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Health-Related Quality of Life after Hysterectomy for Endometrial Cancer: The Impact of Enhanced Recovery after Surgery Shifting Paradigm

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Keywords
Endometrial cancer · Minimally invasive surgery · Hysterectomy · Health related quality of life · Enhanced recovery after surgery

Abstract
Objectives: Enhanced recovery after surgery (ERAS) protocols provide well-known benefits in the immediate recovery with a shorter length of stay (LOS) and also in gynecological surgery. However, the impact of ERAS has not been clearly showed yet regarding long-term consequences and health-related quality of life (HRQL). The aim of this study was to investigate the impact of ERAS on HRQL after hysterectomy for endometrial cancer. ***Design:*** An observational retrospective study with propensity score matching (PSM) was performed. ***Participants:*** We administered the SF-36 validated questionnaire to women underwent hysterectomy and lymph nodal staging before and after introducing ERAS protocol, getting, respectively, a standard practice (SP) and ERAS group. ***Settings:*** The study was conducted at the academic hospital. ***Methods:*** We collected demographic, clinical, surgical and postoperative data and performed a PSM of the baseline confounders. We administered the questionnaire 4 weeks after the surgery. The SF-36 measures HRQL using eight scales: physical functioning (PF), role physical (RLP), bodily pain (BP), general health (GH), vitality (Vt), social functioning (SF), role emotional (RLE) and mental health (MH). ***Results:*** After PSM, we enrolled a total of 154 patients, 77 in each group (SP and ERA). The two groups were similar in terms of age, BMI, anesthetic risk, Charlson comorbidity index (CCI), and surgical technique (minimally invasive vs. open access). Median LOS was shorter for ERAS group (5 vs. 3 days; $p = 0.02$), while no significant differences were registered in the rates of postoperative complications (16.9% vs. 17.4%; $p = 0.66$). Response rates to SF-36 questionnaire were 89% and 92%, respectively, in SP and ERAS group. At multivariate analyzes, the mean scores of SF-36 questionnaire, registered at 28 days weeks after surgery (range 26–32 days), were significantly higher in ERAS group for PF (73.3 vs. 91.6; $p < 0.00$), RLP (median 58.3 vs. 81.2; $p = 0.02$), and SF (37.5 vs. 58.3; $p = 0.01$) domains, when compared to SP patients. ***Limitations:***

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Further follow-up was not possible due to the anonymized data derived from clinical audit. ***Conclusions:*** ERAS significantly increases the HRQL of women who underwent surgery for endometrial cancer. HRQL assessment should be routinely implemented in the ERAS protocol.

Introduction

The concept of enhanced recovery after surgery (ERAS) protocol was first introduced in 1997 and gradually accepted and widely used in nearly as many surgical specialties, including gynecological surgery [1]. Short-term benefits include a faster recovery with a shorter length of hospitalization (LOH) and a reduction of health-care-related cost [2–4]. As a proof of concept, a multitude of factors in the perioperative setting impact short- and probably long-term outcomes and include unmodifiable patient-related risk factors and factors related to surgery and perioperative management [5–7]. Regarding long-term outcomes, the evidence is scarce and mainly encompasses oncological outcomes, such as improvement in the return to intended oncologic treatment after surgery [8]. Few studies could correlate improved overall survival in patients with solid cancers who were fully adherent to the perioperative protocol, even though controversial results have been published [9]. No reports regarding the health-related quality of life (HRQL) were instead reported in those patients who underwent ERAS. Endometrial cancer remains a surgical paradigm disease that can be potentially cured with primary surgery, and currently, ERAS protocol has been showed to be safe and workable in these types of patients [10–12]. The aim of this study was to investigate the HRQL of women affected by endometrial cancer who underwent hysterectomy with lymph nodal staging within an ERAS protocol compared to standard practice (SP) perioperative management.

