Doctoral Thesis

Quality of Life during the Early Period after Diagnosis and Days Spent at Home in the Last Month of Life in Elderly Patients with Advanced Non-Small-Cell Lung Cancer

Mikako Notsu
Oita University of Nursing and Health Sciences

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Abstract

Background

The number of elderly people living with advanced non-small-cell lung cancer (NSCLC) is increasing worldwide, owing to the aging population and advances in cancer treatment. Their treatment goals are defined to maximize survival time, maintain quality of life (QOL), and spend end-of-life as they wish. Many patients prefer to spend their end-of life at home. Providing support for maintaining the QOL and increasing the days spent at home (DASH) near the end-of-life is an important role for nurses but their QOL and DASH was not fully investigated.

Objectives

Study 1 aimed to estimate the QOL during the early period after cancer diagnosis and identify early predictors of its deterioration in elderly patients with advanced NSCLC. Study 2 aimed to estimate the individual DASH near the end-of-life and identify its early predictors among elderly patients with advanced NSCLC.

Methods

In Study 1, the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) was assessed at baseline at the cancer diagnosis and 12 ± 4 weeks from baseline. In Study 2, DASH was defined as 30 days minus the number of days spent in health care facilities in the last 30 days of life.

Results

In Study 1, 20 to 40% of 21 elderly patients with advanced NSCLC had a clinically relevant deterioration of QOL scores from baseline to 12 ± 4 weeks from baseline. The mean of daily steps and incremental shuttle walking distance at baseline can be predictors of clinically relevant deterioration of QOL scores. In Study 2, the median DASH of 44 elderly patients with advanced NSCLC was 8 days (range 0-30 days). The risk factors for reduced DASH were women gender, reduced muscle mass index, and poor physical function at the time of diagnosis for advanced NSCLC.

Conclusion

Our research suggests that elderly patients with advanced NSCLC tend to

have a lower QOL during early period after cancer diagnosis and fewer DASH near the end-of-life. Elderly people ought to improve their physical function and increase their muscle mass before cancer diagnosis. Additionally, after advanced NSCLC diagnosis, early intervention should be provided to elderly patients to improve muscle mass and physical function to maintain QOL and prolong DASH. An example of such an early intervention is the Nutrition and Exercise Treatment for Advanced Cancer (NEXTAC) program. Future researches are warranted on QOL and DASH in elderly patients with advanced NSCLC.

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Chapter 1
Research background and objectives

1. Lung cancer

1.1. *Epidemiology of lung cancer*

In 20 large areas of the world, 18.1 million patients were newly diagnosed as having cancer in 2018 (Ferlay, Colombet et al. 2019). Lung cancer was the most common cancer in the world, both in term of new cases (2.0 million cases, 12% of total) and deaths (1.7 million deaths, 18% of total) because of the high case fatality.

In Japan, approximately 980 thousand new cancer cases occurred in 2017, of which 120 thousand (12.7%) were lung cancer cases (Cancer Information Service, National Cancer Center, Japan (Ministry of Health, Labour and Welfare, National Cancer Registry)). From 2009 to 2011, the 5-year relative survival rate in lung cancer was 29.5% for men and 46.9% for women (Center for Cancer Control and Information Services, National Cancer Center 2020). Lung cancer is more difficult to treat than other cancers.

1.2. *Epidemiology of lung cancer in elderly patients*

In the United States, approximately three-quarters of lung cancer survivors were aged 65 years or older as of January 1, 2019 (Miller, Nogueira et al. 2019).

In Japan, 67% of lung cancer morbidity cases were attributed to elderly individuals aged ≥70 years in 2017 (Cancer Information Service, National Cancer Center, Japan (Ministry of Health, Labour and Welfare, National Cancer Registry)). Lung cancer is mostly a disease of the elderly (Kanesvaran, Roy Chowdhury et al. 2016).

The 1-year relative survival for lung cancer increased from 34% for patients diagnosed during 1975 through 1977 to 47% for those diagnosed during 2011 through 2014 (Miller, Nogueira et al. 2019). With the prolonged survival and aging due to the advances in cancer treatment, the number of elderly patients living with lung cancer are expected to increase markedly.

1.3. *Characteristics of patients with non-small-cell lung cancer*

Lung cancer is classified as small cell (13% of cases) or non-small-cell lung cancer (83% of cases) (Miller, Nogueira et al. 2019).

The goal of therapy with advanced non-small-cell lung cancer is to improve quality of life and prolong survival (DeVita, T. et al. 2019). A large number of patients with lung cancer will develop symptoms related to their disease. More common, symptoms such as pain, dyspnea, cough, anorexia, or fatigue can significantly impact quality of life and may preclude cancer-directed therapy.

2. Deterioration of muscle mass and physical function in patients with lung cancer

2.1. *Deterioration of physical function in patients with lung cancer*

Patients with lung cancer have impaired physical function as compared with healthy people and patients with other cancer types. Hummler et al. showed that most patients with lung cancer had ≥20% reduced muscle strength as compared with the healthy reference data (Hummler, Thomas et al. 2014). Lower values were also observed for the 6-minute walk distance when compared with values for the healthy reference population. Patients with lung cancer have the greatest mean decrease in physical function from baseline to follow-up among patients with cancer (Leach, Bellizzi et al. 2016). Patients with lung cancer had the greatest decline in activities of daily living before and after diagnosis among patients with cancer. Granger et al. reported that patients with non-small-cell lung cancer (mean age, 68.5 ± 9.3 years) had significantly fewer steps per day (2,363 steps/day) and spent less time outdoors than healthy individuals of the same age (Granger, Denehy et al. 2014).

2.2. *Deterioration of muscle mass and physical function from diagnosis in elderly patients with advanced non-small-cell lung cancer*

Elderly patients with advanced non-small-cell lung cancer have reduced muscle mass and physical function from the time of diagnosis. Cancer cachexia is one of the causes of loss of physical function and muscle mass. Cancer cachexia is characterized by a multifactorial syndrome defined as an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that leads to progressive functional impairment. It cannot be fully reversed by conventional nutritional support (Fearon, Strasser et al. 2011). Skeletal muscle depletion accompanied by physical function decline starts in the early phase of chemotherapy in elderly patients with advanced non-small-cell lung cancer (Naito, Okayama et al. 2017).

Elderly patients with advanced non-small-cell lung cancer are a vulnerable population with reduced muscle mass and physical function from the time of diagnosis. Declines in muscle mass and physical function may have negative impacts on the quality of life and end-of-life of elderly patients with advanced non-small-cell lung cancer.

3. *Outcomes in cancer*

Conventionally, the response rate, progression-free and overall survival rates, and so on are used to evaluate the efficacy of cancer treatment. Groff et al. reported that from the results of their survey about preference for dealing with a terminal illness, most people would not want to be receiving ventilator support to gain an extra week of life and are not opposed to drugs that could improve symptoms but potentially shorten life (Groff, Colla et al. 2016). Conventional outcomes are insufficient for evaluating palliative treatments and nursing care for such terminally ill patients. Recently, patient-centered and patient-reported outcomes have received much attention for the evaluation of cancer treatment and nursing care.

Patient-reported outcome is defined as any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else, according to the Food and Drug Administration (FDA) in 2009 (U.S. Department of Health and Human Services Food and Drug Administration 2009). The quality of life and patient-reported outcome version of the common terminology criteria for adverse events developed by the National Cancer Institute (National Cancer Institute) are examples of patient-reported outcome. Quality of life has been used for at least 70 years, but it is for not only patients but also healthy people, so the notion became unclear (Shimozuma 2015). The expression “patient-reported outcome” has been used since around 2005. This expression emphasizes that the evaluation is on the patients’ condition by the patients themselves and not applicable to healthy people.

Patient-centered outcome is meaningful and important to patients and caregivers (Frank, Basch et al. 2014). Days spent at home during the end-of-life is an example of patient-centered outcome. In 2010, The Patient-Centered Outcomes Research Institute was established in the

United States to fund patient-centered outcomes research.

4. *Quality of life*

The World Health Organization defines “quality of life” as individuals’ perception of their positions in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns (The World Health Organization 1997). In oncology, support for such quality of life investigations has been expressed by Japan (Ministry of Health, Labour and Welfare 2014), the United States (Moinpour, Feigl et al. 1989, U.S. Department of Health and Human Services Food and Drug Administration 2009), and Europe (European Medicines Agency 2016). Furthermore, the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) developed in Europe and the Functional Assessment of Cancer Treatment-General (FACT-G) developed in the United States are commonly used as quality of life measurements (Shimozuma 2015).

The history of the notion of quality of life is referenced in Shimozuma (2004), Doi (2004), and Fuji (2015). They noted that a clear definition of quality of life had not been established and that quality of life is a subjective assessment of various patient characteristics in different domains. These domains include, for example, global, physical, psychological, and social aspects. In the present study, we defined and interpreted quality of life based on these studies. Based on the aforementioned definition of quality of life, the EORTC QLQ-C30 was developed to evaluate the quality of life of cancer patients across multiple domains, regardless of the cancer type or stage, and has been widely used as a standard tool. The EORTC QLQ-C30 includes 5 functioning domains (physical, role, emotional, cognitive, and social), and an overall or global quality of life domain (global health status/QoL) based on the patients’ self-evaluation. It is important to evaluate quality of life across multidimensional domains from a variety of perspectives. In addition to EORTC QLQ-C30, some other tools to measure the quality of life have been developed on the basis of the aforementioned definition; FACT-G for cancer patients, EORTC QLQ-LC13 for patients with lung cancer, EORTC QLQ-BR23 for patients with breast cancer, and EQ-5D for the general population. As the present study focused on patients with lung cancer, the quality of life assessment tools that were suitable for this population included the FACT-G, EORTC QLQ-C30, and EORTC

QLQ-LC13. However, we did not choose EORTC QLQ-LC13 due to its low comparability with other cancer types. The other two tools are almost similar, with common domains, and can be used to evaluate quality of life across multidimensional domains from a variety of perspectives (Ikegami et al. 2002). Finally, we selected EORTC QLQ-C30, considering its comparability with previous studies.

We reviewed the literature for studies on quality of life, both nationally and internationally, that were published between 2010 and 2020 (Figure 1, Table 1). Considering the advances in cancer treatment, we included studies published from 2010. We searched the PubMed and CINAHL using the following keywords in November 2020: “advanced” AND “non-small-cell lung cancer” AND “elderly” AND “quality of life.” The prespecified inclusion criteria were articles in the English language; studies involving adults aged ≥65 years. Studies that did not investigate quality of life were excluded. Our search retrieved 40 publications in PubMed and none in CINAHL. Twenty-five research studies were on clinical trials in which quality of life was assessed for evaluation of the efficacy and safety of treatment. Except for clinical trials, 5 research studies remained. The Japanese literature on quality of life were identified by searching the Japan Medical Abstracts Society in November 2020 by using the following keywords: in Japanese “Shinkousei” AND “Hishousaibouhaigan” AND “Koureisha” AND “Seikatsunoshitsu”, which means “advanced” AND “non-small-cell lung cancer” AND “elderly” AND “quality of life” in English. Our search retrieved 4 publications in the Japan Medical Abstracts Society. Two research studies were duplicates, and 1 research was on clinical trial. Finally, one research remained. The literature review revealed that nursing research studies were few on quality of life in elderly patients with advanced non-small-cell lung cancer. We outline the 6 references below. The paper by Miura et al. is about a research protocol. The aim of the research is to investigate the efficacy of multimodal intervention for elderly patients with advanced non-small-cell lung and pancreatic cancers, and quality of life is one of the outcomes used in the research (Miura, Naito et al. 2019). Fiteni et al. reported that patients with higher quality of life scores at baseline had longer overall survival in a study of patients aged ≥70 years with stage III/IV non-small-cell lung cancer who were receiving chemotherapy (Fiteni, Vernerey et al. 2016). Schuette et al. reported that patients with advanced non-small-cell lung cancer, of whom 36% were elderly patients (≥70 years) had maintained or improved self-rated health-related quality of life in the second-line treatment with pemetrexed (Schuette, Tesch et al. 2012). Ngeow et al. reported that patients with non-small-cell lung cancer had improved quality of life over the treatment period, and the presence of comorbidities did not negatively impact the quality of life scores (Ngeow, Leong et al. 2010). Di Maio et al. reported a discrepancy between physician and patient toxicity assessments, in which the EORTC QLQ-C30 (Aaronson, Ahmedzai et al. 1993) was used for patient toxicity assessment (Di Maio, Gallo et al. 2015). Tanaka et al. reported that nutrition interventions might be beneficial to the quality of life of patients with advanced non-small-cell lung cancer (Tanaka, Takeda et al. 2018).

The above literature review revealed that many previous studies used quality of life to assess the efficacy and safety of treatment, and no real-world data were available on the quality of life or the predictors of its deterioration in elderly patients with advanced non-small-cell lung cancer. Some previous studies investigated quality of life to identify predictors of its deterioration in patients with stage III/IV lung cancer. Patients with Stage III cancer tend to aim for curative treatment, although they may sacrifice their quality of life to some extent. On the other hand, treatment goals in Stage IV cancer are broadly defined to maximize the survival time and maintain an acceptable quality of life. The goals on quality of life differ depending on cancer stage, so the data on quality of life should preferably be presented separately.

We did not find any studies in terms of nursing in the aforementioned literature search. We searched for nursing studies with any aged patients with advanced non-small-cell lung cancer. To find studies published between 2010 and 2021, we searched PubMed and CINAHL using the following keywords in February 2021: “advanced” AND “lung cancer” AND “nursing” AND “QOL.” Our search retrieved 13 publications in PubMed and none in CINAHL. Of these, two studies were on early-stage cancer, one was a research protocol and one, a study on caregivers. Hence, we excluded them from the analysis. To find studies published between 2010 and 2021, we searched the Japan Medical Abstracts Society using the following keywords in February 2021: in Japanese “Shinkouhaigan” AND “kango” AND “QOL”, which stand for “advanced lung cancer” AND “nursing” AND “quality of life.” No publication was retrieved. Finally, 9 studies were selected, as outlined below. Table 2 describes the tumor histology, the age and stage of patients in each study. Choi and Ryu reported that age and symptoms were associated with the quality of life

(Choi and Ryu 2018). Additionally, stigma was associated with the quality of life (Johnson, Schreier et al. 2019). An intervention that provides self-care education and monitoring of adverse events depending on the patient's condition, in addition to usual nursing care, improved the quality of life (Zhu, Chen et al. 2021). Dai et al. and Liao et al. reported quality of life for patients with stage III/IV lung cancer and the early predictors of the change of quality of life (Liao, Shun et al. 2014, Dai., Yang. et al. 2017). Mouri et al. reported that a physical activity intervention of the multimodal nutrition and exercise treatment improved the quality of life (Mouri, Naito et al. 2018). Roulston et al. discussed the quality of life of 5 patients with stage III/IV lung cancer in a nurse-led multidisciplinary outpatient clinic using integrative care (Roulston, Bickerstaff et al. 2012). Muscle mass was associated with the quality of life (Bye, Sjoblom et al. 2017). Hamada et al. reported that symptom clusters affected the quality of life with varying degrees of influence (Hamada, Komatsu et al. 2016). Summarizing the 9 studies, a change in quality of life and the early predictors of this change were investigated by Dai et al. and Liao et al., but these studies did not distinguish between patients with stage III and stage IV cancer. As the treatment strategy for stage III patients is different from that for stage IV patients, further studies in stage IV patients are warranted.

5. Days spent at home near the end-of-life

Groff et al. reported that health care organizations need to measure outcomes that matter to patients and proposed days spent at home near the end of life as such an outcome (Groff, Colla et al. 2016, Sayer 2016). They stated that most people indicated that they would prefer to be at home in their final days (LJ. Higginson, G.J.A.SEN-GUPTA et al. 2000). Days spent at home near the end of life reflects the achievement of this preference. Groff and Colla et al. 2016 stated that “Being home at the end of one’s life will never be a universal goal, but our experience and academic research suggest that, all else being equal, patients would rather be at home than in health care facilities.” (Adam C. Groff, Carrie H. Colla et al. 2016). However, whether the above also applies to people in developing countries remains unclear.

We reviewed the literature for studies on days spent at home, both nationally and internationally, that were published between 2010 and 2020 (Figure 2, Table 3). We searched the PubMed and CINAHL by using the following keywords in November 2020: first “days spent at home” AND “end of life”, and second, “times spent at home” AND “end of life.” The prespecified inclusion criteria were articles in the English language and studies involving adults aged ≥19 years. Studies that did not investigate the days spent at home were excluded. Our search retrieved 48 publications in PubMed and none in CINAHL. Except for studies that satisfied the exclusion criteria, 7 studies remained. The Japanese studies on days spent at home were identified by searching the Japan Medical Abstracts Society in November 2020 using the following keywords: in Japanese “Zaitakunissu” AND “Shu-matsuki”, which means “days spent at home” AND “end of life” in English. Our search retrieved 3 publications in the Japan Medical Abstracts Society. One article was a conference paper. We outline the 9 references below. Otsuka reported that days spent at home during the last month of life of patients with advanced cancer were significantly longer for men, patients with a history of using outpatient palliative care services, and users of in-home nursing visits (Otsuka 2017). Gill et al. reported that the number of days spent at home in the last 6 months of life of community-dwelling persons, aged ≥70 years was significantly lower for persons dying from organ failure (Gill, Gahbauer et al. 2019). Andersen et al. reported that the days spent at home in the last 6 months of life of patients who died of cancer were significantly longer for men and for users of palliative care before the last 6 months of life (Andersen, Croxford et al. 2019). Patients with hematological malignancies who received palliative care services prior to their last 6 months of life spent more time at home in the last 6 months of life than those who did not receive such services (Cheung, Croxford et al. 2020). Bjornely et al. reported that in the last 6 months of life, the closer the patients got to death, the lower was the proportion of patients who spent any days at home, and compared with the patients who were never married, the married patients spent more days at home (Bjornelv, Edwin et al. 2020). Wang et al. reported that days spent at home in the last 6 months of life of patients aged ≥65 years were longer for the users of earlier comprehensive palliative care (Wang, Liu et al. 2019). Schuler et al. reported that in the United States, 66% of the study population with small-cell lung cancer spent most of the time between diagnosis and death at home (Schuler, Joyce et al. 2017). Yamada et al. reported days spent at home in patients with terminal cancer with home parenteral nutrition (Yamada, Hara et al. 2015). Nagata et al. reported days spent at home in patients with terminal cancer with home hospice care (Nagata 2010). In summary, men and users of palliative care services tend to spend more days at home near the end of life. To the best of our knowledge, however, no studies have investigated days spent at home near the end of life in elderly patients with advanced non-small-cell lung cancer. Further research on days spent at home near the end-of-life is warranted for better end-of-life nursing care.

