lesion.

In bone cancer, the activation of osteoblasts and osteoclasts is imbalanced, resulting in osteoclast dominance. Osteoclasts destroy bone to make space for cancer growth and release insulin-like growth factor (IGF) and transform growth factor-1β (TGF-1β), fluid factors that promote cancer cell growth, from the destroyed bone. These factors bind to the IGF-1 and TGF-1β receptors on cancer cells, respectively, and promote cell proliferation of cancer cells. The increase and activation of osteoclasts are thought to be factors in the development of bone pain.

Osteoclasts release enzymes such as collagenase and hydrogen ions into the periphery of the cells, making the extracellular environment acidic (pH 4–5) and resorbing the bone matrix. Tumor tissues, including cancer cells and their stromal cells, are known to have a lower pH than normal tissues [17]. Acid activates acid receptors such as transient receptor potential ion channels vanilloid-1 (TRPV1) and acid sensing ion channels-3 (ASIC3) [18]. TRPV1 and ASIC3 are expressed in nociceptive nerves, and activation of these channels is thought to induce pain.

Persistent pain input gradually increases the excitability of spinal nerves, leading to central sensitization. In animal models of bone cancer pain, the synaptic transmission efficiency of nociceptive A-delta and C fibers is increased over a wide area of the spinal cord dorsal horn [19].

17.3.3 Neuropathic Pain

Neuropathic cancer pain results from compression/invasion of peripheral nerves and compression/invasion of spinal and cranial nerves by tumors. Shimoyama et al. [20] created a model of cancer-induced neuropathic pain by implanting sarcoma cells into the muscle tissue adjacent to the sciatic nerve in the corpus callosum of mice and conducted a detailed pathological analysis. In this model, strong degeneration of unmyelinated nerves precedes degeneration of myelinated nerves at the onset of spontaneous pain. In the sciatic nerve ligation model, a non-cancer neuropathic pain model, myelinated nerves are more severely damaged than unmyelinated nerves, whereas in the tumor-induced neuropathic pain model, degeneration of unmyelinated nerves is mainly observed. This difference in neuropathic mechanisms is thought to be the cause of the difference between cancer neuropathic pain and non-cancer neuropathic pain.

In addition, analysis using resected human pancreatic cancer specimens reported that increased expression of nerve growth factor (NGF) in pancreatic cancer cells and increased expression of trkA receptors in the neural network of pancreatic nerves and cancer cells correlated with the degree of nerve invasion and pain of the cancer [21]. These findings suggest that NGF/trkA signaling may be involved in pain associated with tumor invasion.

17.4 Continuous and Breakthrough Pain

17.4.1 Continuous Pain

Continuous pain is pain described by patients as "average pain experienced for more than 12 hours in a 24-hour period." There are two types of continuous pain; pain that is relieved by analgesics and pain that is not relieved by analgesics due to rapidly increasing pain. The degree of persistent pain may change with treatment and cancer progression.

17.4.2 Breakthrough Pain

Breakthrough pain, defined as a transitory exacerbation of nociceptive pain that is superimposed on persistent stabilized chronic pain, has been associated with a low probability of adequate pain control in some groups of cancer patients [22]. This type of pain characteristically has an acute onset (less than 3 min) as well as a severe intensity, but a brief duration (average of 30 min), and occurs an average of four times a day. Because breakthrough pain can negatively affect psychological and functional outcomes, the knowledge of how to successfully manage breakthrough pain can significantly affect the QOL of patients. Cancer-related pain is a progressive chronic pain that gradually worsens with recurrent episodes of breakthrough pain (Fig. 17.1).

Pain associated with deliberate body movement is to be expected. The use of rescue dose 30–60 min before rehabilitation can help prevent protrusion pain. Protrusion pain associated with unintentional body movements, such as myoclonus, coughing, and gastrointestinal or bladder spasms, cannot be predicted. In addition to rapid rescue dose response, we approach the condition in a way that reduces the frequency of pain triggers. Paroxysmal pain associated with neuropathic pain is often difficult to treat with rescue doses alone, so it is necessary to select effective analgesic adjuncts with minimal side effects [22].

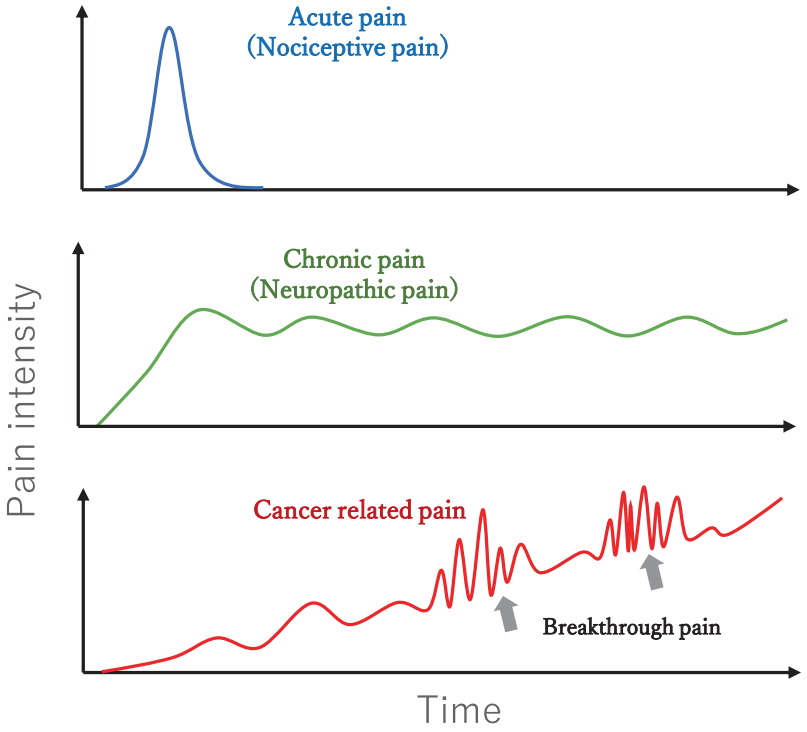


Fig. 17.1 Progress of cancer-related pain. (Figure created with reference to Tomoyuki Kawamata's paper (Pain Clinic 31: S14–25, 2010 [Japanese]))

17.5 Methods of Pain Assessment

Pain assessment requires multifaceted evaluations, including pain patterns, impact on life, location, nature, exacerbating factors, relieving factors, Support Team Assessment Schedule (STAS) [23], and the effects of medications. Regarding impact on daily life, we should ask, "Are you satisfied with the current treatment for your pain?" and "Do you have any problems in your daily life due to the pain?". In order to make a comprehensive evaluation of the patient's pain treatment, the degree to which daily life is interfered with, and to what extent the patient wishes to have the pain addressed, should be confirmed. The effect of the pain on sleep should always be asked. For the pain pattern, we asked "Is the pain present all day, or does it come and go?" and "Does the pain fluctuate?". There are two main types of pain patterns: continuous pain and breakthrough pain. The treatment plan differs depending on the pattern; for continuous pain, regular or increased doses of analgesics are used, whereas rapid-onset opioids are used for breakthrough pain.

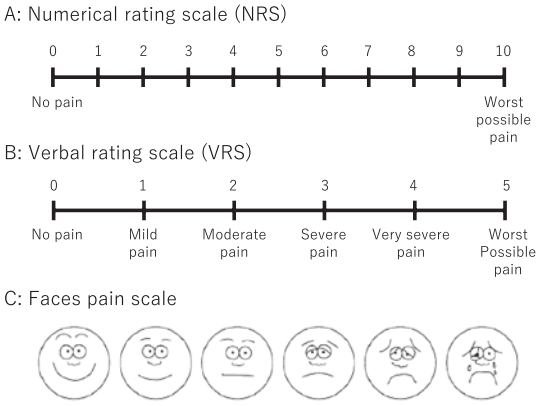


Fig. 17.2 Pain scale. (**a**) Numerical rating scale (NRS). (**b**) Verbal rating scale (VRS). (**c**) Faces pain scale

The numerical rating scale (NRS), visual analogue scale (VAS), and verbal rating scale (VRS) have been validated for reliability and validity and are currently used in clinical practice (Fig. 17.2a, b). The faces pain scale (FPS) has been reported to be useful in the self-assessment of pain in children (Fig. 17.2c). However, because examination using these scales may reflect factors other than pain, such as the patient's mood, and the scale has few steps, it may not be reliable as a detailed evaluation. These evaluation methods can also assess the intensity of pain but cannot record its localization or its effect on ADLs. For multifaceted pain assessment in cancer patients, the Brief Pain Inventory (BPI) is used frequently (Fig. 17.3) [24].

Since cancer-related pain has similar characteristics to chronic pain, it is important to evaluate its psychological aspects. Evaluation using the Hospital Anxiety and Depression Scale (HADS) and Pain Catastrophizing Scale (PCS) is often conducted simultaneously with pain assessment. To assess pain comprehensively, it is important to check the extent to which pain interferes with ADLs. In particular, be sure to ask about the effect of the patient's pain on sleep. STAS can be used to determine if treatment is needed. A comprehensive QOL evaluation chart (e.g., The European Organization for Research and Treatment of Cancer: QLQ-C30) also includes items for evaluating pain. However, if a study focusing on cancer-related pain is to be conducted, it is recommended that pain be assessed separately from the comprehensive QOL evaluation chart.

17.6 Pharmacologic Interventions for Cancer-Related Pain

Pharmacologic options include opioids (oxycodone, morphine, hydromorphone, fentanyl), the mainstay in managing somatic pain, and anticonvulsants (gabapentin, pregabalin) for neuropathic pain. Opioids are necessary and appropriate for patients with advanced cancer and intractable pain. However, fatigue, drowsiness,

Brief Pain Inventory—Short Form

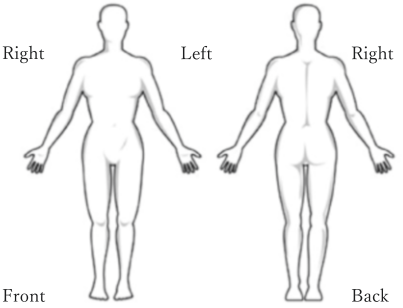
Date / / Time

Name

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that shows how much relief you have received.

0 10 20 30 40 50 60 70 80 90 100%
No relief — Complete relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General activity

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

D. Normal work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

Fig. 17.3 Progress of cancer-related pain

constipation, nausea, and indigestion are common side effects [25]. They are also not appropriate for most cancer survivors who are in remission. Because of exposure to opioids during cancer treatment, cancer survivors are at a higher risk for opioid misuse. Studies have shown that exposure to opioids during treatment for acute pain is a strong risk factor for patients to become long-term opioid users, even when the acute pain has subsided and opioids are no longer necessary [26–30].

On the other hand, acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are used for mild to moderate pain, but they are not favored during chemotherapy due to their potential for liver and kidney toxicity, or their ability to mask a fever that may be an early sign of infection. While antidepressants, anxiolytics, and steroids are sometimes used as adjuncts to enhance pain control, they are associated with their own side effects. Aversion to treatment side effects and fear of developing addiction or tolerance have been cited as reasons why patients may be reluctant to take adequate pain medicine [31, 32].

The WHO method of treating cancer-related pain has become the standard for treating cancer spastic pain, and it is said to improve 80–90% of cancer-related pain [9]. The following five basic principles are important for proper operation: (1) oral (by mouth) administration; (2) regular administration, at the same time(s) each day; (3) according to the analgesic ladder (Fig. 17.4a) [9]; (4) for the individual; and (5) the attention to detail. Proposed modifications based on various studies have also been presented (Fig. 17.4b) [33].

17.6.1 Opioids Rotation and Conversion Ratio

When an opioid does not produce the desired therapeutic effect, it is necessary to consider remedial measures to alleviate the patient's suffering as much as possible.

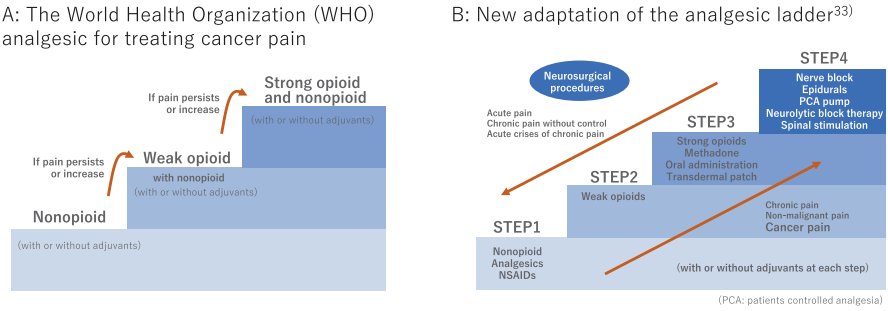


Fig. 17.4 Analgesic ladder for cancer-related pain. *PCA* patients controlled analgesia. (**a**) The World Health Organization (WHO) analgesic for treating cancer pain. (**b**) New adaptation of the analgesic ladder [33]

Table 17.2 Opioid conversion table

Drug	Equianalgesic dose (mg)
Morphine	30
Oxycodone	20
Tapentadol	100
Tramadol	150
Hydromorphone	6
Morphine (suppository)	20
Fentanyl (paste 1 day)	1

When opioid doses are used in study outcomes, use a conversion table to standardize opioids to morphine doses. Values are for reference only

In this case, opioid rotation may be one of the effective methods and is indicated for the following conditions: (1) when there are side effects that are difficult to control or (2) when the analgesic effect is insufficient [34, 35]. When performing opioid rotation, the dose should be converted to the appropriate dose according to the appropriate conversion ratio between each opioid (Table 17.2). The opioid conversion ratio is also very important to research on cancer-related pain. Studies often use the amount of analgesic medication as an outcome of pain interventions. Since there are many different analgesics (opioids) used for treatment, it is difficult to process them statistically. The amount of opioids can be standardized to one type using this opioid conversion ratio. Then, the average value for all patients can be calculated. Usually, the outcome of opioid dosage is unified with morphine in research studies.

17.7 Non-pharmacologic Intervention for Cancer-Related Pain

The Joint Commission, American College of Physicians (ACP), National Comprehensive Cancer Network (NCCN), and American Society of Clinical Oncology (ASCO) guidelines all recommend a combination of pharmacologic and non-pharmacologic modalities. Non-pharmacologic interventions are an important part of a comprehensive pain management plan. Non-pharmacologic interventions include cognitive behavioral therapy, physical exercise, acupuncture, massage therapy, thermal therapy, aromatherapy, music therapy, and transcutaneous electrical nerve stimulation (TENS). There is low to moderate, but not grade A, evidence for these treatments. However, a major advantage of these treatments is the absence of side effects. Once carefully incorporated to standard cancer care, these therapies can complement other treatments and enhance the quality of the cancer care [36–38]. It is important to note that non-pharmacologic intervention is not intended as a substitute for drugs.

In rehabilitation, physical exercise, thermal therapy, cold therapy, and TENS are often employed by physical therapists to alleviate cancer-related pain. These therapies do not require any special skills and are easy to adopt.

17.8 Physical Exercise for Cancer-Related Pain

Exercise has been reported to relieve cancer-related physical symptoms including pain. On the other hand, the effects of exercise on physical symptoms might differ depending on the type of exercise [39]. Pain has been reported to be relieved by aerobic, but not resistance exercise in some RCTs [40–42]. Thus, aerobic and resistance exercises should be distinguished when the effects of exercise on cancer-related physical symptoms are examined. Nakano et al. [39] published the most recent meta-analysis limited to RCTs using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30). They summarized the effect of aerobic and/or general resistance exercises on physical symptoms, including pain, for cancer patients and survivors in any setting. In this systematic review by Nakano et al. [39], it was shown that the most effective exercise program for cancer-related pain was a mixed program of aerobic and resistance exercise (Fig. 17.5) [39].

Part of pain reduction with exercise is explained by "exercise-induced hypoalgesia (EIH)." EIH is characterized by a decrease in pain intensity and an increase in pain threshold and tolerance values during and after exercise. The mechanism by which EIH occurs has been proposed based on exercise-induced plastic changes at the peripheral nerve, spinal cord, and brainstem levels [43]. A useful exercise modality for the emergence of EIH is continuous aerobic exercise, such as running, walking, and swimming. It has been reported that these aerobic exercises improve chronic musculoskeletal pain such as cervical pain, fibromyalgia, and chronic low

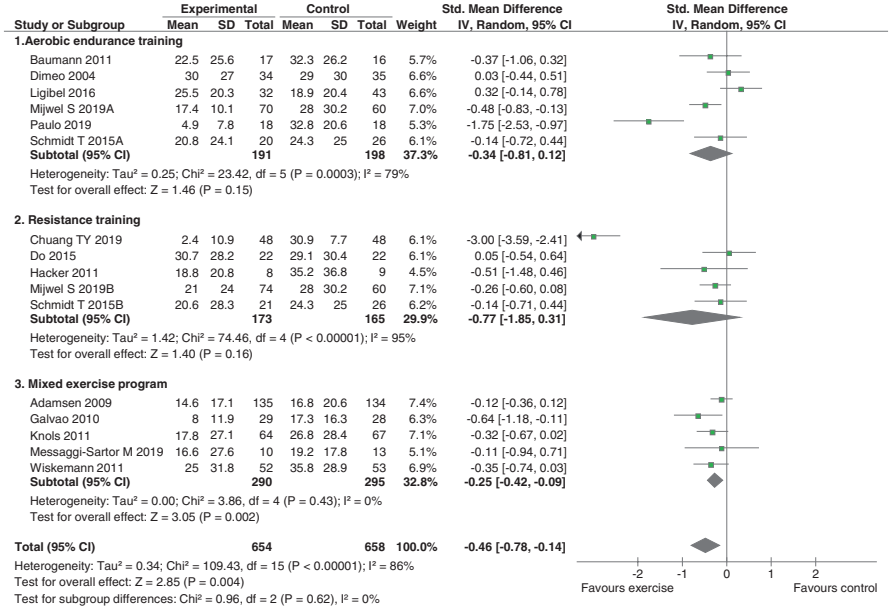


Fig. 17.5 Results of meta-analysis on the effect of exercise for cancer-related pain

back pain [44] and that physical activity level is inversely related to depressive symptoms in fibromyalgia [45]. EIH may also be effective for patients with cancer-related pain.

Inhibiting the production of inflammatory cytokines and increasing the production of anti-inflammatory cytokines seem to be one aspect of the effect of EIH. For example, Bobinski et al. [46] reported that treadmill running in mice with a sprained sciatic nerve improved pain-related behavior and suppressed inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor 1 (TNF1α) in the spinal dorsal horn. In the brainstem-mediated mechanism of EIH, spontaneous exercise reduces muscle pain in a mouse model of chronic myalgia, but this analgesic effect is suppressed by infusion of naloxone (an opioid antagonist) into the periaqueductal gray matter (PAG) and rostroventral medulla (RVM) of the midbrain [47]. It is suggested that brain mechanisms involved in the generation of reward and pleasant emotions play an important role in EIH, because voluntary movements are a kind of reward and produce pleasant emotions in mice. If this phenomenon occurs in humans, we need to provide comfortable exercise for cancer patients. Naturally, the exercise programs will depend on whether the patients regularly exercise or not. Therefore, it is important to understand the exercise habits and preferences of cancer patients.

The effect of exercise therapy on shoulder pain in breast cancer patients is different from EIH. A systematic review by Tatham et al. [48] that examined RCTs, comparing the effects of exercise intervention in breast cancer patients with shoulder pain, showed that exercise is effective for treating shoulder pain in breast cancer and head and neck cancer patients. This effect includes improvement in joint range of motion and lymphedema from shoulder joint exercises and stretching.

Regarding safety, there is agreement that exercise therapy does not cause adverse events in cancer patients. Adverse events rarely occur during exercise, and they are not directly related to the exercise [49]. However, there have been no reports examining the safety of exercise in cancer patients with cancer-related pain. On the other hand, physical therapists need to consider not only pain but also other physical symptoms, as well as mental status, because those physical symptoms are likely to contribute to pain. Systematic reviews that included meta-analyses have shown that exercise not only helps with pain but also with fatigue, dyspnea, sleep disturbance, anxiety, and depression [39, 49]. Therefore, exercise therapy is strongly recommended for cancer patients suffering from pain and other physical symptoms.

17.9 Thermal Therapy for Cancer-Related Pain

Thermal therapy is broadly divided into two types: (1) superficial heat therapy, which transfers heat through direct contact with the skin surface, as typified by hot packs; and (2) deep heat therapy, which is converted into heat within the body (diathermy), such as microwaves and ultrasound. Heat can directly relieve pain by

raising its threshold. In addition, comfortable heating has a relaxing effect; it increases the extensibility of collagen fibers and has an antispasmodic effect on muscles.

The risk of tumor growth and metastasis associated with increased blood flow due to hyperthermia has long been recognized, and many textbooks contraindicate thermal therapy for malignant tumors [50]. However, there are few reports that have evaluated the effects of hyperthermia on cancer from a risk perspective. The Agency for Health Care Policy and Research (AHCPR, US; now the Agency for Healthcare Research and Quality) guidelines state that "the use of heat is recommended" but also suggest to "avoid burns by wrapping the heat source (e.g., hot pack or heating pad) in a towel." It should be noted that diathermy and ultrasound are not recommended for use over tumor sites or tissue irradiated by radiation therapy. On the basis of the recommendations of the AHCPR, surface thermal therapy is commonly used in clinical practice for cancer patients [51].

Surface thermal therapy is the easiest thermal therapy method for families at home. Hot packs that can be heated in a microwave are also readily available. It is recommended to teach a patient's family members about thermal therapy so that they can help them to cope with pain and reduce their anxiety. When using thermal therapy, other precautions are also necessary. Hot packs and hot water bottles should be used with caution to avoid burns and low-temperature burns. If patients are using fentanyl patches, make sure that the patches are not exposed to heat sources (e.g., hot pack or heating pad). In the case of trauma, edema, or bleeding, it is necessary to check if it is safe to heat the patient, as there is a risk of aggravating the symptoms.

Among cancer-related pains, the location of internal pain is ambiguous, and the pain is often felt in the back. In these cases, it is easy for the patient to relax by applying a hot pack to the back. However, it is necessary to confirm the presence of spinal or pelvic metastasis beforehand. In many cases, it is difficult for the patient to lie supine due to their receiving of intravenous infusion, so they should be placed in the intermediate position between the supine and lateral lying positions using a pillow or a position-converting mat. If a hot pack cannot be applied to the back, warming of the hands and feet can be used to help the patient relax.

17.10 Massaging for Cancer-Related Pain

Massage techniques include rubbing, squeezing, light tapping, and pressure. Massaging can reduce muscle tension, improve joint range of motion, promote blood circulation, and help to drain local tissue edema. In addition, touching the patient's body with the hands brings a sense of security and trust, which is expected to be effective in improving cancer-related pain as a secondary effect of mental relaxation (reduction of anxiety and stress). There have been many studies examining the effects of massaging on cancer-related pain. Several systematic reviews for that have also been published [52–55]. According to these studies, although there

are scattered reports that massaging is effective for cancer-related pain, no conclusive evidence has been recognized. A meta-analysis conducted by Pan et al. found no significant effect [55]. Even if massaging doesn't directly improve pain, physical and mental relaxation via massaging is necessary in patients with cancer-related pain.

Massaging is one of the therapies that can be easily introduced in hospitals or at home because it does not involve any tools. Massage for relaxation is usually done with smooth, long, slow strokes; rapid strokes, circular movements, and squeezing of tissues tend to stimulate circulation and increase arousal. However, massager should try several degrees of pressure, along with different types of massage, such as kneading, stroking, and circling, to determine which is preferred. A back rub that effectively produces relaxation for older patients may consist of no more than 3 min of slow, rhythmic stroking (about 60 strokes/min) on both sides of the spinous process from the crown of the head to the lower back. A regular schedule for massage should be decided as it gives the patient something to look forward to and depend on. A massage (3–10 min) may be a whole body massage, or it may be restricted to back, feet, or hands. If the patient is modest or cannot move or turn easily in bed, consider massaging the hands and feet only [55].

In the field of cancer treatment, safety is important when considering massage therapy for patients. Strong pressure should not be applied to soft tissues with underlying tumors or bone metastasis sites. It should also not be applied to patients who are thrombocytopenic or on anticoagulants.

17.11 Transcutaneous Electrical Nerve Stimulation (TENS) for Cancer-Related Pain

Transcutaneous electrical nerve stimulation (TENS) can potentially be used as an adjunct therapy for the treatment of cancer-related pain. TENS is beneficial in the treatment of pain, including acute [56] and chronic [57] pain, in orthopedics. In terms of cancer-related pain, a few reports have shown the beneficial effect of TENS [58–61] against cancer-related pain in various organs. However, no conclusive evidence has been obtained, as studies to date have used insufficient sample sizes [62]; thus, the accumulation of additional data is imperative. Maddocks et al. [63] chose electrical stimulation as the therapy for lung cancer patients with muscle weakness postoperatively to help their rehabilitation. Searle et al. [64] reported a case treated with TENS that resulted in apparent relief of bone pain. Some investigators used TENS and high-frequency electrical stimulation to treat the pain of patients with malignant tumors and achieved satisfying results [60, 65, 66]. It was reported that electrical stimulation could improve the QOL of postoperative cancer patients.

17.11.1 Safety of TENS for Cancer Patients

TENS is thought to be safe to use in cancer patients, but there is no definitive evidence. Whether the pulse electrical field created by TENS will enhance the

proliferation of cancer cells, leading to recurrence and metastasis, what the effect of pulse electrical field on cancer is and whether it is safe for patients remain unanswered questions with no current clinical or experimental data available. Some studies suggest that electrical stimulation promotes vessel formation in vivo by increasing the expression of vascular endothelial growth factor [67]. Electrical characteristics of malignant tumor tissues may change, which affect the metastasis of carcinoma cells in circulation [68]. Additionally, electrical stimulation can promote healing of wounded skin and bones, repair of nerve muscles, spinal repair, and neuronal migration, all of which make us think about the potential migration and proliferation of cancer cells when being electrically stimulated. In order to clarify this issue, Wang et al. [69] conducted an experiment that yielded the following; pulse electrical field by low-frequency electrical nerve stimulation used for rehabilitation does not generate changes in the proliferation or invasion of cancer cells, suggesting that the current clinical application of TENS may not cause recurrence of cervical cancer. Negative results were also obtained in our experiments. TENS (100 Hz, 1.0–3.0 mA, 20 min) was administered for 4 weeks to tumors in a rat model of chemically induced breast cancer. The results showed that tumor size, number of white red blood cells, and hemoglobin were all unaffected by TENS (Fig. 17.6).

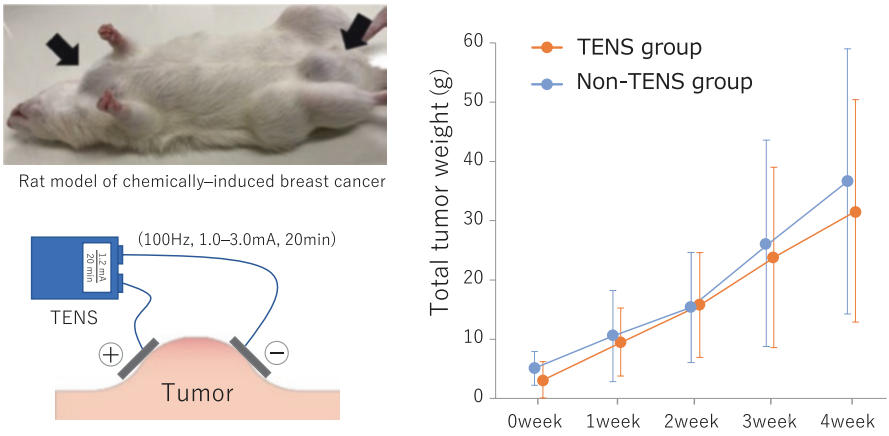


Fig. 17.6 Animal experiments on the safety of TENS for tumors. TENS for 4 weeks had no adverse effects on the tumor, number of white red blood cells, and hemoglobin in a rat model of chemically induced breast cancer. (Numata, et al.: 25th Congress of Japanese Physical Therapy Fundamental, Sendai, Japan, 2020)

17.11.2 Mechanism of Effect of TENS for Pain

Although the mechanism underlying pain reduction by TENS has not been completely clarified, several mechanisms have been postulated based on the results of basic research. Evidence from animal studies show that TENS reduces nociceptor cell activity and sensitization in the central nervous system when applied to somatic receptive fields and after spinal cord transection [70]. First, TENS-induced A-delta activity causes long-term depression of central nociceptor cell activity for up to 2 h. Second TENS-induced activity in small diameter afferents (A-delta) leads to activation of the midbrain periaqueductal gray and rostral ventromedial medulla (i.e., descending pain inhibitory pathways) and inhibition of descending pain facilitatory pathways. Third, antidromic activation of peripheral nerves by TENS generates nerve impulses that have been shown to collide and extinguish afferent impulses arising from peripheral structures. Last, TENS effects are mediated by many neurochemicals including opioids, serotonin, acetylcholine, noradrenaline and gamma-aminobutyric acid (GABA). Low-frequency (10 Hz) TENS has been shown to involve μ opioid and 5-HT2 and 5-HT3 receptors [71]. Additionally, high-frequency (100 Hz) TENS produces antihyperalgesia through δ opioid receptors in the spinal cord [72]. If TENS suppresses visceral pain, it is likely to be mediated by descending pain inhibitory pathways and opioid receptors in the central nervous system.

17.11.3 Introduction of Research on the Effect of TENS for Cancer-Related Pain

We previously conducted an experiment on the effect of TENS for cancer-related pain [73]. This study employed a crossover design involving TENS and non-TENS phases in 24 inpatients with advanced cancer who were undergoing palliative treatment at a hospital. Any participants meeting the eligibility criteria for palliative care were recruited. After screening and enrollment, the participants were randomly allocated to group A or B, and treatment sequences were assigned at random by using a randomized envelope method. The two-arm crossover trial consisted of a first period, washout period, and a second period. The TENS intervention (TENS phase) lasted 5 days and was administered during the first period in group A and during the second period in group B. Both groups received both their usual care and palliative care during all periods in the study. The washout period was 5 days. Evaluations were performed before and after each phase, and individual outcomes were analyzed according to the crossover design, regardless of whether patients dropped out or fully complied with the study.

The outcomes were pain (NRS), QLQ-C15PAL, opioid dose, and frequency. The opioid dose was converted to morphine according to the opioid conversion formula. To confirm the safety of TENS for patients with cancer, blood data, including white and red blood cell counts, platelet count, lymphocyte count, and C-reactive protein, hemoglobin, and albumin levels, were recorded.

17.11.3.1 TENS Application Protocol

TENS was applied to four sites related to the patient's pain and physical symptoms, by a medical researcher using a four-channel electrical stimulation device (Cefar Complex rehab400, DJO France SAS, Mouguerre, France) and adhesive gel pads (Dura-Stick plus, 5 cm × 9 cm, DJO Global, Vista, CA, USA). For treatment of pain, one pair of gel pads was placed on the back at the dermatomal level that corresponded to the painful area or internal organ [74]. When there was metastatic spinal tumor on the vertebra, the gel pads were placed longitudinally to avoid stimulating the tumor directly (Fig. 17.7). In TENS, high-frequency (100 Hz) stimulation was used for all treatments except for constipation [61, 62]. Intensity was increased until the electrical sensation was strong but still comfortable. TENS was delivered for 30 min, once per day, by a physical therapist.

17.11.3.2 Effect of Pain Relief by TENS

The immediate effect of TENS on pain is shown in Fig. 17.8a. Pain immediately after TENS was significantly reduced compared with immediately before TENS (baseline). However, this effect disappeared after 60–120 min. The average and maximum pain NRS scores during the day, the total dose of prescribed opioids per day, and the total number of rescue doses required during the TENS and non-TENS phases are shown in Fig. 17.8b. The average pain scores during the day were reduced significantly. In terms of the maximum pain during the day, there was no significant change between pre- and post-intervention in either the TENS or non-TENS phases.

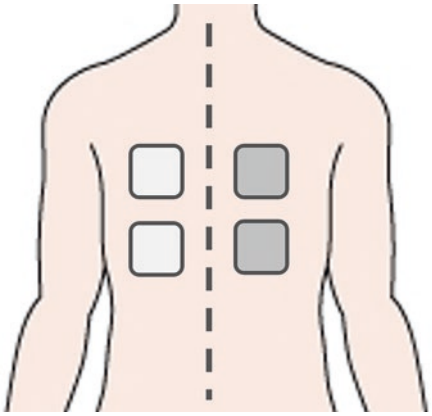


Fig. 17.7 Placement of gel pad of TENS. A gel pad is placed in the center of the back. If the location of the pain is clear, the gel pads were placed on the back at the dermatomal level that corresponded to the painful part or internal organ. The gel pads were placed longitudinally to avoid stimulating the tumor directly

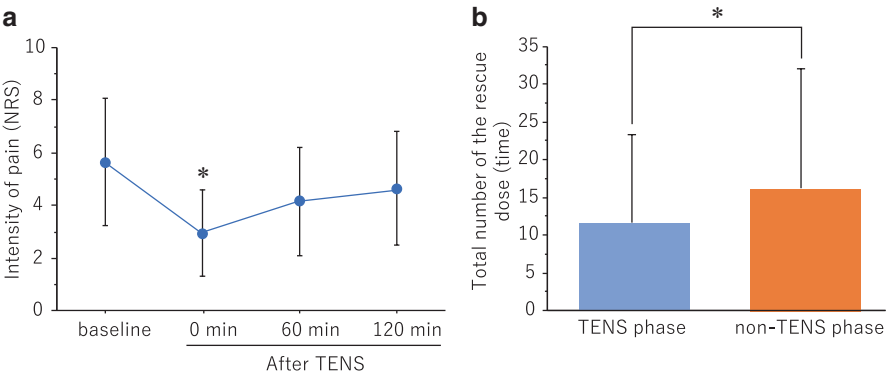


Fig. 17.8 The effect of TENS for cancer-related pain. (**a**) The immediate effect of TENS for pain (NRS: numerical rating pain scale). TENS has immediate but not sustained analgesic effects. (**b**) Comparison in total number of the rescue dose between pre- and post-intervention. Number of rescue dose reduced by TENS. *Compared with pre-TENS ($p < 0.05$)

Table 17.3 Blood data at pre- and post-TENS in cancer patients

	Pre-TENS	Post-TENS	Change
WBC (10^3/μL)	6.4 ± 4.0	6.6 ± 3.6	−0.0 ± 3.5
RBC (10^6/μL)	3.7 ± 1.6	3.6 ± 0.5	−0.0 ± 1.6
PLT (10^3/μL)	238.4 ± 79.4	271.1 ± 117.5	31.5 ± 113.9
Lymphocyte (%)	14.9 ± 9.5	13.1 ± 7.6	−1.6 ± 7.9
CRP (mg/dL)	4.9 ± 4.4	4.2 ± 4.9	−0.7 ± 4.9
Hb (g/dL)	10.7 ± 1.5	10.7 ± 1.3	−0.1 ± 0.7
ALB (g/dL)	2.9 ± 0.3	3.0 ± 0.2	0.0 ± 0.2
TP (g/dL)	6.1 ± 0.5	6.3 ± 0.4	0.3 ± 0.8

No significant differences were found between pre-TENS and post-TENS for all items

The daily dose of prescribed opioids was also not significantly different between the TENS and non-TENS phases. Because the total daily dose of prescribed opioids was not changed, the reduction in the average pain during the day may be due to the effect of TENS. The total number of times of requiring opioid rescue during the TENS phase (11.7 ± 11.6 times) was reduced significantly as compared with that during the non-TENS phase (16.3 ± 15.8 times). This result indicates that TENS reduced the number of cases of breakthrough pain. Thus, the effect of TENS on pain is not dramatic, but it is somewhat promising. In addition, the safety of TENS was proven by the lack of significant changes in blood data (Table 17.3).

17.11.4 Meta-Analysis on the Effect of TENS for Cancer-Related Pain

The efficacy of TENS for cancer-related pain has been expected for some time, and a Cochrane systematic review was published in 2008 and updated in 2012 [74].

However, few RCT studies examining the effect of TENS have been published, and thus no meta-analysis has yet been conducted.

The Cochrane published systematic review included three studies [59, 66, 75]. TENS was performed in 15 participants in one study, 41 participants in another, and 25 participants in a third study, which at present is the most recently reported study. The third study [66] suggested that TENS might improve cancer bone pain during movement, but because it was a pilot study, it was not designed to determine the impact of TENS on pain. The two other studies in the review did not show that TENS significantly improved cancer-related pain. Moreover, one study did not have sufficient participants to determine whether TENS had an effect. There were many differences in participants, treatments, procedures, and symptom measurement tools used in the studies. In two of the studies [59, 75], some participants were able to identify when they received active TENS and when they received placebo. Thus, there is insufficient evidence to judge whether TENS should be used in adults with cancer-related pain. Further research using well-designed clinical trials is needed to improve knowledge in this field [74].

17.11.5 Treatment of Cancer-Related Symptoms Other Than Pain Using TENS

Cancer patients experience a wide range of suffering, for example, nausea, vomiting, loss of appetite, fatigue, constipation, and diarrhea. Cancer-related pain in the broadest sense includes all of these physical symptoms, which physical therapists should work to treat.

The usefulness of TENS for cancer patients may involve not only pain reduction but also alleviation of other physical symptoms during palliative care. For example, the positive effect of TENS on nausea and vomiting in cancer patients has been reported [76, 77]. The effect of TENS on other symptoms has also been reported although not in cancer patients. Lau and Jones [78] reported that TENS improved dyspnea in patients with chronic obstructive pulmonary disease, while Iqbal et al. [79] reported that TENS was effective in patients with chronic constipation. However, whether these effects could be obtained in advanced cancer patients has not yet been investigated.

According to previous studies, low-frequency TENS (4–10 Hz) appears to be effective for physical symptoms other than pain. The stimulation site is the back, but the electrode position is changed according to the expected effect (Fig. 17.9).

A study of actual cancer patients has shown that TENS may reduce nausea and appetite loss in such patients [73]. However, no improvement in constipation was observed. This suggests that the opioid side effects were stronger than the effects of TENS. The effect of TENS on dyspnea has also not been confirmed [73], but adjusting the TENS conditions may help. It was hypothesized that the reduction in dyspnea by TENS may be due to its effect on vagal afferents via hypothalamic stimulation [78].

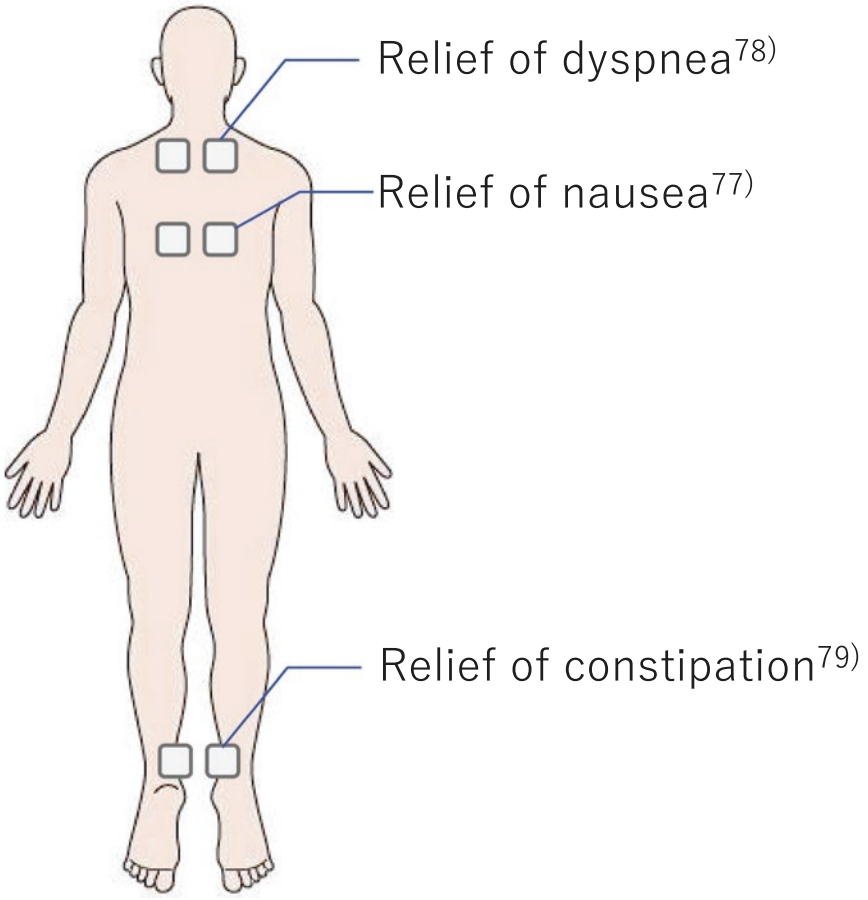


Fig. 17.9 Treatment of cancer-related symptoms other than pain using TENS. For dyspnea and nausea, the gel pads are placed at the back at C6-Th1 and Th4–6 levels. TENS stimulation is at 10 or 100 Hz. For constipation, the gel pads are placed at the inside of the ankle joint (tibial nerve). TENS stimulation is at low frequency (4–10 Hz)

17.12 Other Treatments in Physical Therapy for Cancer Patients

A potential treatment for cancer pain is laser therapy. Laser therapy cannot be used for visceral pain, but it is effective for mucosal damage commonly seen in cancer patients. Bensadoun [80] reported on the importance of low-level laser therapy on wound healing and its role in treatments for cancer therapy-induced mucositis. Maiya et al. [81] subsequently reported that helium–neon laser therapy was effective for reducing pain and improving healing of radiation-induced mucositis after 6 weeks of therapy in head and neck cancer patients. In a recent studies, the

immediate pain-relieving effect of photobiomodulation therapy (low-level laser) in patients with oral ulcers of chronic graft-versus-host disease (cGVHD) refractory was reported [82]. Although not yet in practical use, physical therapy devices may reduce the suffering of cancer patients.

17.13 Clinical Recommendation and Conclusion

An integrative approach is useful in the treatment of cancer-related pain. The basic principle is pharmacologic therapy, in addition to a combination of several non-pharmacologic therapies can provide more effective pain relief. As a result, success in reducing drug dosages may also reduce their side effects. Nondrug therapies should be actively pursued because, unlike pharmacologic therapy, they do not have side effects. Although not included in this chapter, aromatherapy, music therapy, yoga, acupuncture, and hypnosis are also said to be effective. The efficacy of acupuncture and music therapy in particular has been reported and should be included in the program if possible [32, 83, 84].

Physical therapists, nurses, and occupational therapists carry out with each other to implement non-pharmacologic therapy. The treatment that physical therapists should take the lead in is exercise and TENS. Exercise is standardized not only for pain relief but also to prevent disuse muscle atrophy, improve ADLs, and maintain physical fitness. On the other hand, TENS is rarely performed, and few studies have reported its efficacy; thus, further research is necessary. It should be noted, however, that TENS is not a panacea. Patients with severe cancer-related pain may be averse to TENS. In such cases, massaging is more effective. Patients with prior TENS experience are often willing to undergo TENS for cancer-related pain.

Patients who have a strong spiritual need, who wish to have a more naturalistic approach to health, and patients who have benefited from these therapies previously are more open to integrative therapies and appreciate their availability. If a clinician partners with the patient and values their perspective in how to manage pain, they will find the relationship between them enhanced. Only by considering what is truly important to a patient as an individual can we provide optimal patient-centered care, improve the quality of pain management, and comfort the patient to the best of our ability.

17.14 Conclusion

This chapter provided basic information on cancer-related pain, which is often classified into three categories, visceral pain, bone pain, and neuropathic pain. In addition, cancer-related pain is characterized by continuous and breakthrough pain. It is a progressive chronic pain that gradually worsens with recurrent episodes of breakthrough pain.

Treatment for cancer-related pain can be divided into pharmacotherapy and non-pharmacotherapy. Non-pharmacologic interventions that physical therapists can

implement include physical exercise, massage therapy, thermal therapy, and TENS. Exercise performed as part of the patient's rehabilitation routine may reduce pain, and thermal therapy is effective for relaxation and pain relief. Although there is little evidence on TENS, our research showed that the use of TENS for cancer-related pain was safe and provided limited pain relief. Additionally, nausea and appetite were also improved by TENS in cancer patients. It is indicated that TENS may be an effective tool for the treatment of cancer-related pain. However, TENS and other non-pharmacologic interventions are not a substitute for pharmacologic therapy. Pharmacologic therapy should be not to be omitted. An integrative approach combining multiple non-pharmacological interventions and pharmacotherapy is useful and important in the treatment of cancer-related pain.

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Nutrition and Daily Activities in Older Patients After Gastrectomy

18

Tatsuro Inoue

Abstract

Gastric cancer is one of the most common cancers in the world. The total number of gastric cancer patients is increasing with the aging population, and the number of older patients undergoing curative gastrectomy is correspondingly increasing. Geriatric nutritional problems such as malnutrition (undernutrition, obesity), sarcopenia, and frailty are powerful risk factors for the occurrence of complications and mortality after gastrectomy. Nutrition and daily activities are important modifiable factors in both incidence and treatment of gastric cancer. Enhanced recovery after surgery (ERAS) is a concept that has been developed with complex patient conditions, and perioperative nutritional and physical rehabilitations are part of ERAS. Several studies have adapted ERAS to gastric cancer patients, and improved clinical outcomes have been reported as a result. In this chapter, we discuss nutrition and daily activities from the perspectives of both nutrients and geriatric nutritional problems in patients with gastric cancer.

Keywords

Nutrition · undernutrition · sarcopenia · frailty · older adults

18.1 Introduction

Gastric cancer is one of the most common cancers in the world. In 2017, more than 1.22 million cases of gastric cancer were newly diagnosed globally, and it was the cause of death for 865,000 people [1]. The age-adjusted incidence rates are highest

T. Inoue (✉)
Department of Physical Therapy, Niigata University of Health and Welfare, Niigata City, Japan
e-mail: tatsuro-inoue@nuhw.ac.jp

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in the high-income Asia Pacific and East Asia regions [1]. Japan has one of the highest incidence rates of gastric cancer, and the incidence in 2018 was the second highest among men and the fifth highest among women among all cancers in Japan [2]. Early detection in addition to the development of therapeutic agents and minimally invasive surgery have reduced the mortality rate, and the number of cancer survivors is growing rapidly [2, 3]. It has been reported that the 5-year survival rate in Japan is 65% and that in South Korea is 71.5% [1]. Surgery and chemotherapy cause a decrease in physical function [4]. Thus, it is necessary to maintain independent daily living both during and after treatment in patients with gastric cancer.

Age-standardized incidence is decreasing [1], but the total number of gastric cancer is increasing with the aging population [3, 5]. The incidence of gastric cancer increases with age and is highest in those aged 75–84 years [6]. The number of older patients undergoing curative gastrectomy has been increasing [7], and surgeons must be aware of geriatric syndromes such as frailty, sarcopenia, and malnutrition, which need to be considered. Aging is a risk factor for increased mortality after gastrectomy [8]. Older patients who have undergone gastrectomy have poorer postoperative clinical outcomes compared to younger- or middle-aged patients [7]. Thus, interventions to improve postoperative clinical outcomes are important in older patients. In this chapter, we discuss the nutrition and daily activities of gastric cancer patients from the perspectives of both nutrients and geriatric nutritional problems.

