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New insights into early recovery after robotic surgery for endometrial cancer

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HIGHLIGHTS

- The individual woman's baseline score in physical health is predictive for recovery.
- Women with the poorest physical health at baseline demonstrated a fast recovery.
- The recovery to baseline of women with the best physical health is prolonged.
- The EORTC CAT Core allowed sensitive assessment of domains within physical health.

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ABSTRACT

Objective. To assess early recovery of physical health after robotic minimally invasive surgery (RMIS) for early-stage endometrial cancer using the European Organisation of Research and Treatment of Cancer Computer Adaptive Test Core questionnaire (EORTC CAT Core). The EORTC CAT Core provides individualised measurements while maintaining comparability. A hypothesis of individual complete recovery to baseline within three post-surgical weeks was evaluated.

Methods. Ninety-four women who underwent RMIS for early-stage endometrial cancer were included consecutively. The EORTC CAT Core was distributed before surgery and prospectively every week during the first post-operative month. Repeated measures models were fitted for each of the four domains (physical functioning, role function, fatigue, and pain) and tested for impact of age, ASA score, minor/major surgery, and the individual baseline scores (poorest, intermediate, best).

Results. Women with the lowest physical functioning, lowest role function, highest fatigue level, and highest pain level at baseline all recovered within three weeks. Women with the highest physical functioning, highest role function, lowest level of fatigue, and lowest level of pain at baseline did not reach their individual baselines within the first post-operative month but had the most favourable domain-scores three weeks post-operatively.

Conclusion. The individual woman's physical health baseline score is predictive for her postoperative recovery following RMIS for early-stage endometrial cancer. Women with the best physical health had the best postoperative functions and lowest level of symptoms; however their recovery to baseline was prolonged. Computer adaptive testing may be a valuable tool for individualised pre-operative information and supportive care during surveillance.

1. Introduction

Over the past decade, the surgical approach to endometrial cancer treatment has transitioned towards minimally invasive surgery (MIS) with the expectation of early recovery. A large prospective study compared quality-of-life following MIS with open access surgery in early-stage endometrial cancer and demonstrated improved physical and psychological outcomes following MIS up to 12 weeks post-surgery [1]. The assessment of health is complex due to the plurality in the individual's perception and fluctuation over time. Knowledge on the individual recovery following robotic minimally invasive surgery (RMIS) in early-stage endometrial cancer is sparse and may differ from the clinician's perception [2–4]. This knowledge is important to

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optimising pre-operative information and post-operative supportive care [5].

Generic quality-of-life questionnaires encompass multiple scales that cover a broad spectrum of general health aimed towards the majority. The drawback is that questions may appear too general for some individuals and the overall information obtained may be less than desired. Women with early-stage endometrial cancer range from an active workforce in their thirties to retired women in their nineties [6]. Hence, the use of generic questionnaires is particularly challenging within this population. The European Organisation of Research and Treatment of Cancer has developed and validated a computer adaptive test core questionnaire (EORTC CAT Core) that enables adaptation to the individual while maintaining comparability across patients [7–11].

The objective of the present study was to assess the individual early recovery to baseline of physical health among women with early-stage endometrial cancer following RMIS. It was hypothesised that individual recovery to baseline would be obtained within three post-surgical weeks.

2. Material and methods

A prospective cohort of women with early-stage endometrial cancer, International Federation of Gynaecology and Obstetrics (FIGO) stage I-II, who underwent RMIS at Odense University Hospital, Denmark, April 2016–September 2017, was included (Fig. 1). Women who did not speak Danish, suffered from dementia, or who suffered from other cancers were not eligible. Also we subsequently excluded women who had delayed staging lymphadenectomy performed due to unexpected deep myometrial invasion on final histology and those who failed to complete the baseline questionnaire.

