Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Final survival analysis and predictors of treatment discontinuation in patients aged ≥ 80 years receiving adjuvant uracil–tegafur and leucovorin for stage III colorectal cancer: The prospective phase II HiSCO-03 trial

toshiyuki moriuchi

mkqhm857@gmail.com

Hiroshima Daigaku Daigakuin Ikei Kagaku Kenkyuka https://orcid.org/0000-0002-5231-5800

Manabu Shimomura

Hiroshima Daigaku Daigakuin Ikei Kagaku Kenkyuka https://orcid.org/0000-0001-8078-0091

satoshi ikeda

Hiroshima Prefectural Hospital: Kenritsu Hiroshima Byoin

tomoaki bekki

Onomichi General Hospital: JA Onomichi Sogo Byoin

Kouki Imaoka

Hiroshima City North Medical Center Asa Citizens Hospital: Hiroshima Shiritsu Asa Shimin Byoin

Masashi Miguchi

Hiroshima Prefectural Hospital: Kenritsu Hiroshima Byoin

Shintaro Akabane

National Hospital Organization Hiroshima-Nishi Medical Center

Shoichiro Mukai

Chugoku Rosai Hospital: Chugoku Rosai Byoin

Yusuke Sumi

National Hospital Organization Higashihiroshima Medical Center

Daisuke Sumitani

Hiroshima Prefectural Hospital Organization Futabanosato Prefectural Hospital

Haruki Sada

National Hospital Organization Kure Medical Center

Yuji Takakura

Chuden Hospital

Hiroyuki Sawada

Hiroshima City Hiroshima Citizens Hospital: Hiroshima Shiritsu Hiroshima Shimin Byoin

Shinya Kodama
Yoshida Hospital: Yoshida Byoin
Masahiko Fujimori
Kure City Medical Association Hospital
Mamoru Oeda
Cera Central Hospital
Hironori Kobayashi
Hiroshima Memorial Hospital
Hideki Ohdan
Hiroshima Daigaku Daigakuin Ikei Kagaku Kenkyuka

Research Article

Keywords: colorectal cancer, aged 80 and over, adjuvant chemotherapy, uracil–tegafur and leucovorin, treatment discontinuation, skeletal muscle mass

Posted Date: November 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11635534/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations:
Tables 1 to 3 are available in the Supplementary Files section.

Title: Final survival analysis and predictors of treatment discontinuation in patients aged ≥ 80 years receiving adjuvant uracil–tegafur and leucovorin for stage III colorectal cancer: The prospective phase II HiSCO-03 trial

Running title: Final analysis of the HiSCO-03 trial of adjuvant uracil–tegafur and leucovorin in patients aged ≥ 80 years

Toshiyuki Moriuchi[1)], Manabu Shimomura[1)], Satoshi Ikeda[4)], Tomoaki Bekki[2)], Kouki Imaoka[3)], Masashi Miguchi[4)], Shintaro Akabane[5)], Shoichiro Mukai[6)], Yusuke Sumi[7)], Daisuke Sumitani[8)], Haruki Sada[9)], Yuji Takakura[10)], Hiroyuki Sawada[11)], Shinya Kodama[12)], Masahiko Fujimori[13)], Mamoru Oeda[14)], Hironori Kobayashi[15)], Hideki Ohdan[1)], Hiroshima Surgical Study Group of Clinical Oncology (HiSCO)

1) *Department of Gastroenterological and Transplant Surgery, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan*

2) *Department of Surgery, Onomichi General Hospital, Onomichi, Japan*

3) *Department of Surgery, Hiroshima City Asa Citizens Hospital, Hiroshima, Japan*

4) *Department of Surgery, Hiroshima Prefectural Hospital, Hiroshima, Japan*

5) *Department of Surgery, National Hospital Organization Hiroshima-Nishi Medical Center, Hiroshima, Japan*

6) *Department of Surgery, Chugoku Rosai Hospital, Hiroshima, Japan*

7) *Department of Surgery, National Hospital Organization Higashihiroshima Medical Center, Hiroshima, Japan*

8) *Department of Surgery, Hiroshima Prefectural Hospital Organization Futabanosato Prefectural Hospital, Hiroshima, Japan*

9) *Department of Surgery, National Hospital Organization Kure Medical Center, Hiroshima, Japan*

10) *Department of Surgery, Chuden Hospital, Hiroshima, Japan*

11) *Department of Surgery, Hiroshima City Hospital, Hiroshima, Japan*

12) *Department of Surgery, Yoshida General Hospital, Hiroshima, Japan*

13) *Department of Surgery, Kure City Medical Association Hospital, Hiroshima, Japan*

14) *Department of Surgery, Cera Central Hospital, Hiroshima, Japan*

15) *Department of Surgery, Hiroshima Memorial Hospital, Hiroshima, Japan*

Corresponding author:

Manabu Shimomura

Department of Gastroenterological and Transplant Surgery, Graduate School of Biomedical and

Health Sciences, Hiroshima University, Kasumi 1-2-3 Minami-ku, Hiroshima, Hiroshima, Japan

E-mail: mshimo@hiroshima-u.ac.jp

Tel.: +81-82-257-5222

Fax: +81-82-257-5224

Abstract

Background: In the HiSCO-03 trial of adjuvant uracil–tegafur and leucovorin in patients aged ≥ 80 years with stage III colorectal cancer, the treatment completion rate was lower than expected. This final analysis evaluated long-term outcomes and risk factors for treatment discontinuation.

Methods: Of 69 enrolled patients, 65 were included in the survival analysis. In exploratory analyses, skeletal muscle mass was measured on preoperative computed tomography at the third lumbar vertebra, and risk factors for discontinuation due to adverse events or patient refusal were analyzed using logistic regression in 45 patients, excluding those who discontinued treatment because of recurrence.

Results: The 3-year disease-free survival rate was 70.6%, and the 5-year overall, recurrence-free, and disease-free survival rates were 75.9%, 64.5%, and 61.4%, respectively. Of the 45 patients, 30 completed and 15 discontinued treatment. In multivariable analysis, female sex (odds ratio 7.75, 95% confidence interval 1.68–56.59) and low skeletal muscle mass (odds ratio 9.69, 95% confidence interval 1.84–78.11) were independent risk factors for discontinuation. Survival did not differ between patients who completed and those who discontinued treatment.