18.2 Nutrition and Gastric Cancer

Lifestyle factors are closely associated with gastric cancer incidence. High salt intake increases the incidence of gastric cancer [9, 10]. Feng et al. reported in a meta-analysis that high salt intake is associated with approximately twice higher incidents of gastric cancer compared with low salt intake (odds ratio [OR], 2.05; 95% confidence interval [CI], 1.60–2.62) [9]. This tendency is particularly high among the Japanese population [9, 10]. Japanese food is rich in salt [11], with 60% of the average salt intake coming from seasonings [12]. Pickled food (risk ratio [RR], 1.28; 95% CI, 1.05–1.57) and processed meat (RR, 1.24; 95% CI, 1.03–1.49) also increase the incidence of gastric cancer [13]. The mechanism of how these foods affect gastric carcinogenesis is not fully understood, but the destruction of the mucosal barrier, intestinal metaplasia, is thought to be a possible mechanism [9]. On the other hand, a Mediterranean diet (RR, 0.73; 95% CI, 0.55–0.97) [14], high cruciferous vegetable intake (RR, 0.81; 95% CI, 0.75–0.88) [15], and high dietary fiber intake (RR, 0.58; 95% CI, 0.49–0.67) [16] are reported to be significantly associated with a lower risk of gastric cancer.

Gastric cancer is likely to cause nutritional problems. In addition to excessive intake of salt, pickled food, processed meat, and smoking [17], a risk factor for the incidence of gastric cancer is obesity. When a tumor develops in the stomach, it can cause difficulty to intake diet due to tumor-induced stenosis or obstruction, causing undernutrition. Some gastric cancer patients often have difficulty with oral intake

before treatment. Preoperative obesity and undernutrition lead to poor clinical outcomes after gastrectomy. Postoperative complications lead to lower overall survival (HR [hazard ratio], 1.88; 95% CI, 1.26–2.80) and disease-specific mortality (HR, 1.90; 95% CI, 1.19–3.02) [18]. Optimization of nutritional status through preoperative nutritional intervention may improve postoperative clinical outcomes.

Undernutrition after gastrectomy is a serious problem. Body mass index (BMI) and nutritional indices deteriorate after gastrectomy. Billroth I results in the least weight and nutritional loss such as total protein, albumin, the prognostic nutritional index (PNI), and nutritional risk index (NRI). Roux-en-Y is comparable to Billroth I in nutritional indicators, and Billroth II has the most nutritional loss [19]. Higher BMI at 1 year after gastrectomy leads to higher survival rates [20]. Loss of body weight and skeletal muscle mass after gastrectomy decreases the continuity of postoperative adjuvant chemotherapy [21, 22] and affects prognosis. Thus, nutritional intervention after gastrectomy is necessary.

18.3 Physical Activity, Exercise, and Gastric Cancer

Increased physical activity decreases the incidence of gastric cancer. A recent systematic review reported that high physical activity (>3000 METs [metabolic equivalents]) decreases the incidence of gastric cancer (RR, 0.83; 95% CI, 0.76–0.91) [23]. It has also been reported that physical activity increases estrogen and testosterone, enhances antioxidant defense, and may reduce the risk of cancer through biological mechanisms [24].

Physical activity, resistance training, and aerobic exercise during cancer treatment are performed safely and maintain or increase skeletal muscle mass and physical function. Interventions for physical activity during and after treatment are effective for upper and lower extremity muscle strength as well as fatigue in cancer patients [25]. Stene et al. reported in their systematic review that resistance training, aerobic exercise, and a combination of the two increased muscle strength and skeletal muscle mass in cancer patients [25]. Exercise has anti-inflammatory effects in patients with cancer cachexia [26]. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend maintaining and increasing physical activity to maintain skeletal muscle mass, physical function, and metabolic patterns in cancer patients [24]. They also recommend maintaining muscle strength and skeletal muscle mass through aerobic exercise and resistance training [24].

18.4 Malnutrition in Patients with Gastric Cancer Who Underwent Gastrectomy

Patients with gastric cancer are likely to have difficulty eating due to narrowing or obstruction of the gastroesophageal junction caused by the tumor, leading to undernutrition. On the other hand, obesity is also a risk factor for gastric cancer, so many patients with this type of cancer are obese [27]. The prevalence of malnutrition

varies depending on the screening or assessment. BMI, geriatric nutritional risk index (GNRI), subjective global assessment (SGA), and prealbumin are commonly used for nutritional screening and assessment of nutritional status before gastrectomy.

18.4.1 BMI

BMI is the most widely used nutritional assessment in patients with gastric cancer; it is an index that is calculated by dividing the subject's weight (kg) by the square of their height (m). A simple nutrition indicator, BMI, is included in many nutrition screening tools and diagnostic criteria. Globally, patients are classified according to the World Health Organization BMI classification as follows: underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30 kg/m^2) [28]. For Asian populations, <18.5 kg/m^2 indicates that the subject is underweight, 18.5–<23 kg/m^2 is standard, 23–<27.5 kg/m^2 indicates that the subject is overweight, and ≥27.5 kg/m^2 indicates that the subject is obese [29, 30]. The prevalence of being underweight before gastrectomy is 6.4–12.4%. The prevalence of obesity is also high, and it has been reported that up to approximately 30% of all patients undergoing gastrectomy have a BMI of ≥30 kg/m^2 before gastrectomy [31].

18.4.2 GNRI

The GNRI is an objective nutritional screening calculated using serum albumin levels and body weight. The formula is as follows: GNRI = (1.489 × albumin [g/L]) + (41.7 × weight [kg]/ideal body weight) [32]. If the subject's weight/ideal weight is less than 1.0, the ratio is set to 1. The standard staging is a major risk (GNRI <82), moderate risk (GNRI 82–91), low risk (GNRI 92–98), and no risk (GNRI >98) [32]. However, different cutoff values are often set according to studies.

GNRI has been used in several studies to screen preoperative nutritional status in patients who have undergone gastrectomy. In laparoscopy-assisted gastrectomy in patients aged ≥65 years, the reported prevalence was 10.2% when undernutrition was defined as GNRI <85.7 [33]. In a study of curative gastrectomy patients aged >75 years, the prevalence of undernutrition was 45.4% when undernutrition was defined as GNRI <92 [34]. Hirahara et al. reported that the prevalence of low GNRI (<98) was 38.8% before gastrectomy [35]. For patients aged ≥65 years who underwent laparoscopic gastrectomy with R0 resection, the cutoff values of preoperative GNRI to predict overall survival and cancer-specific survival were 94.8 and 90.0, respectively, and the percentage of patients below 90.0 was 22.2–32.7% [36]. The percentage of older patients with cancer cachexia in the low GNRI group (<91.959) was reported to be 50.9% [37].

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

Patient-generated subjective global assessment (PG-SGA) is a nutritional assessment tool for cancer patients that was developed by Ottery et al. in 1994, based on SGA [38]. Items on nutrition-related symptoms and short-term weight change were added to the SGA, and some items were answered by the patients themselves. PG-SGA is composed of self-reported sections (body weight, eating conditions, symptoms, activities, and physical function) and medical personnel assessment sections (nutrition-related disease state, metabolic state, physical examination). In a multicenter study conducted by Guo et al. of 2322 hospitalized patients with gastric cancer in China, 80.4% were malnourished (PG-SGA score ≥4) and 45.1% required urgent nutritional support (score ≥9) [39]. The prevalence of undernutrition was 26.8% using PG-SGA in patients with stage III gastric cancer patients [40].

18.4.4 Prealbumin

The usefulness of prealbumin as a prognostic factor has been reported [41, 42]. Low serum prealbumin (<15 mg/dL) is a predictor of the occurrence of all postoperative complications and infectious complications, even in patients with CRP >0.1 mg/dL [42]. Additionally, in a study by Izumi et al., postoperative complications were significantly lower in a group with a ≥10% increase in serum prealbumin after a mean of 10 days of preoperative nutritional therapy [43]. Thus, preoperative serum prealbumin reflects the early effects of preoperative nutritional intervention and may be a useful predictor of the occurrence of postoperative complications.

18.4.5 Other Nutritional Indicators

Several indices have been used to assess nutritional status in patients with gastric cancer. In a study comparing five nutrition screenings or assessments (Glasgow prognostic score [GPS], Malnutrition Universal Screening Tool [MUST], nutritional risk screening (NRI), PG-SGA and PNI), the prevalence of undernutrition was 63.2%, 43.3%, 20.6%, 26.8%, and 21.8%, respectively. The prevalence of undernutrition according to the Global Leadership Initiative on Malnutrition (GLIM) criteria for undernutrition diagnostic criteria published in 2019 [44] is not clear at present.

18.5 Malnutrition and Clinical Outcomes

18.5.1 Mortality and Complication After Gastrectomy

Malnutrition leads to poor clinical outcomes after gastrectomy. Impact on postoperative outcomes varies with preoperative BMI (Fig. 18.1). BMI <18.5 kg/m^2 increases mortality after gastrectomy [45–48]. On the other hand, obesity is a risk factor for surgery-related complications such as longer operation time, fewer retrieved lymph nodes, and a larger amount of intraoperative blood loss, but it has not been reported to affect long-term survival [46, 49]. In addition, a study of 30,765 patients using the Japanese nationwide inpatient database reported a U-shaped relationship between BMI and both postoperative complications and mortality [50]. In the present study, patients with a BMI of 23 kg/m^2 had the lowest mortality, occurrence of complications, and medical costs after gastrectomy. Thus, appropriate preoperative management of BMI may lead to improved clinical outcomes after gastrectomy. It was previously reported that visceral fat area, but not BMI, was a predictor of the occurrence of complications after gastrectomy [51]. It may be necessary to evaluate not only BMI but also body composition such as visceral fat area and muscle mass.

Low GNRI is a predictor of poor clinical outcomes after gastrectomy. Preoperative low GNRI (<85.7) is a predictor of postoperative poor overall survival and

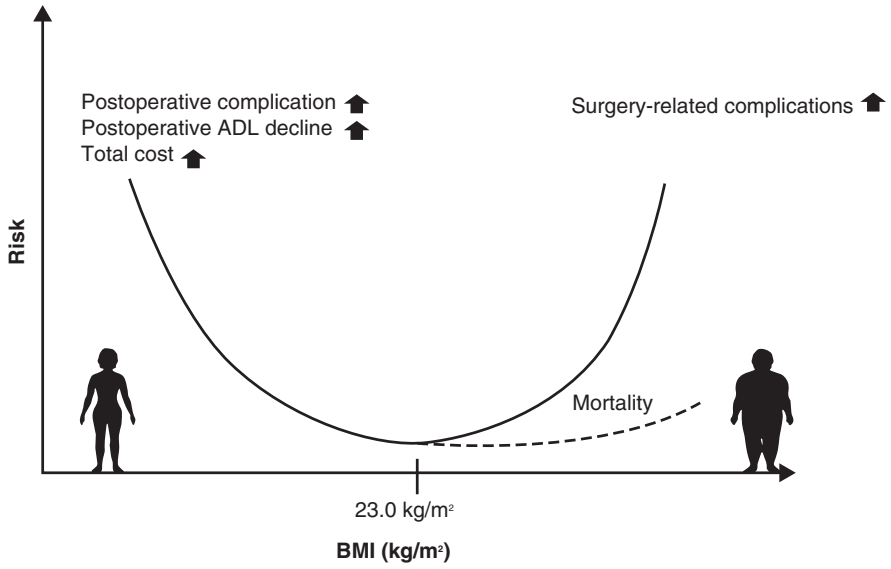

Fig. 18.1 Relationship between preoperative BMI and adverse outcomes after gastrectomy. Preoperative underweight status is a risk factor for many adverse outcomes, including the occurrence of complications, decreased activities of daily living, and increased healthcare costs, as well as a risk factor for long-term mortality. On the other hand, obesity is a risk factor for temporary surgery-related complications, but long-term mortality is low

postoperative complications [33]. Preoperative low GNRI (<92) has been reported to be a predictor of postoperative complications (Clavien-Dindo classification grade II or higher) [34]. The low GNRI group (<91.959) was predictive of overall survival after gastrectomy [37]. Low GNRI (<98) was predictive of poor overall survival and cancer-specific survival [35].

18.5.2 Quality of Life (QOL)

In a cross-sectional observational study of 2322 hospitalized gastric cancer patients, poor nutritional status assessed by the PG-SGA significantly decreased the 30-item European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) of functional categories and overall health status score [39]. The global scores and functional category scores, except for the social and emotional functioning scores, were higher when the nutritional status as well in the PG-SGA is higher [52]. In addition, in the symptom categories, higher PG-SGA was associated with higher QOL in all categories except diarrhea and dyspnea [52].

18.5.3 Activities of Daily Living (ADL)

There are few reports on the impact of nutritional status on activities of daily living in patients with gastric cancer. Inoue et al. performed a Japanese nation survey of 1769 older patients (≥65 years old) who had undergone gastrectomy, and to date, it is the only study to objectively assess ADL after gastrectomy [53]. In that study, 11.9% of subjects were underweight (<18.5 kg/m^2), 46.7% were standard (18.5–<23 kg/m^2), 34.1% were overweight (23–27.5 kg/m^2), and 7.3% were obese (≥27.5 kg/m^2) [53]. In multivariate analysis, a significant association was observed between BMI and Barthel index scores (underweight group, standardized coefficient, −0.040, compared with standard group, $P = 0.013$). Thus, it is necessary to emphasize patient-oriented outcomes such as ADL and QOL in gastric cancer patients. Further research into this is needed.

18.5.4 Malnutrition and Nonsurgical Treatments

Some studies have examined the relationships between nutritional status and radiotherapy-associated toxicities in patients with gastric cancer. Hypoalbuminemia (<3.5 g/dL) is a risk factor for grade 3 and 4 hematological and non-hematological adverse events [54]. Weight loss (≥10%) was a predictor of grade 3/grade 4 non-hematological adverse events [54]. Nutrition risk screening 2002 (NRS-2002), PG-SGA score, and NRI score were not associated with treatment-induced adverse events.

18.6 Sarcopenia in Patients with Gastric Cancer

Sarcopenia is defined as age-related loss of skeletal muscle mass, muscle strength, and physical function. The prevalence of sarcopenia before gastrectomy varies according to the diagnostic criteria. Most studies have defined sarcopenia in patients with gastric cancer only by measuring the skeletal muscle around L3 measured using computed tomography (CT). Figure 18.2 shows CT imaging of the diagnosis of gastric cancer which comprises total skeletal muscles at the L3 level, including the rectus abdominis, internal obliques, external obliques, transversus abdominis oblique, abdominis, quadratus lumborum, erector spinae, and psoas which are imaged. This is the reason for defining sarcopenia solely by skeletal muscle mass in patients with gastric cancer. This differs significantly from the European Working Group on Sarcopenia in Older People (EWGSOP) [55, 56] (Fig. 18.3) and Asian Working Group for Sarcopenia (AWGS) criteria [57, 58] (Fig. 18.4), which are widely used worldwide to include not only skeletal muscle mass but also muscle strength and physical function, in the definition of sarcopenia. Skeletal muscle mass is an indicator that primarily reflects nutritional status, directly reflecting catabolism and anabolism in the muscle. Some studies have defined sarcopenia to include muscle strength and physical function [59, 60] and have reported a lower prevalence of sarcopenia compared to a diagnosis based on skeletal muscle mass alone in patients with gastric cancer. To accurately compare the prevalence of sarcopenia with other

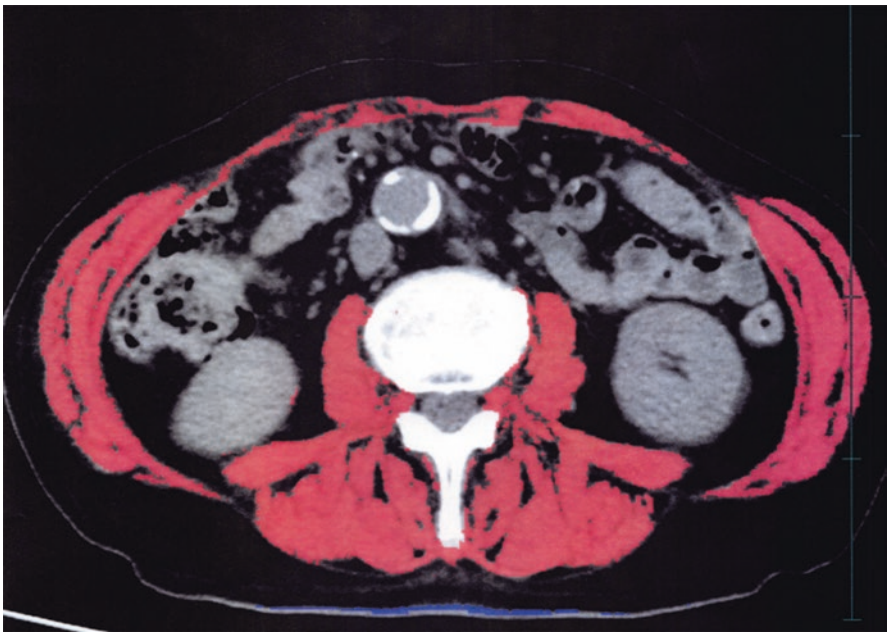

Fig. 18.2 Skeletal muscle mass at L3 level. Red areas are skeletal muscles including the rectus abdominis, internal obliques, external obliques, transversus abdominis oblique, abdominis, quadratus lumborum, erector spinae, and psoas

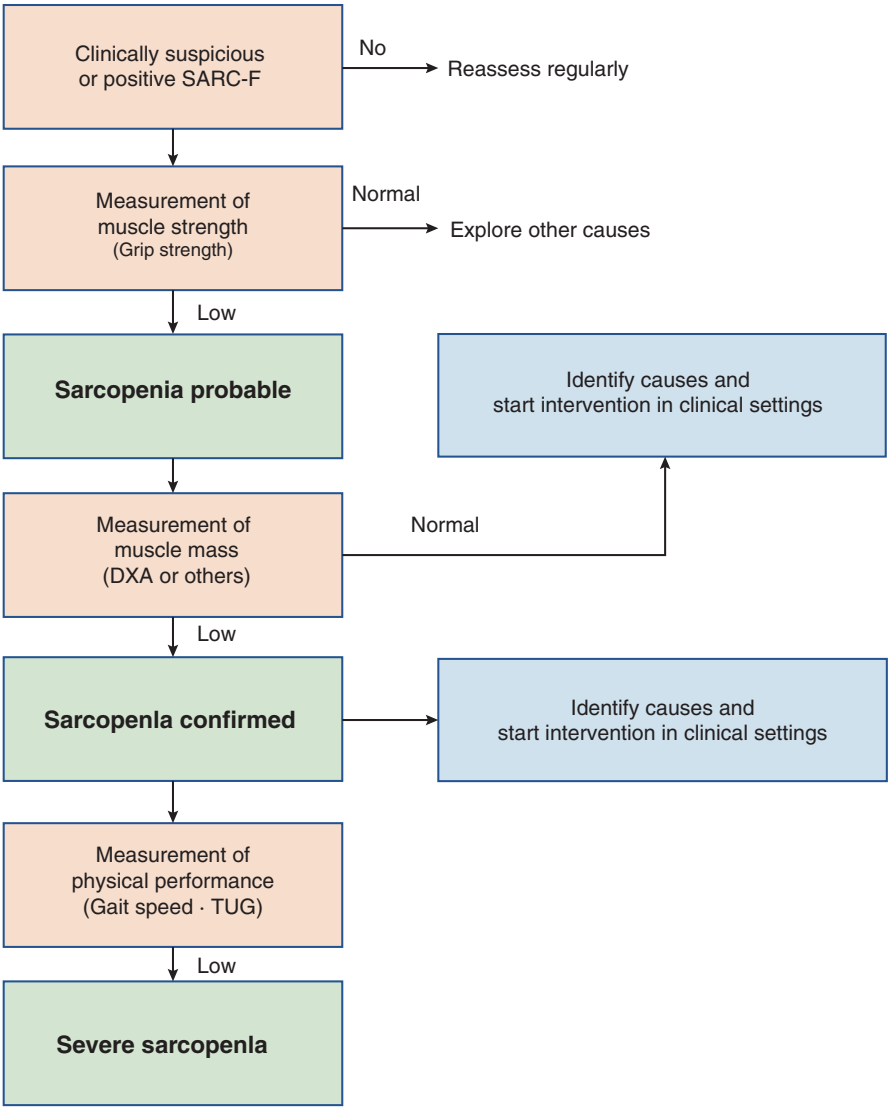

Fig. 18.3 Sarcopenia diagnostic algorithm by the European Working Group on Sarcopenia in Older People (EWGSOP) 2

diseases and to determine its prognostic impact, a diagnosis that takes into consideration muscle strength and physical function may be necessary. In addition, the skeletal muscle mass of the extremities is widely used in the diagnosis of sarcopenia. In particular, the lower extremities are the skeletal muscles most affected by aging. Despite the confirmed correlation between limb and L3 skeletal muscle mass, limb skeletal muscle mass should be taken into consideration when diagnosing sarcopenia.

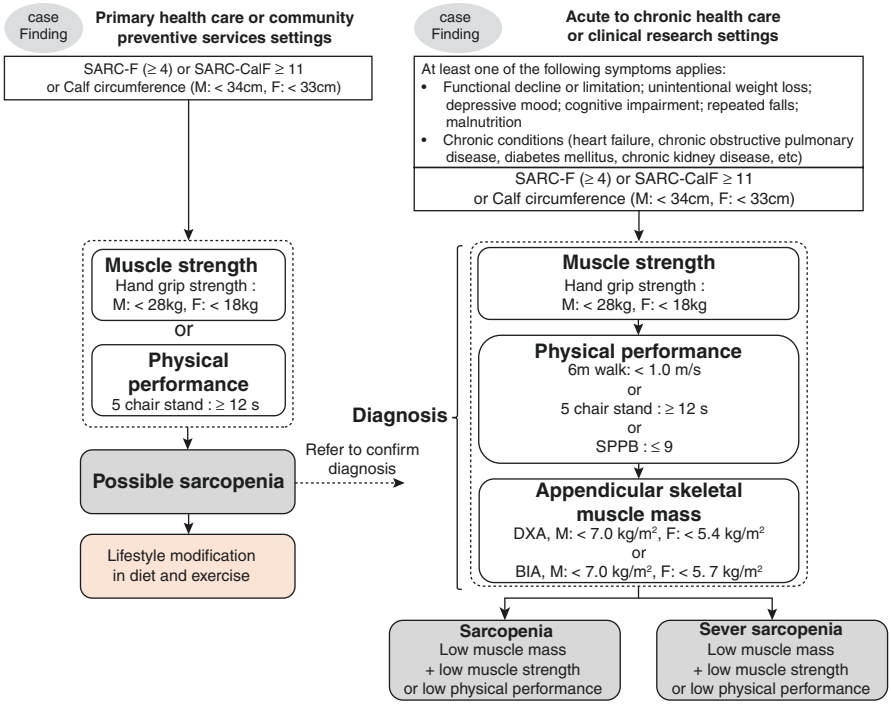

Fig. 18.4 Sarcopenia diagnostic algorithm by the Asian Working Group for Sarcopenia (AWGS) 2019

18.6.1 Sarcopenia and Clinical Outcomes in Patients with Gastric Cancer

Preoperative sarcopenia affects adverse clinical outcomes after gastrectomy. In a recent meta-analysis by Chen et al., preoperative sarcopenia was found to lead to the occurrence of overall complications (RR, 2.89; 95% CI, 1.86–4.49), serious complications (Clavien-Dindo grade ≥3, RR, 3.01; 95% CI, 1.73–5.23), pneumonia (RR, 2.64; 95% CI, 1.71–4.09), and obstruction (RR, 3.96; 95% CI, 2.27–6.90) [61]. In addition, preoperative sarcopenia reduced the overall survival rate (hazard ratio [HR], 1.71; 95% CI, 1.53–1.91) but was not associated with postoperative delayed gastric emptying (RR, 1.44; 95% CI, 0.63–3.25), intra-abdominal infection (RR, 2.09; 95% CI, 0.88–5.00), and anastomotic leakage (RR, 1.26; 95% CI, 0.69–2.32) [61]. In a meta-analysis by Yang et al., sarcopenia was found to be a risk factor of total postoperative complications (OR, 2.17; 95% CI, 1.53–3.08), severe complications (OR, 1.65; 95% CI, 1.09–2.50), and poorer overall survival (HR, 1.70; 95% CI, 1.45–1.99) [62]. Kamarajah et al. reported in their meta-analysis that sarcopenia affects major complications (OR, 1.67; 95% CI, 1.14–2.46) and pulmonary complications (OR, 4.01; 95% CI, 2.23–7.21) and worsens survival (HR, 2.12; 95% CI, 1.89–2.38) after gastrectomy [63]. Thus, sarcopenia is an

important skeletal muscle disease that leads to many adverse outcomes, and preoperative interventions may be effective in improving postoperative outcomes. However, as mentioned above, many studies have defined sarcopenia using only skeletal muscle mass. Sato et al. reported that only preoperative grip strength affected postoperative complications, and skeletal muscle mass had no effect after gastrectomy [64]. Future studies evaluating not only skeletal muscle mass but also skeletal muscle function are needed.

18.7 Frailty in Patients with Gastric Cancer

18.7.1 Prevalence of Frailty in Patients with Gastric Cancer

Frailty is a condition in which vulnerability to stress with aging causes health problems. The definition of frailty and how to assess it are controversial. In general, frailty phenotype [65] and an accumulated deficit model [66] are widely used to assess frailty.

There are few studies on frailty in gastric cancer patients. In a Chinese study of gastric and colorectal cancer inpatients aged ≥60 years evaluated using the Groningen Frailty Indicator, the prevalence of frailty was 43.8%, and the risk factors were older age (OR, 1.065; 95% CI, 1.001–1.132), low handgrip strength (OR, 4.346; 95% CI, 1.739–10.863), no regular exercise habit (OR, 3.228; 95% CI, 1.230–8.469), and low MNA-SF score (OR, 11.090; 95% CI, 5.119–24.024) [67]. Lu et al. defined frailty as consisting of preoperative albumin (<3.4 g/dL), hematocrit (<35%), and creatinine (>2 mg/dL) [68]. The patients aged >80 years in that study were categorized according to the number of positive traits as follows: nonfrailty, up to two traits, and frailty, three traits in patients with gastric cancer [68]. As a result, the prevalence of frailty was 32.7% [68]. Choe et al. reported that in the Study of Osteoporotic Fractures (SOF) frailty index (unintentional weight loss of at least 5% in the past year, inability to stand up five times in a row from a chair without the need for an armrest, a negative answer to the question "Are you feeling well?"), 25.1% were pre-frailty, and 14.8% were determined to be frail [69].

18.7.2 Frailty and Clinical Outcomes in Patients with Gastric Cancer

Preoperative frailty negatively affects clinical outcomes after gastrectomy. Frailty assessed by preoperative laboratory data has been reported to be a predictor of postoperative complications (OR, 3.396; 95% CI, 1.046–11.025), overall survival (OR, 1.613; 95% CI, 1.052–2.473), replace-free survival (OR, 1.859; 95% CI, 1.279–2.703), and cancer-specific survival (OR, 1.859; 95% CI, 1.279–2.703) in patients aged >80 years [68]. In addition, preoperative frailty (pre-frailty and frailty) assessed by SOF was a risk factor of readmission within one year of discharge after gastrectomy (OR, 5.74; 95% CI, 1.78–18.48) [69].

18.8 Perioperative Nutrition and Rehabilitation Intervention

18.8.1 ERAS

The philosophy of ERAS is a multi-modal approach to reduce invasive reactions, achieve early independence in physical activity and nutritional intake, reduce perioperative anxiety, and motivate recovery (Fig. 18.5). Nutritional items in ERAS include perioperative oral intake, stimulation of postoperative bowel movements, prevention of nausea and vomiting, prevention of intestinal edema, and oral intake of carbohydrate solutions both the night before and the morning of surgery. Early mobilization is a component of ERAS, the principles of which have been refined and applied to many types of surgeries.

ERAS has been shown to improve clinical outcomes in patients with gastrointestinal cancer. In a meta-analysis, ERAS was reported to reduce the length of hospital stay (pool weighted mean difference [WMD], 2.47 days, 95% CI, −3.06 to −1.89), time to flatus (WMD, 0.70 days, 95% CI, −1.02 to −0.37), and reduced hospitalized cost (WMD USD$ 4400, 95% CI, −USD$ 5580 to −USD$ 3210) in both open and laparoscopic surgeries in gastric cancer patients [70]. In addition, ERAS significantly reduced C-reactive protein levels on days 3, 4, and 7; interleukin-6 levels on days 1, 3, and 4; and tumor necrosis factor-α levels on days 3 and 4 [70] but raised the readmission rate (RR, 1.95; 95% CI, 1.03–3.67) [70]. In a meta-analysis of ERAS in upper gastrointestinal surgery including gastric cancer, ERAS reduced pneumonia (RR, 0.50; 95% CI, 0.33–0.75), postoperative hospital stay (MD, −2.53; 95% CI, −3.42 to −1.65), and time until first postoperative flatus (MD, −0.64; 95% CI, −0.84 to −0.45) and decreased days to first

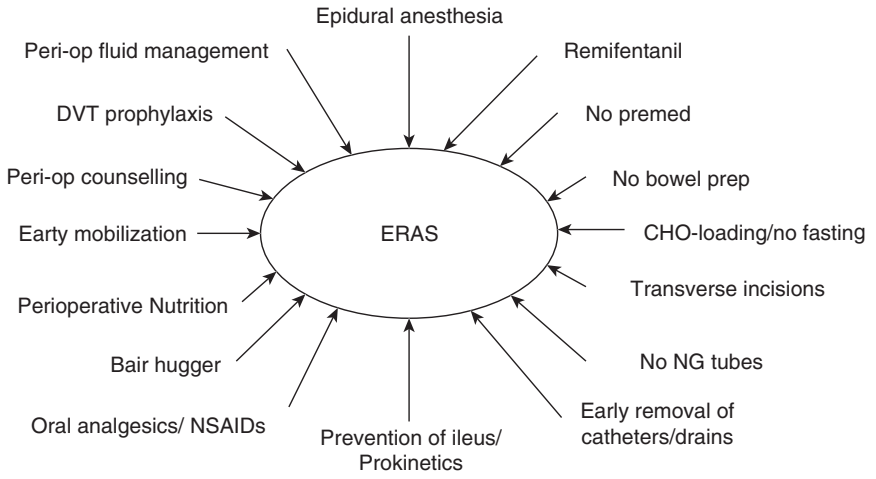

Fig. 18.5 Enhanced recovery after surgery (ERAS)

bowel movement (MD, 1.10; 95% CI, −1.74 to −0.47) compared with standard care [71]. On the other hand, there were no differences regarding urinary tract infection, surgical site infection, postoperative anastomotic leakage, readmissions, or ileus [71].

ERAS is not effective for reducing readmission rates. Wee et al. and Ding et al. in their meta-analysis reported higher rehospitalization rates in ERAS compared to standard care [70, 72]. Moreover, other previous studies reported no significant difference in readmission rates between ERAS and standard care [71, 73, 74]. It is unclear that ERAS can reduce readmission rates; it may be due to the high number of delayed complications in gastric cancer patients [70].

18.8.2 Pre-rehabilitation

Pre-rehabilitation is performed to prevent postoperative complications, especially respiratory complications, and to accelerate postoperative functional recovery. Postoperatively, patients experience decreased skeletal muscle mass, muscle strength, and physical function due to hypercatabolism and inflammation. The preoperative period is regarded as an important opportunity to improve muscle mass, skeletal muscle mass, physical performance, endurance, and nutritional status to compensate for these physiological reserve deficits. Older gastric patients, especially those with coexisting frailty, sarcopenia, and malnutrition, have low reserve capacity, causing a mismatch with the physiological demands placed on the body and delaying postoperative recovery. Frailty and sarcopenic older adults are suitable candidates for pre-rehabilitation. Pre-rehabilitation is a multimodal approach that includes not only physical rehabilitation but also nutritional intervention and psychological support [75].

18.8.3 Pre-rehabilitation in Physical Aspects

Preoperative physical rehabilitation programs are composed of extensive programs. This type of rehabilitation often consists of respiratory muscle training, breathing exercises, upper and lower extremity resistance training, aerobic exercise, and stretching [76]. In a meta-analysis by Tukanova et al., pre-rehabilitation reduced the incidence of pneumonia (pooled OR, 0.70; 95% CI, 0.51–0.95) and incidence of morbidity (Clavien-Dindo grade 2 or higher, pooled OR, 0.68; 95% CI, 0.49–0.95) after gastrectomy [76]. In a meta-analysis by Lambert et al. for hepatobiliary, colorectal, and upper gastrointestinal cancer, pre-rehabilitation decreased length of hospital stay, but no differences were found regarding postoperative complications or mortality, when compared with usual care [77].

18.8.4 Perioperative Nutritional Intervention

In preoperative patients with undernutrition and sarcopenia, optimization of nutritional status through preoperative nutritional intervention may improve clinical outcomes after gastrectomy. The ESPEN guidelines recommend that patients with severe preoperative undernutrition delay surgery for 10–14 days to allow for nutritional therapy [78]. In a randomized controlled trial (RCT) of preoperative nutritional therapy for gastrointestinal cancer patients, oral intake of arginine, u-3 fatty acids, and RNA for 5 days before surgery in patients undergoing pancreatoduodenectomy resulted in fewer serious complications than in a control group receiving a normal diet [79]. In addition, it has been reported that preoperative enteral administration of 2.2 g/day of eicosatetraenoic acid (EPA) for 5 days significantly prevented a decrease in lean body mass in patients undergoing esophagectomy compared to the normal group [80]. In addition, the stress responses of TNFα, IL-10, and IL-8 were significantly reduced in the EPA group compared to the standard group [80]. On the other hand, it is unclear whether preoperative nutritional therapy is effective in patients undergoing gastrectomy. In an RCT of gastrectomy patients who received a 600-kcal diet containing 2.2 g of EPA for 7 days preoperatively and 21 days postoperatively, there was no difference in surgical morbidity or weight loss at 1 and 3 months postoperatively, compared with controls with a normal diet [81]. Thus, the optimal quality of nutrition and the number of days of perioperative administration are not clear. Optimal nutritional therapy in gastric cancer patients needs to be established.

Leucine has been effective in older adults with sarcopenia. Muscle protein synthesis is most enhanced after resistance training, compared to nutrition alone or resistance training alone [82], and this is no exception even among the older adults [83]. Regarding nutritional quality, leucine, branched-chain amino acids [84] and β-hydroxy-β-methyl butyrate (HMB) have been reported to increase muscle mass among older adults [85]. Preoperative nutritional intervention with these nutrients has been conducted in gastric cancer patients [86].

18.8.5 Combination Intervention of Nutritional Management and Rehabilitation After Gastrectomy

Several studies have reported the effects of combined exercise and nutrition interventions in older patients who underwent curative gastrectomy. Minnella et al. suggested that pre-rehabilitation combined with exercise intervention (aerobic exercise and resistance training) and nutritional intervention (nutritional counseling and whey protein supplement of 1.2–1.5 g/kg of ideal body weight) improved the change of preoperative 6-minute walk distance (6MWD) (mean 6MWD change, 36.9 ± 51.4 vs −22.8 ± 52.5 m; $P < 0.001$) and postoperative 6MWD (mean 6MWD change, 15.4 ± 65.6 vs −81.8 ± 87.0 m; $P < 0.001$) in patients with esophageal and gastric

cancer [87]. Yamamoto et al. reported that preoperative exercise interventions (resistance training and increased physical activity) and nutritional interventions (>28 kcal/kg of ideal body weight, protein 1.2 g/kg of ideal body weight, and 2.4 g daily oral supplementation with leucine metabolite hydroxymethyl butyrate) reduced the occurrence of postoperative complications in older patients with sarcopenia who had undergone gastrectomy [86]. Future intervention studies are required to clarify the combined effects of exercise and nutrition in patients with frailty, sarcopenia, and undernutrition.

18.9 Conclusion

Nutrition and daily activities are closely related to the incidence and treatment of gastric cancer. In the treatment of gastric cancer, preoperative geriatric nutritional problems (undernutrition, obesity, sarcopenia, and frailty) are powerful predictors of adverse outcomes after gastrectomy. Therefore, a multi-modal perioperative approach based on nutrition and exercise is needed to maximize clinical outcomes.

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Frailty and Mental Health in Older Patients with Gastrointestinal Cancer

19

Maho Okumura and Rei Ono

Abstract

Frailty is highly prevalent in gastrointestinal cancer patients due to decreased food intake and gastrointestinal symptoms. Frailty is associated with postoperative complications, emergency room visits, and mortality, making preoperative screening important. Gastrointestinal cancer patients also have a high prevalence of postoperative psychiatric disorders due to postoperative complications, poor prognosis, and negative body image. Since psychiatric symptoms affect activities of daily living and quality of life, rehabilitation plays a significant role in treatment. Rehabilitation for gastrointestinal cancer patients is aimed at prevention of postoperative complications and improvement of physical function, and in recent years, pre-rehabilitation has been the focus of attention. The effects of exercise on mental health have been reported in several studies, and exercise is a low-cost and safe method for improving mental health. Finally, we discuss the association between social frailty and mental health, which is the topic of our research.

Keywords

Frailty · Mental health · Gastrointestinal cancer patients · Social frailty Rehabilitation

M. Okumura (✉)
Division of Rehabilitation Medicine, Kobe University Hospital, Kobe, Hyogo, Japan
e-mail: omaho@med.kobe-u.ac.jp

R. Ono
Department of Health Promotion and Exercise, National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health and Nutrition, Shinjuku, Tokyo, Japan

Department of Public Health, Kobe University Graduate School of Health Sciences, Kobe, Hyogo, Japan
e-mail: ono@phoenix.kobe-u.ac.jp

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19.1 Introduction

19.1.1 Gastrointestinal Cancer and Frailty

Colorectal and gastric cancers were the most prevalent cancer types in Japan in 2018 [1]. In 2020, gastrointestinal cancers accounted for the second to fifth highest number of deaths [1], highlighting the need for improved treatment and care. Most affected individuals are older adults. Gastrointestinal cancers are characterized by an increased endogenous energy consumption, due to general chronic inflammation and cachexia. The presence of tumors in the digestive organs leads to symptoms such as decreased food intake, impaired transit of food, worsened nutritional status, weight loss, sarcopenia, and frailty. This text focuses on frailty.

In geriatrics, there are two main theories of frailty: phenotypic and accumulated deficit. Phenotypic frailty theory conceptualizes frailty as a complex age-related clinical condition where a decline in physiological capacity across several organ systems results in increased susceptibility to stressors [2, 3]. This is preventable and reversible. Accumulated deficit theory conceptualizes frailty as a result of accumulated medical, physical, and social conditions that drive the increased vulnerability observed in frailty [4, 5].

In geriatric oncology, frailty is used as a pretreatment screening tool and is associated with postoperative complications, treatment-related toxicity, and mortality [6]. Preoperative frailty predicts postoperative complications in elderly colorectal surgery patients [7]. Among patients with esophageal and head and neck cancers undergoing curative intent concurrent chemoradiotherapy, those with pretreatment frailty had significantly higher rates of adverse events and emergency room visits than those without pretreatment frailty [8]. In a meta-analysis, colorectal cancer (CRC) patients with frailty also had a higher mortality rate than non-frail patients [9]. Screening and response to frailty should be implemented prior to treatment to improve outcomes of elderly cancer patients.

19.1.2 Gastrointestinal Cancer and Psychiatric Symptoms

Psychiatric disorders affect treatment outcomes. Surgical CRC patients who underwent adjuvant chemotherapy for major depression had worse overall survival rates [10]. Similarly, postoperative esophageal cancer patients who developed a new psychiatric disorder during the first 2 years after surgery also had higher mortality rates than those without psychiatric disorders [11].

Mental disorders are highly prevalent in patients following gastrointestinal cancer treatment. Patients with esophageal cancer have a higher prevalence of anxiety and depressive symptoms than other matched patients [12]. Bergquist et al. investigated the prevalence of depression in patients with esophageal or gastroesophageal junction cancer before surgery and 1, 2, 3, 6, and 12 months after surgery and reported an increase in prevalence at 6 months [13]. Hellstadius et al. reported that while the prevalence of depressive symptoms in preoperative esophageal cancer

patients was 20% preoperatively, it was up to 27% at 6 months and 32% at 1 year postoperatively [14]. The high prevalence of postoperative mental disorders in these patients may be owing to complications, such as dysphagia, strictures, and dumping syndrome following surgery, and poor prognoses [15]. In addition, in patients with CRC, stoma surgery may result in a negative body image, sexual problems, and reduced psychosocial adaptation [16]. Therefore, the mental health of patients with gastrointestinal cancers must be monitored not only at the time of diagnosis and treatment but also continuously thereafter.

19.2 Impact of Psychiatric Distress on Physical Function, Activities of Daily Living, and Quality of Life

Among gastrointestinal cancer patients aged ≥60 years, those with moderate to severe depression were more likely to report falls, malnutrition, frailty, fatigue, and dependence in instrumental activities of daily living (IADLs) and in activities of daily living (ADLs) [17]. Depression and anxiety, assessed according to the Beck Anxiety Scale and Beck Depression Scale, are risk factors for a reduced quality of life (QOL) as assessed by the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) within 3–6 months after discharge among esophageal cancer patients following endoscopic submucosal dissection [18]. In addition, a study of esophageal cancer patients revealed that those with psychiatric symptoms, as indicated using the Hospital Anxiety and Depression Scale (HADS), had lower QOL subscale scores, such as those in physical function, dyspnea, and general fatigue (according to EORTC QLQ C-30), both before and after surgery, than patients without psychiatric issues [19]. Since psychiatric conditions of patients with gastrointestinal cancers affect not only postoperative treatment outcomes but also long-term life quality, we believe that rehabilitation plays a significant role in treatment.

19.3 Physical Therapy Evaluation of Physical Frailty and Mental Health

19.3.1 Physical Frailty

The screening tools commonly used in geriatrics are shown in Sects. 19.3.1.1 and 19.3.1.2. In the field of geriatric oncology, frailty screening tools that can be easily measured in daily clinical settings are shown in Sects. 19.3.1.3 and 19.3.1.4 (Table 19.1).

19.3.1.1 Frailty Index

The accumulated deficit theory in the field of geriatrics holds that frailty is caused by a comprehensive abnormality in the accumulation of multiple factors, including disease and functional decline. The frailty index, proposed by Rockwood et al. in Canada, assesses a comprehensive set of factors, including 30–70 ADLs, IADLs,

Table 19.1 Frailty screening tools for elderly cancer patients

	Frailty index	CHS	G8	VES-13
Number of questions	30–70	5	8	13
Muscle weakness/ physical function/ physical activity/falls	• Changes in everyday activities • Problems going out alone • Impaired mobility • Poor standing posture • Irregular gait pattern • Bulk difficulties • Falls	• Physical activity • Gait speed <1.0 m/s • Grip strength <28 kg for men or 18 kg for women	• Mobility	• Stooping, crouching, or kneeling • Lifting of carrying 10 lb • Writing of handling small objects • Reaching or extending the arm above the shoulder • Walking 1/4 mile • Doing heavy housework
ADL/IADL	• Problems cooking • Problems getting dressed • Problems with bathing • Problems grooming oneself • Urinary incontinence • Toileting problems			• Shopping • Managing money • Doing light housework • Transferring • Bathing

Nutrition			• Weight loss	• Food intake declined • Weight loss • Body mass index	
Mental/ cognitive	• Mood problems • Feeling sad, blue, or depressed • History of depressed mood • Tiredness all the time • Depression (clinical impression) • Sleep changes • Restlessness • Memory changes • Short-term memory impairment	• Long-term memory impairment • Changes in general mental functioning • Onset of cognitive symptoms • Clouding or delirium • Paranoid features • History relevant to cognitive impairment or loss • Family history relevant to cognitive impairment or loss	In the past 2 weeks, have you felt tired without a reason?	Neuropsychological problems	

(continued)

Table 19.1 (continued)

	Frailty index		CHS	G8	VES-13
Comorbidity	• Impaired vibration • Tremor at rest • Postural tremor • Intention tremor • History of Parkinson's disease • Family history of degenerative disease • Seizures and partial complex • Seizures and generalized • Syncope or blackouts • Headache • Cerebrovascular problems • Musculoskeletal problems • Bradykinesia of the limbs • Bradykinesia and facial • Poor muscle tone in limbs • Poor limb coordination • Poor coordination and trunk • Rectal problems • Gastrointestinal problems • Sucking problems	• Head and neck problems • Poor muscle tone in the neck • History of stroke • History of diabetes mellitus • Arterial hypertension • Peripheral pulses • Cardiac problems • Myocardial infarction • Arrhythmia • Congestive heart failure • Lung problems • Respiratory problems • History of thyroid disease • Thyroid problems • Skin problems • Malignant disease • Breast problems • Abdominal problems • Presence of snout reflex • Presence of the palmomental reflex • Other medical history			
Others				• Age (<80 or 80–85 or ≥86) • ≥3 drugs/day • Self-rated health status	• Age (75–85 or ≥85) • Self-rated overall health status
Frailty	Score ≥0.25		Score ≥3	Score ≤14	Score ≥3

CHS cardiovascular health study, *G8* Geriatric8, *VES-13* Vulnerable Elders Survey-13

subjective health, comorbidities, and physical abilities [4, 5]. The total number of deficits present in the patient is divided by the total number of variables in frailty index score. The values are ranged from 0 (no frail) to 1 (severely frail), with a score ≥0.25 indicating frailty [20]. However, it is difficult to calculate and is therefore rarely used in clinical practice.

19.3.1.2 Cardiovascular Health Study

In the Cardiovascular Health Study (CHS) proposed by Fried et al., frailty was defined as three or more of the following five conditions: (1) unintentional weight loss, (2) low physical activity, (3) exhaustion, (4) weak grip strength, and (5) slow gait [2]. The Japanese version of the CHS criteria was constructed in 2017 [21] and revised in 2020 [22] as follows:

1. Shrinking: Have you lost 2 kg or more in the past 6 months? ("yes" = 1 point)
2. Low activity:
   (a) Do you engage in moderate levels of physical exercise or sports aimed at health?
   (b) Do you engage in low levels of physical exercise aimed at improving health? ("no" to both questions = 1 point)
3. Exhaustion: In the past 2 weeks, have you felt tired without a reason? ("yes" = 1 point)
4. Weakness: grip strength <28 kg for men or 18 kg for women (1 point)
5. Slowness: gait speed <1.0 m/s (1 point)

As in the CHS criteria, a score ≥3 indicates frailty.

Fried et al.'s definition remains useful in the field of oncology [23]. Their method is recommended in clinical practice over Rockwood's because of its concept of being preventable and reversible and because it consists of only five points, allowing quick patient screening.

19.3.1.3 Geriatric8

The Geriatric8 (G8) is the most widely used frailty screening tool in geriatric oncology. It is an eight-item questionnaire that includes one age-related item (<80 or 80–85 or ≥86 years) and seven items from the 18-item Mini-Nutritional Assessment (MNA®): food intake, weight loss, mobility, neuropsychological problems, body mass index, drugs, and health status [24]. The total scores ranged from 0 to 17, with a score ≤14 indicating frailty. The G8 is an easy tool that can be performed in approximately 3 min, and the Japan Clinical Oncology Group recommends its use [25].

