Gynecologic Oncology Reports 54 (2024) 101441

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Development and feasibility of an exercise therapy intervention for older women with advanced epithelial ovarian cancer referred to neoadjuvant chemotherapy prior to possible interval debulking surgery

Eva Jespersen [a,b,*,1], Cristina Daviu Cobián [c,d,1], Trine L. Jørgensen [a,b], Lisbeth R. Minet [b,e], Tine H. Schnack [b,d,2], Anders Vinther [f,g,2]

[a] Department of Oncology, Academy of Geriatric Cancer Research, AgeCare, Odense University Hospital, Odense, Denmark
[b] Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[c] Department of Gynaecology and Obstetrics, Zealand University Hospital, Roskilde, Denmark
[d] Department of Gynaecology and Obstetrics, Odense University Hospital, Denmark
[e] Geriatric Research Unit, Odense University Hospital, Odense, Denmark
[f] Department of Physiotherapy and Occupational Therapy, Copenhagen University Hospital, Herlev and Gentofte Hospital, Herlev, Denmark
[g] Hospital Secretariat and Communications, Research, Copenhagen University Hospital, Herlev and Gentofte Hospital, Herlev, Denmark

ARTICLE INFO

Keywords:
Ovarian cancer
Chemotherapy
Frailty
Prehabilitation
Exercise feasibility
Exercise acceptability

ABSTRACT

Objective: This study describes the development and examines the feasibility of an exercise therapy program for women aged 70 years or older with advanced EOC, receiving neoadjuvant chemotherapy (NACT) before possible major surgery.

Methods: In this feasibility study, patients participated in a mainly home-based exercise therapy program, including progressive resistance training, physical activity, and support from the supervising physiotherapist. The program included both supervised virtual and face-to-face sessions and self-administered daily exercise. Clinician-reported, patient-reported and physical performance measures were collected before and after NACT. Retention, adherence, and compliance to the program was monitored, and patient acceptability was explored in semi-structured interviews.

Results: Fifteen patients, median age of 77 years (range 70–85) completed the exercise therapy program concurrently to receiving NACT lasting a median of 12 weeks. Patients were physically frail at baseline but improved at follow-up on measures of performance status, level of frailty, patient-reported physical fitness, lower body strength, aerobic functional capacity, basic mobility, balance, and number of steps per day. High levels of participation were found to both supervised and self-administered exercise. Patient interviews highlighted the homebased setting, the individualised tailoring of exercises and the support from the physiotherapist as reasons to complete the exercise therapy program as prescribed.

Conclusions: The exercise therapy program was found to be feasible and acceptable in women aged 70 years or older with advanced EOC, receiving NACT before possible major surgery. The observed improvements and the positive experiences perceived by the patients support future application in research and clinical practice.

1. Background

Epithelial ovarian cancer (EOC) is the seventh most common cancer in women and the deadliest gynaecological malignancy globally, with prognosis worsening significantly with age (Gottschau et al., 2016; Ferlay et al., 2015; Dumas et al., 2021; Ekmann-Gade et al., 2022). EOC is also called the silent killer due to late onset of symptoms leading to diagnosis in advanced stages (Seibaek et al., 2011). A combination of extensive surgery and chemotherapy is the cornerstone of curatively intended treatment, delivered as either primary debulking surgery

* Corresponding author at: Eva Jespersen, Department of Oncology, Odense University Hospital, Kløvervænget 19, Indgang 85, 1. Sal, 5000 Odense C, Denmark.
E-mail address: eva.jespersen@rsyd.dk (E. Jespersen).
[1] Eva Jespersen and Cristina Daviu Cobián share first authorship.
[2] Tine H. Schnack and Anders Vinther share last authorship.

https://doi.org/10.1016/j.gore.2024.101441
Received 8 May 2024; Received in revised form 17 June 2024; Accepted 23 June 2024
Available online 26 June 2024

followed by adjuvant chemotherapy or as neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS). The latter, if primary complete resection is considered impossible or the general condition of the patients does not allow extensive surgery. Optimally, NACT consists of a combination of carboplatin and paclitaxel. Patients considered too frail to tolerate this regimen are offered carboplatin as a monotherapy.

Risk of cancer increases with age, and therefore the number of older patients with cancer is expected to rise (Siegel et al., 2019). The prognosis of advanced EOC is poor and worsens with age (Gottschau et al., 2016; Ør Knudsen et al., 2016). Treatment of older patients is more complex due to comorbidity and age-related frailty. These factors increase the risk of adverse events such as functional decline, postoperative complications, poor quality of life, poor chemotherapy tolerance and survival (Handforth et al., 2015; Kristjansson et al., 2010; Geessink et al., 2017; Kirkhus et al., 2019; Ørum et al., 2018; Aparicio et al., 2013; Hoppe et al., 2013).

Exercise and physical activity have the potential to prevent or improve the underlying factors for physical and psychological frailty in cancer patients undergoing chemotherapy (Campbell et al., 2019; Patel et al., 2019). However, the effect of exercise in older patients receiving chemotherapy is inconclusive due to a limited number of well powered trials and deficits related to selection, intervention, and outcomes (Mikkelsen et al., 2020; Lund et al., 2020; Kilari et al., 2016). Due to heterogeneity among older patients with cancer, ranging from fit to frail, with various cancer burdens and comorbidities, future exercise studies are recommended to be individualised to optimise participation, safety, and efficacy (Kilari et al., 2016). Still, interventions should build on evidence-based guidelines regarding the recommended type, frequency, intensity, and duration to improve physical and psychological cancer-related health outcomes (Campbell et al., 2019; Patel et al., 2019; Kilari et al., 2016). Earlier exercise studies for women with EOC, have pointed towards a poor uptake and several factors hindering adherence to exercise programmes (McGrath et al., 2022; Jones et al., 2020). Barriers were cancer – and treatment related symptoms (i.e. fatigue, abdominal pain, nausea, constipation, neuropathy), as well as logistical concerns, scheduling conflicts, social and mental barriers, and being older (McGrath et al., 2022; Polen-De et al., 2021). Facilitators were a supportive healthcare team and perceived benefits in relation to overall health, to fight cancer disease, to gain symptom control and to have life-saving/-prolonging surgery (McGrath et al., 2022; Polen-De et al., 2021). Building on this knowledge, further studies are warranted to develop and test how exercise interventions for older women with advanced EOC receiving cancer treatment can be feasible.