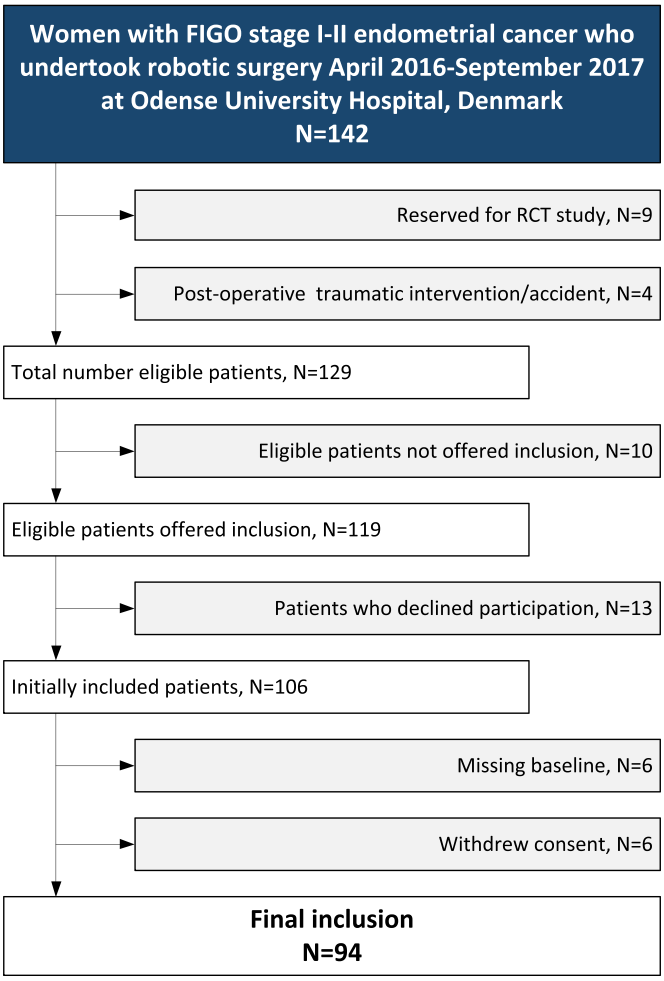

Fig. 1. Patient inclusion.

Individual health was measured using the validated EORTC CAT Core [12]. It encompasses 15 domains with pools of validated questions. Within each pool of questions, the EORTC CAT Core selects and presents the question that is the most informative for the individual woman based on her previous responses. Despite the individually tailored questionnaires, the comparability of scores across participants is maintained due to the underlying statistical model based on item response theory [13].

Physical health was a priori defined as encompassing aspects of physical functioning (PF), role function (RF), fatigue (FA), and Pain (PA) [14]. The PF domain combines measurement of strength, gross mobility, and fine motor skills with an assessment of a wide range of activities, e.g., carrying groceries, walking outdoors and buttoning a shirt [8]. The RF domain encompasses work and leisure activities, e.g., household tasks and cycling [9]. The FA domain involves physical and general fatigue, e.g., physical exhaustion, lack of energy, and the need to rest [15]. The PA domain covers pain intensity and its influence on daily activities [16].

The EORTC CAT Core needs to be completed electronically for the system to individually tailor the questionnaire. In Denmark, women diagnosed with endometrial cancer have a median age of 67 years. We expected that it might be challenging to complete an electronic questionnaire for some women in our population, particularly among the oldest women (70–90 years). For this reason, a paper questionnaire was also generated. If the patient could or would not complete the electronic questionnaire, she was offered to complete the paper version instead. The CAT Core item banks were developed following a thorough stepwise mixed-methods approach including a literature search, expert evaluations, interviews with patients, and psychometric analyses. The development was based on input from nearly 10,000 patients [7]. For the paper questionnaire we selected items from the CAT item banks that were expected to be particularly relevant to women with endometrial cancer. We supplemented the generic EORTC C30 Core questionnaire with the items that were the most informative for women aged 70+. In close collaboration with the developers of the CAT, we decided to ask 100 questions at each assessment. To be consistent, our CAT version was set to present an equivalent number of items within each domain as the number selected for the paper questionnaire. Questionnaires were completed before surgery (baseline) and weekly for the first four post-operative weeks. At each assessment, the woman completed 100 items, 36 of which were within physical health (17 PF, 5 RF, 8 FA, and 6 PA questions). The additional 64 items encompassed psychological well-being, social functioning, and disease-specific issues. These are not reported in the present paper. From the pilot testing the participants required approximately 1/2 h to complete the questionnaire.