Conclusions: In patients aged ≥ 80 years with stage III colorectal cancer, adjuvant uracil–tegafur and leucovorin achieved a 3-year disease-free survival rate comparable to those reported in younger patients. Low skeletal muscle mass and female sex were associated with treatment discontinuation. These factors may help identify, before treatment, patients who are likely to tolerate adjuvant

chemotherapy and those who need early supportive care.

Trial registration: jRCTs061180087 (registered 22 March 2019; retrospectively registered).

Keywords: colorectal cancer, aged 80 and over, adjuvant chemotherapy, uracil–tegafur and leucovorin, treatment discontinuation, skeletal muscle mass

Introduction

The number of older adults with cancer is rising, and determining their optimal treatment has become an important challenge. Because older adults are a heterogeneous population, treatment decisions should consider not only the risk of recurrence but also comorbidities, functional status, and social background, which can be evaluated by geriatric assessment [1]. For stage III colorectal cancer (CRC), adjuvant chemotherapy with fluoropyrimidine plus oxaliplatin after curative resection is the standard treatment [2, 3]. Older patients with good organ function and performance status may also benefit from adjuvant treatment [4], but the additional benefit of oxaliplatin is considered limited in patients aged 70 years or older [5, 6]. Therefore, oral fluoropyrimidines such as capecitabine, S-1, and uracil–tegafur/leucovorin (UFT/LV) are often chosen [7-10], and UFT/LV has shown acceptable tolerability in older patients [8-10]. However, very few patients aged 80 years or older were enrolled in these trials, and no prospective study had evaluated adjuvant chemotherapy in

this age group. We therefore conducted a multicenter phase II study (HiSCO-03) of adjuvant UFT/LV in patients aged ≥ 80 years with stage III CRC [11]. The cumulative treatment continuation rate was 67.3% (95% confidence interval [CI] 54.9–77.6%), with the lower limit of the 95% CI below the prespecified threshold of 60%, and no risk factor for discontinuation was identified among clinical factors [11]. In the parallel HiSCO-04 prospective cohort study of patients aged ≥ 80 years with stage III CRC, completion of adjuvant chemotherapy was associated with better disease-free survival [12], suggesting that identifying patients likely to discontinue treatment is important.

Here, we report the long-term outcomes of this trial (overall survival [OS], recurrence-free survival [RFS], and disease-free survival [DFS], which were secondary endpoints) and risk factors for discontinuation, including nutritional and prognostic indices such as the prognostic nutritional index (PNI), living situation, family or caregiver support, and skeletal muscle mass on computed tomography (CT). Low skeletal muscle mass has been associated with chemotherapy-related toxicity and dose reduction [13-15], but its association with tolerance to oral fluoropyrimidine-based adjuvant chemotherapy in patients aged ≥ 80 years has not been fully examined.

Patients and Methods

Study design and patients

This is the final analysis of HiSCO-03, a multi-institutional phase II trial of adjuvant UFT/LV for

patients aged ≥ 80 years with stage III CRC after curative resection [11]. Eligible patients had histologically proven CRC (excluding tumors in the lower rectum), R0 resection, an Eastern Cooperative Oncology Group performance status (PS) of 0–2, no previous chemotherapy or radiotherapy, and adequate bone marrow, hepatic, and renal function [11]. Stage was defined by the Union for International Cancer Control TNM classification (8th edition). Patients were enrolled from 15 institutions of the Hiroshima Surgical Study Group of Clinical Oncology (HiSCO) between December 2013 and June 2021.

Eligible patients who received protocol treatment formed the full analysis set. Body composition could be measured only at institutions with the image analysis system Synapse Vincent (Fujifilm Medical, Tokyo, Japan). The risk factor analysis included patients with these data, excluding those who discontinued treatment because of recurrence, which differs in nature from intolerance and was censored in the original study [11]. The change in muscle mass was evaluated in patients who also had CT images 6 months after surgery.

The study was approved by the Hiroshima University Certified Review Board (approval no. CRB2018-0027) and registered in the Japan Registry of Clinical Trials (jRCTs061180087), and all patients provided written informed consent.

Protocol treatment

UFT (300 mg/m² per day as tegafur) and LV (75 mg/body per day) were given orally in three

divided doses for 28 days followed by a 7-day rest, for five courses (25 weeks). The criteria for continuing treatment, dose reduction and interruption according to adverse events (AEs), and discontinuation were described previously [11].

Body composition assessment

Body composition was measured using Synapse Vincent on a single preoperative CT slice at the third lumbar vertebra (L3): skeletal muscle area (SMA), skeletal muscle density (SMD; mean CT attenuation of muscle), visceral fat area (VFA), and subcutaneous fat area (SFA), with thresholds of −30 to +150 Hounsfield units (HU) for muscle, −150 to −50 HU for visceral fat, and −190 to −30 HU for subcutaneous fat. The skeletal muscle index (L3-SMI; SMA divided by height squared, cm^2/m^2) and the VFA/SMA and VFA/SFA ratios were calculated.

Low values were defined as values at or below the lowest sex-specific quartile (Q1) in the study cohort (for L3-SMI, ≤39.43 cm^2/m^2 in men and ≤33.33 cm^2/m^2 in women). L3-SMI was also standardized within each sex (z-score). L3-SMI was measured in the same way on CT images 6 months after surgery, and its change (ΔSMI) was calculated as (L3-SMI at 6 months − preoperative L3-SMI) / preoperative L3-SMI × 100 (%).

Inflammatory and nutritional indices

The C-reactive protein-to-albumin ratio (CAR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-

lymphocyte ratio (PLR), and PNI (10 × serum albumin [g/dL] + 0.005 × total lymphocyte count [/mm³]) were calculated from preoperative blood tests.

Endpoints

The endpoints were OS, RFS, and DFS from the date of surgery, which were prespecified secondary endpoints not reported in the primary analysis [11]. OS was defined as the time to death from any cause; RFS, to recurrence or death; and DFS, to recurrence, another cancer (including recurrence of a previously treated cancer), or death. Exploratory analyses examined risk factors for discontinuation and the change in muscle mass. As in the original study, patients who completed five courses formed the completion group, and those who discontinued treatment (because of AEs, refusal, or recurrence) the discontinuation group. Living situation and key support person (a younger family member [child, grandchild, child's spouse] or a spouse or sibling only) were obtained from case report forms.