Currently, a randomized controlled trial (RCT) investigating the impact of FRAilty screening and Geriatric assessment and INtervention in older patients with epithelial Ovarian Cancer (The FRAGINOC study) is being conducted (Daviu Cobián et al., 2024:). The study seeks to explore whether a comprehensive geriatric assessment and intervention in combination with an individualised exercise therapy program can increase the number of patients referred to interval debulking surgery in those receiving NACT (Daviu Cobián et al., 2024:).

The purpose of the present study was to describe the development and feasibility of this exercise therapy program for women aged 70 years or older with advanced EOC, receiving NACT before possible IDS.

2. Methods

2.1. Design

This was a feasibility study to test the exercise intervention in the FRAGINOC study. Patients who were found eligible for NACT after evaluation at a Multidisciplinary Conference were included in the exercise program, and followed until the end of NACT. The FRAGINOC study (including this study) was approved by The Scientific Ethics Review Committee, Region of Southern Denmark (project number: H-17024315) and The Danish Data Protection Agency (22/7471) and adhered to the Declaration of Helsinki.

2.2. Participants

For the feasibility study, The Department of Gynaecology (Odense University Hospital) and the Departments of Oncology (Odense University Hospital and Vejle Hospital) participated, including patients in the period June to December 2022. Inclusion criteria were; women aged 70 years or older with a newly diagnosis of FIGO-stage III-IV (International Federation of Gynecology and Obstetrics) EOC and referred to NACT before possible IDS. Excluding patients who had received antineoplastic treatment (excluding endocrine therapy or surgery alone) for other cancers in the preceding three years or women suffering from severe psychiatric disease or not being able to understand written and oral information in Danish.

2.3. Development of the exercise therapy program

The description of the exercise therapy program adheres to the Consensus on Exercise Reporting Template (CERT) (Slade et al., 2016). An initial version of the exercise therapy program was developed by two physiotherapy senior researchers with clinical and research experience in exercise interventions in cancer and geriatric populations. The program was based on available evidence describing exercise therapy for patients with cancer (Campbell et al., 2019; Patel et al., 2019), including two recent systematic reviews of exercise interventions for patients with EOC (McGrath et al., 2022; Jones et al., 2020) and specific recommendations regarding exercise trials for older adults with cancer (Kilari et al., 2016). Thus, the exercise therapy program was developed to be person-centered, and individualised, meeting the performance abilities and needs of the individual patient throughout the oncological treatment, and included 1) Resistance training aiming to increase the muscle strength and function, 2) Physical activity to increase aerobic capacity and 3) Supportive counselling to optimise the effect, safety, and participation in the program.

To overcome barriers such as travel distances and scheduling conflicts, the exercise therapy program was developed as homebased sessions supervised by a physiotherapist through videoconferencing (Morrison et al., 2020). The set-up was discussed with oncologists, gynaecological surgeons, and geriatricians involved in the project. The possibility of a telephone supported version of the exercise therapy program was added as it was presumed that not all patients would have the digital confidence/devices required for a virtual exercise set-up.

Prior to the feasibility study, three older patients who had just finished NACT, were interviewed. The purpose was to gather information about their experience of going through chemotherapy, its influence on their daily life/activity level and their thoughts on completing a structured exercise and physical activity program while undergoing chemotherapy. Furthermore, patients were asked if they had smartphones, tablets and/or computers and to what degree they could imagine operating virtual exercise sessions using these devices. Eventually, they were asked if it would have been acceptable to wear an activity watch and make notes in a paper diary about the daily amount and type of physical activity.

2.4. The final version of the exercise therapy program tested in the feasibility study

The exercise therapy program started within a week from inclusion and ran during NACT (9–12 weeks). The physiotherapist made a first visit at the patient's home, with the purpose of assessing the current physical capacity of the patients and adjusting the exercise therapy program to the home and local environment. The physiotherapist providing the exercise therapy program had postgraduate expertise in exercise prescription, musculoskeletal health and oncogeriatric

rehabilitation.

The exercise therapy program consisted of resistance training with the supervising physiotherapist lasting approximately 30 min twice weekly, either as virtual sessions or face-to face sessions coinciding with hospital appointments. Patients who were not able to participate in virtual sessions received supportive counselling by telephone once weekly. Four predefined progressive levels of resistance training were used, and the physiotherapist selected the starting level after protocolled criteria, and continuously supervised the progression. If needed, the physiotherapist could modify the program in days with heavy symptoms. Additionally, the exercise program was supported by self-administered daily activity including 1) Two progressive resistance training exercises involving the major muscle groups in lower extremities and 2) Progressive walking and/or other physical activities performed with at least moderate intensity.

The program was progressed as much as possible during the intervention by the supervising physiotherapist. A detailed overview of the program is provided in Supplemental Table 1.

2.5. Clinician-reported, patient-reported and physical performance outcome measures

Baseline information on age, height, weight, living accommodations, cohabitation, planned NACT regimen and registration of patients being considered fit for IDS at follow-up were obtained from medical records. Clinician-reported measures of comorbidity, performance status, geriatric risk profile and level of frailty were gathered. Likewise, patient-reported measures on physical activity levels, physical fitness, functioning, history of falls, and concerns about falling were gathered and physical measures on upper and lower body strength, aerobic functional capacity, basic mobility and standing balance were performed. All measures were repeated at follow-up approximately 3 months later. A detailed description is provided in Supplemental Table 2.

