

# Impact of Physical Inactivity on the Risk of Disability and Hospitalization in Older Patients with Advanced Lung Cancer

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**Purpose:** This prospective observational study aimed to explore the influence of physical inactivity during initial chemotherapy on the risk of disability and hospitalization in later life among older patients with advanced non-small-cell lung cancer (NSCLC).

**Patients and Methods:** Patients aged 70 or above who were scheduled to receive first-line chemotherapy for newly diagnosed advanced NSCLC were recruited for the study. An electronic pedometer was used to measure daily steps; based on the change rate (cutoff: -12.5%) from pretreatment to 12 ± 4 weeks after enrolment, patients were classified as active or inactive. The Barthel Index estimated activities of daily living. We compared disability-free survival time, mean cumulative functions of hospital stays, and medical costs, between the active and inactive groups.

**Results:** Among the 29 patients enrolled, 21 were evaluable. Compared with active patients (n = 11), inactive patients (n = 10) showed shorter disability-free survival (6.4 vs 19.9 months,  $p < 0.05$ ) and tended to have longer hospital stays (23.7 vs 6.3 days/person) and higher inpatient care cost (¥1.6 vs ¥0.3 million/person [US\$16,000 vs US\$3000/person]) during the first year.

**Conclusion:** Physical inactivity during initial chemotherapy may be a risk factor for developing disability and requiring hospitalization in later life for older patients with advanced NSCLC. Our findings may indicate the need for lifestyle interventions with multidisciplinary teams, which include physicians, nurses, and physiotherapists, for older patients with advanced lung cancer during an active cancer treatment. A large-sample-sized study is needed to validate our findings.

**Keywords:** non-small-cell lung cancer, older patients, physical activity, disability-free survival, medical cost, length of hospital stay

## Introduction

The number of older patients with advanced lung cancer has been increasing because of global population aging<sup>1</sup> and a high proportion of metastatic diseases at the time of diagnosis of lung cancer.<sup>2</sup> Further, patients with advanced cancer now live longer because of advances in anticancer treatments, such as molecular targeted therapies and immunotherapies.<sup>3</sup> Thus, these medical conditions may become an economic burden on society. In Japan, approximately half (57%, ¥3.2 hundred million [US\$3.2 million]) of the annual national medical costs for tracheal, bronchial, and lung cancers were associated with older individuals aged 70 years or older, and the majority of the costs (64%, ¥2.0 hundred million [US\$2.0 million]) were associated with their inpatient care.<sup>4</sup>

Older patients are predisposed to sarcopenia<sup>5</sup> and decreased physical function,<sup>6</sup> which are highly associated with disability.<sup>7</sup> Additionally, older patients with advanced lung cancer are prone to multiple comorbidities,<sup>8</sup> malnutrition,<sup>9</sup> muscle depletion,<sup>10</sup> and cancer cachexia,<sup>11,12</sup> thereby resulting in progressive physical inactivity.<sup>13,14</sup> These negative characteristics account for this population's vulnerability and increase their medical dependency from an early cancer trajectory.<sup>12</sup> This complexity in pathogenesis indicates a need for multidisciplinary approaches to prevent worsening physical conditions during cancer treatment in this population.<sup>15</sup> However, there are few previous reports on the longitudinal changes in physical activity in patients with advanced lung cancer.<sup>14</sup> Furthermore information on when physical inactivity occurs and how it affects functional and socioeconomic outcomes is limited. Accordingly, we conducted this prospective observational study to explore the influence of physical inactivity during initial chemotherapy on the risk of disability and hospitalization in later life among older patients with advanced non-small-cell lung cancer (NSCLC).

## Materials and Methods

### Patient Selection

This prospective longitudinal observational study was conducted from February 2014 to October 2017 at the Shizuoka Cancer Center, Japan. To be eligible, patients had to: (1) have histologically or cytologically proven metastatic or postoperative recurrent NSCLC; (2) be aged 70 years or older; (3) be scheduled to receive first-line systemic chemotherapy; (4) not have undergone previous systemic chemotherapy or thoracic radiotherapy (adjuvant chemotherapy was not counted as prior chemotherapy); (5) have an Eastern Cooperative Oncology Group performance status (PS) of 0–1; (6) be able to ambulate, read, and respond to questions without assistance; and (7) have an expected survival of more than twelve weeks. Patients with severe psychiatric disorders, active infectious diseases, unstable cardiac disease, or untreated symptomatic brain or bone metastases hindering accurate assessment were excluded. All patients provided their written informed consent. The study was approved by the Shizuoka Cancer Center's institutional review board (Shizuoka, Japan) and registered on the University Hospital Medical Information Network Clinical Trials Registry in Japan (trial registration number:

UMIN000012845). All assessments were carried out under the ethical principles outlined in the Declaration of Helsinki.

