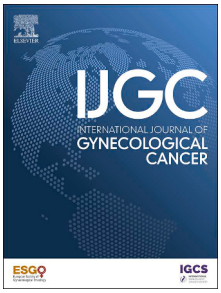
ORIGINAL RESEARCH

Levonorgestrel-releasing intra-uterine device alone for managing early-stage endometrial cancer and endometrial hyperplasia with atypia in patients unfit for surgery: the ENDOIUD study



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ABSTRACT

Objective: This study aimed to clarify the role of levonorgestrel-releasing intra-uterine device as a stand-alone therapy in managing patients with endometrial atypical hyperplasia/endometrial cancer who are not suitable for surgery, through the evaluation of cause-specific survival and the control of vaginal bleeding.

Methods: This is a retrospective, multi-center study conducted in 9 referral gynecologic centers in Italy. Data regarding the clinical and oncological outcomes of patients with endometrial atypical hyperplasia/endometrial cancer (International Federation of Gynecology and Obstetrics Stage I) were analyzed. Patients were judged unsuitable for surgery due to an American Society of Anesthesiologists score $\geq$3 and the presence of multiple severe co-morbidities and, therefore, triaged to receive levonorgestrel-releasing intra-uterine device alone.

Results: A total of 78 women were enrolled. Fifteen patients (19.2%) had a diagnosis of endometrial atypical hyperplasia, whereas the other 63 (80.8%) had endometrial cancer. The baseline hemoglobin levels averaged 11.6 (range; 6-16), increasing to 12.1 (range; 7.8-14.9) during follow-up after levonorgestrel-releasing intra-uterine device insertion ($p = .003$). No patient experienced any side effects, and bleeding control was rated as excellent in most patients. Median disease-free survival was 43 months (range; 5-120) and median overall survival was 45 months (range; 5-120).

Conclusions: Levonorgestrel-releasing intra-uterine device alone is a safe and effective approach, showing no side effects, and a promising oncological outcome in women with early-stage endometrial atypical hyperplasia/endometrial cancer unfit for surgery. Future prospective studies are required to clarify how to select patient candidates for this therapy and how to predict response to levonorgestrel-releasing intra-uterine device.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Levonorgestrel-releasing intra-uterine device has been shown to be effective for treating women with endometrial atypical hyperplasia or early-stage endometrial cancer, yet limited data exist regarding their long-term use as the sole treatment in older, frail patients unfit for surgery.

WHAT THIS STUDY ADDS

This multi-center retrospective study demonstrates that levonorgestrel-releasing intra-uterine device alone is a safe and potentially effective non-surgical option for managing early-stage endometrial cancer and endometrial atypical hyperplasia in patients with significant co-morbidities who are not surgical candidates. The study shows promising oncologic outcomes, excellent control of bleeding, and no reported treatment-related adverse effects.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

These findings support the inclusion of levonorgestrel-releasing intra-uterine device therapy as a viable alternative to surgery in selected frail patients. Future research should focus on prospective validation, the development of predictive markers for treatment response, and the integration of molecular profiling to optimize patient selection.

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ORIGINAL RESEARCH

INTRODUCTION

Endometrial carcinoma is the most common gynecologic tumor, and its incidence is rising mainly due to the obesity epidemic in industrialized countries, which is the most well-known risk factor for endometrioid endometrial cancer,[1] the most prevalent histotype. Endometrial atypical hyperplasia or endometrial intra-epithelial neoplasia is a pre-cancerous condition of the endometrium and a precursor to endometrioid endometrial cancer. About 30% of women with atypical hyperplasia develop endometrial cancer, and up to 40% of women diagnosed with atypical hyperplasia are found to have undetected endometrial cancer at the time of hysterectomy.[2,3]

Over the last few decades, minimally invasive surgery has become widely regarded as the gold-standard approach in managing early-stage endometrial cancer and endometrial atypical hyperplasia.[4,5] The availability of robotic platforms and the broader adoption of sentinel node biopsy have led to a significant decrease in surgical complications and an overall improvement in quality of life.[6-10]

Due to the aging female population and the widespread prevalence of obesity, an increasing number of patients with endometrial cancer/endometrial atypical hyperplasia are affected by significant co-morbidities, making surgery contraindicated due to an increased risk related to general anesthesia and surgery.[11,12] Pathologic conditions, such as obesity, diabetes, and hypertension, are linked to a higher risk of endometrial cancer and increased chances of intra-operative complications and post-operative morbidity and mortality.[13,14]