2.6. Measuring feasibility of the exercise therapy program and monitoring

The rate of retention, adherence, and compliance to the supervised resistance training were used to interpret the feasibility of the program (Cyarto et al., 2006). *Retention rate* was defined as the number of patients who completed follow-up testing divided by the number who completed baseline testing. *Adherence rate* was defined as the number of sessions attended divided by number of sessions prescribed. In case of patients being hospitalised, having pronounced symptoms/adverse events or staff shortage, sessions would not count as prescribed. *Compliance* was defined as the extent to which patients completed the prescribed number of sets and repetitions and/or progressed the intensity (repetitions and/or resistance). This information was gathered by the physiotherapist keeping records of attendance, level of resistance training, including number of sets and repetitions, needs for progression (or reasons for modification).

Patients were instructed to wear a wrist worn activity tracker watch, the Garmin Vivofit 4 (Garmin, Olathe, Kansas, US), from getting up in the morning and until going to bed and to register the daily number of steps and the distance in the training diary. Additionally, data from the watch was downloaded to a data-processing software application (the Fitrockr research platform, Berlin, Germany). Adherence was defined as having worn the watch/completed the diary all or most of the days ($\geq$75 %).

All data was stored in a predefined Research Electronic Data Capture (REDCap) database, administered by University of Southern Denmark and Odense University Hospital, Odense, Denmark.

2.7. Statistical analysis

Baseline characteristics of patients and participation in the exercise therapy program, adherence to monitoring tools and referral to surgery were presented using descriptive statistics. The status of frailty was described using dichotomized or categorized cut-offs validated in earlier studies (Supplemental Table 2). Patients were defined as compliant if they completed the prescribed number of sets and repetitions $\geq$ 75 % of the sessions. Adherence to self-administered daily walking and/or other physical activity, was defined as performing daily walking $>$ 4600 steps (Tudor-Locke et al., 2011) and/or resistance exercises and/or other physical activity.

Due to the small sample size of and the asymmetrical distribution of differences between baseline and 3 months, the change in outcome scores was analysed using non-parametric statistics (Wilcoxon matched-pairs signed-rank test). A 95 % significance level was used throughout the analysis (two-sided p-values $<$ 0.05 were considered statistically significant). All analyses were performed using Stata statistical software (Stata/IC 17.0).

2.8. Patient interviews

Immediately after each patient had completed the exercise therapy program, semi-structured interviews were conducted to evaluate the feasibility, including the acceptance of the program (Kvale and Brinkmann, 2015). An iterative approach to the analysis of the interviews were chosen to be able to improve the program concurrently (O'Cathain et al., 2015). Thus, the findings from interviews were included in the program development and informed the final version of the exercise therapy program. Patients were interviewed to capture their experience of exercising by using a semi-structured approach to evaluate different elements of the exercise therapy program (Kvale and Brinkmann, 2015). All interviews were conducted by EJ in the home of each patient (n = 14) except for one interview conducted by telephone (n = 1). All fifteen interviews were assisted by an interview guide (Supplemental Table 3), including twelve conducted and recorded on audio and three summarised and written down on paper.

2.8.1. Analytic strategy

The interview data was analysed using thematic content analysis inspired by Braun and Clarke (Braun and Clarke, 2006); with manifest interpretation in its focus on the obvious, visible components of the content. The purpose was to identify the main themes in the patients' accounts of their experience with the program. This is a comparative process by which the various accounts gathered from the interviews were compared with each other to classify themes that were common in the data set. EJ carried out the thematic analysis and discussed methodological uncertainties with LRM who has special insights into qualitative research.

3. Results

A total of 17 patients were found eligible for the study and 15 patients (88 %) with a median age of 77 years (range 70–85) agreed to participate. Physical frailty was prevalent at baseline, albeit varying according to the chosen frailty measure (Table 1). All patients were able to perform the physical tests except for the six-minute walk test where four patients were unable to complete at baseline. There were no baseline differences between groups being able to participate in supervised virtual exercise sessions or not, except from differences in neoadjuvant chemotherapy regimen, where all patients participating in a virtual set-up received combination therapy (Carboplatin + Paclitaxel), whereas 75 % of the patients that could not participate in a virtual set-up received monotherapy (Carboplatin) (Supplemental Table 4a). The patients who received monotherapy (40 %) were frailer compared to patients receiving combination therapy as measured by BMI, G8, Clinical Frailty Scale, Six-Minute Walk test, and Timed Up & Go test (Supplemental Table 4b).

All 15 patients completed the exercise therapy program, with seven patients participating in a virtual set-up. A median of 5 supervised

Table 1
Baseline characteristics of patients with EOC receiving neoadjuvant chemotherapy including frequencies of frailty.