Statistical analysis

Categorical variables were compared using Fisher's exact test (the Fisher–Freeman–Halton test for stage), and continuous variables using the Mann–Whitney U test. Survival and the treatment continuation rate were estimated by the Kaplan–Meier method; the proportion of patients who completed treatment was also calculated for comparison with previous studies. Variables with P <

0.05 in univariate logistic regression were entered into the multivariable analysis, with L3-SMI as a binary variable (low [Q1] vs. others [Q2–Q4]; Model 1) or a continuous variable (sex-specific z-score, per 1-standard deviation (SD) decrease; Model 2); P values and 95% CIs were calculated by the likelihood ratio test and profile likelihood method, respectively. Within each group, preoperative and 6-month L3-SMI were compared by the Wilcoxon signed-rank test.

To avoid immortal time bias, survival was compared between the groups using a landmark analysis. Because treatment ended within 255 days after surgery in all patients, the landmark was set at 9 months. In patients who were alive and disease-free at the landmark, OS, RFS, and DFS were estimated by the Kaplan–Meier method and compared using the log-rank test.

All tests were two-sided, and $P < 0.05$ was considered significant. Analyses were performed using JMP Student Edition 19.1.4 (JMP Statistical Discovery LLC, Cary, NC, USA).

Results

Patient flow and characteristics

Of the 69 enrolled patients, 2 who did not meet the eligibility criteria and 2 who did not receive protocol treatment were excluded, leaving 65 patients in the full analysis set (Fig. 1). There were 32 men and 33 women, with a median age of 82 years (range, 80–88 years) (Table 1).

Compared with the 16 patients without body composition data, the 49 with these data more often had carcinoembryonic antigen (CEA) > 5 ng/mL (44.7% vs. 13.3%, P = 0.035) and a younger family

member as their key support person (59.2% vs. 25.0%, P = 0.023); other characteristics did not differ (Online Resource 1).

Treatment completion and reasons for discontinuation

Treatment was completed in 40 patients (61.5%) and discontinued in 25 because of AEs (9 patients), patient refusal (12), or recurrence (4); the cumulative treatment continuation rate was 67.3%, as reported previously [11].

Of the 12 patients who refused treatment, 10 (83.3%) were women. The preceding symptoms were fatigue (5), diarrhea (4), stomatitis (3), and anorexia (2) (including overlaps), all of grade 1 or 2. The median time to refusal was 76 days (range, 24–155), and 5 patients (41.7%) refused within 2 months. Among women, 20.0% of those who refused (n = 10) and 39.1% of those who did not (n = 23) lived alone, and 60.0% and 56.5%, respectively, had a younger family member as their key support person.

Survival outcomes

The median follow-up was 59.9 months (range, 13.9–60.0). The 3-year and 5-year OS rates were 86.0% and 75.9%, RFS rates 72.1% and 64.5%, and DFS rates 70.6% and 61.4%, respectively (Fig. 2). Fifteen patients died (13 of CRC and 2 of other causes). Recurrence occurred in 20 patients: distant lymph nodes (6), lung (6), liver (6), peritoneum (3), ovary (1), brain (1), and local (1)

(including overlaps). Fifteen of them (75.0%) were treated for recurrence (upfront resection, 3 [15.0%]; chemotherapy, 9 [45.0%]; radiotherapy, 3 [15.0%]), and 5 (25.0%) were not. Second cancer developed in 3 patients (breast cancer, 2; hepatocellular carcinoma, 1).

Landmark analysis

At 9 months after surgery, 57 patients (39 in the completion group and 18 in the discontinuation group) were alive and disease-free, with no significant differences in characteristics between the groups (Online Resource 2). OS (P = 0.323), RFS (P = 0.696), and DFS (P = 0.607) did not differ significantly between the groups (Fig. 3).

Risk factors for discontinuation

Of the 45 patients in the risk factor analysis, 30 completed and 15 discontinued treatment (AEs in 8 and refusal in 7). The discontinuation group had more women (73.3% vs. 36.7%, P = 0.029) and more patients with low L3-SMI (46.7% vs. 13.3%, P = 0.026); other characteristics did not differ (Table 2).

Female sex and low L3-SMI were significant in the univariate analysis (Table 3) and remained independent risk factors in the multivariable analysis (Model 1: female sex, odds ratio [OR] 7.75, 95% CI 1.68–56.59, P = 0.007; low L3-SMI, OR 9.69, 95% CI 1.84–78.11, P = 0.006). In Model 2, a 1-SD decrease in L3-SMI was also associated with discontinuation (OR 3.54, 95% CI 1.53–10.87, P

= 0.002), and female sex remained significant (OR 6.55, 95% CI 1.49–37.21, P = 0.012).

Change in skeletal muscle mass

Among the 42 patients with CT images at 6 months, L3-SMI did not change significantly in the completion group (median, 43.1 to 42.2 cm^2/m^2; median ΔSMI, −0.5%; P = 0.409) and tended to increase in the discontinuation group (35.7 to 37.5 cm^2/m^2; P = 0.079) (Fig. 4).

Discussion

This final analysis of the HiSCO-03 trial is, to our knowledge, the first prospective report of long-term outcomes of adjuvant chemotherapy in patients aged ≥ 80 years with stage III CRC. The 3-year DFS rate (70.6%) was comparable to those reported in younger patients. In exploratory analyses, female sex and low preoperative skeletal muscle mass were independent risk factors for discontinuation, whereas no independent risk factor had been identified among conventional clinical factors in the primary analysis [11].

JCOG0205 and ACTS-CC, Japanese phase III trials with a UFT/LV arm using the same five-course regimen, enrolled much younger patients (1,101 and 1,518 patients; median age, 61 and 66 vs. 82 years) [8, 10]. Even so, our 3-year DFS rate (70.6%) was not markedly different from those in their UFT/LV arms (77.8% and 72.5%) [8, 10]. Our completion proportion (61.5%) was lower than theirs (77% and 73.4%) [8, 10]; however, discontinuation due to AEs was similar to that in

JCOG0205 (13.8% vs. 12.0%), whereas refusal was approximately three times more frequent (18.5% vs. 6.5%) [8], so the lower completion rate was mainly due to refusal. The 5-year OS rate (75.9%) was lower than those in JCOG0205 and JFMC33-0502 (87.5% and 84.9%) [8, 9]. The favorable OS in JCOG0205 was partly attributed to resection of recurrent lesions [8], but only 3 of our 20 patients with recurrence (15.0%) underwent resection; curative-intent treatment after recurrence may be less feasible at this age, which may partly explain why 13 of the 15 deaths were due to CRC. These cross-trial comparisons should be interpreted with caution.