Treating these high-risk patients for peri-operative morbidity is a significant clinical challenge. In this context, alternative therapeutic options are currently available for managing frail, surgically unfit women with early-stage endometrial cancer, including radiation therapy alone or combined with hormonal treatment.[11,12,15] Still, radiation therapy could lead to increased toxicity for these patients,[15] making hormone therapy the most viable option. Given the role of unopposed estrogen in the development of endometrial cancer, progesterone is considered an alternative to surgery for fertility-sparing treatment[16] and in early-stage low-grade endometrial cancer when surgery is not an option.[17]

Systemic progesterone (medroxyprogesterone acetate or megestrol acetate) is efficacious in these cases, but its therapeutic duration is relatively short due to the downregulation of progesterone receptors.[17] Moreover, systemic progestin therapy is often associated with low adherence rates due to adverse effects, and patients may discontinue the treatment spontaneously without consulting their physician.[18,19]

Local progesterone delivery systems could achieve the same therapeutic effects, with no adverse reactions. The levonorgestrel-releasing intra-uterine device releases high local concentrations of levonorgestrel (20 μg/day) into the uterine cavity. This leads to decidualization of the stroma, mucosal thinning, and suppression of endometrial growth. These non-surgical strategies have been recognized as valuable therapeutic options.[4,5] Still, very few data are currently available regarding long-term oncological outcomes of very frail patients with endometrial cancer, judged unfit for surgery, and treated with levonorgestrel-releasing intra-uterine device alone.

In this context, the FEMME study,[20] a randomized clinical trial comparing levonorgestrel-releasing intra-uterine device alone versus levonorgestrel-releasing intra-uterine device plus metformin or weight loss, strongly supported the efficacy of levonorgestrel-releasing intra-uterine device in women with well-differentiated early-stage endometrial cancer, documenting a promising rate of complete pathologic response to hormonal therapy.[20] However, in this intriguing scenario, there are little data available regarding long-term disease control and survival outcomes in patients treated with levonorgestrel-releasing intra-uterine device alone,[21] especially regarding patients who opt for this method because they are unfit for surgery. Many studies focus exclusively on levonorgestrel-releasing intra-uterine device in fertility-sparing cases. For these reasons, we present here the results of the ENDOIUD study, the largest Italian multi-center retrospective study aimed at clarifying the oncological safety and long-term efficacy of levonorgestrel-releasing intra-uterine device as a stand-alone treatment in the management of frail women with atypical hyperplasia/well-differentiated early-stage endometrial cancer judged not suitable for surgery

METHODS

This was a multi-center retrospective study conducted in 9 referral gynecologic centers in Italy (Supplementary Material 1).

The investigators retrospectively evaluated patients with histologically confirmed atypical hyperplasia and early-stage endometrial cancer diagnosed through endometrial hysteroscopic biopsy or dilation and curettage who were treated with levonorgestrel-releasing intra-uterine device between January 2012 and December 2022. Seventy-eight patients were enrolled.

The peri-operative risk was estimated using the American Society of Anesthesiologists (ASA) physical status classification. Patients were considered unsuitable for surgery if the ASA risk class was 4 (a disease that is severe, incapacitating, and a constant threat to life)[22] or 3 (severe disease that is activity-limiting but not incapacitating),[22] especially if they had multiple co-morbidities, multiple previous surgeries, or had morbid obesity. The primary objective was to evaluate cause-specific survival. The secondary objective was to verify the control of vaginal bleeding, assessed by maintaining serum hemoglobin levels above the initial level. The inclusion criteria were patients with endometrioid endometrial cancer, International Federation of Gynecology and Obstetrics (FIGO) stage I (regardless of histologic grade) without clinical evidence of extra-corporeal disease spread, or patients with endometrial atypical hyperplasia who were unsuitable for surgery (ASA risk class 3 to 4) and treated with levonorgestrel-releasing intra-uterine device. Patients were considered ineligible if they had previously received other treatments for endometrial atypical hyperplasia or endometrial cancer.