We did not find any studies on nursing in the literature search described above. We searched for nursing studies about days spent at home near the end-of-life. To find studies published between 2010 and 2021, we searched PubMed and CINAHL using the following keywords in February 2021: "days spent at home" AND "end of life" AND "nursing." No publication was retrieved. We revised "days spent at home" to “times spent at home” and searched, but no publication was retrieved. To find studies published between 2010 and 2021, we searched the Japan Medical Abstracts Society using the following keywords in February 2021: in Japanese “Zaitakunissu” AND “Shumatsuki” AND “Kango”, which mean “days spent at home” AND “end of life” AND “nursing.” No publication was retrieved.

Regarding the definition of days spent at home, the meaning of "home" is controversial. For example, in Japan, the number of people living alone or in nursing homes is increasing (Ministry of Health 2009, Ministry of Health 2019). However, it remains unclear whether these people prefer spending their end-of-life at their homes or nursing homes. As "home" did not include nursing homes in most previous studies, we followed them and defined that "home" referred only to private residences, and did not include nursing homes.

6. Clinical issues in cancer nursing

Compared with other diseases, the quality of life in cancer may deteriorate due to treatment with adverse events, even in the terminal stage. Patients may need to be hospitalized for treatment with adverse events, reducing their days spent at home near the end-of-life. Patients with early-stage cancer or non-elderly patients tend to aim for curative treatment, although they may sacrifice their quality of life to some extent. The treatment goals in elderly patients with advanced cancer are broadly defined to maximize survival time, maintain an acceptable quality of life, and spend the end-of-life as they wish (DeVita, T. et al. 2019). The progress or metastasis of small-cell lung cancer are faster than those of non-small-cell lung cancer. Treatments and adverse events in small-cell lung cancer are different from those in non-small-cell lung cancer (DeVita, T. et al. 2019), and such differences may affect quality of life and days spent at home near the end-of-life. Therefore, they should be separately investigated. As the number of patients with non-small-cell lung cancer is larger than that of those with small-cell lung cancer, we decided to focus on non-small cell lung cancer in this study, in order to provide results that can help a larger number of patients

Providing support for maintaining the quality of life and increasing the days spent at home near the end-of-life is an important role for nurses. Many researchers believe that quality of life and days spent at home near the end-of-life are important for elderly patients with advanced non-small-cell lung cancer, but these have not been investigated and reported. Clarifying the early predictors for decreased quality of life and decreased days spent at home near the end-of-life will lead to efficient nursing interventions. For example, to prevent quality of life deterioration, nurses in the hospital can monitor patients at high risk of deterioration more frequently compared with those at low risk and provide care to patients at high risk to enhance their self-efficacy (Liao, Shun et al. 2014). To prevent a decrease in the days spent at home near the end-of-life, nurses can inform high-risk patients of their situation, and discuss the end-of-life with patients, doctors, and social workers. The timing of the start of the discussion about the end-of-life is controversial and the discussion should be carefully initiated.

7. Purposes of our research

The aims of our research were (1) to measure the quality of life during the early period after diagnosis and days spent at home near the end-of-life, (2) to identify early predictors of reduced quality of life, and (3) to identify early predictors of days spent at home in elderly patients with advanced non-small-cell lung cancer. In chapter 2, we report on quality of life during the early period after diagnosis and revealed early predictors of reduced quality of life in elderly patients with advanced non-small-cell lung cancer. In chapter 3, we report on days spent at home near the end-of-life and reveal early predictors of days spent at home. In chapter 4, we summarize our research.

We summarize the studies in chapters 2 and 3 (Figure 3). Details are provided in each chapter and none of the patients participated in both studies. Patients in the study reported in chapter 2 consisted of patients with stage IV advanced cancer, and those in the study reported in chapter 3 consisted of patients with stage III locally advanced cancer and stage IV advanced cancer. Although the treatment goals differ for patients with stage III and IV cancer, we speculated that the terminal stage in both groups is unlikely to largely differ. Therefore, we investigated patients with stage III and IV cancer simultaneously in terms of days spent at home near the end-of-life. The enrollment periods, timings of assessments and evaluations, and study periods are shown in Figure 3. The study presented in chapter 2 evaluates muscle mass, physical function, physical activities, and quality of life, and is ongoing at March, 2021. In this thesis, we reported a part of the study, i.e., the results of quality of life assessment during the early period after diagnosis. The study presented in chapter 3 evaluated muscle mass, physical function, and use of medical services, and finished at December, 2018. In this thesis, we reported the result of a post-hoc analysis of the study on days spent at home near the end-of-life.

8. Tables and Figures

Table 1 List of studies on quality of life

No.	Author (year)	Cancer type	Assessment period for quality of life	QOL measurements
1	Miura et al. (2019)	Advanced non-small-cell lung or pancreatic cancers	Baseline from the entry to the initiation of systemic therapy and T4 at 12 ± 2 weeks from randomization	EORTC QLQ-C30
2	Fiteni et al. (2016)	Stage III/IV non-small-cell lung cancer	At randomization, 6 weeks, and 18 weeks	EORTC QLQ-C30
3	Schuette et al. (2012)	Stage III/IV non-small-cell lung cancer	Baseline before the first treatment to a maximum of 9 treatment courses	EQ-5D
4	Ngeow et al. (2010)	Non-small-cell lung cancer	From baseline to the sixth treatment cycle	EORTC QLQ-C30, LC13
5	Maio et al. (2015)	Early breast and advanced non-small-cell lung cancers	Three times at the end of each treatment cycle	EORTC QLQ-C30, LC13, BR23
6	Tanaka et al. (2018)	Stage IIIB/IV or recurrence non-small-cell lung cancer	At baseline and after 90 days of intervention	EQ-5D

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30

LC 13: lung cancer module

BR 23: breast cancer module

EQ-5D: European Quality Of Life Five Dimensions

Table 2 List of studies on quality of life in terms of nursing

No.	Author (year)	Tumour histological type	Age, year	Stage
1	Choi and Ryu. (2016)	Non-small-cell lung cancer, Small-cell lung cancer	Mean 54.0 (SD ±8.7)	StageIV
2	Johnson et al. (2019)	No detailed description	Mean 64.45 (SD ±8.69)	StageIII/IV
3	Zhu et al. (2021)	Non-small-cell lung cancer (92.5%), The others (8.5%)	Age ≥ 65 (69%), <65 (31%),	StageIII/IV
4	Dai et al. (2017)	Non-small-cell lung cancer	Mean 61.9 (SD ±10.63)	StageIII/IV
5	Liao et al. (2014)	Non-small-cell lung cancer (90%)	Mean 60.4 (SD ±10.79)	StageIII/IV
6	Mouri et al. (2018)	Non-small-cell lung cancer (80%), Pancreatic cancer (20%)	Median 75 (range 70 - 84)	StageIII/IVor metastatic
7	Roulston et al. (2016)	Non-small-cell lung cancer	Mean 74	StageIIIB/IV
8	Bye et al. (2017)	Non-small-cell lung cancer	Mean 65.4 (SD ±9.4)	StageIIIB/IV
9	Hamada et al. (2016)	Non-small-cell lung cancer	Mean 64.33 (SD ±11.40)	StageIIIB/IV

Table 3 List of studies on days spent at home

No.	Author (year)	Subjects	Assessment period for days spent at home	Definition of home
1	Otsuka (2017)	Patients with advanced cancer	Last month of life	Home only
2	Gill et al. (2019)	Community-dwelling persons, aged ≥70 years	Last 6 months of life	Home only
3	Andersen et al. (2019)	Patients with cancer	Last 6 months of life	Home only
4	Cheung et al. (2020)	Patients with hematological malignancies	Last 6 months of life	Home only
5	Bjornely et al. (2020)	Patients with colorectal cancer	Last 6 months of life	Home only
6	Wang et al. (2019)	Patients aged ≥65 years	Last 1 and 6 months of life	Home only
7	Schuler et al. (2017)	Patients with small-cell lung cancer	From diagnosis to death	Home only
8	Yamada et al. (2015)	Patients with terminal cancer	No detailed description	No detailed description
9	Nagata et al. (2010)	Patients with terminal cancer	No detailed description	No detailed description

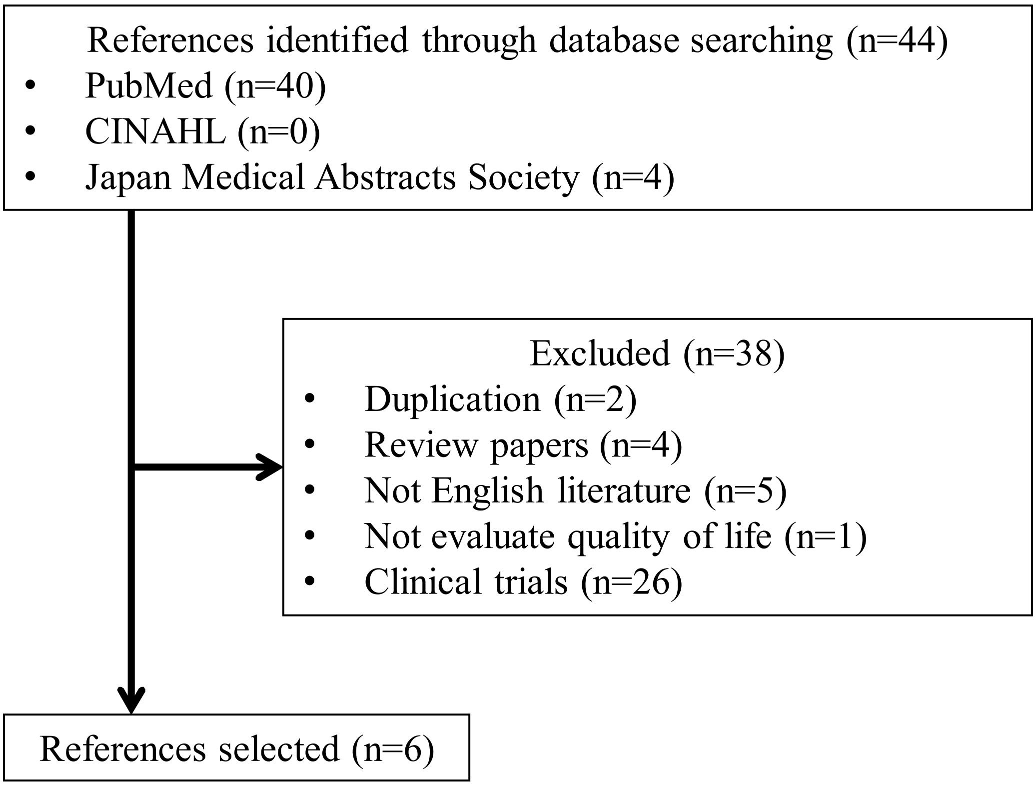

Figure1 Flow diagram of literature review on quality of life

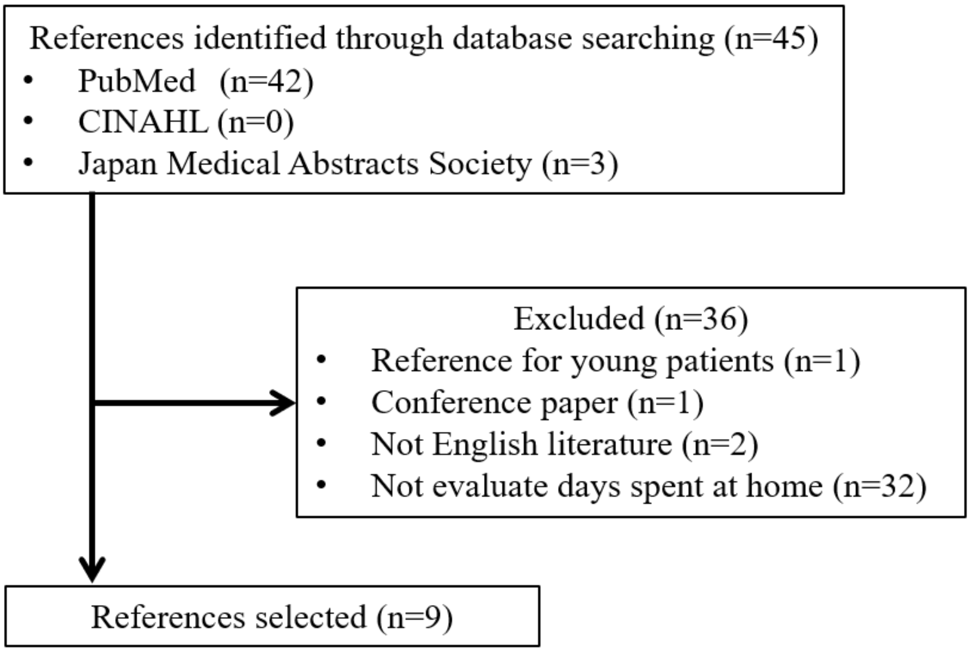

Figure 2 Flow diagram of literature review on days spent at home

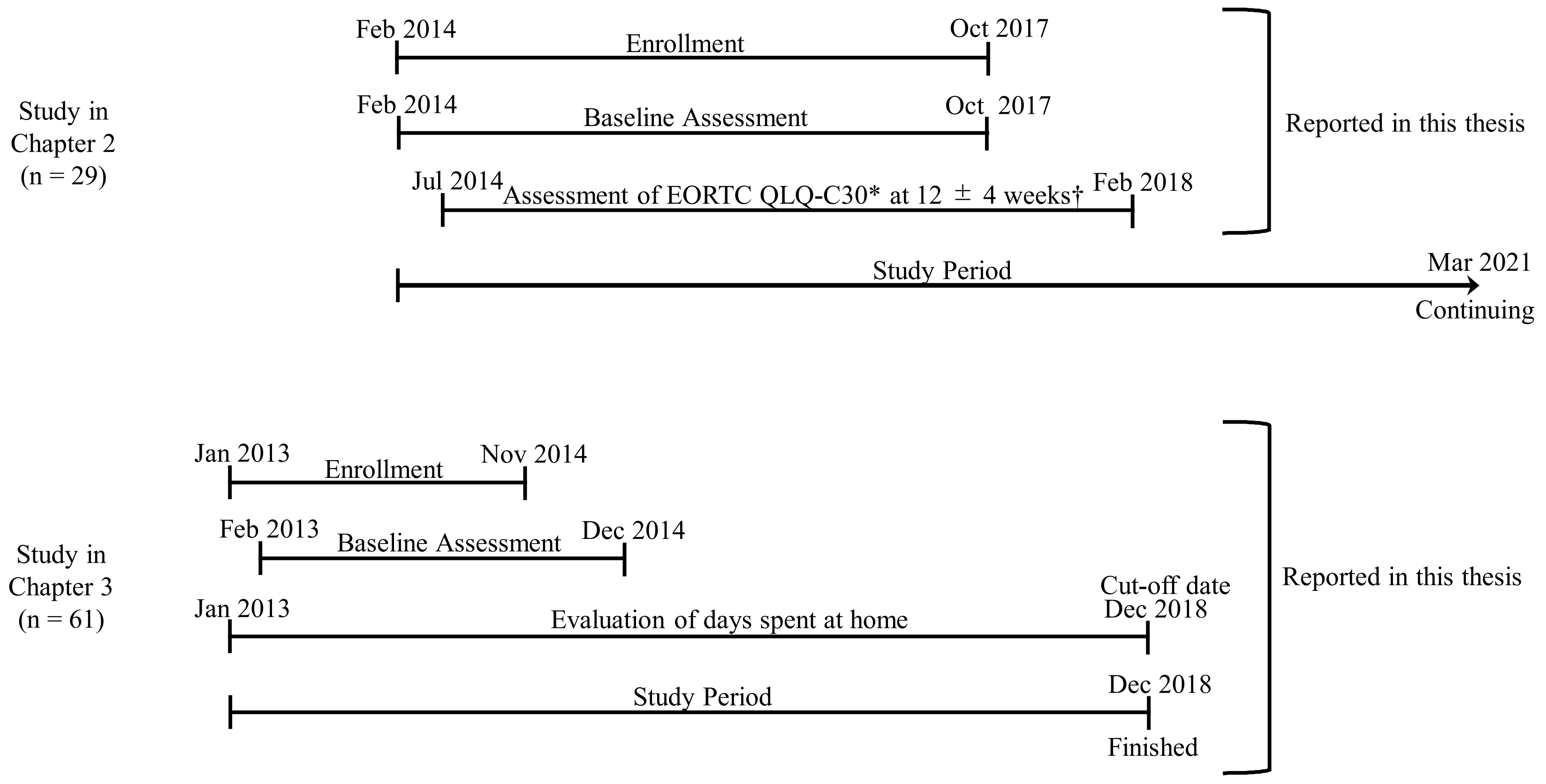

Figure 3 Enrollment period, timing of assessments, and study period of the studies presented in Chapter 2 and 3

*EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30

†12 ± 4 weeks means the period from 8 to 16 weeks from the baseline

9. References

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Chapter 2

Quality of life during the early period after diagnosis in elderly patients with advanced non-small-cell lung cancer

1. Introduction

The number of elderly people living with advanced lung cancer is increasing worldwide, owing to the aging population and advances in cancer treatment (Petrelli, Winer et al. 2009, Miller, Siegel et al. 2016). Therapeutic outcomes such as tumor response, time to progression, and disease-free and overall survival rates have been used to evaluate the efficacy of cancer treatment (Aaronson, Ahmedzai et al. 1993). Growing attention has been paid to the assessment of the impacts of diseases and their treatments on the physical, psychological, and social functioning of patients. Support for such "quality of life" investigations has been expressed internationally (Ministry of Health, Labour and Welfare 2014). The distress associated with symptoms arising from lung cancer has been centered as the most intense, compared with that in other types of cancer (Akin, Can et al. 2010). Maintaining or improving quality of life is an important goal in patients with advanced cancer, for whom the main goal of treatment is palliation rather than cure (Michael and Tannock 1998, Belani, Pereira et al. 2006).