Because previous analyses mostly defined older patients as those aged ≥ 70 or ≥ 75 years [4–6], the survival benefit of adjuvant chemotherapy in patients aged ≥ 80 years remains unclear. Our landmark analysis showed no survival difference by treatment completion, but the small number of events precluded firm conclusions from these data alone. However, in the HiSCO-04 prospective cohort of patients aged ≥ 80 years with stage III CRC, which included most of our patients, the completion rate was 52%, but completion was associated with better DFS after propensity score matching [12]. Our DFS, comparable to that in trials of younger patients, further supports the potential efficacy of adjuvant chemotherapy even at this age. Although most deaths in our study were due to CRC, the high risk of death from other causes at this age should also be considered. Taken together, although not conclusive, these findings suggest a meaningful survival benefit of adjuvant chemotherapy in this population, highlighting the critical importance of identifying patients who are likely to tolerate it.

Sarcopenia, the loss of skeletal muscle mass and function, is a marker of physical reserve [16, 17], and low muscle mass has been associated with chemotherapy-related toxicity, dose reduction [13-15, 18], and poor prognosis [19]. 5-Fluorouracil (5-FU) is distributed mainly in lean tissue, which correlates poorly with body surface area; thus, dosing by body surface area may cause up to a threefold variation in the volume of distribution relative to lean body mass [20], and a higher dose per kilogram of lean body mass causes more dose-limiting toxicity [13]. Low muscle mass was also associated with early discontinuation of adjuvant FOLFOX (5-FU, leucovorin, and oxaliplatin) [18]. Because UFT was also dosed by body surface area, patients with low muscle mass may have received a relatively higher dose. However, Williams et al. found that 5-FU exposure was not higher in patients with sarcopenia [21], so reduced physical reserve may also contribute. Our findings extend this association to oral fluoropyrimidine monotherapy in patients aged ≥ 80 years.

Female sex remained an independent risk factor after adjustment for muscle mass. Women experience more fluoropyrimidine toxicity: in the ACCENT database, women receiving adjuvant 5-FU had more grade ≥ 3 nausea, vomiting, stomatitis, diarrhea, and neutropenia than men [22], and in a Japanese study, female sex was the only independent predictor of early dose-limiting toxicity of adjuvant CAPOX (capecitabine and oxaliplatin) [23]. Women have lower lean body mass relative to body surface area, and thus receive a higher 5-FU dose per unit of lean body mass [13, 20], and may have lower 5-FU clearance [24]. These findings were mainly obtained with intravenous 5-FU, but a similar mechanism may apply to UFT, as sarcopenia is also associated with toxicity of capecitabine,

an oral 5-FU prodrug [14]. Because low L3-SMI was defined within each sex, the two factors may reflect different aspects: relative muscle mass, and sex differences in body composition and pharmacokinetics. Age was not associated with discontinuation, consistent with the finding that age does not affect 5-FU clearance [24], suggesting that tolerability at age ≥ 80 years is better estimated by muscle mass and sex than by age.

Muscle mass may recover after resection even during adjuvant chemotherapy: SMI increased by a median of 8.7% over 210 days of adjuvant FOLFOX in patients mostly younger than 65 years [25], and adjuvant chemotherapy was associated with increased muscle area after surgery [26]. In contrast, muscle mass did not increase in our patients who completed treatment (median ΔSMI, −0.5%, within the approximately 2% measurement error of CT-based SMI [25]), suggesting that adjuvant chemotherapy may delay muscle recovery at this age. In a different setting of colorectal liver metastases, muscle loss during preoperative chemotherapy was associated with a lower rate of subsequent adjuvant chemotherapy in one study and with shorter recurrence-free survival in another [27, 28], suggesting that maintaining muscle mass may matter for both treatment delivery and prognosis. Whether nutritional or exercise support can improve the effectiveness of adjuvant chemotherapy in older patients warrants further investigation.

Patient refusal was the main reason for the low completion rate. Most patients who refused were women, many refused early, and all preceding symptoms were grade 1 or 2, suggesting that even non-severe AEs can lead to refusal at this age, especially in women. As living alone and the key

support person were not associated with discontinuation, refusal may depend more on how patients perceive AEs than on family support. Because female sex and low muscle mass predicted discontinuation, patients with these factors could be identified before treatment and offered early supportive and psychological care; muscle mass can be assessed on routine preoperative CT without additional burden.

This study has several limitations. First, this was a small single-arm study, and the exploratory risk factor analysis (45 patients, 15 discontinuations) had wide CIs, indicating imprecise estimates, and allowed only a few variables in the multivariable model. Second, body composition was available only at some institutions, and some characteristics differed by data availability (Online Resource 1), so selection bias cannot be excluded. Third, because widely used cut-off values for muscle mass [19, 20] were derived from younger Western populations, we used sex-specific quartiles within the cohort, which have not been externally validated. Fourth, we did not assess muscle strength, physical function, patient-reported outcomes, or 5-FU concentrations, so the proposed mechanisms could not be directly evaluated. Fifth, the narrow age range (80–88 years) may have masked an effect of age. Sixth, the change in muscle mass was evaluated in only 42 patients. Finally, all patients were Japanese, which may limit generalizability.

Conclusion

In patients aged ≥ 80 years with stage III CRC, adjuvant UFT/LV achieved a 3-year DFS rate

comparable to those reported in younger patients. Preoperative low skeletal muscle mass assessed on CT and female sex were independent risk factors for discontinuation of adjuvant UFT/LV. These factors may help identify, before treatment, patients who are likely to tolerate adjuvant chemotherapy and those who need early supportive care.

Acknowledgments: We thank all patients who participated in this trial and their families. The following departments and hospitals participated in the trial: Department of Gastroenterological and Transplant Surgery, Graduate School of Biomedical and Health Sciences, Hiroshima University; Department of Surgery, Onomichi General Hospital; Department of Surgery, Hiroshima City Asa Citizens Hospital; Department of Surgery, Hiroshima Prefectural Hospital; Department of Surgery, National Hospital Organization Hiroshima-Nishi Medical Center; Department of Surgery, Chugoku Rosai Hospital; Department of Surgery, National Hospital Organization Higashihiroshima Medical Center; Department of Surgery, JR Hiroshima Hospital; Department of Surgery, National Hospital Organization Kure Medical Center; Department of Surgery, Chuden Hospital; Department of Surgery, Hiroshima City Hospital; Department of Surgery, Yoshida General Hospital; Department of Surgery, Kure City Medical Association Hospital; Department of Surgery, Cera Central Hospital; and Department of Surgery, Hiroshima Memorial Hospital.