	Total N = 15
Age, y, median (IQR*) [range]	77 (73–78) [70–85]
Living alone, n (%)	9 (60 %)
Living accommodations, n (%)	
House, rural	5 (33 %)
House, urban	7 (47 %)
Flat, urban	2 (13 %)
Nursing home (temporary)	1 (7 %)
BMI, median (IQR) [range]	25 (21–30) [16–39]
Neoadjuvant chemotherapy regimen, n (%)	
Combination therapy (Carboplatin + Paclitaxel)	9 (60 %)
Monotherapy (Carboplatin)	6 (40 %)
Charlson Comorbidity Index	
Score (points), median (IQR) [range]	6 (6–7) [6–8]
Frail; ≥1 comorbidities, n (%)	7 (47 %)
Performance status, n (%)	
0	1 (7 %)
1	8 (53 %)
2	6 (40 %)
Frail; 2 points	6 (40 %)
G8 score	
Score (points), median (IQR) [range]	10 (9–12) [7–16]
Frail; ≤ 14 points n (%)	13 (87 %)
G8 modified score	
Score (points) median (IQR) [range]	14 (7–25) [4–27]
Frail; ≥ 6 points	14 (93 %)
Clinical Frailty Scale, n (%)	
Score (points), median (IQR) [range]	4 (4–5) [3–7]
3, Managing well	1 (7 %)
4, Vulnerable	7 (46 %)
5, Mildly frail	5 (33 %)
6, Moderately frail	1 (7 %)
7, Severely frail	1 (7 %)
Frail; ≥ 5 points	7 (47 %)
Saltin-Grimby Physical Activity Scale, n (%)	
1 = Physical inactive/sedentary	7 (47 %)
2 = Light physical activity	8 (53 %)
3 = Moderate physical activity	–
4 = Vigorous physical activity	–
Frail; <2 (being physical inactive/sedentary)	7 (47 %)
Physical fitness, n (%)	
1 = Very good	–
2 = Good	1 (7 %)
3 = Fair	8 (53 %)
4 = Poor	6 (40 %)
5 = Very poor	–
Frail; ≥ 4 points	6 (40 %)
Falls, n (%)	
Frail; ≥1 falls within last six months	1 (7 %)
FES-1 – concerns about falling, n (%)	
Score (points), median (IQR) [range]	19 (16–23) [16–30]
Low concern (16–19)	8 (53 %)
Moderate concern (20–27)	6 (40 %)
High concern (28–64)	1 (7 %)
Frail; ≥20	7 (47 %)
ELFI – the Elderly Functional Index, median (IQR) [range] (1 missing)	
Physical function scale	63 (40–80) [27–100]
Role function scale	33 (17–83) [0–100]
Social function scale	92 (67–100) [33–100]
Mobility scale	61 (44–89) [22–100]
ELFI score	63 (39–90) [25–96]
Frail; <80	10 (67 %)
Handgrip strength test	
Score (kilogram), median (IQR) [range]	21 (18–25) [16–31]
Frail; ≤ age/gender specific ref material, n (%)	4 (27 %)
30 sec Chair Stand Test	
Score (no of stands without using armrest), median (IQR) [range] (n = 12)	9 (8–12) [5–14]
Score (no of stands with use of armrest), median (IQR) [range] (n = 3)	6 (3–8) [3–8]
Frail; < age/gender specific ref material or using the armrest, n (%)(n = 15)	11 (73 %)
Six-Minute Walk test (4 missing)	
Distance walked (meters), median (IQR) [range]	387 (309–420) [120–442]
Percentage of age/gender/weight/height specific reference material (%)	91 (67–97) [31–104]
Frail; ≤ age/gender/weight/height specific reference material, n (%)	3 (20 %)
Timed Up & Go test	
Score (seconds), median (IQR) [range]	9 (7–11) [6–14]
Frail; > 10 s, n (%)	5 (33 %)
Tandem balance test	
Score (seconds), median (IQR) [range]	28 (22–30) [12–30]
Frail; < 30 s, n (%)	8 (53 %)

* Inter Quartile Range.

resistance training sessions were attended, with a wide individual range from three to 34 sessions. Patients with a virtual exercise set-up attended a higher number of supervised resistance training with a median of 14 sessions and thus progressed the intensity more compared to patients with no virtual exercise set-up who attended a median of three sessions (Supplemental Table 5). Cancelling sessions would primarily be due to hospitalisations and to a lesser degree pronounced symptoms/adverse events or staff shortage.

Attending more than 18 sessions would imply that NACT treatment was extended due to blood profile or decision to give additional NACT treatments before reassessing referral to surgery. A high degree of participation to the supervised resistance training was found with patients adhering to 87 % of the prescribed sessions and completing the

Table 2
Participation in the exercise therapy program, adherence to monitoring tools and referral to surgery.

	Total N = 15
Retention rate, n (%)	
Patients who completed the exercise therapy program, n (%)	15 (100 %)
Adherence virtual exercise set-up	7 (47 %)
Adherence rate, supervised resistance training	
Sessions attended, median (inter quartile range)[range]	5 (3–14) [3–34]
Total sessions attended/ total sessions prescribed, n	149/172
Adherence rate (%)	87 %
Compliance to supervised resistance training	
Completed the prescribed number of sets and repetitions ≥ 75 % of sessions, n (%)	15 (100 %)
Adherence rate self-administered daily walking and/or resistance exercises and/or other physical activity, n (%)	
Performed self-administered daily walking > 4600 steps and/or resistance exercises and/or other physical activity	
≥30 % of the intervention days	13 (87 %)
≥50 % of the intervention days	8 (53 %)
≥75 % of the intervention days	4 (27 %)
Missing*	2 (13 %)
Adherence to Training diary, n (%)	
Completed all or most of the time (≥75 %)	12 (80 %)
Not or only partly completed	1 (7 %)
Not handed out**	2 (13 %)
Adherence to Activity watch, n (%)	
Worn all or most of the time (≥75 %)	12 (80 %)
Not worn or only worn part of the time	1 (7 %)
Not handed out (pronounced poor vision or 'technical anxiety')	2 (13 %)
Referral to surgery, n (%)	
Operation possible	8 (53 %)
Operation not possible***	7 (47 %)

*Missing because of not having worn a watch due to pronounced poor vision (n = 1) and technical anxiety (n = 1).
** Training diary not handed out because they did not wear an activity watch due to pronounced poor vision (n = 1) and technical anxiety (n = 1) and therefore lacked the information asked for in the diary.
***Operation not possible includes non-sufficient NACT response (n = 5) and non-sufficient general condition (n = 2).

prescribed number of sets and repetitions ≥ 75 % of sessions (Table 2).

Most patients did some kind of physical activity with moderate intensity at least 30 % of the days, whereas one fourth were physically active at least 75 % of the days. All the monitored patients improved the mean number of steps per day with at least 30 % with one third of the group reaching a double up on step counts during the intervention period (Table 2).

Two patients did not wear an activity watch because of pronounced poor vision and fear of technical devices. Of the remaining thirteen patients, 12 patients wore the watch and completed the training diary ≥ 75 % of the time. One patient had memory problems that made adherence to activity watch and training diary incomplete.