### Patient Enrolment and Data Collection

The study period was defined as the duration from the enrolment date to either the final visit or the cutoff date (August 31, 2018). Daily steps (steps/day) and duration of moderate to vigorous physical activity (MVPA, in minutes) were assessed at pretreatment and  $12 \pm 4$  weeks (T2) after enrolment. Body mass index ( $\text{kg}/\text{m}^2$ ), lumbar skeletal muscle index ( $\text{cm}^2/\text{m}^2$ ), incremental shuttle walking distance (m), and hand-grip strength (kg) were assessed at pretreatment. Pretreatment assessments were performed during the period from enrolment to the first chemotherapy session. The attending physicians and physiotherapists performed all assessments. The best response to chemotherapy was evaluated by the Response Evaluation Criteria in Solid Tumors version 1.1.<sup>16</sup>

### Assessment of Physical Activity

Daily steps and intensity of physical activity were continuously measured using an electronic pedometer (Kenz Lifecorder-GS, Suzuken Co., Ltd., Nagoya, Japan). Under laboratory conditions, this instrument can determine step counts with intra-model reliability of 0.998 and accuracy within 3% of the actual number of steps taken.<sup>17</sup> After providing their informed consent, the patients wore the device on the side of their waist.<sup>18</sup> We instructed patients to wear the device for as long as possible, from when they change clothes in the morning until they change into nightclothes. The device recorded the daily steps and intensity of physical activity every 4 s throughout the day. The data, including the number of daily steps, intensity of physical activity, and time during which the device was worn, were collected during regular visits to the outpatient department, pretreatment and T2. Days on which the device was worn for less than five hours were excluded from the analysis.<sup>14,19,20</sup> Daily steps and intensity of physical activity were monitored throughout the study period until the cutoff date. Physical activity which included three or more metabolic equivalents (METs) was defined as MVPA.<sup>21</sup> The average number of daily steps and duration of MVPA for the seven days before the pretreatment assessment was set as the parameter for daily steps and duration of MVPA during the pretreatment period. Likewise, the average number of daily steps and duration of MVPA for the seven days before T2 was set as

the parameter for T2. The change rate in daily steps from pretreatment to T2 was derived using the following formula:

$$\left[ \frac{\text{changerateindailysteps}(\%) = \left\{ \frac{(\text{dailystepsatT2} - \text{pretreatmentdailysteps})}{\text{pretreatmentdailysteps}} \right\} \times 100}{\right]$$

The patients were classified into two groups based on the change rate as follows: those with an equal or higher median change rate in daily steps were classified as active, while those with a lower median change rate in daily steps were classified as inactive.

## Assessment of Skeletal Muscle Mass

Lumbar skeletal muscle mass was estimated by analyzing electronically stored computed tomography (CT) images using sliceOmatic software (version 5.0, TomoVision, Montreal, Quebec, Canada). The CT images were contrast-enhanced or unenhanced with a slice thickness of 5 mm. Furthermore, two consecutive CT images at the third lumbar vertebra (L3) were selected to measure the skeletal muscle's cross-sectional area identified based on the Hounsfield unit thresholds from  $-29$  to  $+150$ . The cross-sectional areas ( $\text{cm}^2$ ) of the L3 region muscle were computed for each image. The mean value of two images was normalized for height in square meters and reported as lumbar skeletal muscle index.<sup>22</sup>

## Definition of Skeletal Muscle Depletion and Cancer Cachexia

Skeletal muscle depletion was defined based on lumbar skeletal muscle index cutoffs of less than  $43.0 \text{ cm}^2/\text{m}^2$  and  $53.0 \text{ cm}^2/\text{m}^2$  for men with a body mass index of less than  $25.0 \text{ kg}/\text{m}^2$  and  $25.0 \text{ kg}/\text{m}^2$  or higher, respectively, and the cutoff was  $41.0 \text{ cm}^2/\text{m}^2$  for women.<sup>23</sup> According to the consensus criteria, we defined cancer cachexia as an unintentional weight loss of higher than 5% in the preceding six months, weight loss of higher than 2% in patients with a body mass index of less than  $20.0 \text{ kg}/\text{m}^2$ , or the presence of skeletal muscle depletion.<sup>24</sup> The patients' weight six months before enrolling in the study were obtained through interviews with them and their family members before the study's commencement.

## Assessment of Physical Function

An incremental shuttle walking test was conducted based on a recent guideline<sup>25</sup> and an original protocol presented

by Singh et al.<sup>26</sup> A 10 m course was created in the hospital corridor. Walking speed was indicated by a timed signal played on a compact disk 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 with careful observation to ensure that they did not exceed their exercise limits. An instructor accompanied the patients along the course during the assessments but did not interfere with the process by encouraging them. 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 (ie, walk for more than 0.5 m away from the cone within the set time), or (3) when the patient experienced 85% or higher heart rate than the predicted maximal heart rate derived using the formula  $[210 - (0.65 \times \text{age})]$ . Incremental shuttle walking distance denoted the maximum walking distance.

