



# Medically unfit women with early-stage endometrial cancer treated with the levonorgestrel intrauterine system

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## Objective

To assess the clinical efficacy of the levonorgestrel intrauterine system (LNG-IUS) in the treatment of early-stage endometrial cancer in elderly morbidly obese women, whose multiple co-morbidities made the standard surgical treatment too risky to undertake.

## Methods

A retrospective review was conducted and case series reports were prepared of all women diagnosed with endometrial cancer, from April 2011 to December 2016 at the Queen's Hospital, London, to identify women unfit for surgery and treated with the LNG-IUS.

## Results

Out of 438 women with endometrial cancer, Eight women with early-stage endometrial cancer were deemed unfit for surgery and underwent treatment with the LNG-IUS. All had grade 1 endometrioid endometrial adenocarcinoma, radiologically staged as 1a. Four women died of their co-morbidities, not related to endometrial cancer. One of them had 68 months of progression-free survival before death due to co-morbidities. One patient required a hysterectomy after 32 months of treatment with LNG-IUS and oral progestogens due to heavy vaginal bleeding. Three women have continued the LNG-IUS treatment with no evidence of progressive disease symptoms till date at a mean follow-up of 35.7 months.

## Conclusion

For women with multiple co-morbidities, the LNG-IUS offers an effective and safe treatment for early-stage, low-grade endometrial cancer, with no cases of symptomatic progression reported in our case series. In the frail and elderly, where the quality of life is of paramount importance, surgical treatment may not offer additional long-term survival benefits.

**Keywords:** Endometrial cancer; Quality of life; Elderly; Levonorgestrel; Mirena

## Introduction

Endometrial carcinoma is currently the most common gynecological malignancy in women in the Western world, and endometrioid adenocarcinomas represent the majority of these cases [1,2].

Endometrioid adenocarcinoma of the endometrium is directly associated with an estrogen-related pathway, and several risk factors such as obesity, nulliparity, early menarche and late menopause, increasing age, hypertension, and eth-

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nicity are the risk factors in the development of this type of endometrial cancer [3].

Excess of estrogen, regardless of the source, has a mitogenic effect on the endometrial glands and can lead to premalignant endometrial disease, atypical hyperplasia, or endometrial intraepithelial neoplasia, and eventually endometrial carcinoma. Progesterone antagonizes the estrogen-mediated proliferation of the glands, leading to secretory changes and decidualization of the endometrial stroma [3]. Lack of this negative effect due to stimulation of the endometrium is associated with the development of endometrial neoplasia. This phenomenon may occur in women with excess estrogen due to obesity, unopposed estrogen exposure, and insulin resistance, or in women with anovulatory disorders [4].

Women with endometrial cancer or atypical endometrial hyperplasia with an increased risk of future or co-existent cancer have routinely been treated with hysterectomy and bilateral salpingo-oophorectomy [5]. Progestin therapy, specifically the levonorgestrel intrauterine system (LNG-IUS), and high-dose oral progestogen have reportedly reverted early-stage, low-grade endometrial cancer (caused by unopposed estrogen stimulation) to benign endometrium in young women seeking fertility-sparing treatment [5]. Numerous published retrospective studies have demonstrated high conversion rates of affected endometrium to normal endometrium in pre-menopausal women, with subsequent successful pregnancies [6-9] and no increase in the recurrence rates [10]. Progesterone treatment is also used in to treat metastatic or recurrent diseases.

There are also case reports of the use of the LNG-IUS in women with early-stage endometrial cancer who are not medically fit to undergo standard surgical treatments, such as hysterectomy and bilateral salpingo-oophorectomy, due to multiple co-morbidities [11,12]. With an increasingly ageing population and growing levels of morbid obesity, the incidence of patients too frail or unfit to undergo surgery is becoming a more frequent and causing dilemma during treatment planning. Obesity, hypertension, and diabetes are risk factors of endometrial cancer and increase perioperative morbidity and mortality [3,5,13,14]. Treatment with progesterone (systemic, intrauterine, or both) may be a preferred alternative to surgery in women with multiple life-limiting co-morbidities.

Nevertheless, the use and success of the LNG-IUS in elderly, morbidly obese women with multiple co-morbidities, with

high risk in undergoing the standard treatment of hysterectomy and bilateral salpingo-oophorectomy, is still unclear. This study aimed to assess the clinical response and long-term benefit of the use of LNG-IUS in women diagnosed with early-stage, low-grade endometrioid adenocarcinoma of the endometrium, and who were medically unfit for surgical treatment.