19.3.1.4 Vulnerable Elders Survey-13

The Vulnerable Elders Survey-13 (VES-13) is a 13-item self-administered questionnaire that includes questions on age, self-rated overall health status, functional limitations in six domains of physical functioning, and five domains of functional disabilities [26]. A total score ≥3 indicates frailty. The Japanese version has been previously verified [27].

19.3.2 Mental Health

An appropriate questionnaire that screens mental health disorders should be easily assessed and interpreted by physical therapists who are not mental health professionals. They have an advantage of being less burdensome to the patient owing to their quick completion. The following is a list of questionnaires currently used in clinical and research settings in Japan (Table 19.2).

19.3.2.1 Hospital Anxiety and Depression Scale

HADS is a questionnaire consisting of 14 items, 7 for anxiety and 7 for depression [28], and its reliability and validity have been reported in Japan [29]. Each item has a 0–3 score; the higher the total score, the stronger the psychological symptom. For patients with cancer, previous studies have recommended cutoffs of 5, 7, and 13 points for anxiety, depression, and in total, respectively [30].

19.3.2.2 The Center for Epidemiologic Studies Depression Scale

The Center for Epidemiologic Studies Depression Scale (CES-D) is a self-assessment scale for depression developed by the National Institute of Mental Health for epidemiological studies. It is easy to use [31, 32], and its validity in the Japanese version has been reported [33]. Indeed, the Japan Clinical Oncology Group refers to CES-D as a typical geriatric assessment (GA) [25]. The survey consists of 20 items, and for each item, respondents are asked to indicate the frequency of their experience in the past week on a 0–3-point scale: 0, rarely or none of the time (<1 day during the past week); 1, some or a little of the time (1–2 days); 2, occasionally or a moderate amount of time (3–4 days); and 3, most or all of the time (5–7 days). Scoring is reversed for question 4. A higher score indicates a tendency toward depression, and a total score of ≥16 is the cutoff.

19.3.2.3 Geriatric Depression Scale-15

The Geriatric Depression Scale-15 (GDS-15) is a shortened version of the original consisting of 30 items [34], and the Japan Clinical Oncology Group also refers to this a typical GA [25]. It is easy for elderly patients to answer each question with a "yes" or "no." The total score is calculated as "yes" = 1 and "no" = 0 points. Scoring is reversed for questions 1, 5, 7, 11, and 13. Total scores range from 0 to 15, with a score ≥5 indicating depressive symptoms, and symptom severity increases with increasing scores [35].

19.3.2.4 Distress and Impact Thermometer

The Distress and Impact Thermometer (DIT) is a screening tool for adjustment disorders and depression in patients with cancer. Using two pictures of a thermometer, patients are asked by the following two questions: "Please circle the number that represents the average of how hard you have been feeling over the past week" and "How much did the painful feeling interfere with your daily life?" The higher the number, the greater the distress or interference. Each test is scored between 0 and 10. The cutoff value for distinguishing adjustment disorder or depression from

Table 19.2 Psychological distress screening tools for elderly cancer patients

	HADS	CES-D	GDS-15	DIT
Number of questions	14	20	15	2
Contents	*Depression* 1. Enjoy the thing I used to enjoy 2. Laugh and see the funny side of things 3. Feel cheerful 4. Feel slowed down 5. Have lost interest in my appearance 6. Look forward to enjoyment of things 7. Enjoy a good book or radio or TV program *Anxiety* 1. Feel tense or "wound up" 2. Get sort of a frightened feeling as if something awful is about to happen 3. Worrying thoughts go through my mind 4. I can sit at ease and feel relaxed 5. Get sort of a frightened feeling like "butterflies" in the stomach 6. Feel restress as I have to be on the move 7. Get sudden feelings of panic	1. I was bothered by things that usually do not bother me 2. I did not feel like eating 3. I felt I could not shake off the blues even with help from my family or friends 4. I felt that I was just as good as other people 5. I had trouble keeping my mind on what I was doing 6. I felt depressed 7. I felt everything I did was an effort 8. Hopeful about the future 9. I thought my life had been a failure 10. I felt fearful 11. My sleep was restless 12. I was happy 13. I talked less than usual 14. People were unfriendly 15. I felt lonely 16. People were unfriendly 17. I had crying spells 18. I felt sad 19. I feel people dislike me 20. I could not get going	1. Are you satisfied with life 2. Have you dropped many of your activities and interests 3. Feel that life is empty 4. Get bored 5. Be in a good spirits most of the time 6. Be afraid that something bad is going to happen to you 7. Feel happy most of the time 8. I feel helpless 9. I would rather stay home than going out 10. Feel I have more problems with memory than most 11. Feeling wonderful to be alive 12. Feeling pretty worthless the way you are now 13. Full of energy 14. Hopeless 15. I think I am better off than most people	Please circle the number that represents the average of how hard you have been feeling over the past week. How much did the painful feeling interfere with your daily life?
Cutoff	Score ≥5, 7, and 13 points for anxiety, depression, and total	Score ≥16	Score ≥5	Score ≥4 for distress and ≥3 for interference

HADS Hospital Anxiety and Depression Scale, *CES-D* Center for Epidemiologic Studies Depression Scale, *GDS-15* Geriatric Depression Scale-15, *DIT* Distress and Impact Thermometer

cases without a psychiatric diagnosis is a score of ≥4 for distress and ≥3 for interference, with a sensitivity of 0.82 and a specificity of 0.82 [36]. It takes approximately 1–2 min to complete and is easily scored.

19.4 Rehabilitation for Gastrointestinal Cancer Patients

19.4.1 Early Postoperative Rehabilitation

Open thoracic and abdominal surgery may result in complications, such as pneumonia, pulmonary thromboembolism, and disuse syndrome. Rehabilitation following gastrointestinal cancer surgery is performed to prevent these and improve physical function. Enhanced recovery after surgery (ERAS) has been widely recognized [37], and Shida et al. reported that patients with CRC who underwent ERAS had a shorter postoperative hospital stay than those who did not [38]. Similarly, Handa et al. reported that early postoperative ambulation reduced the incidence of pulmonary atelectasis in esophageal cancer patients who underwent video-assisted thoracoscopic surgery of the esophagus [39]. Rehabilitation is therefore essential and should involve a cooperation among nurses and other healthcare providers to ensure that an optimal environment is provided, for example, without restricting the patient's ability to move by the placement of various drains and devices.

In addition, the increased circulating plasma volume, based on the refilling phenomenon, may cause atelectasis, pneumonia, arrhythmia, and complaints of fatigue during the first 2–3 days after surgery. Such risks must be managed so that rehabilitation can be performed safely [40].

19.4.2 Rehabilitation Before Discharge

Muscle strength and physical fitness of patients must be improved prior to discharge, ensuring that they are able to walk, drink, and feed themselves. Despite rehabilitation interventions during hospitalization, there are reports of a significant decrease in the 6-min walking test performance prior to discharge compared with that before gastrointestinal cancer surgery [41]. Hara et al. investigated the minimal clinically important difference in the 6-min walking test result (conducted before surgery and 4 weeks after surgery) of gastrointestinal cancer patients, and a 7.8-m decline or 1.5% difference was considered clinically relevant [42].

In addition, evidence from prospective studies has consistently suggested that physical activity after CRC diagnosis reduces the risk of mortality [43]. Jeffrey et al. reported that, compared with CRC patients who reported unchanged levels of physical activity before and after diagnosis, those who reported more physical activity after had an approximately 50% lower risk of CRC-specific and all-cause mortality [44]. Hence, it is important that patients with gastrointestinal cancer continue home-based exercises following discharge. When CRC survivors received a 7-day home-based exercise program, their moderate physical activity levels increased, and physical fitness significantly improved compared with those of the control group without the program [45]. Similarly, among CRC survivors who completed standard surgery and adjuvant chemotherapy, life quality was improved by 12 weeks of aerobic and resistance training exercises at home [46]. Ichijo et al. showed that present occupational status and past leisure-time physical activity behavior before the cancer diagnosis were related to current leisure-time physical activity in patients

with esophageal cancer [47]. This indicates that we need to focus on occupational status and past leisure-time physical activity before diagnosis to promote appropriate physical activity. A review article recommended the following exercises:

1. Perform at least 150 min/week of aerobic activity, such as brisk walking, where every bout of activity lasting ≥10 min counts toward the weekly goal. More intense or longer durations of physical activity may have additional benefits (e.g., 6 h/week of walking and 90 min/week of running).
2. When 150 min of aerobic activity per week is not feasible, the aim is to be as physically active as possible.
3. Perform muscle-strengthening exercises ≥2 days/week [43].

19.4.3 Pre-rehabilitation

In recent years, pre-rehabilitation has been the focus of attention, suggesting that overall health can be improved by physical therapy interventions prior to surgery. These are expected to reduce postoperative respiratory complications, improve survival rates, shorten hospital stays, reduce readmission rates, and reduce medical costs. A study showed that preoperative rehabilitation for >7 days for patients with esophageal cancer resulted in a significantly lower incidence of postoperative pulmonary complications than that of those not receiving such rehabilitation [48]. Similarly, preoperative respiratory rehabilitation and exercise therapy for at least 1 week reduced postoperative complications in patients with esophageal cancer [49]. Among patients with colon cancer scheduled for surgery during the COVID-19 pandemic, patients who opted for home pre-rehabilitation significantly prevented loss of lean body mass and reduced hospital stay and postoperative complications [50]. However, a randomized controlled trial reported that the effect of preoperative rehabilitation was comparable with that of postoperative rehabilitation in patients 30 days postoperatively [51]. Therefore, preoperative interventions require further investigations to analyze their methods and efficiency.

19.5 Exercise and Mental Health

19.5.1 Effects of Exercise on Mental Health

The effects of exercise on mental health have been reported in several studies. In mild to moderate depression, the effects of exercise seem to the same or better than those of antidepressants and psychotherapy [52–54] and with a lower rate of relapse [55]. Indeed, moderate-intensity aerobic training performed three times per week for at least 12 weeks, or combined aerobic and resistance training twice weekly lasting 6–12 weeks, can significantly reduce depressive symptoms and anxiety in cancer survivors during and after treatment [56–63]. Studies have also investigated the effects of such exercise programs on the mental health of patients with gastrointestinal cancer (Table 19.3).

Table 19.3 Association between exercise and mental health among patients with gastrointestinal cancer

Author (year)	Subjects	Frequency	Intensity	Duration	Contents	Outcome	Results
Kim et al. (2019) [46]	Colorectal cancer survivors who completed surgery and adjuvant chemotherapy	Every day	~18 MET h/week during the first 6 weeks; ~27 MET h/week during the last 6 weeks	12 weeks	• Two of exercise DVDs, including both moderate and vigorous intensities • They recommended brisk walking, hiking, stationary bike, and swimming for aerobic exercises	QOL: FACT-C scale	Emotional well-being of FACT-C subscale scores increased in the exercise group when compared with baseline scores
Vallance et al. (2015) [64]	Colon cancer survivors			7 days	Objectively assessed physical activity	Depression: PHQ-9 SWL: SWLS Anxiety: SAI	Higher levels of MVPA were associated with greater SWL and lower anxiety
Loh et al. (2019) [65]	Cancer other than leukemia with a plan to initiate chemotherapy	Every day	• Progressively increase their steps by 5–20% every week • Progressively increase the intensity, sets, and/or number of repetitions of resistance band exercises	6 weeks	• Walking • Ten required resistance exercises and four optional exercises	Anxiety: STAI Mood: POMS Social and emotional well-being: FACT-G	A 6-week structured exercise program improved anxiety, mood, and social and emotional well-being

Li et al. (2019) [66]	Colon cancer receiving adjuvant chemotherapy	3–5/week	Low-intensity + high-intensity	6 months (including education, exercise, and telephone counseling)	• Over the first 3 months: Relaxation (30 min five times a week), body awareness and restorative exercise (90 min once a week), and massage (30 min twice a week) • Over the subsequent 3 months: high-intensity physical exercise; 30 min of warm-up exercises, 45 min of resistance exercise, and 15 min of cardiovascular exercise and +30 min of relaxation exercise three times a week	Anxiety and depression: HADS	Intervention group has significant improvement of depression at 6 months vs. before intervention. The depression grade was reduced compared with that of the control group at 6 months
Zopf et al. (2022) [67]	Colorectal cancer undergoing adjuvant chemotherapy	2/week cycling + 3/week walking	"Somewhat hard" to "hard" intensity, measured based on the Borg Rating of Perceived Exertion Scale (modified depending on patient's well-being)	6 months	• 30 min of cycling on a stationary bicycle • 15-min home-based walking	Fatigue: MFI-20	Aerobic exercise intervention group significantly improved motivation and metal fatigue

(continued)

Table 19.3 (continued)

Author (year)	Subjects	Frequency	Intensity	Duration	Contents	Outcome	Results
Lee et al. (2021) [68]	Gastric cancer			6 months	Observation study Regular exercise was defined as regularly maintained aerobic exercise of at least moderate intensity consuming ≥4 metabolic equivalents for ≥150 min/week for 6 months	Depression: PHQ-9 QOL: QLQ-C30	Patients who maintained regular exercise were less likely to have depression and more likely to have improved global QOL, as well as physical, role, and emotional functioning

MET metabolic equivalent of task, *FACT-C* Functional Assessment of Cancer Therapy-Colorectal, *PHQ-9* Patient Health Questionnaire-9, *SWL* Satisfaction With Life, *SWLS* Diener's Satisfaction With Life Scale, *SAI* Spielberger's State Anxiety Inventory, *MVPA* moderate-to-vigorous intensity physical activity, *STAI* State Trait Anxiety Inventory, *POMS* Profile of Mood States, *FACT-G* Functional Assessment of Cancer Therapy–General subscales, *MFI-20* Multidimensional Fatigue Inventory, *QLQ-C30* European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30, *HADS* Hospital Anxiety and Depression Scale, *QOL* quality of life

In colon cancer survivors, moderate-to-vigorous intensity physical activity, assessed using the ActiGraph GT3X (ActiGraph, LLC, Pensacola, FL, USA) accelerometer, was associated with anxiety symptoms and life satisfaction [64]. In patients aged ≥60 years who received chemotherapy, including that for colon cancer, a home-based, low-to-moderate-intensity progressive walking and resistance training program resulted in significantly greater improvements in anxiety and mood at 6 weeks when compared with those of patients receiving standard care [65]. A 12-week home-based exercise program was shown to significantly improve QOL, as assessed using the Functional Assessment of Cancer Therapy-Colorectal scale in colon cancer patients [46]. Patients with CRC in a 6-month Increment Patient Care Program, including the physical exercise group, exhibited a significant improvement in HADS scores post intervention, while the depression grade also reduced when compared with that of the control group of patients receiving adjuvant chemotherapy [66]. Similarly, in CRC patients undergoing adjuvant chemotherapy, significant improvements were observed in cardiorespiratory fitness, reduced motivation, and mental fatigue in the group that also participated in a 6-month supervised aerobic exercise program [67]. Patients with gastric cancer who maintained aerobic exercise with moderate intensity for at least 150 min/week for at least 6 months were less likely to have depression [68]. A meta-analysis reported that compared with usual care, exercise significantly affects depression, sleep, fatigue, aerobic fitness, upper-body strength, and reduced body fat in patients with colon cancer [69]. Exercise is a low-cost and safe method for improving mental health. As a physical therapist, promoting exercise and physical activity plays an important role in the mental health of patients with cancer.

19.5.2 Mechanisms for the Effects of Exercise on Mental Health

Exercise is considered to impact mental health through various ways and modulators, as follows: (1) physiological and biochemical changes due to endorphins, mitochondria, mammalian target of rapamycin (mTOR), brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1), vascular endothelial growth factor (VEGF), and hypothalamic-pituitary–adrenal (HPA) axis; (2) reduction of inflammation due to effects on cytokines, adipocytes, toll-like receptors (TLR), vagal tone, and kynurenine (Kyn); and (3) distraction from negative thoughts, improvement of self-efficacy, self-esteem, body image, coping strategies with stress, and sleep volume and quality [52, 70–74] (Fig. 19.1).

Endorphins are endogenous opioids that help the body to endure pain and stress, and several studies have reported that physical activity increases the release of these [75–77]. Exercise is also linked to increased mitochondrial numbers, responsible for neurogenesis [78, 79]. A previous study proposed that major depression might result from a disturbance in neural plasticity and adult hippocampal neurogenesis [80]. mTOR is an important translational regulator of cell growth, proliferation, and survival [81] and has been implicated in learning and memory enhancement with antidepressant effects [82, 83]. Exercise may also lead to improved mental health

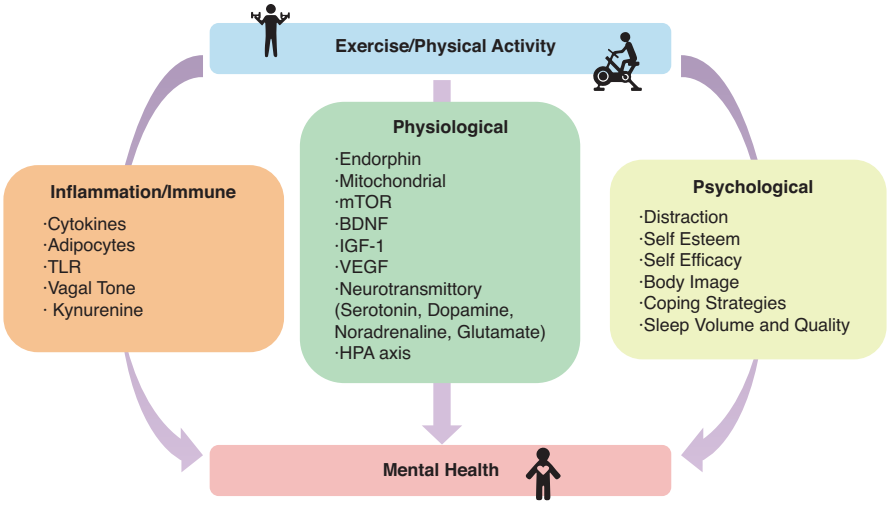

Fig. 19.1 Mechanism of the effect of exercise/physical activity on mental health. *TLR* toll-like receptors, *mTOR* mammalian target of rapamycin, *BDNF* mammalian target of rapamycin, *IGF-1* the insulin-like growth factor, *VEGF* vascular endothelial growth factor, *HPA* hypothalamic-pituitary-adrenal

status through an increase in mTOR signaling [82]. BDNF, IGF-1, and VEGF regulate neurogenesis and angiogenesis and increase with exercise [71, 84]. HPA overactivity and long-term elevation of cortisol levels may contribute to the pathophysiology of depression, and exercise could help negate these effects [74].

The immune system regulates the mood and inflammatory responses associated with depression [85]. Exercise upregulates anti-inflammatory cytokines, reduces adipose tissue and TLRs, and increases vagal tone. Kyn and its metabolites are known to affect the central nervous system and have been linked to several psychiatric disorders, such as depression and schizophrenia [86]. Exercise training reduced the symptoms of depression in patients with gastroesophageal junction cancer, and this effect was associated with exercise-dependent attenuation of the inflammation-induced conversion of Kyn to neurotoxic metabolites [87].

In another study, an 8-week exercise program reduced depressive symptoms and increased self-efficacy when compared with that of an inactive control group [88]. Similarly, a 7-week exercise intervention increased self-esteem and decreased depressive symptoms when compared with those of a control group among women with elevated depressive symptoms [89]. A previous study reported that among older female cancer survivors, body image concerns mediated the association between physical activity and psychological health outcomes [90]. A 12-week training intervention increased sleep duration and sleep efficiency in obese adolescents [91]. In addition, a systematic review reported that exercise training participation had a beneficial effect on sleep quality, improved sleep latency, and reduced the use of sleep medication in middle-aged and older adults with sleep problems [92]. These studies highlight the importance of exercise in the mental health of cancer patients.

19.6 Our Research Topics: Social Frailty and Mental Health

19.6.1 Social Frailty

In recent years, cognitive and social frailty have also been comprehensively assessed, along with physical frailty. Although no uniform measure for social frailty exists, as it is a new concept, a scoping review article published in 2017 defined it as follows: "a continuum of being at risk of losing, or having lost, resources that are important for fulfilling one or more basic social needs during the life span" in addition to "not only the absence of social resources, but also the absence of social behaviors and social activities, as well as the absence of self-management abilities" [93]. Social frailty is also associated with adverse health outcomes: in a cross-sectional study, it was linked with cognitive deficits (assessed considering memory, attention, executive function, and processing speed) and with a reduction in physical function (characterized by slow walking speed and/or lower grip strength) among community-dwelling elderly people in Japan [94]. Among adults in similar settings who had no physical frailty or pre-frailty at baseline, social frailty was associated with an increased risk of developing physical frailty during the 4-year follow-up period [95]. In addition, among community-based older adults, social frailty is linked with mortality and disability over 6 years [96].

19.6.2 Social Frailty in Patients with Cancer

Social frailty in patients with cancer is an area that requires further attention. In our previous study, the rate of social frailty in elderly patients with gastrointestinal cancer was 46.8% [97], which is higher than the rate of 3.6–18% in the elderly living in the community [95, 96, 98]. Avoidance and withdrawal behaviors can be seen in the relationships between patients diagnosed with cancer and colleagues [99]. During the COVID-19 pandemic in Germany, individuals with cancer were more likely to report anxiety symptoms, suicidal ideation, and loneliness than the general population [100]. In Japan, women and temporary employees are more likely to lose their jobs following cancer diagnoses [101], making them particularly prone to feeling lonely.

19.6.3 Social Frailty and Mental Health

We investigated the impact of preoperative social frailty in older patients with gastrointestinal cancer on new-onset depressive symptoms 1 year postsurgery [102]. The participants' depressive symptoms were assessed both presurgery and 1-year postsurgery using the 15-item GDS, and those with a score <5 before surgery were included. Patients with a GDS score ≥5 at the 1-year follow-up were classified as "new-onset," and those with <5 at follow-up were classified as "not depressed." Social frailty was examined using five yes/no questions, including "going out less

frequently than that last year" (yes), "visiting friends sometimes" (no), "feeling helpful to friends or family" (no), "living alone" (yes), and "talking with someone every day" (no) [98]. Social frailty was considered in patients with two or more of the above responses. In the multiple logistic regression analysis, after adjusting for age, sex, and postoperative complications, preoperative social frailty was significantly associated with new-onset depressive symptoms 1-year postsurgery (odds ratio, 4.13; 95% confidence interval, 1.01–16.8). Similarly, among community-dwelling elderly people in Japan, social frailty was also reported to be a risk for new depressive symptoms during the 4-year follow-up period [103]. During the COVID-19 pandemic in Japan, social frailty has been associated with depression in older adults [104]. In addition, we found that preoperative social frailty affected survival of elderly patients with gastrointestinal cancer [97]. Based on this, psychological problems may be an important factor in the influence of preoperative social frailty on survival.

Several papers have reported the relationship between social decline and mental health. Among older adults including cancer survivors aged ≥65 years without depression at baseline, social isolation was significantly associated with new-onset depression for 2 years in Japan and for 2.5 years in England [105]. In a study, anxiety and depression significantly correlated with social isolation in patients with breast cancer [106].

However, there are reports on the impact of social support on mental health as follows. Here, social support played a mediating role in the relationship between social isolation and symptoms of anxiety or depression, highlighting its vital role in improving patient mental health [106]. Another study investigating the relationship between preoperative social support and changes in anxiety and depression in colorectal cancer patients 1 year after surgery reported that patients with more preoperative social support had improved results [107]. Therefore, in terms of mental health among patients with cancer, the introduction of appropriate social resources may be effective for patients with social frailty. A community-based 3-year longitudinal study on the elderly suggested not only that each of the three types of activity—physical, social, and religious activity—is individually associated with a lower risk of depression but also that the combination of two or three types of activity is associated with a much lower risk of depression [108]. Additionally, in a previous study, the relationship between social support and leisure-time physical activity was reported for middle-aged office staff [109].

We discuss the association between physical activity/exercise and mental health in Sect. 19.5, and it is possible that social support may lead to improved mental health by allowing an increase in physical activity [110].

19.7 Future Physical Therapy Research in This Field

Pre-rehabilitation is a recently emerged topic, and much remains unknown. We investigated the association between preoperative social frailty and new-onset depressive symptoms 1 year after surgery. However, our sample size was small, and

confounding factors such as pain, physical activity, and complications after discharge could not be assessed, calling for a new study to address these. In addition, it is necessary to compare the prevalence of social frailty in elderly cancer patients and the elderly living in the community to identify problems and guide the development of appropriate interventions.

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Physical Function and Nutrition in Patients with Hematological Malignancies

20

Shin Kondo and Jiro Nakano

Abstract

Physical function and nutritional status may potentially affect hematopoietic stem cell transplantation (HSCT) or intensive chemotherapy outcomes. This chapter aimed to summarize the impact of pretreatment physical function and nutritional status on the clinical outcomes of HSCT and intensive chemotherapy. We also researched reports that exercise and/or nutritional support interventions during treatment for these patient population significantly improved treatment outcomes, quality of life, and physical function. The summaries in this chapter will promote the detection of physical function and nutritional problems in patients with hematological malignancy and help improve clinical outcomes and quality of life.

Keywords

Hematological malignancy · Physical function · Nutritional status · Hematopoietic stem cell transplantation · Intensive chemotherapy · Sarcopenia · Muscle strength Overall survival · Non-relapse mortality

S. Kondo (✉)
Division of Rehabilitation, Tokushima University Hospital, Tokushima, Japan

Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan
e-mail: skondo@tokushima-u.ac.jp

J. Nakano
Department of Rehabilitation, Kansai Medical University, Hirakata, Japan

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20.1 Introduction

In 2017, the worldwide incidence of hematological malignancies was 518,000, 488,000, 101,000, and 153,000 cases of leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma, and multiple myeloma, respectively, all of which corresponded to the total number of cases of gastric cancer, the sixth most common cancer [1]. The total number of deaths associated with these hematological malignancies was 737,000, which is greater than those secondary to breast cancer, the fifth leading cause of death [1].

Treatment for hematological malignancies usually includes intensive chemotherapy or intensive chemotherapy combined with hematopoietic stem cell transplantation (HSCT). The intensity of these treatments is greater than that used for solid cancers, and patients' physical function and nutritional status often decline secondary to infections caused by immunosuppression and fatigue. HSCT particularly is highly invasive and is therefore often associated with treatment-related mortality. Furthermore, treatment-related adverse events such as acute and chronic graft-versus-host disease (GVHD) may result in specific disabilities in patients who undergo allogeneic HSCT (allo-HSCT). Assessment of physical functioning and nutritional status prior to treatment and appropriate intervention during treatment serve as supportive therapies for these hematological malignancies. In this chapter, we describe the role of physical function and nutrition in patients who undergo HSCT and intensive chemotherapy, both pre- and posttreatment.

20.2 Physical Function and Nutritional Status in Adults Who Undergo Allogeneic Hematopoietic Stem Cell Transplantation

20.2.1 Pretransplantation Physical Function and Nutritional Status Assessment

Pre-HSCT physical function and nutritional status may potentially affect HSCT outcomes. These qualitative evaluation methods based on observations by medical staff and questionnaires obtained from patients are feasible and do not require special equipment. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) and Karnofsky Performance Status (KPS) scales are widely used to evaluate the general condition of patients with cancer, including those with hematological malignancies. Sorror et al. [2] investigated the association between the KPS and comorbidity (hematopoietic stem cell comorbidity index) and 3-year overall survival (OS) and non-relapse mortality (NRM) in patients who underwent non-myeloablative allo-HSCT; multivariate analysis showed that the KPS alone was not an independent factor for OS and NRM. Although ECOG PS and KPS are easily measurable, systematic reviews have reported conflicting results with regard to inter-rater reliability among healthcare professionals [3]. Reportedly, a systematic

review and meta-analysis showed fair-to-moderate inter-rater reliability between healthcare professionals and patients (ECOG PS, correlation 0.584; KPS, correlation 0.449) [4]. However, physical functions assessed from questionnaires administered to the patients have been reported to be beneficial. Wood et al. [5] investigated the prognostic effects in patients who underwent allo-HSCT ($n = 310$) using physical function component scores of the Short Form 36 Health Survey. The hazard ratio (HR) for each ten-point decrease in the physical function component score was 1.4, which was shown to be a significant predictor of OS. Patient-reported physical function, which can be evaluated at any facility, does not require special equipment and may be a useful pretransplantation physical function assessment tool.

Pre-HSCT instrumental assessment of physical function and nutritional status can provide objective and quantitative data, although availability of equipment may serve as a limitation. Recent studies have implicated sarcopenia as a significant factor that affects transplantation outcomes [6–8]. Armenian et al. [6] investigated the effects of sarcopenia (defined using computed tomography [CT]-based measurement of skeletal muscle mass at the level of the L3 vertebra) on 2-year NRM, OS, and relapse-related mortality (RRM) rates in 859 patients who underwent allo-HSCT for acute leukemia and myelodysplastic syndromes and observed that patients with sarcopenia had a significantly higher risk of NRM (HR 1.58, 95% confidence interval [CI] 1.16–2.16). Furthermore, OS was significantly lower in patients with sarcopenia (55.2% vs. 66.9%, $p = 0.001$), although no difference was observed in the RRM (19.5% vs. 17.3%, $p = 0.41$). Therefore, the authors concluded that the NRM contributed to the difference in OS observed in patients who underwent allo-HSCT. Although the authors did not discuss the physiological mechanisms underlying the effects of muscle mass loss on survival, they were of the opinion that sarcopenia represents a state of frailty associated with greater susceptibility to infection and organ failure, which affects long-term posttransplantation outcomes. Ando et al. [7] investigated the effects of sarcopenia (defined using CT-based measurement of skeletal muscle mass at the level of the L3 vertebra) on a 2-year OS and NRM in 125 patients who underwent allo-HSCT for acute myeloid leukemia (AML) and myelodysplastic syndromes. The authors observed that patients with sarcopenia had a significantly higher risk of OS (HR 2.30, 95% CI 1.20–3.30) and NRM (HR 1.88, 95% CI 1.20–3.41) and significantly longer length of hospitalization (88 days vs. 74 days, $p = 0.026$). Sakatoku et al. [8] investigated the effects of sarcopenia (defined using CT-based measurement of skeletal muscle mass at the level of the L3 vertebra) on OS and NRM in 60 patients who underwent allo-HSCT and observed that patients with sarcopenia had significantly lower 1-year OS (56.0% vs. 93.0%, $p < 0.001$) and higher NRM (17.0% vs. 0.0%, $p = 0.023$). Skeletal muscle mass was assessed using both CT and bioelectrical impedance analysis (BIA). No significant difference was observed in the posttransplantation outcomes in patients with sarcopenia using BIA-documented measurement of muscle mass. The number of patients in the CT and BIA groups differed in the study; however, it is suggested that CT may show greater reliability for measurement of skeletal muscle mass in patients who undergo transplantation. However, the

Table 20.1 Study of sarcopenia with CT imaging and hematological malignancy

Authors	Year	Country	Study design	*n*	CT level	Hounsfield unit threshold	Definition of sarcopenia
Armenian et al. [6]	2019	USA	Retrospective	859	L3	−29 to 150	Male (BMI ≥25): <53.0 cm^2/m^2 Male (BMI <25): <43.0 cm^2/m^2 Female: <41.0 cm^2/m^2
Ando et al. [7]	2020	Japan	Retrospective	125	L3	−29 to 150	Male: <51.0 cm^2/m^2 Female: <48.5 cm^2/m^2
Sakatoku et al. [8]	2020	Japan	Retrospective	60	L3	–	Male: <34.4 cm^2/m^2 Female: <23.4 cm^2/m^2
Go et al. [35]	2016	Korea	Retrospective	187	T4	−29 to 100	Male: <440 cm^2/m^2 Female: <310 cm^2/m^2
Lanic [37]	2014	France	Retrospective	82	L3	−29 to 150	Male: <55.8 cm^2/m^2 Female: <38.9 cm^2/m^2
Nakamura [38]	2015	Japan	Retrospective	207	L3	−29 to 150	Male: <47.1 cm^2/m^2 Female: <34.4 cm^2/m^2
Nakamura [39]	2019	Japan	Retrospective	90	L3	−29 to 150	Male: <48.4 cm^2/m^2 Female: <33.5 cm^2/m^2
Jung [40]	2021	Korea	Retrospective	96	L1	−29 to 150	Male: <40.8 cm^2/m^2 Female: <31.6 cm^2/m^2

cutoff values of the skeletal muscle mass measurement used to diagnose sarcopenia differed across the aforementioned studies (Table 20.1). Future studies are warranted to conclusively establish CT-based diagnostic criteria for sarcopenia, based on race and sex.

Several studies have reported the usefulness of the body mass index (BMI) for determination of the pretransplantation nutritional status and its association with transplantation outcomes and prognosis. Fuji et al. [9] investigated the association between pretransplantation BMI and acute GVHD, NRM, relapse, and OS after transplantation in 12,050 patients who underwent allo-HSCT. The incidence of acute GVHD (grades II–IV) was significantly higher in the overweight (25.0 kg/m^2 ≤ BMI < 30.0 kg/m^2) than in the normal weight group (18.5 ≤ BMI < 25.0 kg/m^2). The incidence of NRM was significantly higher in the overweight and obesity groups (BMI ≥30.0 kg/m^2) than in the normal weight group. In contrast, the incidence of relapse was significantly higher in the underweight (BMI <18.5 kg/m^2) and significantly lower in the overweight and obesity groups than in the normal weight group. Furthermore, OS was significantly poorer in the underweight (BMI <18.5) than in the normal weight group. A higher BMI was associated with poorer prognosis with regard to the incidence of acute GVHD and NRM. Obese patients have a greater degree of tissue injury secondary to high-dose chemotherapy, which contributes to cytokine storms that precipitate severe acute GVHD. In contrast, patients with low BMI showed poorer prognosis with regard to relapse and OS. The authors hypothesized that this may reflect the advanced stage of the disease in patients with low BMI or inadequate drug doses during chemotherapy. Other studies have also investigated the association between pretransplantation BMI and treatment prognosis. With regard to the effects on long-term prognosis, Yang et al. [10] reported a significantly

lower HR for OS in patients with BMI ≥23 kg/m^2. With regard to the effect on short-term prognosis, Suck et al. [11] reported that lower BMI tended to be associated with fewer posttransplantation adverse events. Studies have also reported the effects of pretransplantation weight loss on long-term prognosis. Brauer et al. [12] reported a significantly higher NRM and shorter OS in patients with a decline in BMI >2 kg/m^2 between the time of diagnosis and transplantation. Tamaki et al. [13] reported a significantly higher NRM and shorter OS in patients who lost >13.2% of body weight between the time of diagnosis and transplantation. Therefore, maintenance of body weight to ensure that the BMI is approximately normal to overweight may be important when considering the effects of BMI on OS.

Several studies have reported the association between comprehensive nutritional assessment and allo-HSCT outcomes. Sagou et al. [14] investigated the effects of nutritional status on the prognosis of allo-HSCT using a nutritional risk index based on estimation of serum albumin values and current body weight per ideal body weight in 160 patients who underwent allo-HSCT and observed that malnutrition (<97.5 points) was an independent predictor of prognosis, and the incidence of NRM and skin GVHD was significantly high within 1 year post-transplantation. El-Ghammaz et al. [15] reported the effect of nutritional status on transplantation outcomes using the Patient-Generated Subjective Global Assessment tool in 50 patients who underwent allo-HSCT and poor nutritional status (stages B and C) at pretransplant, and 180 days posttransplant was a significant factor affecting OS.

Many studies have reported the effects of pretransplantation motor function on posttransplantation prognosis. Salas et al. [16] performed frailty and functionality tests in 169 patients (median age 58 years) who underwent allo-HSCT and investigated the effects of motor function on OS and NRM 1 year posttransplantation. The Timed Up and Go test (TUGT) (>10 s) was an independent prognostic factor for OS and NRM. Deschler et al. [17] also reported an association between the TUGT and a 2-year OS in patients in whom the test duration was >20s in a study of 106 patients aged >60 years, who underwent allo-HSCT. Muffly et al. [18] also investigated the effects of activities of daily living and the Fried Frailty Index on OS and NRM 2 years post-allo-HSCT in 203 patients aged >50 years and observed that declining walking speed (a component of the frailty index) served as an independent predictor of a 2-year OS. Using assessment of walking ability as a motor function, Jones et al. [19] investigated the effects of pretransplantation 6-min walk distance (6 MWD) on OS and NRM in 407 patients who underwent allo-HSCT and observed that the 6 MWD (<400 m) was a significant factor on univariate analysis but not on multivariate analysis. Mishra et al. [20] also investigated the association between the 6 MWD and OS and NRM that was recorded pretransplantation and on days 30, 90, and 180 in 47 patients who underwent allo-HSCT and reported that patients with a 6 MWD value < the median value on day 30 posttransplantation had a significantly lower OS. However, the 6 MWD pretransplantation on days 90 and 180 was not a significant predictor of OS. Although the walking ability test is a simple method to evaluate pretransplantation motor function, the TUGT is reportedly more useful to determine OS or NRM. Notably, the sensitivity of these tests may be higher in older patients.

Some previous studies have suggested that walking ability tests are useful indicators of motor function, which affects posttransplantation prognosis; however, the sensitivity may be lower in relatively young patients. Allo-HSCT is performed in adults across a wide age range of 18–70 years. Therefore, it is important to determine the risk before transplantation at the same scale, independent of age. We investigated the effects of pretransplant lower extremity muscle strength (LEMS) on posttransplantation 5-year OS and NRM in 87 patients who underwent allo-HSCT [21]. We used a handheld dynamometer (μ-TAS F-1, ANIMA, Tokyo, Japan) to measure the isometric knee extension force (IKEF, expressed in kg) for 5 s. The IKEF was measured twice, and the higher value was used and divided by the subject's body weight (kg) to determine the LEMS (%). The LEMS was measured by trained physiotherapists within 2 weeks before allo-HSCT in all patients. We used the "maxstat" package [22] to calculate the optimal sex-specific LEMS cutoff value. Calculations showed that the cutoff value for LEMS associated with OS was 42.8% in women and 51.2% in men. Patients were categorized into low and high LEMS groups based on the cutoff values determined by the aforementioned method. Intergroup comparison showed a significant difference in the 5-year OS rates (low LEMS group [25.8%] vs. high LEMS group [66.4%]) (Fig. 20.1a). We also observed a significant difference in the NRM (low LEMS group [41.4%] vs. high LEMS group [11.1%]) (Fig. 20.1b). Multivariate analysis showed that low LEMS was an independent predictor of OS (HR 2.48, 95% CI 1.20–5.12) and NRM (HR 4.49, 95% CI 1.28–15.68). These results suggest that pretransplantation exercise interventions may improve posttransplantation outcomes.

However, a study has reported that pretransplantation physical activity did not produce any effect on posttransplantation survival. Wingard et al. [23] investigated the effects of pretransplantation physical activity on OS 180 days posttransplantation in 310 adults who underwent allo-HSCT. Physical activity was assessed using the Leisure Score Index (LSI) of the Godin Leisure-Time Exercise Questionnaire.

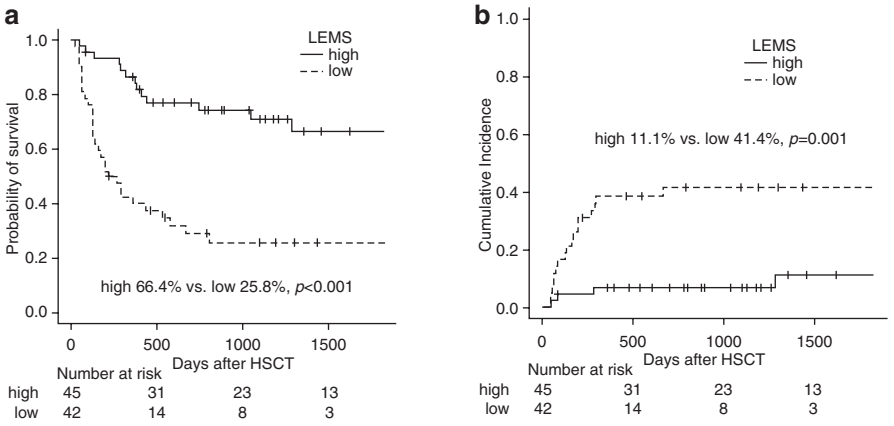

Fig. 20.1 (**a**) Probability of overall survival and (**b**) cumulative incidence of non-relapse mortality in patients with high and low pretransplant lower extremity muscle strength (LEMS)

The LSI monitors an individual's exercise over the preceding week, with exercise categorized as mild/light, moderate, and strenuous, depending on the load. Based on the scoring method, physical activity was classified into three intensities, and the weekly leisure time activity score was calculated. A score of ≥24 indicated an active status, 14–23 was considered moderately active, and <14 was considered inadequately active/sedentary. Inadequate activity or sedentariness was not a predictor of the day 180 OS compared with an active status (HR 1.70, 95% CI 0.96–2.99). On multivariate analysis using psychological stress and the physical functioning subscale of health-related quality of life (HRQOL) as covariates, inadequate activity level/sedentariness was not observed to be a predictor of the day 180 OS (HR 1.44, 95% CI 0.81–2.56). However, the physical function subscale of the HRQOL remained a significant predictor of the day 180 OS on multivariate analysis (HR 2.24, 95% CI 1.10–4.55). Therefore, the authors concluded that actual physical function is more strongly associated with posttransplantation survival than the quantity of pretransplantation physical activity. The authors also cited the limitations of the study, including the fact that the study was a questionnaire-based survey, participants were enrolled into the study only 1 week prior to transplantation, and it was necessary to use special equipment to measure the actual physical activity and to evaluate physical activity over time.

20.2.2 Interventions for Physical Function and Nutrition After Transplantation

Several studies have reported the usefulness of exercise and nutritional interventions for patients hospitalized for HSCT [24]. The reason for this could be that GVHD [25–28] and systemic steroids used for its treatment are characteristic side effects of allo-HSCT. Hamada et al. [25] reported that the rehabilitation rate was significantly lower in patients with severe GVHD (grades III–IV) than in others and that LEMS and exercise capacity did not recover in the former group even at the time of hospital discharge. Ishikawa et al. [26] investigated the effects of the acute GVHD (grades III–IV) on posttransplantation LEMS. Corticosteroids, which are routinely administered to patients with acute GVHD, are known to produce catabolic effects on skeletal muscles [29], thereby reducing muscle mass and strength in patient population. Hamada et al. [25] also reported a weak correlation ($r = 0.37$, $p = 0.03$) between LEMS and the total corticosteroid dose. Morishita et al. [28] investigated the rate of change in grip strength, knee extensor strength, and total steroid dose pre- and posttransplantation and reported a slightly stronger correlation in the grip strength (Rt: $r = -0.39$, $p < 0.001$; Lt: $r = -0.43$, $p < 0.001$) than that observed with regard to knee extensor strength (Rt: $r = -0.36$, $p < 0.001$; Lt: $r = -0.30$, $p = 0.001$). Lee et al. [27] observed steroid myopathy in 40.8% ($n = 29$) of 70 patients who underwent allo-HSCT and that compared to walking ($n = 1$), sit-stand ($n = 5$) and supine-sit ($n = 4$) were the most common activities for which these patients required assistance.

Exercise and nutritional interventions for patients with cancer are one of the important aims of improved survival. Wiskemann et al. [30] performed a randomized controlled trial that included 105 patients who underwent allo-HSCT and were assigned to an intervention group (IG, $n = 52$) or a control group (CG, $n = 53$). Exercise therapy interventions included aerobic training through walking or the use of a bicycle ergometer three to five times/week and resistance training using a stretch band two times/week for at least 20–40 min each. Patients assigned to the IG were provided an exercise manual and DVD 1–4 weeks prior to admission and were encouraged to exercise at home. After discharge, the patients continued home-based self-managed exercise for up to 8 weeks, during which the staff confirmed patient compliance with the intervention via telephone calls every week and identified any difficulties with the exercise program. Exercise intensity was set at a rating of 12–14 on the Borg scale. Adherence to exercise was 87.0% before admission, 83.0% during admission, and 91.0% after discharge. Patients assigned to the CG were instructed to perform moderate physical activity throughout the transplantation process, without any further exercise recommendations or instructions. The frequency of social contact (e.g., telephone interviews and hospital visits) with trained research staff was the same in both the CG and exercise groups to avoid sociopsychological bias. The study outcomes were total mortality (TM) after discharge, NRM after discharge, TM after transplantation, and NRM evaluated 2 years after transplantation. Two participants from the IG withdrew from the study, and 50 participants were included in the final analysis, with 53 participants included in the CG. TM after discharge was 12.0% in the IG and 28.3% in the CG, which represented a significant difference ($p = 0.034$). NRM after discharge was 4.0% in the IG and 13.5% in the CG; however, the difference was statistically nonsignificant ($p = 0.086$). TM after transplantation was 34.0% in the IG and 50.9% in the CG, which was a statistically nonsignificant difference ($p = 0.112$). NRM after transplantation was 26.0% in the IG and 36.5% in the CG, which was not significantly different ($p = 0.293$). The authors concluded that these results may be attributable to exercise-induced anti-inflammatory and immunological effects.

Enteral nutrition (EN) has received much attention as a useful posttransplantation nutritional support intervention in recent times. Although EN was recommended previously, owing to lack of strong evidence-based research to support its use, parenteral nutrition (PN) was the primary nutritional support provided in many facilities. Zama et al. [31] performed a systematic review and meta-analysis of previous studies that compared the usefulness of EN and PN in patients who underwent allo-HSCT. The search yielded 13 articles, of which 10 compared posttransplantation clinical outcomes, two compared gut microbiota composition, and one compared systemic metabolic profiles. Analysis of eight studies that included 495 patients with acute GVHD showed that the relative risk (RR) for acute GVHD was significantly lower in the EN than in the PN group (RR 0.69, 95% CI 0.56–0.86). Analysis of five studies that included 522 patients with severe acute GVHD (grades III–IV) showed that the incidence was significantly lower in the EN than in the PN group (RR 0.44, 95% CI 0.30–0.64). Analysis of four studies that included 396 patients with acute GVHD of the gut showed that the risk of acute GVHD was

significantly lower in the EN than in the PN group (RR 0.44, 95% CI 0.30–0.66). Other outcomes including oral mucositis and OS on day +100 were compared between the EN and PN groups, and no significant intergroup difference was observed (oral mucositis, RR 0.95; OS at day +100, RR 1.07). Suppression of gut GVHD in the EN group was attributed to the increased production of short-chain fatty acids, which reduce translocation of microbial molecules and microbes, with consequent anti-inflammatory and immunomodulatory effects.