The severity of post-operative impairment was measured on a 4-point Likert scale. The EORTC CAT Core measurements were translated into so-called T-scores [17]. For each domain, the EORTC CAT T-scores are scaled so that the European general population has a mean of 50 and a standard deviation of 10 [17]. This means that if a patient has, for example, a PF score of 40, her PF is 1 SD below the European average. In this paper, the T-scores for each domain will be referred to as domain-scores.

PF and RF are functional scales; the higher the domain-score, the better the function. FA and PA are symptom scales whereby high scores correspond to high levels of symptoms. The primary outcome was the weekly difference-scores which were estimated individually by subtracting the post-surgical domain-score from the baseline domain-score. A difference of 3.5 points was considered the clinical minimally important difference corresponding to about 8 points on the traditional 100-point EORTC-QLQ scale [17]. To obtain at least 90% power, simulations showed that at least 85 patients had to complete the trial.

Patient characteristics were compared between participants and non-participants using the Wilcoxon rank-sum test for continuous variables and chi-squared test for categorical variables, respectively. The scores within each domain (PF, RF, FA and PA) were repeatedly measured (Baseline, week 1, 2, 3, and 4). A linear mixed-effects model with autoregressive structure was used to estimate the difference-scores with 95% confidence intervals (95%CI). The normal distributions were checked using Q-Q plots.

Surgical type, age, and the American Society of Anaesthesiologists physical status score (ASA score) and baseline measurement in physical health were assumed to potentially affect patient recovery. The physical health baseline was grouped in tertiles for each domain; those who performed best, intermediate, and poorest. Surgical type was classified as minor (hysterectomy with bilateral salpingo-oophorectomy) and major surgery including additional lymphadenectomy or the sentinel node mapping procedure ± omentectomy. Age was used as a continuous variable and ASA score was categorised in healthy (I), mild systemic disease (II), and severe systemic disease (III-IV) [18]. The likelihood ratio test was used to test whether the predefined variables affected the difference-scores. The current study evaluates the early recovery of physical health including the initial 4 postoperative weeks. Due to unexpected short term results among women with the best baseline scores, explorative analyses of the long term results were performed to assess whether the differences persisted at 3 and 6 months postsurgery. Explorative analyses of the small sample size with restricted possibilities for adjustments were approached by simple two-sided paired *t*-tests that tested whether the change from baseline to the long term scores differed significantly from zero.

The study was approved by the National Board of Health (3-3013-803/1) and the Data Protection Agency (13/15219). All women provided written informed consent. Data were entered in Research Electronic Data Capture, a secure web application that manages online surveys provided by the Odense Explorative Network (OPEN) at Odense University Hospital, Denmark. The online survey linked to the computer adaptive platform at the headquarters of the Quality of Life Group that developed and validated the EORTC CAT Core in Copenhagen, Denmark [12].

3. Results

Overall, 142 women with early-stage endometrial cancer met the inclusion criteria. Of these, 9 women were reserved for a competing study, 3 patients had delayed lymphadenectomy and 1 patient was involved in an accident just after the operation, leaving 129 eligible women. Of these, 10 women were not approached for administrative reasons and 13 women declined to participate, leaving 106 women in the study, corresponding to a participation rate of 82% (Fig. 1). Following inclusion, a total of six women withdrew their consent and six women did not complete the baseline questionnaire. Thus, a total of 94 women (73%) participated in the study. Each participant received five questionnaires and the overall response rate was 93%; 440 out of 475 questionnaires were returned, 105 (24%) of which were paper forms. Participants and non-participants did not differ in age, ASA score, histological type or Stage, but did in Grade and surgical type (Table 1).

The mean baseline domain-scores and the three-week estimates from the linear mixed effects models of the repeated difference and domain-scores are presented by baseline groups for each domain (Table 2). For a graphical presentation, the difference-scores with 95% confidence intervals estimated from the linear mixed-effects models are presented relative to the mean baseline domain-score for each baseline group within each domain (Fig. 2).