Materials and Methods

We enrolled patients treated for endometrial cancer (EC) before and after ERAS implementation and treated with primary surgery across multiple centers between January 2019 and December 2022. All the data used in this manuscript derives from auditing databases in service evaluation for endometrial cancer and is hence already anonymized at the moment of data extraction. The design, analysis, interpretation of data, drafting, and revisions conform to the Helsinki Declaration, the Committee on Publication Ethics guidelines (http://publicationethics.org/), and the reporting of studies conducted using observational routinely collected health data (RECORD) statement, validated by the Enhancing the Quality and Transparency of Health Research Network (www.equator-network.org). No personal data that could lead to formal identification of the patient was stored in the databases. The study was not advertised.

We fetched baseline demographic data such as age, American Society of Anesthesiologists (ASA) score, body mass index (BMI), and age-adjusted Charlson comorbidity index (CCI). We further extracted treatment details, such as the technique of access, the types of surgical procedures (minimally invasive surgery – MIS – vs. open surgery), the rate of postoperative complications and blood transfusion rate, and the need of adjuvant treatment (external beam radiotherapy with or without vaginal brachytherapy).

We included patients with confirmed early stage disease (FIGO I) and endometrioid histotype, classified according to European Society of Gynecological Oncology (ESGO) – European Society for Radiotherapy and Oncology (ESTRO) – European Society of Pathology (ESP) risk stratification model, that underwent hysterectomy, bilateral salpingo-oophorectomy, and lymph nodal assessment (including lymph node sampling, sentinel lymph node technique, and systematic pelvic bilateral lymphadenectomy). We included all the patients regardless of the type of lymph nodal staging based on the current evidence that a minimalistic approach, such as the use of sentinel lymph node technique, is the standard [13]. Unfortunately, even with the recent advances in the classification of endometrial cancer, we cannot include molecular data for the evaluation because of the enrolling period of the study and the purposes of the service evaluation of the auditing [14]. We included women that were managed according to ERAS protocol or standard perioperative practice (SP). We performed a propensity score matching with a 1:1 ratio between matched subjects (SP vs. ERAS) using nearest neighbor matching with a caliper width of 0.20 standardized mean difference of the logit of the propensity scores using age, ASA, BMI, CCI, and the use of MIS.

The SF-36 questionnaire, also known as the 36-Item Short Form Health Survey, is a widely used self-reported survey instrument for measuring HRQL [15]. It assesses various aspects of a person's physical and mental health, functioning, and well-being. The SF-36 questionnaire comprises 36 items that cover eight different domains or subscales: (i) physical functioning (PF): that assesses limitations in physical activities, such as walking, climbing stairs, and carrying objects; (ii) role limitations because of physical problems (RLP): measure the extent to which physical health affects a person's ability to perform daily activities or work; (iii) bodily pain (BP): that evaluates the intensity and impact of pain experienced by an individual; (iv) general health perceptions (GH): assess the individual's subjective evaluation of their overall health and well-being; (v) vitality (Vt): measures energy levels, fatigue, and overall vitality; (vi) social functioning (SF): assesses the extent to which physical or emotional health interferes with social activities; (vii) role limitations because of emotional problems (RLE): measures the impact of emotional health on daily activities or work; and, finally, (viii) mental health (MH): evaluates psychological distress, mood, and overall mental well-being.

Table 1. Demographic and clinical characteristics of the two groups

	SP (n = 77)	ERAS (n = 77)	Standardized mean difference	p value
Age	63 (52–69)	61 (51–70)	0.15	0.83
ASA	3 (2–3)	3 (2–3)	0.00	–
BMI	29.5 (26.5–31)	28.8 (27.2–31.4)	0.19	0.82
CCI	3 (2–8)	3 (2–7)	0.00	0.73
MIS, n (%)	55 (72)	54 (71)	0.09	0.65
Blood transfusion, n (%)	4 (5.2)	3 (4.3)	–	0.76
Complications, n (%)	13 (16.9)	14 (18.1)	–	0.66
EBRT +/– VB, n (%)	8 (10.4)	10 (13)	–	0.51
LOH	5 (4–6)	3 (3–5)	–	0.02*
RR to SF-36, n (%)	68 (89)	71 (92)	–	0.74

Values are presented as median and interquartile range (IQR) or absolute count and rate. SP, standard practice; ERAS, enhanced recovery after surgery; ASA, anesthesiologist score risk; BMI, body mass index; CCI, Charlson comorbidity index; MIS, minimally invasive surgery; EBRT +/– VB, external beam radiotherapy with or without vaginal brachytherapy; LOH, length of hospitalization in days; RR, response rate; SF-36, 36-Item Short Form Health Survey. *Statistically significant values.