The investigators retrospectively collected the following data: age at diagnosis, body mass index, diagnosis date, hemoglobin

levels at diagnosis and post-therapy, co-morbidities according to the Charlson index, pre-operative ASA physical status classification score,[22] histology (hyperplasia vs carcinoma), myometrial infiltration, tumor size, stage, grading, risk class according to European Society of Gynaecological Oncology/European Society for Medical Oncology/European SocieTy for Radiotherapy and Oncology criteria, levonorgestrel-releasing intra-uterine device placement and removal date, therapy duration, post-therapy re-evaluation (biopsies, magnetic resonance imaging, ultrasound), overall response to levonorgestrel-releasing intra-uterine device, post-therapy hysterectomy and time to relapse in months, recurrence, follow-up/death, overall survival, disease-free survival, and control of bleeding.

Adverse events were retrospectively identified through review of medical records and hospital databases, including any treatment-related complications requiring medical attention. Bleeding control was evaluated by clinical notes and by comparing hemoglobin levels. In particular, hemoglobin levels were collected at baseline and at the first available follow-up evaluation after levonorgestrel-releasing intra-uterine device insertion, which was variable with a range of 4 to 12 months. The width of this range reflects the variability of clinical practices across the different centers and the retrospective nature of the study. The same applies to biopsy follow-up, which was performed at variable intervals across centers (4-8 months). Unfortunately, information on blood transfusions or iron supplementation was not consistently available across centers and, therefore, could not be analyzed.

The relevant data were collected through computerized hospital systems and medical records and were entered into a specially designed and anonymized data collection database.

The institutional review board approved the study at all participating centers. Specifically, the study at the leading center was approved by the institutional review board of the Department of Medicine at the University of Udine, with protocol number 223/2024. Because the study was retrospective and involved no direct patient contact or diagnostic or therapeutic interventions, a waiver of informed consent and a waiver of authorization were requested. The ethics committee of the principal investigator determined that obtaining informed consent from patients was unnecessary for this retrospective study because all patients had previously provided consent for the use of their data in research. All patient information was kept confidential. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

The sample was characterized in terms of its clinical and demographic features using descriptive statistical methods. Quantitative variables were summarized with the mean, standard deviation, minimum, and maximum values. Qualitative variables were described with frequency tables, showing absolute counts and percentages. Cause-specific survival was estimated using Kaplan-Meier curves. Disease-free survival was defined as the interval from levonorgestrel-releasing intra-uterine device insertion to documented recurrence (or progression in cases of atypical hyperplasia) or last follow-up if no event occurred. Cause-specific survival was defined as the interval from insertion to death attributable to endometrial cancer, with deaths from other causes censored. Overall survival was defined as the interval from levonorgestrel-releasing intra-uterine device insertion to death from any cause or last follow-up.

Table 1 Clinical-Pathological Characteristics of the Study Population

Characteristics	All patients
	n (%)
All cases	78
Age, median (range), y	72 (37-91)
Body mass index, median (range)	41 (22-65)
ASA classification	
ASA = 3	65 (83.3)
ASA = 4	13 (16.7)
Hemoglobin levels, median (range), g/dL	11.6 (6-16)
Charlson index, median (range)	6 (2-11)
Histology	
Complex atypical hyperplasia	15 (19.2)
Endometrioid adenocarcinoma	63 (80.8)
Tumor grade[a]	
G1	32 (50.7)
G2	22 (34.9)
G3	9 (14.3)
Lymphovascular space invasion[a]	
No	51 (81.0)
Yes	12 (19.0)
Myometrial infiltration[a]	
<50%	47 (74.6)
>50%	16 (25.4)
Patients per center (*n*)	
Bologna	5
Chieti	4
Palermo (ARNAS)	9
Parma	3
Sassari	15
Udine	5
Milano (INT)	17
Bari (F. Miulli)	12
Rome (A. Gemelli)	8

Abbreviations: ASA, American Society of Anesthesiologists; ARNAS, Azienda di Rilievo Nazionale ad Alta Specializzazione; INT, Istituto Nazionale Tumori.
[a] Calculated only on patients with endometrial cancer.

Kaplan-Meier survival curves were generated with censoring at the date of last follow-up for patients alive and disease-free. Patients lost to follow-up were censored at the time of their last documented clinical contact. No formal competing risk analysis was performed due to the limited sample size; however, deaths unrelated to endometrial cancer were recorded separately and discussed as an important factor influencing overall survival.