The patients participated in the exercise therapy program with a median of 12 weeks (interquartile range 10–14 weeks, range: 7–21 weeks). Statistically significant improvements were found for clinician reported ECOG-PS, CFS, patient-reported physical fitness and 30 s-CST, 6MWT, TUG, Tandem test, and steps per day in the beginning versus the end of the intervention period. All other estimates also showed promising improvements, albeit they did not reach statistical significance (Table 3). The eight patients exercising without a virtual supervised exercise set-up, still improved on several physical performance outcomes and did not differ from the patients exercising with a virtual set-up (Supplemental Table 6a). In relation to change in outcomes from baseline to follow-up, by neoadjuvant chemotherapy regimen, there were no differences in the improvements measured in patients receiving monotherapy compared to patients receiving combination therapy (Supplemental Table 6b).

The individual variation in outcome scores from baseline to approximately three months later for each of the 15 patients is illustrated in Fig. 1.

The patients found the exercise therapy program acceptable and mentioned positive effects like hope, confidence, a way to feel in control, a way of doing something active to improve the situation, a way to change mood/handle sadness, feeling the gradual physical improvements and being relatively fit. Most patients thought that they would not have exercised if they had not been in the program. The home-based exercise, the individualised tailoring and the empathy and support from the supervising physiotherapist were perceived to be essential for participation. More detailed patient responses are presented in Table 4.

Table 3
Changes in outcomes from baseline to follow-up approximately 3 months later, prior to interval debulking surgery or further chemotherapy in patients not undergoing surgery.

	Baseline (n = 15)	Follow-up (n = 15)	P-value*
Clinician-reported, median (IQR) [range]			
Performance status	1 (1–2) [0–2]	1 (0–1) [0–2]	**0.02**
G8 score	9.5 (9–12) [7–15.5]	11.5 (9.5–13.5) [8–16]	0.15
G8 modified score	14 (7–25) [4–27]	13 (6–16) [0–22]	0.09
Clinical Frailty Score	4 (4–5) [3–7]	4 (3–4) [2–6]	**0.01**
Patient-reported, median (IQR) [range]			
Physical fitness	3 (2–3) [2–4]	4 (3–4) [2–4]	**0.01**
FES-1 (concerns about falling)	19 (16–23) [16–30]	18 (16–21) [16–25]	0.35
ELFI (the Elderly Functional Index) (1 missing)	63.2 (39–90) [25–96]	78.3 (69–89) [39–100]	0.09
Physical tests median (IQR) [range]			
Handgrip strength test (1 missing)	21.2 (18–25) [16–31]	22 (21–23) [16–27]	0.16
30 sec Chair Stand Test	9 (8–12) [5–14]	13 (10–15) [8–18]	**0.001**
Six-Minute Walk Test (4 missing)	387 (309–420) [120–442]	432 (409–483) [350–506]	**0.004**
Timed Up & Go test	8.8 (7–11) [6–14]	6.9 (6–9) [6–11]	**0.000**
Tandem balance test	28 (22–30) [12–30]	30 (28–30) [20–30]	**0.03**
Physical activity, Steps per day, mean (SD)			
The mean number of steps per day averaged over three consecutive days in beginning versus end of intervention period (3 missing)	2595.6 (1138.4)	4419.1 (1949.7)	**0.001**

*Wilcoxon matched-pairs signed-rank test (nonparametric analysis). P-values of < 0.05 in bold.

4. Discussion

This study provided a detailed description of the development and feasibility of an exercise therapy program for women aged 70 years or older with advanced EOC, receiving NACT before possible major cancer surgery. Quantitative as well as qualitative evaluation of the exercise program was performed. The program was found feasible, with a high degree of patient perceived acceptance and improved outcome measures at follow-up.

While the feasibility of exercise programs has been reviewed in earlier studies involving all adult women with EOC in all disease and treatment stages (McGrath et al., 2022; Jones et al., 2020), this study is the first to target a specific population of older women with advanced EOC in the initial and crucial state of treatment. It illuminates earlier research gaps in cancer exercise studies regarding geriatric oncology patients overcoming exercise adherence, previously acknowledged to be negatively associated with older age (Loh et al., 2018).

The qualitative interviews contributed to one specific change (addition of two daily unsupervised resistance exercises), but also to important perspectives on acceptability and perceived benefits of the exercise therapy program. This study adds to the evidence that exercising during chemotherapy is perceived acceptable, safe, and effective (Campbell et al., 2019; Patel et al., 2019; Adamsen et al., 2009). Contextual factors theorised to be important when developing the exercise therapy program, e.g. supervision, individualisation, the program being primarily home-based and conformed to hospital schedule, were confirmed by patient statements and the high level of retention, adherence, and compliance. This is in line with a theoretical model on how exercise adherence are thought to be enhanced for women with EOC (McGrath et al., 2022).

Most patients in this study were physically frail at baseline, as measured by clinician-reported, patient-reported, and physical performance tests, supporting the need for interventions targeting this. Within the last decade, there has been an increasing interest in optimising patients' physical condition before undergoing extensive surgery (Miralpeix et al., 2016; Nelson et al., 2019). The exercise therapy intervention in this study serves not only as prehabilitation, but also as an intervention to avoid functional decline while undergoing NACT. The latter is especially important to the group of patients not considered candidates for IDS after NACT, as they will continue with palliative intended chemotherapy if performance status allows this. Indeed, the patients described how they experienced disabling symptoms and frailty when starting the exercise therapy program, but felt that they had benefitted from exercise achieving better functioning in their daily living. Similar perceived benefits were reported among older patients with advanced pancreas, biliary tract, and lung cancer after having completed a multimodal exercise-based intervention (Mikkelsen et al., 2022).