Patients are known to experience long-term health-related issues such as chronic GVHD and infections posttransplantation. Recent studies have also reported post-transplantation osteoporosis [32] and bone fractures [33]. Pundole et al. [33] investigated the incidence of fractures in 7620 patients (allo-HSCT [3729] and auto-HSCT [3891]) who underwent allo-HSCT or auto-HSCT between 1997 and 2011 and compared these values with the annual incidence of fractures in the USA. The authors observed that 602 patients (8.0%) developed fractures during a median follow-up period of 85 months (allo-HSCT, 183 patients, and auto-HSCT, 419 patients). The fracture rate per 1000 was approximately eightfold higher in women aged 45–64 years than in the general population of the same age (24.1/1000 population vs. 3.0/1000 population). Similarly, the fracture rate was approximately ninefold higher in men aged 45–64 years than in the general population of the same age (25.2/1000 population vs. 2.9/1000 population). Multivariate analysis showed that age (>50 years, HR 1.94, 95% CI 1.63–2.31), indication for HSCT (multiple myeloma, HR 6.50, 95% CI 5.37–7.86, and solid cancer, HR 1.79, 95% CI 1.29–2.46), and auto-HSCT (HR 2.09, 95% CI 1.75–2.49) were predictors of fractures. Therefore, patients who undergo HSCT are at a high risk for fractures for many years posttransplantation. Therefore, it is preferable that posttransplantation rehabilitation should include nutritional and exercise interventions aimed at bone formation and should also focus on fall prevention programs.

20.3 Physical Function and Nutritional Interventions in Adults Administered Chemotherapy

20.3.1 Pre-chemotherapy Physical Function and Nutritional Status Assessment

Intensive chemotherapy for hematological malignancies often involves administration of high-dose anticancer drugs, which are associated with a variety of adverse events. Disturbances of physical function and nutritional status may precipitate adverse events and can necessitate reduction in the intensity of treatment or may interrupt treatment [34, 35]. Therefore, the prognosis of patients receiving chemotherapy may be affected by physical function and nutritional status at initiation of treatment, as well as while receiving HSCT.

Reportedly, sarcopenia is an important physical and nutritional factor that affects prognosis, even in patients treated with chemotherapy. Go et al. [35] investigated the effects of sarcopenia on 5-year OS, progression-free survival (PFS), treatment

toxicity, compliance, and treatment response in 187 patients with diffuse large B-cell lymphoma (DLBCL) who received induction rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone chemotherapy. Sarcopenia was evaluated based on CT-documented measurement of muscle mass at the level of the T4 vertebra. Patients with sarcopenia showed significantly lower OS (37.3% vs. 68.1%, $p < 0.001$) and PFS (35.3% vs. 65.8%, $p < 0.001$). Multivariate analysis showed that sarcopenia was also an independent predictor of OS (HR 2.11, 95% CI 1.30–3.44) and PFS (HR 2.07, 95% CI 1.30–3.31). Furthermore, patients with sarcopenia showed a significantly higher incidence of anemia, febrile neutropenia, and grades IV–V non-hematologic toxicity, treatment-induced mortality, and a significantly lower treatment completion rate. Therefore, the authors concluded that poor prognosis in this patient population was not due to a decrease in the anticancer effect of treatment but was attributable to treatment toxicity that limited optimal therapy. Go et al. [36] performed a comparative study to determine the effects of CT imaging of muscles at the L3 vertebral level (which is frequently used in studies on sarcopenia) and CT imaging of the pectoralis muscle, on treatment prognosis. The difference in 5-year survival rates was similar in both groups (L3 muscle-defined sarcopenia, 40.5% vs. 67.8%, $p < 0.001$, and pectoralis muscle-defined sarcopenia, 35.9% vs. 69.0%, $p < 0.001$). Furthermore, multivariate analysis showed that sarcopenia ceased to be a significant prognostic factor when exclusively defined by the L3 or pectoralis muscle level measurements, which suggests the usefulness of skeletal muscle mass measurements at two levels for accurate diagnosis of sarcopenia. In a study that included patients with DLBCL, Lanic et al. [37] investigated the effects of sarcopenia on 2-year OS and PFS determined by CT-based muscle mass measurement at the level of the L3 vertebra in 82 patients aged >70 years. Multivariate analysis showed that sarcopenia was an independent predictor for OS (HR 2.07, 95% CI 1.01–4.26) and PFS (HR 2.24, 95% CI 1.21–4.12). Subgroup analysis was performed with categorization of patients into the good ECOG PS (0–1) and poor ECOG PS (2–4) groups. Results showed that sarcopenia was a significant predictor of a 2-year OS in the good ECOG PS but not in the poor ECOG PS group, which suggests that sarcopenia may be a useful prognostic tool in patients with relatively good PS. Nakamura et al. [38] investigated the effect of sarcopenia on OS and PFS in patients with DLBCL, who underwent CT-based muscle mass measurement at the level of the L3 vertebra. Men with sarcopenia had a significantly reduced 3-year OS and PFS; however, no significant difference in a 3-year OS or PFS was observed in women. Multivariate analysis showed that sarcopenia was an independent prognostic factor for PFS in men (HR 2.55, 95% CI 1.16–6.09) but was not significantly associated with OS (HR 2.34, 95% CI 0.96–6.66). The authors concluded that the lack of difference in prognosis between women with and without sarcopenia was attributable to the fact that the response to rituximab-based chemotherapy was better in women than in men. Several studies have investigated the usefulness of CT-documented muscle mass measurements for diagnosis of sarcopenia as a prognostic factor associated with treatment of patients with AML. Nakamura et al. [39] investigated the effects of sarcopenia on OS, event-free survival (EFS), and disease-free survival (DFS) in 90 patients with AML, who underwent remission induction

therapy, and observed that on multivariate analysis, sarcopenia was an independent factor for OS (HR 2.27, 95% CI 1.11–4.79), EFS (HR 3.01, 95% CI 1.58–5.91), and DFS (HR 9.39, 95% CI 3.19–30.62). The study also investigated the effects of the adipose tissue index (which represents adipose tissue loss) on prognosis; however, it was not shown to be a significant factor for OS, EFS, and DFS, on multivariate analysis. Therefore, the authors concluded that sarcopenia is a more accurate predictor of prognosis than the adipose tissue mass or BMI. Jung et al. [40] investigated the effects of sarcopenia based on determination of skeletal muscle mass, subcutaneous adipopenia determined by subcutaneous fat mass, and visceral adipopenia determined by visceral fat mass on OS, PFS, and treatment-related mortality (TRM) in 96 patients diagnosed with AML. Multivariate analysis showed that sarcopenia was significantly associated with OS (HR 2.64, 95% CI 1.38–5.07) and TRM (HR 10.00, 95% CI 2.04–49.07), subcutaneous adipopenia was significantly associated with OS (HR 2.92, 95% CI 1.48–5.75) and PFS (HR 2.46, 95% CI 1.34–4.51), and visceral adipopenia was an independent predictor of OS (HR 2.59, 95% CI 1.31–5.12) and PFS (HR 2.09, 95% CI 1.15–3.80). The study also included patients who underwent HSCT after chemotherapy. The authors observed that sarcopenia also affects TRM, which suggests that muscle mass measurement may be useful in decision-making regarding treatment strategies early during treatment planning.

Some studies have focused on muscle quality rather than on muscle quantity. Chu et al. [41] investigated the effects of skeletal muscle radiodensity (SMD) on OS and PFS based on CT-documented measurements at the level of the L3 vertebra in patients with follicular lymphoma. Multivariate analysis showed that SMD was an independent predictor of OS (HR 3.40, 95% CI 1.58–7.32) but was not significantly associated with PFS (HR 1.65, 95% CI 0.98–2.79). Sarcopenia (defined based on the muscle mass quantity) was not a significant prognostic factor. The authors speculated that compared with the SMI, the SMD is a more accurate determinant of muscle function and is more sensitive for detection of muscle dysfunction.

Several reports have discussed the association between comprehensive nutritional assessment and post-chemotherapy outcomes. Using the prognostic nutritional index (PNI), which is calculated using serum albumin levels and the total lymphocyte count, He et al. [42] investigated the association between nutritional status and PFS and OS in patients with DLBCL. Multivariate analysis showed that low PNI (scores <44.85) was an independent predictor of PFS (HR 2.20, 95% CI 1.20–4.03). In addition to the PNI, the authors also established a novel prognostic index (NPI) based on the Ann Arbor stage and lactate dehydrogenase levels. They reported that the NPI score is a better predictor than the National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI), which is conventionally used to predict prognosis in patients with DLBCL, who receive rituximab-based chemotherapy. Zhou et al. [43] discussed the effects of PNI-determined nutritional status on the prognosis of patients with DLBCL and observed that a low PNI (scores <44.68) was an independent predictor of OS (HR 2.34, 95% CI 1.36–4.03) and EFS (HR 1.56, 95% CI 1.04–2.44). Go et al. [44] investigated the effect of PNI-determined nutritional status on PFS and OS in 228 patients with DLBCL and observed that on multivariate analysis, a low PNI (scores <40) was an

independent predictor of PFS (HR 2.03, 95% CI 1.34–3.09) and OS (HR 2.18, 95% CI 1.42–3.33). Patients with a low PNI also had significantly higher rates of treatment-related toxicity and treatment interruption. Therefore, the PNI is a feasible and useful nutritional assessment tool in patients with hematological malignancies because it can be easily calculated using serum albumin levels and the total lymphocyte count. In the future, it is expected that a consensus will be reached on the optimal cutoff value for predicting prognosis in patients with hematological malignancies. Go et al. [45] also investigated the effects of the Geriatric Nutritional Risk Index (GNRI, based on serum albumin levels and the ratio of the actual to the ideal body weight) on treatment outcomes in patients with DLBCL. The risk of cachexia was defined based on a combination of nutritional status and sarcopenia, which is defined by the skeletal muscle mass. Patients with a higher risk of cachexia showed significantly greater rates of treatment-related toxicities, treatment-related mortality, and early treatment interruptions. Therefore, patients at a high risk of cachexia had a significantly lower complete response rate (46.5% vs. 86.6%). The results showed that a high risk of cachexia was an independent predictor of PFS (HR 2.77, 95% CI 1.83–4.21) and OS (HR 3.35, 95% CI 2.17–5.17). Kanemasa et al. [46] investigated the effects of nutritional status based on the GNRI on the prognosis of patients with DLBCL. The GNRI usually stratifies patients into four groups; however, in this study, the optimal cutoff value for the GNRI score for prediction of prognosis was calculated as 96.8. The results showed that low GNRI was a significant predictor of OS (HR 2.05, 95% CI 1.31–3.22) on multivariate analysis. Additionally, analysis following stratification based on the NCCN-IPI risk showed a significant difference in prognosis based on nutritional status among patients at high intermediate and high risk. Some studies have investigated the effects of nutritional status assessed using the controlling nutritional status (CONUT) score (which is calculated using serum albumin [g/dL] levels, total cholesterol [mg/dL] levels, and the total lymphocyte count), on prognosis in patients with hematological malignancies. Nagata et al. [47] investigated the effects of a CONUT score ≥4 (defined as malnutrition) on 5-year OS and PFS in 476 patients with DLBCL. The authors observed that a CONUT score ≥4 was an independent predictor of OS (HR 1.86, 95% CI 1.24–2.80). The study also reported that following analysis of patients after stratification based on the NCCN-IPI risk, a significant difference was observed in the prognosis based on nutritional status in patients at high intermediate and high risk. Therefore, the prognostic reliability of nutritional assessment using serum albumin levels may be more sensitive in patients with more advanced-stage malignancies. Senjo et al. [48] assessed nutritional status using the simplified CONUT score, which excludes the total lymphocyte count from the CONUT score, and observed an association between the nutritional status and 2-year OS in 174 patients aged >65 years diagnosed with AML. The results showed that a simplified CONUT score (score ≥3) was an independent predictor of OS (HR 1.76, 95% CI 1.11–2.78).

Several reports have discussed the effects of motor function on treatment outcomes in patients who undergo chemotherapy. Klepin et al. [49] investigated the

effects of physical function decline (assessed by the Short Physical Performance Battery [SPPB]) on OS in 74 patients aged >60 years diagnosed with AML, who received remission induction therapy. The median OS in patients with low physical function (SPPB scores <9) was 6.0 months and that in patients with good physical function (SPPB scores ≥9) was 16.8 months, which represented a statistically significant difference ($p = 0.018$). Multivariate analysis showed that low SPPB scores (scores<9) independently predicted OS (HR 2.2, 95% CI 1.1–4.6). In this study, cognitive function assessed using the Modified Mini-Mental State Examination was also an independent predictor of OS, which suggests that in addition to physical function, cognitive function should be considered for therapeutic decision-making in patients aged >60 years with diagnosis of AML. The study also assessed patients' self-reported physical function, which was not a predictor of OS. Therefore, the authors emphasize the importance of objective assessment of physical function. Liu et al. [50] investigated the effect of usual walking speed and grip strength on OS and unplanned hospital readmissions and emergency care utilization in 448 patients aged ≥75 years, with hematological malignancies. Multivariate analysis showed that every 0.1 m/sec decrease in walking speed was associated with a significant increase in the HR for OS (HR 1.20, 95% CI 1.12–1.29). The HR for OS also increased significantly with each 5 kg decrease in grip strength (HR 1.24, 95% CI 1.07–1.43). Furthermore, grip strength was a significant predictor of OS (HR 1.24, 95% CI 1.02–1.51) even in patients with good ECOG PS scores (0–1). In contrast, walking speed was not a significant predictor of OS in patients with a good PS score. Decreased walking speed was a significant predictor of emergency medical care use (odds ratio 1.33, 95% CI 1.10–1.61); however, grip strength did not show a significant association. The authors emphasize the usefulness of the aforementioned tests for physical function screening because these tests are user friendly and can be performed in less than a minute. Some studies have shown no association between motor function and treatment outcomes. Tamilshina et al. [51] investigated the association between motor function (grip strength, 10 timed chair stand test, 2 min walk test) and short-term treatment outcomes (60-day mortality, intensive care unit admission, and remission after intensive chemotherapy) in 239 adults with AML and observed that motor function did not affect short-term treatment outcomes. The authors suggest that a higher load (e.g., maximal oxygen uptake [VO2max]) should have been used for evaluation of motor function and that the test showed low power because of the small number of outcomes. Tamilshina et al. [52] also investigated the association between physical function and 1-year survival in 97 patients aged ≥60 years diagnosed with AML and observed that no indicator of motor function (grip strength, 10 timed chair stand test, 2 min walk test, and SPPB) independently predicted a 1-year survival. The authors mentioned that compared with previous studies, the study included a greater percentage of young patients and a small percentage of patients with comorbidities. These findings suggest that physical functioning significantly affects treatment outcomes in older patients with hematological malignancies, who undergo chemotherapy.

20.3.2 Exercise Intervention and Motor Function Changes During Chemotherapy

Chemotherapy-induced decline in various physical functions has been reported in patients with AML [53] and lymphoma [54], and various studies have investigated the role of concurrent exercise therapy interventions in reduction of such decline. Courneya et al. [55] performed a randomized controlled trial in which 122 patients with lymphoma were randomized to 12 weeks of supervised aerobic exercise training (AET, $n = 60$) and usual care (UC, $n = 62$). The AET intervention commenced with a load of 60.0% of VO2max, using a bicycle ergometer three times/week, and the load was increased by 5.0% every 4 weeks. Exercise time commenced at 15–20 min for the first 4 weeks and was increased by 5 min each week. Participants in the UC group were instructed not to increase exercise from baseline and restarted exercise after post-intervention evaluation. Patients in the AET group showed significant post-intervention improvement in patient-rated motor function, overall QOL (quality of life), fatigue, happiness, depression, and overall health. Furthermore, patients who received AET showed significantly better overall QOL, well-being, and depression at a 6-month follow-up. Chang et al. [56] performed a randomized controlled trial that included 24 patients with AML who received remission induction therapy. Patients were assigned to a 3-week walking exercise program (WEP, $n = 12$) and a control group (CG, $n = 12$). The WEP intervention included a 12 min walk through the hospital corridors five times a week. The walking speed was set at a target heart rate of resting +30. Results showed that the mean 12 min walking distance tended to decrease each week in the CG (day 1, 399.3 m; day 7, 300.7 m; day 14, 280.3 m; day 21, 269.4 m). In contrast, the mean 12 min walking distance increased from baseline in the WEP group and was maintained at a stable level thereafter (day 1, 329.1 m; day 7, 409.6 m; day 14, 407.2 m; day 21, 377.2 m). Klepin et al. [57] performed a pilot study to investigate the effects of exercise therapy during chemotherapy hospitalization in 24 patients aged >50 years diagnosed with AML. A total of 12 interventions were scheduled three times/week, with each exercise session lasting 30–45 min. Exercise included walking and strength training using resistance bands. Study outcomes included feasibility of intervention, SPPB scores, HRQOL assessed using the Functional Assessment of Cancer Therapy-Leukemia questionnaire, and depressive symptoms evaluated using the 11-item Center for Epidemiologic Studies Depression Scale Short Form scale. With regard to adherence to the exercise program, 70.8% of patients participated in the exercise program at least once. The mean number of interventions was 2.7. Poor physical condition (71.0%) was the most common contributor to nonparticipation in the exercise program. The mean SPPB score increased from 7.3 to 8.6; however, the difference was statistically nonsignificant. A significant improvement was observed in the physical well-being and leukemia subscales of the HRQOL. Additionally, depressive symptoms tended to improve significantly. No adverse events were observed during the exercise intervention. The authors proposed frequent visits and a more flexible exercise schedule to improve adherence to the intervention. Wehrle et al. [58] performed a randomized controlled trial that included 29 patients with

AML who were assigned to endurance (EG, $n = 9$), resistance (RG, $n = 10$), or control (CG, $n = 10$) groups. Patients in the EG performed aerobic exercise on a bicycle ergometer or treadmill, with the load set at 60.0–70.0% of the maximum heart rate. Patients in the RG performed supervised resistance exercises using body weights, such as squats, dumbbells, elastic bands, and machines. The exercise load was controlled in both the EG and RG to maintain a rated perceived exertion scale of 12–14. These interventions were performed for 30–45 min three times/week during hospitalization for remission induction therapy. Patients in the CG underwent low-intensity mobilization and stretching to avoid psychological bias. Exercise capacity expressed as the change in individual anaerobic threshold was not significantly different between the intervention group and the CG; however, the decrease in the intervention group was less than that in the CG (EG, −0.05 W/kg, vs. RG, −0.04 W/kg, vs. CG, −0.22 W/kg). In contrast, no significant change was observed in knee flexion strength in the EG (−0.02 Nm/kg, $p = 0.701$) and CG (−0.12 Nm/kg, $p = 0.117$); however, a significant improvement was observed in the RG (+0.15 Nm/kg, $p = 0.008$). Moreover, the authors observed a significant decrease in knee extensor strength in the EG (−0.13 Nm/kg, $p = 0.019$) and CG (−0.19 Nm/kg, $p = 0.003$) but not in the RG (+0.14 Nm/kg, $p = 0.209$). The authors concluded that the resistance exercise component is particularly important for maintenance of physical function in patients who undergo remission induction, even with complex exercise therapy interventions. Fukushima et al. [59] performed an observational study in patients with various hematological malignancies; based on the frequency of exercise therapy, patients were categorized into a high-frequency group (HF, mean intervention frequency 93.0%) and a low-frequency group (LF, mean intervention frequency 66.0%). Exercise included a combination of resistance and aerobic exercise, with each session lasting 20–40 min. The exercise intensity was based on the Karvonen formula, which defines low-intensity exercise as one associated with heart rate reserve ≤40.0%. The results showed that muscle function (handgrip strength, isometric knee extensor strength, and muscle thickness) did not change significantly in patients from the HF group, although a significant decrease was observed in isometric knee extensor strength and muscle thickness in patients in the LF group. Significant improvement in physical function (10 m walking test and TUGT) was observed in patients from the HF group; however, no significant difference was observed in patients from the LF group. The authors therefore concluded that high frequency of even low-intensity exercise therapy can maintain and improve muscle and physical function in patients hospitalized for chemotherapy.

Most exercise methods described by previous studies were conventionally used for resistance and aerobic training, although recent reports have discussed new training devices. Bewarder et al. [60] investigated the effects of electrical muscle stimulation (EMS) in 45 patients with hematological malignancies, who received various treatments, including chemotherapy, to determine its effects on physical function (6 MWD, SPPB), as well as the safety and feasibility of this approach. Electrodes were placed on both thighs and upper arms, and stimulation was performed at a pulse width of 300 μs, 60 Hz frequency, 5 s on, and off of 5 s. Interventions were performed for at least 15 min per session at least five times/week. The intervention and

pre- and posttreatment assessments were successfully completed in 34 patients (76.0%). The 6 MWD decreased by a mean of 24 m after the intervention. No differences were observed in means SPPB scores. One patient developed hematoma, and three patients developed petechial hemorrhage; however, major bleeding events (defined as grade > I on the World Health Organization bleeding scale) did not occur in any patient. Among the patients who successfully underwent EMS over more than 66.0% of all sessions, 70.6% of patients performed this exercise therapy for the lower extremities and 64.7% for the upper extremities. Schink et al. [61] investigated the effects of EMS-based exercise therapy on physical function in patients pre- and post-HSCT. Patients who could participate in the exercise program at least twice a week for 12 weeks were assigned to the IG and those who could not participate in the aforementioned program were assigned to the CG. Nutritional support was provided to both groups in a similar manner, and the CG did not receive any exercise intervention. EMS was performed on the extremities and trunk, with stimulation at 350 μs pulse width, 85 Hz frequency, 6 s on, and 4 s off. The IG (whole-body EMS group: WEG) included 22 and the CG included 9 patients. A total of 59.1% of the patients in the WEG and 33.3% in the CG withdrew from the study at 12 weeks. Study withdrawal was primarily secondary to chemotherapy-induced toxicity. No intervention-induced adverse effects or discomfort occurred in the WEG, except for mild muscle pain. The muscle mass of patients in the WEG, who successfully completed the intervention, showed an increasing trend, in contrast to the decreasing trend in muscle mass in the CG after 12 weeks. Muscle mass in the WEG increased significantly at a mean of 1.51 kg. The body weight tended to increase in both groups; however, the increase in fat mass showed an effect on patients in the CG. With regard to the 6 MWD, no change was observed in the CG, in contrast to a significant increase in this parameter (mean 48.4 m) in the WEG.

A large body of evidence-based knowledge is available with regard to physical function and nutritional management in patients with hematological malignancies, and the effects of these interventions are increasingly being understood in clinical practice. Patients experience various symptoms such as fatigue, fever, and nausea during HSCT and intensive chemotherapy treatments. Therefore, improved adherence to exercise and nutritional interventions may be a future focus area. Additionally, it is necessary to establish the role of supportive care in these patients; therefore, interventions that affect treatment outcomes, such as improved survival, reduction in treatment-related mortality, and reduced GVHD, and other complications specific to the treatment of hematological malignancies need to be investigated in greater detail.

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Physical Function and Nutrition in Patients with Esophageal Cancer and Head and Neck Cancer

21

Masayuki Suzuki and Nao Hashida

Abstract

Esophageal cancer and head and neck cancer (HNC) are prone to poor nutritional status due to their anatomical location and side effects of treatment, resulting in decreased skeletal muscle mass in many patients. Computed tomography and bioelectrical impedance assessments have become the main methods for assessing muscle mass. In recent years, ultrasound devices have made it easier to assess the muscle mass both quantitatively and qualitatively. Since both cancers are common in the elderly, there are many cases in which physical function is low before treatment. For the assessment of physical function, handgrip strength, walking speed, and exercise tolerance capacity should be assessed to manage the risks. Patients with poor nutritional status and physical function are less likely to tolerate treatment and usually have poor survival rates. However, nutritional status and physical function are generally reversible, and there may be room for improvement in outcomes if physical and nutritional interventions are successful. Physical and nutritional intervention in various phases (before/after surgery, during chemo/RT (radiation therapy)) for patients with both esophageal cancer and HNC is important.

Keywords

Esophageal cancer · Head and neck cancer · Skeletal muscle mass · Physical function · Nutrition

M. Suzuki (✉) · N. Hashida
Department of Rehabilitation, Osaka International Cancer Institute, Osaka, Japan
e-mail: suzukimas@opho.jp

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21.1 Esophageal Cancer

21.1.1 Introduction

Esophageal cancer is a common cancer worldwide and has a poor prognosis. In Japan, it has a 5-year relative survival rate of 41.5% [1]. It is more likely to occur in males than in females (male-to-female ratio of approximately 5:1) and has a higher incidence in older males [2]. The major histological types are classified into adenocarcinoma and squamous cell carcinoma. Adenocarcinoma tends to be more common in Oceania and North America, whereas squamous cell carcinoma tends to be more common in Asia, Africa, and South America [3]. The incidence and mortality rates are predicted to increase in all regions, most notably in Asia [3]. In Japan, the number of patients diagnosed with esophageal cancer is approximately 26,000 per year, with an incidence rate of 20.5 cases per 100,000 persons [2]. Esophageal cancer is often asymptomatic in the early stages; however, dysphagia, unintentional weight loss, chest pain, and hoarseness appear with the progression of the disease. The risk factors for esophageal cancer are lifestyle-related and vary according to the different histological types. Squamous cell carcinoma is mainly associated with smoking and alcohol consumption, whereas adenocarcinoma is associated with gastroesophageal reflux disease, obesity, and smoking [4–7]. Drinking alcohol and smoking are also risk factors for pharyngeal cancer and gastric cancer [8, 9], so there are often multiple primary cancers in patients with esophageal cancer [10].

21.1.2 Treatments and Complications

Typical treatments for esophageal cancer are endoscopic resection, surgical operation, chemotherapy, and radiation therapy (RT). Multidisciplinary treatment is selected depending on the cancer progression, surgical tolerance, and patient's performance status. The actual treatment strategy varies according to the tissue type and the country [11–13].

21.1.2.1 Endoscopic Resection

Endoscopic mucosal resection and endoscopic submucosal dissection are the two endoscopic resection methods for esophageal cancer. Endoscopic resection is indicated for tumors that are confined to the mucosa. Additional treatment may be necessary if the lesion that needs resection is located in the submucosa. In the Japanese reports, the frequency of the overall complications was approximately 5%, and esophageal stricture was reported to be the most common complication (2.7%) [14].

21.1.2.2 Surgery

Esophageal cancer surgery involves resection and reconstruction. Therefore, it is one of the most invasive surgeries among those for the other types of gastrointestinal cancers. The esophagus is anatomically located near vital organs such as the lungs and the heart, so the resection approach requires careful operative

manipulation. Esophageal cancer frequently metastasizes to nearby lymph nodes, thus requiring lymph node dissection [15]. The surgical procedure varies depending on whether the cancer is located in the cervical, thoracic, or abdominal esophagus. In cervical esophageal cancer, the pharynx and larynx may be removed along with the entire esophagus. If the pharynx and larynx are removed, permanent tracheal stoma is created in the neck. Thoracic and abdominal esophageal cancer generally have similar surgical procedures. In open thoracotomy (McKeown approach), the right chest, neck, and upper abdomen are generally incised, and the entire thoracic esophagus and part of the stomach are removed. At the same time, lymph node dissection across the neck, chest, and abdomen is performed. In addition, after esophagectomy, the esophagus is reconstructed in the stomach or the intestine. The Esophageal Complications Consensus Group, a group of 24 high-volume centers for esophageal cancer surgery in 14 countries, reported that complications occurred in 59% of postoperative patients (31% had Clavien–Dindo classification ≥grade III) [16]. The most common complication was pneumonia (14.6%) in the pulmonary system [16]. Other complications included atrial dysrhythmia (14.5%), anastomotic leakage (11.4%), chyle leakage (4.7%), and recurrent laryngeal nerve palsy (4.2%) [16]. The reported readmission rate was 11.2% and the 30-day postoperative mortality was 2.4% [16]. Recently, minimally invasive procedures using thoracoscopy, laparoscopy, or surgical assist robotics have been developed [17]. Therefore, surgical progress has decreased the incidence of pulmonary complications [18]. Recurrent laryngeal nerve palsy occurs more frequently with upper mediastinal lymphadenectomies [19]. Upper mediastinal lymph node dissection is considered important in East Asia, and thus recurrent laryngeal palsy is high [20]. The postoperative complications vary widely, depending on the surgical method and the country.

21.1.2.3 Chemotherapy

The purpose of chemotherapy for esophageal cancer is threefold: preoperative or postoperative adjuvant therapy, curative treatment with RT, and to prolong survival and improve the quality of life (QoL) [11–13]. The main drugs used are platinum-based agents (cisplatin, carboplatin, oxaliplatin, and nedaplatin), taxane microtubule inhibitors (paclitaxel and docetaxel), and pyrimidine antimetabolites (fluorouracil, capecitabine, and S-1). Two-drug regimens combining platinum-based agents and pyrimidine antimetabolites are used, and three-drug regimens are recommended for patients with good performance status [11]. In addition to cytotoxic agents, monoclonal antibodies against HER2 (trastuzumab) and immune checkpoint inhibitors (nivolumab or pembrolizumab) have been reported to be effective [21–23]. Adverse events vary in frequency and intensity of toxicity depending on the drug used. Fatigue and gastrointestinal symptoms such as nausea, loss of appetite, myelosuppression, and hair loss are common. Adverse events associated with these drugs include renal dysfunction with cisplatin, peripheral neuropathy with taxanes and oxaliplatin, hand-foot syndrome with capecitabine, edema with docetaxel, and cardiac dysfunction with trastuzumab. Although the frequency of immune-related adverse events associated with immune checkpoint inhibitors is relatively low, they affect various organs [21, 22].

21.1.2.4 Radiation Therapy (RT)

RT is a localized treatment, similar to surgery. It can preserve the function and form of the esophagus, and the procedure itself is less invasive than surgery. The two aims of RT are radical treatment (in combination with chemotherapy) and relief of symptoms. Chemoradiation therapy (CRT) can be regarded as a neoadjuvant therapy [11, 13]. It is suggested as a curative treatment when patients either do not tolerate surgery due to frailty and comorbidities or decline surgery [11–13]. The radiation dose varies between countries, but it is usually between 50.4 and 60 Gy (1.8–2.0 Gy/day) for about 6 weeks [24]. In radiation alone, this dose may reach 60–66 Gy [12]. Side effects include dermatitis and esophagitis in the acute phase, in addition to the side effects associated with chemotherapy. Esophagitis is inevitable and occurs with >30 Gy of radiation for pain and dysphagia [25]. Late-phase side effects include radiation pneumonitis and cardiovascular disease, but intensity-modulated RT reduces the radiation dose reaching the lungs and the heart [26].

21.1.3 Physical Function and Rehabilitation

Patients with esophageal cancer do not suffer direct impairment of physical function due to the tumor, as do patients with bone or brain tumors. Their physical function is often indirectly affected by the side effects of the cancer treatment. Since many patients with esophageal cancer are elderly [27], we have clinically experienced that those patients with low physical function may require assistance in activities of daily living and self-care after treatment. Physical function in esophageal cancer patients is important not only in relation to activities of daily living but also in relation to outcomes such as complications [28–33], treatment modification [34], unplanned readmission [35], and survival [29, 32, 36, 37]. Thus, it is necessary to evaluate and rehabilitate the physical function of patients with esophageal cancer.

21.1.3.1 Skeletal Muscle Mass

Decreased skeletal muscle mass is increasingly recognized as sarcopenia [38], which leads to poor outcomes. There are several methods for measuring muscle mass. Computed tomography (CT) has been reported to be a common method in recent studies [39]. In many reports, muscles in CT images are identified by defining a range of −29 to 150 Hounsfield units [39]. The most commonly reported measurement is at the level of the L3 vertebra and is based on the skeletal muscle mass index, which is the cross-sectional area of the abdominal wall muscles divided by the square of their height [39]. Although the abdominal wall muscles consist of the transversus abdominis, external oblique, internal oblique, rectus abdominis, psoas major, erector spinae, and quadratus lumborum, previous studies have only evaluated the psoas muscle (Fig. 21.1d) [39]. Some studies have reported the use of free software or manual traces for analysis [39, 40]. Although CT has a high accuracy for the evaluation of the muscle mass, the risk of radiation exposure and economics have to be considered. Dual-energy X-ray absorptiometry is commonly

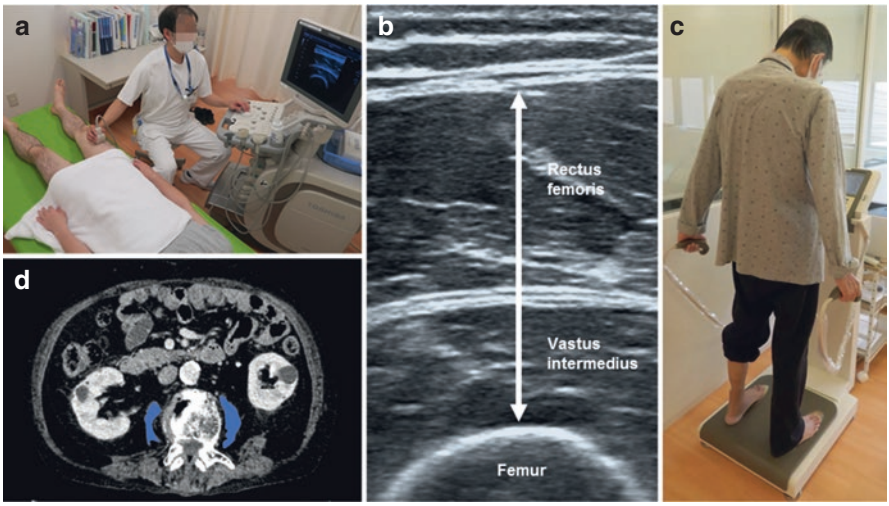

Fig. 21.1 Measurements of skeletal muscle mass. (**a**) Ultrasound measurements, (**b**) femoral muscle thickness on ultrasound imaging, (**c**) bioelectrical impedance analysis (BIA), and (**d**) cross-sectional area of the psoas muscle on computed tomography (CT) imaging

used to measure the muscle mass [41]. However, it is difficult to move the device, and radiation exposure poses a risk similar to that of CT. Bioelectrical impedance analysis (BIA) determines body composition based on the difference in the electrical impedance to alternating currents (Fig. 21.1c). Fat tissue has high impedance, whereas lean tissue with high water content has low impedance. Since most lean tissues are composed of muscles, the muscle mass is estimated from this difference in impedance of both measurements. The BIA method is not invasive, and medical staff can move the equipment and operate it quickly. Therefore, it is clinically easy to use and is used for the prospective evaluation. However, the BIA method has a limitation in that it is significantly affected by the amount of water in the body [42]. If there is an imbalance of fluid in the body, such as edema or dehydration, the error in measuring the muscle mass will increase; thus, the measurement conditions must be kept constant. In addition, the CT method may overestimate the muscle mass in patients with edema; therefore, the measurement results should be interpreted with caution [43]. Measuring the muscle mass using an ultrasound device has also been reported (Fig. 21.1a, b) [44]. Being portable and noninvasive, similar to the BIA method, the significant advantage of this method is that it can visualize the quality of muscles [45]. There is no doubt that muscle strength correlates with muscle mass, but one of the other important factors is intramuscular fat, which defines the muscle quality. This is because muscles having the same cross-sectional area with more fat have a relatively low muscle cell mass. Although thigh thickness measurements using ultrasound devices may be considered for the diagnosis of sarcopenia [46], the clinical significance of muscle mass and quality measured by ultrasound in patients with esophageal cancer is unclear, and thus further studies are needed.

21.1.3.2 Muscle Strength and Physical Performance

Physical vulnerability is a significant factor in the assessment of treatment tolerance in patients with cancer. In the elderly, muscle strength and gait speed are more strongly associated with survival than skeletal muscle mass loss [47]. In patients with esophageal cancer, muscle weakness (rather than skeletal muscle mass) has been reported to be an effective predictor of survival, postoperative complications, and treatment modifications [29–31, 33–36, 48]. Muscle strength is generally correlated with muscle mass, but other factors can affect the muscle strength. Muscle strength can increase with strength training, even if the muscle mass does not change [49, 50]. It also has a clinically significant contribution to activities of daily living and QoL [51]. Therefore, in addition to muscle mass measurement, assessing muscle strength and performance can provide a more detailed assessment of the physical vulnerability of patients with esophageal cancer. Grip strength is the most commonly used assessment tool for muscle strength. Given the anatomical location of esophageal cancer, it is unlikely that grip strength declines alone, and thus a concomitant systematic decline in the lower extremity muscle strength is likely to occur [52]. Although previous studies evaluated lower extremity muscle strength using the 30-s chair stand test and a handheld dynamometer, many reports did not indicate clinically meaningful cutoff values [36, 52]. Physical performance can be assessed using the 6-m walk speed test, 400-m walk test, short physical performance battery (SPPB), Timed Up and Go Test, and five-chair stand test, as well as the other diagnostic criteria for sarcopenia [53, 54]. In addition to the skeletal muscle mass loss, both muscle weakness and poor physical performance are defined as severe sarcopenia according to the revised diagnostic criteria [53, 54]. After gastrectomy, severe sarcopenia has been reported to be a stronger predictor of postoperative complications than sarcopenia in patients with gastric cancer [55]. No study has examined the clinical difference in the severity of sarcopenia between patients with esophageal cancer.

21.1.3.3 Exercise Capacity

Exercise capacity is a comprehensive function that includes pulmonary function, cardiac function, peripheral circulation, pulmonary circulation, and skeletal muscle function, rather than assessing the function of a single organ, such as the heart, lungs, or blood vessels. Patients with greater exercise capacity are reported to be physically able to tolerate surgery and have fewer postoperative complications [56, 57]. Exercise capacity is used as one of the risk management assessments in the perioperative period. In the case of highly invasive surgeries such as esophagectomy, exercise capacity was found to be associated with postoperative cardiopulmonary complications, unplanned ICU admissions, and a 1-year survival following esophagectomy [32]. A cardiopulmonary exercise test assesses exercise capacity and is a typical index of peak oxygen consumption (VO_{2peak}). VO_{2peak} is highly load-dependent and is underestimated in patients with physical vulnerability. The anaerobic threshold and minute ventilation/carbon dioxide production (VE/VCO_2) slope indices can be stably measured even in tests performed under submaximal loads.

Alternative assessments for exercise capacity are the field walking tests, such as the incremental shuttle walking test (ISWT) and the 6-minute walk test (6MWT). In a study comparing VO_{2peak} and each walking test in patients with lung cancer, ISWT was linearly correlated with VO_{2peak}, but the 6MWT had a weaker VO_{2peak} correlation [58]. The weak correlation with VO_{2peak} is because the 6MWT is a self-controlled exercise load compared to the ISWT or cardiopulmonary exercise testing [58]. In addition, the 6-minute walk distance showed a moderate correlation with respiratory function, whereas the ISWT did not show a significant correlation [58]. The field walking test is associated with survival in patients with esophageal [59], but there is no consensus on the relationship between the walking test and postoperative complications [60, 61]. No studies have examined which assessment for exercise capacity is best for patients with esophageal cancer. The field walking test is easy to administer in clinical practice and research because it does not require specialized equipment or staff.

21.1.3.4 Rehabilitation

Preoperative Period

The goal of preoperative intervention in patients with esophageal cancer is to maintain or improve the physical function and reduce the incidence of postoperative complications, especially pulmonary complications. Physical therapy consists of resistance exercise, aerobic exercise, and respiratory muscle training. Programs that include inspiratory muscle training have been particularly effective for postoperative complications [62, 63]. Similarly, respiratory muscle training with incentive spirometry is often used, although its effect is still in question [63, 64]. In the preoperative period, esophageal cancer patients often undergo neoadjuvant chemotherapy or CRT. Patients with physical frailty are more prone to toxicity [65], resulting in lower intensity and rates of interventions, and their physical function is more likely to deteriorate. Previous studies have shown that preoperative interventions with reduced load intensity and compliance are not effective [62], so it is important to maintain the intensity and rate of the exercise.

Postoperative Period

Rehabilitation consists of ambulation, squeezing, and positional drainage to improve the airway clearance and prevent respiratory complications during the early postoperative period. This period requires careful attention to circulatory dynamics, pain, and delirium. Moreover, gradual mobilization from the first postoperative day with the aid of nurses in our hospital is encouraged (Fig. 21.2a). Although protocols vary among different institutions, early mobilization is an essential component of enhanced recovery after surgery and has been introduced in various surgeries. The physical functions of esophageal cancer survivors do not improve quickly after discharge [66, 67]. The decrease in postoperative physical activity leads to the decline in physical function [66, 68], so it is important to actively implement exercise therapy during hospitalization to improve the physical function as much as possible. In

Fig. 21.2 Physical therapy: (**a**) early mobilization at the ICU, (**b**) exercise at the rehabilitation room, and (**c**) assessment of exercise capacity

our hospital, exercise therapy was carried out to improve the physical function of patients during hospitalization (Fig. 21.2b, c). After esophageal cancer surgery, time is needed to improve inflammation and nutritional status; therefore, we started with three METs (metabolic equivalents) or less training and exercise for 20–30 min/day.

During Chemotherapy and RT

Poor physical function may lead to a decline in performance status, affecting the continuation of treatment in patients undergoing chemotherapy or RT to prolong life or relieve symptoms [69]. In particular, a treatment regimen that is likely to cause chemotherapy-induced peripheral neuropathy will likely result in decreased balance and falls. Exercise therapy may improve the completion rate of chemotherapy treatment in patients with breast cancer [70]. To continue the treatment, it is suggested that maintaining the physical functions by exercise therapy contributes not only to activities of daily living and QoL [71] but also indirectly to the improvement of prognosis. During chemotherapy, various problems arise with exercise therapy, including hematologic toxicity (anemia, febrile neutropenia, and high bleeding

tendency), gastrointestinal toxicity (anorexia, nausea, and vomiting), and cancer-related fatigue (CRF). Patients with low physical function are especially prone to exacerbation of CRF [65]. Therefore, patients tend to be less active and have a further decline in physical function. Consequently, it is necessary to maintain exercise intensity under supervision or regular counseling for patients with frailty.

21.1.4 Nutritional Status

All cancer types, especially esophageal cancer, increase the risk of malnutrition. About 67–85% of patients with esophageal cancer have malnutrition [72, 73]. Malnutrition can be classified into tumor-induced malnutrition and treatment-induced malnutrition. Cachexia, which is the most common type of tumor-induced malnutrition, leads to anorexia, hypercatabolism, and substantial weight loss, primarily due to the loss of skeletal muscle mass. In addition, locally advanced esophageal cancer can lead to dysphagia due to the obstructive nature of the tumor. Therefore, there are many cases of malnutrition at the time of treatment initiation for esophageal cancer. Patients who received chemoradiotherapy have risks of malnutrition for a variety of reasons, such as anorexia and esophageal mucositis. Moreover, malnutrition can occur after esophagectomy due to dysphagia, anorexia, reduced oral intake, or dumping syndrome. Consequently, patients with esophageal cancer can experience malnutrition for many reasons at different stages; thus, interventions according to the underlying reasons are necessary.

21.1.4.1 Pretreatment Malnutrition

Cancer cachexia, which is associated with metabolic abnormalities leading to hypercatabolism, anorexia, and other nutritional disorders, causes malnutrition with skeletal muscle loss. Cachexia affects approximately half of patients with cancer, causing poor nutritional status, physical dysfunction, poor response to chemotherapy, and mortality. Along with cancer progression, cancer cachexia causes an irreversible nutritional disorder that does not improve even after nutritional intervention because of the high level of metabolic abnormalities and hypercatabolism caused by systemic inflammatory reactions. In contrast, nutritional intervention may be effective during pre-cachexia with mild hypermetabolism. Psychological cancer-related factors may also have an effect on pretreatment malnutrition. Depression and anxiety can lead to anorexia and nutritional disturbances. Moreover, some patients with locally advanced esophageal cancer suffer from tumor obstruction, thus resulting in poor appetite. Therefore, there are many cases of malnutrition at the time of treatment initiation for esophageal cancer.

21.1.4.2 Postsurgery Malnutrition

Esophagectomy, one of the most invasive surgeries, causes hypermetabolism and increases resting energy expenditure as a physiological alteration. Most patients develop malnutrition after esophagectomy. A previous study reported that

postoperative hypermetabolism remained 2 weeks after surgery [74]. In addition, esophagectomy can lead to a variety of symptoms such as dysphagia, pneumonia, anorexia, pain, digestive symptoms, and delirium. These symptoms can cause malnutrition, which adversely affects postoperative wound healing, physical function, infection, and the length of hospital stay [75]. Persistent weight loss after esophageal cancer surgery is associated with poor prognosis. In addition to the clinical stage and incomplete resection, weight loss 1 year after surgery has been reported to be a factor affecting the 5-year recurrence-free survival [76]. Thus, patients routinely receive nutritional support, including nutritional counseling and enteral feeding, in many hospitals. Despite that, most patients experience weight loss following esophagectomy. A study conducted in Sweden reported significant weight loss within 6 months after surgery, with 64% of patients having a body mass index loss of 10% or more due to anorexia.

21.1.4.3 Malnutrition During and After Radiotherapy

RT plays an important role in the treatment of esophageal cancer. It can have both positive and negative effects on the nutritional status of patients with esophageal cancer. The side effects of RT, such as radiation pneumonitis, radiation esophagitis, sore throat, and esophageal stricture, can cause malnutrition and further worsen the nutritional status [77]. However, RT can improve dysphagia and food intake when obstructive tumors show improvement, although radiation esophagitis can cause or worsen patients' oral intake problems. Both positive and negative effects are present during radiotherapy, resulting in the interference with the achievements of nutritional therapy.

21.1.4.4 Malnutrition During Chemotherapy

Depending on the regimen, chemotherapy can cause anorexia and gastrointestinal symptoms. The main anticancer drugs used for esophageal cancer treatment are cisplatin, 5-fluorouracil (5-FU), docetaxel, and paclitaxel. Advanced esophageal cancer is treated with preoperative anticancer chemotherapy, most commonly with FP (combination of 5-FU and cisplatin) as a standard treatment, and also with the three-drug DCF regimen (combination of cisplatin, 5-FU, and docetaxel) as neoadjuvant chemotherapy in Japan. Chemotherapy also has nutritional benefits as well as disadvantages. Advanced esophageal cancer patients may have difficulty eating prior to treatment because of the tumor obstruction, but oral intake may increase following successful chemotherapy and tumor shrinkage. However, nausea, loss of appetite, taste and smell disorders, diarrhea, and fatigue due to the side effects of chemotherapy lead to reduced oral intake and activity, resulting in nutritional impairment and physical dysfunction. In a safety study of DCF therapy, 7.1% of patients reported loss of appetite, and 4.8% reported mouth ulcers [78]. Clinically, the inadequate nutritional intake in patients is likely to be much higher than that reported in the mentioned study. In addition, since edema is a common side effect of anticancer drug treatment, body weight often temporarily increases, making it difficult to monitor the nutritional status adequately and accurately. Therefore, it is necessary to monitor changes in oral intake and body weight. If there is a significant or a prolonged decrease in oral intake, nutritional assistance is necessary. In many

cases, patients are discharged at the end of the first course of chemotherapy. It is thus important to assess whether the patient has lost weight, maintained weight, or recovered when the second course of chemotherapy is started. If weight gain does not improve by the beginning of the second course of chemotherapy, it is likely that the nutritional deficits will continue to worsen.

21.1.4.5 Intervention

Improved nutritional status can reduce anxiety and depression in patients with cancer [79–83]. There is no standardized and widely used nutritional assessment tool for patients with esophageal cancer. An Asian study reported that the Patient-Generated Subjective Global Assessment (PG-SGA) score is recommended in patients with advanced esophageal cancer. It also correlates with the Karnofsky Performance Status Scale and the ECOG Performance Status [84].