## Materials and methods

### 1. Patients and study design

All patients with stage 1 endometrioid adenocarcinoma of the endometrium at the Queen's Hospital, London, UK were identified from the pathology database from January 2011 to December 2016. This review of clinical service provision/audit (as defined by the Health Research Authority) was registered at the clinical audit department of the Queen's Hospital.

Data was extracted via online medical records, written case notes, histology, and radiology reports. This included demographic and risk factors data of women included age, ethnicity, body mass index (BMI), and medical co-morbidities including hypertension, diabetes, previous history of breast cancer, and tamoxifen use. Documentation included the clinical presentation and tumor data (endometrial thickness, histology results, staging) including the treatment undertaken. Women who were medically unfit for standard surgical treatment of total hysterectomy and bilateral salpingo-oophorectomy with stage 1 endometrioid adenocarcinoma of the endometrium were offered treatment with the LNG-IUS/Mirena IUS, which contains 52 mg levonorgestrel with an initial release of approximately 20 µg per day.

Clinical oncologists reviewed the patients and considered them unsuitable for primary radiotherapy given multiple co-morbidities, morbid obesity, reduced mobility, anesthetic fitness issues, and increased risk of associated morbidity. The diagnosis was confirmed histologically on endometrial biopsy, and the disease was staged using the magnetic resonance imaging (MRI) scans of the pelvis before commencing treatment (computed tomography [CT] was performed if MRI was contraindicated). Regular follow-ups were conducted every 4 months in the first year and every 6 months after that, with clinical examination and symptom review. MRI or CT scan imaging was considered if the patient had symptoms suggestive of disease progression. Explicitly, the absence of

symptoms (vaginal bleeding, abdominal and pelvic pain, or abdominal bloating) and signs suggesting metastasis (palpable lymph nodes or palpable mass) are likely to indicate the absence of disease progression. In cases of concerning symptoms and patients' request due to anxiety, imaging and/or biopsy were performed. Repeat endometrial biopsies were not planned, as the management would not change with respect to the extreme co-morbidities of our patients. Change of the LNG-IUS was advised no later than thrice a year.

## Results

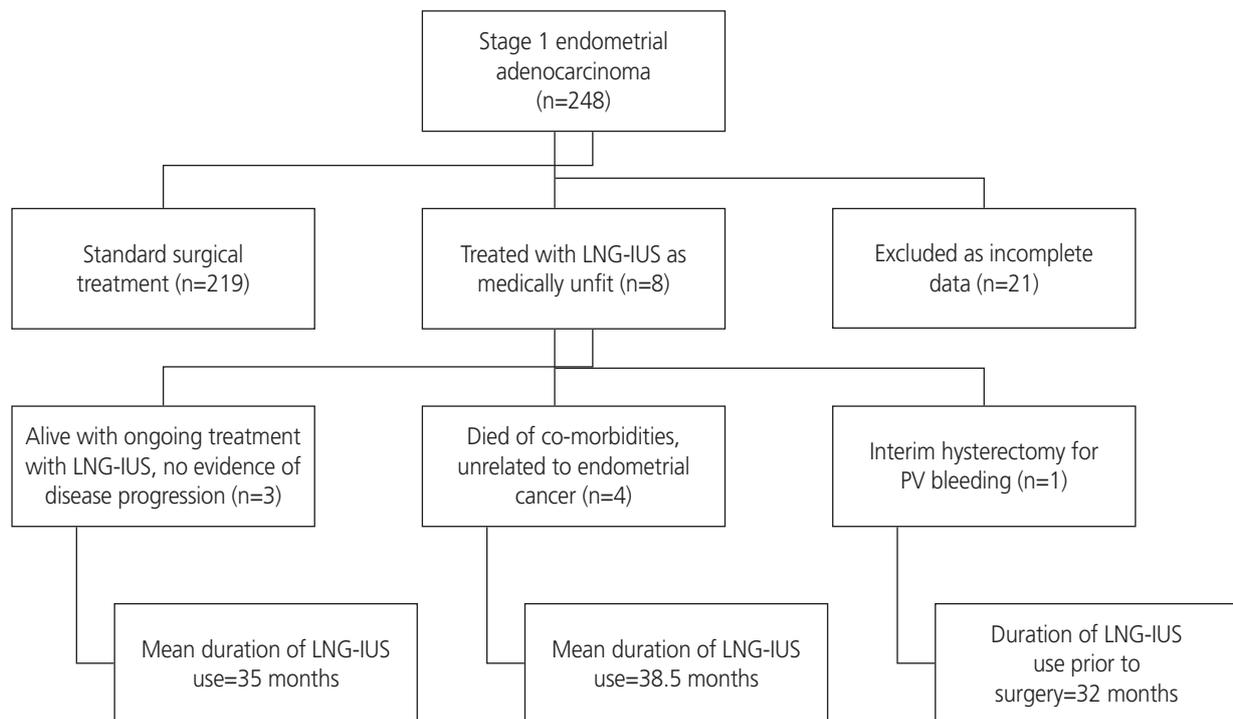
Between January 2011 and December 2016, 438 women were diagnosed with endometrial cancer, of which 248 had stage 1 endometrioid adenocarcinoma of the endometrium as diagnosed on MRI imaging, except for one patient who underwent CT imaging because of her pacemaker. Of the 248 women, 8 (3.2%) were post-menopausal, and surgically unfit women with stage 1 grade 1 endometrial cancer were treated with LNG-IUS. These women were the focus of this study. Three of these women also received concurrent oral