Identifying early predictors for deterioration of quality of life allows for its prevention by early intervention, although only a few are reported. Bade et al. reported that the number of daily steps and quality of life scores positively correlated in patients with locally advanced and advanced lung cancer (Bade, Brooks et al. 2018). Bye et al. reported that low muscle mass negatively affected the quality of life of patients with locally advanced and advanced non-small-cell lung cancer (Bye, Sjoblom et al. 2017). Based on the studies, muscle mass and physical function at diagnosis could be predictors of quality of life deterioration for elderly patients with locally advanced or advanced lung cancer. However, the quality of life goals in locally advanced cancer are different from those in advanced cancer, as mentioned in Chapter 1. Therefore, the predictors of the deterioration of quality of life for elderly patients with advanced non-small-cell lung cancer and those for the patients with locally advanced non-small-cell lung cancer should be investigated separately.

However, information is limited on the quality of life during the early period after diagnosis in elderly patients with advanced non-small-cell lung cancer. Accordingly, this study aimed to estimate the quality of life during the early period after diagnosis and identify its early predictors of deterioration, including muscle mass and physical function, in elderly patients with advanced non-small-cell lung cancer.

2. Methods

2.1. Patient selection

This study on quality of life was a part of a prospective observational study that recruited patients from February 2014 onwards and was conducted at the Shizuoka Cancer Center, Japan. The study was approved by the institutional review board and was registered on the University Hospital Medical Information Network Clinical Trials Registry in Japan (registration No. UMIN000012845). The eligibility criteria were as follows: (1) histologically and/or cytologically proven metastatic or postoperative recurrent non-small-cell lung cancer; (2) patients aged ≥70 years, with planned first-line systemic chemotherapy; (3) no previous systemic chemotherapy or thoracic radiotherapy (adjuvant chemotherapy was not counted as prior chemotherapy); (4) Eastern Cooperative Oncology Group performance status (PS) of 0–2 (Supplementary material 1); (5) ability to ambulate, read, and respond to questions without assistance; and (6) expected survival of >12 weeks. Patients were excluded if they had severe psychiatric disorder, active infectious disease, unstable cardiac disease, or untreated symptomatic brain or bone metastases that prevented safety assessment. The attending physicians screened patients with newly diagnosed advanced non-small-cell lung cancer to ascertain their eligibility. The staff of the research office double-checked the patients' eligibility and explained the clinical study to them. Finally, patients participated in the study after providing written informed consent.

2.2. Data collection

Body mass index (kg/m^2), incremental shuttle walking distance (m), hand-grip strength (kg), number of daily steps (steps/day), muscle mass (kg), age, PS, and treatment were assessed at baseline. The baseline period was between the time of diagnosis to the initiation of the first chemotherapy cycle. At baseline, patients may feel nervous about the future due to their cancer diagnosis and may fear chemotherapy, but they do not suffer from chemotherapy-related adverse events. Patients who could not start chemotherapy received baseline assessment during diagnosis to the scheduled initiation of the first chemotherapy cycle. The attending physicians and physiotherapists assessed the body mass index, incremental shuttle walking distance, hand-grip strength, and muscle mass of the patients. Quality of life scores were assessed at two points, at baseline and 12 ± 4 weeks from baseline. The notation 12 ± 4 weeks means the period from 8 weeks to 16 weeks. For patients who received cytotoxic regimens, 12 ± 4 weeks usually corresponded to the period from the end of the first chemotherapy cycle to the start of the second cycle. At 12 ± 4 weeks, patients treated with chemotherapy may suffer from chemotherapy-related adverse events, and feel nervous or relieved about the future due to their response to the first chemotherapy cycle.

2.3. Assessment of physical function

Physiotherapists assessed the incremental shuttle walking distance and hand-grip strength on both sides. An incremental shuttle walking test was conducted on the basis of the recent guidelines (Singh, Puhan et al. 2014) and the original protocol presented by Singh et al (Singh, Morgan et al. 1992). The physiotherapists set a 10-m course in the hospital corridor. The walking speed was dictated by a timed signal played on a compact disc recorder provided by the manufacturer (Japanese version, the Graduate School of Biomedical Sciences, Nagasaki University, Japan, 2000). Assessments for all patients were conducted once under standardized conditions while ensuring that the patients did not exceed their exercise limit. An instructor accompanied the patients along the course during the assessments but did not interfere with the process by providing encouragement. The assessment was concluded (1) by the patient when they were exhausted and unable to maintain the required walking speed, (2) by the instructor when the patient could not complete a shuttle within the allotted time (i.e., walk for >0.5 m away from the cone within the set time), or (3) when the patient presented a heart rate ≥ 85% of the predicted maximal heart rate derived using the formula [210 − (0.65 × age)]. Shuttle walking distance denotes the maximum walking distance. Hand-grip strength was measured using a grip strength dynamometer (GRIP-D, Takei Scientific Instruments Co., LTD, Niigata, Japan). The patients stood in an upright position and held the dynamometer in one hand in accordance with the adjusted grip range to ensure that the second joint of the forefinger was bent at 90°. The instrument was then held down beside the patient, with the arm completely extended and not touching the body. The patients were then asked to exert complete force with their hand for approximately 3 seconds to yield the maximum kilogram-force. Here, the instructor provided verbal encouragement to elicit a maximum response from the patients. A trial was performed for each hand, and the result from the maximum grip strength was used for the analysis.

2.4. Assessment of physical activity

Physical activity was continuously measured using an electronic pedometer/accelerometer (Kenz Lifecorder-GS, Suzuken Co., Ltd., Nagoya, Japan). After providing informed consent, the patients wore the device on the side of their waists. The patients were instructed to wear the device for as long as possible from the time they change clothes for daily activity in the morning until they change into nightclothes when sleeping. The device recorded the number of daily steps and intensity of physical activity at every 4 s throughout the day. Regular visits to the outpatient department of each institution allowed data collection. The collected data included the number of daily steps and time for which the device was worn. Days on which the device was worn for less than 5 h were excluded from the analysis. The mean number of daily steps for the 7 days prior to the baseline was set as parameters for the physical activity at the baseline. Patients were not offered any incentives for increasing physical activity or walking during the study period.

2.5. Anthropometric and muscle mass measurements

The body weight (kg) was measured to the nearest 0.1 kg, and the body mass index was subsequently calculated. The muscle mass (kg) and body weight were measured by bioelectrical impedance analysis using the Body Composition Analyzer BC-118 (Tanita Corp., Tokyo, Japan). The recommended conditions for bioelectrical impedance analysis measurement were explained to the subjects: (1) fasting for 4 h, and no consumption of alcohol for 8 h before measurement; (2) bladder to be voided before measurement; and (3) no exercise to be performed within 8 h prior to the measurement (Kyle, Bosaeus et al. 2004). Patients stood on the footplate electrodes and grasped the hand-grip electrodes with both hands. The electrodes emitted current through both feet and hands distally, and the current was detected at the heels of both feet and palms of both hands. This system applies electricity at frequencies of 5, 50, 250, and

500 kHz through the body. The whole-body impedance was measured using an ipsilateral foot-hand electrical pathway. Appendicular skeletal muscle mass (kg) was derived as the sum of the muscle mass of the arms and legs. The appendicular skeletal muscle mass was converted to an appendicular skeletal muscle mass index by dividing it by the square of height in meters (kg/m^2) (Tanimoto, Watanabe et al. 2012).

2.6. Definition of sarcopenia and cancer cachexia

Sarcopenia was defined as reduced grip strength (men: < 28 kg, women: < 18 kg) and reduced limb skeletal muscle mass (men: < 7.0 kg/m^2, women: < 5.7 kg/m^2) calculated from bioimpedance, according to the consensus criteria (Chen, Woo et al. 2020). Cancer cachexia was defined as the unintentional weight loss > 5% in the preceding 6 months, weight loss > 2% in patients with a body mass index < 20.0 kg/m^2, or the presence of skeletal muscle depletion according to the consensus criteria. The weight of the patients 6 months before enrolling in the study was provided the by patient and their family members through interviews before the study.

2.7. Quality of life measurement

The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) was used to evaluate quality of life (Aaronson, Ahmedzai et al. 1993). The reason why we selected EORTC QLQ-C30 among the many quality of life assessment tools is described in Chapter 1. The EORTC QLQ-C30 is a 30-item self-report questionnaire that assesses 5 functioning domains (physical, role, emotional, cognitive, and social), an overall or global quality of life domain (global health status/QoL), 3 symptom domains (pain, fatigue, and nausea/vomiting), and 6 single items (dyspnea, insomnia, anorexia, diarrhea, constipation, and financial impact). The scores range from 0 to 100 after linear transformation of the raw scores (Supplementary material 2). A high score for a functional scale represents a high level of functioning (healthier), whereas a high score for a symptom scale represents a high level of symptoms/problems. The reliability and validity of the Japanese version of EORTC QLQ-C30 has been confirmed by Kobayashi, Takeda et al. (1998).

2.8. Statistical analyses

The full analysis set consisted of patients with quality of life assessments evaluable at baseline. The change analysis set consisted of patients with quality of life assessments evaluable at baseline and 12 ± 4 weeks. Patient baseline characteristics were presented as medians, ranges, counts, and percentages for the full and change analysis sets. The quality of life scores at baseline were presented as median, range, mean, and standard deviation for the full analysis set, and were compared with EORTC QLQ-C30 reference value (EORTC Quality of Life Group 2008). The reference values were on patients with cancer at pretreatment in 49 countries, including Japan. The quality of life scores at baseline and 12 ± 4 weeks and the changes of the scores were presented as median, range, mean, and standard deviation for the change analysis set. The change of the scores was calculated as the quality of life score at 12 ± 4 weeks minus the quality of life score at baseline. The Wilcoxon signed-rank test was used to examine whether the median of change in quality of life score was zero. A clinically relevant deterioration of quality of life score was defined as a change ≤ -10 points (Osoba, Bezjak et al. 2005, Maringwa, Quinten et al. 2011). The proportion of patients with such deterioration was calculated for each quality of life score in the change analysis set. To identify the predictors of clinically relevant deterioration of quality of life, we compared the patient characteristics at baseline between the two groups of patients, one consisting of patients with deterioration, the other consisting of patients without deterioration. For the comparison of the two groups, the Wilcoxon rank-sum test was used to analyze continuous variable, and the Fisher exact test was used to analyze qualitative variables. The odds ratio and 95% confidence interval were estimated for the qualitative variables. A two-sided p-value < 0.05 was considered statistically significant. The R statistical package version 3.6.3 (R Core Team, February 2020, www.r-project.org) was used for the statistical analysis.

3. Results

3.1. Patient characteristics at baseline

In the study, 29 patients were enrolled from February 27, 2014, to October 13, 2017 (Figure 1). One patient was excluded from the analysis because the patient did not continue the study. Twenty-eight patients were assessed for quality of life at baseline. Of the 28 patients, 7 patients were not assessed for quality of life at 12 ± 4 weeks after baseline because (1) the patient died by 12 ± 4 weeks from baseline (n = 1), (2) the patients was transferred to other hospitals (n = 3), (3) the patient was not followed up owing to safety reason (n = 2), and (4) the patient had missing data on the quality of life assessment at 12 ± 4 weeks from baseline (n = 1). Finally, 28 patients were included in the full analysis set, and 21 patients were included in the change analysis set. No large differences in patient characteristics were found between the full and change analysis sets. The median age at diagnosis was 75 years (range, 70–83 years) for the full analysis set (Table 1). Seventeen patients (61%) were men, and 11 (39%) were women. Most of the patients had a PS of 0−1 (96%). Fifteen patients (54%) received cytotoxic regimens, while 7 (25%) received targeted regimens. Six patients (21%) received best supportive care. The cytotoxic regimens included docetaxel (n = 6), cisplatin + pemetrexed (n = 4), vinorelbine (n = 2), cisplatin + etoposide (n = 1), and carboplatin + paclitaxel (n = 2). The targeted regimen included gefitinib (n = 4) and erlotinib (n = 3). The median body mass index was 21.8 kg/m^2 (range, 16.9–28.1). The median appendicular skeletal muscle mass index was 6.4 kg/m^2 (range, 5.0–8.3). The median of mean of daily steps was 3,542 steps/day (range, 882–19957). The median incremental shuttle walking distance was 340 m (range, 120–550). Sarcopenia was diagnosed in 3 patients (11%). Cancer cachexia was diagnosed in ≥50% of the patients at baseline.

3.2. Quality of life score and change

In this study, the patients in full analysis set had good quality of life scores at baseline compared with the reference (EORTC QLQ-C30 Reference Values) (Table 2). The patients in change analysis set had similar quality of life scores compared with patients in full analysis set (Figure 2). In change analysis set, approximately half of the patients had improvement in global health status/QoL score, whereas the other half did not, and 8 patients (38%) had clinically relevant deterioration (Table 3,

Figure 3). Of the patients, 20% to 30% had clinically relevant deteriorations of physical, role, cognitive, and social functioning (n = 6, 29%; n = 4, 24%; n = 4, 19%; and n = 5, 24%, respectively). The physical functioning score significantly deteriorated (p = 0.001, median of change = −6). Only 1 patient had a clinically relevant deterioration of emotional functioning score, and the score significantly increased (p = 0.014, median of change = 8). Only 1 patient had a clinically relevant deterioration of insomnia score, and the score significantly increased (p = 0.027, median of change = 0, mean of change = −16).

3.3. Predictor of deterioration of quality of life

The patient with a clinically relevant deterioration of physical function had a lower incremental shuttle walking distance at baseline than the patient without a clinically relevant deterioration (p = 0.002; Table 5). In addition, the patients who did not receive chemotherapy had a higher risk of clinically relevant deterioration of physical function than those who received cytotoxic regimens (odds ratio = 0, p = 0.018). The patient with a clinically relevant deterioration of role function had fewer daily steps at baseline than the patient without a clinically relevant deterioration (p = 0.007, Table 6). No factors were significantly associated with a clinically relevant deterioration of global health status/QoL, emotional, cognitive, or social functioning (Tables 4, 7–9).

4. Discussion

To the best of our knowledge, this is the first study to report comprehensively on the quality of life of elderly patient with advanced non-small-cell lung cancer. This study offered four major findings. First, approximately 40% of patients had a clinically relevant deterioration of global health status/QoL. Second, the physical functioning score significantly deteriorated. Third, only 5% of the patients had a clinically relevant deterioration of emotional functioning score, and the score significantly increased. Finally, incremental shuttle walking distance and number of daily steps can be predictors of deterioration of physical and role functioning, respectively.

Dai et al. reported that patients with stage IIIB/IV non-small-cell lung cancer (average age, 61.90 years; standard deviation, 10.65) had no significant change in global health status/QoL score from prechemotherapy to the first chemotherapy cycle (Dai, Yang et al. 2017). Patients in this study were younger than our patients. Additionally, our study results indicated that patients did not show any statistically significant change in global health status/QoL score from baseline to 12 weeks, which was consistent with the results of the study by Dai et al. However, approximately 40% of patients had a clinically relevant deterioration of global health status/QoL. Maringwa et al. reported that a 4-point decrease in global health status/QoL score corresponded to a decrease of ≥1 point in PS and 5% to 20% weight loss in lung cancer patients (Maringwa, Quinten et al. 2011). Braum et al. reported that a 10-point decrease in global health status/QoL score corresponded to a 9% decrease in survival (Braun, Gupta et al. 2011). Therefore, approximately 40% of patients showed a severe deterioration in global health status/QoL, and some interventions may be needed for such patients.

In our study population there was a statistically significant decrease in physical functioning score from baseline to 12 weeks. Conversely, Dai et al. reported that patients with stage IIIB/IV non-small-cell lung cancer (average age, 61.90 years; standard deviation, 10.65) showed no significant change in physical functioning score from prechemotherapy to the first chemotherapy cycle (Dai, Yang et al. 2017). This difference in results may be caused by the fact that the patients in Dai et al. were younger than our patients. In our study population, although statistical significance was not observed, patients showed a decrease in the symptom scale scores for fatigue and dyspnea. These lung cancer symptoms may have resulted in the reduced physical functioning score.

Dai et al. reported that patients with stage IIIB/IV non-small-cell lung cancer (average age, 61.90 years; standard deviation, 10.65) showed little improvement in emotional functioning score from prechemotherapy to the first chemotherapy cycle, but statistical significance was not observed (Dai, Yang et al. 2017). Consistent with the findings of Dai et al, only 1 patient in our study population had a clinically relevant deterioration of emotional functioning score, with the score significantly increasing. The symptom scale score for insomnia showed the same tendency. At the time of diagnosis, the patients might have had vague anxiety about their treatment plan and prognosis, but it might have been relieved by deciding on a treatment plan and establishing a new lifestyle over the next 3 months.