Pretreatment Intervention

Patients with esophageal cancer often have nutritional deficits prior to treatment, which may be either due to the metabolic abnormalities caused by cachexia or dysphagia caused by the tumor itself. Esophageal dyspepsia is clinically common, but in such cases, patients may be able to consume liquid foods; thus, oral nutritional supplements (ONS) may be effective. However, in cases where they are difficult to administer or the risk of aspiration is high, tube feeding should be considered. If a patient has advanced cancer and is expected to have worsening dyspepsia, percutaneous endoscopic gastrostomy should be considered as early as possible.

Nutritional Interventions During CRT for Esophageal Cancer

Nutritional interventions during CRT for esophageal cancer are based on a combination of nutritional counseling, dietary modification, intravenous nutrition, and guidance and use of ONS. Nutritional management requires individualized and dynamic adjustment of the target intake of energy, protein, and other nutrients for patients with cancer undergoing radiotherapy and chemotherapy, according to various factors such as tumor volume, stress status, and acute radiation injury. Prealbumin is a sensitive nutritional biomarker for assessing the nutritional status of patients with esophageal cancer undergoing concurrent chemoradiotherapy [85]. Nutritional intervention with periodic nutritional assessment is based on the dietary intake, weight loss, and prealbumin levels [85]. It has been reported that patients undergoing radiation chemotherapy for esophageal cancer cannot maintain an adequate nutritional status with regular nutritional counseling and guidance alone; consequently, active nutritional intervention such as parenteral nutrition and providing ONS is necessary [86].

Perioperative Nutritional Interventions

Parenteral and Enteral Nutrition

In the perioperative period, patients with esophageal cancer may present with nutritional disorders for various reasons, requiring multidisciplinary interventions. Oral intake is not possible in the early postoperative period. Therefore, nutritional

management using parenteral and enteral nutrition is necessary. In some cases, oral intake begins immediately. However, various factors such as dysphagia, suture insufficiency, and chylothorax may delay the initiation of oral intake. Consequently, it is important to evaluate alternative nutrition approaches. Many patients experience diarrhea when they start enteral feeding. However, in most cases, this improves within a few days by adjusting the speed of enteral feeding. If symptoms do not improve, it is necessary to consider the type of nutrients administered through enteral feeding. In many cases, enteral nutrition must be continued after discharge from the hospital; therefore, patient education is also important. Compared with oral intake alone, enteral nutrition at home has been reported to improve nutritional status and physical function, in addition to reducing nausea, vomiting, fatigue, anorexia, diarrhea, and sleep disturbances in postoperative patients with esophageal cancer [87]. Because many elderly patients with esophageal cancer require practice in the self-management of enteral nutrition, it is important to begin practice after the patient's general condition has settled.

Oral Intake

After esophagectomy, patients often have a limited oral intake. Therefore, it is necessary to assess the reasons for the difficulty in receiving oral nutrition. Many patients undergo surgery with gastric tube reconstruction, leading to the loss of the ability to digest, store, and prevent reflux of food. Therefore, it is necessary to educate them about how to swallow well and eat slowly. In addition, it is necessary for patients to rest in a sitting position rather than lying down after eating.

In addition, patients who undergo esophagectomy often have swallowing dysfunction. Therefore, evaluation of the swallowing function, selection of an appropriate diet, and dysphagia rehabilitation are necessary. Patients often present with recurrent nerve palsy and laryngeal elevation problems that may lead to aspiration and pharyngeal retention problems.

21.1.5 Combined Therapy

As previously mentioned, loss of muscle mass in patients with cancer leads to poor outcomes. Therefore, we are currently conducting a randomized controlled trial of exercise therapy and nutritional intervention to maintain muscle mass in patients with esophageal cancer during neoadjuvant chemotherapy (jRCTs051190016). The intervention combines nutritional supplements and exercise therapy, focusing on resistance training. The primary endpoint is the rate of change in muscle mass before and after neoadjuvant chemotherapy. Previous studies have examined the feasibility of exercise and nutritional interventions during chemotherapy in patients with advanced lung and pancreatic cancer [88, 89]. These studies conducted unsupervised home exercise programs (compliance rate of 60–91% of the patients) and reported no serious adverse events. The implementation rate was higher in trials conducted with regular counseling. However, there was no significant difference in the change of muscle mass in the intervention group compared to that of the control

group. Moreover, muscle mass loss was also observed in the intervention group. Studies examining drugs designed to improve cachexia reported that they were successful in improving anorexia and lean mass but did not improve muscle strength [90–92]. The main reason is that skeletal muscle mass is not the only component of strength. In addition, there was no exercise intervention. NEXTAC-III (jRCTs041210053), a clinical study combining drugs, nutrition, and exercise, has been initiated in patients with advanced lung and pancreatic cancer. Further studies are needed for esophageal cancer patients with multimodal interventions, including exercise, nutritional therapy, and drugs.

21.2 Head and Neck Cancer

21.2.1 Introduction, Treatment, and Complications

Head and neck cancer (HNC), which consists mainly of squamous cell carcinoma of the mouth, pharynx, and larynx, is becoming increasingly prevalent worldwide. Although the number of newly diagnosed HNC cases was approximately 700,000 in 2005, more than 900,000 new cases were diagnosed in 2015 [93]. Since the head and neck region contains important organs for communication, swallowing, and breathing, the treatment of HNC requires a balance between treatment efficacy and side effects. The treatment of locoregional HNC has evolved with respect to the role of radiation, surgery, and systemic therapy. In the first half of the twentieth century, RT was the primary treatment; however, in the middle of the twentieth century, there was a shift to surgery with or without adjuvant radiation [94]. This strategy demonstrated high locoregional and distant failure rates of approximately 30% and 20%, respectively, with 5-year survival rates around 40% [95, 96]. In the 1990s, a shift toward functional outcomes and introduction of chemotherapy has led to the development of organ preservation strategies [97–99]. The survival benefit noted with the addition of concomitant chemotherapy to radiation occurs predominantly through the improved locoregional control [100]. Definitive therapy with concurrent CRT has become a standard treatment approach for locoregional HNSCC (head and neck squamous cell cancer). Despite these important advances, acute and late complications of concurrent CRT are major concerns. Late toxicities of CRT can have a significant impact on the function and QoL of long-term HNSCC survivors. Despite the improvements in the techniques of RT, late toxicities such as xerostomia, long-term poor dental and oral health, fibrosis, trismus, and esophageal stenosis greatly impact survivorship [101–106]. Cisplatin concurrent with radiation results in long-term secondary ototoxicity in approximately 20% of the patients. Ototoxicity is a limiting factor in delivering optimal cumulative doses of cisplatin [107]. A pooled analysis from three RTOG (Radiation Therapy Oncology Group) trials of patients with locally advanced HNSCC treated with concurrent CRT suggested that 43% of patients had a severe late toxicity [108]. Moreover, several studies have shown that long-term complications of treatment have a significant impact on the QoL of long-term HNC survivors [109–111]. Treatment of HNC, including surgery, RT, and

CRT, often causes dysphagia, which may affect the QoL or lead to poor prognosis [112–115]. Patients who undergo RT are at a high risk of developing malnutrition and muscle wasting due to pain in the oral and pharyngeal mucous membranes, dry mouth, dysgeusia, and dysphagia [116–118]. A pilot study has reported that within 4–5 weeks of starting RT, patients experience mucositis, pain, copious mucous production, xerostomia, and edema of the soft tissues, which may cause aspiration, malnutrition, and feeding tube dependency. The study also demonstrated that even prior to receiving CRT, stage III, IVa, or IVb Indian patients with HNC may have been at a high risk of sarcopenia and sarcopenic-related adverse events compared to their age-matched peers. These effects become much more pronounced by the completion of 7 weeks of CRT [119]. Newer treatment strategies, such as reduced irradiation field and intensity-modulated radiotherapy, have reduced the risk or severity of dysphagia or nutritional matters in patients with HNC but have not offset against the development of these side effects yet [120, 121].

21.2.2 Physical Function and Rehabilitation

The head and neck region has essential functions, such as swallowing, speech, and respiration. The difficulty in oral intake caused by the tumor and its treatment methods results in a significant weight loss. About 70% of the weight loss during CRT is reported to be due to loss in muscle mass [122, 123]. Low muscle mass is a poor prognostic factor in HNC [124]. In addition, physical frailty is associated with severe postoperative complications and prolonged hospital stay [125]. Since muscle mass and physical function affect the postoperative outcomes and prognosis, there may be room for those indications for prehabilitation similar to the case of patients with esophageal cancer; however, there are no relevant previous reports in the field of HNC. HNCs are often treated with curative CRT because of their morphology, functional preservation, and sensitivity to treatment. Resistance and aerobic exercise have been reported to counter the physical and QoL declines during CRT [126, 127]. In the postoperative period, shoulder dysfunction, such as having a limited range of motion and pain, often occurs with accessory nerve palsy. In HNC, more attention should be paid to the shoulder function, as many patients require physical therapy.

21.2.2.1 Shoulder Dysfunction and Rehabilitation

In levels II–V lymph node dissection, paralysis of the trapezius and sternocleidomastoid muscles may occur due to excision, traction, or injury of the accessory nerve by intraoperative manipulation. As the trapezius muscle plays a role in the fixation and movement of the scapula, paralysis of the trapezius muscle causes an imbalance with other muscle groups, resulting in a winged scapula (Fig. 21.3). In addition, scapulohumeral rhythm failure limits shoulder flexion, especially abduction [128]. Even when the accessory nerve is preserved, recovery takes approximately 4 months to a year [129]. If the shoulder joint is left immobile during this period, contracture occurs, resulting in irreversible shoulder joint disorders. A

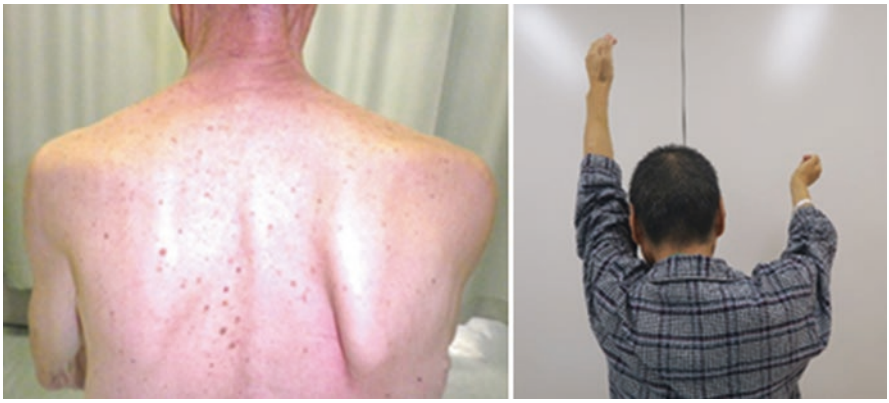

Fig. 21.3 Winged scapula and limited shoulder flexion

systematic review reported that patients who underwent a pain-free resistance training program and regular rehabilitation functioned better [128]. If patients are likely to overuse joints and muscles, resulting in the induction of pain and shoulder joint damage, it is critical to correctly induce movement by a physical therapist.

21.2.2.2 Exercise Intervention During RT or CRT

The structure and content of exercise is different in previous studies; however, it mostly consists of resistance and/or aerobic exercise, corresponding to the American College of Sports Medicine Guidelines (i.e., intensity, moderate; frequency, aerobic training 3–5 days/week; and resistance training, 2–3 days/week) [127]. Supervised and home exercises were often combined, and monitoring was conducted via phone. In all the previous studies, there were no reported serious adverse events during the exercise sessions. The adverse events associated with CRT tended to appear more strongly in the latter half of the treatment period and continued after the end of CRT [130, 131]. In our patients' cohort, the exercise rate was also reduced due to the increase in the incidence of adverse events. During CRT, it is difficult to improve the physical function; consequently, the goal is to maintain the exercise intensity. To achieve this goal, it is essential to educate patients before treatment to improve and promote their health literacy and strengthen monitoring when adverse events are likely to occur [132–134].

21.2.3 Nutritional Status

Many patients lose body weight after being diagnosed with cancer [135]. Orell-Kotikankas et al. reported that 34% of patients with HNC had malnutrition when assessed by the PG-SGA score, 31% had cachexia, and 46% had sarcopenia [136]. Malnutrition is common in patients with cancer owing to the symptoms and the side effects of treatments, such as radiation, chemotherapy, and surgery [116, 117].

Combined treatment strategies in many patients lead to nutritional issues due to swallowing difficulty, dysgeusia, anorexia, or pain on swallowing [137, 138]. Unsal et al. reported a malnutrition rate of 88% in patients with HNC after RT [118]. Malnutrition leads to a decrease in the skeletal muscle mass and sarcopenia, which are the risk factors for dysphagia [139–142]. Malnutrition in patients with HNC is associated with the increased rate of treatment side effects, treatment interruption, increased length of hospital stays, increased medical charges, and mortality [135, 136, 143]. In addition, malnutrition in HNC may be associated with depression and poor QoL [144, 145]. Nutritional issues in patients with HNC can continue after the end of treatment or occur several years after treatment and can also become chronic [137]. Moreover, malnutrition can lead to social frailty and can have negative effects on the patients' daily life [146].

21.2.3.1 Assessment

Patients with HNC are continuously at risk of malnutrition, before, during, and after treatment. Patients with HNC are prone to nutritional disorders owing to the many aforementioned factors. Therefore, nutritional intervention during treatment requires multidisciplinary interventions by physicians, dentists, nurses, dental hygienists, physical therapists, speech language pathologists, palliative care departments, nutrition support teams, registered dietitians, psychologists, and other healthcare professionals. Nutritional screening includes screening assessments such as the MSF Screening and PG-SGA score that are important to be performed on a regular basis. However, since patients with HNC are at a very high risk of nutritional disorders, screening is not deemed necessary, and thus consultation with a nutritionist or nutrition support team is always required. Dual-energy X-ray absorptiometry and BIA are widely used in the diagnosis of sarcopenia because of their ease of evaluation. There are various methods for measuring the muscle mass. Magnetic resonance imaging and CT are the gold standards for measuring skeletal muscle mass. In many studies on patients with cancer, the cross-sectional area of the psoas muscle at the L3 level has been measured. Many patients with HNC have not undergone abdominal CT; thus, some studies have measured and evaluated the masseter muscle (Fig. 21.4a) or geniohyoid muscle (Fig. 21.4b) mass to assess muscle atrophy or sarcopenia. Ultrasound imaging was also used to assess the muscle mass of the quadriceps, geniohyoid (Fig. 21.4c), and masseter muscles, which are all easy to evaluate using ultrasonography.

21.2.3.2 Intervention

Pretreatment Nutritional Intervention

Patients with HNC often have nutritional problems before treatment, which may be due to the metabolic abnormalities caused by cachexia or dysphagia caused by the tumor. If patients suffer from dysphagia, it is necessary to evaluate its severity and the food texture that can be swallowed. Tumor-induced motor dysfunction of the tongue and obstructive tumors of the hypopharynx are clinically common; however, in such cases, patients may be able to swallow fluid-rich foods and ONS. Nevertheless,

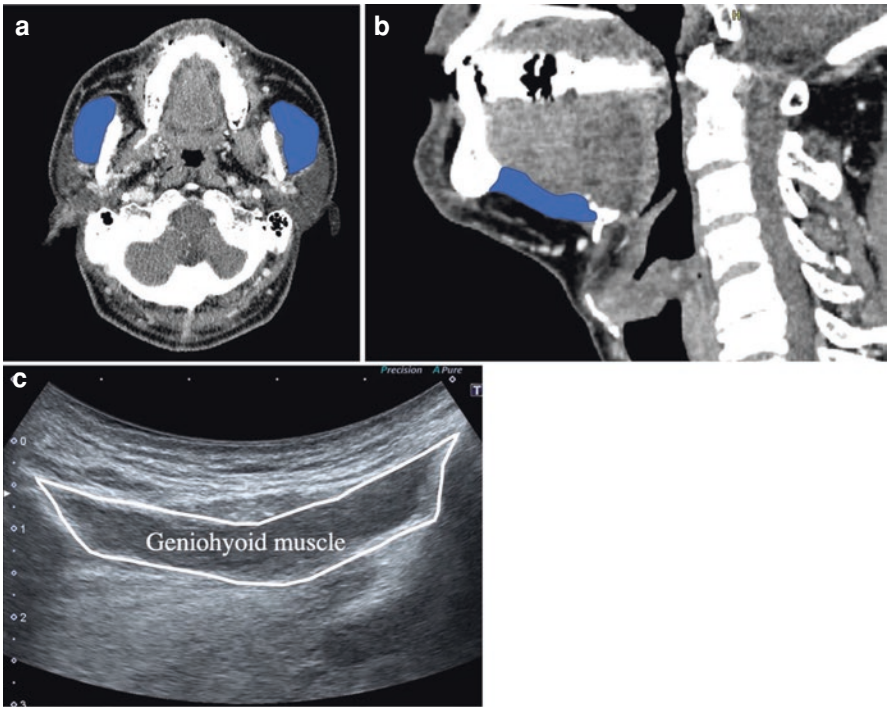

Fig. 21.4 Measurements of head and neck muscle mass. (**a**) Cross-sectional area of masseter muscle using CT, (**b**) cross-sectional area of geniohyoid muscle mass using CT, and (**c**) geniohyoid muscle mass using ultrasound imaging

if the patient is unable to swallow these supplements or is at a high risk of aspiration, tube feeding should be considered. If the patient has difficulty swallowing prior to treatment, the underlying cause of dysphagia should be analyzed. When short-term oral intake is deemed difficult, performing percutaneous endoscopic gastrostomy before RT may be considered for nutritional management.

Nutritional Intervention During Treatment

Nutritional interventions during treatment are important because chemotherapy, RT, and CRT are long-term treatment approaches, unlike surgery. The nutritional expertise provided by registered dietitians improves the nutritional outcomes and QoL. Nutritional counseling is the first-line approach of nutritional therapy to help patients with nutritional problems through patient education and other interventions to address the problems caused by permanent changes in the dietary intake associated with HNC treatment [116]. The UK guidelines recommend weekly nutritional counseling during RT [147]. The recommended nutritional intake is 25–35 kcal/kg/day and 0.8–2.0 g/kg/day of protein. The nutritional intake amounts should be adjusted by monitoring the patient's general condition, activity, and weight change. Clinically, a nutritional dose of 30 kcal/kg/day during RT often results in weight

loss. The best nutritional goals are achieved through the regular food and water intake. However, ONS or tube feeding may be considered in patients experiencing difficulties in consuming enough food due to pain, loss of appetite, or difficulty in swallowing.

Swallowing Interventions

There are some positive reports on the prophylactic swallowing training before and during RT. Prehabilitation aims to minimize dysphagia due to RT or CRT by maintaining muscle mass, strength, range of motion, coordination, and function, particularly in the structures of the oral cavity such as the jaw, tongue, pharynx, and larynx. Swallowing protocols have been found to improve functional swallowing outcomes, including the ability to manage a wider variety of foods and drinks; maintain muscle mass; improve mouth opening; improve taste, smell, and salivary function; and reduce the need for tube feeding [148, 149]. However, a number of studies have shown no difference in outcomes related to food intake following swallowing exercises [149–151]. The effectiveness of prophylactic swallowing therapy can be attributed to the patients' adherence to the program. During treatment, side effects such as pain, fatigue, changes in salivary compounds, and other treatment-related toxicities can affect a patient's ability to complete a prophylactic swallowing program, as prescribed. Owing to the high treatment burden of RT and chemotherapy in HNC, many studies have reported a high dropout rate among participants [149, 152]. Exercise participation generally declines gradually during RT and CRT and even after the end of treatment. To examine the adherence rates, another preventive exercise model was examined. Wall et al. reported that face-to-face clinician-directed therapy had significantly higher adherence rates than patient-directed therapy. Additionally, a supported telemedicine model tended to improve adherence [153]. The observed low level of adherence suggests the need for a multidisciplinary collaborative strategy, including face-to-face instructions and psychological support, rather than simply training the patients on swallowing exercises. In our retrospective backward design study, we showed that a multidisciplinary approach that included swallowing exercises and nutritional monitoring was useful for dietary patterns in the first 6 months after treatment, during surgery and postoperative RT and CRT for oral and oropharyngeal cancer. This approach included face-to-face meetings at least once a week to train the patients on swallowing exercises and continue oral intake whenever possible [154]. There is not a definitive structure for the components of a prophylactic swallowing program, with regard to the number of repetitions, number of sets, or duration of the program. Furthermore, there is limited evidence regarding the long-term consequences of completing swallowing therapy during CRT therapy. Prophylactic swallowing exercise programs are usually intensive, and patients are instructed to perform a series of exercises several times a day for several weeks before or during CRT and RT. To understand the potential benefits of routine prophylactic exercise protocols, large multicenter studies examining similar protocols for exercise intensity, frequency, and follow-up are required.

Oral Mucositis and Oral Care

Unlike chemotherapy, which affects the entire body, RT only affects the irradiated field. The radiation field involving the oral cavity affects the oral mucosa and salivary glands, resulting in oral mucositis and xerostomia. In most cases, symptoms begin to appear 2–3 weeks after the start of RT and gradually worsen and persist during the treatment period. Symptoms do not improve with the completion of RT but rather take a few months to resolve and show improvement after treatment. If the patient experiences severe pain due to oral mucositis, this often leads to malnutrition due to difficulties in oral intake. In addition, oral mucositis and salivary gland disorders may in turn lead to dysphagia. In some cases, complications such as aspiration pneumonia may occur. Currently, there is no method to prevent the RT-induced oral mucositis, but it is possible to manage the symptoms to some extent by providing early care, such as oral care and pain control. It is necessary to provide the patients with education to observe and care for their oral cavities on a daily basis. RT-induced oral mucositis is caused by the direct effects of irradiation and chemotherapeutic agents (if combined with chemotherapy) as well as the released cytokines and free radicals that damage the mucosal epithelial basal cells and induce apoptosis [155]. Therefore, RT-induced oral mucositis occurs regardless of whether oral hygiene is good or bad. Nonetheless, if local or systemic immunity is lowered due to poor oral hygiene, secondary infection from ulcers may occur, and oral mucositis may worsen. Oral care and management are expected to suppress the exacerbation of RT-induced oral mucositis. Oral care is recommended by many guidelines, including the MASCC/ISOO guidelines [156]. However, a review article on oral mucositis reported no evidence for a specific method that is able to reduce the severity of the disease [157]. Therefore, it is important to prevent the secondary infections by using antiseptic-containing gargles and to maintain the oral function by controlling pain so that oral intake can continue for as long as possible for patients with HNC during RT. Clinically, disinfectant mouthwashes are often difficult to use because of the associated pain. In such cases, saline rinses or rinses containing local anesthetics such as xylocaine can be prepared. Episil, a topical hydrogel wound dressing and protector, is often useful for pain management. GC4419, a superoxide dismutase mimetic, has been studied for its ability to prevent oral mucositis in patients undergoing concomitant cisplatin RT for locally advanced oral and oropharyngeal cancer [158]. A 90-mg dose of GC4419 significantly reduced the incidence, duration, and severity of oral mucositis and had an acceptable safety profile. Currently, a phase 3 trial is underway and future reports are expected.

Posttreatment Nutrition Support

After HNC treatment, patients are at a high risk for nutritional disorders, and many patients experience weight loss. The severity of nutritional impairment peaks in the first few weeks after the end of treatment and, therefore, requires special intervention in the early posttreatment period [159, 160]. This supports the importance of

the continuation of nutritional interventions and supportive care to address nutritional deficits after HNC treatment. In the early posttreatment phase, enteral nutrition or ONS is often required. It is recommended that enteral nutrition be phased out as quickly and safely as possible to improve the swallowing function. After HNC treatment, patients have increased oral intake and improved forms of food as their feeding ability improves [116]. However, improvements in eating patterns and taste disturbances vary widely among individuals, and the nutritional intake as well as the severity of eating disturbances may vary daily [159]. In our study, the mass of the swallowing muscles was measured using CT in male patients after RT for HNC. The median geniohyoid muscle's sagittal cross-sectional area was 3.13 mm^2, and the median masseter muscle's coronal cross-sectional area was 4.70 mm^2 at a median of 21 months after RT. The measured muscle mass was lower than that in previous studies, despite most patients being able to eat normal food at the time of admission (assessed by a median functional oral intake scale [FOIS] score of 7) [154]. In addition, our case report of patients who had undergone subtotal tongue resection showed a significant weight loss in patients due to other diseases >1 year posttreatment, which led to nutritional disorders and dysphagia. It can be concluded that patients are very vulnerable to the nutritional status after HNC treatment [161]. Similar to other diseases, patients with HNC require adequate energy and protein intake. For this purpose, it is necessary to not only collaborate with dietitians but also with speech pathologists, dentists, dental hygienists, and other experienced feeding and swallowing professionals [147]. Supportive care needs during and after HNC treatment are also multifaceted and go far beyond nutrition and swallowing therapy. The supportive care needed to cope with acute or long-term side effects includes psychological support, management of anxiety and depression, physical training, and management of fatigue [162]. In our study, a multidisciplinary team was recruited to intervene. Severe swallowing dysfunction with tongue atrophy and sarcopenia, weight gain, increased muscle mass, improved physical function, increased volume of atrophied reconstructed skin valves, and improved swallowing function were observed after the intervention [161]. Interventions in other professions are important as nutritional impairment may occur several years after HNC treatment, thus requiring monitoring. Additionally, some survivors of HNC may permanently need enteral feeding or ONS [163]. The benefits of using an interdisciplinary team are the shorter treatment duration and improved outcomes [164]. The multidisciplinary team can improve coordination, contribute to the continuity of care, and identify issues in a timely manner to initiate an appropriate adjunctive care. A coordinated multidisciplinary approach can be synergistic and, thus, more efficient than the sum of individual strategies. Multidisciplinary approaches should be continued after the treatment. However, a scoping review published in 2018 on rehabilitation interventions used in clinical studies with survivors of HNC identified only three studies with comprehensive multidisciplinary/interdisciplinary rehabilitation interventions [165]. Combined multidisciplinary HNC evidence on the effectiveness of rehabilitation remains scarce and further research is needed.

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Part IV

Skeletal Muscle

Skeletal Muscle Oxygenation in Patients with Malignant Hematopoietic Disease

22

Tatsushi Wakasugi, Yuki Uchiyama, and Shinichiro Morishita

Abstract

The noninvasive near-infrared spectroscopy (NIRS) technique has enabled a way to measure oxidative metabolism in muscle during exercise. Therefore, the NIRS technique has been used in research and clinical fields around the world to investigate the dynamic changes of hemoglobin and myoglobin in the skeletal muscle.

Our study used the NIRS technique to investigate hemodynamics in the muscle of patients with hematological malignancy who had undergone allogeneic transplantation. We chose the measurements of the tibialis anterior muscle during an isometric contraction task that induced muscle fatigue. Muscle fatigue is a very useful sign in the clinical setting because it was induced in either a supine or sitting posture setting. This protocol made it possible to measure muscle oxidative metabolism at bedside in a sterile isolation room during treatment for hematopoietic transplantation. Fatigue is an important clinical sign for interpreting oxidative metabolism in the muscle and leads to inevitably reduced exercise capacity in patients with hematological malignancy. NIRS parameters may be a useful outcome to interpret the clinical symptoms.

T. Wakasugi (✉)
Department of Rehabilitation, Hyogo Medical University Hospital, Nishinomiya, Japan
e-mail: waka-t2s@hyo-med.ac.jp

Y. Uchiyama
Department of Rehabilitation Medicine, Hyogo Medical University, Nishinomiya, Japan

S. Morishita
Department of Physical Therapy, School of Health Sciences, Fukushima Medical University, Fukushima, Japan

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Keywords

NIRS · Muscle · Hemoglobin · Cancer · Hematopoietic disease

22.1 Introduction

To date, the noninvasive near-infrared spectroscopy (NIRS) technique has enabled a way to measure oxidative metabolism in the muscle during exercise. Therefore, this technique has been used in research and clinical fields around the world to investigate the dynamic changes of hemoglobin and myoglobin in the skeletal muscle [1, 2]. Our study used the NIRS technique to investigate hemodynamics in the muscle of patients with hematological malignancy [3]. We chose the measurements of the tibialis anterior (TA) muscle, because it is a monoarticular muscle and is able to increase intramuscular pressure by itself [4]. Therefore, patients could restrict the blood flow to induce muscle fatigue by themselves during muscle contraction. Muscle fatigue in the TA is a very useful sign in the clinical setting because it can be induced with the patient in the supine position [5]. NIRS is a portable device; therefore, it is possible to measure muscle oxygenation status at bedside in a sterile isolation room during treatment for hematopoietic transplantation. Fatigue is an important clinical sign for interpreting oxidative metabolism in the muscle, which leads to the inevitably reduced exercise capacity that occurs in hematological malignancy patients [6–9]; muscle oxidative metabolism may be useful when interpreting clinical symptoms and assessing the patient's quality of life. It may also be an important predictor of mortality.

Hemoglobin plays a role of oxygen transporter in red blood cells, and myoglobin is an iron- and oxygen-binding protein in the skeletal muscle, responsible for intracellular oxygen transport to muscle tissue [10]. The NIRS device was used to measure the dynamics of hemoglobin and myoglobin in our study. The absorption spectra of hemoglobin and myoglobin largely overlap. Therefore, it is impossible to distinguish between the dynamics of hemoglobin and myoglobin measured by NIRS [11]. The estimates of the relative contribution of hemoglobin and myoglobin to the NIRS signal vary and may depend on whether the muscle works or not [12] and on the adipose layer [13] and skin blood flow [13]. Therefore, we have to be careful when interpreting the results of the NIRS signal.

The oxygenated and deoxygenated hemoglobin (oxy-Hb and de-oxy-Hb) have different absorption spectra; thus, it is possible to obtain information about oxygenation of muscle tissue by transmitting near-infrared light into the tissue and measuring the reflected light [14].

In general, assessment of anemia in patients with hematological malignancy is based on limb blood sampling. NIRS can estimate the local muscle oxidative metabolism at the level of microcirculation and muscle interface [15]. NIRS is able to directly measure the oxy-Hb and de-oxy-Hb of the microcirculation blood vessels and myoglobin.

Muscle oxidative metabolism is determined by oxygen consumption due to mitochondria and supply due to microcirculation [16]. Mitochondria use oxygen in skeletal muscle cells to produce an adenosine triphosphate (ATP) [17, 18]. During exercise, skeletal muscle increases the oxidative consumption according to mitochondrial activity [17]. This characteristic of skeletal muscle activity was able to be appeared by the dynamics of NIRS trace which composed by oxy or de-oxy hemoglobin [19]. To understand the oxidative metabolism of the muscle during exercise, the NIRS is a very useful device [20, 21].

NIRS traces are represented by concentration changes in oxy-Hb, de-oxy-Hb, total hemoglobin (tHb), and muscle tissue saturation (StO_2) (see Fig. 22.1). StO_2 reflects the dynamic balance between oxygen consumption in the skeletal muscle and oxygen supply by the microcirculation [22]. The changes in tHb represent dynamics of muscle blood volume or flow. The parameters of StO_2 and tHb are represented in the following equations [14]:

$$StO_2 = oxy - Hb / tHb \times 100$$

$$tHb = oxy - Hb + de - oxy - Hb$$

- StO_{2rest}: Average of StO_2 resting values (baseline signal).
- $\Delta StO_{2D\text{-}slope}$: StO_2 desaturation slope trace (this is a negative slope of the least-squared regression line: amplitude of StO_{2min}/$StO_{2D\text{-}slope\ time}$). A higher $StO_{2D\text{-}slope}$ angle represents greater oxygen consumption and consequently greater energy consumption in the muscle.
- $StO_{2D\text{-}slope\ time}$: Oxygen consumption time during muscle contraction.
- ΔStO_{2min}: StO_2 minimum amplitude is the difference between the minimum StO_2 value reached during muscle contraction and $StO_{2rest.}$ This is an oxygen consumption parameter during muscle contraction. ΔStO_{2min} represents the dynamic balance of oxygen consumption by mitochondria and oxygen supply from the microcirculation.
- ΔStO_{2max}: StO_2 maximum is the difference between the maximum StO_2 value reached during the relaxation phase and $StO_{2rest.}$ A higher StO_{2max} represents increased oxygen supply relative to oxygen consumption.
- $\Delta StO_{21/2RT}$: Oxygen half-recovery time, a parameter of muscle oxidative metabolism. This is a time it takes to reach 50% of the difference between the ΔStO_{2min} value at the end of the contraction phase and the ΔStO_2 maximum value in the relaxation phase.
- tHb_{rest}: Average of total hemoglobin resting values (baseline signal).
- ΔtHb_{mean}: This is the difference between the average of the tHb values during contraction and tHb_{rest}. This is a muscle blood flow parameter owing to the increased intramuscular pressure of the contraction. tHb_{mean} value indicates the level of blood flow over the exercise duration.
- ΔtHb_{max}: This is the difference between the maximum tHb value during the relaxation phase and tHb_{rest}. A higher tHb_{max} represents great hyperemia after muscle contraction.

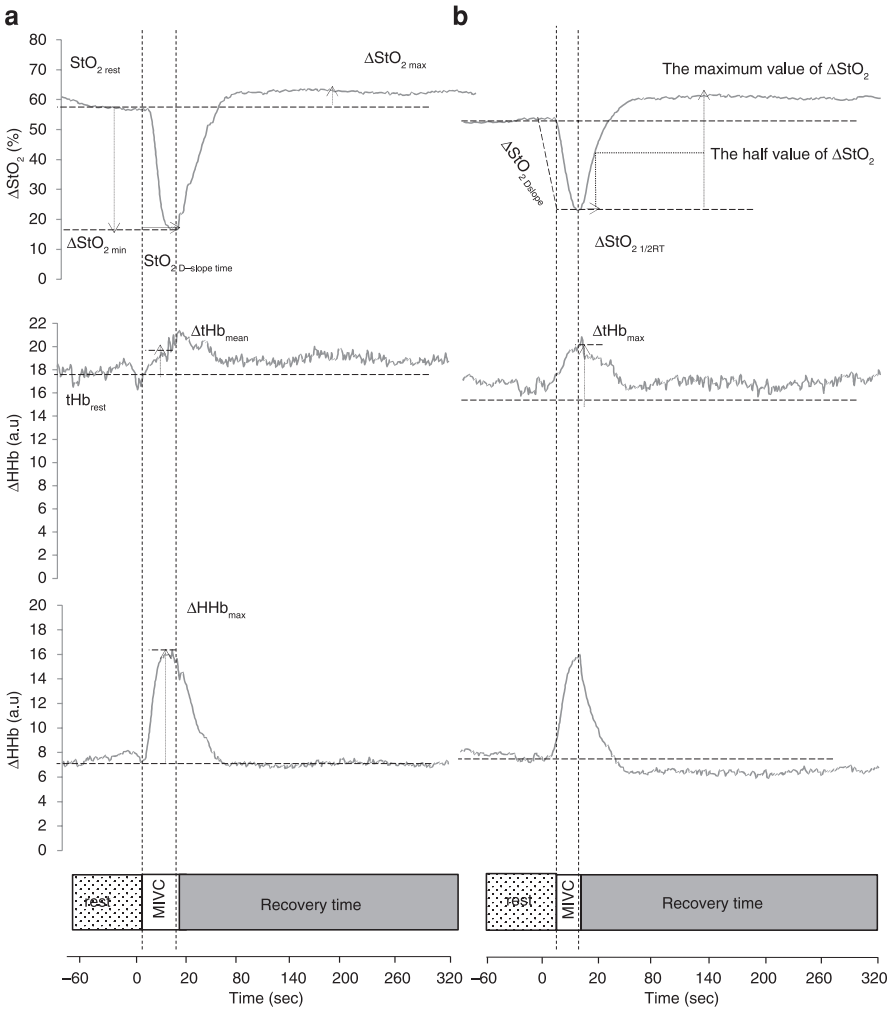

Fig. 22.1 Typical raw data of NIRS parameter in the tibialis anterior muscle. This figure represents muscle tissue saturation (ΔStO_2), total hemoglobin (tHb) and de-oxy hemoglobin (HHb) during maximal voluntary isometric contraction (MVIC) during (**a**) pre-transplantation and (**b**) post-transplantation. The vertical dotted lines delimit the duration of the contractions. StO_{2rest}, average of StO_2 resting values; ΔStO_{2min}, minimum ΔStO_2 amplitude; ΔStO_{2max}, maximum ΔStO_2 amplitude; $\Delta StO_{21/2DT}$, ΔStO_2 half desaturation time; $\Delta StO_{21/2RT}$, ΔStO_2 half-recovery time; tHb_{rest}, average of tHb resting values; ΔtHb_{mean}, ΔtHb mean increase; ΔtHb_{max}, ΔtHb maximum increase; ΔHHb_{max}, maximum Δdeoxy hemoglobin amplitude

- De-oxy Hb_{max} (HHb_{max}): This is the difference between maximum HHb value reached during the contraction phase and baseline. A higher HHb_{max} represented great muscle extraction function during the contraction phase.

According to the wheel gear model theory [23], exercise capacity is determined by cardiopulmonary function, muscle oxidative function, and hemoglobin levels.

Wasserman reported that exercise capacity was associated with the lung, heart, muscle, and mitochondria due to their roles in tissue oxygen transport based on the wheel gear model [24].

Regarding mitochondrial function, it is apparent that mitochondrial oxygen consumption is closely related to muscle ATP utilization [25]. Fick reported that the major physiological variable theory in muscle oxidative metabolism is represented as the following equation:

$$\text{Muscle oxygen consumption} = \left(\text{arterial} - \text{venous oxygen difference}\right) \times \left(\text{blood flow}\right)$$

From the Fick's equation above, the oxygen metabolic demand is increased by muscle oxygen extraction from the blood and the rate of blood flow through the muscle.

In anemic patients with hematological cancer, they have no symptoms at rest, but fatigue is one of the symptoms that frequently occur during exercise. Fatigue in hematological cancer is associated with several factors (i.e., cancer-related fatigue [26], cachexia, hematopoietic stem cell transplantation, treatment side effects [27], steroid-induced myopathy [28, 29], and anemia [15]). To assess fatigue, the NIRS device is a very useful tool for obtaining real-time information regarding the signal trace.

22.2 NIRS Measurements

We measured NIRS signaling trace using an NIRS device (BOM-L1 TRW; OMEGAWAVE, Inc., Tokyo, Japan) and synchronized with the maximum voluntary isometric contraction (MVIC) [30] using a handheld dynamometer (μ-tas F1; ANIMA, Inc., Tokyo, Japan). We also measured an exercise task of intermitted 50% MVIC using another dynamometer (System4; Biodex Medical Systems, Inc., USA) (see Fig. 22.2). This task was also synchronized with NIRS measurements.

22.2.1 Experimental Protocol in a Sterile Isolation Room

Patients were made to lie down in the supine position with the ankle attachment device connected to their foot. The right lower leg was placed parallel to the bed, with the ankle joint straight (0°) and the knee joint slightly flexed (10–20°). The rubber-covered NIRS probe was placed 100 mm from the lower edge of the patella on the TA muscle belly and held in place with double-sided adhesive tape (see Fig. 22.3).

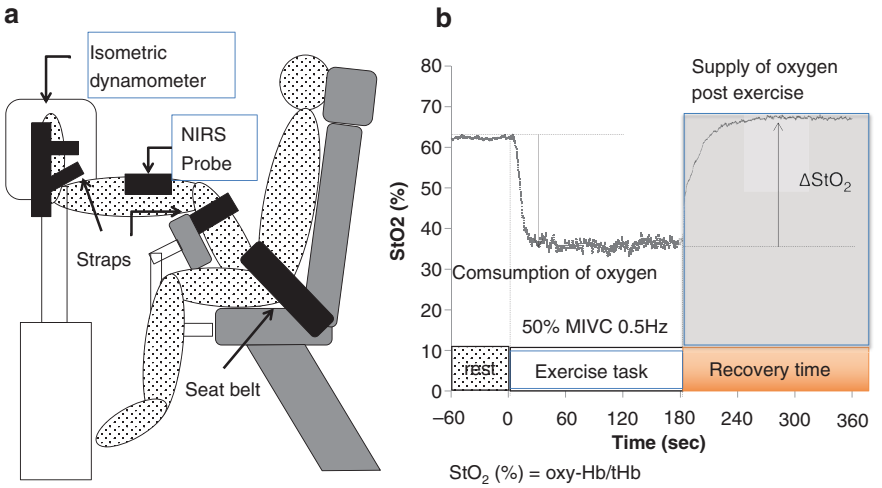

Fig. 22.2 Experimental setting in a physical therapy room. This figure represents muscle tissue saturation (StO_2) during 50% maximal voluntary isometric contraction (MVIC). (**a**) Experimental setting and (**b**) NIRS trace. *Abbreviations*: *oxy-Hb* oxygenated hemoglobin, *tHb* total-hemoglobin

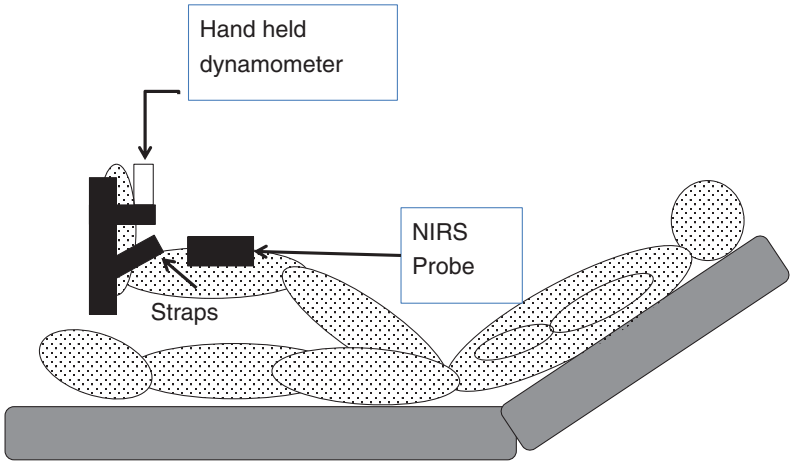

Fig. 22.3 Experimental setting of the right leg of patients during exercise task in the clean room

22.2.2 Experimental Protocol in a Physical Therapy Room

All patients performed a repeated dorsiflexor muscle contraction task at 50% MVIC. The right lower leg was placed parallel to the floor with the ankle joint at 0° and both the knee and hip joints flexed according to the seated position. The peak

torque value of the three contractions was used to set for the 50% MVIC target. A line representing the 50% MVIC target torque level was displayed on the computer screen with actual torque output, which ensured real-time feedback of torque to both the evaluator and the patient. The workload performed was adjusted to 50% MVIC of ankle dorsiflexion at a 50% duty cycle (1 s of contraction/1 s of release) for 180 s (90 times) (see Fig. 22.2). The NIRS probe was set at the same position on the TA muscle in bedside setting (see Fig. 22.3).

22.2.3 Creatine Kinase (CK) Activity

In general, if the skeletal muscle is damaged, abnormally high circulating levels of muscle-specific proteins such as creatine kinase (CK) are present. In clinical practice, however, hematological malignancy patients did not appear to have high CK levels due to the immunosuppressive effect of steroids or appropriate exercise load. Our previous rehabilitation program can be seen below.

Physical therapy for patients with hematological malignancy:

- Cycle ergometer (target heart rate is set at 40–60% using the Karvonen's method).
- Stretching on a stretching board and manual stretching by physiotherapist
- Balance exercise tasks on a balance board
- Closed kinetic chain exercise (squats, calf raises, and high knees)
- Respiratory muscle training (Silvester's method)
- Walking (using a pedometer)
- Stair climbing (patient engaged in stair climbing if they were able)

22.3 Comparison of the Muscle Oxidative Metabolism in Patients and Age-Matched Healthy Controls

Blood is a circulating tissue composed of fluid plasma and cells (i.e., red blood cells, white blood cells, and platelets). Blood cells are derived from hematopoietic stem cells. Among them, red blood cells are responsible for the role of transport oxygen to muscle cells. Patients with hematological malignancy have reduced hematopoietic function [31]. This severely increases the risk of bleeding, infection, and anemia, resulting in fatigue. Fatigue is one of the most frequent symptoms reported by patients with hematological malignancy and may be associated with a reduction of exercise capacity [32]. However, the real-time effect of changes in hemoglobin dynamics on fatigue is not yet understood. Using the TA muscle, we monitored Hb dynamics using NIRS. This study investigated whether changes in total Hb parameters (tHb) were different between patients with malignant hematopoietic disease and age-matched healthy controls.

We used an experimental protocol of intermitted 50% MVIC using BIODEX (see Fig. 22.2). NIRS was measured during exercise. Sixteen patients and 21 age- and sex-matched healthy controls were enrolled. A paired *t*-test was used to compare muscle strength between the patients and controls. We used Pearson's and

Spearman's correlation tests to evaluate the relationship between muscle strength and tHb parameters.

Statistical analyses were performed with statistical significance set at $P < 0.05$.

We have measured NIRS in 16 hematological malignancy patients. Of the 16 patients, 7 patients had acute leukemia, 6 had malignant lymphoma, 1 had myelodysplastic syndrome, 1 had chronic myelogenous leukemia, and 1 had Hodgkin's lymphoma. The patients' muscle strength was decreased compared with that of the healthy controls (peak torque: 22.57 ± 9.86 Nm vs. 38.09 ± 6.74 Nm; $P < 0.001$). All members of the control group were males. In the patients, there were no associations between muscle strength and tHb parameters (ΔtHb_{mean} $r = 0.203$, $P = 0.415$, and ΔtHb_{max} $r = 0.112$, $P = 0.634$). However, in the controls, there was one such association observed (ΔtHb_{mean}, $r = 0.42$, $P < 0.05$, and ΔtHb_{max}, $r = 0.575$, $P < 0.01$).

In the present study, TA muscle strength was significantly decreased in patients with hematological malignancy compared to age-matched healthy controls. Several studies have reported that muscle strength is influenced by factors including immobility [33], chemotherapy and radiation side effects [34], steroid induced myopathy [35], and cachexia. In the present study, muscle strength in patients with hematological malignancy was associated with anemia ($r = 0.547$, $P = 0.028$). However, no correlations between NIRS-derived tHb parameters and muscle strength were found. These results suggest muscle strength is more strongly associated with anemia than muscle blood flow in patients with malignancy. On the other hand, a correlation between muscle strength and blood flow was found in the age-matched controls. In the controls, an association was observed between muscle strength and blood flow. The results of the present study suggest that muscle blood flow during exercise was different between patients and healthy people.

Our results suggested that muscle blood flow (tHb parameter) in patients with hematopoietic malignancy was different from that in healthy controls.

22.4 Hematological Malignancy: Muscle Oxygen Saturation (StO_2)

Patients with hematological malignancy may already have decreased muscle oxygen saturation at rest and when exercising [36] using 6-minute walking test (6MWT). We here investigated the relationship between 6MWT and NIRS resting value in patients with hematological malignancy. The present study included 60 male hematological malignancy patients, who performed a 6MWT to determine their exercise capacity [37]. The purpose of the present study was to investigate the relationship between 6MWT and anemia and NIRS resting value (StO_{2rest}).