progestogens (medroxyprogesterone acetate 100–200 mg twice daily or megestrol acetate 80mg to 160 mg per day, depending on the co-morbidities).

The mean age was 74.75 years (range 62–82 years). No patient had previously used any hormone replacement therapy. All women presented initially with post-menopausal bleeding, and all of them were multiparous. Only one patient had BMI less than 30 (Fig. 1).

Table 1 shows the characteristics (age, BMI, co-morbidities, and cause of death) of these 8 women. Four women died of their co-morbidities, not related to endometrial cancer, and 4 women are alive with no progressive disease symptoms.

Patient 1 (Table 1) had known metastatic breast cancer with lung, bone, and liver metastases at the time of diagnosis of endometrial cancer and was receiving capecitabine as a palliative treatment for breast cancer. The patient decided against surgery after discussion of all the treatment options, as quality of life was understandably her main concern and preferred to continue first with chemotherapy for breast cancer. Primary radiotherapy would have been an alternative treatment, but the patient preferred the insertion of LNG-IUS for control of symptoms of vaginal bleeding, despite hav-



**Fig. 1.** Study flow chart of the medically very high risk and/or unfit women treated with LNG-IUS for stage 1, grade 1 endometrial adenocarcinoma. LNG-IUS, levonorgestrel intrauterine system.

ing hormone receptor-positive breast cancer. The oncologist was made aware of this management. During subsequent visits, the patient did not report vaginal bleeding following the insertion of the LNG-IUS. Follow-up CT scan showed the already known metastases, with no pelvic lymphadenopathy or progression of the uterine disease. A repeat endometrial biopsy was not considered appropriate in this scenario. The patient died of metastatic breast cancer 10 months after the insertion of the LNG-IUS.

Patient 2 (Table 1) was an elderly woman with frailty, immobility, and severe dementia. A medical power of attorney was available with the family and surgery was considered inappropriate in her case; hence, LNG-IUS insertion was preferred. An abdominal ultrasound scan of the pelvis at 6 months after LNG-IUS insertion showed the LNG-IUS in situ and no disease progression. Her care-providers reported no vaginal bleeding. A chest radiograph close to her time of death from medical causes had shown no evidence of metastases. Although primary radiotherapy was an alternative option in this scenario, it would be extremely challenging in

the background of severe dementia and reduced mobility.

Patient 3 (Table 1) had multiple co-morbidities. She was morbidly obese weighing 155 kg and had congestive cardiac failure. She had a single cardiac chamber pacemaker, because her obesity prevented her from lying flat and inserting a dual-chamber pacemaker. Moreover, she had type 2 respiratory failure and a history of recurrent deep vein thrombosis requiring lifelong anti-coagulation therapy with warfarin. She was not medically fit to undergo general anesthetic procedures for surgery and had the LNG-IUS inserted under local anesthesia. The patient was not keen on a surgical approach during follow-up, given the high risks associated with anesthesia and surgery. Six months after insertion of the LNG-IUS, a subsequent biopsy was performed that only showed atypical hyperplasia. The patient declined further endometrial biopsies. She regularly attended her follow-up appointments and reported no vaginal bleeding. Five years after diagnosis of cancer, she was admitted to the hospital following a fall at home, and the chest radiograph and limited abdominal ultrasound did not show any obvious evidence of endome-