Fifteen patients were included with a high recruitment rate of 88 %. This contrasts with similar studies with lower rates (Lund et al., 2021; Mikkelsen et al., 2022). The explanation could be that patients were not at risk of going into a control group and were probably aware that being physical fit could increase the chances of referral to IDS (Polen-De et al., 2021). The latter might also explain the high retention, adherence and compliance rates with no patients withdrawing from the program and

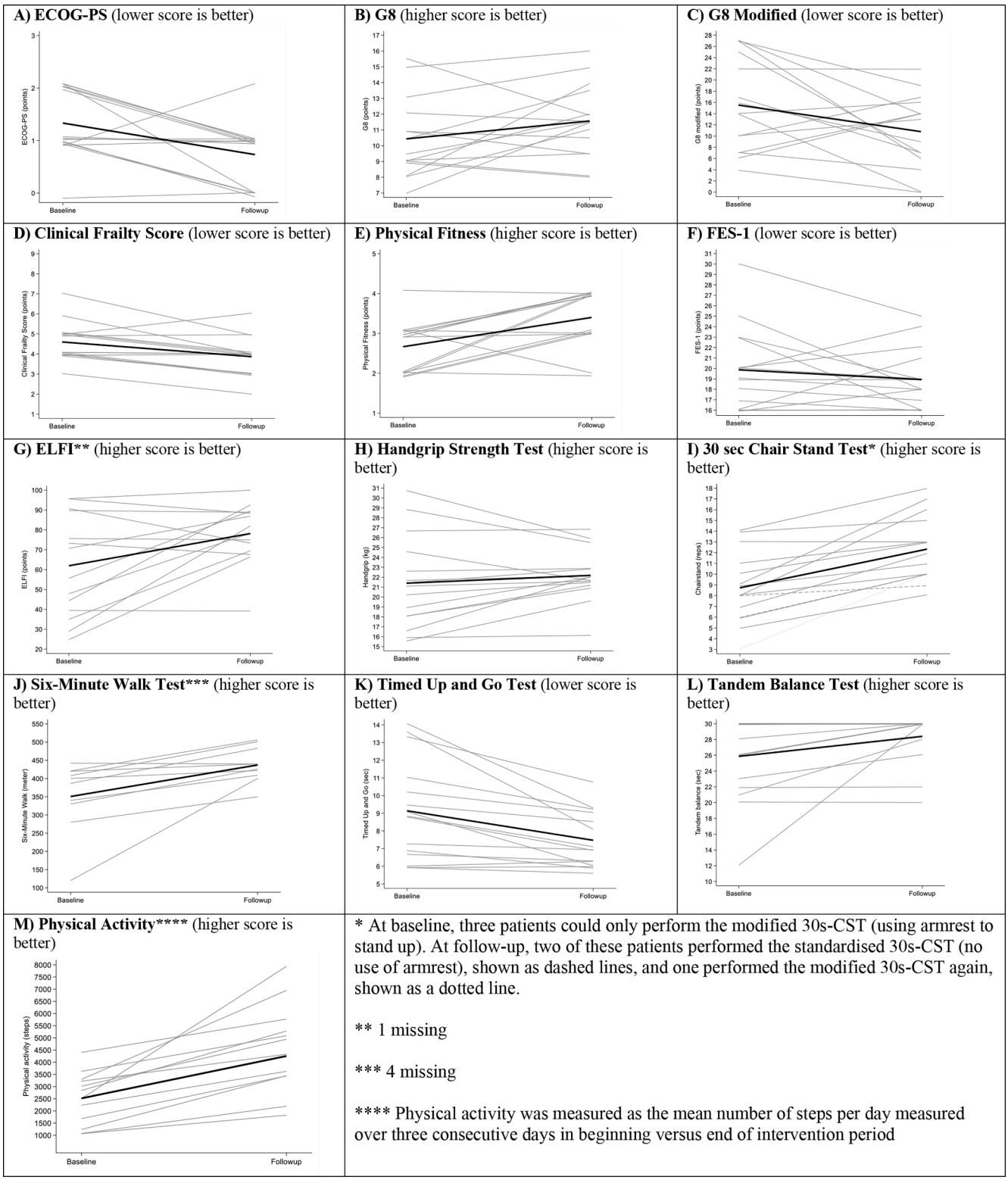

Fig. 1. Individual changes in outcome measures (n = 15) from baseline to follow-up (approximately 3 months). Black thick line is mean group change.

most patients performing the prescribed exercise. Patient interviews highlighted the homebased exercise setting and the support from the physiotherapist as other reasons to adhere, comply and stay in the exercise therapy program.

Almost half the patients in this study participated in the virtual exercise set-up, receiving almost five times more supervised resistance training sessions compared to the non-virtual set-up. Digital solutions have been suggested as a critical tool to deliver timely and ongoing support for exercise interventions for those affected by cancer (Morrison et al., 2020). However, knowledge gaps have been identified regarding older adults with cancer (Shaffer et al., 2023). This study shows that some patients aged 70 years or older do not have the digital competency and/or the devices to participate in a virtual exercise set-up and future programs still need to accommodate for this. Encouraging, the eight

Table 4
Patients responses on acceptability of the exercise therapy program, the facilitating and impeding factors for participation in the program and illustrative quotes from the patient interviews.