Statement & Declarations

Funding:

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests:

The authors declare that they have no competing interests.

Data availability:

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Ethics approval:

This study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. The study was approved by the Hiroshima University Certified Review Board (approval no. CRB2018-0027).

Consent to participate:

Written informed consent was obtained from all individual participants included in the study.

Author contributions:

All authors contributed to the study conception and design. Material preparation and data collection were performed by all authors. Statistical analysis was performed by Toshiyuki Moriuchi and supervised by Manabu Shimomura. The first draft of the manuscript was written by Toshiyuki Moriuchi and Manabu Shimomura, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1.Liposits G, André T, Aparicio T, et al (2026) Management of colorectal cancer in older adults: an expert panel recommendation to guide daily clinical practice. Lancet Gastroenterol Hepatol 11:627-644. https://doi.org/10.1016/s2468-1253(26)00041-5

2.Kuebler JP, Wieand HS, O'Connell MJ, et al (2007) Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 25:2198-2204. https://doi.org/10.1200/jco.2006.08.2974

3.André T, Boni C, Mounedji-Boudiaf L, et al (2004) Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350:2343-2351. https://doi.org/10.1056/NEJMoa032709

4.Haller DG, O'Connell MJ, Cartwright TH, et al (2015) Impact of age and medical comorbidity on adjuvant treatment outcomes for stage III colon cancer: a pooled analysis of individual patient data from four randomized, controlled trials. Ann Oncol 26:715-724. https://doi.org/10.1093/annonc/mdv003

5.Tournigand C, André T, Bonnetain F, et al (2012) Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. J Clin Oncol 30:3353-3360. https://doi.org/10.1200/jco.2012.42.5645

6.Yothers G, O'Connell MJ, Allegra CJ, et al (2011) Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol 29:3768-3774. https://doi.org/10.1200/jco.2011.36.4539

7.Twelves C, Wong A, Nowacki MP, et al (2005) Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 352:2696-2704. https://doi.org/10.1056/NEJMoa043116

8.Shimada Y, Hamaguchi T, Mizusawa J, et al (2014) Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil and levofolinate in patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection: final results of JCOG0205. Eur J Cancer 50:2231-2240. https://doi.org/10.1016/j.ejca.2014.05.025

9.Sadahiro S, Tsuchiya T, Sasaki K, et al (2015) Randomized phase III trial of treatment duration for oral uracil and tegafur plus leucovorin as adjuvant chemotherapy for patients with stage IIB/III colon cancer: final results of JFMC33-0502. Ann Oncol 26:2274-2280. https://doi.org/10.1093/annonc/mdv358
10.Yoshida M, Ishiguro M, Ikejiri K, et al (2014) S-1 as adjuvant chemotherapy for stage III colon cancer: a randomized phase III study (ACTS-CC trial). Ann Oncol 25:1743-1749. https://doi.org/10.1093/annonc/mdu232
11.Okuda H, Shimomura M, Ikeda S, et al (2023) A prospective feasibility study of uracil-tegafur and leucovorin as adjuvant chemotherapy for patients aged ≥ 80 years after curative resection of colorectal cancer, the HiSCO-03 study. Cancer Chemother Pharmacol 91:317-324. https://doi.org/10.1007/s00280-023-04526-7
12.Mochizuki T, Shimomura M, Nakahara M, et al (2024) Survival outcomes of patients with stage III colorectal cancer aged ≥ 80 years who underwent curative resection: the HiSCO-04 prospective cohort study. Int J Clin Oncol 29:159-168. https://doi.org/10.1007/s10147-023-02440-9
13.Prado CM, Baracos VE, McCargar LJ, et al (2007) Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clin Cancer Res 13:3264-3268. https://doi.org/10.1158/1078-0432.Ccr-06-3067
14.Prado CM, Baracos VE, McCargar LJ, et al (2009) Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res 15:2920-2926. https://doi.org/10.1158/1078-0432.Ccr-08-2242
15.Barret M, Antoun S, Dalban C, et al (2014) Sarcopenia is linked to treatment toxicity in patients with metastatic colorectal cancer. Nutr Cancer 66:583-589. https://doi.org/10.1080/01635581.2014.894103
16.Chen LK, Woo J, Assantachai P, et al (2020) Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. J Am Med Dir Assoc 21:300-307.e302. https://doi.org/10.1016/j.jamda.2019.12.012
17.Cruz-Jentoft AJ, Bahat G, Bauer J, et al (2019) Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 48:16-31. https://doi.org/10.1093/ageing/afy169
18.Cespedes Feliciano EM, Lee VS, Prado CM, et al (2017) Muscle mass at the time of diagnosis of nonmetastatic colon cancer and early discontinuation of chemotherapy, delays, and dose reductions on adjuvant FOLFOX: The C-SCANS study. Cancer 123:4868-4877. https://doi.org/10.1002/cncr.30950
19.Martin L, Birdsell L, Macdonald N, et al (2013) Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 31:1539-1547. https://doi.org/10.1200/jco.2012.45.2722
20.Prado CM, Lieffers JR, McCargar LJ, et al (2008) Prevalence and clinical implications of

sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 9:629-635. https://doi.org/10.1016/s1470-2045(08)70153-0
21. Williams GR, Deal AM, Shachar SS, et al (2018) The impact of skeletal muscle on the pharmacokinetics and toxicity of 5-fluorouracil in colorectal cancer. Cancer Chemother Pharmacol 81:413-417. https://doi.org/10.1007/s00280-017-3487-2
22. Wagner AD, Grothey A, Andre T, et al (2021) Sex and Adverse Events of Adjuvant Chemotherapy in Colon Cancer: An Analysis of 34 640 Patients in the ACCENT Database. J Natl Cancer Inst 113:400-407. https://doi.org/10.1093/jnci/djaa124
23. Nozawa H, Kawai K, Sasaki K, et al (2021) Women are predisposed to early dose-limiting toxicities during adjuvant CAPOX for colorectal cancer. Int J Clin Pract 75:e14863. https://doi.org/10.1111/ijcp.14863
24. Milano G, Etienne MC, Cassuto-Viguier E, et al (1992) Influence of sex and age on fluorouracil clearance. J Clin Oncol 10:1171-1175. https://doi.org/10.1200/jco.1992.10.7.1171
25. Chung E, Lee HS, Cho ES, et al (2019) Changes in Body Composition During Adjuvant FOLFOX Chemotherapy and Overall Survival in Non-Metastatic Colon Cancer. Cancers (Basel) 12:60. https://doi.org/10.3390/cancers12010060
26. Pardes HY, Ali MS, Dolin TG, et al (2026) Changes in psoas muscle area in patients with colorectal cancer three years after surgery: a longitudinal approach. Langenbecks Arch Surg 411:123. https://doi.org/10.1007/s00423-026-04002-9
27. Eriksson S, Nilsson JH, Strandberg Holka P, et al (2017) The impact of neoadjuvant chemotherapy on skeletal muscle depletion and preoperative sarcopenia in patients with resectable colorectal liver metastases. HPB (Oxford) 19:331-337. https://doi.org/10.1016/j.hpb.2016.11.009
28. Okuno M, Goumard C, Kopetz S, et al (2019) Loss of muscle mass during preoperative chemotherapy as a prognosticator for poor survival in patients with colorectal liver metastases. Surgery 165:329-336. https://doi.org/10.1016/j.surg.2018.07.031