**Table 1.** Medical history and outcome of the patients treated with LNG-IUS

Patient/age (yr)	BMI	Co-morbidities	Duration of use of LNG-IUS (mon)	Outcome
#1 62	34	Metastatic breast cancer, palliative chemotherapy, atrial fibrillation	10	Died of metastatic breast cancer
#2 82	27	Frailty immobility, severe dementia	32	Died of causes not related to cancer
#3 69	50	Heart failure EF <20%, morbid obesity, sleep apnoea, atrial flutter, pacemaker, recurrent hypothyroidism, DVT (on lifelong-warfarin), bilateral leg lymphoedema	68	Died of heart failure
#4 77	49	Morbid obesity, bed bound, hypertensive, atrial fibrillation on rivaroxaban	32	Alive, no progression/hysterectomy due to recurrent vaginal bleeding, severe anaemia requiring admission and blood transfusion
#5 74	41	Morbid obesity, cerebral palsy, wheel-chair bound, chronic b-cell lymphocytic leukaemia	31	Alive, no progression
#6 80	33	Frailty, wheel-chair bound, low sodium, diabetes, hypertension	43	Alive, no progression
#7 78	37	Diabetes, hypertension, pacemaker, stroke, pulmonary hypertension, aortic stenosis, bilateral renal angle stenosis, tricuspid regurgitation, bilateral internal carotid artery stenosis	25	Alive, no progression
#8 76	48	Severe COPD, atrial fibrillation, diabetes, reduced mobility, chronic kidney disease	44	Died due to co-morbidities

LNG-IUS, levonorgestrel intrauterine system; BMI, body mass index; EF, ejection fraction; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis.

trial cancer progression or metastases. She died of heart failure 68 months after diagnosis of endometrial cancer and treatment with LNG-IUS. Primary radiotherapy, including brachytherapy, is associated with very high morbidity in the presence of morbid obesity and co-morbidities, and hence deemed unsuitable.

Patient 4 (Table 1) presented with heavy vaginal bleeding and a performance status of 3 (bed-bound due to severe arthritis, morbid obesity, and atrial fibrillation requiring anti-coagulation). An endometrial biopsy and insertion of the LNG-IUS were performed with difficulty due to the patient's joint stiffness. The patient was offered a hysterectomy for the treatment of endometrial cancer, but she declined. She agreed to the treatment with LNG-IUS and oral progestogens. Primary radiotherapy would not be possible because of morbid obesity, reduced mobility, and lack of flexibility of the knee joints for lithotomy positioning during brachytherapy. Thirty-two months after insertion of the LNG-IUS, the woman presented with 2 heavy vaginal bleeds, causing severe anemia that required blood transfusion and hospital admission. Notably, this patient had a large endometrial tumor at presentation, and her anti-coagulation treatment may have contributed to the heavy vaginal bleeding. A CT scan of the chest, abdomen, and pelvis for staging did not show any evidence of disease progression or distant metastasis, and the patient opted for surgery this time. An uncomplicated total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed, with an uneventful surgical recovery. It was difficult to assess on the pre-operative CT if the cancer was at stage Ia or Ib, and the final histology revealed stage Ib with no lymphovascular space invasion.

Patient 5 (Table 1) was morbidly obese and unable to stand due to cerebral palsy. Management planning involved all treatment options. She decided against surgery, as she was concerned about the risks of anesthesia and stroke. She was seen by an oncologist for consideration of radiotherapy option, but given her morbid obesity and reduced mobility, radiotherapy was considered extremely difficult. The patient chose treatment with LNG-IUS and oral progestogens. She is well without any symptoms and declined repeat biopsy or surgery. She underwent CT of the chest, abdomen, and pelvis 1 year after diagnosis and treatment of cancer for re-staging, and this showed an unchanged uterine lesion with no evidence of distant metastasis. She has subsequently developed chronic lymphocytic leukemia

Co-morbidities of patient 6 are as shown in Table 1. The patient opted for medical management following discussion of all treatment options. Treatment was performed with LNG-IUS and oral progestogens, and the LNG-IUS was changed after 3 years. She has been followed-up and showed no signs or symptoms of disease progression.

Patient 7 was treated with LNG-IUS because of multiple co-morbidities (Table 1). She was satisfied with the medical treatment approach in view of extremely high morbidity and mortality risk associated with anesthesia and surgery. Two years after diagnosis, the patient suffered a new right lacunar stroke while she was on warfarin, and remains at an exceptionally high-risk for surgery. She attends her follow-up appointments and has no complains of vaginal bleeding or discharge. During a recent examination, the uterus was mobile with no obvious palpable pelvic or abdominal masses, and coil threads were present. Chest radiograph for other indications did not show chest metastasis.