The PF difference-score was influenced by time and baseline group but not by ASA score or surgical type (Table 2 and Fig. 2). A significant interaction between age and weeks since surgery was found. Women over age 80 and women with poor – intermediate PF baseline reached their baselines within three weeks post-surgery, while women with the best PF baseline did not. An analysis of the post-operative PF domain-score demonstrated that women with the best PF baseline did not recover to baseline but their domain-scores were the highest within the cohort. The RF difference-score was influenced by time since surgery, the baseline group, and ASA score (Table 2 and Fig. 2). Women with poor RF baselines and those with high ASA scores reached their individual baselines within three weeks post-operatively. In contrast, women with the intermediate – best RF baseline and those with low ASA scores did not recover to baseline within three weeks. Analysis of the post-operative RF domain-scores demonstrated that the scores three weeks post-surgery were highest among women with intermediate – best RF baseline and low ASA scores.

The FA and PA difference-scores were both influenced by time and baseline group (Table 2 and Fig. 2). Women who reported intermediate – high level of fatigue at baseline and women with the highest pain level at baseline had recovered to their baseline scores three week post-operatively. In contrast, women who reported the lowest levels of fatigue at baseline and women with low – intermediate pain levels before surgery did not recover to their individual baseline levels of fatigue and pain within three weeks. Analyses of the post-operative FA and PA domain-scores demonstrated that women who reported low symptom levels at baseline had the lowest levels of fatigue and pain three weeks post-surgery although they had not recovered to baseline values.

Results of the long-term data (3 and 6 months postoperatively) of women with the best baselines are given in Table 3. As described in the methods section a difference of 3.5 points was considered the clinical minimally important difference (MID). The results indicate that women with the best PF had recovered to baseline levels of PF within six months and possibly already after three months. Women with the best RF have a mean difference smaller than the clinical MID of 3.5 six months postsurgery but as reflected by the CI and the *t*-test, we are unable to reject that there still may be a clinically significant difference from the RF baseline. A difference larger than 3.5 points and a significant *p*-value indicate that women with the best FA have not recovered to baseline FA within three months and possibly not within six months. A mean difference of 3.3 among women with the least pain at baseline indicates a trend towards more pain six months after the surgery.

Table 1
Eligible patients characteristics.

Characteristic	Participants (n = 94)	Non-participants (n = 129)	P-value
Age, mean [SD]	66.7 [8.8]	68.3 [14.5]	NS[a]
ASA score			
1	10 (10.7%)	2 (5.7%)	NS[b]
2	60 (63.8%)	20 (57.2%)	
3	24 (25.5%)	13 (37.1%)	
Stage			
IA	71 (75.5%)	22 (62.8%)	NS[b]
IB	16 (17.0%)	10 (28.6%)	
II	7 (7.5%)	3 (8.6%)	
Histology			
EAC	75 (79.8%)	30 (85.7%)	NS[b]
Non-EAC	19 (20.2%)	5 (14.3%)	
Grade[c]			
1–2	74 (98.7%)	25 (83.3%)	
3	Low number	5 (16.7%)	.002[b]
Surgical type			
Minor	65 (69.1%)	15 (42.9%)	.006[b]
Major	29 (30.9%)	20 (57.1%)	

Abbreviation: endometrioid adenocarcinoma, EAC.
[a] Wilcoxon rank-sum test.
[b] Chi-squared test.
[c] Endometrioid adenocarcinoma.

4. Discussion

To our knowledge, this is the first study that evaluates the short-term impact of RMIS on the individual level of physical health. The

Table 2
Mixed model linear regression outputs of difference-scores and domain-scores three weeks post-surgery within physical health presented by baseline groups.

Scale	Domain	Score (95% CI)					
		Poorest baseline		Intermediate baseline		Best baseline	
Functional	Physical functioning						
	Difference-score week 3[a]	−2.76	(−5.52 to 0.00)	0.49	(−2.32 to 3.29)	10.20	(7.42 to 12.99)
	Domain-score week 3[a]	38.87	(36.35 to 41.39)	46.90	(44.35 to 49.45)	51.16	(48.62 to 53.70)
	Domain-score baseline	36.04	(34.69 to 37.38)	47.29	(46.27 to 48.32)	61.58	(59.86 to 63.31)
	Role function						
	Difference-score week 3[b]	−1.05	(−4.58 to 2.48)	7.02	(3.90 to 10.15)	11.09	(8.07 to 14.10)
	Domain-score week 3[b]	38.77	(35.39 to 42.15)	46.15	(43.16 to 49.14)	47.98	(45.10 to 50.87)
	Domain-score baseline	36.62	(34.56 to 38.69)	52.77	(50.85 to 54.68)	58.63	(58.63 to 58.63)
Symptom	Fatigue						
	Difference-score week 3	6.55	(3.90 to 9.21)	−1.90	(−4.51 to 0.71)	−9.69	(−12.30 to −7.09)
	Domain-score week 3	56.96	(54.58 to 59.34)	49.31	(46.05 to 51.66)	43.38	(41.03 to 45.73)
	Domain-score baseline	60.85	(59.02 to 62.67)	47.48	(46.29 to 48.67)	36.04	(35.08 to 37.01)
	Pain						
	Difference-score week 3	6.46	(3.61 to 9.30)	−4.53	(−7.38 to −1.68)	−5.84	(−8.67 to −3.01)
	Domain-score week 3	53.49	(51.03 to 55.94)	46.02	(43.55 to 48.48)	43.88	(41.43 to 46.34)
	Domain-score baseline	57.51	(54.78 to 60.23)	42.52	(41.33 to 43.71)	39.46	(39.44 to 39.47)

Domain-score: physical functioning (PF) and role function (RF) are function-scales i.e. the higher the score the better the function. Fatigue (FA) and pain (PA) are symptom scales, i.e. higher scores correspond to more symptoms. PF and RF are functional scales, i.e. the higher the domain-score the better the function. FA and PA are symptom scales, i.e. high scores correspond to a high level of symptoms. The difference-scores were estimated individually by subtracting the post-surgical domain-score from the baseline domain-score.
[a] Patients aged 80 years or above have recovered within three weeks.
[b] Women with high ASA scores recovered within the first week.

EORTC CAT core allowed sensitive assessment across a wide range of physical health domains. Measuring the individual changes in women with early-stage endometrial cancer, we demonstrated that the individual recovery to baseline level is prolonged among women with the best physical health. Women with the lowest functions and highest symptom levels recovered to baseline within three post-operative weeks. Hence, our hypothesis of complete recovery within three weeks following robotic surgery was only partially confirmed. This knowledge challenges the standardised pre-operative information usually provided and may prompt changes in post-operative supportive care. The EORTC CAT Core was a useful tool for preoperative screening of physical functioning before surgery.

The randomised GOG-LAP2 trial reported improved quality of life measurements during the early postoperative phase among women who underwent MIS compared with those who underwent laparotomy. In line with our results, not all patients who underwent MIS had

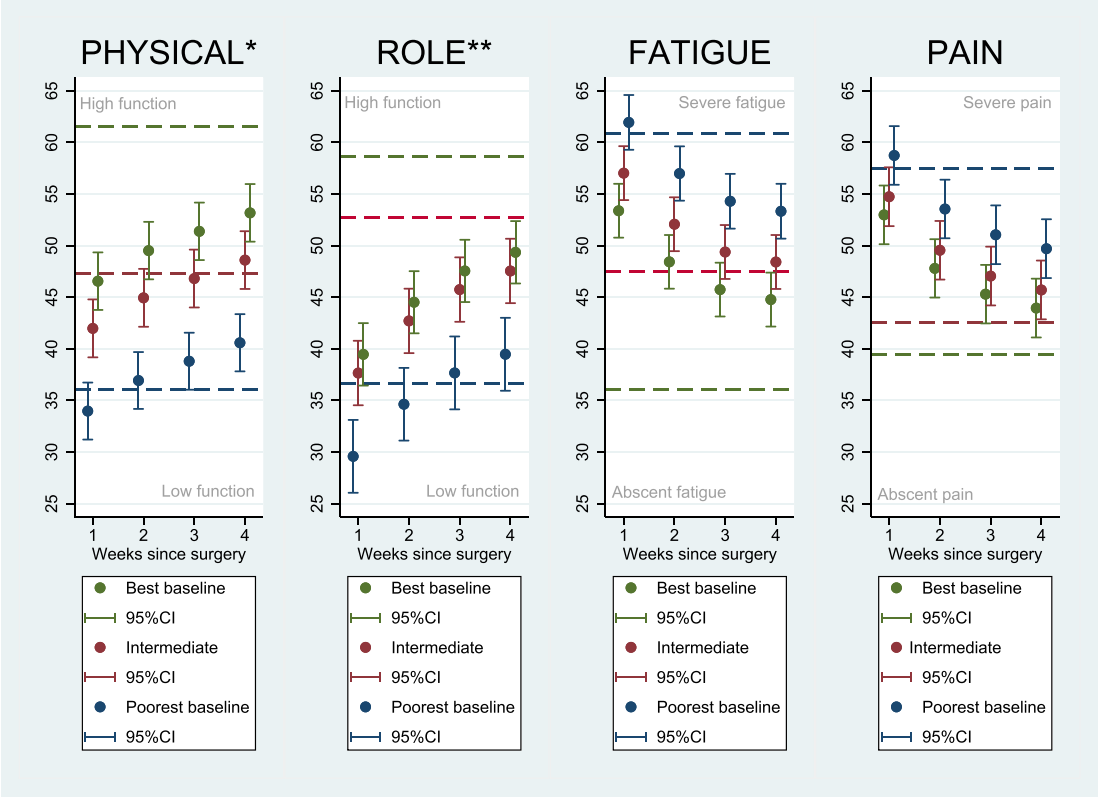

Fig. 2. The post-surgical recovery differs between women with the best, intermediate and poorest baselines within conceptualised physical health domains. The color-coded mean baseline domain-score (stippled lines) subtracted the results of the mixed model regression of the difference-scores (color coded dots) and confidence intervals (whiskers). *Patients aged 80 years or above recovered within the first week. **Women with high ASA scores had all recovered within three weeks.

Table 3
Explorative analyses of long term data of women with the best baselines.

Domain	Mean baseline score (95% CI)	Mean score 3 months (95% CI)	Mean score 6 months (95% CI)	Mean difference-score 3 months[a] (95% CI)	*P* value 3 months	Mean difference-score 6 months[a] (95% CI)	*P* value 6 months
PF	61.58 (59.86 to 63.31)	58.38 (55.04 to 61.73)	60.38 (57.73 to 63.03)	3.03 (−0.34 to 6.41)	0.08	1.36 (−1.22 to 3.93)	0.29
RF	58.63 (58.63 to 58.63)	55.12 (52.39 to 57.85)	55.88 (53.53 to 58.22)	3.51 (0.78 to 6.24)	0.014	2.76 (0.41 to 5.10)	0.023
FA	36.04 (35.08 to 37.01)	40.37 (37.05 to 43.68)	39.43 (36.66 to 42.20)	−4.29 (−7.64 to −0.93)	0.014	−3.46 (−6.17 to −0.75)	0.014
PA	39.46 (39.44 to 39.47)	45.23 (41.20 to 49.26)	42.78 (39.77 to 45.80)	−5.77 (−9.80 to −1.74)	0.007	−3.32 (−6.34 to −0.31)	0.032

Abbreviation; physical function, PF; role function, RF; fatigue, FA; pain, PA.
[a] Difference score (Baseline – post operative measurement): a difference score above 3.5 points within PF and RF indicate a clinically lower function while a difference score below −3.5 within FA and PA indicate clinically more symptoms.

recovered to baseline physical levels within the initial three weeks [19]. Kornblith et al. adjusted their analyses for the baseline scores but they did not report physical health on a stratified level regarding baseline off-set. Measurements of individual changes adjusted for the baseline may detect differences and even opposing effects among subgroups [20]. Such detection may reveal areas in which supportive care could be enforced. The finding of prolonged recovery among women with the best preoperative physical health was unexpected. However, they reported the best domain-scores four weeks after surgery, and our finding may simply reflect that it takes longer to regain the ability to perform more physically demanding tasks such as running following surgery. The possible differences between baseline and long term measurements observed among women with the best offset in RF, FA, and PA could be explained by regression towards the mean, as we extract information on those women who peaked with the best offset at baseline. Hence, a change towards the average may be expected due to the natural variation between point estimates [21–23]. Currently, women who undergo RMIS receive standardised information on sick-leave, physical activity, and analgesic use for post-operative pain. A Cochrane review on quality-of-life for people with cancer during active treatment has demonstrated the beneficial effects of exercise on quality-of-life domains, including physical functioning, role function, and fatigue [24]. It is likely that the perception of recovery following surgical intervention is influenced by the patient's expectations and that those who have the highest expectations for their own (fast) recovery are also in the best physical health [25,26]. Hence, women with the best physical health at baseline are likely to under-estimate their postoperative functions and over-estimate their postoperative symptoms due to their high level of expectation to performance and vice versa among women with the poorest physical health. Different priming has been demonstrated to modify Patient-Reported Outcome Measures [27]. Our data indicate that individualised pre-operative information and postoperative support should be considered in women with early-stage endometrial cancer. Individualised post-surgical programs that actively advise and recommend resuming physical activity soon after surgery may improve the functioning and lower their fatigue and pain level. In light of the current focus on opioid usage, the baseline data derived from the EORTC CAT Core may be important for optimisation of the post-operative distribution of narcotics. Overall, individualised post-surgical programs may potentially shorten the time and resources required for recovery and reduce long-term impairment of physical health [28–30]. Implementing the EORTC CAT Core to pre-surgically assess physical health may be a useful screening tool for guiding individualised pre-operative information and postoperative rehabilitation.