We demonstrated that decrease in the number of daily steps and incremental shuttle walking distance at baseline were associated with a deterioration of quality of life in this study. We speculated that patients with impaired physical functioning at baseline experience decreased physical and outdoor activity after cancer diagnosis, which may result in worsened physical and role functioning scores. Furthermore, the number of daily steps and incremental shuttle walking distance at baseline may become predictors of quality of life deterioration during the early period after diagnosis. Consistently, Bade et al. reported that a higher step count correlated with a higher quality of life in all domains in lung cancer patients (average age, 66 years; standard deviation, 7.75) (Bade, Brooks et al. 2018). Mouri et al. reported that among elderly patients with advanced non-small-cell lung and pancreatic cancers, those with increased outdoor activity had significantly increased global health status/QoL and role and emotional functioning (Mouri, Naito et al. 2018). In our population, patients who did not receive chemotherapy because of worsening of their condition showed a higher risk of clinically relevant deterioration of physical functioning than those who received cytotoxic regimens. Whether receiving no chemotherapy is a predictor of the deterioration of physical functioning remains controversial.

Our study has several limitations. First, this was a small study and included only Japanese patients who were treated at a single cancer center. Second, our study population was heterogeneous with regard to the treatment regimens received. Third, patients who were transferred to another hospital were excluded from our analyses, which may have caused a selection bias. Finally, we did not investigate the association between the deterioration of quality of life and social factors, such as marital status, educational level, perceived income level, and employment status at diagnosis.

Maintenance of quality of life has increasingly become important. First, a large observational study would be needed to clarify the quality of life of elderly patients with advanced non-small-cell lung cancer. This will reveal the risk factors of impaired quality of life. As quality of life is a physical, social, and mental assessment, not only therapeutic interventions by physicians but also multidisciplinary interventions involving social workers, psychologists, dieticians, and physiotherapists will be needed. Nurses have first contact with patients and can be successfully involved in collecting symptom information because of their direct relationship with the patient (Baratelli, Turco et al. 2019). Baratelli et al. reported that introduction of patient-reported outcomes in clinical practice, thanks to an active role of nurses, was feasible, produced high patients' satisfaction, and a significantly improved quality of life. Nurses may play a central role in these multidisciplinary interventions.

5. Conclusion

Twenty to 40% of the patients had a clinically relevant deterioration of quality of life score from baseline to 12 ± 4 weeks. The mean of daily steps and incremental shuttle walking distance can be predictors of clinically relevant deterioration of quality of life. These findings may promote early intervention to prevent quality of life deterioration. Further prospective studies are needed to validate our findings.

6. Tables and Figures

Table 1 Patient characteristics at beseline

Variable	Full analysis set (n = 28)	Change analysis set (n = 21)
Age, years, median (range)	75 (70–83)	74 (70–83)
Sex, n (%)		
Men	17 (61)	13 (62)
Women	11 (39)	8 (38)
ECOG-PS, n(%)		
0	9 (32)	6 (29)
1	18 (64)	15 (71)
2	1 (4)	0 (0)
Treatment, n (%)		
Cytotoxic regimen	15 (54)	13 (62)
Targeted regimen	7 (25)	5 (24)
No chemotherapy	6 (21)	3 (14)
Body composition, median (range)		
Body mass index, kg/m2	21.8 (16.9–28.1)	21.2 (16.9–28.1)
Appendicular skeletal muscle mass index, kg/m^2	6.4 (5.0–8.3)*	6.4 (5.0–8.3)
Physical function, median (range)		
Steps per day, steps	3542 (882–19957)*	4077 (882–19957)*
Incremental shuttle walking distance , m	340 (120–550)*	360 (120–550)
Hand-grip strength, kg	28.3 (19.0–37.2)*	28.3 (19.0–35.9)
Sarcopenia, n (%)	3 (11)*	3 (14)
Cancer cachexia, n (%)	14 (50)**	11 (52)**

*Not evaluable in 1 patient

**Not evaluable in 2 patients

ECOG-PS: Eastern cooperative oncology group performance status.

Appendicular skeletal muscle mass index was defined as muscle mass (kg) divided by height squared (m2).

Sarcopenia: Diagnosis was based on the international consensus criteria.

Cancer cachexia: Diagnosis was based on the international consensus criteria.

The full analysis set consisted of patients with quality of life assessments evaluable at baseline.

The change analysis set consisted of patients with quality of life assessments evaluable at baseline and 12 ± 4 weeks.

Table 2 EORTC QLQ-C30 score at baseline (Full analysis set)

	Full analysis set (n = 28)		Reference (lung cancer: equal 70 years or more)		Reference (lung cancer: recurrent/metastatic)	
	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)
Global health status/QoL						
Global health status/QoL	67 (25–100)	65 (21)	58.5 (33.3–75)	54.4 (26.7)	50 (16.7–66.7)	43.5 (28.2)
Functional scales						
Physical functioning	93 (60–100)	89 (12)	73.3 (53.3–86.7)	68.2 (25.6)	NA*	
Role functioning	100 (50–100)	89 (16)	66.7 (33.3–100)	61.3 (33.9)	50 (16.7–66.7)	47.0 (33.9)
Emotional functioning	92 (50–100)	83 (13)	75 (58.3–91.7)	72.9 (24.8)	66.7 (50–83.3)	64.7 (25.7)
Cognitive functioning	83 (50–100)	85 (16)	83.3 (66.7–100)	79.8 (23)	83.3 (66.7–100)	74.6 (26.6)
Social functioning	100 (33–100)	89 (17)	83.3 (58.3–100)	74.9 (28.8)	66.7 (33.3–100)	64.6 (31.4)
Symptom scales/items						
Nausea and vomiting	0 (0–17)	2 (5)	0 (0–16.7)	9.9 (19.8)	0 (0–16.7)	16.1 (26.2)
Fatigue	28 (0–78)	24 (19)	33.3 (22.2–66.7)	43.0 (28.7)	44.4 (33.3–66.7)	51.6 (28.7)
Dyspnea	0 (0–100)	23 (29)	33.3 (33.3–66.7)	42.2 (32.5)	33.3 (0–66.7)	42.8 (34.3)
Pain	17 (0–83)	16 (21)	16.7 (0–50)	25.4 (30.6)	33.3 (16.7–66.7)	40.5 (33.5)
Insomnia	33 (0–100)	25 (25)	33.3 (0–33.3)	28.9 (32.7)	33.3 (0–66.7)	36.4 (32.8)
Appetite loss	16 (0–100)	23 (27)	0 (0–66.7)	29.4 (36)	33.3 (0–66.7)	34.7 (37)
Constipation	16 (0–33)	16 (17)	0 (0–33.3)	25.5 (33)	33.3 (0–66.7)	34.0 (36.5)
Diarrhea	0 (0–33)	7 (14)	0 (0–0)	6.4 (17)	0 (0–33.3)	12.4 (23.4)
Financial difficulties	0 (0–33)	6 (13)	0 (0–0)	8.7 (21)	0 (0–33.3)	22.3 (31.3)

EORTC QLQ-C30: The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire

The full analysis set consisted of patients with quality of life assessments evaluable at baseline.

Reference were from EORTC QLQ-C30 reference values. The reference values were on patients with concer at pretreatment in the world.

*NA: Not available

SD: standard deviation

Table 3 EORTC QLQ-C30 scores at baseline and 12 ± 4 weeks and change of scores (Change analysis set)

	Change analysis set (n = 21)								
	Baseline		12 ± 4 weeks after baseline		Change				
	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	p-value*	Deterioration, n (%)	95% CI (%)**
Global health status/QoL									
Global health status/QoL	67 (33–100)	67 (22)	50 (0 - 100)	56 (27)	0 (-83 to 25)	–11 (28)	0.176	8 (38)	18–62
Functional scales									
Physical functioning	93 (67–100)	90 (9)	87 (33–100)	82 (20)	−6 (−60 to 7)	–9 (16)	0.011	6 (29)	11–52
Role functioning	100 (67–100)	91 (14)	100 (33–100)	87 (20)	0 (−34 to 33)	–3 (17)	0.453	5 (24)	8–47
Emotional functioning	89 (50–100)	81 (14)	92 (42–100)	88 (15)	8 (–25 to 33)	7 (13)	0.014	1 (5)	0–24
Cognitive functioning	83 (50–100)	86 (17)	83 (33–100)	86 (17)	0 (–34 to 33)	1 (16)	1.000	4 (19)	5–42
Social functioning	100 (33–100)	86 (19)	100 (0–100)	83 (26)	0 (–100 to 34)	–3 (28)	0.939	5 (24)	8–47
Symptom scales/items									
Nausea and vomiting	0 (0–17)	2 (6)	0 (0–100)	9 (23)	0 (–17 to 100)	6 (23)	0.375	3 (14)	3–36
Fatigue	22 (0–78)	22 (22)	33 (0–89)	30 (22)	0 (–34 to 89)	9 (25)	0.140	9 (43)	22–66
Dyspnea	0 (0–67)	16 (20)	0 (0–100)	25 (33)	0 (–33 to 100)	10 (35)	0.240	6 (29)	11–52
Pain	17 (0–83)	18 (24)	17 (0–50)	13 (16)	0 (–33 to 17)	–5 (13)	0.188	2 (10)	1–30
Insomnia	33 (0–100)	28 (26)	0 (0–33)	13 (16)	0 (–67 to 33)	–16 (27)	0.027	1 (5)	0–24
Appetite loss	0 (0–100)	19 (27)	33 (0–100)	30 (30)	0 (–67 to 100)	11 (36)	0.230	8 (38)	18–62
Constipation	0 (0–33)	16 (17)	0 (0–100)	22 (34)	0 (–33 to 67)	6 (27)	0.148	5 (24)	8–47
Diarrhea	0 (0–33)	6 (13)	0 (0–33)	16 (17)	0 (–33 to 33)	9 (24)	0.146	9 (43)	22–66
Financial difficulties	0 (0–33)	8 (14)	0 (0–33)	8 (14)	0 (–33 to 33)	0 (15)	1.000	2 (10)	1–30

EORTC QLQ-C30: The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire

The change analysis set consisted of patients with quality of life assessments evaluable at baseline and 12 ± 4 weeks.

The change of the scores was calculated as the quality of life score at 12 ± 4 weeks minus the quality of life score at baseline.

The deterioration quality of life score was defined as a change equal –10 points or less.

SD: standard deviation

* p-value was based on the Wilcoxon signed-rank test. Null hypothesis was the median of change was zero.

**The 95% confidence interval of the proportion of patient with the deterioration.

Table 4 Predictor of deterioration of global health status/QoL (Change analysis set)

Variable	Deterioration (n = 8)	Non deterioration (n = 13)	Odds ratio	95% CI	p-value
Age, years, median (range)	75 (72–82)	74 (70 to 83)			0.708
Sex, n (%)					
Men	5 (38)	8 (62)	1.0	0.1–9.8	1.000
Women	3 (38)	5 (63)	1.0		
Body composition, median (range)					
Body mass index, kg/m^2	22.4 (19.2–25.2)	20.5 (16.9–28.1)			0.310
Appendicular skeletal muscle mass index, kg/m^2	6.1 (5.7–7.3)	6.5 (5.0–8.3)			0.929
Physical function, median (range)					
Steps per day, steps*	2734 (1212–6818)	4240 (882–19957)			0.311
Shuttle walk distance, m	360 (140–480)	350 (120–550)			0.737
Hand-grip strength, kg	28.1 (19.0–34.9)	28.3 (20.5–35.9)			0.846
Treatment, n (%)					
Cytotoxic regimen	7 (54)	6 (46)	2.2	0.1–156.8	1.000
Targeted regimen	0 (0)	5 (100)	0.0	0.0–23.4	0.375
No chemotherapy	1 (33)	2 (67)	1.0		
Sarcopenia, n (%)					
Yes	2 (67)	1 (33)	3.7	0.2–254.7	0.531
No	6 (33)	12 (67)	1.0		
Cancer cachexia, n (%)**					
Yes	3 (27)	8 (73)	0.4	0.0–3.7	0.377
No	4 (50)	4 (50)	1.0		

The change analysis set consisted of patients with quality of life assessments evaluable at baseline and 12 ± 4 weeks.

The change of the scores was calculated as the quality of life score at 12 ± 4 weeks minus the quality of life score at baseline.

The deterioration quality of life score was defined as a change equal −10 points or less.

Appendicular skeletal muscle mass index was defined as muscle mass(kg) divided by height squared(m^2).

Sarcopenia: Diagnosis was based on the international consensus criteria.

Cancer cachexia: Diagnosis was based on the international consensus criteria.

*Not evaluable in 1 patient

**Not evaluable in 2 patients

Inf indicates infinity.

Table 5 Predictors of the deterioration of physical functioning (Change analysis set)

Variable	Deterioration (n = 6)	Non deterioration (n = 15)	Odds ratio	95%CI	p-value
Age, years, median (range)	80 (70–83)	74 (70–80)			0.169
Sex, n (%)					
Men	4 (31)	9 (69)	1.3	0.1–19.0	1.000
Women	2 (25)	6 (75)	1.0		
Body composition, median (range)					
Body mass index, kg/m^2	22.1 (16.9–28.1)	20.8 (19–26.4)			0.804
Appendicular skeletal muscle mass index, kg/m^2	5.9 (5.3–7.0)	6.6 (5.0–8.3)			0.147
Physical function, median (range)					
Steps per day, steps*	1870 (882–6262)	4382 (1212–19957)			0.142
Shuttle walk distance, m	230 (120–360)	400 (260–550)			0.002
Hand-grip strength, kg	27.1 (21.2–31.7)	29.2 (19.0–35.9)			0.634
Treatment, n (%)					
Cytotoxic regimen	2 (15)	11 (85)	0.0	0.0–0.9	0.018
Targeted regimen	1 (20)	4 (80)	0.0	0.0–1.9	0.143
No chemotherapy	3 (100)	0 (0)	1.0		
Sarcopenia, n (%)					
Yes	2 (67)	1 (33)	6.2	0.3–439.9	0.184
No	4 (22)	14 (78)	1.0		
Cancer cachexia, n (%)**					
Yes	2 (18)	9 (82)	0.4	0.0–4.7	0.603
No	3 (38)	5 (63)	1.0		

The change analysis set consisted of patients with quality of life assessments evaluable at baseline and 12 ± 4 weeks.

The change of the scores was calculated as the quality of life score at 12 ± 4 weeks minus the quality of life score at baseline.
The deterioration quality of life score was defined as a change equal −10 points or less.

Appendicular skeletal muscle mass index was defined as muscle mass(kg) divided by height squared(m^2).
Sarcopenia: Diagnosis was based on the international consensus criteria.
Cancer cachexia: Diagnosis was based on the international consensus criteria.
*Not evaluable in 1 patient
**Not evaluable in 2 patients
Inf indicates infinity.

Table 6 Predictors of deterioration of role functioning (Change analysis set)

Variable	Deterioration (n = 5)	Non deterioration (n = 16)	Odds ratio	95%CI	p-value
Age, years, median (range)	78 (73–82)	74 (70–83)			0.386
Sex, n(%)					
Man	5 (38)	8 (62)	Inf	0.6–Inf	0.111
Women	0 (0)	8 (100)	1.0		
Body composition, median (range)					
Body mass index, kg/m^2	22.0 (19.2–25.2)	20.7 (16.9–28.1)			0.505
Appendicular skeletal muscle mass index, kg/m^2	6.6 (5.8–7.3)	6.2 (5.0–8.3)			0.364
Physical function, median (range)					
Steps per day, steps*	1566 (1212–2285)	4805 (882–19957)			0.007
Shuttle walk distance, m	260 (140–520)	370 (120–550)			0.323
Hand-grip strength, kg	29.2 (21.2–34.9)	28.3 (19.0–35.9)			0.592
Treatment, n (%)					
Cytotoxic regimen	3 (23)	10 (77)	0.6	0.0–47.1	1.000
Targeted regimen	1 (20)	4 (80)	0.6	0.0–58.7	1.000
No chemotherapy	1 (33)	2 (67)	1.0		
Sarcopenia, n (%)					
Yes	2 (67)	1 (33)	8.6	0.4–624.3	0.128
No	3 (17)	15 (83)	1.0		
Cancer cachexia, n (%)**					
Yes	2 (18)	9 (82)	0.7	0.0–11.9	1.000
No	2 (25)	6 (75)	1.0		

The change analysis set consisted of patients with quality of life assessments evaluable at baseline and 12 ± 4 weeks.

The change of the scores was calculated as the quality of life score at 12 ± 4 weeks minus the quality of life score at baseline.

The deterioration quality of life score was defined as a change equal −10 points or less.

Appendicular skeletal muscle mass index was defined as muscle mass(kg) divided by height squared(m^2).

Sarcopenia: Diagnosis was based on the international consensus criteria.

Cancer cachexia: Diagnosis was based on the international consensus criteria.

*Not evaluable in 1 patient

**Not evaluable in 2 patients

Inf indicates infinity.