All descriptions were summarized with descriptive statistics. All statistical tests used a 2-tailed significance level of .05.

In accordance with the journal's guidelines, we will provide our data for independent analysis by a designated team chosen by the Editorial Team, either for additional data analysis or to facilitate the reproducibility of this study at other centers if requested.

Table 2 Details of Death Distribution in the Study Population.

Characteristics	All patients	Atypical hyperplasia	Endometrial cancer
	n (%)	*n* (%)	*n* (%)
All cases	78	15 (19.2)	63 (80.8)
Hemoglobin levels post-therapy, median (range), g/dL	12.1 (7.8-14.9)		
Death of disease	7 (9)	0 (0.0)	7 (11.1)
Death not of cancer disease	23 (29.5%)	4 (26.7)	19 (30.1)
Cerebral ischemia	8 (10.2)	2 (13.3)	6 (9.5)
Acute myocardial infarction	6 (7.7)	1 (6.7)	5 (7.9)
Pulmonary embolism	4 (5.1)	1 (6.7)	3 (4.7)
COVID disease	2 (2.5)	0	2 (3.1)
Other malignancy	1 (1.3)	0	1 (1.6)
Suicide	1 (1.3)	0	1 (1.6)
Other	1 (1.3)	0	1 (1.6)
Overall survival (range), mo	45 (5-120)	42 (24-82)	46 (5-120)
Disease-free survival (range), mo	43 (5-120)	42 (24-82)	44 (5-120)

Abbreviation: COVID, coronavirus.

RESULTS

Seventy-eight patients deemed unsuitable for surgery and assigned to receive levonorgestrel-releasing intra-uterine device alone were included in the study. The median age of the included patients was 72 years (range; 37-91), with a median body mass index of 41 kg/m^2 (range; 22-65). Sixty-five patients (83.3%) were classified as ASA 3, whereas the remaining 13 (16.7%) were classified as ASA 4, and all were considered unfit for surgery. Fifteen patients (19.2%) had a diagnosis of endometrial hyperplasia with atypia, whereas the other 63 (80.8%) had endometrial carcinoma. Of these, the majority (32 patients, 50.7%) had FIGO G1 endometrial cancer, whereas 22 (34.9%) were FIGO G2 and 9 (14.3%) were FIGO G3. Considering only patients with endometrial cancer, 51 (81%) had negative lymphovascular spaces on histological examination, whereas 12 (19%) had positive lymphovascular spaces (Table 1). The median follow-up was 40 months (interquartile range [IQR] 30.5-52; mean 45.1, range; 5-120).

The baseline hemoglobin levels averaged 11.6 (range; 6-16), rising to 12.1 (range; 7.8-14.9) during follow-up after levonorgestrel-releasing intra-uterine device insertion ($p = .003$). No major complications or clinically significant side effects requiring discontinuation or medical intervention were reported. Minor adverse events may have been underreported due to the retrospective nature of data collection. Bleeding control was rated as optimal in most patients ($n = 58$, 74%), adequate in 10 patients (13%), and inadequate in another 10 patients (13%).

Histologic follow-up data were available for 65 of 78 patients (83.3%), whereas in 13 cases (16.7%), information was missing due to the retrospective and multi-center nature of the study. Among evaluable patients, 32 (49.2%) achieved a complete response, 12 (18.5%) showed partial regression, 19 (29.2%) had persistence of disease, and 2 (3.1%) experienced progression. These findings should be interpreted with caution because the presence of missing data may introduce bias and reduce the statistical power of sub-group analyses.

A total of 21 patients (26.9% of the evaluable cohort) underwent hysterectomy after an initial period of levonorgestrel-releasing intra-uterine device treatment. These women had initially been considered medically inoperable, but surgery was later performed after optimization of their general condition or due to changes in their clinical scenario. The median duration of levonorgestrel-releasing intra-uterine device treatment before hysterectomy was 27.5 months (IQR 12.6-32.8, range; 6.2-77.2). Data on adjuvant therapies were not consistently available across centers; however, the main rationale for hysterectomy in these patients was local disease control rather than systemic management.