The advantages of the EORTC CAT Core include increased measurement precision, reduced response burden, increased flexibility, and avoidance of uninformative questions, compared with the traditional core questionnaire [7]. The use of the CAT Core can be accommodated to each specific purpose depending on the study design, the population, and the demand for measurement precision. This means that in a study with e.g. participation of a well-defined group of younger patients and the full availability of all items in the CAT core, a significantly reduced number of items are required to obtain a high level of measurement precision. In the study by Petersen MA et al. it was demonstrated that the number of items required to obtain the same level of information as in the generic questionnaire (C30) was reduced with 20–35% when using the CAT core version [7]. The EORTC CAT Core has several features for customising the CAT to the individual study, including pre-specifications of questions presented for all patients, the maximum number of questions presented within each domain, and pre-specification of the degree of precision that is desired within each domain [7]. The comparability of scores allows researchers to evaluate patients' perceptions of physical health at the individual or group level in different settings. Hence, because of its high precision and flexibility, the tool may be valuable for assessment at the individual level (e.g. for symptom monitoring) and for longitudinal studies in which the patient's condition changes over time and hence, the most informative questions also change.

A possible drawback of the EORTC CAT Core usage is that the electronically completion may challenge an ageing population. However, patients that are unable to complete questionnaires electronically may be provided with pre-tailored paper versions that still maintain score comparability [8–10,12,16]. In the present study, the majority (76%) of the women were able to complete questionnaires electronically. Paper-versions were administered to the remaining patients and constituted 24% of the returned questionnaires. The use of paper questionnaires in an electronic setting may generate a risk of bias and decrease the generalisation of our results. However, the paper questionnaire used in the present study allowed us to assess a group of women who was otherwise excluded. When designing the study, it was decided not to select the youngest patients only, as the purpose of the study was to provide an evaluation of the early recovery in a representative sample of consecutive women with early stage endometrial cancer. The scores obtained by paper versions and CAT are directly comparable due to the underlying item response theory and with higher precision than the generic EORTC QLQ-C30 questionnaire. At present, CAT may be most applicable for the younger generations. However, this is expected to change in the coming years as most women aged 50–60 years today are familiar with electronic devices.

Our study yielded a high completion rate of questionnaires among participants and repeated measurements with short time intervals. The number of participants was in accordance with the power calculation. However, the generalisation of our results could be questioned as only 2/3 of the eligible women were enrolled in the study. Non-participants had more often grade III disease and underwent major surgery, which indicates the possibility of selection bias towards the physically and psychologically strongest women. The question load in the present study may be challenging, thus preventing those undergoing

major surgeries from participating. Despite the potential selection bias, the EORTC CAT Core was able to differentiate between the scores of the included women.

5. Conclusion

The individual woman's baseline score in physical health is predictive for her postoperative recovery. The recovery to baseline of women with the best physical health is prolonged, although they had the best postoperative functions and lowest level of symptoms. The EORTC CAT Core allowed sensitive assessment and comparison of physical health across women with early-stage endometrial cancer.

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Role of the funding source

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Conflict of interest statement

The authors have no conflicts of interest to declare.

The article has not been published and is not under consideration for publication elsewhere.

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