We administered the SF-36 questionnaire after 4 weeks after surgery and registered the scores of the eight scales, which are the weighted sums of the questions in their section. We directly transformed each scale into a 0–100 scale on the assumption that each question carries equal weight, assuming that a lower score corresponds to more disability. We used independent samples t test to compare continuous variables or the U test Mann-Whitney as appropriate, based on data distribution. We used the Pearson χ^2 or Fisher's extract test for categorical variables. Multivariate analysis was performed using a general linear model, and data was normalized as appropriate. All statistical analyzes were performed using IBM © SPSS Statistics 22.0. Statistical significance was considered for $p < 0.05$.

Results

During the study period, a total of 154 patients were extracted and matched from the database, with, respectively, 77 patients in each group (SP and ERAS). The two groups were similar in terms of age, ASA, BMI, CCI, and surgical technique (rate of MIS). No differences were noted in term of blood transfusion and postoperative complications rates, neither in the rate of adjuvant treatment needed after surgery. As expected, the length of stay (LOH) in the hospital was shorter in the ERAS group (see Table 1). The SF-36 questionnaire was administered after a median of 28 days from surgery (range 26–32 days) to the patients and the response rate was respectively 89% (68 patients) and 92% (71 patients) in SP and ERAS groups (p = 0.74). The results from the SF-36 questionnaire were extracted, calculated according to the declared methods, and finally expressed as means for each domain in Table 2.

As seen in Table 2, we found a significant difference in PF, role limitation physical and social functioning, with lower scores in the SP group. At multivariate analysis, we found that ERAS protocol was the only predictor for a lower score of PF (Table 3).

Regarding the domain role limitation because of physical problems, we found multiple independent predictors. In fact, age and the need for adjuvant treatment are linked to lower scores, while the use of minimally invasive surgery and perioperative management, according to ERAS, were linked with higher scores for this domain (see Table 4).

In the domain of social functioning, we found two independent predictors of the score. Respectively, a higher CCI is an independent predictor of low score, while, again, perioperative management according to ERAS was linked to a higher score for this domain (see Table 5).

Discussion

This study showed that the health-related quality of life of women affected by endometrial cancer and treated with surgery is significantly better when a perioperative management strategy according to ERAS is adopted. In recent years, introducing a novel molecular classification for endometrial cancer has led to an important shift toward tailoring of the adjuvant treatment that is based not only on pathological data [13, 14, 16]. In this context, the need for an improvement in the HRQL after surgery for this type of cancer is of paramount importance to deliver the most appropriate post-operative treatment by

Table 2. SF-36 results (expressed as "points") in the eight domains

	SP (n = 68)	ERAS (n = 71)	p value
Physical functioning (PF)	73.3	91.6	<0.00*
Role limitation – physical (RLP)	58.3	81.2	0.02*
Bodily pain (BP)	74.2	79.1	0.29
General health (GH)	64.6	68.7	0.69
Vitality (Vt)	66.7	68.3	0.84
Social functioning (SF)	37.5	58.3	0.01*
Role limitation – emotional (RLE)	41.7	45.8	0.71
Mental health (MH)	56.7	60	0.65

Values are presented as means. SP, standard practice; ERAS, enhanced recovery after surgery.

Table 3. Multivariate analysis of "physical functioning – PF – domain"

	HR	95% CI		p value
Age	0.99	0.98	1.00	0.10
BMI	0.99	0.96	1.02	0.53
CCI	0.96	0.80	1.14	0.59
MIS	1.10	0.72	1.19	0.54
ERAS	1.28	1.11	1.44	0.00*
EBRT +/– VB	0.90	0.76	1.04	0.14

HR, hazard ratio; 95% CI, confidence interval at 95%; BMI, body mass index; CCI, Charlson comorbidity index; MIS, minimally invasive surgery; EBRT +/– VB, external beam radiotherapy with or without vaginal brachytherapy.