Table 7 Predictors of deterioration of emotional functioning (Change analysis set)

Variable	Deterioration (n = 1)	Non deterioration (n = 20)	Odds ratio	95%CI	p-value
Age, years, median (range)	70 (70–70)	75 (70–83)			0.238
Sex, n(%)					
Man	1 (8)	12 (92)	Inf	0.0–Inf	1.000
Women	0 (0)	8 (100)	1.0		
Body composition, median (range)					
Body mass index, kg/m^2	16.9 (16.9–16.9)	21.6 (19.0–28.1)			0.095
Appendicular skeletal muscle mass index, kg/m^2	5.3 (5.3–5.3)	6.5 (5.0–8.3)			0.191
Physical function, median (range)					
Steps per day, steps*	6262 (6262–6262)	3914 (882–19957)			0.400
Shuttle walk distance, m	330 (330–330)	360 (120–550)			0.667
Hand-grip strength, kg	29.7 (29.7–29.7)	28.3 (19.0–35.9)			0.762
Treatment, n (%)					
Cytotoxic regimen	0 (0)	13 (100)	0.0	0.0–9.0	0.187
Targeted regimen	0 (0)	5 (100)	0.0	0.0–23.4	0.375
No chemotherapy	1 (33)	2 (67)	1.0		
Sarcopenia, n (%)					
Yes	0 (0)	3 (100)	0.0	0.0–233.2	1.000
No	1 (6)	17 (94)	1.0		
Cancer cachexia, n (%)**					
Yes	1 (9)	10 (91)	Inf	0.0–Inf	1.000
No	0 (0)	8 (100)	1.0		

The change analysis set consisted of patients with quality of life assessments evaluable at baseline and 12 ± 4 weeks.

The change of the scores was calculated as the quality of life score at 12 ± 4 weeks minus the quality of life score at baseline.

The deterioration quality of life score was defined as a change equal −10 points or less.

Appendicular skeletal muscle mass index was defined as muscle mass(kg) divided by height squared(m^2).

Sarcopenia: Diagnosis was based on the international consensus criteria.

Cancer cachexia: Diagnosis was based on the international consensus criteria.

*Not evaluable in 1 patient

**Not evaluable in 2 patients

Inf indicates infinity.

Table 8 Predictors of deterioration of cognitive functioning (Change analysis set)

Variable	Deterioration (n = 4)	Non deterioration (n = 17)	Odds ratio	95%CI	p-value
Age, years, median (range)	81 (72–83)	74 (70–81)			0.110
Sex, n(%)					
Men	3 (23)	10 (77)	2.0	0.1–125.7	1.000
Women	1 (13)	7 (88)	1.0		
Body composition, median (range)					
Body mass index, kg/m^2	22.1 (21.2–25.2)	20.6 (16.9–28.1)			0.310
Appendicular skeletal muscle mass index, kg/m^2	7.1 (5.7–7.3)	6.2 (5.0–8.3)			0.148
Physical function, median (range)					
Steps per day, steps*	2588 (1212–5345)	4311 (882–19957)			0.249
Shuttle walk distance, m	235 (140–440)	360 (120–550)			0.115
Hand-grip strength, kg	31.3 (28.3–34.9)	26.1 (19.0–35.9)			0.054
Treatment, n (%)					
Cytotoxic regimen	3 (23)	10 (77)	0.62	0.0–47.1	1.000
Targeted regimen	0 (0)	5 (100)	0.0	0.0–23.4	0.375
No chemotherapy	1 (33)	2 (67)	1.0		
Sarcopenia, n (%)					
Yes	0 (0)	3 (100)	0.0	0.0–11.7	1.000
No	4 (22)	14 (78)	1.0		
Cancer cachexia, n (%)**					
Yes	1 (9)	10 (91)	0.2	0.0–3.0	0.262
No	3 (38)	5 (63)	1.0		

The change analysis set consisted of patients with quality of life assessments evaluable at baseline and 12 ± 4 weeks.

The change of the scores was calculated as the quality of life score at 12 ± 4 weeks minus the quality of life score at baseline.

The deterioration quality of life score was defined as a change equal −10 points or less.

Appendicular skeletal muscle mass index was defined as muscle mass(kg) divided by height squared(m^2).

Sarcopenia: Diagnosis was based on the international consensus criteria.

Cancer cachexia: Diagnosis was based on the international consensus criteria.

*Not evaluable in 1 patient

**Not evaluable in 2 patients

Inf indicates infinity.

Table 9 Predictors of deterioration of social functioning (Change analysis set)

Variable	Deterioration (n = 5)	Non deterioration (n = 16)	Odds ratio	95%CI	p-value
Age, years, median (range)	78 (70–82)	74 (70–83)			0.405
Sex, n (%)					
Men	4 (31)	9 (69)	3.0	0.2–174.5	0.606
Women	1 (13)	7 (88)	1.0		
Body composition, median (range)					
Body mass index, kg/m^2	22.7 (16.9–25.2)	20.7 (19.0–28.1)			0.485
Appendicular skeletal muscle mass index, kg/m^2	6.2 (5.3–7.3)	6.5 (5.0–8.3)			0.827
Physical function, median (range)					
Steps per day, steps*	2822 (1212–6262)	4077 (882–19957)			0.494
Shuttle walk distance, m	330 (140–400)	370 (120–550)			0.216
Hand-grip strength, kg	30.3 (25.8–34.9)	27.2 (19.0–35.9)			0.106
Treatment, n (%)					
Cytotoxic regimen	4 (31)	9 (69)	0.9	0.0–65.4	1.000
Targeted regimen	0 (0)	5 (100)	0.0	0.0–23.4	0.375
No chemotherapy	1 (33)	2 (67)	1.0		
Sarcopenia, n (%)					
Yes	1 (33)	2 (67)	1.7	0.0–41.6	1.000
No	4 (22)	14 (78)	1.0		
Cancer cachexia, n (%)**					
Yes	1 (9)	10 (91)	0.2	0.0–3.0	0.262
No	3 (38)	5 (63)	1.0		

The change analysis set consisted of patients with quality of life assessments evaluable at baseline and 12 ± 4 weeks.

The change of the scores was calculated as the quality of life score at 12 ± 4 weeks minus the quality of life score at baseline.

The deterioration quality of life score was defined as a change equal −10 points or less.

Appendicular skeletal muscle mass index was defined as muscle mass(kg) divided by height squared(m^2).

Sarcopenia: Diagnosis was based on the international consensus criteria.

Cancer cachexia: Diagnosis was based on the international consensus criteria.

*Not evaluable in 1 patient

**Not evaluable in 2 patients

Inf indicates infinity.

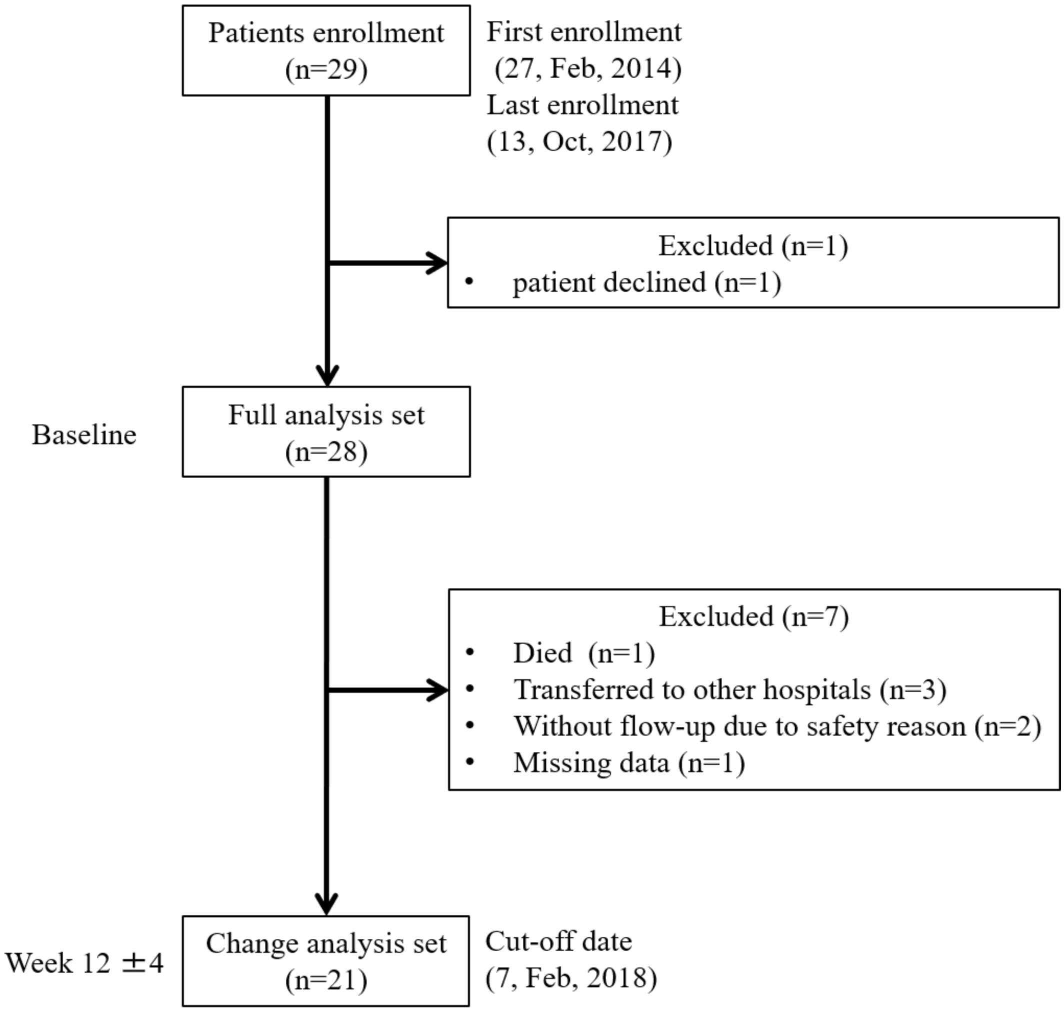
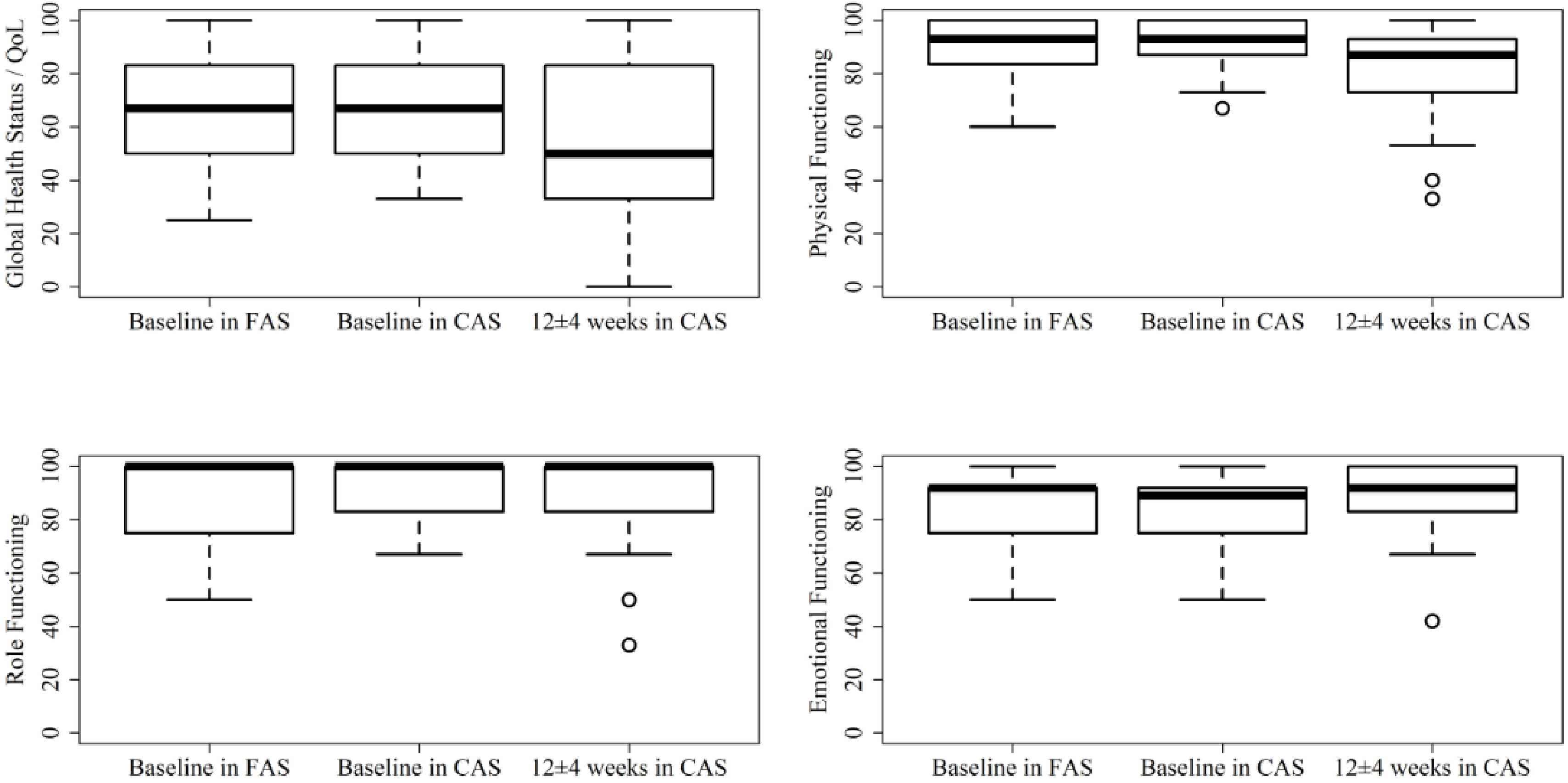


Figure 1 Patient flow diagram



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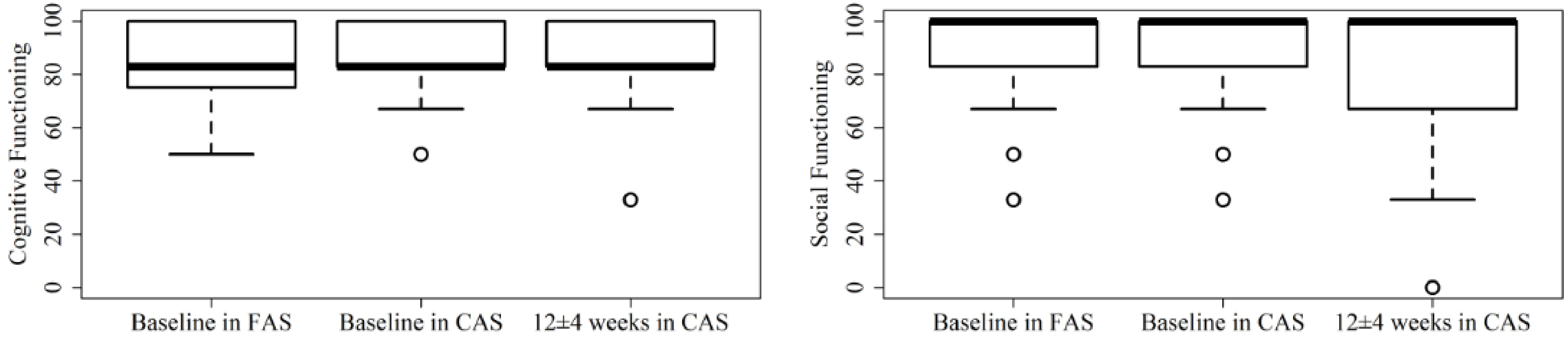

Figure 2 EORTC QLQ-C30 scores at baseline and 12 ± 4 weeks in full analysis set (FAS, n = 28) and change analysis set (CAS, n = 21)

EORTC QLQ-C30: The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire.

The full analysis set consisted of patients with quality of life assessments evaluable at baseline.

The change analysis set consisted of patients with quality of life assessments evaluable at baseline and 12 ± 4 weeks.

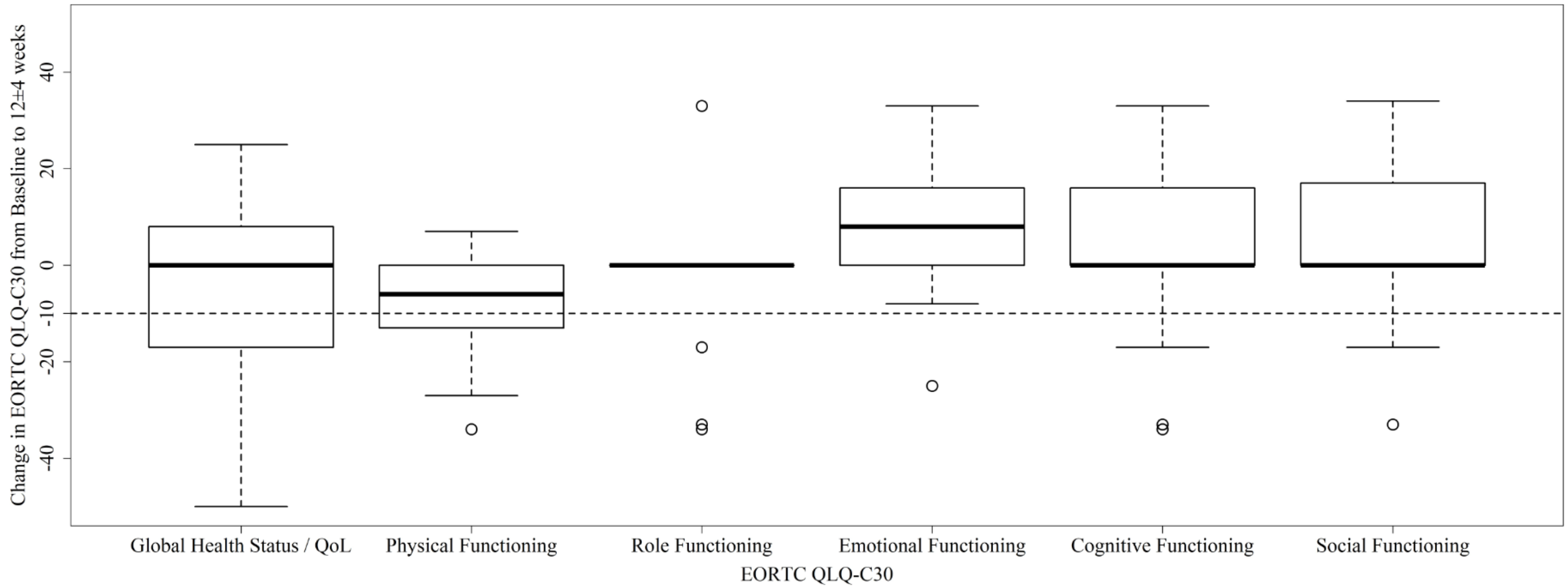

Figure 3 Change in EORTC QLQ-C30 score from diagnosis to 12 ± 4 weeks in the change analysis set

EORTC QLQ-C30: The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire.
The change analysis set consisted of patients with quality of life assessments evaluable at baseline and 12 ± 4 weeks.
The change of the scores was calculated as the quality of life score at 12 ± 4 weeks minus the quality of life score at baseline.