	Acceptability	Facilitating factors and impeding factors	Illustrative quotes from patient interviews
The supervised part of the exercise therapy program (warm-up, four resistance exercises and stretching)	The patients found the frequency, intensity, duration of sessions and type of exercises in the supervised resistance training acceptable.	Facilitating factorsThe presence of a supervising physiotherapist (virtually or face-to-face) was thought to facilitate the performance of the program. The exercises were thought to be easy to perform at home. Impeding factors Especially in the beginning of the program, symptoms from cancer/cancer treatment could impede the participation (e.g. abdominal ascites and/or pleural fluid leading to breathlessness)	*"It has been easy enough to perform (the type of exercises), something you can do without special equipment." (patient no. 3)* *"I thought the exercises were a bit difficult the first times. But then that was also the time where I still felt ill … It also helped a lot once the swelling of my stomach and legs had disappeared." (patient no. 14)*
The daily self-administered part of the exercise therapy program (two resistance exercises, walking and/or other physical activities)	In the beginning of the feasibility period, patients spontaneously suggested that the program should be supplemented with a few self-administered exercises to do on a daily basis. This need especially emerged when they could not exercise in the virtual set-up. Thus, two daily resistance exercises for the lower body were added to the self-administered part of the program, which all patients found acceptable.	Facilitating factors The possibility of spreading the resistance training sets across the day increased the possibility of completing the prescribed program. Patients described that it was a satisfying feeling to complete the self-administered program and gave a sense of taking control. On their own initiative, a few patients started to use walking sticks as a way to walk longer, faster and feel steadier. Impeding factors Outdoor walking and/or otherwise being physically active outdoor could be difficult for various reasons: E.g. dizziness, severe diarrhoea, feeling unsteady and in risk of falling, swollen legs, having severe lumbal stenosis, afraid to run out of breath and/or walking on their own, having other appointments. Moreover, both too warm and too cold weather could be reasons not to leave the house.	*"The type of exercises have been good and it has been good to be able to do some of the exercises and then leave them and do the rest later." (patient no. 4)* *"Some days it (outdoor walking) was not easy and other days it went really fine … If I had stomach problems or a busy day with hospital appointments, I just didn't have the energy to do more:" (patient no. 4)* *"When the swelling in my legs had disappeared it went well (the self-administered part of the program). Also, the snow kept me indoors some days. But I think that doing the exercises alone took around 30 min and I also did other things. … And if I walk more than 3 km, it is also around half an hour." (patient no. 14)*
The role of the physiotherapist	The patients doubted that they would have had the motivation and energy to exercise on their own and experienced the support from the physiotherapist as helpful and acceptable. They also expressed that it was nice to share the experience with someone and that someone cared and expressed empathy about their situation.	Facilitating factors Both the support to modify the exercise program on days with pronounced adverse effects and on the reverse the push to progress the program when possible, was believed to be important to always perform what was physical possible in a safe way. The patients appreciated that the physiotherapist could also remedy other problems, e.g. need for assistive devices, respiratory problems and referrals to lymphedema therapists.	*"It has actually been good, because it motivates you when you know that now is the time! (taps her finger into the table). And then you are just ready!" (patient no. 6)* *"Also the fact that you could talk about different things at the same time (as exercising) … and also just someone to share your thoughts with." (patient no. 6)* *"It was worth a lot that the physio was in the other end. I was really happy about that. It also gives you the feeling that you are not forgotten. It gave a sense of feeling safe and that someone was interested in what I did." (patient no. 14)*
The experience of the exercise therapy program being delivered primarily at home and individually	All patients appreciated the possibility of exercising at home and could not point towards any disadvantages. They argued that they would not have had the energy to leave the house more than they already did in relation to hospital attendances in relation to receiving chemotherapy, blood tests, scans, genetic analysis etc.	Facilitating factors The patients mentioned various reasons for preferring to exercise at home in an individual set-up, including: that even though they felt tired and in lack of mental energy, they could still participate in the home-based program that even though they had problems like uncontrolled diarrhoea or not feeling safe in relation to a newly acquired stoma they could still	*"Even though I got more energetic as the weeks went by, I would have been too tired to leave the house and go somewhere and do exercising. Also I hate to exercise in machines (referring to some training she did when she had a hip replacement)." (patient no. 2)* *"It has suited me well that there was no travelling and waiting time*

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Table 4 (*continued*)

	Acceptability	Facilitating factors and impeding factors	Illustrative quotes from patient interviews
	The one-to-one relation with the physiotherapist was also found acceptable and valued for the ongoing need for individual adjustments of the exercise therapy program.	exercise that they would have had logistic challenges in relation to leaving home	*and all that. It's been tough enough to go for blood tests and have to sit and wait there." (patient no. 9)*
The experience of exercising in a virtual set-up (n = 7)	All of the seven patients who were able to exercise in a virtual set-up found it acceptable and appreciated the fact that they could be supervised and supported without leaving their home.	Facilitating factors The patients believed that exercising in a virtual set-up at home enabled a high participation rate. Impeding factors One patient expressed that the face-to-face sessions at the hospital were better than virtual sessions when corrections to exercises were needed.	*"Both ways (virtual – and face-to-face sessions) were equally fine for me after we got into the routine. When I first started and figured it out, it was no problem, it was okay." (patient no. 7)* *"The exercising by screen worked out really fine, but I also liked the physical meetings. Especially when I needed corrections to the exercises." (patient no. 10)*
Monitoring of the exercise therapy program using an activity watch and training diary	The wear of an activity watch was found acceptable to all 13 patients who wore one. The training diary was accepted primarily as a tool to report daily activity to the researchers in the project, but also as a way of keeping track for one self.	Facilitating factors Most patients mentioned the activity watch as a motivating factor, because they kept track of steps and distance walked every day. Impeding factors Comorbidity e.g. Parkinson, where range of arm motion when walking can be decreased, could result in poorer step counts (due to watch being wrist worn). This could be demotivating.	*"It was no problem, when I was ready to go to bed I just sat down with the diary and the watch and wrote down … The watch made me walk just a little more." (patient no. 6)* *"The counting steps was good and it was also okay to fill out the diary as it only took me a few minutes every night. Motivating on good days, but a little annoying on days with low step counts." (patient no. 1)*
The experience of exercising/ being physically active while receiving chemotherapy	All patients found it acceptable to exercise during chemotherapy treatment and they did not mention any further discomfort related to	Facilitating factors The physiotherapist supervised adjustments of the exercise program on days with pronounced adverse effects	*"What impressed me the most was the time when I was asked to exercise right after having received chemotherapy. I must admit, my*

Table 4 (*continued*)