Sixty men were enrolled, and their mean age, height, and body mass were 38.5 years, 170.9 ± 7.0 cm, and 64.0 ± 11.1 kg, respectively. The subjects were evaluated by StO_{2rest} using NIRS at the tibial anterior muscle. StO_{2rest} was determined by measuring the NIRS for 1 minute at rest. The hemoglobin level (Hb) was evaluated by lime blood sampling at the same time NIRS was used. 6MWT was evaluated using

20 m slope routes in a physical therapy room. The subjects walked the maximum distance they could.

Our statistics indicated that there was a significant correlation between StO_{2rest} and Hb (r = 0.36, P < 0.01). Furthermore, StO_{2rest} was correlated with 6MWT (r = 0.275, P < 0.05). Anemia was correlated with exercise capacity (Hb vs. 6MWT: r = 0.294, P < 0.05).

Previous studies suggested that anemia was associated with exercise intolerance in patients with hematopoietic malignancy [38]. This study suggest that a NIRS device was able to capture the dynamics of hemoglobin, because the values of StO_{2rest} were associated with blood sample of the limb in hemoglobin [37]. A previous study suggested that exercise capacity was predicted by using StO_{2rest} measured by NIRS [15]. Recently, NIRS has been used to measure real-time absolute values using time-resolved spectroscopy (TRS) methods [39, 40]. The values of NIRS continuous wave (CW) may be useful for measuring physical function in patients with hematopoietic malignancy.

NIRS CW could be used to investigate exercise intolerance using StO_{2rest} values in patients with hematological malignancy.

22.5 Relationship Between StO_2 and Exercise Load in Patients with Hematological Malignancy

An anemia is a frequently occurring symptom of hematological malignancy. We have determined whether there was a correlation between exercise load using a dynamometer and muscle oxygen saturation parameter (StO_2). Hemoglobin plays the role of oxygen transporter to the tissue. Therefore, we also investigated the relationship between anemia and exercise load [41].

This study included 19 male patients with hematological malignancy, who performed an isometric repeated dorsiflexion exercise at 50% MVIC for 180 s to determine their exercise load. This exercise task was done using the Biodex System. Intermittent exercise was set at 50 Hz (1 s contraction and 1 s relaxation). The patients focused on the target line (50% MVC) on the computer screen as real-time monitoring was performed. At the same time, we monitored NIRS trace during the exercise task.

Exercise load was calculated using the mean values of peak torque during the exercise task (units = Nm/kg × 100).

The %MVIC represented the ratio of the mean values of peak torque during the exercise task to peak torque during MVIC, as represented in the following formula:

$$\%\mathrm{MVIC}(\%) = \text{mean peak torque value during the exercise task}(\mathrm{Nm/kg}) / \text{peak torque}(\mathrm{Nm/kg}) \times 100$$

There was a significant correlation between the exercise load and StO_{2min} (r = 0.537, P < 0.05). Furthermore, %MIVC was correlated with StO_{2min} (r = 0.484, P < 0.05). However, there was no correlation between hemoglobin level and exercise load (r = 0.05, P = 0.84) [41].

Patients with hematological malignancy performed an intermitted dorsiflexion exercise for 3 min set at 50%. Our previous study reported that oxygen consumption reached its peak at 20–30 s during isometric contraction in the skeletal muscle [36]. Squats is frequently used as an exercise intervention. In the clinical setting, the patients performed ten squats with 3 s muscle contractions instructed by physiotherapist. Squats may provide evidence regarding oxygen transport for patients with malignant hematopoietic disease. Regarding oxygen dynamics of the skeletal muscle, our results suggested that ten repetitions of squats with muscle contractions lasting 3 s of squats may be an appropriate amount of exercise load for patients. Our results show that muscle oxygen consumption increases according to exercise load value [41]. They also indicate that the activation of mitochondria by exercise depletes oxygen in the muscle and that the activity of oxygen is proportional to the exercise load. This is because the cumulative amount of ankle dorsiflexion movement and the hemoglobin value from blood sampling did not correlate. Complaints of exercise fatigue by patients with hematological malignancies are not explained solely by hemoglobin levels.

Hemoglobin level sampling by the limb is a factor that determines exercise tolerance, but it is not a factor of muscle oxidative metabolism.

This suggests that we can determine exercise load not only hemoglobin but also muscle oxidative metabolism as the ability to take up oxygen. This ability may be an important factor for producing energy.

22.6 Hematological Malignancy Following Hematopoietic Cell Transplantation

Impaired skeletal muscle oxygenation potentially contributes to reduced exercise capacity in patients with hematological malignancy and may explain altered hemoglobin responses to exercise following allogeneic hematopoietic stem cell transplantation (allo-HSCT). While it is an effective medical treatment option for patients with high-risk hematopoietic malignancy [42], allo-HSCT is associated with numerous treatment complications, including infections and graft-versus-host disease (GvHD) [43]. These complications reduce physical performance and function. A previous study reported that cancer-related fatigue negatively affects the patient's quality of life [44]. The allo-HSCT involves high-dose chemotherapy in combination with total body irradiation (TBI), followed by infusion of donor-harvested hematopoietic stem cells [45] (i.e., bone marrow, cord blood cells, and peripheral blood cells). This procedure results in a 2–4-week period of severe marrow suppression and high-risk infection [46]. Therefore, patients must be isolated in a sterile room for about 4–7 weeks, leading to immobility that may result in impaired skeletal muscle function as disuse syndrome [47]. Severe marrow suppression increases the risk of bleeding, infection, and anemia. Previous studies have reported that the combination of chemotherapy and TBI leads to microvascular injury, which over time may result in endothelial dysfunction [34]. However, the direct effects on the peripheral vascular system are not yet understood. We here investigated whether

skeletal muscle oxygenation parameters following allo-HSCT were impaired and whether these results were associated with declines in exercise capacity using 6MWT.

We used NIRS during a repetitive isometric contraction task at 50% of MVIC. The patients performed a dorsiflexor exercise task, and a fatigue test on the TA muscle was used. The TA muscle is suitable for clinical NIRS measurement because of its relatively small size and thin adipose layer, suggesting that the area beneath the probe is more representative of the whole muscle than it would be in a muscle like the quadriceps. The study population included 18 patients with hematological malignancy before and after allo-HSCT. Furthermore, we assessed a 6MWT as an exercise capacity test.

22.7 Transplantation Protocol

For HSCT from human leukocyte antigen (HLA) identical donors, myeloablative conditioning included cyclophosphamide 120 mg/kg and TBI (12 Gy). Patients received the bone marrow as the stem cell source. GvHD prophylaxis consisted of cyclosporine and short-term methotrexate. For umbilical cord blood transplantation, the non-myeloablative regimen included fludarabine, cyclophosphamide, and TBI (3 Gy). In these cases, the stem cell source was umbilical blood. GvHD prophylaxis consisted of cyclosporine or tacrolimus and methotrexate. For HSCT from HLA-mismatched donors [48], myeloablative conditioning included fludarabine, cytarabine, cyclophosphamide, and TBI (8 Gy). The non-myeloablative regimen included fludarabine, busulfan or melphalan, antithymocyte globulin, and TBI (3 Gy). In these cases, the stem cell source was bone marrow or peripheral blood stem cells. GvHD prophylaxis consisted of methylprednisolone or tacrolimus. In HSCT patients, corticosteroids were tapered after hematopoiesis engraftment. The tapering rate was adjusted individually depending on lymphocyte recovery.

22.8 Physical Therapy Intervention

The patients began physiotherapy intervention 1–4 weeks before allo-HSCT and continued after being discharged from the hospital. The exercise routine included between 20 and 40 min of exercise per day, 5 days/week. The physical therapy program consisted of stretching exercises, resistance training, and endurance training. Stretching was conducted mainly for the lower limb and trunk muscles. Resistance training intensity was chosen by determining the rating of perceived exertion using a modified Borg scale [32]. Endurance training intensity was set at 40% of the patient's target heart rate, as calculated using Karvonen's equation.

Our research show that the StO_{2min} was significantly lower after allo-HSCT (the rate of decrease was 49.7%). However, total hemoglobin as a blood flow parameter was not decreased after allo-HSCT.

Ankle dorsiflexor muscle strength was associated with 6MWT ($r = 0.706$, $P < 0.05$).

The StO_{2min} was associated with exercise capacity using 6MWT (r = 0.648, $P < 0.05$) and ankle dorsiflexor muscle strength ($r = 0.487$, $P < 0.05$).

The present study showed that muscle function (e.g., muscle strength and muscle oxygenation using NIRS) and exercise capacity in patients with malignant hematopoietic disease were significantly decreased following allo-HSCT. Furthermore, the StO_{2min} value, as the ability of muscle consumption, was associated with exercise capacity and muscle strength.

A previous NIRS study reported that StO_{2min} represents an estimated arterial-venous O2 concentration difference across the muscle [49]. Previous studies reported that the decrease of muscle oxygen extraction was skeletal muscle disease (e.g., muscle dystrophy [50], metabolic myopathies, mitochondrial myopathies [49], and McArdle's disease [51]), which may have been due to the decline in muscle oxygen extraction. We have found that StO_{2min} was strongly related to reduced exercise capacity and muscle strength. The skeletal muscles following allo-HSCT have confounding factor included by steroid-induced myopathy [35], sarcopenia [52], cachexia, and catabolism caused by malnutrition [17]. These results suggest that allo-HSCT patients with hematopoietic malignancy may be experienced by not only muscle atrophy but also ATP production inefficiency due to fractional oxygen extraction dysfunction.

There was correlation between impaired muscle oxygenation and a decline in exercise capacity after allo-HSCT.

22.9 Hematological Malignancy During Exercise Tolerance Test (Ramp Protocol)

We reported that impaired skeletal muscle oxygenation occurred following allogeneic hematopoietic stem cell transplantation (allo-HSCT) [36]. Patients need to be isolated in a sterile isolation room for about 2–3 weeks until donor stem cell engraftment. High-dose chemotherapy and TBI cause cytotoxic adverse effects in systemic organs, as well as severe bone marrow suppression with anemia, leukocytopenia, and thrombocytopenia. Therefore, it is difficult to assess exercise capacity using the 6MWT due to limitations regarding space for physical activity at the time of engraftment. We hypothesized that exercise capacity is impaired due to multiple organ-related factors in the muscular, pulmonary, cardiovascular systems and mitochondrial function at the engraftment phase. A previous study reported that exercise capacity is determined by cardiopulmonary function, muscle oxidative function, mitochondrial function, and hemoglobin level in the exercise physiology research field [23]. Wasserman reported that exercise capacity was associated with the lung, heart, muscle, and mitochondria with regard to oxygen transport to the tissue, based on the wheel gear model theory [24]. This theory was used in the ramp protocol. The amount of oxygen extracted increases and is exhausted when the workload increases. In the ramp protocol, the distribution of blood flow to the working tissues is workload dependent.

22.10 Exercise Tolerance Test

We used ramp protocols reference to the American Thoracic Statements (ATS) [53]. This protocol consisted of increases in exerted workload by 10 W/min until the patients reached voluntary exhaustion. The initial work load was set at 5 W/min. We used a stationary cycle ergometer in a sterile isolation room and instructed the patients to try to maintain a pedal speed of 50–60 rotation/min (rpm). During the exercise tolerance test, the patients' cardiac activities were monitored using electrocardiography (DS-7500; FUKUDA, Tokyo, Japan). The end points of the exercise tolerance test were determined to be the following: (1) the patient could not keep at least 50 rpm or (2) the patient's pulse rate reached >85% of the age-predicted maximum (220 − age × 0.85). The double product corresponding to the heart load was calculated by multiplying the HR by the SBP.

22.11 Exercise Protocols

We investigated the physical function of the patients before allo-HSCT.

In a sterile isolation room setting, anthropometric body measurements were evaluated, with the patient in the supine position, using an eight-contact electrode bioimpedance analysis device (In Body S10; Inbody Japan Inc., Tokyo, Japan).

The skeletal mass index (SMI) was calculated using the following formula:

$$\mathrm{SMI} = \mathrm{height}\left(\mathrm{meters}\right) / \mathrm{muscle\ mass}\left(\mathrm{kg}\right)$$

Measurements of pulmonary function were carried out using a handheld spirometer (AS-302 Auto-spiro, Minato Medical Science, Osaka, Japan) based on the ATS guidelines.

Fourteen patients met our inclusion criteria. In the exercise tolerance test, peak workload decreased by 17.4% following allo-HSCT. The Borg scale (leg item 5.8–6.8) after peak workload was considered a statistically significant change following allo-HSCT. Body weight and lower leg circumference decreased by 5.3% and 7.4%, respectively, following allo-HSCT. However, the SMI parameters were not significantly decreased. The pulmonary function was remained, however, and %VC was found to be associated with peak workload during exercise tolerance test ($r = 0.643$, $P < 0.05$). In muscle consumption function using the values of StO_{2min}, the kinetic values of StO_2 revealed a shorting time until exhaustion, and the StO_2 amplitude was decreased. Furthermore, StO_{2min} was associated with peak workload during the exercise tolerance test. The parameter of muscle oxygen extraction as HHb_{max} was decreased after allo-HSCT. Furthermore, HHb_{max} was associated with peak workload during the exercise tolerance test.

The results of the present study indicate that weight loss and progressive calf muscle atrophy occur in patients following allo-HSCT. Furthermore, weight loss following HSCT was correlated with calf atrophy and decreased muscle volume.

However, there was no correlation between weight loss and body fat ratio. Thus, we believe that weight loss following allo-HSCT is associated with a loss in skeletal muscle mass rather than a loss of body fat. We previously reported that the prevalence of sarcopenia was 50.6%, even before allo-HSCT [52], and that corticosteroid dose affected muscle mass and strength but not exercise tolerance.

Muscle dysfunction following allo-HSCT is attributed to steroid-induced myopathy, cachexia, and malnutrition. In the present study, there was a 7.1% reduction in muscle mass and a 27.5% reduction in muscle strength 17 days after HSCT. Our previous study reported a 27.7% reduction in knee extensor muscle strength following allo-HSCT (HLA-mismatched donor group) at 41 days after HSCT. Our results suggest that muscle dysfunction at the time of engraftment occurs early due to changes in muscle strength rather than changes in muscle mass. This may be biologically plausible because muscle dysfunction affects muscle strength as a motor unit more than muscle mass.

Sustained TA muscle contraction led to exhaustion in the first 30 s of MVIC in healthy participants. Furthermore, intramuscular pressure during exercise decreased linearly beyond 30 s of sustained isometric contraction. It took 20.2 ± 4.2 s for patients with hematological malignancy to reach minimum StO_2 values during MVIC. This was significantly shorter following allo-HSCT (17.3 ± 4.2 s). These results suggest that the speed of exhaustion of oxygen in the skeletal muscle was faster following allo-HSCT. Patients with malignant hematological malignancy had impaired muscle oxidative metabolism due to mitochondrial dysfunction.

Impaired muscle oxidative metabolism is determined by the following factors:

- Endothelial dysfunction and capillary reduction
- Changes in type of muscle fiber
- Mitochondrial dysfunction

Our results demonstrated that hemoglobin level (blood sampling) and NIRS-derived t-Hb (blood flow) did not change. However, HHb_{max} as a measure of muscle oxygen extraction was significantly lower following allo-HSCT [54]. Hence, we propose that the muscle oxidative dysfunction following HSCT occurs due to mitochondrial dysfunction and not endothelial dysfunction secondary to capillary reduction. This suggests that exercise in a sterile isolation room prevented the reduction of blood flow during exercise. Muscle oxidative dysfunction may be induced by severe myopathy as steroid myopathy, cachexia, and disuse syndrome.

The present study revealed an association between exercise intolerance, muscle oxidative metabolism dysfunction (muscle oxygen consumption and extraction), and lung function (vital capacity). Wasserman reported that exercise capacity was determined by cardiopulmonary function, muscle oxidative metabolism, and hemoglobin with regard to oxygen transport and the by-product ATP in the mitochondria. Our results indicate that exercise capacity in patients with hematological malignancy was associated with oxygen uptake by the lungs and muscle oxygen extraction by the mitochondria.

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Sarcopenia and Physical Performance in Patients with Cancer

23

Shinya Tanaka and Noriatsu Tatematsu

Abstract

Recently, sarcopenia has become an area of interest in oncology research due to its high prevalence and association with adverse outcomes. Although the prevalence of sarcopenia varies widely among studies owing to a lack of uniform definitions, it consistently results in poor prognosis across a variety of cancers and cancer stages. Early detection and intervention are important because exercise and nutritional therapy are effective in preventing the incidence and progression of sarcopenia.

Keywords

Sarcopenia · Physical performance · Physical function · Muscle mass · Muscle strength · Exercise · Nutrition · Physical activity · Rehabilitation · Prognosis

23.1 Introduction

23.1.1 What Is Sarcopenia?

One of the most significant changes associated with aging is loss of skeletal muscle mass, which leads to decreased muscle strength and function. In 1989, Irwin Rosenberg proposed the term "sarcopenia" (from the Greek word *sarx* for flesh and

S. Tanaka (✉)
Department of Rehabilitation, Nagoya University Hospital, Nagoya, Aichi, Japan
e-mail: s-tanaka@med.nagoya-u.ac.jp

N. Tatematsu
Department of Integrated Health Sciences, Graduate School of Medicine, Nagoya University, Nagoya, Aichi, Japan
e-mail: tatematsu@met.nagoya-u.ac.jp

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penia for loss) to describe this age-related decrease in muscle mass [1]. Sarcopenia is a progressive, systemic skeletal muscle disorder that increases the likelihood of adverse events such as falls, fractures, disability, and mortality and decreases the health-related quality of life [2]. The prevalence of sarcopenia varies widely among reports, but there is no consistent view. In some reports, the prevalence of sarcopenia is thought to range from 6% to 12%, in large cohort studies involving older adults living in the community [2]. Factors thought to contribute to sarcopenia include age-related inactivity, poor nutritional intake, decreased exercise, chronic inflammation, increased oxidative stress, decreased satellite cells, hormonal changes, deoxyribonucleic acid (DNA) damage, trauma, and insulin resistance (Fig. 23.1) [3]. Sarcopenia is classified into age-related (primary sarcopenia) sarcopenia and sarcopenia related to low activity, chronic disease, and malnutrition (secondary sarcopenia) (Table 23.1). Sarcopenia is common among older adults but can also occur earlier in life. Sarcopenia costs the US health-care system approximately US $18.5 billion per year, as it often results in disability requiring caregiver assistance, loss of independence, and the need for long-term care [4]. Sarcopenia is now listed in the ICD-10 as a muscle disease and can be billable in some countries [5].

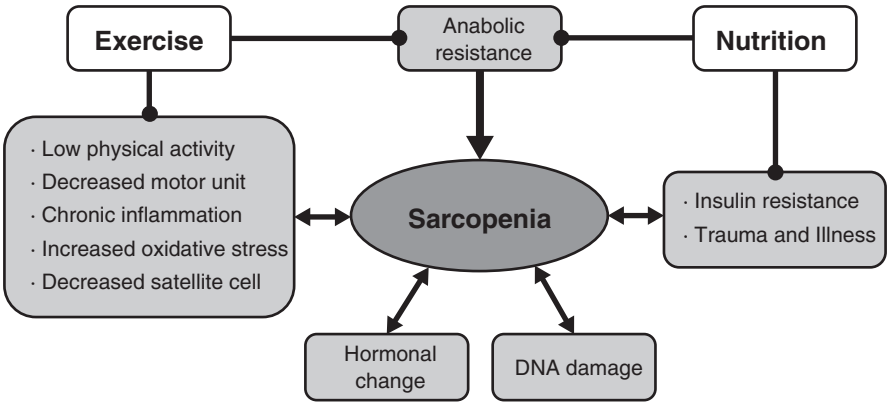

Fig. 23.1 Mechanisms of sarcopenia. *DNA* deoxyribonucleic acid

Table 23.1 Sarcopenia categories by cause

Primary sarcopenia	Age-related sarcopenia	No other causes evident except aging
Secondary sarcopenia	Activity-related sarcopenia	Can result from bed rest, sedentary lifestyle, deconditioning, or zero-gravity conditions
	Disease-related sarcopenia	Associated with advanced organ failure (heart, lung, liver, kidney, brain), inflammatory disease, and malignancy or endocrine disease
	Nutrition-related sarcopenia	Results from inadequate dietary intake of energy and/or protein, as with malabsorption, gastrointestinal disorders, or the use of medications that cause anorexia

Inactivity and malnutrition are considered points of intervention [6]. Optimal care for people with sarcopenia is essential because the condition results in high personal, social, and economic burden when left untreated.

23.1.2 Definition of Sarcopenia

The diagnosis of sarcopenia requires both findings of low muscle mass and impaired muscle function (reduced muscle strength and physical performance) to be present. Sarcopenia is often defined using the European Working Group on Sarcopenia in Older People (EWGSOP) (Fig. 23.2 and Table 23.2) or Asian Working Group for Sarcopenia (AWGS) definitions (Fig. 23.3) [2, 7]. Several techniques can be used to assess muscle mass. However, cost, availability, and ease of use determine whether the techniques are better suited for clinical practice or for research. Either dual-energy X-ray absorptiometry (DXA) or multifrequency bioelectrical impedance analysis (BIA) is recommended for measuring muscle mass, while handgrip strength is used for measuring muscle strength in sarcopenia. Various tests are used to measure physical performance, including short physical performance battery, gait speed, 6-minute walk test, stair climb power test, timed up-and-go test, and five times

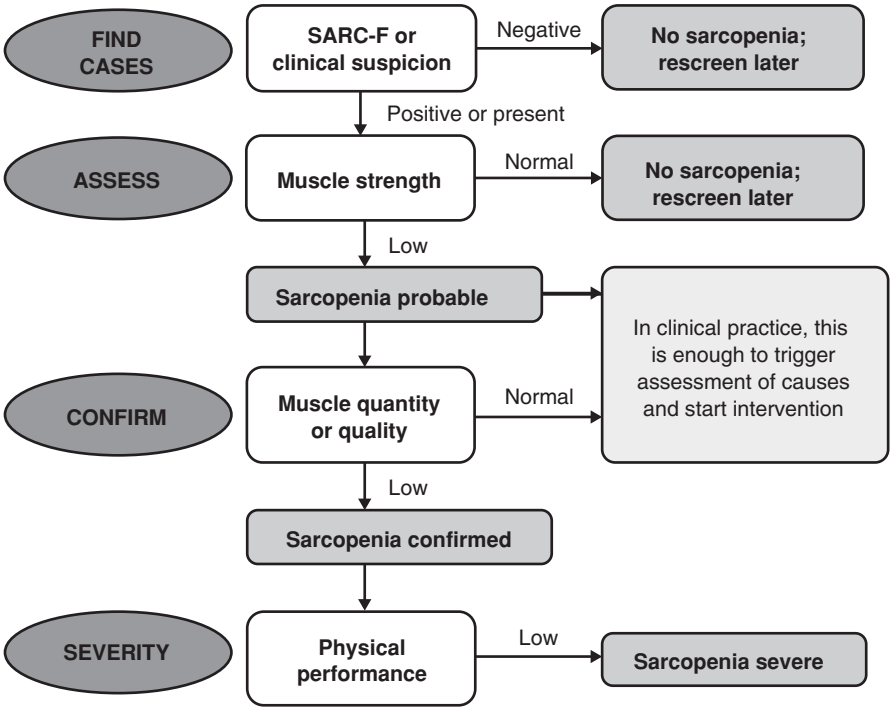

Fig. 23.2 Definition of sarcopenia in EWGSOP2. *EWGSOP* European Working Group on Sarcopenia in Older People

Table 23.2 EWGSOP2 sarcopenia cutoff points

Test	Cutoff points
Low muscle strength	
Grip strength	<27 kg (male), <16 kg (female)
Chair stand	>15 s for five rises
Low muscle quantity	
Appendicular skeletal muscle mass	<20 kg (male), <15 kg (female)
Appendicular skeletal muscle mass/height^2	<7.0 kg/m^2 (male), <5.5 kg/m^2 (female)
Low physical performance	
Gait speed	≤0.8 m/s
Short physical performance battery	≤8 point score
Time	≥20 s
400 m walk test	Non-completion or ≥6 min for completion

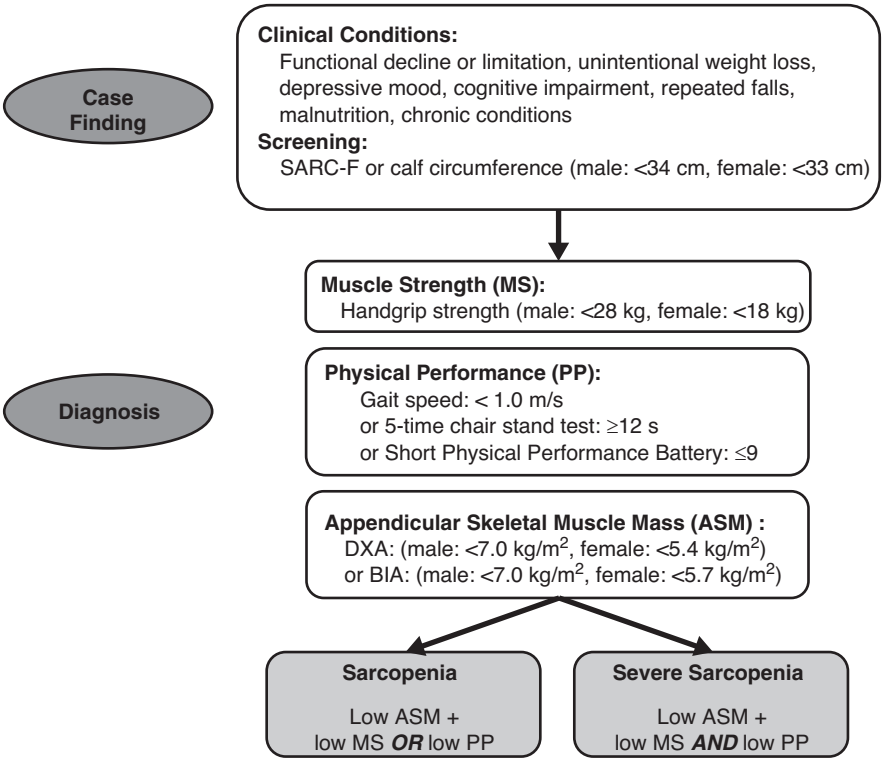

Fig. 23.3 Definition of sarcopenia in AWGS2019. *AWGS* Asian Working Group for Sarcopenia, *DXA* dual-energy X-ray absorptiometry, *BIA* bioelectrical impedance analysis

sit-to-stand test. Gait speed is the most frequently used and recommended test because it is strongly associated with disability, severe mobility limitations, and mortality. In addition, guidelines recommend using SARC-F as a tool in clinical practice for the assessment and treatment of sarcopenia [2, 7]. The SARC-F is a five-item questionnaire to screen for sarcopenia risk (Table 23.3). In sites where it is difficult to measure skeletal muscle mass, screening can be performed using the

Table 23.3 SARC-F score

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 lb?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0 Some = 1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of ten stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1–3 falls = 1 ≥4 falls = 2

A total score of ≥4 was taken to indicate sarcopenia (probable)

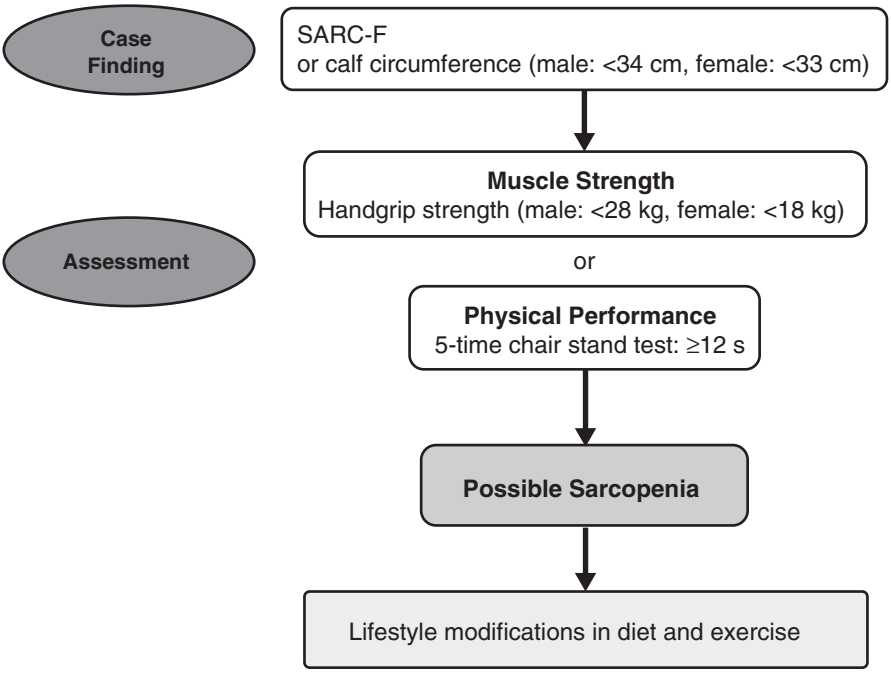

Fig. 23.4 AWGS2019 algorithm for sarcopenia in primary health-care and preventive service users

calf circumference and SARC-F. If low values are found, skeletal muscle function can be measured using handgrip strength and five times sit-to-stand test. If either is reduced, a diagnosis of sarcopenia (probable) can be made (Fig. 23.4). Lifestyle

interventions and related health education are recommended for patients diagnosed with sarcopenia (probable). In addition, referral to a hospital for definitive diagnosis is encouraged.

23.1.3 Prevention of Sarcopenia

Guidelines recommend exercise and protein intake for the prevention of sarcopenia. However, few interventional studies have examined the prevention of sarcopenia. Recommendations are based on observational studies. Many studies have examined the benefits of resistance exercise. A meta-analysis has shown that resistance exercise increases muscle strength and skeletal muscle mass in healthy older adults [8]. Another meta-analysis examining the effects of protein supplementation on muscle strength and skeletal muscle mass in healthy older subjects found no benefit with protein supplementation [9]. In healthy older adults who consume sufficient amounts of protein in their daily diet, protein supplementation was not found to be beneficial. Increasing physical activity and maintaining a healthy body weight have been shown to be effective in preventing sarcopenia [10].

23.1.4 Treatment of Sarcopenia

Exercise, essential amino acid, and/or protein intake or a combination of these interventions are recommended in the guidelines for the treatment of sarcopenia. Few studies have examined interventions only in sarcopenic patients, and the recommendations are weak. In this context, resistance exercise has been shown to be useful in the treatment and prevention of sarcopenia and has been shown to improve skeletal muscle mass, muscle strength, and physical performance [11]. In general, when resistance exercise is performed for the purpose of increasing muscle strength, it is ideal to perform it at a high load of 70–80% of the repetition maximum (1RM). However, recent studies have shown that the effects of muscle protein synthesis and muscle strengthening can be obtained by performing high-repetition exercises even at low loads, rather than focusing on high-load exercises in older adults [12, 13]. In particular, it has been shown that high- and low-load resistance exercises are almost equally effective if the workload calculated by the amount of load and the number of repetitions is the same. When prescribing exercise regimens for older adults who are at risk, it is important to note that increasing the number of repetitions, even at low workloads, can help prevent sarcopenia. Muscle strength and muscle mass gained by resistance exercise are almost halved after 12 weeks and almost lost after 24 weeks [14, 15]. Therefore, it is important to continue exercise and to promote awareness and behavioral change so that low-load and high-repetition exercise becomes sustainable.

Protein supplementation was not found to be superior in the prevention of sarcopenia in healthy older adults but was found to have a superior effect on the skeletal muscle in participants with sarcopenia [16]. Protein intake of 1.0–1.5 g/kg/day is

recommended. Although amino acid and protein intake have been confirmed to be beneficial in the treatment of sarcopenia, the route of administration also needs to be considered. In general, amino acid and protein intake immediately after exercise are considered to be beneficial. Recently, however, there has been a renewed emphasis in the guidelines on balancing the three meals. This is based on the idea that by maintaining uniform protein intake in all three meals, the amino acid levels in the blood are kept as high as possible throughout the day [17]. In the case of treatment, it is necessary to increase the daily protein intake while maintaining balance among the three meals.

Sarcopenic dysphagia, which is closely related to nutritional disorders, is defined as dysphagia resulting from sarcopenia of the entire body- and swallowing-related muscles [18]. The treatment of sarcopenic dysphagia requires both dysphagia rehabilitation, such as resistance training of the swallowing muscles and nutritional intervention. Sarcopenic dysphagia is a significant issue; however, its diagnosis remains a challenge. More discussion is required on issues such as the relationship between dysphagia and secondary sarcopenia as well as the diagnostic criteria and methods for diagnosing dysphagia caused by sarcopenia.

23.2 Sarcopenia in Cancer

Cancer, a major cause of death globally, is often caused by the accumulation of genetic abnormalities in cells. Consequently, it is more likely to occur in the older population. Approximately 70% of all cancer patients are 65 years or older. In an aging population, sarcopenia has attracted interest in oncology because of its high prevalence and association with adverse outcomes [19].

23.2.1 Epidemiology of Sarcopenia in Cancer

The number of publications on sarcopenia in patients with cancer has been steadily increasing. Table 23.4 shows the results of a meta-analysis examining the association between sarcopenia and clinical outcomes in patients with cancer published between 2021 and 2022 [20–31]. Notably, the definition of sarcopenia is one of the most important aspects. The definition of sarcopenia includes the assessment of muscle strength and physical function and the assessment of skeletal muscle mass using DXA or BIA. In the field of oncology, computed tomography (CT) examinations are frequently performed in daily clinical practice. Many studies have defined sarcopenia solely in terms of skeletal muscle mass through CT images [19] (Fig. 23.5). As the evaluation of skeletal muscle mass using CT images does not have a uniform cutoff value to discriminate sarcopenia, generalization and comparison of study results should be done with caution. The prevalence of sarcopenia varies widely among studies, ranging from a few percent to nearly 80%. However, an average prevalence of 40–50% is often reported. The prevalence in cancer patients is higher than in community-dwelling people. Although many reports have focused

Table 23.4 Meta-analysis examining the association between sarcopenia and clinical outcomes in cancer patients

Study	Type of cancer	Number of cases	Subject	Average age	Prevalence of sarcopenia	Definition method	Impact of sarcopenia on outcomes	Reference number
Takenaka (2021)	Head and neck cancer	18 studies (n = 3233)	Preoperative (7 studies)	51–72 years	14–75%	CT images	Risk of decreased disease-free survival for surgical patients: 2.59 times (95% CI 1.56–4.31) and death 2.50 times (95%CI 1.95–3.21) Risk of decreased disease-free survival for radiotherapy patients: 1.56 times (95% CI 1.24–1.97) and death 1.63 times (95% CI 1.40–1.90)	[20]
Findlay (2021)	Head and neck cancer	7 studies (n = 1059)	Radiation therapy	57–66 years	Pretreatment: 7–65% Posttreatment: 12–66%	CT images	Risk of death (pretreatment sarcopenia): 2.07 times (95% CI 1.47–2.92) Risk of death (posttreatment sarcopenia): 2.93 times (95% CI 2.00–4.29)	[21]
Kawaguchi (2021)	Lung cancer	10 studies (n = 2643)	Preoperative	NA	13–55%	CT images	Risk of postoperative complications: 1.86 times (95% CI 1.42–2.44) Risk of decreased disease-free survival: 1.66 times (95% CI 1.00–2.74) Risk of death: 3.07 times (95% CI 2.45–3.85)	[22]

Chen (2022)	Esophageal cancer	26 studies (n = 4515)	Preoperative	60–71 years	14–85%	CT images (22 studies) BIA (4 studies)	Risk of complications: 1.15 times (95% CI 1.08–1.22) Risk of decreased recurrence-free survival: 1.79 times (95% CI 1.12–2.87) Risk of death: 1.12 times (95% CI 1.04–1.20)	[23]
Jin (2021)	Esophageal cancer	11 studies (n = 1485)	Neoadjuvant therapy	54–67 years	26–80%	CT images	Sarcopenia rate increased 15% after preoperative adjuvant therapy Risk of decreased disease-free survival: 1.55 times (95% CI 1.18–2.05) Risk of death: 1.29 times (95% CI 1.08–1.54)	[24]
Chen (2022)	Gastric cancer	20 studies (n = 7615)	Preoperative	56–78 years	7–45%	CT images (13 studies)	Risk of complications: 2.89 times (95% CI 1.86–4.49) Risk of death: 1.71 times (95% CI 1.53–1.91)	[25]
Xie (2021)	Colorectal cancer	19 studies (n = 15,889)	Preoperative	58–72 years	12–68%	CT images	Risk of complications: 1.82 times (95% CI 0.36–2.44) Risk of decreased disease-free survival: 1.59 times (95% CI 1.32–1.92) Risk of death: 1.40 times (95% CI 1.25–1.58)	[26]

(continued)

Table 23.4 (continued)

Study	Type of cancer	Number of cases	Subject	Average age	Prevalence of sarcopenia	Definition method	Impact of sarcopenia on outcomes	Reference number
Watanabe (2021)	Biliary tract cancer	29 studies ($n = 4443$)	Preoperative (18 studies)	57–76 years	15–80%	CT images (28 studies) DXA (1 study)	Risk of postoperative complications: 1.23 times (95% CI 1.07–1.41) Risk of decreased recurrence-free survival: 2.20 times (95% CI 1.75–2.75) Risk of death: 2.26 times (95% CI 1.75–2.92)	[27]
Ibilibor (2021)	Bladder cancer	5 studies ($n = 1447$)	Preoperative	61–73 years	25–68%	CT images	Risk of death: 1.41 times (95% CI 1.22–1.62)	[28]
Li (2021)	Gynecological cancer	23 studies ($n = 3495$)	NA	54–67 years	47%	CT images	Risk of decreased progression-free survival: 1.32 times (95% CI 1.02–1.70) Risk of death: 1.78 times (95% CI 1.38–2.30)	[29]
Deng (2021)	Advanced cancer	9 studies ($n = 740$)	Immune checkpoint inhibitor	56–72 years	22–55%	CT images	Response rate trended decreased (30.5% vs. 15.9%, $P = 0.095$) Risk of decreased progression-free survival: 1.31 times (95% CI 1.18–1.46) Risk of 1-year mortality: 1.71 times (95% CI 1.10–2.30)	[30]
Au (2021)	All cancers	100 studies	NA	NA	NA	CT images	Risk of death: 1.69 times (95% CI 1.56–1.83)	[31]

DXA dual-energy X-ray absorptiometry, *CT* computed tomography, *L3* third lumbar vertebra, *CI* confidence interval, *NA* not applicable

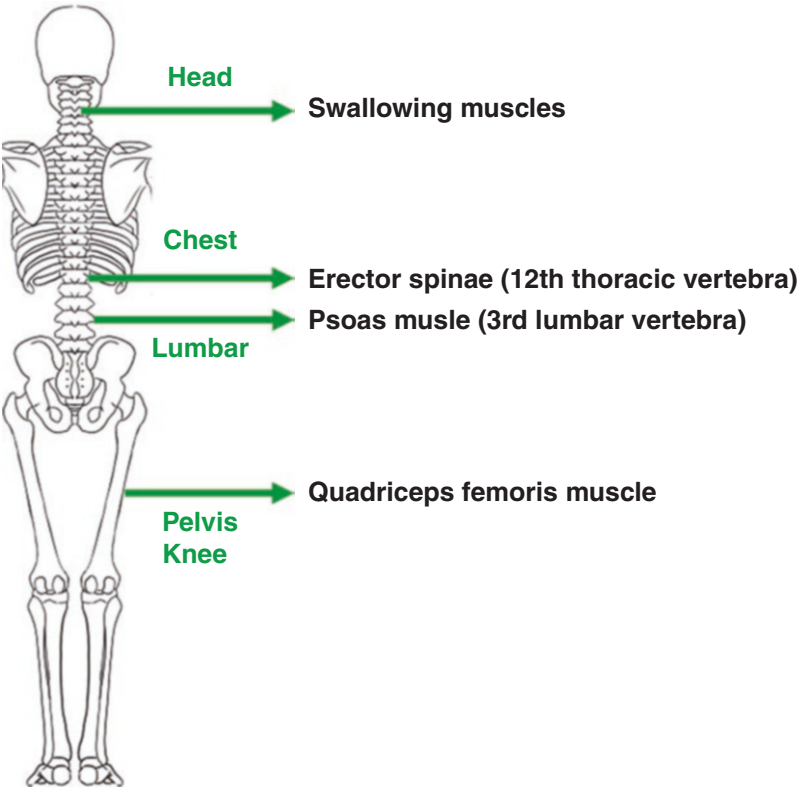

Fig. 23.5 Evaluation of skeletal muscle mass by CT imaging. *CT* computed tomography

on preoperative patients, some studies have also included patients treated with chemotherapy, radiotherapy, and immunotherapy. In clinical practice, early detection of sarcopenia in high-risk patients is essential for timely and appropriate intervention.

23.2.2 Impact of Sarcopenia on Clinical Outcomes in Cancer

The impact of sarcopenia on clinical outcomes has been investigated in different types of cancer. Prognosis has been consistently poor (Table 23.4). The presence of sarcopenia in the preoperative assessment increases the risk of postoperative complications and death, prolongs the length of hospital stay, and increases the probability of discharge from the hospital to a nonhome location. In addition, it is important to maintain a high level of physical performance because a decline in activities of daily living (ADL) may limit the options for cancer treatment.

23.2.3 Impact of Sarcopenia on Clinical Outcomes in Non-small Cell Lung Cancer

Lung cancer is one of the main causes of mortality worldwide and accounts for 1.7 million deaths every year [32]. Approximately 80% of primary lung cancer cases are classified as non-small cell lung cancer (NSCLC), for which the standard treatment of choice for early stage disease is surgical resection [33]. In spite of improvements in survival rates brought about by advances in diagnostics and treatment strategies, the outcome following resection for NSCLC remains poor [34]. This may be attributed to cancer-specific factors and individual differences in physical status [35]. In an aging population, it is necessary to develop more accurate methods for preoperative evaluation, prognostication, and physical performance following surgery. Assessment of the psoas muscle at the level of the third lumbar vertebra (L3) on a single-slice CT is often used to screen for sarcopenia [36, 37]. However, the standard imaging modality in the preoperative evaluation of NSCLC, chest CT, does not routinely visualize the L3 level. Supplementary abdominal CT would result in additional medical costs and radiation exposure to the patient. There is increasing interest in the measurement of skeletal muscle mass at the level of the 12th thoracic vertebra (T12) on chest CT. Sarcopenia in the thoracic area correlated with poor survival in various patient populations [38–41].

We examined the prognostic significance of preoperative thoracic sarcopenia and physical performance status in patients with NSCLC [42]. In this retrospective cohort study, patients with NSCLS were divided into four groups according to skeletal muscle index (SMI) (sarcopenia [lowest sex-specific tertile] and non-sarcopenia) and 6-minute walking distance (6MWD) (short distance [<400 m] and long distance [≥400 m]). Preoperative cross-sectional areas of the right and left paraspinous muscles at the level of the 12th thoracic vertebra on CT images were used to screen for sarcopenia. Physical performance was determined by the preoperative 6MWD. The 587 patients (mean age 68.5 ± 8.8 years, 399 men [68%]) included in the study were divided into the normal group (58%), sarcopenia group (26%), short-distance group (9%), and sarcopenia and short-distance group (7%) (Fig. 23.6). A body mass index of <18.5 kg/m^2 was associated with a greater likelihood of positivity for both sarcopenia and short-distance 6MWD. A total of 109 (18.6%) deaths were observed over a mean follow-up of 3.1 years. The risk of death in patients with sarcopenia alone, in those with short distance on 6MWD test alone, and in those with both conditions was 1.78, 2.26, and 3.38 times higher, respectively, than that in patients with neither sarcopenia nor short distance on the 6MWD test (Fig. 23.7). The combination of

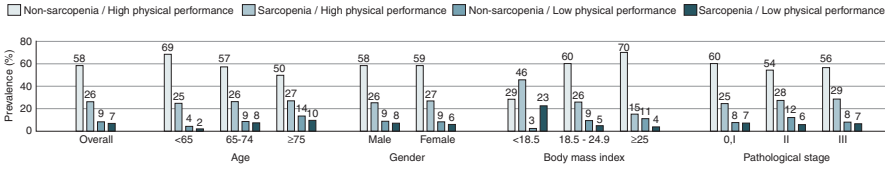

Fig. 23.6 Prevalence of sarcopenia and low physical performance

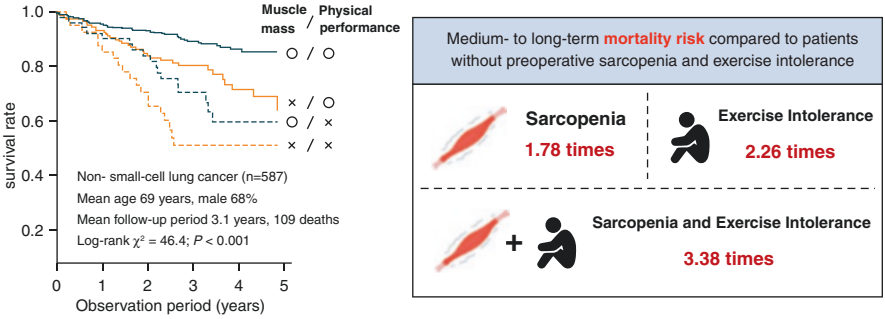

Fig. 23.7 Impact of sarcopenia and physical performance on mortality in patients with NSCLC. *NSCLC* non-small cell lung cancer

muscle loss and 6MWD of <400 m is defined as "sarcopenia with limited mobility" [43], which is included in the concept of frailty [44]. Alternatively, the consensus of the EWGSOP also defines persons with sarcopenia who cannot walk 400 m within 6 min as having "severe sarcopenia." In this study, these vulnerable patients were found to have poor prognosis. Furthermore, the combination of SMI and 6MWD after two years of surgery had prognostic predictive capability complementary for pre-existing prognostic factors such as age, sex, smoking status, cancer progression, and respiratory function. These observations emphasized that a comprehensive evaluation that considers both preoperative sarcopenia and physical performance is required in patients with NSCLC. It is important to accurately assess preoperative sarcopenia and physical performance because both can be targeted for treatment before and after surgery with various interventions, including nutritional recommendations and exercise therapy.

23.2.4 Disease Specificity

Cancer and its treatment exacerbate many factors that cause sarcopenia, including anorexia, decreased activity, and accelerated inflammatory responses (Fig. 23.8). In addition, many cancer treatments, especially chemotherapy, cause direct damage to the muscle tissue, such as mitochondrial dysfunction, in addition to indirect damage, such as anorexia, nausea, and fatigue [19]. Cachexia is frequently observed in cancer patients, and similar to sarcopenia, it is associated with decreased skeletal muscle function and physical function. Its pathophysiology, however, is different (Table 23.5). Cachexia is caused by an accelerated catabolic state under the influence of tumor metabolism and inflammatory cytokines and is accompanied by loss of the adipose tissue and skeletal muscle.