Seven patients (9%) died due to the disease (Table 2). All these patients initially received a diagnosis of endometrial cancer. Twenty-three patients (4 with endometrial atypical hyperplasia and 19 with endometrial cancer) died from causes unrelated to the underlying malignancy. The 2 leading causes of non–tumor-related death were cerebral ischemia and acute myocardial infarction. The overall survival was 45 months (range; 5-120), specifically, 42 months for patients with endometrial atypical hyperplasia and 46 months for those with endometrial cancer. The disease-free survival was 43 months, with 42 months for patients with endometrial atypical hyperplasia and 44 months for those with endometrial cancer.

DISCUSSION

Summary of Main Results

In this study, treatment with levonorgestrel-releasing intra-uterine device alone showed promising results. Hemoglobin levels stayed

stable or improved in all patients, with most reporting excellent bleeding control. No treatment-related side effects were observed.

Results in the Context of Published Literature

It is well known that most women with endometrial cancer are affected by a hormone-dependent cancer. As global obesity rates increase, the need for safe and effective conservative treatments for this condition grows.[23] Because unopposed hyperestrogenism plays a crucial role in the development of endometrial atypical hyperplasia/endometrial cancer, progesterone is the most common and well-studied medical treatment for these conditions, and it can serve as a good alternative to surgery in cases of endometrial atypical hyperplasia and early-stage, low-grade endometrial cancer.[24]

Oral progesterone treatment has been suggested, but many women experience intolerable side effects from systemic progesterone or have difficulty sticking with the therapy.[20] The use of the levonorgestrel-releasing intra-uterine device for treating atypical hyperplasia and early-stage endometrial carcinoma is included in the main and most recent guidelines (American College of Obstetricians and Gynecologists[5] and European Society of Gynaecological Oncology/European Society of Human Reproduction and Embryology/European Society for Gynaecological Endoscopy).[25] However, this type of treatment is primarily mentioned for fertility-sparing in young women.[26] Only the American College of Obstetricians and Gynecologists guidelines[5] recommend it for patients who are generally not candidates for surgery. Both guidelines, however, highlight the lack of data regarding the use of levonorgestrel-releasing intra-uterine device. The currently available literature on non-surgical candidates mainly consists of small retrospective studies. It seems to show higher regression rates with levonorgestrel-releasing intra-uterine device than oral progestins, with pathological response rates ranging from 37% to 66%.[27-30] In addition, the adverse effects of levonorgestrel-releasing intra-uterine device are lower than those of systemic therapy, leading to better adherence to treatment.[30,31]

In this study, analyzing the Kaplan-Meier curves (Fig.), it is evident that overall survival steadily declines over time, with an estimated 5-year survival rate of approximately 60%. The widening of the confidence interval during more extended follow-up periods aligns with the fact that many patients die during follow-up, although not necessarily from the disease under study. In fact, the included patients often have multiple co-morbidities, which is why they are excluded from surgical treatment. Disease-free survival consistently remains higher than overall survival, with a noticeable plateau after approximately 60 months at around 77% to 78%, indicating that many patients stay in remission. This suggests that treatment with the levonorgestrel-releasing intra-uterine device may be effective in controlling disease progression for a significant number of patients. The overall survival was lower due to non-oncologic health issues, highlighting the vulnerability of the study group.

The results of this study align with the literature, which reports a 5-year relative survival rate of 76% for European women diagnosed with endometrial carcinoma between 2000 and 2007.[32] In another study conducted on a Spanish population, the 5-year disease-free survival was 82.3%, and the overall 5-year survival was 81%.[33] This discrepancy between these data and the 5-year overall survival observed in this cohort ($\approx$60%) is mainly explained by the demographics of our study population, characterized by advanced age, high body mass index, multiple co-morbidities, and ASA $\geq$3. Consistently, the majority of deaths were unrelated to cancer but due to competing co-morbidities, underscoring the frailty of these patients.