	Acceptability	Facilitating factors and impeding factors	Illustrative quotes from patient interviews
	exercising and staying physically active.	from the chemotherapy helped complete the entire or a modified program. Impeding factorsMost patients experienced periods where they needed to modify the exercises and/ or other physical activities because of the adverse effects from chemotherapy (e. g. tiredness, nausea, digestive problems, unsteadiness and pain in joint and muscles) .	*body actually felt much better when I returned home afterwards" (patient no. 7)* *"The days when I was dizzy I couldn't exercise. I really couldn't! I had to stop and I almost had to lean against the walls when walking in my house." (patient no. 5)*
The perceived effects of the exercise therapy program	All patients felt that they had benefitted from having completed the exercise therapy program and that the perceived effects were worth the effort. This was regardless of whether they were going to be operated or not. They had felt the gradual physical improvements during the program, including coping better with the adverse effects of the chemotherapy.	Facilitating factors Patients found it motivating to exercise once they had felt the benefits of being relatively fit.This was expressed as the ability to independent daily living and to perform activities that were important to them (e.g. being active with grandchildren, going for long walks in nature, baking and cooking, visiting/ receiving visits from friends and family etc.) .	*"I am sure the effort has been worthwhile,* e.g. *now I can get up from the chair without difficulties." (patient no. 2)* *"It seems that I don't run out of breath as easily as in the beginning." (patient no. 8)* *"My motor skills where not really good in the beginning. But it is now …* e.g. *when I started the program I had to walk backwards down the stairs but not anymore. Now I walk forwards one foot on each step and likewise up (the stairs)." (patient no. 10)*
Miscellaneous	A few patients felt reluctant to participate at the time of inclusion but were convinced to do so by their spouses and/or children. When evaluating these patients were satisfied to have participated and found the mode of delivery acceptable. Also, earlier experiences of	Facilitating factorsThe support from family and friends was highlighted as both a direct help (e.g. taking walks together) and an indirect help (e.g. encouragement, appraisals, technical assistance to virtual set-up) . Further, patients with a history of	*"My daughter-in-law has been a great help to me. She lived with me this summer and dragged me out of the house to do something active. My sons were also very supportive." (patient no. 1)* *"The reason why I decided to participate in the project was because I had*

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Table 4 (*continued*)

	Acceptability	Facilitating factors and impeding factors	Illustrative quotes from patient interviews
	being physically active was mentioned to be an advantage in the current situation	being physically active or who had participated in physical rehabilitation in other situations found it a useful experience to draw on in the current situation.	*some good experience with exercising after my hip replacement." (patient no. 2)*

patients exercising without virtual set-up, still improved on several physical performance outcomes. However, it is unclear whether these improvements were due to the intervention (three supervised exercise sessions, daily self-administered physical activity and weekly supportive counselling) or the effect of the neoadjuvant chemotherapy.

Having only single agent carboplatin implies that the patient is assessed to be too vulnerable to receive both carboplatin and paclitaxel. In this study, baseline measures confirm the larger prevalence of physical frailty among the group of 6 patients (40 %) receiving monotherapy. Promising, these patients also experienced improved outcome measures at follow-up.

In this study, 13 patients wore an activity tracker watch to measure the daily step count and reported it to be feasible and for some patients also motivational for increasing physical activity. Physical activity monitors have a moderate positive effect on the physical activity behaviour in older adults (Larsen et al., 2019). A statistically significant increase in step count was found in this study, but notably the mean follow-up step count of 4.419 steps (baseline 2596 steps) was still low considering the WHO-recommended 7.000 to 10.000 steps per day in older adults (Tudor-Locke et al., 2011). This may illustrate the negative impact of advanced cancer disease and a toxic treatment and underlines the need for support to prevent physical inactivity and deterioration in this vulnerable phase.

The patients found the exercise therapy program acceptable, maybe reinforced by feeling the gradual physical improvements during the program allowing them to resume their normal everyday life. Research looking into the lived experience of women undergoing surgery for EOC finds that sustaining some sense of normality in a period of great uncertainty and being able to occupy themselves with meaningful activities and feeling physical well are experienced as important and enforces the experience of hope (Seibaek et al., 2012).

4.1. Strengths and limitations

This feasibility study was strengthened by a range of both quantitative and qualitative measures supporting the feasibility, including patient acceptance and individual beneficial changes on follow-up outcomes.

Reports on the effectiveness of exercise intervention trials for older people often only include discussion of outcomes (Cyarto et al., 2006). In this study both retention, adherence and compliance to the exercise therapy program were reported and found high, allowing for a more accurate interpretation of the program's potential for more widespread adoption.

It is a limitation that the supervising physiotherapist did the interviews, as the patients might have felt inclined to comment positively on the program. However, this allowed for the program to be improved concurrently (O'Cathain et al., 2015). The differences between two subgroups; virtual versus no-virtual exercise set-up and monotherapy versus combination therapy, should be read with reservations as the numbers participating in this feasibility study are small. Finally, the lack of a control group makes it impossible to decide if the significant improvements on several outcome measures were due to the exercise therapy program, the chemotherapy and/or other supportive care interventions derived from being in standard oncologic care.

5. Conclusion

The present exercise therapy program was found to be feasible in women aged 70 years or older with EOC, receiving NACT before possible cancer surgery. The observed improvements on clinician-reported, patient-reported and physical performance outcomes in combination with the positive experiences perceived by the patients support the application of the exercise therapy program in the FRAGINOC RCT.

CRediT authorship contribution statement

Eva Jespersen: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cristina Daviu Cobián:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Trine L. Jørgensen:** . **Lisbeth R. Minet:** . **Tine H. Schnack:** . **Anders Vinther:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are very grateful to the patients who participated in this study. We would like to thank the Departments of Gynecology and Obstetrics at Odense University Hospital and Zealand University Hospital, the Departments of Oncology at Odense University Hospital and Vejle Hospital, the Department of Geriatric Medicine at Odense University Hospital, the Department of Physiotherapy and Occupational Therapy, Herlev and Gentofte Hospital and Vejle Hospital, for their enthusiasm and involvement in the project.

This work is supported by the Region Sjælland and Region Syddanmarks research fund, the Danish Comprehensive Cancer Center, and the Academy of Geriatric Cancer Research. None of the funding bodies influenced the study design, data analysis, and interpretation or writing of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2024.101441.

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