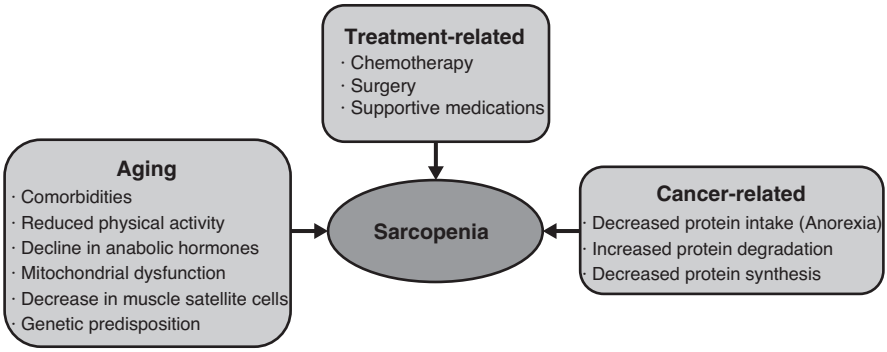

Fig. 23.8 Multifactorial causes of sarcopenia in the patients with cancer

Table 23.5 Features of sarcopenia, cachexia, and frailty

Features	Sarcopenia	Cachexia	Frailty
Muscle mass	↓	↓	↓ or ↔
Muscle strength and function	↓	↓	↓ or ↔
Fat mass	↔	↓	↔
Basal metabolic rate	↓	↑	↓
Inflammation	↔	↑	↑
Overall body weight	↔	↓	↓

↑, increase; ↓, decrease; ↔, can be increased, decreased, or unchanged with no real effect

23.2.5 Prevention and Treatment of Sarcopenia in Cancer

Exercise therapy has been reported to be effective in improving muscle strength, exercise tolerance, and quality of life (QOL) in patients during and after cancer treatment, regardless of cancer type [45, 46]. Exercise therapy is more effective when supervised and performed at least three times a week, with over 60 min per session, and with a combination of resistance training and aerobic exercise [45, 47]. Few randomized controlled trials (RCTs) have examined the effects of exercise therapy on skeletal muscle mass. In an RCT of exercise therapy intervention (median 17 weeks, 95% confidence interval 9–24 weeks) for breast cancer patients undergoing adjuvant chemotherapy, the resistance training group significantly increased skeletal muscle mass compared with the aerobic exercise and usual care groups. Increased skeletal muscle mass was significantly associated with improved QOL [48]. Exercise therapy has been shown to have a positive effect on the effectiveness of cancer treatment itself [49]. In addition, exercise therapy and psychological interventions, rather than pharmaceutical interventions, are more effective in treating cancer-related fatigue [50]. Furthermore, exercise therapy has been reported to improve physical function, exercise tolerance, QOL, and fatigue even in patients with advanced cancer who are eligible for palliative care [51]. However, high dropout rates and low adherence to intervention programs have been cited as problems

[52, 53]. The effects of exercise therapy on advanced cancer patients with cachexia are not yet clear. Nutritional disorders are a characteristic finding in sarcopenia and cachexia, and nutritional intervention is considered important; however, the effects of nutritional therapy alone on skeletal muscle mass and physical function are not agreed upon in patients with cancer [54–56].

23.2.6 Nutrition and Exercise Treatment for Advanced Cancer (NEXTAC) Program

In Japan, the NEXTAC study was conducted to test the feasibility of early introduction of new non-pharmacological multimodal interventions specifically for older patients with advanced cancer [57]. This was a multicenter, prospective, single-arm study of patients aged ≥70 years who were scheduled to receive first-line chemotherapy for newly diagnosed advanced pancreatic cancer or NSCLC. An eight-week educational intervention comprised three exercise and three nutritional sessions by a multidisciplinary team including medical doctors, nurses, nutritionists, physical or occupational therapists, psychotherapists, and/or medical social workers (Table 23.6). The exercise interventions combined home-based low-intensity resistance training and counseling to promote physical activity. The muscle training programs included five exercises: sit-to-stand, calf raise, knee extension, knee raise, and side-leg-raise with or without 1 kg ankle weight. One set included ten repetitions per exercise. Patients performed each exercise at the prescribed level three

Table 23.6 Nutrition and exercise treatment for advanced cancer (NEXTAC) program

Sessions and time allocation	Assessments	Interventions
Exercise session	• Six-minute walking distance	• Prescription and modification of exercise program
30 min at baseline	• Gait speed	• Instruction of exercise procedures
20 min at 4 and 8 weeks after baseline	• Handgrip strength	• Education of self-modification
	• Five time sit to stand test	• Prescription and modification of target daily step
	• Exercise diary collection	• Physical activity counseling
	• Physical activity measurement	• Education of fall prevention
	• Physical activity interview	
Nutritional session	• Food intake	• Nutritional advice
30 min at baseline	• Nutritional status (Mini Nutritional Assessment)	• Support for symptom management, food environment, and eating-related distress
20 min at 4 and 8 weeks after baseline	• Nutritional checklist (symptom, problems, distress)	• Oral nutritional supplement prescription
	• Skeletal muscle analysis	
	• Diet diary collection	

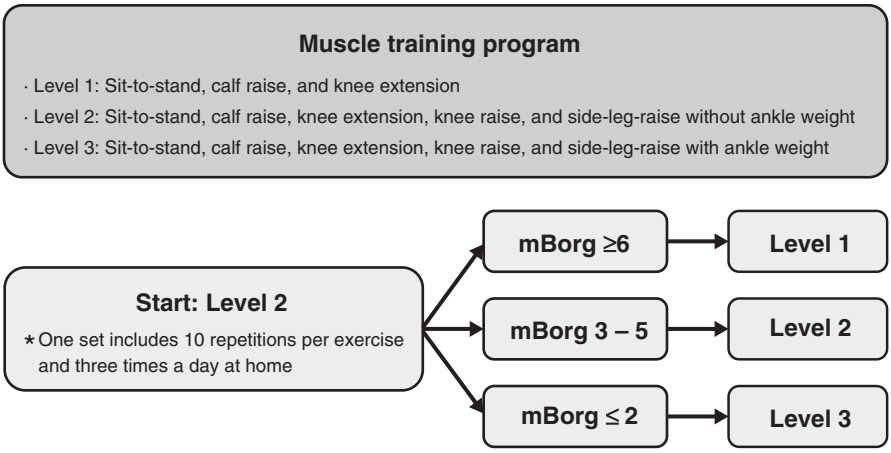

Fig. 23.9 Muscle training program and prescription algorithm for advanced cancer in NEXTAC study. *NEXTAC* Nutrition and Exercise Treatment for Advanced Cancer, *mBorg* modified Borg scale

times a day at home (Fig. 23.9). The physical activity program consisted of lifestyle consultations and prescribed targets to encourage the patients to engage in the daily activities. The target step was the average steps plus 2000 steps to a maximum of 8000 steps. Nutritional interventions included standard nutritional counseling and instructions on how to manage symptoms that interfere with the patient's appetite and oral intake. Supplements rich in branched-chain amino acids were provided. The study concluded that early induction of multimodal interventions showed excellent compliance and safety in older patients with newly diagnosed pancreatic cancer and NSCLC receiving concurrent chemotherapy.

Based on these results, a multicenter, randomized phase II trial (NEXTAC-TWO) is currently underway to evaluate the effects of the program in older patients with advanced cancer [58]. The primary endpoint of this study was disability-free survival. The results of this study will provide interventions to improve ADL, QOL, and prognosis for patients with advanced cancer.

23.2.7 Our Recent Activities

In our hospital, rehabilitation is introduced before surgery. Aerobic exercise, resistance training, and essential amino acid supplementation are taught and recommended. Perioperative physical activity is measured using a triaxial accelerometer (Fig. 23.10). The use of a pedometer to manage and guide physical activity and to assess physical function at appropriate times is likely to improve the patient's motivation to exercise and their ability to manage their physical condition. In addition, quantitative physical activity assessment enables health-care providers to share

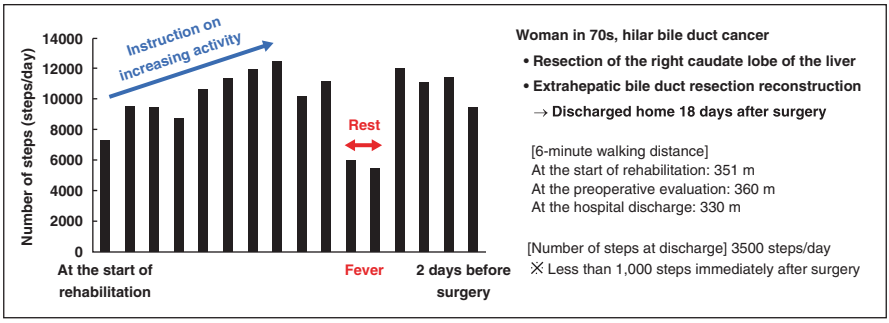

Fig. 23.10 A case in which perioperative decline in physical function was prevented by management and guidance of physical activity

information on the amount of activity with other professionals using language such as "number of steps." We are currently conducting an RCT in which patients undergoing highly invasive surgery are randomized to receive preoperative conventional rehabilitation therapy or goal-directed rehabilitation therapy. In addition, an RCT on the usefulness of a health app for rehabilitation in gastrointestinal surgery patients has been planned. Through these RCTs, we hope to prevent the development and progression of sarcopenia and to improve the functional and life outcomes of patients.

23.2.8 Future Perspectives

There are several unresolved issues in the study of sarcopenia in oncology. How do the mechanisms and processes of muscle loss differ between patients with cancer and those without cancer? Which factors or interventions ameliorate sarcopenia related to cancer and cancer treatment? How can we best treat and maintain muscle mass and physical performance? Caring for cancer patients is challenging; it consists of a dual focus on maintaining the quality of life and functional independence as much as possible while maintaining treatment efficacy.

23.3 Conclusion

This issue provides an overview of sarcopenia in patients with cancer. Further research on sarcopenia is encouraged to prevent or delay adverse events, which can be a significant burden to patients and health-care providers. When applying previous research to clinical practice, care should be taken regarding the target diseases, timing of interventions, and definitions and intervention methods. As more evidence accumulates in the future, it is suggested that knowledge be kept up-to-date.

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Cachexia and Postoperative Outcomes in Elderly Patients with Gastrointestinal Cancer

24

Akimasa Fukuta and Rei Ono

Abstract

Cachexia is a multifactorial syndrome that is common in patients with cancer. In particular, gastrointestinal cancer and elderly cancer patients have a high prevalence of cachexia. Although several definitions of cancer cachexia have been developed, such as the international consensus of the European Palliative Care Research Collaborative, the definitions used for each clinical trial are not unified. Additionally, the assessments and treatment for cancer cachexia vary greatly. Cancer cachexia adversely affects mortality and morbidity, physical function, and the quality of life of patients. Cancer cachexia is present not only in the terminal stage but also in the perioperative period. Moreover, preoperative cancer cachexia can negatively affect postoperative outcomes. One treatment for gastrointestinal cancer is surgery, and an enhanced recovery after surgery protocol and prehabilitation are important for promoting recovery in patients. Since cancer cachexia is a multifactorial syndrome, multimodal interventions, including nutritional, pharmacological, or other interventions, including exercise, are important. There are some trials on the management of cancer cachexia. However, the available evidence is insufficient. Physical therapy as part of multimodal interventions can be a potentially effective management for patients with cancer cachexia and may lead to improved postoperative outcomes. Further research is needed to accumulate further evidence.

A. Fukuta (✉)
Department of Rehabilitation, Nagoya University Hospital, Nagoya, Japan
e-mail: a.fukuta@med.nagoya-u.ac.jp

R. Ono
Department of Physical Activity Research, National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health and Nutrition, Tokyo, Japan
e-mail: ono@nibiohn.go.jp

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Keywords

Cancer cachexia · Postoperative outcomes · Gastrointestinal cancer · Elderly patients · Enhanced recovery after surgery · Prehabilitation · Multimodal interventions

24.1 Introduction

Cancer cachexia is a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass [1]. It can have adversely affect patient outcomes [2–4]. Cancer cachexia is especially common in patients with gastrointestinal cancer and the elderly [5, 6]. Recent studies have also reported that preoperative cancer cachexia can be a prognostic factor for postoperative outcomes [7–9]. Assessments and treatment vary, and an international standard care guideline for cancer cachexia with perfect efficacy does not exist [10]. Recently, the number of trials on multimodal interventions has been increasing. It is important for physical therapists to understand the definition, assessment, and treatment of cancer cachexia when prescribing exercise interventions as part of multimodal interventions.

This chapter describes the definition, assessment, and management of cancer cachexia and the effect of cancer cachexia on postoperative outcomes in elderly patients with gastrointestinal cancer.

24.2 Definitions and Classifications

Cachexia is the result of complex interactions between underlying diseases, disease-related metabolic alterations, and reduced availability of nutrients [11]. Currently, there are various definitions and classifications for cancer cachexia (Table 24.1).

In 2006, cachexia was defined by at least two of the following three factor profiles: weight loss, reduced food intake, and systemic inflammation [2]. In 2008, the diagnostic criteria for cachexia in patients with chronic illnesses, such as chronic heart failure, chronic obstructive pulmonary disease, and cancer, were published [12]. Cachexia was defined as >5% weight loss in the previous 12 months or a body mass index (BMI) <20 kg/m^2 in patients with a chronic disease and at least three of the following five criteria: decreased muscle strength, fatigue, anorexia, low fat-free mass index, and abnormal biochemistry about systemic inflammation. In 2009, the screening the nutritional status in oncology (SCRINIO) working group defined cancer-specific cachexia as 10% weight loss with symptoms of anorexia, early satiety, and fatigue [13].

In 2011, the European Palliative Care Research Collaborative (EPCRC) developed an international consensus. In the international consensus, cancer cachexia was defined as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass), which cannot be fully reversed by conventional nutritional support, and leads to progressive functional impairment [1].

Table 24.1 Definitions and classifications of cancer cachexia

Number	Study	Year	Criteria
1	Fearon et al. [2]	2006	At least two out of three factors: • Weight loss (≥10%) • Low food intake (≥1500 kcal/day) • Systemic inflammation (CRP ≥10 mg/L)
2	Evans et al. [12]	2008	>5% weight loss in the previous 12 months with a chronic disease or BMI <20 kg/m^2 and At least three of the five criteria: • Decreased muscle strength • Fatigue • Anorexia • Low fat-free mass index • Abnormal biochemistry
3	SCRINO Group [13]	2009	Weight loss (≥10%) from the usual body weight and The presence/absence of at least one symptom of anorexia, fatigue, and early satiation
4	EPCRC [1]	2011	Weight loss (>5%) in the previous 6 months without starvation or Weight loss (>2%) and BMI <20 kg/m^2 or Weight loss (>2%) and sarcopenia
5	Argilés et al. [17]	2011	The cachexia score (CASCO) Components (percent of total score): • Body weight loss and composition (40%) • Inflammation/metabolic disturbances/immunosuppression (20%) • Physical performance (15%) • Anorexia (15%) • QOL (10%) The scoring scale goes from 0 to 100: Mild cachexia (less than 25), moderate (more than 26 and less than 50), severe (more than 51 and less than 75), and terminal phase (more than 76 and up to 100)
6	Douglas and McMillan [15]	2014	The Glasgow prognostic score (GPS) No cachexia (GPS = 0): albumin (>35 g/L) and CRP (<10 mg/L) Undernourished (GPS = 0): albumin (<35 g/L) and CRP (<10 mg/L) Pre-cachexia (GPS = 1): albumin (>35 g/L) and CRP (>10 mg/L) Refractory cachexia (GPS = 2): albumin (<35 g/L) and CRP (>10 mg/L)
7	Wiegert et al. [14]	2021	The system classified cachexia into three stages, precachexia, cachexia, and refractory cachexia, based on a combination of percentage weight loss in the past 6 months (<15% or ≥15%), BMI (<21.0, 21.0–26.4, >26.4 kg/m^2), and MUAMA (≥38.0/≥35.5 or <38.0/<35.5 cm^2 in men/women, respectively)

Abbreviations: *SCRINIO* screening the nutritional status in oncology, *EPCRC* European Palliative Care Research Collaborative, *CRP* C-reactive protein, *BMI* body mass index, *QOL* quality of life, *MUAMA* mid-upper arm muscle area

Modified from Mohammadamin Sadeghi, Mahsa Keshavarz-Fathi, Vickie Baracos, Jann Arends, Maryam Mahmoudi, Nima Rezaei. Cancer cachexia: Diagnosis, assessment, and treatment. In: Critical Reviews in Oncology/Hematology, Volume 127, July 2018, Pages 91–104, copyright Elsevier

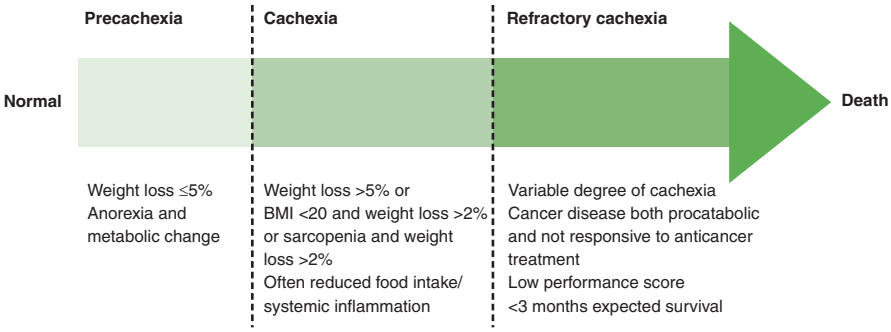

Fig. 24.1 Stages of cancer cachexia. (Reprinted from The Lancet Oncology, Volume 12(5), Kenneth Fearon, Florian Strasser, Stefan D Anker, Ingvar Bosaeus, Eduardo Bruera, Robin L Fainsinger, Aminah Jatoi, Charles Loprinzi, Neil MacDonald, Giovanni Mantovani, Mellar Davis, Maurizio Muscaritoli, Faith Ottery, Lukas Radbruch, Paula Ravasco, Declan Walsh et al. Definition and classification of cancer cachexia: an international consensus. Pages 489–495, Copyright (2011), with permission from Elsevier)

According to this international consensus, cancer cachexia is a continuum that can be categorized into three stages: precachexia, cachexia, and refractory cachexia (Fig. 24.1). In precachexia, patients experience substantial involuntary weight loss, anorexia, and metabolic changes, such as changed glucose metabolism. The diagnostic criteria for cachexia are patients with >5% loss of stable body weight over the previous 6 months, a BMI <20 kg/m^2 and ongoing weight loss >2%, or sarcopenia and ongoing weight loss >2%. Refractory cachexia may be refractory because of advanced cancer or rapidly progressive cancer that is unresponsive to anticancer therapy. It is characterized by a low performance status and life expectancy of less than 3 months. Although an international consensus is available, few studies utilize these diagnostic criteria.

Another system classified cancer cachexia into three stages based on a combination of percentage weight loss in the previous 6 months, BMI, and mid-upper arm muscle area (MUAMA) [14]. Since systemic inflammation is an aspect of cancer cachexia, the Glasgow prognostic score (GPS) and the modified GPS (mGPS) combined with C-reactive protein (CRP) and albumin levels should also be used to identify and classify cancer cachexia [15].

Recently, the Cachexia Score (CASCO) was developed as a validated screening tool for cachexia that performed well against the consensus definition [16]. The CASCO is mainly based on the following: body weight loss and composition, inflammation/metabolic disturbances/immunosuppression, physical performance, anorexia, and quality of life (QOL) [17]. The CASCO considers not only body composition but also the presence of elevated inflammatory markers and QOL compared to other diagnostic tools. The CASCO and MiniCASCO (MCASCO), a simple version of CASCO, significantly correlated with each other [16]. Hence, MCASCO may be an easy validated tool for staging cachectic cancer patients.

Sensitivities and specificities for CASCO have not yet been verified. Further research is expected in the future.

Some definitions of cachexia do not consider systemic inflammation markers, anorexia, or physical performance. One study suggested that significant weight loss alone is sufficient and reliable enough for defining cachexia in elderly patients [18]. Overall, the symptoms necessary for the diagnosis of cachexia remain controversial.

Furthermore, the Asian body types differ from that of Western populations [19]. Therefore, when considering the cutoff values for body composition as defined in the diagnostic criteria for cachexia, it is necessary to consider specific body types in Asian populations.

Therefore, the development of a valid definition of cancer cachexia and further research in cachexia according to regional and racial characteristics are expected in the future.

24.3 Epidemiology

Cachexia affects 50–80% of cancer patients and accounts for up to 20% of cancer deaths [20]. The prevalence of cachexia varies according to different definitions, cancer types, treatment types, and timing of diagnosis [21]. In patients with advanced cancer, approximately 36% of patients were classified as having cachexia [5]. The same study reported that pancreatic, gastric, and esophageal cancers had the highest prevalence (88.9%, 76.5%, and 52.9%, respectively). Additionally, in a nationwide French cross-sectional survey of older cancer patients, aged ≥70 years, cachexia was present in 51.8% of 1030 patients [4]. The common cancer types associated with cachexia were upper gastrointestinal and colorectal cancer. The prevalence of cachexia was higher in patients with gastrointestinal cancer than in those with other cancer types. Moreover, the prevalence of cancer cachexia is as high as 65% in elderly patients with cancer [6]. Cancer cachexia is present not only in the terminal stage but also in the perioperative period. Some studies have reported that the prevalence of preoperative cancer cachexia is 16.6–35.8% [7–9]. To date, there are insufficient studies on the prevalence of preoperative cancer cachexia. Hence, further research in this area is needed.

24.4 Treatment

The primary endpoints of cancer cachexia treatment are improvements in lean body mass (LBM), resting energy expenditure, fatigue, anorexia, QOL, performance status, and reduction in pro-inflammatory cytokines [22]. Three global surveys reported that approximately two-thirds of patients with cancer did not receive any cancer cachexia prescription medication before the disease reached stage IV [23]. Additionally, more than half of the patients with cachexia and advanced cancer did

not receive any treatment for cachexia [5]. Several trials have been conducted to develop effective interventions for cancer cachexia. Similar to the diagnostic criteria for cachexia, an international standard care guideline for the management of cancer cachexia with perfect efficacy does not exist [10]. In 2020, the American Society of Clinical Oncology (ASCO) published guidelines for the management of cancer cachexia in patients with advanced cancer [24]. The ASCO guidelines recommended nutritional, pharmacological, and other interventions including exercise. Although several trials have investigated treatment strategies for cachexia and reported positive effects on weight, appetite, food intake, and LBM, there were few improvements in physical function.

24.4.1 Nutritional Interventions

Nutritional interventions include dietary counseling, nutritional supplementation, and artificial nutrition. The ASCO guidelines concluded that dietary counseling, the routine use of parental or enteral nutrition, and omega-3 fatty acids, vitamins, minerals, and other dietary supplements are recommended with a low level of the evidence [24].

24.4.1.1 Dietary Counseling

The ASCO guidelines, based on systematic reviews, stated that the strength of recommendation for dietary counseling was moderate. One key limitation was the lack of a clear definition of what nutritional counseling interventions entail [24]. Additionally, a systematic review concluded that there was insufficient evidence to support the benefit of dietary counseling for patients with advanced cancer for improving weight or energy balance [25]. A small randomized pilot trial suggested that nutrition therapy based on patient-specific biophysical parameters compared to regular dietary counseling helped to maintain body weight and induced a more optimal nutritional balance among patients with cachectic cancer [26].

24.4.1.2 Parenteral Nutrition (PN) or Enteral Nutrition (EN)

A 1990 meta-analysis concluded that routine total PN (TPN) in cancer patients undergoing chemotherapy should be discouraged because TPN is associated with decreased survival and increased infectious complications [27]. A prospective randomized crossover trial has suggested that PN with branched-chain amino acids (BCAA) improved whole-body leucine kinetics, fractional rates of albumin synthesis, and leucine balance and thus may favorably influence protein metabolism in cancer cachexia [28]. However, a 2019 systematic review of the effects of PN in patients with advanced cancer reported no survival benefit in using PN and concluded that the level of evidence was weak [29].

24.4.1.3 Omega-3 Fatty Acids

The ASCO guidelines concluded that the evidence for the recommendation of omega-3 fatty acids remained insufficient [24]. However, fish oil, as well as omega-3 fatty acids,

such as eicosapentaenoic acid (EPA) and docosapentaenoic acids, may potentially affect cancer cachexia. A systematic review reported that the use of omega-3 fatty acids in patients with colorectal cancer reduced certain inflammatory markers, such as interleukin (IL)-6 and CRP, but the benefits of omega-3 fatty acids depended on specific supplementation protocols with particular considerations for the duration, dose, route of administration, and concomitant anticancer treatment adopted [30].

In a 2018 meta-analysis evaluating the effects of oral nutritional intervention during chemo(radio)therapy, an analysis of four randomized controlled trials showed that intervention with high-energy oral nutritional supplements (ONS) containing high protein levels and omega-3 fatty acids improved body weight [31]. Additionally, a systematic review focusing on patients with unresectable pancreatic cancer suggested that the consumption of omega-3 fatty acids was safe and had a positive effect on body weight, LBM, resting energy expenditure, and overall survival (OS) [32].

24.4.1.4 Vitamins, Minerals, and Other Dietary Supplements

A systematic review evaluated the effects of supplements, including magnesium, vitamin E, vitamin C, vitamin D, ß-hydroxy-ß-methyl butyrate (HMB), arginine, glutamine, and L-carnitine for improving cancer cachexia [33]. Some studies have reported that these supplements have a positive effect on patient outcomes. However, evidence is still inadequate, although the use of these supplements did not result in serious adverse effects. Administration of HMB, a metabolite of the essential amino acid, leucine, attenuated body weight and muscle loss in an experimental model of cancer cachexia [34]. Many studies have shown increased lean mass and strength when elderly patients used HMB [35]. However, at present, there is insufficient consistent clinical data to recommend HMB [36].

24.4.2 Pharmacological Interventions

A 2018 systematic review evaluated the effectiveness of pharmacological treatment used to manage cachexia in adult patients with cancer [37]. Agents, such as anamorelin or enobosarm, are effective in improving weight, LBM, and QOL. However, no agents have successfully improved functions. The ASCO guidelines also suggested that the evidence supporting pharmacological interventions for cancer cachexia remained insufficient. Moreover, the guidelines recommended that clinicians offer a short-term trial of a progesterone analog, such as megestrol acetate or a corticosteroid, to patients experiencing anorexia and/or body weight [24].

24.4.2.1 Megestrol Acetate (MA) and Corticosteroids

MA is a synthetic progestogen agent [38]. MA has been shown to be superior to other drugs in terms of efficacy and tolerability [39]. Some reviews have reported positive effects of MA in patients with anorexia-cachexia syndrome, citing that MA improved appetite, weight gain, and QOL [38, 40]. Additionally, the combination of MA and olanzapine improved weight, appetite, nausea, and QOL in patients with

advanced gastrointestinal or lung cancer and cachexia [41]. In particular, two systematic reviews supported the use of MA and short courses of corticosteroids as appetite stimulants in patients with cancer [37, 42]. However, corticosteroids, such as dexamethasone, have higher toxicity and an increased rate of drug discontinuation than MA [43]. Thus, corticosteroids have been recommended for use only in selected cases, and long-term side effects were considered [39]. Many aspects of using appetite stimulants remain unknown, including the optimal dose, treatment duration, and the most appropriate time to start [42].

24.4.2.2 Anamorelin

Anamorelin, a novel selective ghrelin receptor agonist, significantly improved LBM, appetite, and body weight compared with placebo in patients with non-small cell lung or gastrointestinal cancer [44, 45]. Similarly, anamorelin significantly improved the LBM and body weight in patients with non-small cell lung cancer [46, 47]. A systematic review on anamorelin as a single agent showed promising results in improving cachexia [37]. Thus, anamorelin may have a positive effect on body composition but not physical performance. The use of anamorelin for cancer cachexia was approved in Japan in 2020. However, its use has not yet been approved in Europe. To enhance the availability of anamorelin for cancer cachexia, more clinical studies on anamorelin are needed [48].

24.4.2.3 Enobosarm

Enobosarm is an oral nonsteroidal selective androgen receptor modulator [49]. In a randomized controlled trial (RCT) for patients with advanced cancer and cachexia, both enobosarm arms (1 and 3 mg) showed significant improvement in the median LBM compared with baseline [50]. In contrast, no improvement was observed in the placebo arm. Additionally, in both enobosarm arms, the median time to climb 12 stairs also significantly decreased, and the QOL as assessed using the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) score also improved significantly.

24.4.2.4 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Chronic inflammation is an important aspect of cancer cachexia. Therefore, anti-inflammatory agents may improve cachexia. Two systematic reviews suggested that NSAIDs may improve or maintain body composition, including body weight, muscle mass, QOL, and survival [51, 52]. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines concluded that more evidence based on well-designed large clinical trials is necessary before recommending the routine use of NSAIDs for cancer cachexia [36].

24.4.2.5 Other Pharmacologic Agents

Other pharmacological agents for the management of cachexia include androgens, thalidomide, cyproheptadine, cannabinoids, melatonin, tumor necrosis factor (TNF) inhibitors, hydrazine sulfate, and insulin [37, 42]. Although some studies have evaluated the effect of these agents and reported a positive effect, there is currently insufficient evidence supporting their benefit in cancer cachexia [24].

24.4.3 Psychosocial Interventions

One narrative review reported that cancer cachexia had a direct impact on self-image, self-esteem, social relationships, relationships with one's partner, and sexuality [39]. Therefore, psychosocial support is essential as part of integrative treatment of cancer cachexia. In a mixed methods qualitative research study, a family-centered psychosocial intervention was developed and delivered by a single nurse researcher to help patients with advanced cancer and their families or caregivers cope with involuntary weight loss and anorexia [53]. This study demonstrated the potential of psychosocial interventions for improving patient-reported outcomes. Therefore, the clinical practice guidelines recommended that psychosocial interventions by trained healthcare professionals be considered as early as possible in cachexia management [54].

24.4.4 Multimodal Interventions

As cancer cachexia is a complex and multifactorial condition, a multimodal approach that includes nutritional support, exercise, and pharmacological intervention is important [55]. In recent years, clinical trials of multimodal interventions for cancer cachexia have increased (Table 24.2). A randomized phase II feasibility trial reported that multimodal interventions (including exercise, nutritional supplements, and anti-inflammatory medication) for cachexia in patients with advanced cancer resulted in the prevention or attenuation of cachexia [56]. Additionally, a larger phase III trial, the MENAC (Multimodal Intervention-Exercise, Nutrition and Anti-inflammatory medication for Cachexia) study, is currently ongoing [57]. A national, prospective, multicenter, single-arm study on the early introduction of non-pharmacological multimodal interventions for elderly patients with advanced cancer receiving chemotherapy, namely, the Nutrition and Exercise Treatment for Advanced Cancer (NEXTAC) program, demonstrated the feasibility and safety of multimodal interventions [58]. This trial supported the use of multimodal interventions for the prevention or attenuation of weight and muscle loss, and improvement of physical functions, in patients with lung and pancreatic cancer receiving anticancer treatment. The randomized phase II of this study, the NEXTAX-TWO study, is ongoing and is designed to evaluate the efficacy of a multimodal intervention program [59]. A single-center study of multimodal intervention, including fish oil intake (EPA or docosahexaenoic acid) and physical exercise, showed feasibility and increased skeletal muscles in some patients [60]. However, a major limitation of multimodal interventions, including exercise, is the poor compliance among patients with cancer cachexia, especially in performing regular exercise, due to their compromised psychological and health status [61]. Most trials have focused on patients with advanced cancer or those receiving anticancer treatments. Cancer patients scheduled for surgery often have early-stage cancer or a good performance status and are more likely to complete multimodal interventions. More research studies on multimodal interventions for patients with cancer cachexia in the perioperative period are warranted in the future.

Table 24.2 Multimodal interventions including physical exercise for cancer cachexia patients

Reference	Year	Study design	Number of patients	Cancer type and anticancer treatment	Intervention	Main results
Solheim et al. [56]	2017	Phase II, randomized, open-label feasibility trial	46	Incurable lung or pancreatic cancer undergoing chemotherapy	Celecoxib (300 mg/day) + EPA (2 g/day) + home-based aerobic (30 min, two times/week) and resistance training (20 min, three times/week) for 6 weeks	A multimodal intervention showed feasible and safe improvement in body weight
Naito et al. [58]	2019	Multicenter prospective single arm, phase II	30	Newly diagnosed, advanced pancreatic, or non-small cell lung cancer undergoing first-line chemotherapy	Branched-chain amino acids (2.5 g/day), coenzyme Q10 (30 mg/day), and L-carnitine (50 mg/day) + supervised home-based low-intensity resistance training (20–30 min/day) and counseling to promote physical activity for eight weeks	A multimodal intervention showed excellent compliance and safety
Tobberup et al. [60]	2021	Single-center study	58	Inoperative non-small cell lung cancer undergoing primary antineoplastic treatment	fish oil intake (2 g/day of EPA or DHA) + regular dietary counseling + aerobic and resistance training (two times/week) during the first three cycles of primary anti-neoplastic treatment	A multimodal intervention showed feasible improvement in the skeletal muscle

Abbreviations: *EPA* eicosapentaenoic acids, *DHA* docosahexaenoic acid

24.5 Impact of Cachexia on Patient Outcomes

Cancer cachexia can negatively affect the patient in terms of functional status [3] and QOL [2], responsiveness to chemotherapy [62], length of stay (LOS) [8, 63, 64], hospitalization costs [9, 63–65], and OS [9]. Many of these outcomes have been validated in patients with advanced cancer. Further studies on patients with cancer cachexia in the perioperative period are needed. Routine use of patient-reported outcome measures (PROMs) is important in cancer care. A systematic review

reported that PROMs are associated with improved symptom control, increased supportive care measures, and patient satisfaction [66]. Therefore, the use of PROMs as a primary endpoint in the management of cancer cachexia, such as the evaluation of novel agents, is recommended [24].

24.6 Assessment of Cachexia

Cancer cachexia is a multifactorial syndrome that requires extensive assessment before appropriate treatment is decided for each patient [10]. The international consensus and reviews described key features, nutrition, muscle mass and strength, functional and psychosocial effects, and biomarkers such as catabolic drivers, which should be evaluated for cachexia [1, 10].

24.6.1 Nutritional Assessment

Anticancer treatments, including surgery, radiation therapy, and chemotherapy, can reduce food intake through various unfavorable gastrointestinal abnormalities [67]. Malnutrition negatively affects the physiological and psychosocial aspects and reduces the QOL of patients with cancer [68, 69]. In clinical practice guidelines, regular nutritional screening and nutritional support are recommended for all patients receiving cancer treatment and for those with an expected survival of more than a few months [54]. Recently, a study suggested that the Malnutrition Screening Tool (MST) had the greatest ability to detect cancer cachexia among patients with gastric cancer compared to the Malnutrition Universal Screening Tool (MUST), Nutrition Risk Screening 2002 (NRS-2002), and Short Nutritional Assessment Questionnaire (SNAQ) [70]. Other nutritional assessment tools, such as the Mini Nutritional Assessment Short-Form (MNA-SF) [71] or Patient-Generated Subjective Global Assessment (PG-SGA) [72], have also been used in cancer patients. However, there is no consensus on the best assessment tools [73, 74]. The recommended nutritional measures are body weight, weight change during the preceding months, body composition with a focus on muscle mass, food intake with a focus on energy and protein, performance status, and information regarding the presence and degree of systemic inflammation [54]. Symptoms, such as anorexia, nausea, taste and smell alterations, mucositis, constipation, dysphagia, chronic pain, abdominal pain, diarrhea, gastrointestinal abnormalities, fatigue, physical activity, shortness of breath, and psychosocial distress, may potentially impact nutrition status and should also be evaluated [36, 54]. Regular monthly nutritional assessments are recommended [54].

24.6.2 Muscle Mass and Strength

Muscle depletion is an important feature of cancer cachexia. There are several methods of muscle mass assessment. Cross-sectional imaging, including computed tomography (CT) or magnetic resonance imaging (MRI), dual-energy X-ray

Table 24.3 Methods of muscularity assessment in cachectic patients

Assessment method	Indication of muscle depletion
Lumbar (L3) skeletal muscle index determined by CT imaging [79]	Men <55 cm^2/m^2 Women <39 cm^2/m^2
Appendicular skeletal muscle index determined by DEXA [80]	Men <7.26 kg/m^2 Women <5.45 kg/m^2
Whole-body fat-free mass (FFM) index without the bone determined by BIA [81]	Men <14.6 kg/m^2 Women <11.4 kg/m^2

Abbreviations: *CT* computed tomography, *DEXA* dual-energy X-ray imaging, *BIA* bioimpedance analysis

Modified from Mohammadamin Sadeghi, Mahsa Keshavarz-Fathi, Vickie Baracos, Jann Arends, Maryam Mahmoudi, Nima Rezaei. Cancer cachexia: Diagnosis, assessment, and treatment. In: Critical Reviews in Oncology/Hematology, Volume 127, July 2018, Pages 91–104, copyright Elsevier

imaging (DEXA), anthropometry (mid-arm muscle area), and bioimpedance analysis (BIA) are preferred. The international consensus included cutoff values for defining sarcopenia as one of the diagnostic criteria for cachexia [1] (Table 24.3). BIA is a commonly used method due to its low cost and simplicity. However, it does not distinguish the skeletal muscles of fat-free tissues, such as the liver, or metastases, which may be responsible for increased energy expenditure; thus BIA provides less information than MRI and CT [39]. CT and MRI allow a more accurate separation of the skeletal muscle and adipose tissue, but they have some unwanted effects, such as radiation and/or cost [75]. Recently, a study on the prevalence and prognostic impact of cachexia defined sarcopenia as one of the diagnostic criteria for cachexia as per the international consensus and used the Strength, Assistance with walking, Rise from chair, and Climb stairs and Falls (SARC-F) questionnaire to diagnose sarcopenia [4]. The SARC-F score is a highly specific screening tool for low muscle strength [76]. The 2019 revised European consensus on the definition and diagnosis of sarcopenia recommended its use for case finding [77]. SARC-F is a potential method for assessing muscle mass to diagnose cancer cachexia because of its low cost and convenience. As muscle strength should be measured directly to diagnose and monitor cachexia [78], upper-limb handgrip dynamometry is preferred to lower-limb extension strength for the assessment of muscle strength [1].

24.6.3 QOL and Psychosocial Assessment

Although cancer cachexia can have a direct impact on self-image, self-esteem, social relationships, relationships with one's partner, and sexuality [39], there is no relevant psychosocial assessment for cancer patients with cachexia [10]. One method of psychosocial assessment is to use a QOL assessment tool because it includes psychosocial components. FAACT is cancer cachexia-specific [82]. However, a systematic review concluded that the tool was not fully validated for measuring health-related QOL (HRQOL) in patients with cancer cachexia [83].

Since there is no HRQOL instrument to assess all the factors, including psychosocial factors, that impact HRQOL in patients with cancer cachexia, further research to establish an internationally validated tool is necessary [83].

24.6.4 Biomarkers

A key aspect of cachexia is the hypercatabolism caused by tumor metabolism, systemic inflammation, or other tumor-mediated effects [1]. The most widely used index of systemic inflammation is serum CRP level [1]. Pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6, and interferon (IFN)-γ, are associated biomarkers of cancer cachexia [10]. Several other markers, including markers for hormonal dysregulation such as ghrelin, adipose-derived factors such as adiponectin, and tumor-derived factors, are associated with anorexia, lipolysis, and muscle depletion [10]. GPS and mGPS are simple objective frameworks for the investigation and treatment of cancer cachexia [15, 84]. However, one study reported that patients with inoperable pancreatic cancer classified as cachexia by the international consensus-based classification system did not have higher levels of inflammatory biomarkers compared with non-cachectic patients [85]. In contrast, in patients with metastatic cancer and cachexia, these biomarkers had a higher association with OS [86]. Most of these markers do not have cutoff values. Moreover, there are insufficient evidence to support their use as prognostic and predictive markers because of the heterogeneity and small sample size of patients in available studies [10]. Therefore, more studies with larger study groups are needed.

24.7 Research About Physical Therapy for Cachexia

Exercise for cancer patients during and after treatment can improve muscle strength, fatigue, and QOL [87]. Additionally, exercise may modulate muscle metabolism, insulin sensitivity, and levels of inflammation [88, 89].Therefore, physical therapy may be an effective intervention for cancer cachexia. A Cochrane review of exercise for cancer cachexia was published in 2021. At that time, no studies met the inclusion criteria, and the review concluded that there was insufficient evidence to determine the safety and effectiveness of exercise for patients with cancer cachexia [90]. Similarly, the ASCO guidelines concluded that exercise was not recommended because there were no eligible trials identified in the systematic review conducted [24]. However, some studies have reported exercise as a potential intervention for cancer cachexia. Resistance training, which is a potent stimulator of muscle protein synthesis, is a non-pharmacologic therapy [91]. Resistance training is a potentially effective intervention for cancer cachexia. A randomized controlled trial reported that a 3-month resistance training improved mobility, muscle strength, and LBM in patients with pancreatic cancer-induced cachexia [92]. Aerobic and resistance training have also been implicated in the reduction of systemic inflammation in many

chronic diseases [93]. A previous study reported that aerobic exercise reduced inflammation in cachectic rats [94]. Recently, a pilot study evaluated the effect of whole-body electromyostimulation (WB-EMS) to simultaneously stimulate muscles in patients with advanced cancer undergoing anticancer treatment [95]. This study reported that 20 min of WB-EMS twice a week for 12 weeks combined with a supervised exercise program and individualized nutritional support was safe and showed effects against muscle wasting and physical function. The study concluded that WB-EMS may be an effective exercise program for patients with advanced cancer undergoing treatment.

Recently, physical exercise was evaluated as part of a multimodal intervention for patients with cancer cachexia. In the MENAC trial, home-based exercise interventions for cachexic patients with lung or pancreatic cancer consisted of functional resistance training and aerobic training [56]. The exercise program was devised by a physical therapist. Resistance training consisted of six exercises using weights, targeting major muscle groups in the upper body and legs, to be performed three times weekly for approximately 20 min. Aerobic training consisted of 30 min of aerobic exercise twice a week. The results of this trial showed that although there was a positive effect on weight, there was no statistically significant effect on physical activity (PA) or muscle mass. Patient compliance with exercise that combines resistance training and aerobic training was 44%, and the compliance with all three interventions was only 12%. Therefore, the NEXTAC program aimed to improve and maintain compliance with exercise interventions [58]. Three levels were prepared in the program, and the individualized exercise program prescribed by the physical therapist or occupational therapist consisted of 3–5 of the five exercise components. The level 3 exercise program used ankle weights. The instructors determined the exercise level using the modified Borg scale. At each time point, the instructors examined the patient's exercise diary and conducted direct interviews to modify the exercise program to the optimal level for patients who had not discontinued exercise completely. The instructors also recommended self-modification according to the patient's condition. In terms of PA, the initial target step count was determined using the prescription algorithm according to the average number of daily steps during the screening period. The instructors modified the target step count according to the average steps between each time point. With this intervention, the median proportion of days when patients performed full or self-modified exercises was as high as 91%. The patients wore an accelerometer for a median of 98% of the total intervention days, and 93.3% of all patients completed all sessions on time. One systematic review reported that the adherence to the exercise intervention among patients with advanced cancer varied from 65% to 95% as measured by attendance at exercise sessions [96]. It was not clear whether the reported adherence rate included all potential participants or only those considered to have participated in a sufficient amount of exercise to be included in the analysis. Overall, it is necessary to consider exercise interventions that are easier for patients with cancer cachexia to complete. Physical therapists should assess each patient's physical performance and optimize the customized exercise programs. Physical therapists should play an important role in the management of patients with cancer cachexia.

24.8 Cachexia and Postoperative Outcomes

Recent studies have reported that preoperative cancer cachexia is an important predictor of postoperative outcomes. Three studies reported that preoperative cancer cachexia was associated with the postoperative outcomes (Table 24.4). Preoperative cachexia is associated with higher odds of postoperative complications in surgical cancer patients with normal or underweight BMI [7]. In patients with gastric and colorectal cancer, aged 60 years and older, preoperative cachexia significantly affects postoperative LOS [8]. In patients with gastric cancer, preoperative cachexia was associated with OS in patients younger than 50, 51–61, and 61–70 years old but not in those older than 71 years old [9]. Furthermore, in patients aged ≤50 years, cachexia significantly affected the postoperative LOS and hospitalization costs. These studies have some limitations. Two of the studies used the definition of the international consensus and defined sarcopenia as low muscle mass according to the Asian consensus definition [97]. In contrast, one study defined weight loss ≥5% over a 6-month period before surgery as cachexia. Additionally, the postoperative outcomes investigated in these studies were inconsistent. Patient characteristics, such as age and cancer type, also varied between these studies. They were not large-scale trials. Therefore, the findings could not be generalized. Additionally, the mechanism of cachexia on postoperative outcomes is unclear. One of the mechanisms may be delayed wound healing after surgery because cachexia is associated with delayed wound healing, malnutrition, and inflammation [98, 99]. Preoperative cancer cachexia is a risk and modifiable factor of postoperative outcomes. Hence, the management of preoperative cancer cachexia is important.

Treatment for gastrointestinal cancer mainly involves surgery. The enhanced recovery after surgery (ERAS) protocol is important for reducing surgical stress and facilitating postoperative recovery. The ERAS protocol for cancer patients may reduce LOS, hospital costs, postoperative complications, and readmissions [100, 101]. Postoperative complications in patients with surgical colorectal cancer have been shown to be associated with a decline in long-term QOL [102]. In elderly patients, after elective major abdominal operations, 10–50% of patients had protracted disability and did not recover to preoperative functional capacity even after 6 months [103]. Additionally, poor preoperative physical performance, such as cardiorespiratory fitness, has been associated with postoperative complications, LOS [104], and mortality [105]. Thus, interventions in the preoperative period are important for enhancing the physical performance of patients and improve postoperative outcomes. Prehabilitation is defined as a process on the cancer continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment and includes physical and psychological assessments [106]. Prehabilitation aims to establish a baseline functional level, identify impairments, and provide interventions that promote physical and psychological health to reduce the incidence and/or severity of future impairments. Prehabilitation includes nutritional, exercise, or pharmacological intervention, similar to multimodal interventions. Recently, some studies reported the effect of prehabilitation for cancer patients scheduled for surgery. Prehabilitation contributed to shortening the postoperative

Table 24.4 The association between preoperative cancer cachexia and postoperative outcomes

Reference	Year	Study type	Number of patients	Cancer type	Diagnostic criteria of cachexia	Measured postoperative outcomes	Main results
Mason et al. [7]	2016	Prospective cohort study	253	Gastrointestinal (colorectal, hepato-pancreato-biliary, gastric), skin-soft tissue, breast, or other cancers	Patients with a change ≥5% from baseline body weight (6 months before surgery)	Postoperative complications within 60 days of surgery, transitional care needs at discharge, and mortality within 6 months of operation	Preoperative cachexia: 16.6% In multivariate analysis, in patients with normal or underweight BMI, cachexia was associated with higher odds of postoperative complications (OR, 5.08 [95% CI, 1.18–21.88])
Fukuta et al. [8]	2019	Prospective cohort study	98	Gastric or colorectal cancer	The international consensus Sarcopenia was defined as low muscle mass (SMI of <7 kg/m^2 for men and <5.7 kg/m^2 for women) according to the Asian consensus definition	Postoperative complications within 30 days after surgery and postoperative LOS	Preoperative cachexia: 22.4% In multivariate analysis, cachexia was significantly associated with prolonged postoperative LOS (2.41 days [95% CI, 0.28–4.55])

Chen et al. [9]	2019	Prospective cohort study	575	Gastric cancer	The international consensus Sarcopenia was defined as low muscle mass (SMI of <7 kg/m^2 for men and <5.7 kg/m^2 for women) according to the Asian consensus definition	OS, LOS, hospitalization costs, readmission, and postoperative complications	Preoperative cachexia: 35.8% In multivariate analysis, cachexia was independently associated with worse OS (HR, 1.46 [95% CI 1.07–1.98]). After grouping by age, cachexia was associated with OS in patients younger than 50 years old (HR = 4.95 [95% CI 1.18–20.73]), patients 51–60 years old (HR = 2.23 [95% CI 1.10–4.52]), and patients 61–70 years old (HR = 1.81 [95% CI 1.05–3.09]) but not in patients older than 71 years old (HR = 1.41 [95% CI 0.92–2.17]). Further, cachexia only significantly affected the postoperative LOS and hospitalization costs in patients younger than 50 years old

Abbreviations: *BMI* body mass index, *SMI* skeletal muscle mass index, *LOS* length of stay, *OR* odds ratio, *CI* confidence interval, *OS* overall survival, *HR* hazard ratio

LOS [107, 108] and improving postoperative complications [109] or functional capacity [110]. In contrast, a 2021 meta-analysis evaluated the impact of prehabilitation in hepatobiliary, colorectal, and upper gastrointestinal cancer surgery and reported that prehabilitation can reduce patient LOS but had no effect on functional capacity as determined using the 6-minute walk test, postoperative complications, or mortality rates [111]. The same meta-analysis concluded that the number of RCTs for prehabilitation was small, and there were insufficient studies to determine minimum amount, type, intensity, and frequency of aerobic or strength training for improving functional capacity or optimizing clinical outcomes.