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Chapter 3

Days spent at home near the end-of-life in Japanese elderly patients with lung cancer: Post-hoc analysis of a prospective study

1. Introduction

The number of elderly people living with advanced lung cancer is increasing worldwide, owing to the aging population and advances in cancer treatment (Petrelli, Winer et al. 2009, Miller, Siegel et al. 2016). These patients frequently visit the emergency room and are usually hospitalized during the last few months of their lives, which reduces their quality of life and inflates health care costs near the end-of-life (Cheung, Earle et al. 2015, Meghani and Hinds 2015). Optimal psychosocial support, home care, and hospice care may alleviate this burden, and improve the quality of life near the end-of-life for both patients and their families. Besides, it may reduce the use of health care resources (Department of Health 2008, Temel, Greer et al. 2010, Wright, Keating et al. 2010, Mitchell, Chan et al. 2011, Lindqvist, Tishelman et al. 2012).

Statistics on hospital deaths and hospitalizations near end-of-life for patients with cancer reflect the quality of end-of-life care (Barbera, Paszat et al. 2006, Fukui, Yoshiuchi et al. 2011). Recently, days spent at home (DASH) near the end-of-life has drawn attention as an important quality measure (Groff, Colla et al. 2016, Sayer 2016). DASH is considered an important patient-centered goal (Groff, Colla et al. 2016, Sayer 2016) because many cancer patients prefer to stay at home toward the end-of-life (Higginson and Sen-Gupta 2000). Therefore, identifying the predictors of DASH at the time of diagnosis could allow us to provide early support to improve the quality of end-of-life care. For patients with cancer, women and non-users of palliative care reportedly have less DASH (Otsuka 2017, Andersen, Croxford et al. 2019). However, the predictors for decreased DASH for elderly patients with advanced non-small-cell lung cancer (NSCLC) have not been reported.

Elderly patients with advanced non-small-cell lung cancer have been reported to have reduced skeletal muscle mass and physical function at the time of diagnosis (Naito, Okayama et al. 2017). Besides, these patients have been reported to be more frequently disabled in later life, and require prolonged hospitalization (Naito, Okayama et al. 2017). Therefore, we hypothesized that reduced muscle mass and physical function at the time of diagnosis might shorten DASH near the end-of-life.

However, there is limited information on individually measured DASH in populations with specific cancer types. Besides, the early predictors of DASH at the time of diagnosis are not precisely known.

Accordingly, this study aimed to estimate the individual DASH near the end-of-life and identify its early predictors, including muscle mass and physical function, among elderly patients with advanced NSCLC.

2. Methods

2.1. *Patient selection*

We performed post-hoc analysis of the results of a prospective observational study (Naito, Okayama et al. 2017) that recruited patients from January 2013 at the Shizuoka Cancer Center, Japan. This prospective observational study was approved by the institutional review board and was registered on the University Hospital Medical Information Network Clinical Trials Registry in Japan (registration No.: UMIN000009768). The eligibility criteria used in the original observational study were as follows: (1) histologically and/or cytologically proven stage III or IV NSCLC, including postoperative recurrence; (2) patients aged $\geq$ 70 years, with planned first-line systemic chemotherapy; (3) no previous systemic chemotherapy or thoracic radiotherapy (adjuvant chemotherapy was not counted as prior chemotherapy); (4) Eastern Cooperative Oncology Group performance status (PS) of 0–2; (5) ability to ambulate, read, and respond to questions without assistance; and (6) expected survival of >12 weeks. Patients were excluded if they had severe psychiatric disorder, active infectious disease, unstable cardiac disease, or untreated symptomatic brain or bone metastases that prevented safety assessment. The attending physicians screened patients with newly diagnosed advanced NSCLC to ascertain if they were eligible. Staff of the research office double-checked each patient’s eligibility and explained the clinical study to the patients. Finally, patients participated in the study after proving written informed consent. This post-hoc analysis was planned and conducted from 2019 to 2020. Patients in the original observational study whose DASH and baseline measurement of muscle mass and physical function were available were included in this post-hoc analysis.

The treatment goals for patients during the early period after the initial diagnosis with stage III cancer and stage IV cancers were different from each other; hence the data on the quality of life during the early period after the initial diagnosis should be presented separately. On the other hand, we speculated that the terminal stages of patients with stage

III cancer at the initial diagnosis and those with stage IV cancer at the initial diagnosis were not extremely different. Hence, we investigated patients who were initially diagnosed with stage III and stage IV cancer simultaneously on DASH near the end-of-life, where we consided the difference in the stage as a possible predictor variable for DASH near the end-of-life.

2.2. *Data collection*

Body mass index (BMI, kg/m^2), incremental shuttle walking distance (ISWD, m), hand-grip strength (kg), muscle mass (kg), age, PS, stage, treatment, comorbidities, and family structures were assessed at baseline in the original prospective observational study. The baseline period was between enrollment into the study to initiation of the first session of chemotherapy. The attending physicians and physiotherapists assessed the BMI, ISWD, hand-grip strength, and muscle mass of the patients. These variables were treated as potential predictors of DASH in the post-hoc analysis, according to the previous studies (Otsuka 2017, Andersen, Croxford et al. 2019, Gill, Gahbauer et al. 2019). DASH, place of death, and frequency of hospitalization were collected retrospectively from electronic medical records and used in this post-hoc analysis.

2.3. *Assessment of physical function*

Physiotherapists assessed the ISWD and hand-grip strength on the dominant side. An incremental shuttle walking test was conducted based on the recent guideline (Singh, Puhan et al. 2014) and the original protocol presented by Singh et al (Singh, Morgan et al. 1992). We set a 10-m course in the hospital corridor. The walking speed was dictated by a timed signal played on a compact disc recorder provided by the manufacturer (Japanese version, the Graduate School of Biomedical Sciences, Nagasaki University, Japan, 2000). Assessments for all patients were conducted once under standardized conditions while ensuring that the patients did not exceed their exercise limit. An instructor accompanied the patients along the course during the assessments but did not interfere with the process by providing encouragement. The assessment was concluded (1) by the patient when they were exhausted and unable to maintain the required walking speed, (2) by the instructor when the patient could not complete a shuttle within the allotted time (i.e., walk for > 0.5 m away from the cone within the set time), or (3) when the patient presented a heart rate ≥ 85% of the predicted maximal heart rate derived using the formula $[210 - (0.65 \times \text{age})]$. ISWD denotes the maximum walking distance. Hand-grip strength was measured using a grip strength dynamometer (GRIP-D, Takei Scientific Instruments Co., LTD, Niigata, Japan). The patients stood in an upright position and held the dynamometer in one hand in accordance with the adjusted grip range to ensure that the second joint of the forefinger was bent at 90°. The instrument was then held down beside the patient, with the arm completely extended and not touching the body. The patients were then asked to exert complete force with their hand for approximately 3 s to yield the maximum kilogram-force. Here, the instructor provided verbal encouragement to elicit a maximum response from the patients. A trial was performed for each hand, and the result from the dominant hand was used for the analysis.

2.4. *Anthropometric and muscle mass measurements*

The body weight (kg) was measured to the nearest 0.1 kg, and the BMI was subsequently calculated. The muscle mass (kg) and body weight were measured by bioelectrical impedance analysis using the Body Composition Analyzer BC-118 (Tanita Corp., Tokyo, Japan). The recommended conditions for bioelectrical impedance analysis measurement were explained to the subjects: (1) fasting for 4 h, and no consumption of alcohol for 8 h before measurement; (2) bladder to be voided before measurement; and (3) no exercise to be performed within 8 h prior to the measurement (Kyle, Bosaeus et al. 2004). Patients stood on the footplate electrodes and grasped the hand-grip electrodes with both hands. The electrodes emitted current through both feet and hands distally, and the current was detected at the heels of both feet and palms of both hands. This system applies electricity at frequencies of 5, 50, 250, and 500 kHz through the body. The whole-body impedance was measured using an ipsilateral foot-hand electrical pathway. Appendicular skeletal muscle mass (kg) was derived as the sum of the muscle mass of the arms and legs. Trunk muscle mass (kg) was calculated by subtracting the appendicular skeletal muscle mass from the overall muscle mass. The overall muscle mass, trunk muscle mass, and appendicular skeletal muscle mass were converted to an overall muscle mass index, trunk muscle mass index, and appendicular skeletal muscle mass index, respectively, by dividing them by the square of height in meters (kg/m^2) (Tanimoto, Watanabe et al. 2012). Muscle depletion was defined as appendicular skeletal muscle mass index of < 7.0 kg/m^2 in men and < 5.8 kg/m^2 in women (Tanimoto, Watanabe et al. 2014).

2.5. *Calculation of DASH*

The data on days between admission and discharge from the health care facilities were obtained from electronic medical records. DASH was defined as 30 days minus the number of days spent in health care facilities in the last 30 days of life, including the date of death. Health care facilities included a hospital, palliative care facility, or nursing home. The date of admission and the date of discharge were considered as days spent in health care facilities. In the case of multiple admissions and discharges, the total number of days spent in the facilities was defined as the sum of the number of days in each facility.

2.6. *Place of death and frequency of hospitalization*

The place of death and the number of hospitalizations in the last 30 days of life were obtained from electronic medical records.

2.7. *Statistical analyses*

Patient baseline characteristics were presented as medians, ranges, counts, and percentages for the entire cohort and then by sex. The median, first and third quartiles, and range of DASH were calculated. Distributions of the place of death and the number of hospitalizations in the last 30 days of life were evaluated. We performed univariate linear regression analyses to evaluate the predictors of DASH. Candidate predictors included age, sex, PS, stage, treatment, comorbidities, sarcopenia, family structures, muscle mass indexes, physical function, and BMI. To adjust for confounding factors, we performed multivariate linear regression analyses with DASH as the outcome variable. In multivariate regression analyses, sex was used as a predictor variable because it was considered a potential confounding factor and a significant variable in the univariate regression analysis. Muscle mass indexes and physical function were separately included in multivariate regression analyses to avoid multicollinearity because the muscle mass indexes and physical function are correlated. In summary, we conducted multivariate linear regression analyses five times with two predictor variables (one was sex and the other was one of two muscle mass indexes and three physical functions). We did not have the clinically relevant cut-off value of DASH and hence we did not apply logistic regression analysis. The R-square values were calculated to evaluate the goodness of fit in the multivariate linear regression models. A two-sided p-value < 0.05 was considered to be statistically significant. We used the R statistical package version 3.5.1 (R Core Team, July 2018; www.r-project.org) for statistical analyses.

3. Results

3.1. *Patient characteristics at baseline*

In the original observational study, a total of 61 patients were screened between January 2013 and November 2014, and 60 were enrolled in the study (Figure 1). In this post-hoc analysis, fifteen patients were excluded from the analysis because DASH could not be measured in: (1) patients who were transferred to other hospitals (n=11), (2) patients who were alive until the cut-off date (n=3), (3) patient who died within 30 days from enrollment (n=1). One patient was excluded from this analysis because of missing data on muscle mass and physical function. Finally, 44 patients were included in this post-hoc analysis. The median age at diagnosis was 76 years (range, 70–87; Table 1). Twenty-eight patients (64%) were men, and 16 (36%) were women. A majority of the patients had PS of 0−1 (97%). Eighteen patients with locally advanced disease (41%) received curative intent radiotherapy with or without chemotherapy, while 26 with metastatic disease (59%) received palliative chemotherapy. The chemotherapy regimens included carboplatin (n=11), docetaxel (n=8), carboplatin + paclitaxel (n=5), gefitinib (n=6), cisplatin + pemetrexed (n=4), cisplatin + vinorelbine (n=2), carboplatin + paclitaxel + motesanib (n=2), and cisplatin + gemcitabine (n=1). The most common comorbidities were chronic obstructive pulmonary disease in 22 patients (50%) and type 2 diabetes mellitus in 10 patients (23%). Men had a higher incidence of comorbidities than women. Most of the patients (n=41, 93%) lived with their families, whereas 3 patients (7%) lived alone. There were no gender differences in terms of age, BMI, PS, stage, initial treatment, and family structure. The overall, trunk, and appendicular skeletal muscle mass index and hand-grip strength were higher among men than among women (Table 2). Muscle depletion was diagnosed in 26 (59%) patients at baseline and was comparable between men and women (57% in men and 63% in women) according to the gender-specific diagnostic criteria. There was no difference in ISWD between men and women.

3.2. *DASH and other end-of-life situations*

All 44 patients in the analyses died before the data cut-off date (December 2018). The median overall survival was 15.5 months (range, 2.9−58.9). A majority of the patients died at the hospital (n=25, 57%) or palliative care unit (n=17, 39%; Table 3). One patient died at home and a nursing facility each. Thirty-nine patients (89%) were hospitalized once, whereas 4 (9%) were hospitalized twice in the last 30 days of their life. Only one patient did not require hospitalization and died at home. Nineteen patients (43%) did not spend a single day at home in the 30 days of life (Figure 2). The median DASH in the last 30 days of life was 8 days (range, 0–30; interquartile range, 0–23).

3.3. *Clinical predictors of DASH near the end-of-life*

Men had a longer DASH than women by 7.3 days (p=0.035, Table4, Figure3). Patients who had good trunk muscle mass index and hand-grip strength had longer DASH than those who did not [4.7 days per kg/m^2 increase (p=0.017) and 0.4 days per kg increase (p=0.032), respectively]. Finally, muscle mass indices and physical function were found to be positively associated with DASH after adjustment for gender in the multivariate linear regression analysis, although the association was not statistically significant (Figure 4). In all multivariate analyses, men had longer DASH than women, but the association was not statistically significant except ISWD. The R-square values were near 0.1 in all multivariate linear regression analyses.

4. Discussion

To the best of our knowledge, this is the first study to investigate DASH and end-of-life care among elderly patients with advanced NSCLC. We found that our study population stayed at home for a median of 8 days in the last 30 days of life, and only 2% of the patients died at home. The risk factors for reduced DASH were women gender, reduced muscle mass, and poor physical function at the time of diagnosis for advanced NSCLC.

Although most Japanese people desire home to be the place for end-of-life care or dying (Ministry of Health, Labour and Welfare 2004, Fukui, Yoshiuchi et al. 2011, Yamagishi, Morita et al. 2012), only 12.4% of Japanese people died at home in 2009 (Ministry of Health, Labour and Welfare 2009). The remaining people died at the hospitals (78.4%), nursing homes (4.3%), or other health care facilities (2.4%) (2009). Similar gaps between the preferred places of death and the actual places of death were reported in other countries, including the UK and Korea (Karlsen and Addington-Hall 1998, Higginson and Sen-Gupta 2000, Gao, Ho et al. 2013, Lee and Jang 2018). In our study population, patients stayed at home for a median of 8 days in their last 30 days of life, and only 2% of the patients died at home. Oosterveld-Vlug et al. reported that patients with solid tumors who were receiving active cancer treatment near the end-of-life tended to get hospitalized in the last 30 days of life (odds ratio of 4.32) and die in a hospital (odds ratio of 3.98) more often than those receiving palliative care alone (Oosterveld-Vlug, Donker et al. 2018). Additionally, lung cancer led to a higher number of hospitalizations in the last 30 days of life and death in a hospital than other cancers (Oosterveld-Vlug, Donker et al. 2018). The peculiarities of lung cancer as mentioned above may have contributed to the reduced rate of dying at home and short DASH in our study population.

Reduced physical function (Guerriere, Husain et al. 2016) and dependent ADL (Brazil, Bedard et al. 2003) in patients may increase the caregiver’s burden for home care, which negatively impacts the decision of place for care near the end-of-life (Tang 2003, Gott, Seymour et al. 2004, Yamagishi, Morita et al. 2012). Moreover, physical function and independence are supported by adequate muscle mass in the trunk and limbs (Al Snih, Markides et al. 2004, Tanimoto, Watanabe et al. 2012, Granacher, Gollhofer et al. 2013, Naito, Okayama et al. 2017, Shahtahmassebi, Hebert et al. 2017). We showed that a shortage of muscle mass and physical function at baseline were associated with shorter DASH in this study. We speculate that patients with a small physical reserve at baseline may run out of muscle and function to maintain physical independence until days near the end-of-life. Furthermore, the overall or trunk muscle mass and physical function at baseline may become the predictors of DASH at the end-of-life.

Previous studies have reported that women with cancer had less

DASH than men with cancer (Otsuka 2017, Andersen, Croxford et al. 2019, Cheung, Croxford et al. 2020). Consistently, in our study population, we found that women had less DASH than men. Women generally play a central role in palliative and end-of-life care at home for family members (Brazil, Bedard et al. 2003, Brazil, Thabane et al. 2009, Sugiura, Ito et al. 2009). These facts may be associated with the gender norms, namely women are expected to care for their families (Williams, Giddings et al. 2017). This tendency in the familial role may apply to Japanese community, and it may have led to a short DASH in this study. More research is thus warranted to confirm this speculation.