Table 4. Multivariate analysis of "role limitation due to physical problems – RLP – domain"

	HR	95% CI		p value
Age	0.97	0.95	0.98	0.00*
BMI	1.02	0.97	1.07	0.37
CCI	1.07	0.82	1.40	0.59
MIS	1.63	1.12	2.38	0.01*
ERAS	1.47	1.19	1.81	0.00*
EBRT +/– VB	0.78	0.62	0.77	0.03*

HR, hazard ratio; 95% CI, confidence interval at 95%; BMI, body mass index; CCI, Charlson comorbidity index; MIS, minimally invasive surgery; EBRT +/– VB, external beam radiotherapy with or without vaginal brachytherapy.

ensuring an optimal well-being of the woman. Currently, in the literature, there is no evidence available that correlates the achievement of a better HRQL after surgery for endometrial cancer, with an earlier initiation of adjuvant treatment [17].

Table 5. Multivariate analysis of "social functioning – SF – domain"

	HR	95% CI		p value
Age	1.00	0.98	1.02	0.94
BMI	0.97	0.92	1.01	0.12
CCI	0.76	0.59	0.98	0.04*
MIS	0.93	0.64	1.34	0.66
ERAS	1.66	1.36	2.04	0.00*
EBRT +/– VB	1.21	0.71	1.52	0.09

HR, hazard ratio; 95% CI, confidence interval at 95%; BMI, body mass index; CCI, Charlson comorbidity index; MIS, minimally invasive surgery; EBRT +/– VB, external beam radiotherapy with or without vaginal brachytherapy.

The first experience of HRQL after surgery can vary depending on several factors, including the type of surgery performed, the individual's overall health, the purpose of the surgery, and the expectations of the patient [18–20]. In particular, in women affected by endometrial cancer, the perception of disease is of utmost importance; since often surgery is by itself the most relevant treatment act, after hysterectomy, a feeling of good prognosis is very common [21, 22]. In this setting, the impact of surgical treatment is paradigmatic given that these women are typically elderly with co-morbidities, and the maintenance of good HRQL should be integrated into the postoperative recovery [23]. For example, the women underwent robotic surgery easily overcome and recover shortly after; however, they expressed uncertainty about the normal postoperative course and reported changes in functions and short-term symptoms after surgery [23, 24]. These changes should be addressed in the preoperative information and at the post-operative follow-up, and the ERAS protocol seems a perfect framework to ensure these objectives [25, 26].

Immediately after surgery, patients may initially experience pain, discomfort, and limitations in their PF because of the surgical procedure itself. This can include difficulties with mobility, performing daily activities, and self-care tasks [27]. However, as the recovery progresses, HRQL tends to improve, and the specific improvements and timeline can vary, such as PF, that can be limited because of pain and post-operative restrictions; as the body heals and rehabilitation progresses, individuals typically regain their physical abilities and gradually return to their normal activities [28]. Immediately after surgery, pain is common and can vary in intensity depending on the procedure performed. Besides medical pain management strategies, over time, pain typically subsides as healing progresses [29]. ERAS protocols focus on optimizing patients' preoperative health and addressing modifiable risk factors, which can lead to a reduction in surgical complications. Fewer complications mean less postoperative morbidity, reduced pain, and improved physical well-being, ultimately enhancing HRQL [10]. ERAS protocols emphasize early mobilization and appropriate nutrition both before and after surgery. By encouraging patients to move and resume normal activities as soon as possible, ERAS helps maintain muscle strength, improve physical function domain, and minimize the negative impact of immobility on HRQL [30]. Effective pain control not only enhances PF but also contributes to better psychological well-being [6]. In specific settings, the same-day discharge policy can be easily applied where optimal mental and physical status, permitting sociodemographic factors, and a safe place to recover after discharge are mandatory [31, 32].