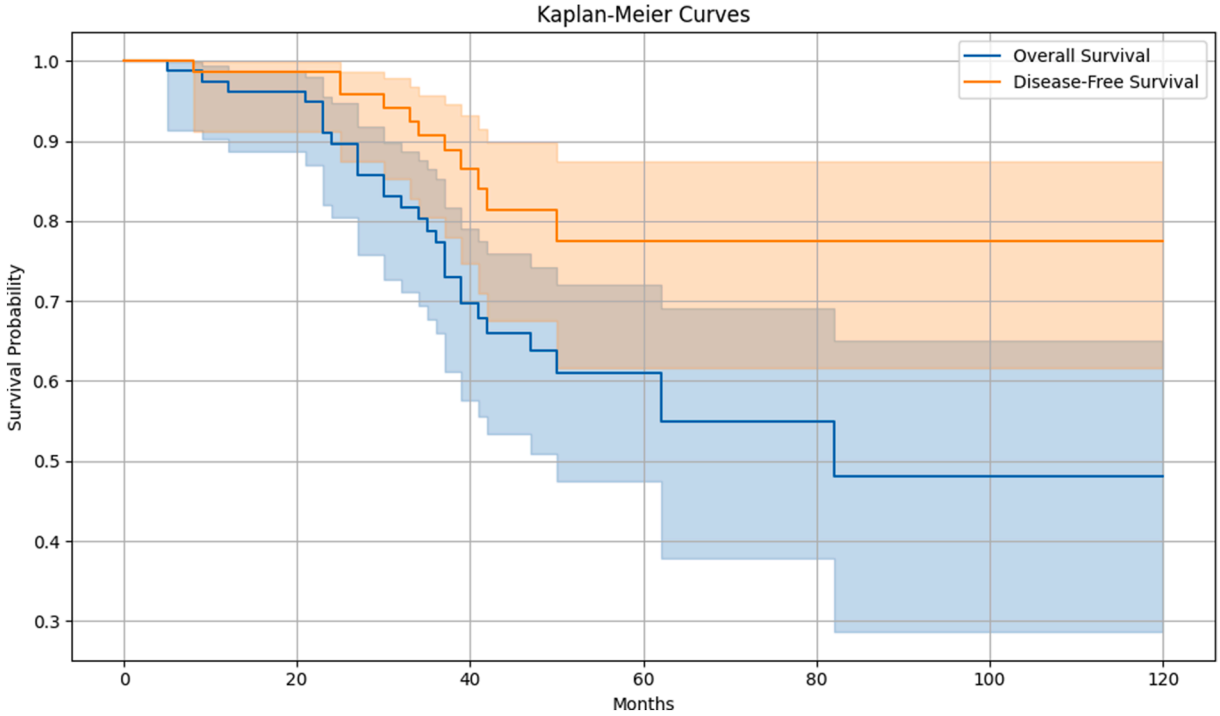

Figure Kaplan-Meier survival curves for overall survival and disease-free survival (95% CI). CI, confidence interval.

It would have been beneficial to correlate the patients' response to the levonorgestrel-releasing intra-uterine device with their disease' molecular profile, especially in cases of endometrial cancer. However, this was not possible due to the retrospective nature of the study and because many cases date back to a time when the participating centers were unable to perform molecular analysis of endometrial cancer. As a result, the available molecular data were too limited to draw any meaningful or statistically valid conclusions.

Furthermore, the placement of the levonorgestrel-releasing intra-uterine device is a straightforward procedure that can be done in an outpatient setting. For patients with severe obesity, anatomical challenges (eg, a narrow and deep vaginal canal or a small cervix) or a history of cesarean delivery, an outpatient hysteroscopic method has also recently been identified as a viable option alternative.[34] As a final note, the authors would like to specify that the current preferred terminology for endometrial atypical hyperplasia is based on endometrial intra-epithelial neoplasia schema.[35] Nonetheless, we chose to use the previous terminology in this study because it is retrospective in nature, and most clinical management decisions were made initially based on the old classification.

Strengths and Weaknesses

The strength of this study lies in its multi-center design, involving 9 Italian centers, which increases the generalizability and applicability of the findings. Although the sample is relatively small, to the best of our knowledge, this is the largest Italian series in this selected population to date. Additionally, another strength is the strict selection of patients, which only consists of those with multiple co-morbidities and an ASA risk score of 3 or higher, who are unfit for surgery, ensuring that the cohort truly reflects women at high peri-operative risk. Moreover, the oncologic end points and clinically relevant symptomatic end points were evaluated. Furthermore, the distinction between cancer-specific and non-cancer deaths provides additional insight into the impact of competing co-morbidities in this fragile population. Finally, this study focuses on a particularly important and clinically relevant growing group of frail, inoperable women, for whom therapeutic options are limited.