Hand-grip strength was measured using a grip strength dynamometer (GRIP-D, Takei Scientific Instruments Co., LTD, Niigata, Japan). The device's handle was adjusted according to participants' hand size such that the index finger of each hand was at  $90^\circ$  flexion between the proximal and middle phalangeal joint. Additionally, an instructor demonstrated the proper form—placing the feet hip-width apart and holding the dynamometer away from the body and in line with the forearm at thigh level so that it did not touch the body, while ensuring that the arm was fully extended—and emphasized a quick and hard squeeze of the handle.<sup>27</sup> Patients did not perform any practice tests. A trial was performed for each hand and the results from the hand yielding the highest force were used for this analysis.

## Disability-Free Survival and Overall Survival

To assess daily living activities, the Barthel Index was estimated by the attending physician or physiotherapist for each hospital visit. The assessment interval was at least once in twelve weeks. The disability-free survival (DFS)<sup>28</sup> duration was calculated as the time between T2 and the onset of a disabling event. A disabling event is defined as a decrease in the Barthel Index from the pretreatment value by ten points or higher. The event was considered an actual event when the condition

persisted for more than two weeks from the initial report. In confirmed events, the initial reports' dates were used as the event dates in the analysis. The overall survival duration was calculated as the time between T2 and death. The DFS and overall survival were censored on the final visit for patients whose disabling events or deaths were not confirmed.

## Assessment of Healthcare Resource Utilization

Medical claims data, including the numbers of hospitalization and outpatient visits, length of hospital stays, healthcare resource utilization, and medical costs were obtained from hospital electronic medical records.<sup>12</sup> Medical claims data were obtained through the local clinics and hospitals' institutional coordination offices for patients receiving medical care at another hospital. Certified medical accountants estimated inpatient medical costs. In this study, medical costs refer to the hospital's actual revenue from the health insurance funds of the Japanese healthcare system. We did not include medical costs for home care. For healthcare utilization analysis, visits (or hospitalizations) for supportive care included all visits (or hospitalizations) involving physical examinations, excluding visits (or hospitalizations) for chemotherapy, radiotherapy, or surgery.

## Statistical Analysis

Since this was an exploratory study, the sample size was determined based on the feasibility of the study. Pretreatment patient characteristics of both groups were compared using Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The overall survival and DFS rates from a landmark point (ie, T2) were estimated using the Kaplan-Meier method and compared using a Log rank test. Cox proportional hazard models were used to estimate the association between the change in daily steps and overall survival or DFS. We used the mean cumulative function for the recurrent event analysis<sup>29</sup> of the cumulative length of hospital stays and medical costs related to cancer care from a landmark point, as performed in previous studies.<sup>12,30,31</sup> For all analyses, the level of statistical significance was set at  $p = 0.05$ . Statistical analyses were performed using JMP Pro 14.0.0 for Mac (SAS Institute Inc., USA).

## Results

### Patient Characteristics

Twenty-nine patients were enrolled in the study from February 27, 2014 to October 13, 2017. One patient discontinued participation for personal reasons, whereas seven patients did not undergo initial chemotherapy, opting for the best possible supportive care. Therefore, the remaining 21 patients were included in the analyses (Figure 1). The median period from the diagnosis of metastatic or postoperative recurrent disease to study enrolment was 1.9 weeks (range: 0.0–29.9 weeks). The median age was 75 years (range: 70–82 years; Table 1). Seventeen patients (81.0%) had stage IV, and four (19.0%) had postoperative recurrence. Seven and fourteen patients exhibited a PS of 0 and 1, respectively, and fifteen and six patients received cytotoxic and targeted regimens as the first-line chemotherapy, respectively. The median body mass index was 21.9 kg/m<sup>2</sup> (range: 19.0–28.1 kg/m<sup>2</sup>). Skeletal muscle depletion and cancer cachexia were diagnosed in fourteen (66.7%) and thirteen (61.9%) patients. The median incremental shuttle walking distance was 360 m (range: 140–550 m) in men and 355m (range: 120–480 m) in women. The median hand-grip strength was 30.6 kg (range: 25.6–37.2 kg) in men and 23.7 kg (range: 19.0–30.3 kg) in women. The median number of daily steps and duration of MVPA at pretreatment was 3389.6 steps (range: 1141.6–17,711.3 steps) and 4.4 minutes (range: 0–60.9 minutes), respectively.