The preoperative pain status, psychological condition, and reduction of acute postsurgical pain and surgery-related infection lead to improvement in outcomes in the "PF domain" [33]. Our results confirmed that the engagement of patients affected by endometrial cancer in the ERAS protocol provides an early and increasing benefit in SF-36 measures of this domain as the only independent predictor. Similarly, in the "role limitation because of physical problems" domain, the adoption of ERAS is an independent predictor of a better outcome; of note, also, the use of minimally invasive approach is connected with an improvement in the score. On the contrary, with the increasing age and CCI, we registered a detrimental impact of the score, meaning that most fragile and older patients are exposed to an increased risk of lowering their HRQL. These findings are consistent with the known impact of CCI on different clinical settings, ranging from chronic conditions such as obstructive sleep apnea or renal disease to acute events such as stroke or surgery for colorectal cancer [34–38].

Emotionally, some individuals may feel relief or a sense of accomplishment after a successful surgery, while others may experience temporary emotional challenges such as anxiety, depression, or frustration because of the recovery process [39]. Emotional support and coping strategies can be beneficial during this time [40]. Informed and engaged patients are more likely to have a positive outlook and experience better HRQL during the perioperative period, and as a paradigm, ERAS protocol is devoted to early engagement of the patient before the surgical procedure, enabling also the active recruitment of the family and caregivers [5, 41]. Regarding the "social functioning domain," we found that the adoption of ERAS improves the domain's score, and this is probably because of a faster return to daily activities that include social interactions, hobbies, and daily routines, leading to a quicker reintegration into social life, also helped by the early engagement of caregivers [42]. As a matter of concept, HRQL is an important outcome after surgery for colorectal cancer, and accurate assessment is required to fully inform clinical decision making [43]. The increase in the CCI is instead related to a worse scoring in this domain, and this finding enforces the need for stronger action in the pre-habilitation setting, especially in those patients affected by cancer [44]. Based on our experience, the contribution to a positive HRQL trajectory after hysterectomy for endometrial cancer seems deeply related to the adoption of ERAS protocol, regardless of the surgical route strategy, as confirmed for other surgical specialties [15]. In particular, for elderly women affected by endometrial cancer, the introduction of a systematic evaluation of HRQL after surgery can improve the long term oncological outcomes thanks to an early resume of the planned treatment, with a potentially greater compliance [45].

The strengths of our work are the selection and propensity score matching of the patients that were collected prospectively for auditing purpose, hence ensuring a high quality of the data provided; so far, a high rate of response to the SF-36 questionnaire, enclosed to the auditing data, is a further point of strength. The main limitation is the retrospective nature of the study, and hence we cannot ensure the results are exempt from selection bias, even though the collection of the patients' data was consecutive. Finally, further follow-up is not possible due to the anonymized data used for the study, and this is a point of weakness because the long-term HRQL in these women cannot be assessed, requiring hence a new study.

Conclusions

In women affected by endometrial cancer and candidates for surgical treatment, the optimization of perioperative care and the focus on patient-centered

outcomes, as planned by ERAS protocol, produce a significant positive impact on HRQL. In particular, benefits have been seen in selected domains such as PF, role limitation because of physical problems, and social functioning; these findings can be implemented in the counseling strategy of the ERAS protocol.

Statement of Ethics

The Local Ethical Review Board (Comitato Etico degli Spedali Civili of Brescia) considered exempt the study given the data derived from a clinical auditing. The Local Ethical Review Board (Comitato Etico degli Spedali Civili of Brescia) considered exempt the study from requiring written informed consent given the data derived from a clinical auditing.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: F.F. and E.G.; methodology: F.F., E.G., and H.S.M.; formal analysis: F.F., A.F., and A.S.L.; investigation: F.F., H.S.M., A.G., A.F., and A.S.L.; writing – original draft preparation: F.F. and H.S.M.; writing – review and editing: all authors; visualization: F.F. and F.O.; and supervision: F.F., H.S.M., and F.O. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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