Our study has several limitations. First, this was a small study and included only Japanese patients who were treated at a single cancer center. Second, our study population was heterogeneous with regard to the treatment regimens received. Third, survivors at the time of analyses and patients who were transferred to another hospital were excluded from our analyses, which may have caused a selection bias. Fourth, we did not consider other types of cancer or physical and social situations at the time of the patient’s decision on the place of death. Fifth, we did not ask the patient’s preference of place for end-of-life care or death in this study. Finally, we did not investigate the interaction among the predictors when analyzing the predictors of DASH, because, even if we divide the patients into subgroups by a variable, the sample size of each subgroup would be too small to determine meaningful evidence. For example, the association of muscle mass and physical function and DASH may have been different in stage III or IV cancer patients. These limitations should be delt with in future researches.

Early discussion regarding end-of-life care has increasingly become important in geriatric oncology (Weathers, O'Caoimh et al. 2016, O'Caoimh, Cornally et al. 2017, Lin, Cheng et al. 2018). This discussion is part of advance care planning and enables patients, their familes, and health-care providers to define goals and preferences for future medical treatment and care (Rietjens, Sudore et al. 2017). If patients with risk factors for short DASH are ready and able to discuss the risk, our findings may promote these discussions from the time of diagnosis and improve the quality of end-of-life care.

Naito et al. recently reported the feasibility of a combined regimen with exercise and nutritional interventions for elderly Japanese patients with advanced cancer (Mouri, Naito et al. 2018, Naito, Mitsunaga et al. 2019). Exploratory analysis showed preservation of physical function, skeletal muscle mass, and physical activity during the study period. The promotion of these programs could lead to improved quality of end-of-life for elderly patients with advanced NSCLC. Clinical trials testing the efficacy of active interventions, such as advance care planning and Nutrition and Exercise Treatment for Advanced Cancer (NEXTAC) programs, may be the next step in end-of-life care for patients with advanced lung cancer.

5. Conclusion

Elderly patients with advanced NSCLC had limited DASH at the end-of-life and died in the hospital. Women and patients with poor muscle mass or physical function were more likely to have short DASH. These findings may promote early discussion about end-of-life care. Further prospective studies are needed to validate our findings.

6. Tables and Figures

Table 1. Baseline characteristics of the patients

Variables	All (n=44)	Men (n=28)	Women (n=16)
Age, years, median (range)	76 (70−87)	75 (70−87)	76 (70−86)
BMI[*], kg/m^2 median (range)	21.7 (14.4−29.3)	22.3 (16.1−29.3)	21.4 (14.4−27.0)
ECOG-PS[†], n (%)			
0	16 (36)	10 (36)	6 (38)
1	27 (61)	18 (64)	9 (56)
2	1 (2)	0 (0)	1 (6)
Stage[‡], n (%)			
locally advanced	18 (41)	12 (43)	6 (38)
metastatic	26 (59)	16 (57)	10 (63)
Treatment, n (%)			
Curative radiotherapy ± chemotherapy	18 (41)	12 (43)	6 (38)
Palliative chemotherapy	26 (59)	16 (57)	10 (63)
Comorbidities, n (%)			
COPD[§]	22 (50)	17 (61)	5 (31)
Type 2 diabetes mellitus	10 (23)	9 (32)	1 (6)
Ischemic heart disease	6 (14)	4 (14)	2 (13)
Cerebrovascular disease	3 (7)	3 (11)	0 (0)
Family structures, n (%)			
Living alone	3 (7)	1 (4)	2 (13)
Living with family	41 (93)	27 (96)	14 (88)

[*] BMI: Body mass index.

[†] ECOG-PS: Eastern cooperative oncology group performance status.

[‡] Locally advanced means stage IIIA or IIIB and metastatic means stage IV or postoperative recurrence.

[§] COPD: Chronic obstructive pulmonary disease.

Table 2. Baseline body composition and physical function

Variables	All (n=44)	Men (n=28)	Women (n=16)
Body composition[*], kg/m^2, median (range)			
Overall muscle mass index	14.7 (10.5−19.2)	15.8 (13.4−19.2)	13.8 (10.5−14.8)
Trunk muscle mass index[†]	8.5 (6.5−10.7)	9.0 (7.7−10.7)	8.0 (6.5−8.5)
Appendicular skeletal muscle mass index	6.3 (4.0−8.5)	6.9 (5.6−8.5)	5.6 (4.0−6.6)
Muscle depletion[‡], n (%)	26 (59)	16 (57)	10 (63)
Physical function, median (range)			
Hand-grip strength, dominant side, kg	28.3 (14.6−46.9)	31.5 (14.6−46.9)	20.8 (16.3−29.8)
Incremental shuttle walking distance, m	290 (80−640)	290 (80−640)	280 (170−450)

[*] The muscle mass index was defined as the muscle mass (kg) divided by the square of height (m).

[†] The trunk muscle mass was defined as the overall muscle mass minus the appendicular skeletal muscle mass.

[‡] Muscle depletion was defined as appendicular skeletal muscle mass index < 7.0 kg/m^2 in men and < 5.8 kg/m^2 in women.

Table 3. Place of death and frequency of hospitalization in the last 30 days of life

Variables	All (n=44)
Place of death, n (%)	
Hospital	25 (57)
Palliative care unit	17 (39)
Nursing facility	1 (2)
Home	1 (2)
Frequency of hospitalization, n (%)	
0	1 (2)
1	39 (89)
2	4 (9)

Table 4. Clinical predictors of days spent at home (univariate analysis)

Variables	β[*]	95% CI[†]	p-value
Age (years, per one year increase)	−0.1	−0.9 to 0.8	0.901
Sex			
Men (reference, women)	7.3	0.6 to 14.1	0.035
ECOG-PS[‡] (reference, 0)			
1	2.5	−4.6 to 9.7	0.479
2	−9.3	−32.6 to 14.1	0.429
Stage			
Metastatic (reference, locally advanced)	0.2	−6.7 to 7.2	0.943
Treatment			
Curative radiotherapy ± chemotherapy (reference, palliative chemotherapy)	−0.2	−7.2 to 6.7	0.943
Comorbidities			
COPD[§] (reference, no COPD)	−0.9	−7.8 to 5.9	0.790
Type 2 diabetes mellitus (reference, no type 2 diabetes mellitus)	7.6	−0.2 to 15.5	0.056
Ischemic heart disease (reference, no ischemic heart disease)	3.8	−6.2 to 13.7	0.450
Cerebrovascular disease (reference, no cerebrovascular)	−2.1	−15.7 to 11.5	0.761
Sarcopenia: muscle depletion (reference, no muscle depletion)	−3.7	−10.6 to 3.2	0.284
Family structures			
Living with family (reference, living alone)	2.1	−11.5 to 15.7	0.761
Body composition (per one unit increase)			
Overall muscle mass index, kg/m^2	2.1	0.2 to 4.0	0.028
Trunk muscle mass index, kg/m^2	4.7	0.9 to 8.5	0.017
Appendicular skeletal muscle mass index, kg/m^2	3.5	−0.1 to 7.0	0.054
Physical function (per one unit increase)			
Hand-grip strength, dominant side, kg	0.4	0.0 to 0.8	0.032
Incremental shuttle walking distance, m	0.0	0.0 to 0.0	0.274
BMI[‖] (kg/m^2, per one unit increase)	0.3	−0.7 to 1.4	0.518

The predictive variables were measured at baseline.

[*] β: Regression coefficient. For a continuous variable such as a muscle mass index, DASH increased by β on the average if the continuous variable increased by one unit. For a nominal variable such as sex and stage, DASH

[†] CI: Confidence interval.

[‡] ECOG-PS: Eastern cooperative oncology group performance status was considered as a continuous variable.

[§] COPD: Chronic obstructive pulmonary disease.

[‖] BMI: Body mass index.

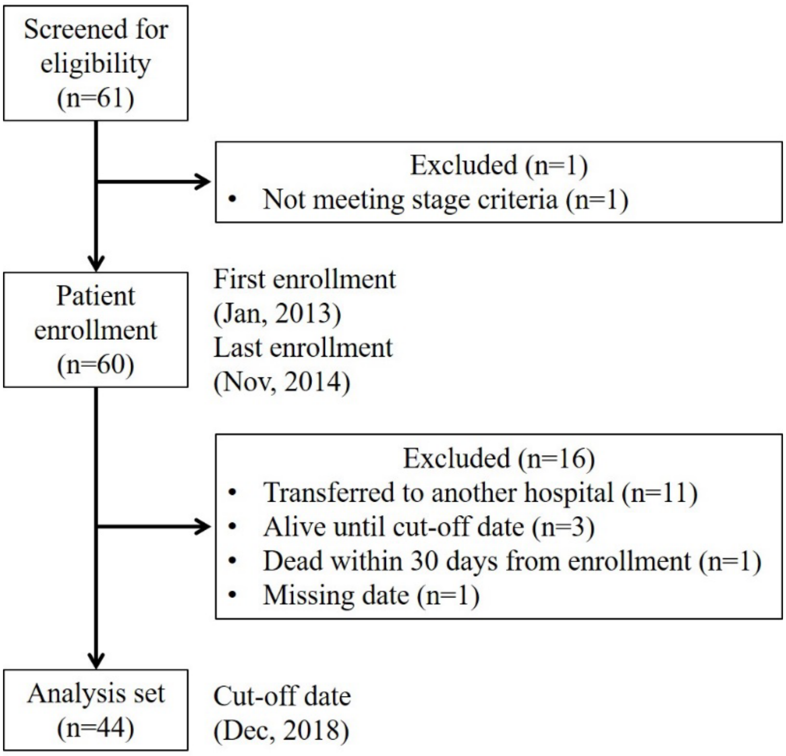


Figure 1. Flow diagram of patient screening, enrollment, follow-up, and analysis set.

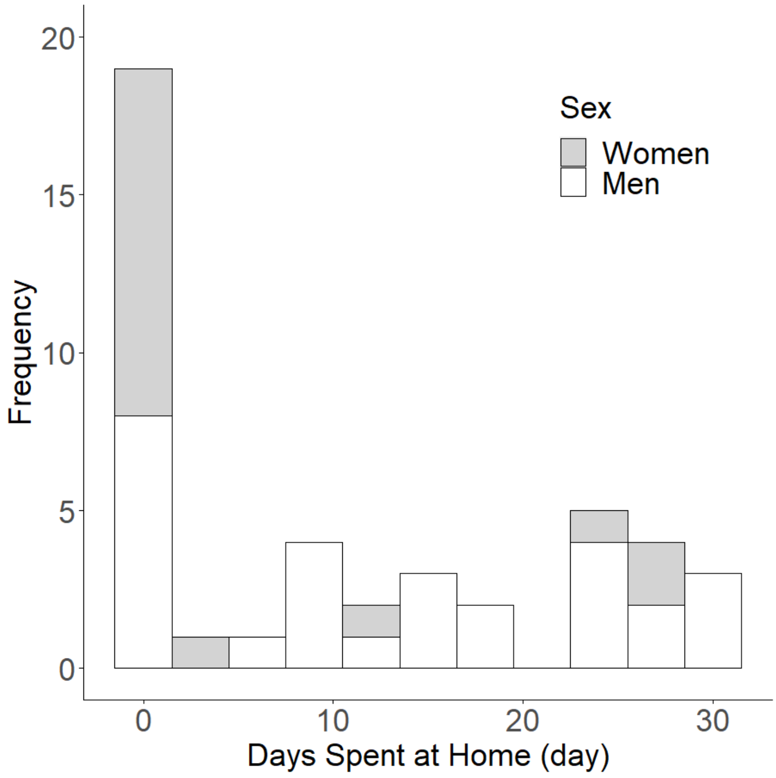


Figure 2. Distribution of DASH in the last 30 days of life (n=44). Women and men are represented by the gray and white colors, respectively.

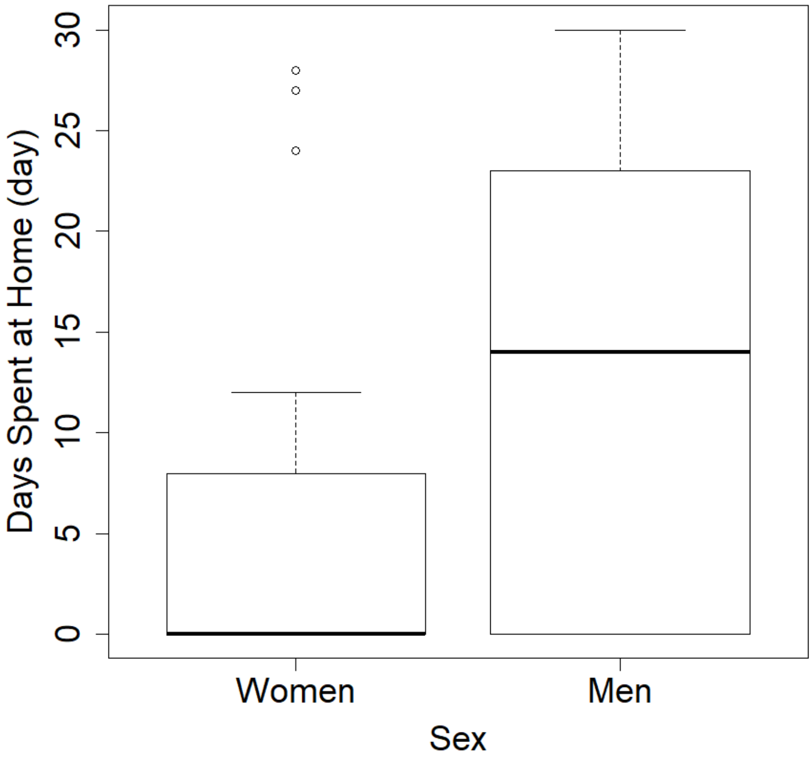
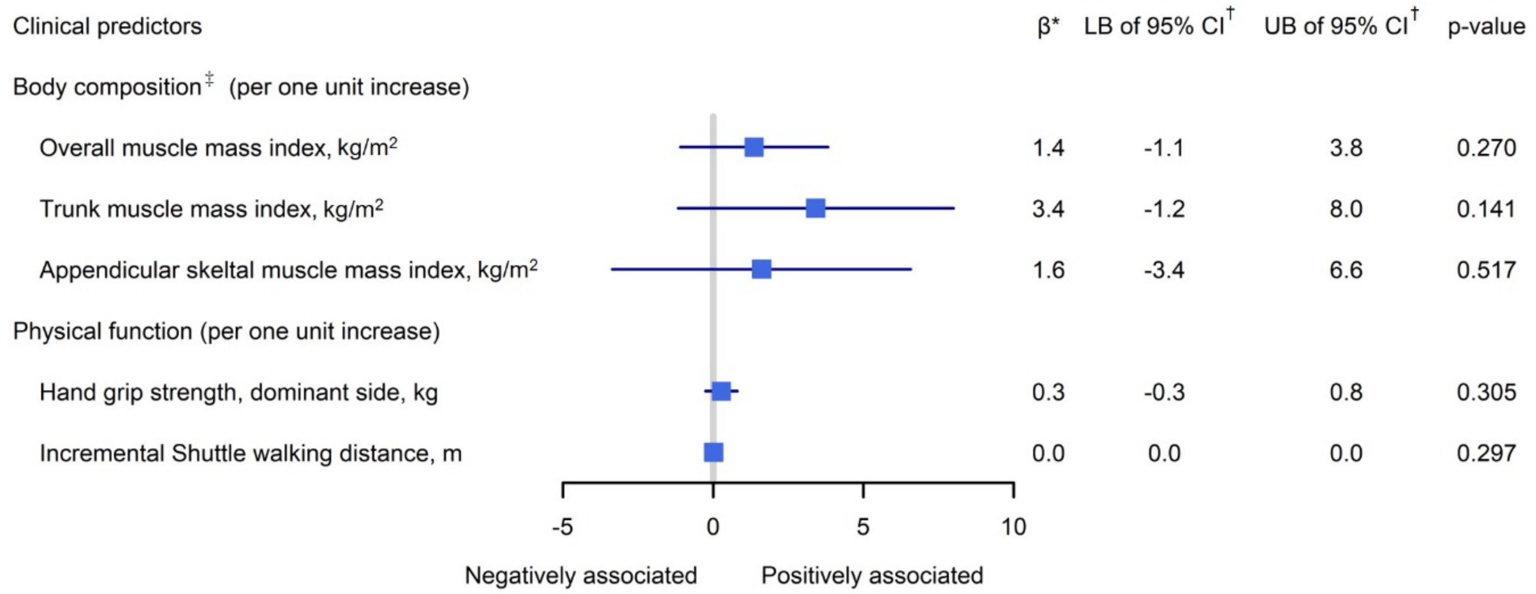


Figure 3. Comparison of DASH in the last 30 days of life between men and women.

The bold line inside the box indicates the median. The top and bottom of each box represent the third and first quartile (Q3 and Q1), respectively. The two bars outside the box represent the lowest datum still within 1.5 × (Q3−Q1) of Q1, and the highest datum still within 1.5 w (Q3−Q1) of Q3. Any data not within the two bars are outliers and are represented by empty circles.



Clinical predictors	β*	LB of 95% CI[†]	UB of 95% CI[†]	p-value
Body composition[‡] (per one unit increase)				
Overall muscle mass index, kg/m^2	1.4	-1.1	3.8	0.270
Trunk muscle mass index, kg/m^2	3.4	-1.2	8.0	0.141
Appendicular skeltal muscle mass index, kg/m^2	1.6	-3.4	6.6	0.517
Physical function (per one unit increase)				
Hand grip strength, dominant side, kg	0.3	-0.3	0.8	0.305
Incremental Shuttle walking distance, m	0.0	0.0	0.0	0.297

Figure 4. Clinical predictor of DASH (adjusted for gender).