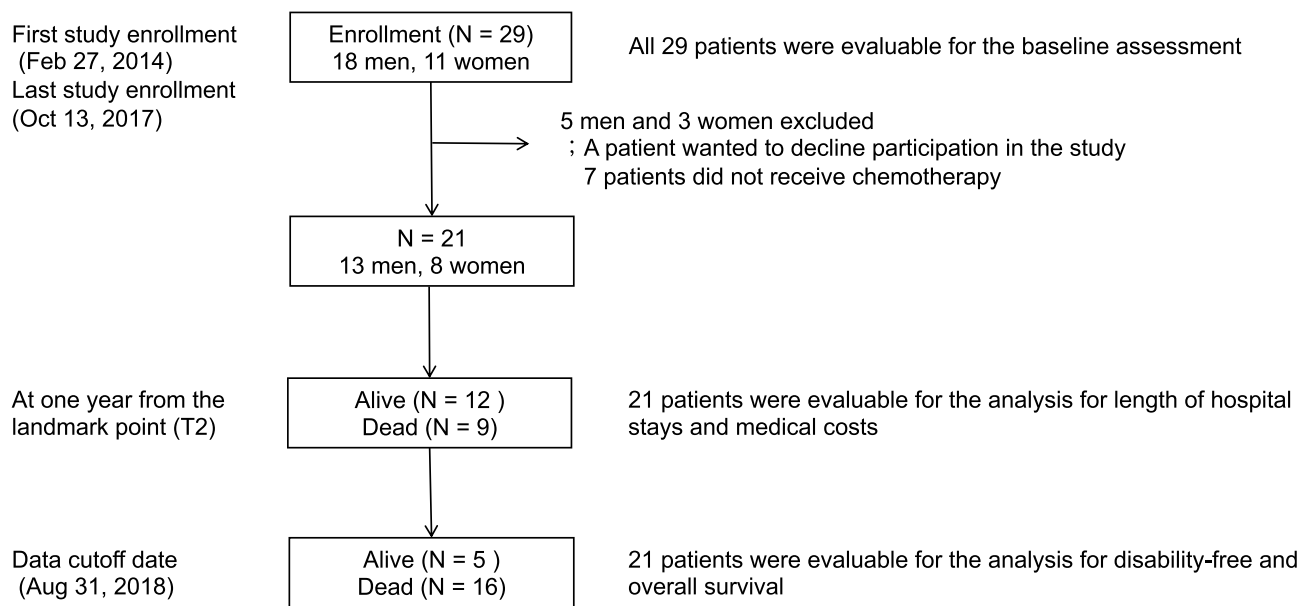
### Change in Physical Activity

The median change rate in daily steps from pretreatment to T2 was –12.5% (range: –89.5 to +91.7%) in all patients (Table 2). Furthermore, eleven and ten patients were classified as active and inactive, respectively. The median change in daily steps was +490 steps (+6.4%) and –1333 steps (–35.6%) for active and inactive patients, respectively. The duration of MVPA at T2 was 2.3 minutes (range: 0.0–52.6 minutes), and the median change rate in the duration of MVPA from pretreatment to T2 was –24.3% (range: –100.0 to 45.5%) in all patients (Table 2).

### Differences in Patient Characteristics

The pretreatment lumbar skeletal muscle index among men was significantly lower for active patients than for inactive patients (39.4 vs 45.2 cm<sup>2</sup>/m<sup>2</sup>,  $p < 0.05$ , Table 1). No significant difference was noted between the groups in terms of pretreatment PS, chemotherapy regimen types, the incidence of skeletal muscle depletion, cancer





**Figure 1** Patient flowchart. Flow diagram of patient recruitment and follow-up.

cachexia, and physical function. Objective tumor response was observed in four cases (40.0%) for inactive patients and four cases (36.4%) for active patients without statistically significant differences.

## Overall Survival and Disability-Free Survival

Of the 21 patients, sixteen (76.2%) had a disability and passed away by the cutoff date. The median follow-up period was 18.7 months (95% confidence interval [CI], 15.1–21.8). Inactive patients exhibited significantly shorter overall survival than active patients (8.8 vs 20.4 months,  $p < 0.05$ ; [Figure 2A](#)). The one-year survival rates were 40.0% in inactive patients and 72.7% in active patients. Inactive patients also exhibited significantly shorter DFS than active patients (6.4 vs 19.9 months,  $p < 0.05$ ; [Figure 2B](#)). The one-year DFS rates were 20.0% in inactive patients and 72.7% in active patients. The hazard ratio for overall survival in inactive patients was 1.92 (95% CI, 0.59–7.07) adjusted for known prognostic factors<sup>32,33</sup> including PS and the presence of mutations in the epidermal growth factor receptor (EGFR). The hazard ratio for DFS in inactive patients was 2.17 (95% CI, 0.66–8.2) after adjustment for PS and EGFR mutation. In the subset analyses of patients who had received cytotoxic chemotherapy ( $n = 15$ ), similar differences between groups were observed regarding overall survival and DFS

([Supplemental Figure 1](#)). In addition, the patients were divided into two groups based on their median MVPA duration at pretreatment (4.4 minutes per day). Furthermore, overall survival and DFS were compared between the two groups and there was no significant difference between the two groups. ([Supplemental Figure 2](#)).