On the other hand, the primary limitations of the study were its retrospective design and the absence of a control group, preventing us from drawing direct comparative conclusions. However, the study was specifically conducted on a frail population frequently not eligible for alternative treatments, making it unfeasible to establish a matched control cohort. Despite this, these findings provide valuable real-world evidence supporting the safety and feasibility of levonorgestrel-releasing intra-uterine device alone in surgically unfit patients. Another limitation is the potential variability in data collection across the participating centers, which is inherent to the study design. To mitigate this issue, all centers used a standardized data collection form, and anonymized information was centrally reviewed for consistency and completeness. Nevertheless, some degree of heterogeneity cannot be excluded. Another limitation is the histopathological heterogeneity of the cohort because patients with higher-risk features (G2/G3 tumors and lymphovascular space invasion-positive disease) were included alongside G1 carcinoma or atypical hyperplasia. This choice reflects real-world practice in surgically unfit women but inevitably introduces biological variability that should be considered when interpreting the results, particularly, for patients with higher-risk characteristics.

A further limitation is the lack of complete histologic follow-up data, which were missing in about 17% of cases due to the retrospective and multi-center design. This inevitably reduces the robustness of the analysis of histologic response rates and may introduce bias. Future prospective studies with standardized histologic re-assessment are warranted to provide more accurate estimates of treatment efficacy. There was also a potential for selection bias: due to the retrospective and multi-center design, the choice of levonorgestrel-releasing intra-uterine device versus other non-surgical options was not based on uniform, stringent criteria, although it is assumed that all participating centers made treatment decisions in accordance with international guidelines.

The relatively small sample size, despite the multi-center design and long study duration, can be another limitation. This can be explained by the rarity of the clinical scenario under investigation. Only a limited proportion of women with atypical hyperplasia or early-stage endometrial cancer are deemed medically inoperable, and the strict eligibility criteria adopted in our study further reduced the pool of eligible patients. Moreover, the progressive diffusion of minimally invasive and robotic surgery, together with advances in anesthesiologic management, has led to a decreasing number of patients being considered unfit for surgery over the past decade.

A potential selection bias of our study is represented by the small sub-group of patients ($n = 21$) who underwent hysterectomy after an initial period on levonorgestrel-releasing intra-uterine device. These women, initially considered inoperable due to their co-morbidities, later became eligible for surgery after clinical optimization or re-assessment. Although hysterectomy may have ultimately contributed to improved oncologic outcomes in these cases, it should be noted that the median duration of local treatment before surgery was 27.5 months (IQR 12.6-32.8), indicating that the levonorgestrel-releasing intra-uterine device provided disease control for a considerable period before surgery was reconsidered.

Implications for Practice and Future Research

In the Kaplan-Meier analysis, the levonorgestrel-releasing intra-uterine device shows effective local control. However, the lower overall survival rate indicates that the treatment might not be sufficient for all patients, emphasizing the need for careful case selection. Although the levonorgestrel-releasing intra-uterine device has proven to be an effective therapy for endometrial atypical hyperplasia/endometrial cancer, with high regression rates, some patients still do not respond, leading to persistent, progressive disease or early recurrence. Currently, there are no predictive markers for this progesterone resistance. Some studies have explored molecular markers to predict non-response. For example, a 2021 study found that non-responders exhibited lower DKK3 gene expression than responders.[30]

In the future, conducting prospective, multi-center studies on patients receiving levonorgestrel-releasing intra-uterine device therapy who are unfit for surgery would be valuable to allow multivariable analyses and competing risk approaches, particularly, to

explore outcomes according to histopathologic risk factors. In addition, performing molecular analyses on these patients and examining the relationship between molecular sub-types and therapy response would be of interest. It would also be helpful to explore the potential of predicting medical therapy response, including through micro-RNA analysis, to determine whether offering these patients a surgical option is advisable or if continuing with medical therapy is more appropriate, thereby avoiding the loss of valuable time that could allow disease progression.

CONCLUSIONS

Levonorgestrel-releasing intra-uterine device alone appears to be a feasible, pragmatic, and potentially effective option for disease control in women with early-stage endometrial cancer or endometrial atypical hyperplasia who are unfit for surgery, showing no side effects and promising oncological outcomes. This study opens the way to considering levonorgestrel-releasing intra-uterine device as a potentially valuable therapeutic strategy in this fragile population and highlights the need for prospective trials to confirm its efficacy, define appropriate patient selection, and predict the response to the treatment.

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Declaration of Competing Interests None declared.

Appendix A. Supplementary data Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijgc.2025.102785.

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