[*] β: Partial regression coefficient. For a continuous variable such as a muscle mass index, DASH increased by β on the average if the continuous variable increased by one unit. For a nominal variable such as sex and stage, DASH increased by β on the average compared with the reference.

[†] CI: Confidence interval; LB: lower bound; UB: upper bound.

[‡] The muscle mass index was defined as the muscle mass (kg) divided by the square of height (m).

[§] The trunk muscle mass was defined as the overall muscle mass minus the appendicular skeletal muscle mass.

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Chapter 4
Conclusion

1. Summaries of our research

The aims of our research were (1) to measure the quality of life during the early period after diagnosis and days spent at home near the end-of-life, (2) to identify early predictors of reduced quality of life, and (3) to identify early predictors of days spent at home in elderly patients with advanced non-small-cell lung cancer. In chapter 2, we reported that many patients had a clinically relevant deterioration of quality of life score. The mean of daily steps and shuttle walking distance can be predictors of clinically relevant deterioration of quality of life. In chapter 3, we reported that many patients had limited days spent at home at the end-of-life. Women and patients with poor muscle mass or physical function were more likely to have short days spent at home. To the best of our knowledge, this study is the first to report the quality of life and days spent at home near the end-of-life of elderly patients with advanced non-small-cell lung cancer.

Patients investigated in chapter 2 and 3 were elderly non-small-cell lung cancer patients in stage III and stage III/IV at initial diagnosis, respectively. The treatment goals for patients during the early period after initial diagnosis with stage III cancer and stage IV cancer differ; hence, data on the quality of life during the early period after initial diagnosis should preferably be presented separately. Additionally, we speculated that the terminal stages of patients with stage III cancer and those with stage IV cancer at initial diagnosis are not substantially different. This is the reason why we investigated patients who were initially diagnosed with stage III cancer and stage IV cancer simultaneously in terms of days spent at home near the end-of-life in chapter 3. We reported that days spent at home and cancer stage were not statistically significantly associated. There was a limitation to our research, that is, we did not investigate the interaction between muscle mass and physical functions, and cancer stage in chapter 3.

2. Concluding discussion

We present the prospective studies of a small number of patients at a single institution. Therefore, the level of evidence of our study is low compared with that of large prospective observational studies or interventional studies. The findings of our study should be confirmed by future large, multicenter prospective observational studies. In such a research, the problem untreated in our research, for example, preference of place of end-of-life, must be taken into consideration. Although the present study had the abovementioned limitations, our findings can be applied to prevent decreases in quality of life and the number of days spent at home near the end-of-life for elderly patients with advanced non-small-cell lung cancer.

First, our research suggests that elderly patients with advanced non-small-cell lung cancer, who have reduced muscle mass and physical function at diagnosis, tend to have a lower quality of life and fewer days spent at home near the end-of-life. Therefore, people ought to improve their physical function and increase their muscle mass before cancer diagnosis. Nurses can encourage community-dwelling elderly people to maintain and improve their muscle mass and physical functions before cancer diagnosis. For example, nurses working in hospitals treating elderly cancer patients can be presenters at workshops held by the local government to teach the community-dwelling elderly about the importance of increasing muscle mass and physical functions. Based on their own experiences with elderly patients with advanced non-small-cell lung cancer, they can explain the importance of increasing muscle mass and physical functions in a concrete manner.

Second, after advanced non-small-cell lung cancer diagnosis, early intervention should be provided to elderly patients to improve muscle mass and physical function. An example of such an early intervention is the Nutrition and Exercise Treatment for Advanced Cancer (NEXTAC) program (Naito, Mitsunaga et al. 2019). This program consists of interventions by hospital nutritionists, physical therapists, physicians, and nurses, and begins with the first chemotherapy cycle. In the NEXTAC program, hospital nurses collect data on the lifestyle of patients, including their daily physical activity, and explain the importance of daily physical activity, muscle mass, and physical functions, and teach the patients how to increase them and prevent falls. Hospital nurses must play a central role in the management of medical workers, because they are the first health care providers to come in contact with patients, and can be successfully involved in gathering patient information through nursing care.

Other aspects should be discussed in order to maintain the quality of life and prolong the days spent at home near the end-of-life. Patients may converse with healthcare providers and family members about their end-of-life preferences. These processes are recognized as advance care planning and require further research. Expanding social resources is important in order to fulfill the end-of-life preferences of patients. These social resources include home medical care, palliative care, home nursing, and training of medical care team members.

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Mikako Notsu, Tateaki Naito, Keita Mori, Akifumi Notsu, Ayumu Morikawa, Takanori Kawabata, Taro Okayama, Yusuke Yonenaga, Miwa Sugiyama, Hirotsugu Kenmotsu, Haruyasu Murakami, Tomoko Ito, Michiaki Kai, Toshiaki Takahashi (2021). “Days spent at home near the end-of-life in Japanese elderly patients with lung cancer: Post-hoc analysis of a prospective study.” Asia-Pacific Journal of Oncology Nursing. 8(3):228-236.

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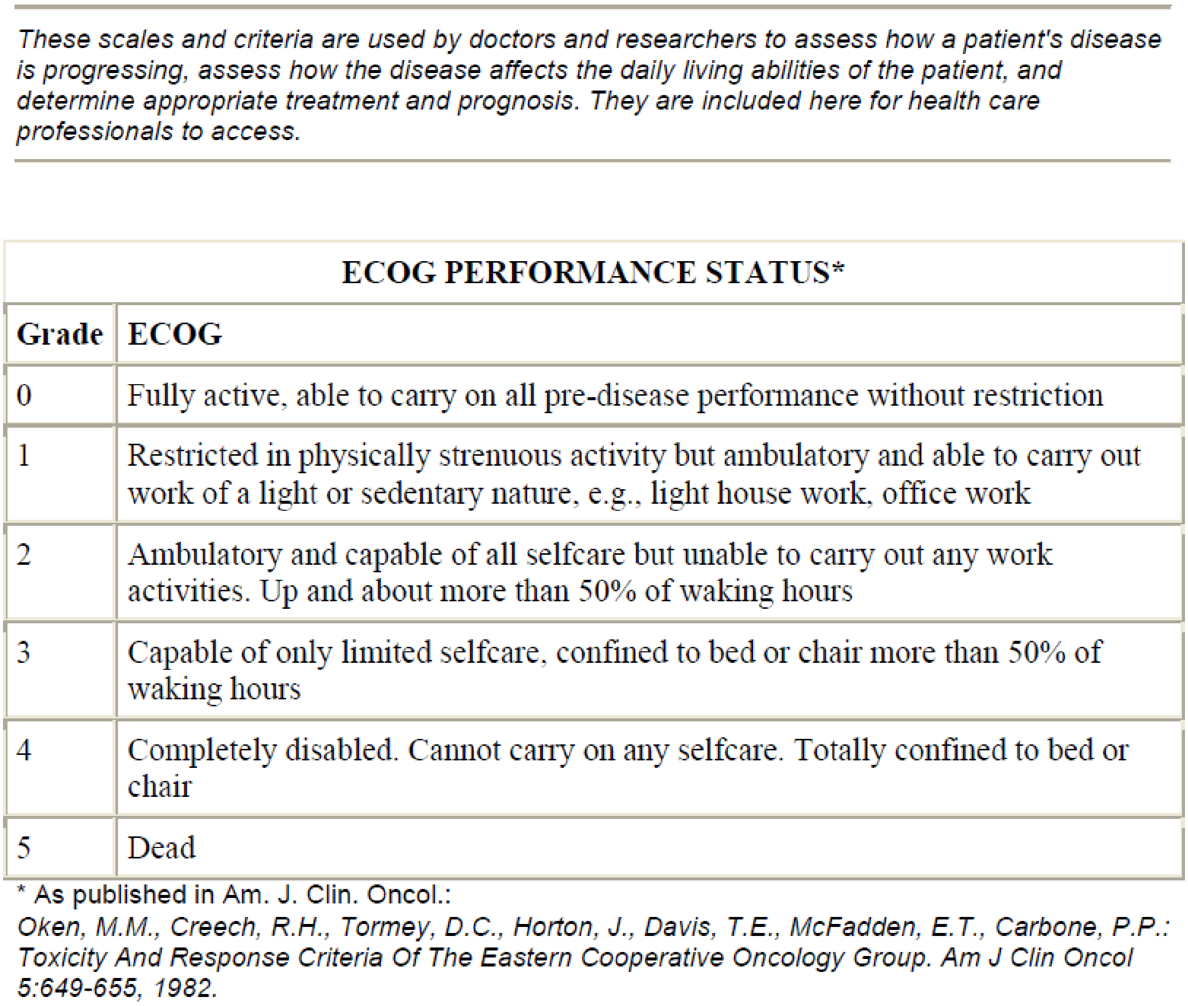
Supplementary materials

Supplementary material 1. Eastern Cooperative Oncology Group performance status



These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

(continued on following page)

ECOG のPerformance Status（PS）の日本語訳

Performance Status Score

Score	定義
0	全く問題なく活動できる。 発病前と同じ日常生活が制限なく行える。
1	肉体的に激しい活動は制限されるが、歩行可能で、軽作業や座っての作業は行うことができる。 例：軽い家事、事務作業
2	歩行可能で自分の身の回りのことはすべて可能だが作業はできない。 日中の50%以上はベッド外で過ごす。
3	限られた自分の身の回りのことしかできない。日中の50%以上をベッドか椅子で過ごす。
4	全く動けない。 自分の身の回りのことは全くできない。 完全にベッドか椅子で過ごす。

出典 Common Toxicity Criteria, Version2.0 Publish Date April 30, 1999
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf
JCOG ホームページ http://www.jcog.jp/

Supplementary material 2. Japanese questionnaire EORTC QLQ-C30 (version 3.0)

JAPANESE

質問表　EORTC QLQ-C30 (version 3)

私達は、あなたとあなたの健康状態について関心を持っています。 あなたの状態に、もっともよく当てはまる番号一つを○で囲み、全設問にお答え下さい。「正しい」答えや「誤った」答え、といったものはありません。 なお、お答え頂いた内容については秘密厳守とさせていただきます。

あなたの名前の頭文字を書いて下さい。　姓:___ 名:___ (例:山田花子さん。姓:や 名:は)
あなたの生年月日を書いて下さい。　19___年(明・大・昭・平___年)___月___日生
今日の日付を書いて下さい。　20___年(平成________年)___月___日

		まったく ない	少し ある	多い	とても 多い
1.	重い買い物袋やスーツケースを運ぶなどの力仕事に支障がありますか。	1	2	3	4
2.	長い距離を歩くことに支障がありますか。	1	2	3	4
3.	屋外の短い距離を歩くことに支障がありますか。	1	2	3	4
4.	一日中ベッドやイスで過ごさなければなりませんか。	1	2	3	4
5.	食べること、衣類を着ること、顔や体を洗うこと、トイレにいくことに人の手を借りる必要がありますか。	1	2	3	4

この一週間について		まったく ない	少し ある	多い	とても 多い
6.	仕事をすることや日常生活活動に支障がありましたか。	1	2	3	4
7.	趣味やレジャーをするのに支障がありましたか。	1	2	3	4
8.	息切れがありましたか。	1	2	3	4
9.	痛みがありましたか。	1	2	3	4
10.	休息をとる必要がありましたか。	1	2	3	4
11.	睡眠に支障がありましたか。	1	2	3	4
12.	体力が弱くなったと感じましたか。	1	2	3	4
13.	食欲がないと感じましたか。	1	2	3	4
14.	吐き気がありましたか。	1	2	3	4
15.	吐きましたか。	1	2	3	4
16.	便秘がありましたか。	1	2	3	4

次のページにお進みください

JAPANESE

	この一週間について	まったくない	少しある	多い	とても多い
17.	下痢がありましたか。	1	2	3	4
18.	疲れていましたか。	1	2	3	4
19.	痛みがあなたの日々の活動のさまたげになりましたか。	1	2	3	4
20.	ものごとに集中しにくいことがありましたか。 たとえば新聞を読むときや、テレビを見るようなときなど。	1	2	3	4
21.	緊張した気分でしたか。	1	2	3	4
22.	心配がありましたか。	1	2	3	4
23.	怒りっぽい気分でしたか。	1	2	3	4
24.	落ち込んだ気分でしたか。	1	2	3	4
25.	もの覚えが悪くなったと思いましたか。	1	2	3	4
26.	身体の調子や治療の実施が、家族の一員としてのあなたの生活のさまたげになりましたか。	1	2	3	4
27.	身体の調子や治療の実施が、あなたの社会的な活動のさまたげになりましたか。	1	2	3	4
28.	身体の調子や治療の実施が、あなたの経済上の問題になりましたか。	1	2	3	4

次の質問では、1から7の数字のうち、あなたにもっともよく当てはまる数字を〇で囲んで下さい。

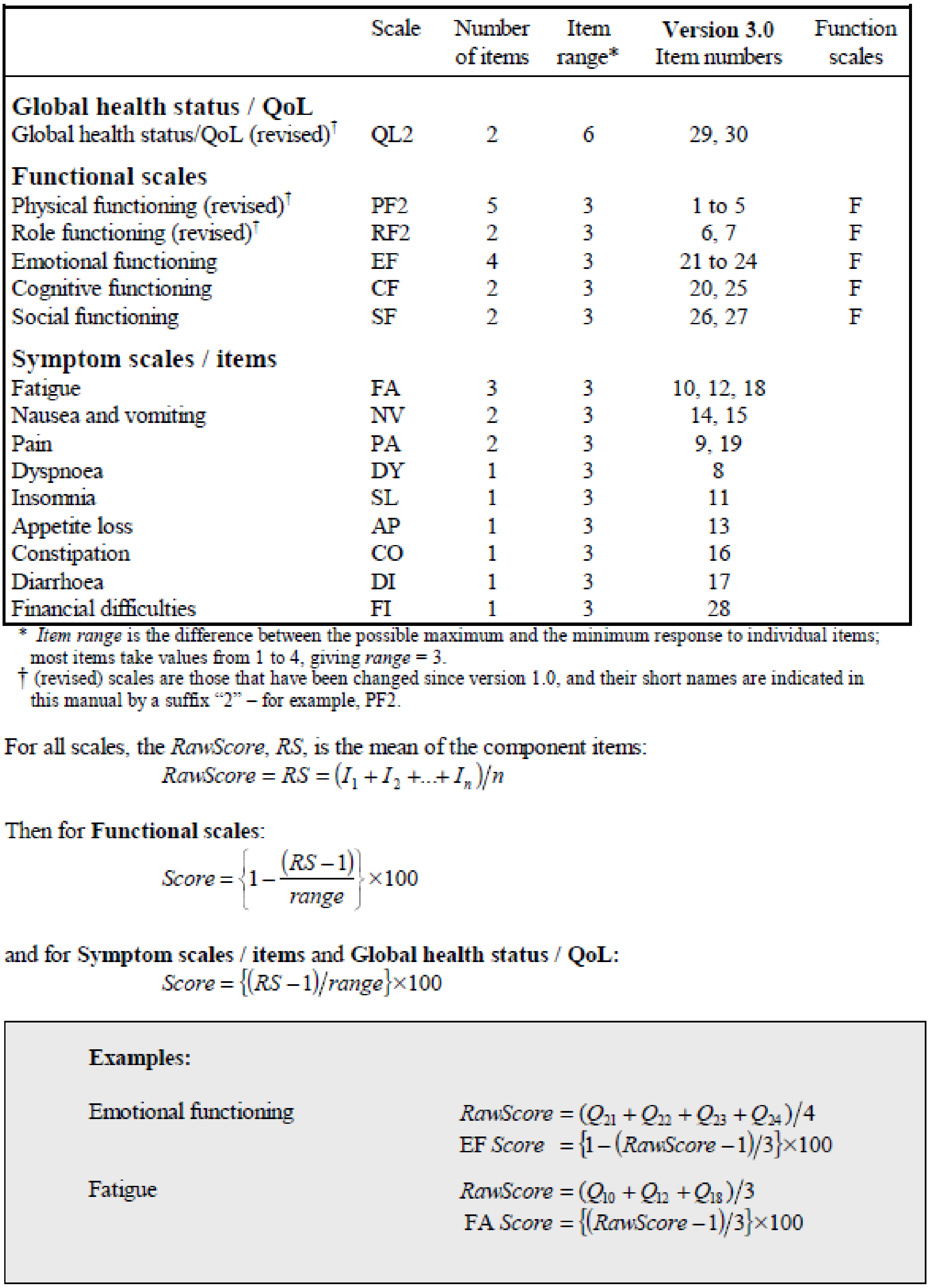
29. この一週間のあなたの健康状態は全体としてどの程度だったでしょうか。

1	2	3	4	5	6	7
とても悪い						とてもよい

30. この一週間、あなたの全体的な生活の質はどの程度だったでしょうか。

1	2	3	4	5	6	7
とても悪い						とてもよい

Supplementary material 3. Scoring of the EORTC QLQ-C30 version 3.0



	Scale	Number of items	Item range*	Version 3.0 Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + \ldots + I_n)/n$$

Then for **Functional scales**:

$$Score = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$$

and for **Symptom scales / items** and **Global health status / QoL**:

$$Score = \{(RS-1)/range\} \times 100$$

Examples:

Emotional functioning

$$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$$
$$\text{EF } Score = \{1 - (RawScore - 1)/3\} \times 100$$

Fatigue

$$RawScore = (Q_{10} + Q_{12} + Q_{18})/3$$
$$\text{FA } Score = \{(RawScore - 1)/3\} \times 100$$

EORTC (2001). EORTC QLQ-C30 Scoring Manual Third edition. https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf