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Preoperative physical activity and frailty in older patients undergoing cancer surgery – PREsurgery study

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1. Introduction

Prehabilitation, a preoperative care program to optimize the physical condition, might improve surgical outcomes. Physical exercise is the cornerstone of most prehabilitation programs [1]. Older patients with physical frailty are expected to benefit the most from such a program [2]. Low physical activity is one of the hallmarks of the frailty phenotype described by Fried et al. [3], and a potentially modifiable target before surgery. However, physical activity data specifically in older presurgical patients are sparse. Furthermore, solid evidence regarding prehabilitation in this population is limited by the quality and methodological heterogeneity of the studies [4]. In order to establish prehabilitation in the older oncological-surgical patients, knowledge of the baseline physical status and activity levels of this population is essential. Therefore, in this study, we used thigh-worn accelerometry to quantify preoperative physical activity levels of older patients undergoing surgery for colorectal cancer (CRC) or gynecological cancer. We described associations between low physical activity and other determinants of frailty. The results of this study can contribute to the development of prehabilitation programs for older oncological-surgical patients.

2. Methods

2.1. Study Design and Setting

This prospective cohort study was performed between December 2018–January 2021 in three hospitals in the Netherlands: Gelre Hospitals, Isala Hospital, and University Medical Center Groningen.

2.2. Participants

Patients aged ≥70 years with CRC or ≥ 60 years with (a high suspicion of) gynecological cancer (Risk of Malignancy Index >200 [5] or complex atypical endometrial hyperplasia) were eligible for inclusion if they were planned for elective, potentially curative surgery. The lower age threshold for patients in the gynecological group aimed to increase the number of eligible study candidates. Patients were ineligible if they were wheelchair users (as thigh-worn accelerometry does not reflect their physical activity).

2.3. Procedures and Data Collection

Potentially eligible patients were identified during multidisciplinary oncological meetings and were given information about the study at the outpatient clinic. After provision of written informed consent, baseline assessment took place one to six weeks before surgery and the patients received the accelerometer. Baseline assessment consisted of physical tests, filling out questionnaires and collecting data from the electronic medical files (Table 1). Study visits took place at the patient's home or at the outpatient clinic. During the COVID-19 pandemic (from March 2020 onwards) study visits were conducted by telephone/videoconferencing. The study was approved by the local Medical Research Ethics Committee and institutional review boards.

2.4. Accelerometry

Physical activity was quantified with MOX1-accelerometers (Maastricht Instruments, Maastricht, The Netherlands), which were attached on the thigh 10 cm above the knee to measure continuously for seven

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days. MOX1 measures raw acceleration data on three orthogonal axes at a sampling rate of 25 Hz. It can accurately estimate the time spent in different postures (sitting/lying or upright) and activities (dynamic versus non-dynamic) [6]. Accelerometry data were analyzed using IDEEQ software (Maastricht Instruments) [6]. The total number of hours spent in a sedentary position, standing or performing dynamic activities was divided by the number of hours the sensor was worn. The results were reported as the number of hours spent sedentary, standing or moving per 24-h period.

2.5. Statistical Analysis

Patients who spent most of the time in sedentary position based on >1 standard deviation (SD) difference compared to the rest of the group were assigned to the sedentary group. Baseline and treatment characteristics were compared between sedentary and non-sedentary patients using Chi squared test, Fisher's exact test, *t*-test or Mann Whitney *U* test. A two-tailed *p*-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 25.0.

Table 1
Comparison of baseline characteristics, accelerometry and physical assessment results between sedentary and non-sedentary patients.

Variable	Overall ($n = 73$)	Sedentary ($n = 12$)	Non-sedentary ($n = 61$)	p-value
Baseline characteristics				
Age, median (IQR)	74 (70–79)	79 (75–81)	73 (70–76)	**0.007**
Female sex	48 (66)	6 (50)	42 (69)	0.32
ASA III-IV, $n = 69$	18 (26)	8 (67)	10 (18)	**0.001**
Charlson Comorbidity Index, median (IQR)	0 (0–1)	0 (0–2)	0 (0–1)	0.32
Anemia [a], n = 61	33 (54)	6 (60)	27 (53)	0.74
Polypharmacy [b]	23 (32)	3 (25)	20 (33)	0.74
Tumor location				1.00
Colorectal	47 (64)	8 (67)	39 (64)	
Gynecological	26 (36)	4 (33)	22 (36)	
Tumor stage				**0.02**
AJCC I-II/FIGO I-II	31 (43)	9 (75)	41 (67)	
AJCC III/FIGO III	16 (22)	1 (8)	19 (31)	
Benign	3 (4)	2 (17)	1 (2)	
Depressive symptoms (GDS ≥6) [c]	4 (5)	1 (8)	3 (5)	0.52
Cognitive problems (CIT ≥11) [d]	1 (1)	0 (0)	1 (2)	1.00
KATZ-ADL score ≥ 2 [e]	2 (3)	1 (8)	1 (2)	0.30
Accelerometry data				
Number of days measured, median (IQR)	7.0 (6.5–7.0)	7.0 (5.9–7.0)	7.0 (6.7–7.0)	0.37
Non-sedentary time per 24 h, *h*, mean (SD)	4.7 (1.4)	2.5 (0.7)	5.1 (1.1)	–
Dynamic activity time per 24 h, *h*, mean (SD)	1.6 (0.6)	0.9 (0.4)	1.8 (0.6)	–
Physical assessment				
BMI, kg/m^2, median (IQR)	25.9 (23.3–29.1)	27.6 (23.6–34.0)	25.1 (23.1–28.4)	0.26
Risk for malnutrition (MNA ≤11) [f]	45 (62)	9 (75)	36 (59)	0.35
SPPB score [g], median (IQR)	11 (10−12)	10 (7–12)	11 (10–12)	**0.04**
Low HGS [h], $n = 61$	27 (44)	8 (80)	19 (37)	**0.03**
Frail (Fried score ≥ 3) [i], $n = 72$	2 (3)	2 (17)	0 (0)	**0.03**
SF-36 physical functioning score [j], median (IQR)	90 (78–100)	60 (50–94)	90 (80–100)	**0.007**
Motivation for movement [k], median (IQR)	8 (7–8)	6.5 (5.3–8.0)	8 (7–8)	**0.02**
Motivation for prehabilitation [k], median (IQR)	7 (5–8)	5 (1–7)	7 (5–8)	**0.03**
Subjective activity, *h/week*, median (IQR)	11.5 (7.0–19.5)	7.8 (3.3–10.7)	14.0 (7.4–20.6)	**0.01**
Walking, *h/week*, median (IQR)	2.0 (0.0–4.3)	0.0 (0.3–1.8)	2.5 (0.5–5.1)	**0.004**
Cycling, *h/week*, median (IQR)	0.7 (0.0–2.0)	0.0 (0.0–2.8)	0.7 (0.0–2.0)	0.30
Sports, *h/week*, median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.1)	0.74
Household chores, *h/week*, median (IQR)	6.0 (2.0–14.0)	3.5 (0.9–6.6)	7.0 (2.2–14.0)	0.06

All values are reported as number and percentage unless otherwise indicated. Boldface data are statistically significant. If a variable has missing values, the number presented behind an outcome variable represents the number of patients included in this analysis.
Abbreviations: ADL *Activities of Daily Living*, ASA *American Society of Anesthesiologists*, BMI *body mass index*, CIT *Cognitive Impairment Test*, GDS *Geriatric Depression Scale*, h *hours*, HGS *hand grip strength*, IQR *interquartile range*, MNA *Mini Nutritional Assessment*, SF-36 *Short Form-36*, SPPB *Short Physical Performance Battery*, SD *standard deviation*.

[a] Preoperative anemia: hemoglobin level <7.5 mmol/L for females and <8.5 mmol/L for males.
[b] Polypharmacy was defined as the use of ≥5 different prescription medicines.
[c] Depressive symptoms were assessed with the Geriatric Depression Scale (GDS-2, and if positive the GDS-15); a score of ≥6 was considered at risk for depression.
[d] Cognitive problems were assessed with the 6-item Cognitive Impairment Test (6-CIT); a score of ≥11 indicated cognitive impairment.
[e] Physical impairment was assessed with KATZ-ADL questionnaire ranging from 0 to 6, a score ≥ 11 indicated physical impairment.
[f] Nutritional status was determined with MNA; a score of ≤11 was considered at risk for undernutrition.
[g] The SPPB consists of three components: balance, 4-m walking speed, and 5-repetition chair stand test. Each component results in a maximum of four points and a total maximum score of 12 points can be obtained. If the inclusion was done by phone/teleconferencing, patients performed the tests themselves while they were given clear instructions over the phone.
[h] Hand grip strength was measured using Jamar hydraulic hand dynamometer on the dominant hand. If the inclusion was done by phone, a nurse performed the measurements preoperatively at the outpatient clinic of during the admission.
[i] Physical frailty was measured with Fried criteria (one point each for: presence of weight loss, low hand grip strength (with sex- and BMI-specific cut-offs), slow gait speed on the 4-m gait speed test (with sex- and height-specific cut-offs), subjective physical exhaustion (a positive answer on at least one of two questions: 1. Did you feel like everything you did was an effort?; 2. Do you feel like you cannot get going?), and low energy use (less than one walk a month; more than four hours a day sedentary behavior; and no sports activities)). A score of ≥3 was considered indicative of frailty.
[j] Subjective problems with physical functioning were assessed with the SF-36 physical functioning questionnaire (10 questions) for which a total score of 0–100 could be obtained.
[k] Patients were also asked to rate their motivation for movement/exercise and for participation in a prehabilitation program (involving exercise and/or nutritional enhancement) on a scale of 0–10.

3. Results

3.1. Study Participants

A flow chart of study inclusion is depicted in Fig. 1. Compared to patients who provided informed consent, patients who declined to participate were more often female (81% versus 65%, $p = 0.03$). Age did not differ between the groups (74 versus 74 years, $p = 0.59$).

3.2. Comparisons between Sedentary and Non-Sedentary Patients

Table 1 shows comparisons of baseline characteristics, accelerometry results and physical assessment data between sedentary and non-sedentary patients. Sedentary patients were older (median 79 versus 73 years, $p = 0.007$) and had higher American Society of Anesthesiologists (ASA)-scores (ASA 3–4: 67% versus 18%, $p = 0.001$). Sedentary patients scored lower on the Short Physical Performance Battery (SPPB) (median 10 versus 11, $p = 0.04$) and were more often frail according to the Fried criteria (17% versus 0%, $p = 0.03$). Sedentary patients had lower scores on the Short Form-36 (SF-36) questionnaire (median 60 versus 90, p = 0.007). Sedentary patients reported less overall activity on the physical activity questionnaire (median 7.8 versus 14.0 h per week, $p = 0.01$), were less motivated to move (median score 6.5/10 versus 8/10, $p = 0.02$), and their motivation for prehabilitation was lower (median score 5/10 versus 7/10, p = 0.03).

3.3. Comparison between Patients Undergoing Colorectal and Gynecological Surgery

Supplementary table S1 shows the treatment characteristics of included patients, and supplementary table S2 shows a comparison of baseline characteristics between patients with CRC and gynecological cancer. Patients with CRC had anemia more often (62% versus 29%, $p = 0.04$). One patient with gynecological cancer was receiving neoadjuvant chemotherapy at the time of assessment, versus none of the patients with CRC. No differences were detected in accelerometry results, HGS, SPPB, frailty, or SF-36 scores between the groups.

4. Discussion

In older patients undergoing surgery for colorectal of gynecological cancer, accelerometry-measured preoperative sedentary behavior was associated with frailty and worse physical functioning irrespective of cancer type. A multidisciplinary prehabilitation program targeting sedentary, physically frail patients across surgical specialties may therefore be promising. To the best of our knowledge, this is the only study that has measured preoperative physical activity in older patients undergoing gynecologic oncological surgery, and one of the first in CRC surgery.

Previously, sedentary behavior has been linked to frailty in older adults [7] and to worse health-related quality of life in CRC survivors [8]. It would be interesting to use accelerometry to explore whether there is a threshold for harmful sedentary behavior with regard to adverse outcomes and whether decreasing overall sedentary time would be enough to prevent negative outcomes. Results of a recent study suggest that older frail patients should reach 400 m on the 6-min walking test to lower the risk for postoperative complications [9]. It should be determined if a specific training program is necessary or if increasing normal daily activity is enough to reach this goal.

Looking at sedentary behavior alone may not have enough discriminative value in the more active subset of older oncological-surgical patients. Therefore, it might be useful to determine the minimum amount of low, moderate or vigorous physical activity that would be required to mitigate perioperative risks. To do so, it is necessary to be able to distinguish between these activity intensity thresholds in older patients. Algorithms to differentiate between these thresholds in older patients using the MOX1-accelerometer are currently in development. In spite of the current absence of validated thresholds, we believe that looking at sedentary behavior is a relevant initial step, as these data provide first insights into preoperative physical activity in a population at risk for adverse postoperative outcomes.

There were no differences regarding physical functioning, frailty characteristics or activity patterns between the gynecological and colorectal groups. These findings might imply that prehabilitation interventions not necessarily need to be tailored differently between surgical specialties. A certain volume of patients is needed for a care pathway such as prehabilitation program to be efficient and cost-effective. The

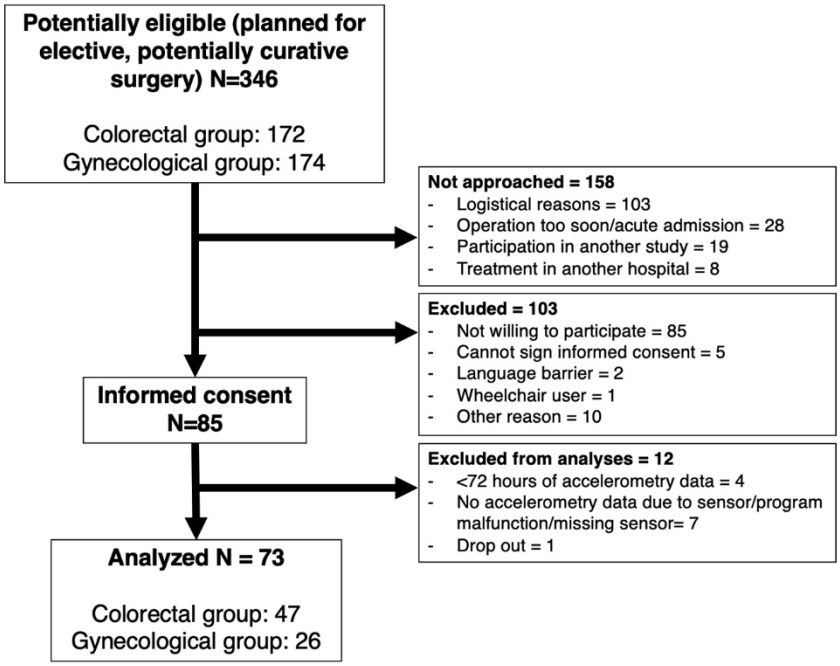

Fig. 1. Flow chart of study inclusion.

development and implementation of specific prehabilitation program for different types of cancer surgery may be a waste of resources. The risk profile of the surgery should also be taken into account: prehabilitation may not be necessary for patients undergoing relatively minor procedures with a low baseline complication risk [10] even in the presence of frailty.

Some limitations have to be addressed. Only half of the eligible patients were included, which hinders the generalizability of the conclusions. It is possible that the more inactive and frail patients declined to participate in the study. Also, the participants in the study were a preselected group of patients already deemed fit for surgery. It would be interesting to measure physical activity levels in patients who are not considered surgical candidates due to patient-related factors. There may be an opportunity to increase the physical resilience of these patients so that (curative) surgery becomes possible. Furthermore, we did not have data on sleep and wake times, which would have allowed us to look at waking hours only. Lastly, the small size of the sedentary group limits the strength of the conclusions. However, in the absence of validated thresholds for what constitutes substantial sedentary behavior, we chose to define the sedentary group based on one standard deviation difference from the group mean in an attempt to achieve a clinically relevant sample.

5. Conclusions

In this prospective multicenter exploratory study in older patients with colorectal and gynecological cancer undergoing surgery, preoperative accelerometry-measured sedentary behavior was associated with frailty and worse physical functioning irrespective of cancer type. Developers of future prehabilitation programs across surgical specialties may benefit from these baseline data as we demonstrated that sedentary behavior and physical parameters are comparable between surgical groups. Future studies should investigate whether there are minimum thresholds of physical activity required to prevent negative postoperative outcomes.

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Authorship Contributions

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Writing – review and editing: T.E. Argillander, V. van der Zanden, H.J. van der Zaag-Loonen, K.M. Paarlberg, W.J. Meijer, A.J. Kruse, H.L. van Westreenen, P. van Duijvendijk, M.J.E. Mourits, B.C. van Munster.

Sponsor's Role

None.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2021.09.008.

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