## Hospital Stays and Medical Costs

The cumulative length of hospital stays for the first year tended to be longer for inactive patients than active patients (23.7 vs 6.3 days/person/year), and the difference continued to widen over the available follow-up period ([Figure 3A](#)). Moreover, inactive patients tended to require more frequent hospitalizations (1.9 vs 0.8 times/person/year) and unplanned outpatient visits or emergency hospitalizations (1.7 vs 0.9 times/person/year) than active patients ([Table 3](#)). Conversely, cumulative medical costs for the first year were similar for inactive and active patients (¥3.0 vs ¥2.5 million/person/year [US\$30,000 vs US\$25,000/person/year], [Table 3](#)); however, the curves of cumulative medical costs of both groups were different in the second year and continued to diverge over the available follow-up period ([Figure 3B](#)). For the breakdown of healthcare utilization in the first year, active patients had higher expenses for outpatient care (¥2.2 vs ¥1.4 million/person/year [US\$22,000 vs US\$14,000/

**Table 1** Baseline Patient Characteristics

	All n=21	Active <sup>d</sup> n=11	Inactive <sup>e</sup> n=10	p-value <sup>f</sup>
Age, median (range)	75 (70–82)	73 (70–81)	76 (72–82)	NS
Gender (Women: Men)	8: 13	6: 5	2: 8	NS
Stage, n (%)				NS
Stage IV	17 (81.0)	9 (81.8)	8 (80.0)	
Postoperative recurrence	4 (19.0)	2 (18.2)	2 (20.0)	
PS, n (%)				NS
0	7 (33.3)	5 (45.5)	2 (20.0)	
I	14 (66.7)	6 (54.5)	8 (80.0)	
Treatment, n (%)				NS
Cytotoxic regimen	15 (71.4)	6 (54.5)	9 (90.0)	
Targeted regimen	6 (28.6)	5 (45.5)	1 (10.0)	
Never smoke, n (%)	8 (38.1)	5 (45.5)	3 (30.0)	NS
Comorbidities, n (%)				NS
Cardiovascular disease	6 (28.6)	2 (18.2)	4 (40.0)	
Cerebrovascular disease	1 (4.8)	1 (9.1)	0 (0.0)	
Pulmonary disease	2 (9.5)	2 (18.2)	0 (0.0)	
Bone and joint disorder	6 (28.6)	1 (9.1)	5 (50.0)	
Type 2 diabetes	5 (23.8)	2 (18.2)	3 (30.0)	
Other cancer	2 (9.5)	1 (9.1)	1 (10.0)	
BMI (kg/m <sup>2</sup> ), median (range)	21.9 (19.0–28.1)	21.9 (19.0–28.1)	21.6 (19.2–25.2)	NS
LSMI (cm/m <sup>2</sup> ), median (range)				
Women	36.7 (31.5–46.2)	36.1 (31.5–46.2)	36.7 (36.5–37.0)	NS
Men	43.9 (38.2–50.6)	39.4 (38.2–45.1)	45.2 (39.9–50.6)	< 0.05
Skeletal muscle depletion, n (%) <sup>a</sup>	14 (66.7)	9 (81.8)	5 (50.0)	NS
Cachexia, n (%) <sup>b</sup>	13 (61.9)	6 (54.5)	7 (70.0)	NS
ISWD (m), median (range)				
Women	355 (120–480)	355 (120–480)	335 (270–400)	NS
Men	360 (140–550)	340 (270–550)	370 (140–460)	NS
HGS (kg), median (range)				
Women	23.7 (19.0–30.3)	21.4 (19.0–26.1)	28.1 (25.9–30.3)	NS
Men	30.6 (25.6–37.2)	29.2 (25.6–37.2)	30.8 (25.8–34.9)	NS
Daily steps, median (range)	3389.6 (1141.6–17,711.3)	3034.4 (1141.6–17,711.3)	4638.8 (1297.6–5824.1)	NS
MVPA <sup>c</sup> (minutes), median (range)	4.4 (0–60.9)	4.3 (1–60.9)	5.2 (0–13.3)	NS

**Notes:** <sup>a</sup>Skeletal muscle depletion was defined based on LSMI cutoffs of less than 43.0 cm<sup>2</sup>/m<sup>2</sup> and 53.0 cm<sup>2</sup>/m<sup>2</sup> for men with a BMI of less than 25.0 kg/m<sup>2</sup> and 25.0 kg/m<sup>2</sup> or higher, respectively, and the cutoff was 41.0 cm<sup>2</sup>/m<sup>2</sup> for women. <sup>b</sup>Cancer cachexia was defined as the unintentional weight loss of higher than 5% in the preceding six months, weight loss of higher than 2% in patients with a BMI of less than 20.0 kg/m<sup>2</sup>, or the presence of skeletal muscle depletion. <sup>c</sup>MVPA was defined as physical activity of 3 metabolic equivalents (METs) or more. <sup>d</sup>Active was defined as a patient group with the change rate in daily steps from pretreatment to T2 of –12.5% or higher. <sup>e</sup>Inactive was defined as a patient group with the change rate in daily steps from pretreatment to T2 of less than –12.5%. <sup>f</sup>Significant difference (P < 0.05) tested by Fisher's exact tests or Wilcoxon rank-sum test.

**Abbreviations:** PS, eastern cooperative oncology group performance status; BMI, body mass index; LSMI, lumbar skeletal muscle index; ISWD, incremental shuttle walking distance; HGS, hand-grip strength; MVPA, moderate to vigorous physical activity.