Tables

Table 1. Baseline characteristics of patients in the full analysis set (n = 65). Some data were reported previously [11]

Table 2. Characteristics of patients included in the body composition analysis, by completion of adjuvant chemotherapy (n = 45)

Table 3. Univariate and multivariable logistic regression analyses of risk factors for discontinuation of adjuvant chemotherapy (n = 45)

Figure legends

Fig. 1 Flow diagram of the study population. Of 69 enrolled patients, 65 were included in the full analysis set after excluding 2 patients who did not meet the eligibility criteria and 2 who did not receive protocol treatment. Body composition was assessed in 49 patients treated at institutions where the Synapse Vincent system was available; after excluding 4 patients who discontinued chemotherapy because of recurrence, 45 patients were included in the analysis of risk factors for discontinuation, and 42 of them who had CT images 6 months after surgery were included in the analysis of the change in L3-SMI

Fig. 2 Kaplan–Meier curves for (a) overall survival, (b) recurrence-free survival and (c) disease-free survival in the full analysis set (n = 65). Tick marks indicate censored observations

Fig. 3 Kaplan–Meier curves for (a) overall survival, (b) recurrence-free survival and (c) disease-free survival from the landmark time point (9 months after surgery) in the completion (n = 39) and discontinuation (n = 18) groups. P values were calculated using the log-rank test. Tick marks indicate censored observations

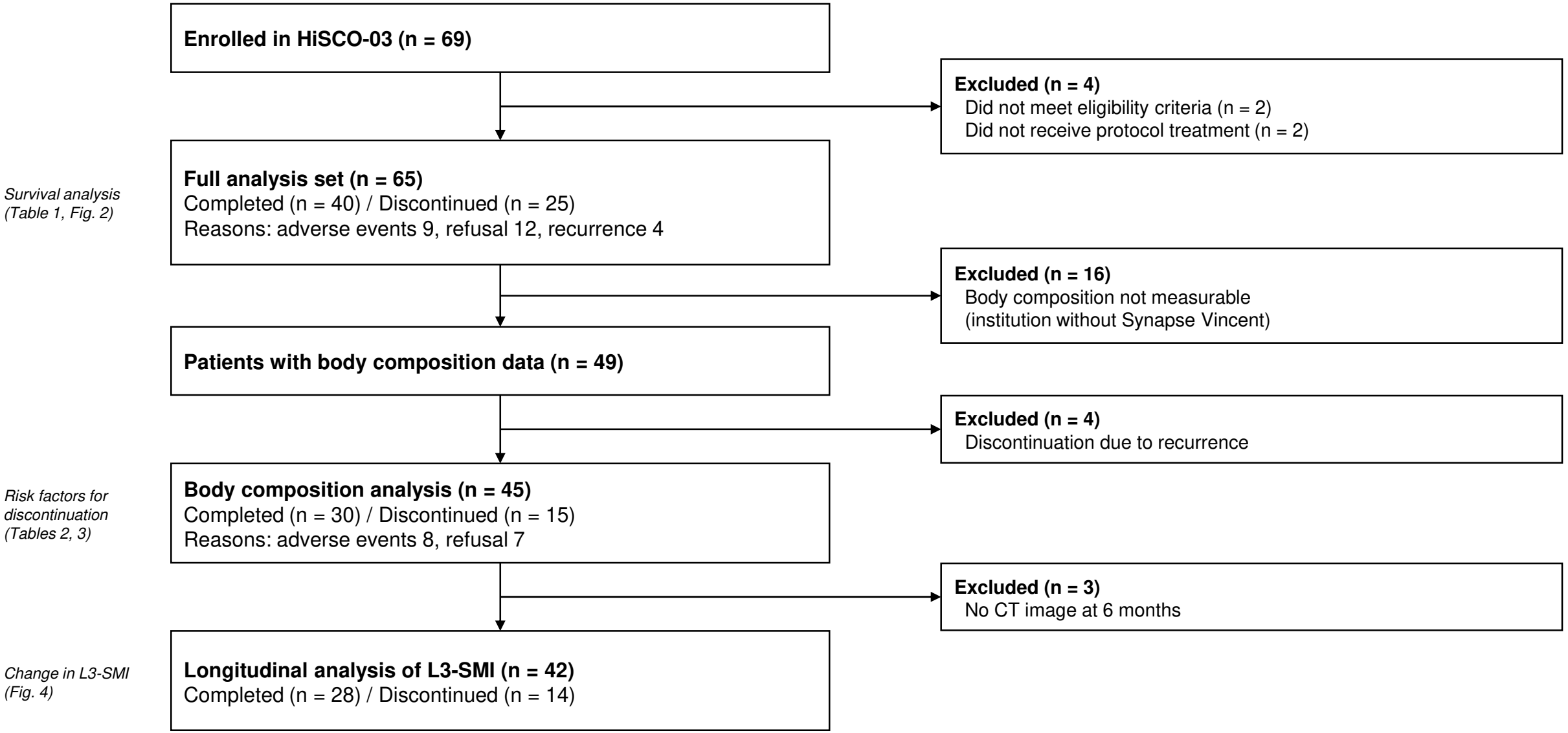
Fig. 4 L3-SMI before surgery and 6 months after surgery in the completion (n = 28) and

discontinuation (n = 14) groups. Gray lines connect values from the same patient, and black lines indicate median values. P values were calculated using the Wilcoxon signed-rank test