Trials investigating the interventions for preoperative cancer cachexia are insufficient. Further studies on multimodal interventions, such as prehabilitation, for patients with cancer cachexia are warranted. In particular, studies that examine the postoperative complications and postoperative recovery rate of multimodal interventions, including prehabilitation, are necessary.

24.9 Conclusion

Management of cancer cachexia is an important challenge in cancer treatment. To date, various assessments and interventions are available. Moreover, there are various diagnostic criteria for cachexia. Patient characteristics, such as cancer type, stage of cancer, and treatment type, may also vary. Since cancer cachexia is particularly common in elderly patients and in patients with gastrointestinal cancer, more management approaches targeting these patients are needed. Preoperative cancer cachexia is an important modifiable factor in improving postoperative outcomes and facilitating postoperative recovery in patients. Hence, we must pay attention to this and develop a mechanism to identify cancer cachexia early, before anticancer treatment. Certain pharmacological agents and nutritional support have been reported to be effective with a single intervention; adding exercise to the combination may be helpful. Physical therapists should collaborate with doctors, nurses, pharmacists, and nutritionists as part of multimodal interventions for cancer cachexia. Further research in the management of cancer cachexia is warranted in the future.

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Mechanism of Skeletal Muscle Atrophy Using a Mice Cancer Cachexia Model

25

Takuya Mori, Jiro Nakano, and Hiroki Kuniyasu

Abstract

Cancer cachexia is one of the major complications that mainly induces skeletal muscle atrophy, worsens the prognosis of patients with cancer, and deteriorates their physical function and quality of life. Cancer cachexia is known to be frequently associated with cancer progression, but it has also been found to play an important role in cancer treatment because of its ability to reduce tolerability of anticancer drugs. Therefore, although elucidation of cancer cachexia mechanisms is clinically beneficial, there are still no definitive reports, and human clinical trials for cancer cachexia have been lagging behind. Consequently, an appropriate animal model is indispensable for conducting innovative research pertaining to the mechanism of cachexia and development of innovative treatment options. This chapter describes cancer cachexia skeletal muscle atrophy, focusing on the results of a mouse cachexia model developed by the authors.

Keywords

Cancer cachexia · Skeletal muscle atrophy · Inflammatory cytokines · Energy metabolism · Mice cancer cachexia model

T. Mori (✉)
Department of Molecular Pathology, Nara Medical University, Kashihara, Nara, Japan

Graduate School of Medicine, Faculty of Medicine, Kyoto University and Kyoto University Hospital, Kyoto, Japan
e-mail: mori.takuya.7y@kyoto-u.ac.jp

J. Nakano
Department of Physical Therapy, Faculty of Rehabilitation, Kansai Medical University, Hirakata-shi, Osaka, Japan

H. Kuniyasu
Department of Molecular Pathology, Nara Medical University, Kashihara, Nara, Japan

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25.1 Relationship Between Cancer Cachexia and Skeletal Muscle Atrophy

Cancer cachexia affects 40% of patients with cancer at all stages of the disease and 80% of elderly and patients with advanced cancer [1, 2]. It has been reported that the onset of cancer cachexia is associated with inflammatory cytokines [3, 4], oxidative stress [5], increased catabolism [6], and anorexia [7, 8]. These are considered to be syndromes that result in a decline in quality of life and impaired physical function. Cachexia was first defined at the 2008 Cachexia Consensus Conference as "a complex metabolic syndrome characterized by muscle loss with or without loss of fat mass" [9].

Consequently, skeletal muscle atrophy is considered to be a major pathogenic factor in cancer cachexia, and more importantly, skeletal muscle mass in patients with cancer is also considered to be a strong survival factor [10, 11]. Blocking myostatin expression via activin IIB receptor inhibitors was found to increase skeletal muscle mass in a mouse cachexia model [11]. Unlike mice in the cachexia group, which became moribund, the survival rate in mice with increased skeletal muscle mass due to the activin IIB receptor inhibitors increased to 80%, despite the fact that no tumor suppression was noted. This result suggests that suppression of skeletal muscle atrophy due to cancer cachexia is directly linked to improved prognosis in patients with cancer [4, 8]. In recent years, studies focusing on skeletal muscle mass from the perspective of suppressing treatment of skeletal muscle atrophy in patients with cancer have also reported the importance of skeletal muscle mass on the daily performance and quality of life of patients with cancer [12]. Conventionally, skeletal muscle mass correlates with high physical function and maintenance of QOL in healthy individuals or individuals suffering from diseases other than cancer. Hence, it is expected that nutritional intervention and strength training will improve the skeletal muscle.

In recent years, several studies have been conducted with the expectation that these factors would improve survival prognosis and quality of life even in patients with cancer [13, 14].

25.2 Relationship Between Inflammatory Cytokines and Skeletal Muscle Atrophy in Cancer Cachexia Obtained from Autopsy Cases

Colorectal cancer (CRC) is the third leading cause of cancer-related death in Japan, and its incidence is continuously increasing. Despite recent advances in adjuvant therapy, prognosis remains poor in patients with advanced disease [15, 16]. Skeletal muscle atrophy has been associated with decreased survival rates of end-stage CRC and stage I–III CRC in CRC patients [17, 18]. The clinical diagnosis of cancer

cachexia was previously based on weight loss, body composition, and body function, but various molecular biomarkers have been sought to elucidate the mechanism of cachexia [19]. Early diagnosis of cancer cachexia with molecular biomarkers may reflect the clinical process of skeletal muscle atrophy, facilitating early detection and treatment of skeletal muscle atrophy in cachexia [20]. However, at present, there are no definitive clinical biomarkers for the diagnosis of cancer cachexia. A study using eight autopsy cases with CRC focused on known cancer cachexia skeletal muscle atrophy-related cytokines, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and high mobility group box 1 (HMGB1). Serum cytokine levels were compared with the skeletal muscle index (SMI) [21] and the biochemical markers of skeletal muscle maturity, SDS-soluble myosin light chain 1 (SDS-MYL1), weight loss, body mass index (BMI), and serum carcinoembryonic antigen (CEA) [22] (Fig. 25.1). These cytokines induce inflammation, catabolism, and increased oxidative stress [3–8, 23]. In addition, SDS-MYL1 has also been reported as a candidate marker for sarcopenia and cachexia in both in vitro and in vivo models [24]. The results of these studies showed that SMI was positively correlated with SDS-MYL1 and negatively correlated with TNF-α. TNF-α and HMGB1 were correlated in a multivariate analysis for SMI, whereas SDS-MYL1 was negatively correlated with TNF-α and HMGB1 but not with IL-6. Furthermore, the multivariate analysis revealed that only TNF-α was associated with SDS-MYL1. A positive correlation was found between TNF-α and HMGB1. Thus, TNF-α was inversely correlated with SMI and SDS-MYL1, and it was suggested to be an effective serum marker for skeletal muscle atrophy in CRC (Table 25.1). Interestingly, SMI, a clinical marker of skeletal muscle atrophy, was not shown to significantly correlate with weight loss, BMI, or lean body mass (LBM). This is thought to be because weight loss and BMI are associated with various factors, such as adipose tissue loss, fluid fluctuations, such as edema and ascites, and skeletal muscle mass loss. In fact, all cancer cases in this study showed the development of marked edema in the lower extremities [25]. TNF-α and HMGB1 correlate with cachexic skeletal muscle atrophy, and both TNF-α and HMGB1 are thought to be involved in the malignant cycle of mutual feedback-induced inflammation enhancement [26]. In particular, HMGB1 is also secreted from CRC cells and is known to promote the development of cancer [25, 27, 28]. Therefore, in patients with terminal cancer, overexpression of HMGB1 and TNF-α is observed even in cases where infection is unclear [29]. It has been reported that HMGB1 induces autophagy in the skeletal muscle through activation of nuclear factor-κB (NF-κB) together with TNF-α, using the receptor for advanced glycation end product (RAGE) and Toll-like receptor-4 (TLR4) as receptors [30].

Based on these facts, serum HMGB1 and TNF-α in patients with cancer can be used as effective biomarkers for cancerous skeletal muscle atrophy but also as important mechanisms for the progression of cancer cachexia. Consequently, targeting TNF-α and HMGB1 and their interactions is expected to enable prevention and amelioration of skeletal muscle atrophy and cancer cachexia.

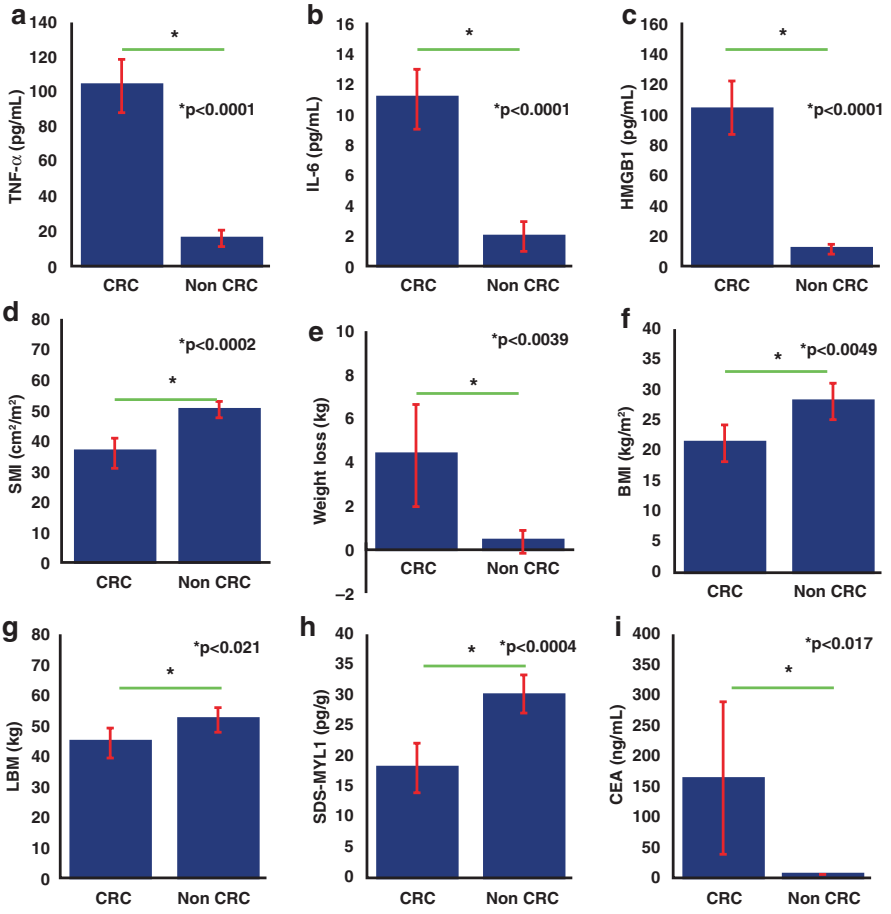

Fig. 25.1 All data were compared between each group. CRC, cancer cases ($n = 8$); and non-CRC, non-cancer cases ($n = 5$). (**a**–**c**) and (**h**) indicated serum concentration. (**a**) TNF-α in serum. (**b**) IL-6 in serum. (**c**) HMGB1 in serum. (**d**) SMI was calculated as skeletal muscle area at L3/body height. Skeletal muscle area was measured by computed tomography. (**e**) Weight loss was calculated as body weight at operation-body weight at death. (**f**) BMI was calculated by dividing the weight value by the square of the height. (**g**) LBM was calculated as 0.32810 × body weight (kg) + 0.33929 × height (cm), 29.5336 in males, or 0.29569 × body weight (kg) + 0.41813 × height (cm), 43.2933 in females. (**h**) SDS-MYL1 was measured by ELISA of SDS-soluble whole lysates of the muscles. (**i**) CEA in serum. *TNF-α* tumor necrosis factor-α, *IL-6* interleukin-6, *HMGB1* high mobility group box 1, *SMI* skeletal muscle index, *BMI* body mass index, *LBM* lean body mass, *SDS-MYL1* SDS-soluble myosin light chain 1, *CEA* carcinoembryonic antigen. (Adapted from [22])

Table 25.1 Relationship between physical indicators and SMI, SDS-MYL1, and cytokines and the relationship between cytokines

		p value	*R*
SMI (cm^2/m^2)	Weight loss (kg)	0.8149	0.099369
	BMI (kg/m^2)	0.8524	0.079057
	CEA (ng/mL)	0.1546	0.55356
	TNF-α (pg/mL)	0.0215	0.78326
	IL-6 (pg/mL)	0.47	0.30023
	HMGB1 (pg/mL)	0.4987	0.28193
	SDS-MYL1 (pg/g)	0.0269	0.76532
SDSMYL1 (pg/g)	TNF-α (pg/mL)	<0.0001	0.97
	IL-6 (pg/mL)	0.4052	0.34326
	HMGB1 (pg/mL)	0.194	0.7912
HMGB1 (pg/mL)	TNF-α (pg/mL)	0.236	0.776
	IL-6 (pg/mL)	0.8708	0.06916
IL-6 (pg/mL)	TNF-α (pg/mL)	0.5263	0.2647

Each parameter was obtained within 2 months of death. The relationship was examined by Spearman regression analysis

BMI body mass index, *SMI* skeletal muscle index, *SDS-MYL1* SDS-soluble myosin light chain 1, *TNF-α* tumor necrosis factor-α, *IL-6* interleukin-6, *HMGB1* high mobility group box 1, *CEA* carcinoembryonic antigen

Adapted from [22]

25.3 Skeletal Muscle Atrophy and Energy Production in a Mouse Cancer Cachexia Model

Patients with advanced cancer exhibit symptoms of malnutrition, weight loss, and cachexia, suggesting that cancer affects the host's energy production pathways. In order to elucidate the relationship between complex metabolic syndrome and cachexia in patients with cancer, it is important to clarify the changes in the energy production mechanism with cancer. HMGB1 is a multifunctional protein that functions as a growth factor in cancerous patients by binding to RAGE, thus promoting proliferation, infiltration, and metastasis [25]. HMGB1 is released from necrotic cells and induces inflammation [31, 32]. In addition, our past reports have shown that HMGB1 increases from the early stages of colorectal carcinogenesis, confirming that its values escalate with stage progression (Fig. 25.2). From these findings, the relationship between HMGB1 and cachexia, which worsens with cancer progression, is interesting. This section shows the results of verifying the effect of high mobility group box 1 HMGB1 on energy metabolism of both tumor and skeletal muscle using a mouse cancer cachexia model. The results of this study showed that HMGB1 expression, a secretory autophagy-induced stress protein, increased in the skeletal muscle of cancer-bearing animals with the onset and progression of colorectal cancer. This effect was associated with reduced expression and activity of pyruvate kinase M 1 (PKM1) in the skeletal muscle via RAGE of the HMGB1 receptor.

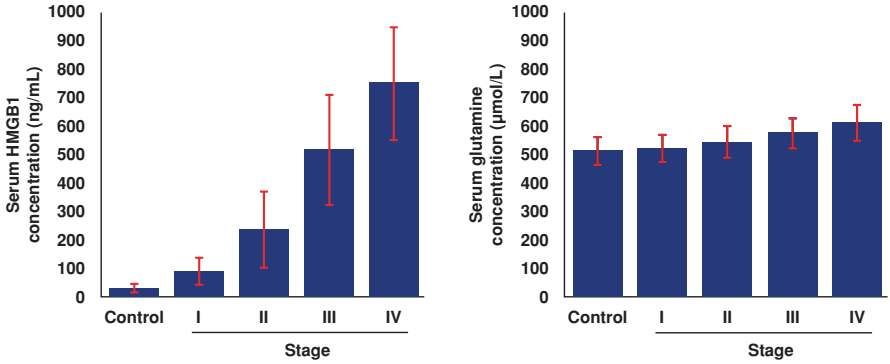

Fig. 25.2 Concentration of serum HMGB1 in patients with colorectal cancer. Stage: Pathology stage was classified according to the TNM classification. Stage I, tumor within the mucosae propria or submucosal layers; stage II, tumor invades beyond the muscularis propria without lymph node metastasis; stage III, tumor shows lymph node metastasis; and stage IV, lymph node metastases may or may not be observed; distant metastases may be observed. (Adapted from [3])

In addition, addition of HMGB1 in skeletal muscle cells was found to reduce active mammalian target of rapamycin (mTOR) levels. Furthermore, uptake of autophagy-related proteins, plasma glutamate, and 13C-glutamine into acetyl-CoA (AcCoA) was increased, inducing autophagy. In a colorectal carcinogenesis mice model, HMGB1 increased temporally in serum and colonic mucosa, and autophagy increased with changes in plasma-free amino acid levels, increased glutamine, and decreased PKM1 levels. However, administration of HMGB1 neutralizing antibody cancelled these findings. Similar results have also been obtained with a mouse xenograft model of human colorectal cancer. Interestingly, addition of HMGB1 to colorectal cancer cells increased lactate fermentation, suggesting that HMGB1 released during tumor formation promotes skeletal muscle autophagy and supplies glutamine released from the skeletal muscle to cancer cells (Fig. 25.3). These findings highlight a cancer-host energy production relationship. Thus, depletion of skeletal muscle protein due to cancer and skeletal muscle interactions is an important mechanism that causes cachexia. Especially in such situations, therapeutic targets for HMGB1 and glutamine can also be important targets for tumor growth suppression and skeletal muscle atrophy suppression. In the future, HMGB1 and glutamine may also prove to be clinical markers for the progression of cachexic skeletal muscle atrophy. It is very important to focus on changes and interactions related to the energy metabolism of tumors and the skeletal muscle as an aid to the mechanism of cachexia.

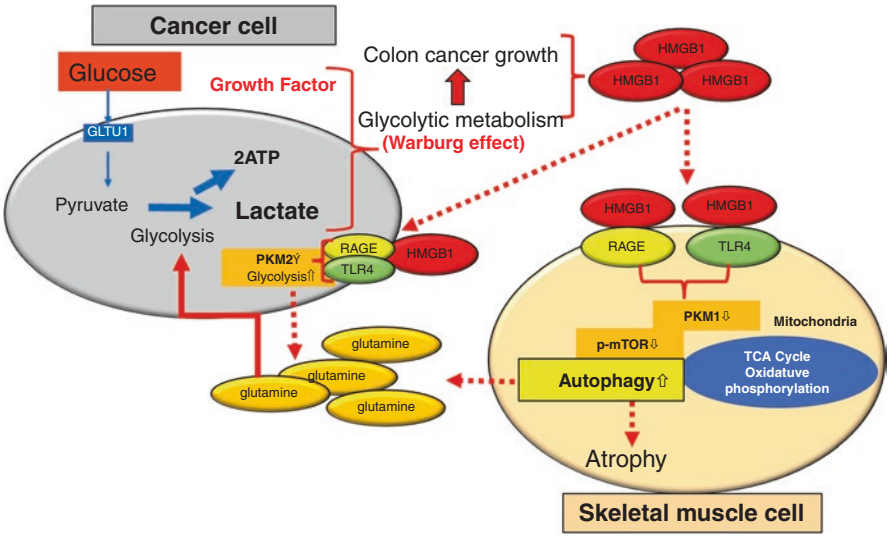

Fig. 25.3 HMGB1 released from tumor cells promotes skeletal muscle autophagy and activates tumor glucose metabolism. HMBG1 is an inflammatory cytokine released with tumor growth. HMGB1 activates autophagy in the skeletal muscle via RAGE and TLR4. In contrast, glycolytic metabolism in tumors is enhanced. Tumors metabolize glutamine released into the blood by skeletal muscle autophagy through glycolytic metabolism

25.4 Carbohydrate-Induced Nutritional Intervention and Skeletal Muscle Atrophy in Cancer-Bearing Mice

In recent years, nutritional intervention has been emphasized as a treatment for patients with cancer with cachexia and malnutrition [8]. However, some nutrients, such as carbohydrates and linoleic acid, can promote tumors [33–35]; thus attention should be paid to the effects of nutritional interventions on both the skeletal muscle and tumors. Glucose is an essential nutrient for skeletal muscle cells, which is known to promote skeletal muscle contraction, homeostasis, and skeletal muscle cell growth [34]. Glucose uptake into skeletal muscle cells depends on insulin via glucose transporter 4 (GLUT4) [33]. In contrast, glucose is also known to have a growth-promoting effect on tumor cells, and tumor cells more selectively prefer glycolytic metabolism as a Warburg effect to generate energy [36]. In addition, glucose uptake by tumor cells is insulin-independent via glucose transporter 1 (GLUT1), which has a high affinity for glucose, and blood glucose levels are thought to promote tumor growth [37]. Thus, although carbohydrates are used as trophic factors, slight differences exist in their metabolism (Fig. 25.4). Although a tumor-suppressing effect of carbohydrate restriction has been reported [38], it has

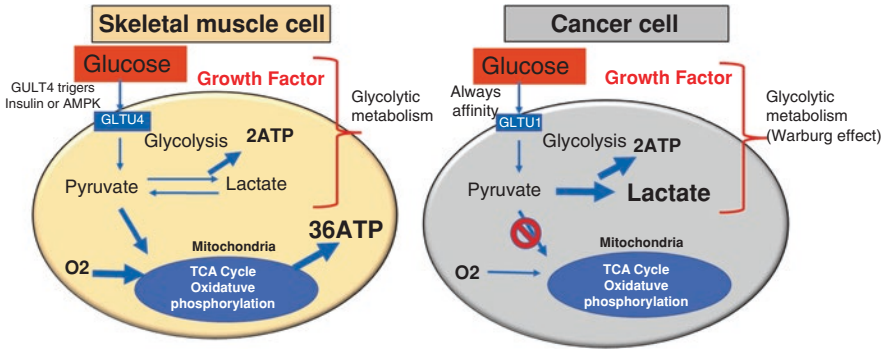

Fig. 25.4 Differences in glucose metabolism between tumor cells and skeletal muscle cells. Glucose metabolism is useful as a growth factor for both cells. In the skeletal muscle, GLUT4 moves to the cell surface, and glucose uptake occurs via insulin- or AMPK-dependent pathways. In contrast, in tumor cells, GULT1, which has a high affinity, is always expressed at the cell boundary and undergoes signal-independent uptake. Regarding metabolism, skeletal muscle converts glucose to pyruvate, and aerobic metabolism is performed by the TCA cycle; however, tumors only undergo glycolytic metabolism

also been suggested that simple carbohydrate restriction generally suppresses skeletal muscle differentiation and causes muscle atrophy [39]. In other words, limiting carbohydrates to cancer-bearing bodies is thought to inhibit energy production in skeletal muscle and exacerbate cachexic skeletal muscle atrophy. However, there are no reports that have simultaneously investigated the effects of carbohydrate load on tumors and skeletal muscle in cancer-bearing bodies. Therefore, this section introduces the results of examining the effects of carbohydrate loading on tumors and skeletal muscle in a mouse cancer-bearing model [40]. CT26 cells, a syngeneic mouse colon cancer cell line, were subcutaneously inoculated into the backs of BALB/c mice. Mice were allowed to freely drink sugar water (0%, 10%, and 50% glucose) for 2 weeks, and tumors and skeletal muscles were analyzed.

As shown in Table 25.2, the subcutaneous tumor diameter increased in a glucose concentration-dependent manner. Skeletal muscle weight was significantly lower in the tumor group, but SDS-MYL1, which indicates the functional maturity of skeletal muscle, showed a significantly higher value depending on glucose concentration. However, when sugar concentration increased to 50%, improvement of SDS-MYL1 was observed to the same level as that of the control group (noncancerous mice) [40]. The above findings reveal that despite the fact that the glucose load of the cancer-bearing body enhances functional maturity and improves skeletal muscle atrophy, it also promotes tumor growth. In mouse myoblasts, glucose has been reported to promote myoblast proliferation and myotube differentiation in a concentration-dependent manner, facilitating skeletal muscle growth [36]. In addition, insulin is important for the growth and differentiation of muscle cancer cells along with glucose intake [37]. In this study, mice showed normal blood glucose levels, suggesting that glucose was taken up by the skeletal muscle and metabolized for muscle remodeling and improving skeletal muscle atrophy in cancer-bearing

Table 25.2 Effects of drinking glucose on CT26 mice

CT26 tumor	Glucose	*n*	Tumor diameter (mm)	Muscle weight (mg)	SDS-MYL1 (pg/g)
(–)	0%	3	–	221 ± 38	71 ± 1
	10%	2	–	258 ± 32	87 ± 2
	50%	2	–	243 ± 30	98 ± 2*
	Average	7	–	241 ± 41*	–
(+)	0%	3	7 ± 4	185 ± 18	41 ± 1
	10%	3	20 ± 8	181 ± 20	72 ± 1
	50%	3	18 ± 7	194 ± 15	103 ± 2*
	Average	9	–	186 ± 16*	–
	(–)	3	7 ± 4	–	–
	(+)	6	19 ± 7*	–	–

The animals were divided into CT26 (−) and CT26 (+) groups, and glucose was provided at concentrations of 0%, 10%, and 50%. Each parameter is presented as mean ± SD. The tumor diameter was measured 2 weeks after inoculation in BABL/c mice. The weight of quadriceps femoris muscles was measured, and muscle weight was measured 2 weeks after inoculation. SDS-MYL1 was measured by ELISA using whole cell lysate solubilized with RIPA buffer containing 0.1% SDS. All data were calculated by Steel–Dwass test after ordinary ANOVA
* $p < 0.05$

mice. Hence, this underlines the importance of glucose in suppressing skeletal muscle atrophy. In contrast, tumor growth was observed with glucose loading. Tumors are known for their Warburg effect, which is characterized by a shift in energy production to glycolysis and lactic acid fermentation. In the above experiment, the tumor diameter and blood glucose levels showed a negative correlation, which is considered to be the result of excessive glucose uptake by the tumor. Thus, glucose suppresses skeletal muscle atrophy in cancer-bearing bodies but should be used with caution because it promotes tumor growth. It is currently difficult to define an appropriate dose of glucose in patients with cancer. However, by reexamining the administration method of glucose and the amount of glucose which is actually taken up into tumors and skeletal muscle, cancer cachexia is expected to be useful in suppressing qualitative skeletal muscle atrophy.

25.5 MCFA-Induced Nutritional Intervention and Skeletal Muscle Atrophy in Cancer-Bearing Mice

The previous section highlighted that sugar intake was found to suppress skeletal muscle atrophy. However, it is important to be very cautious of nutritional interventions that may promote tumor growth [41]. In addition to sugar, lipids are very interesting nutrients sources for the skeletal muscle, and among them, medium-chain fatty acid (MCFA) has recently attracted significant attention due to its metabolic mode. Carbohydrates are generally metabolized by glycolysis, but lipids are taken up by mitochondria, subsequently promoting oxidative phosphorylation. Unlike long-chain fatty acids that are commonly used in dietary supplements, MCFA is carnitine shuttle-independently incorporated into mitochondria, undergoes β-oxidation, and is used for oxidative phosphorylation in the TCA cycle

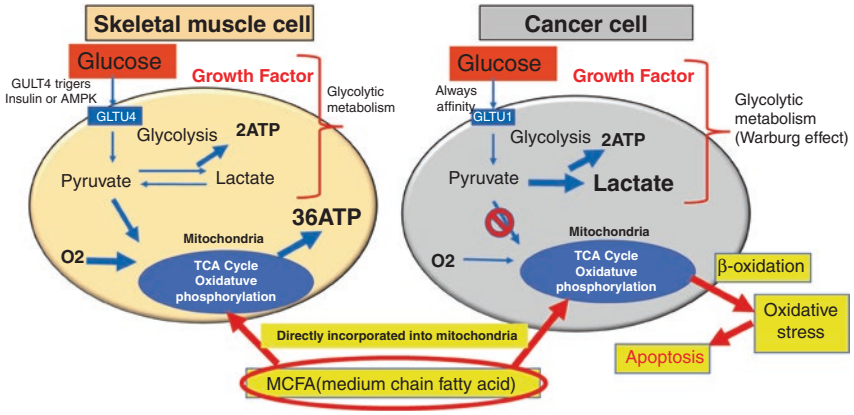

Fig. 25.5 Differences in medium-chain fatty acid between tumor cells and skeletal muscle cells. Medium-chain fatty acids (MCFA) are taken up directly into the mitochondria of both cells independent of the carnitine shuttle. In the skeletal muscle, MCFA is metabolized in the mitochondria by the TCA cycle, enabling efficient energy sharing. In contrast, due to abnormal mitochondrial quality in tumor cells, it promotes oxidative stress due to β-oxidation and induces apoptosis

[42–44]. This feature suggests the possibility of forcibly inducing oxidative phosphorylation (Fig. 25.5). Therefore, we investigated the effect of MCFA on tumor growth and skeletal muscle atrophy in the same individual using a mouse cachexia model. A cachexia model of mouse peritoneal metastasis using CT26 mouse colorectal cancer cells and HT29 human colorectal cancer cells was used [24]. We show the effect of oral intake of glucose (0%, 10%, and 50%) and 2% lauric acid (LAA, C12: 0) on tumor growth and skeletal muscle atrophy in a cachexia mouse model (Table 25.3). Ingestion of 2% LAA alone was found to increase skeletal muscle protein levels. Pertaining to the underlying mechanism, it has been reported that the formation of glycolytic muscle fibers is promoted via the TLR4 signal of LAA [45]. Conversely, for cancer cells, LAA suppressed tumor growth by inducing oxidative stress production. Combined intake of glucose and LAA increased skeletal muscle mass and suppressed tumor growth. Therefore, ingestion of LAA could suppress tumor growth, and the combined use with glucose could offset the tumor-promoting effect of glucose, thereby promoting skeletal muscle mass and maturation without promoting tumor growth. Furthermore, MCFA does not show an increase in oxidative stress or inhibition of glycolytic metabolism in the skeletal muscle, and it efficiently promotes adenosine triphosphate (ATP) production by oxidative phosphorylation. It is considered to be an effective energy source for the skeletal muscle. In the CT26 cells used in this experiment, the gene expression of the electron transport system derived from mitochondria is imbalanced, which is considered to induce oxidative stress due to LAA [45]. In addition, since mitochondrial gene expression disorders and gene abnormalities are frequently observed in other cancer cells [46], LAA is expected to exhibit antitumor effects in many types

Table 25.3 Effect of dietary interventions using glucose and/or lauric acid on a mouse cancer cachexia model

Tumor cell line	Diet	Tumor weight (g)[a]	Muscle weight (g)[b]	SDS-MLC (pg/g)[c]
CT26	No tumor/control	–	0.15 ± 0.002	23 ± 1.3
	Control	1.35 ± 0.15	0.11 ± 0.002	13 ± 1.2
	LAA	0.63 1 0.06	0.13 ± 0.01	22 ± 3.5
	LAA + glucose	1.58 ± 0.16	0.14 ± 0.01	27 ± 3.1
HT29	No tumor/control	–	0.15 ± 0.01	21 ± 2.2
	Control	1.2 ± 0.11	0.09 ± 0.002	11 ± 1.2
	LAA	0.3 ± 0.04	0.14 ± 0.01	21 ± 2.7
	LAA + glucose	1.25 ± 0.13	0.15 ± 0.01	23 ± 2.5

A mouse cachexia model was created by seeding CT26 cells or HT29 cells in the peritoneum. LAA alone or in combination with glucose was provided for 2 weeks, and both tumor and skeletal muscles were analyzed

LAA lauric acid

Adapted from [24]

[a] To measure tumor weight, the peritoneal tumors were dissected from the intestine, mesenterium, diaphragm, and abdominal wall, removing nontumoral tissues

[b] The quadriceps femoris muscle was cut at the muscle end on the upper edge of the patella, peeled off from the femur, and separated at the muscle origin on the frontal surface of the anterior lower iliac spine. The excised quadriceps femoris muscle was weight immediately, avoiding drying

[c] Whole cell lysate solubilized with 0.1% SDS-RIPA buffer from sonicated muscle tissue was analyzed with ELISA for myosin light chain 1/3 isoform

of cancers [47, 48]. In contrast, in normal cells, such as skeletal muscle cells, there is no mutation or expression imbalance in the mitochondrial gene; hence, it is difficult for LAA to induce oxidative stress. We then examined LAA safety, and we found that 2% LAA was effective in increasing skeletal muscle weight, as opposed to 5% LAA which was ineffective. In addition, 5% or 10% LAA to the myocardium resulted in atrophy. It is considered that excessive LAA administration may induce oxidative stress even in normal cells, causing significant damage. Consequently, it is necessary to establish an appropriate dose when applying the LAA-added diet to humans. This study suggests that glucose and MCFA combination may suppress cancerous skeletal muscle atrophy without promoting tumor growth. In the future, it is expected that glucose- and MCFA-based nutritional interventions will be applied in clinical settings for cachexia skeletal muscle atrophy, provided that the appropriate dose, administration method, and administration time are established.

25.6 Vitamin B and Vitamin E Metabolism and Skeletal Muscle Atrophy in a Mouse Cancer Cachexia Model

There are various reports on the effects of vitamins on sarcopenia. For example, individuals who do not meet the recommended intake of riboflavin and vitamin (V) C are known to be at increased risk of developing sarcopenia [49]. The effectiveness of VC and VD has been reported for skeletal muscle atrophy in patients with cancer

[50, 51]. Previous studies have shown that skeletal muscle and myocardium disorders in cachexia are associated with impaired energy metabolism and increased oxidative stress [24, 52]. However, no studies have verified the effectiveness of VB2 and VE, which demonstrate antioxidant effects, on the cancer-derived skeletal muscle. Therefore, we examined the efficacy of VB2 and VE against cancerous sarcopenia. VB2, VB12, calcium, and essential fatty acids contained in dairy products are considered to be more biologically useful than other nutrients [53, 54]. For example, VB2 has distinct antioxidant properties, and it has been reported to reduce oxidative stress associated with lipid peroxides and reperfusion [55], and it is used to improve nutritional levels in individuals with chronic disease [56]. In contrast, VB2 deficiency has been reported to promote increased oxidative stress and carcinogenesis [55]. Hence, the VB2 derivative flavin adenine dinucleotide is most commonly used as a riboflavin nucleotide [57] and exhibits redox activity [58], and it is involved in the epigenetic regulation of gene expression [59, 60]. VE, which exists in eight chemical forms, acts as a peroxy radical scavenger that protects polyunsaturated fatty acids that are present in cell membranes and lipoproteins [61]. Although α-tocopherol, which is mainly used clinically, has a certain antioxidant effect, there are few reports on its carcinogenic suppressive effect and carcinogenic preventive effect [62]. The protective effect of VB2 and VE on the skeletal muscle is expected to be effective in the prevention and treatment of cancer-derived skeletal muscle atrophy [63]. Since VB2 is hydrophilic, as opposed to VE which is lipophilic, antioxidant activity is expected to vary according to its transferability to intracellular organelles such as mitochondria. Therefore, we investigated the effects of VB2 and VE on CT26 mouse colon cancer cells and the skeletal muscle both in vitro and in vivo. VB2 increased the production of ATP and ROS in tumors and suppressed tumor growth mainly by inducing apoptosis. In contrast, VE reduced ATP and ROS production and suppressed tumor growth mainly by suppressing cell proliferation. Pertaining to the skeletal muscle, VB2 and VE exacerbated cancer cachexia skeletal muscle atrophy by activating macrophages and promoting the production of TNFα, HMGB1, and NO. These inflammatory cytokines are involved in the development of cachexia in patients with colorectal cancer as described above [64]. VB2 and VE showed tumor suppressive effects, yet at the same time, they promoted cachexia inflammation and exacerbated sarcopenia (Fig. 25.6). Thus, the proinflammatory effects of VB2 and VE may suppress tumor progression while exacerbating cachexic skeletal muscle atrophy. Consequently, the use of VB2 and VE in patients with cancer may require an efficient risk assessment for the potential development of skeletal muscle atrophy. Herein, we examined the effects of using VB2 and VE alone; however, it seems that VB2 and VE are often used in the form of multivitamins in actual clinical situations. In the future, it is necessary to comprehensively examine the vitamin group for cancer-induced sarcopenia. It is also desirable to study the combined use of vitamins with glucose and medium-chain fatty acids. Collective consideration of these comprehensive nutrients will allow the development of effective nutritional interventions for skeletal muscle atrophy caused by cancer.

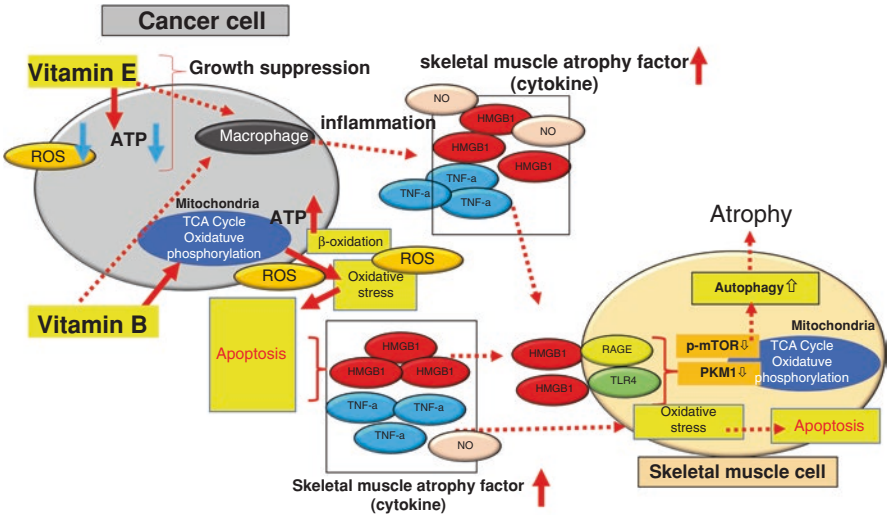

Fig. 25.6 Vitamin B or vitamin E suppresses tumor but also induces inflammation and promotes skeletal muscle atrophy. VB2 increased the production of ATP and ROS in tumors and suppressed tumor growth mainly by inducing apoptosis. In contrast, VE reduced ATP and ROS production and suppressed tumor growth mainly by suppressing cell proliferation. For skeletal muscle atrophy, VB2 and VE exacerbated cancer cachexia skeletal muscle atrophy by activating macrophages and promoting the production of TNFα, HMGB1, and NO

25.7 Myocardial Damage Due to Cancer Cachexia

Weight loss is an important phenotype of cachexia; however, weight loss in patients with cancer is associated with myocardial atrophy [65, 66]. Therefore, myocardial atrophy is considered to be one of the phenotypes of cancer cachexia. In fact, myocardial damage is a common cause of cancer death [67], and cancer-derived myocardial damage is an integrated condition of myocardial atrophy, remodeling, and dysfunction [68, 69]. Cancer-derived myocardial disorders may involve thinning of the left ventricular (LV) wall and decreased cardiac volume and myocardial fibers, as reported in gastrointestinal cancer, pancreatic cancer, and non-small cell lung cancer. In other words, it features remodeling of the left ventricle [68]. In addition, the underlying causes that promote cancer-induced myocardial damage may be related to the effect of cancer itself, the concurrent cardiovascular disease, the cancer treatment-related effects, etc.; however, in clinical settings, the efforts to develop for specific treatment are delayed. In recent years, research studies have underlined the role of cytokines derived from cancer itself, oxidative stress, depletion of antioxidants, and protein catabolism due to AKT/mTOR inhibition in the development of cancer-derived myocardial damage [70]. Furthermore, energy metabolism disorders due to mitochondrial dysfunction are also considered to be one of the causes of

Table 25.4 Myocardial atrophy and oxidative stress in the CT26 mouse cachexia model

	Heart weight (g)	Left ventricular area (%)	Myocardial area (%)	L/M radio (%)	4HNE (pg/g)
Control	0.113 ± 0.006	100	100	5.898 ± 0.99	98.151 ± 3.25
CT26	0.084 ± 0.004	135.818 ± 12.955	90.656 ± 1.638	8.815 ± 0.729	217.343 ± 29.929

The data of the CT26 mouse peritoneal dissemination model after 2 weeks are shown. All parameters are compared between the control and CT26 groups, and all data are indicated by mean ± SD. Heart weight is measured as the total heart mass. LV area and myocardial area were calculated with the control as 100%. L/M ratio divided LV area by the myocardial area. 4HNE is an oxidative stress marker that was measured using anti-4-HNE antibody after homogenization of myocardial tissue

cancer-derived myocardial disorders [8]. Mitochondrial dysfunction in cancer includes mitochondrial uncoupling, reduced ATP production, and NF-kB-mitogen-activated protein kinase (MAPK)-dependent mitochondrial disorders [71, 72]. It has also been reported that cardiomyocyte atrophy, apoptosis induction, autophagy enhancement, and ubiquitin-proteasome system activation can reduce protein synthesis [73]. Despite this, the multifactorial mechanism of cancer-derived myocardial damage has not yet been fully understood, and the molecular mechanism for preventing myocardial damage in patients with cancer has been elucidated. Therefore, we investigated the details of nondrug-induced cancerous myocardial damage using the mouse cachexia model described above [74]. In cachexic mice, decreased heart weight and myocardial volume, dilation of the LV space, and atrophy of cardiomyocytes were observed, which were similar to the outcomes of human cancerous myocardial damage (Table 25.4). Similar findings have been published by previous reports. In a mouse cachexia model, thinning of the LV septum, LV dilation, impaired contractility, and myocardial fibrosis have been observed [75, 76]. In addition, tapering of LV myocardial mass, decreased pump function, increased cardiovascular neurohormones, and protein denaturation have also been noted [77, 78]. Functionally, literature also outlines a decrease in contraction and relaxation force at the cardiomyocyte level [78]. Accumulation of 8-hydroxy-2-deoxyguanosine (8-OhdG), which is ROS, is observed in myocardial cells, and a decrease in the mitochondrial marker Leucin zipper-EF-hand containing transmembrane protein 1 (LETM-1) and an increase in the autophagy marker microtubule-associated proteins 1A/1B light chain (LC) 3-II have also been observed. Furthermore, 8-OHdG, which showed an increase in mitochondrial damage and oxidative stress, has been recently attracting significant attention as a marker for heart failure. 8-OhdG has been shown to increase with higher New York Heart Association Classification (NYHA) classes [79, 80]. In a cancer-bearing rat model, proteins involved in glycolysis, ATP production, muscle contraction, and mitochondrial function due to oxidative strain are oxidized, causing cardiac dysfunction [81]. Oxidative stress also contributes to the atrophy of type II muscle fibers in the skeletal muscle [82]. Furthermore, DNA damage caused by reactive oxygen species in

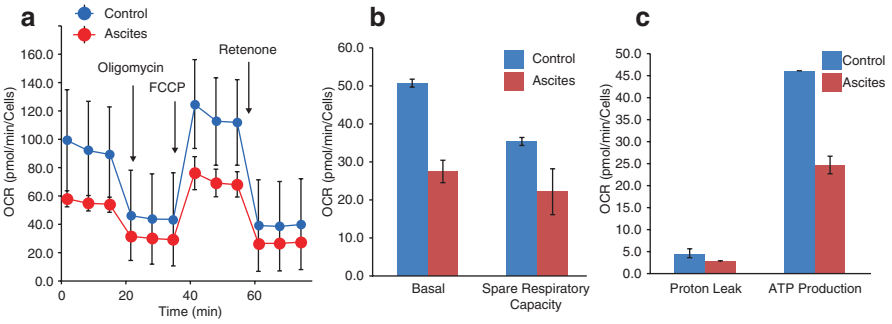

Fig. 25.7 Energy metabolism in the myocardium of H9C2 treated with ascites of CT26-inoculated mice. (**a**) Mitochondrial respiration: Mitochondrial stress test (Seahorse assay) of CT26-inoculated BALB/c mice (ascites) or H9c2 culture medium (control). (**b**) Basal OCR and spare OCR. (**c**) Proton leak and ATP production

a rat cachexia model induced extensive systemic organ damage [83]. Sjöström reports a decrease in cardiomyocyte mitochondria in a mouse cachexia model [81]. LETM1 is present in the inner mitochondrial membrane, and it is believed to be involved in the regulation of mitochondrial network, metabolic function, and cell death. Due to increased autophagy, loss of mitochondria due to mitophagy may be the cause of these metabolic abnormalities [84]. When investigating the mitochondrial metabolism of rat myocardial blast cells (H9c2 cells) that were treated with mouse cachexia model ascites, both oxidative phosphorylation and glycolysis were suppressed, and a quiescent state was induced (Fig. 25.7). The underlying causes of these disorders were increased myocardial TNF-α and HMGB1 protein production and activation of the downstream signaling molecule NF-κB. TNFα is thought to suppress the expression of manganese superoxide dismutase (Mn-SOD) and catalase in cardiomyocytes, reduce glutathione peroxidase, increase intracellular reactive oxygen species and lipid peroxides, and cause cardiomyocyte damage associated therewith. NF-kB activated by TNFα and HMGB1 has been found to suppress apoptosis and increase oxidative stress [85].

It is considered that such intracellular signal enhancement leads to an increase in mitochondrial damage and oxidative stress, which in turn facilitates damage to cardiomyocytes. In addition, myocardial damage in the mouse cachexia model was ameliorated by the combined use of LAA and glucose, similar to skeletal muscle damage [52]. The phenotypes of skeletal muscle and myocardium in cachexia have complex differences, such as cell metabolism. However, mitochondrial disorders and oxidative stress are deeply involved in both skeletal muscle and myocardial disorders. Thus, cancer cachexia causes both skeletal and myocardial atrophies at the same time. It has been suggested that treatment for cancerous skeletal muscle atrophy may also improve cancerous myocardial damage [52], and thus it deemed necessary to be attentive of potential myocardial damage in exercise interventions.

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