**Table 2** Changes in Physical Activity from Pretreatment to T2

	Pretreatment	T2 <sup>b</sup>
Daily steps, median (range)	3389.6 (1141.6–17,711.3)	3398.6 (345.1–18,847.3)
MVPA <sup>a</sup> (minutes), median (range)	4.4 (0–60.9)	2.3 (0–52.6)

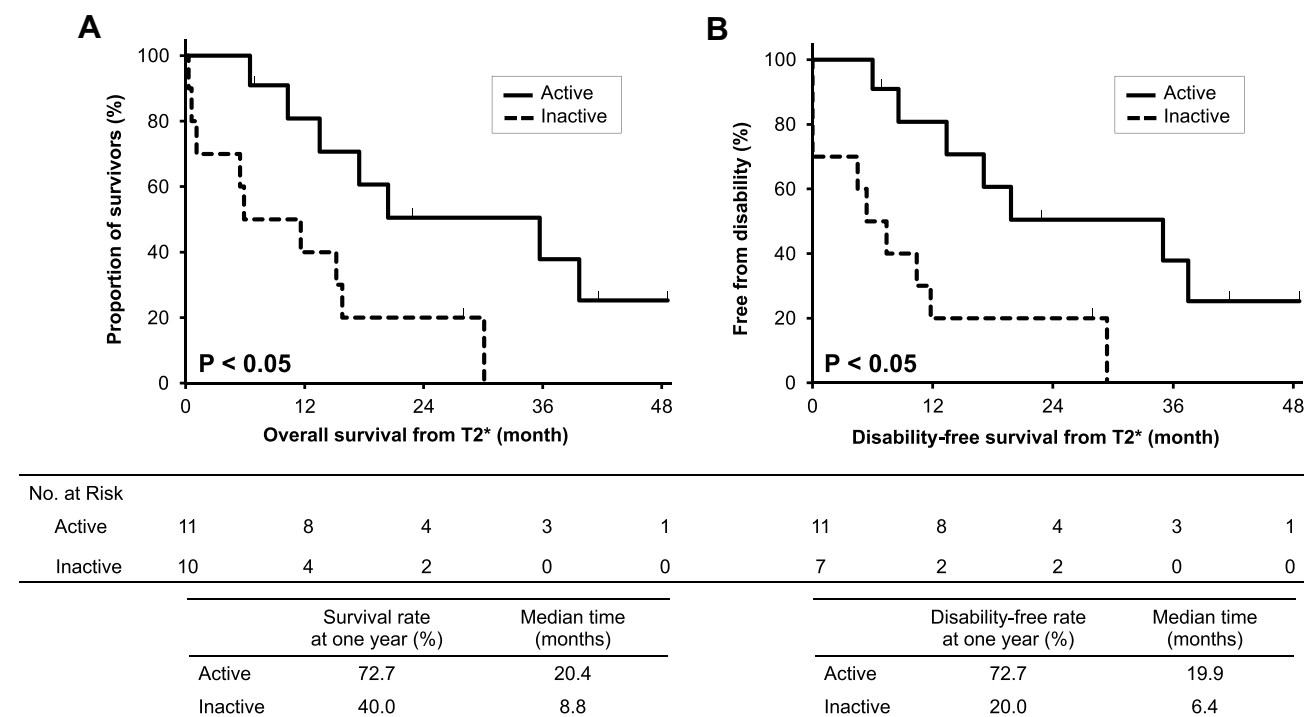
**Notes:** <sup>a</sup>MVPA was defined as physical activity of 3 metabolic equivalents (METs) or more. <sup>b</sup>T2 was 12 ± 4 weeks from enrolment.

**Abbreviation:** MVPA, moderate to vigorous physical activity.

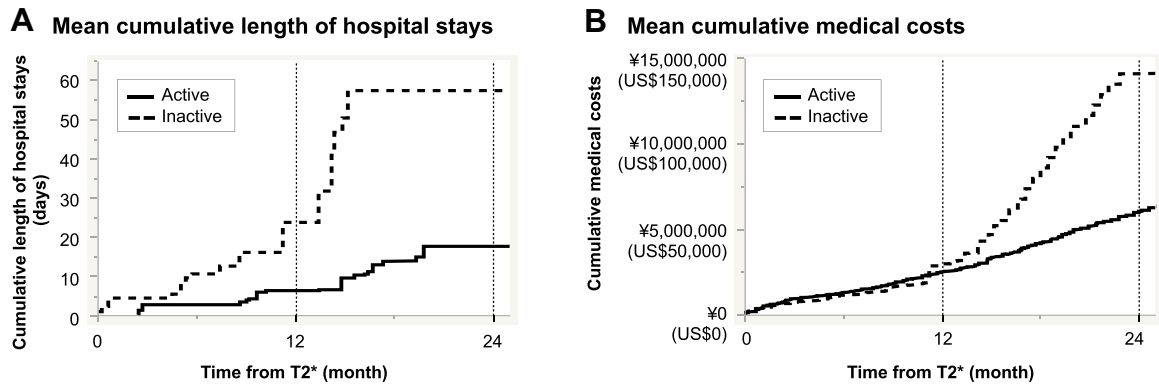
person/year],  $p < 0.05$ ) and chemotherapy (¥2.0 vs ¥0.8 million/person/year [US\$20,000 vs US\$8000/person/year],  $p < 0.05$ ) than inactive patients. In comparison, inactive patients had higher costs for inpatient care (¥1.6 vs ¥0.3 million/person/year [US\$16,000 vs US\$3000/person/year]), palliative radiation therapy or operation (¥1.4 vs ¥0.1 million/person/year [US\$14,000 vs US\$1000/person/year]), and supportive care (¥0.7 vs ¥0.4 million/person/year [US\$7000 vs US\$4000/person/year]). The difference was not statistically significant.