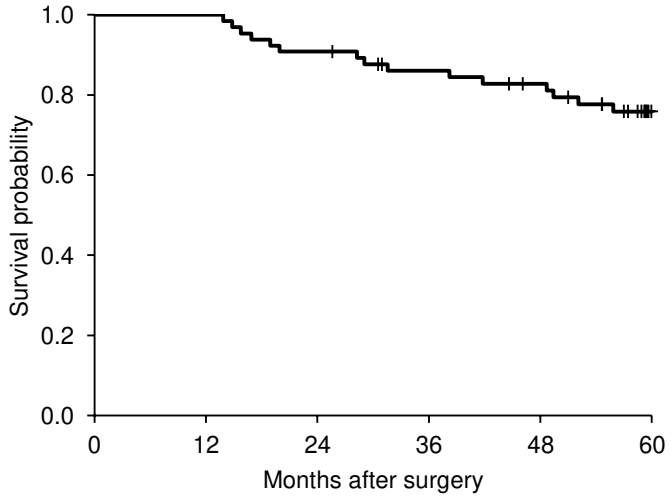
Online Resources

Online Resource 1. Comparison of baseline characteristics between patients with and without body composition data (n = 65)

Online Resource 2. Baseline characteristics of the completion and discontinuation groups in the landmark cohort (n = 57)


Enrolled in HiSCO-03 (n = 69)
Excluded (n = 4)
Did not meet eligibility criteria (n = 2)
Did not receive protocol treatment (n = 2)
Survival analysis
(Table 1, Fig. 2)
Full analysis set (n = 65)
Completed (n = 40) / Discontinued (n = 25)
Reasons: adverse events 9, refusal 12, recurrence 4
Excluded (n = 16)
Body composition not measurable
(institution without Synapse Vincent)
Patients with body composition data (n = 49)
Excluded (n = 4)
Discontinuation due to recurrence
Risk factors for
discontinuation
(Tables 2, 3)
Body composition analysis (n = 45)
Completed (n = 30) / Discontinued (n = 15)
Reasons: adverse events 8, refusal 7
Excluded (n = 3)
No CT image at 6 months
Change in L3-SMI
(Fig. 4)
Longitudinal analysis of L3-SMI (n = 42)
Completed (n = 28) / Discontinued (n = 14)

a Overall survival

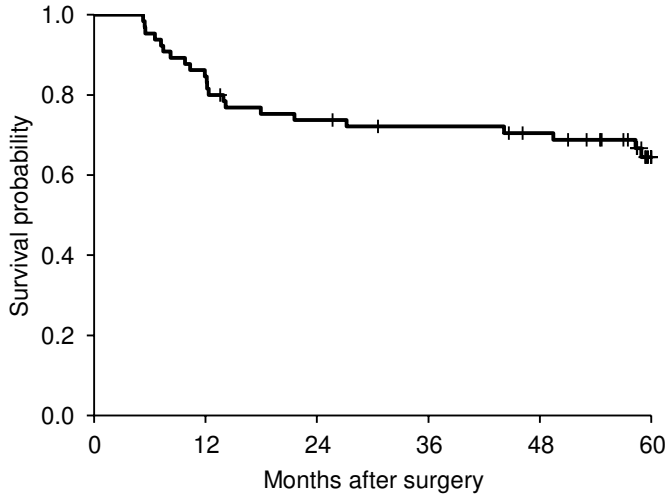


No. at risk

Months	0	12	24	36	48	60
	65	65	59	53	49	31

3-year OS: 86.0% 5-year OS: 75.9%

b Recurrence-free survival

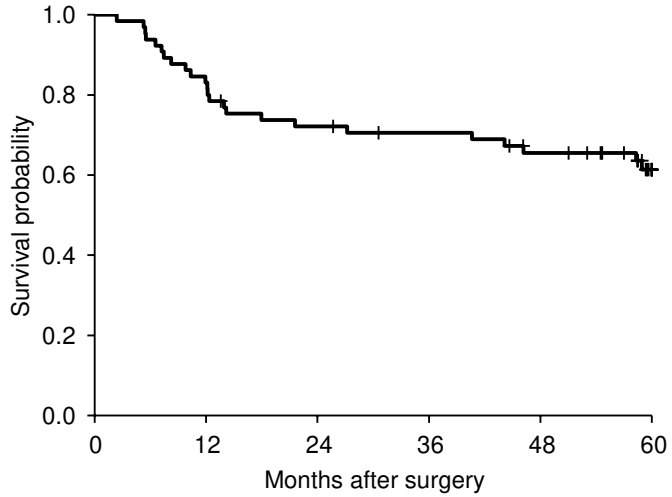


No. at risk

Months	0	12	24	36	48	60
	65	55	47	44	41	23

3-year RFS: 72.1% 5-year RFS: 64.5%

c Disease-free survival

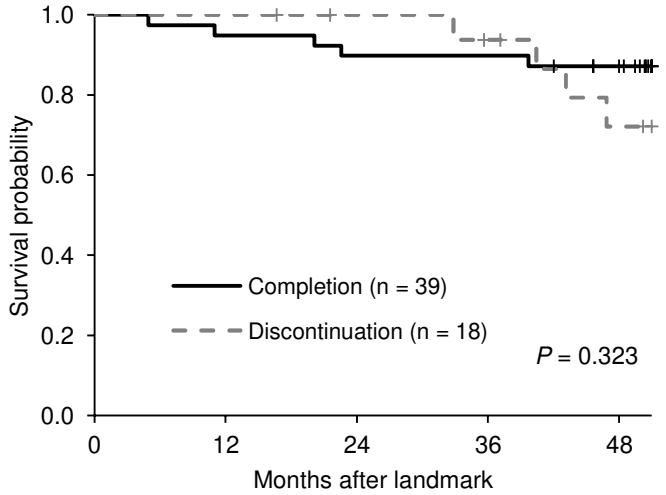


No. at risk

Months	0	12	24	36	48	60
	65	54	46	43	38	22

3-year DFS: 70.6% 5-year DFS: 61.4%

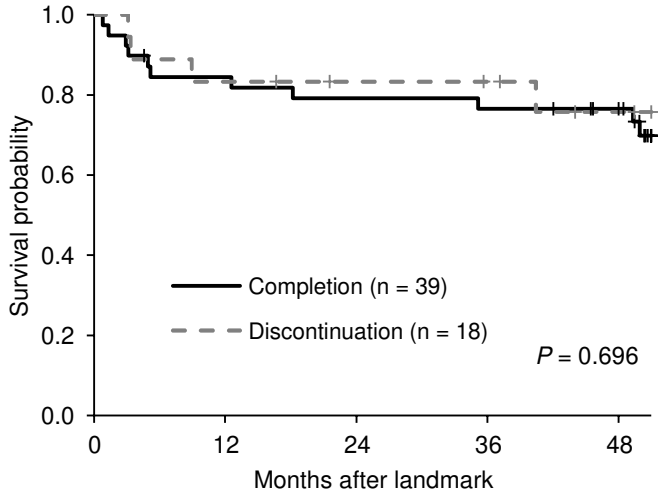
a Overall survival



No. at risk

Months	0	12	24	36	48	51
Completion	39	37	35	35	31	21
Discontinuation	18	18	16	14	10	9

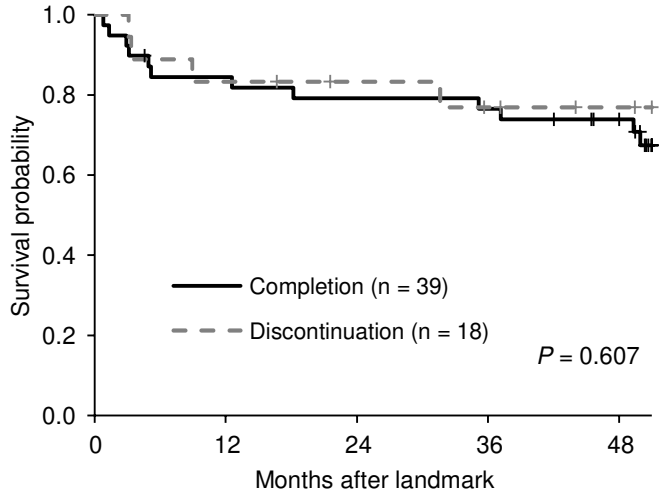
b Recurrence-free survival



No. at risk

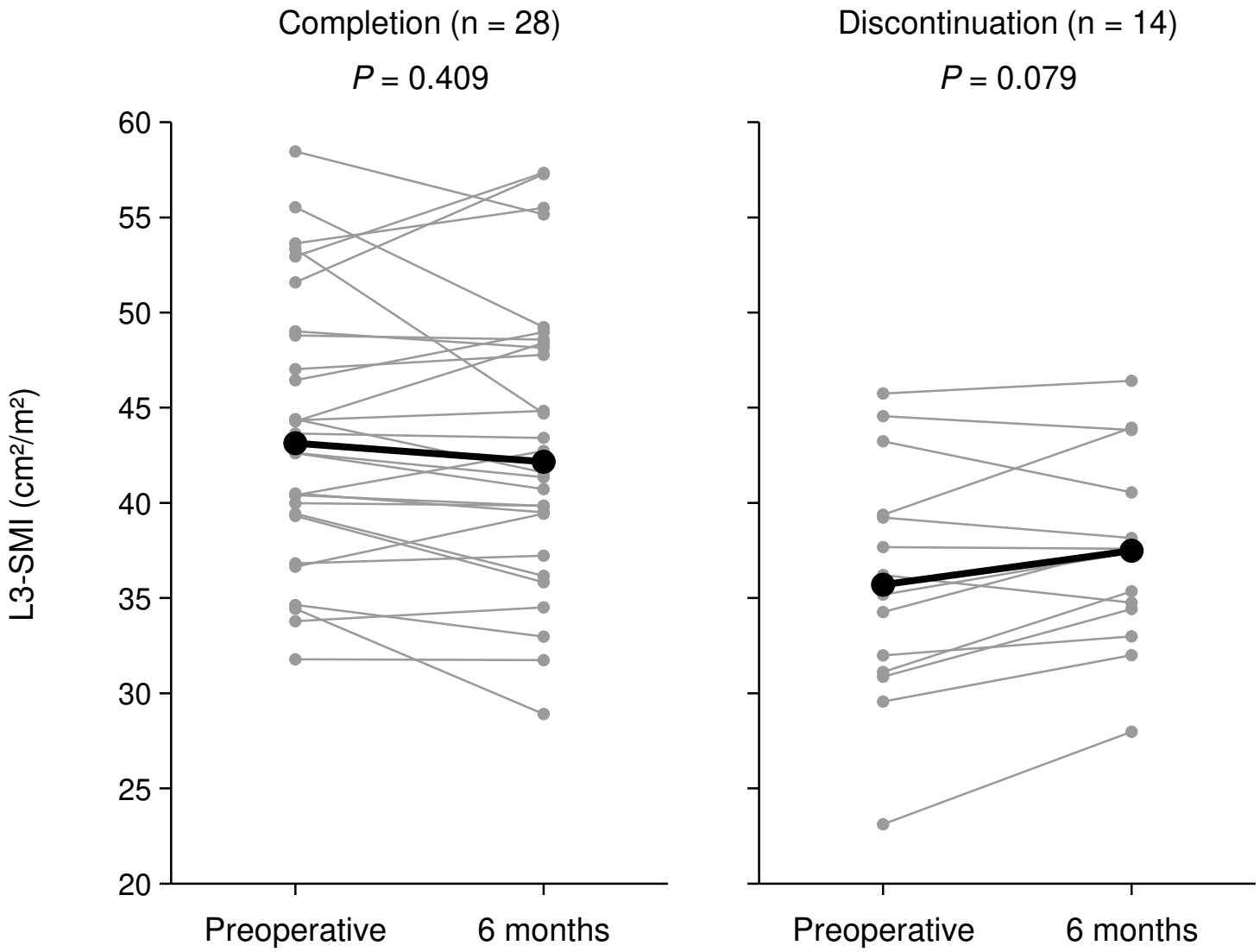
Months	0	12	24	36	48	51
Completion	39	32	30	29	26	14
Discontinuation	18	15	13	12	9	8

c Disease-free survival



No. at risk

Months	0	12	24	36	48	51
Completion	39	32	30	29	25	14
Discontinuation	18	15	13	11	9	8


Completion (n = 28)
P = 0.409
Discontinuation (n = 14)
P = 0.079
L3-SMI (cm²/m²)
60
55
50
45
40
35
30
25
20
Preoperative
6 months
Preoperative
6 months

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- HiSCO03Tables1320261026.docx
- OnlineResource1.docx
- OnlineResource2.docx