## Discussion

To the best of our knowledge, this study is the first attempt to evaluate the influence of physical inactivity during initial chemotherapy on the risk of disability and hospitalization in later life among older patients with advanced NSCLC. First, we found that most of our patients experienced decreased physical activity, with a median decrease of 12.5% in daily steps and 24.3% in the duration of MVPA. Second, active patients lived longer without disability than inactive patients. Finally, inactive patients required long and frequent inpatient care and spent less on outpatient chemotherapy than active patients.



**Figure 2** Overall and disability-free survival curves. Panel (A) Kaplan-Meier curve of overall survival from T2. Panel (B) Kaplan-Meier curve of disability-free survival from T2. A solid line indicates active patients and a dotted line indicates inactive patients. P-values were calculated using Log rank tests. A disabling event is defined as a decrease in Barthel Index from the pretreatment value by 10 points or higher. The overall and disability-free survival was censored on the final visit for patients whose deaths or disabling events were not confirmed. \*T2 was 12 ± 4 weeks from enrolment.



**Figure 3** Difference between active and inactive patients in terms of cumulative length of hospital stays and medical costs from T2. Curves of cumulative functions for the length of hospital stays panel (A) and medical costs panel (B) in active patients (solid line) and inactive patients (dotted line). \*T2 was 12 ± 4 weeks from enrolment.

Patients with lung cancer have been reported to have decreased physical activity than healthy adults throughout the cancer trajectory.<sup>34</sup> Specifically, in patients with advanced NSCLC, physical inactivity has been shown to affect prognosis negatively.<sup>35,36</sup> However, few studies have focused on physical inactivity in the early phase of the cancer trajectory. Our study indicated that physical inactivity during initial chemotherapy may deteriorate the overall survival and DFS of older patients with advanced NSCLC. Their behavior during treatment may be more important, for better long-term outcomes, than their physical condition before treatment. Although the multivariate analysis' results demonstrated that physical inactivity was not an independent prognostic factor for overall survival and DFS, this may have been a false negative due to the small sample size, since the 95% CI for overall survival and DFS was wide.

The use of medical resources by patients with cancer has been reported to increase with the presence of sarcopenia,<sup>37</sup> cachexia,<sup>12</sup> frailty,<sup>38</sup> and unsatisfactory PS.<sup>39</sup> Several studies have reported the association between physical inactivity and medical resources in patients with cancer.<sup>36,40</sup> As per the present study results, inactive patients required more extended hospital stays and had higher costs than active patients. Moreover, medical treatments were considerably different between active and inactive patients. Although the total annual costs were similar in the first year, most medical expenses in active patients were related to outpatient chemotherapy, whereas, for inactive patients, these were related to inpatient supportive care.

This study has several limitations. First, this was an observational prospective study with a small number of

**Table 3** Differences in Socioeconomic Parameters of Cancer Treatment in the First Year

Socioeconomic Parameters for the First Year <sup>a</sup>	Active	Inactive	p-value
Cumulative no. of the length of hospital stays <sup>b</sup>	6.3 ± 3.7	23.7 ± 10.1	NS
Cumulative times of hospitalization <sup>c</sup>	0.8 ± 0.5	1.9 ± 0.7	NS
Cumulative no. of unplanned visits or emergency hospitalizations <sup>c</sup>	0.9 ± 0.4	1.7 ± 0.5	NS
Cumulative medical costs <sup>d</sup>			
Total	2.5 ± 0.4	3.0 ± 1.0	NS
Outpatient care	2.2 ± 0.3	1.4 ± 0.2	< 0.05
Inpatient care	0.3 ± 0.2	1.6 ± 0.9	NS
Cumulative costs for resource utilization <sup>d</sup>			
Chemotherapy	2.0 ± 0.3	0.8 ± 0.3	< 0.05
Radiotherapy/Operation	0.1 ± 0.1	1.4 ± 0.9	NS
Supportive care	0.4 ± 0.2	0.7 ± 0.2	NS

**Notes:** <sup>a</sup>A mean cumulative function was used for recurrent event analysis of cumulative length of hospital stays and medical costs related to cancer care for the first year from T2. T2 was 12 ± 4 weeks from enrolment. <sup>b</sup>Days per person. <sup>c</sup>Times per person. <sup>d</sup> × 10<sup>6</sup> JP yen per person (× 10<sup>4</sup> US\$ per person).



participants, and, therefore, it may not have had sufficient power to draw definite conclusions. In addition, because this study included only Japanese patients who received treatment, our results may not be generalizable to all older patients with advanced NSCLC in other health care settings. Second, the chemotherapy administered during the study included different types of regimens, which possibly influenced the measured outcomes. Third, the health insurance system in Japan is different from those in other countries. Moreover, the standard of care and the medical environment is rapidly changing with advances in medicine. Thus, our results cannot be generalized to other populations in differing medical situations across countries. Fourth, since this study evaluated daily steps using only a pedometer, physical activity assessment may not be completely accurate. While a pedometer is an objective method of assessing daily steps, wearing it on the waist may have underestimated upper body movements and activities such as cycling, swimming, and resistance exercise.<sup>41</sup> Therefore, the simultaneous use of a pedometer and a questionnaire such as the Physical Activity Scale for the Elderly (PASE)<sup>42</sup> is recommended to assess daily physical activity in patients with cancer.<sup>41</sup> Finally, biases such as those involved in selection and measurement could not be avoided. However, there are few previous reports on changes in physical activity over time in older patients with advanced NSCLC, and the results of this study are valuable in demonstrating the importance of maintaining physical activity in these patients during treatment.

The vulnerability of older patients with advanced lung cancer is influenced by multiple factors and requires a multidisciplinary team approach rather than a single intervention.<sup>15</sup> Since exercise is one of the most critical interventions for the frail older population,<sup>43</sup> it must be incorporated into the supportive program for older patients with advanced cancer. The disease's status and treatment-related side effects are major factors that inhibit cancer patients from participating in physical activities.<sup>44</sup> However, physical activity has been reported to improve cardiorespiratory fitness, muscular strength, body composition, quality of life, anxiety, and depression, and help mitigate treatment-related side effects such as nausea, vomiting, peripheral neuropathy, fatigue, arthralgia, and myalgia.<sup>45</sup> A recent systematic review reported that exercise appears to be an effective intervention for improving physical function, quality of life, fatigue, body composition, psychosocial function, and sleep quality in patients

with advanced cancer.<sup>46</sup> Due to the physical vulnerability of patients with advanced cancer, even an increase in light physical activity may foster their ability to be more functional and active in everyday life.<sup>47</sup> The importance of promoting physical activity using pedometers or accelerometers has been recognized in geriatric medicine<sup>48</sup> and walking is classified as a low-intensity exercise intervention for older patients with cancer. Monitoring physical activity, using devices, can positively impact numerous clinically meaningful outcomes in cancer patients.<sup>49</sup> In addition to using equipment to promote physical activity, multidisciplinary promotive counseling is needed for positive behavioral change in physical activity.<sup>20,44</sup>

Naito et al recently reported the feasibility of a regimen combining exercise and nutritional interventions for older Japanese patients with advanced cancer.<sup>19,20</sup> Their exercise prescription combined promotive counseling for physical activity with home-based resistance training and nutritional advice by multidisciplinary team, which was initiated just after diagnosing the advanced pancreatic or NSCLC. Exploratory analysis showed the preservation of physical function, muscle mass, and daily steps during the study period. The intervention is being tested in an ongoing randomized controlled trial (trial registration number: UMIN000028801).<sup>50</sup> The current results support early physical activity intervention by multidisciplinary team, which is aimed not only at maintaining physical function, but also improving long-term outcomes, including disability, medical dependency, and cost-effectiveness in the care of older patients with advanced cancer.

## Conclusion

Physical inactivity during initial chemotherapy may be a risk factor for developing disabilities and requiring hospitalization in later life for older patients with advanced NSCLC. Our findings may indicate the need for lifestyle interventions with multidisciplinary teams, which include physicians, nurses, and physiotherapists, for older patients with advanced lung cancer during active cancer treatment. A large-sample-sized study is needed to validate our findings.

## Abbreviations

NSCLC, non-small-cell lung cancer; PS, eastern Cooperative Oncology Group performance status; MVPA, moderate to vigorous physical activity; METs, metabolic

equivalents; CT, computed tomography; DFS, disability-free survival; EGFR, epidermal growth factor receptor.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Ethics Approval and Informed Consent

The study was approved by the Shizuoka Cancer Center's institutional review board (Shizuoka, Japan) and registered on the University Hospital Medical Information Network Clinical Trials Registry in Japan (trial registration number: UMIN000012845). All patients provided written informed consent. All assessments were carried out under the ethical principles outlined in the Declaration of Helsinki. There were no major changes in the study methods after trial commencement.

## Consent for Publication

All authors and their affiliations consented to publication of the study in this journal.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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