Patient 8 (Table 1) had multiple medical co-morbidities, including morbid obesity, which made general anesthetic procedures highly risky. Primary radiotherapy would be extremely challenging given her BMI, medical conditions, and anesthetic risks. After discussion, the patient opted for medical treatment along with LNG-IUS. She requested a repeat hysteroscopy, endometrial biopsy, and change of LNG-IUS after 24 months. The biopsy showed no evidence of malignancy and inactive endometrium and pseudodecidualization. Another biopsy and insertion of a new LNG-IUS at 44 months showed no malignancy or endometrial pseudodecidualization. A MRI of the pelvis at 44 months after endometrial cancer diagnosis showed a normal size uterus with LNG-IUS in-situ, and no endometrial thickening, focal lesion, or evidence of disease progression. She died recently of complications related to her medical conditions.

Four women are alive with no clinical and or radiological evidence of disease progression (3 women have continued their treatment with LNG-IUS, while 1 woman had a hysterectomy in the interim). The overall mean follow-up time for all 8 patients was 35.6 months and for the women who are alive was 35 months.

## Discussion

Our case series demonstrates that long-term progression-free

survival is achievable in unfit older women treated with the LNG-IUS for early-stage endometrioid adenocarcinoma of the endometrium. Overall, 3.2% of women with stage 1 grade 1 endometrial cancer underwent non-surgical treatment with the LNG-IUS, which is comparable to a Scottish study that treated 3.6% of patients with LNG-IUS due to their medical co-morbidities [15]. Results of the Scottish study were similar to our study, although the success rate was higher in our hospital with 50% of women continuing with LNG-IUS as primary treatment during their third year of follow-up versus the 25% of women in their second year [15].

Four women are still alive at a mean follow-up of 35 months, of which 3 have no signs and symptoms of progression or post-menopausal bleeding, and 1 had interval surgery.

Only 1 of the 8 women in this study continued to have heavy vaginal bleeding requiring treatment with hysterectomy. Heavy vaginal bleeding may have resulted from the rivaroxaban medication given to the patient for atrial fibrillation and/or due to larger tumor size at presentation. Anti-coagulation therapy and large tumor size may hinder the successful treatment with LNG-IUS due to high risk of significant vaginal bleeding. Nevertheless, there was no evidence of distant metastatic disease after 32 months of treatment with LNG-IUS.

Additionally, the 4 women who died of their co-morbidities did not show any evidence of clinical or symptomatic progression. One woman treated with LNG-IUS lived for 68 months but died of heart failure. We are not aware of any documented longer progression-free survival period with the use of LNG-IUS in any elderly, co-morbid woman with early-stage endometrial cancer.

Progestin treatment of patients with atypical hyperplasia has been studied previously, with recent meta-analyses showing disease remission in 66–85.6% patients, and LNG-IUS once again showed better therapeutic results [7,16]. Recent prospective studies have been conducted regarding the treatment of patients with endometrial cancer stage 1a, who were unfit for surgery, with LNG-IUS and concurrent radiotherapy [17] or only LNG-IUS [18]. The former study showed good remission rate with an overall 2-year survival greater than 75% and well-controlled bleeding in all the cases. Radiotherapy-related toxicity was unfortunately present in most patients, although characterized as mild. In the latter study, Montz et al [18]. published a series comprising of patients undergoing endometrial Pipelle biopsy every 3 months

during the treatment with LNG-IUS, which showed complete disease remission in 50% of the patients within 1 year. In our series, only 2 out of 8 women underwent repeat endometrial biopsy. One woman had complete histological remission at 24 months and the other underwent biopsy at 6 months that showed reversion to atypical hyperplasia, but declined any further biopsies. Compared to a historical control group with similar characteristics that underwent surgical treatment, there were clear advantages of using the LNG-IUS. Severe complications occurred in the control group, including one death in the postoperative period, and the quality of life was affected significantly in the extensive recovery period and by the postoperative complications [18].

Baker et al. [4] conducted the most extensive retrospective study so far in the literature regarding the treatment of endometrial cancer with the LNG-IUS/Mirena IUS in surgically unfit patients. In a total of 16 patients with stage 1 grade 1 endometrioid carcinoma, complete response was confirmed with endometrial sampling in 6 patients (38%) and partial response in 2 (13%), with a mean follow-up of 46 months. Four patients died, 3 due to medical co-morbidities and 1 due to perioperative complications, after proceeding to total abdominal hysterectomy and bilateral salpingo-oophorectomy. Symptomatic relief was comparable to our study where post-menopausal bleeding was well controlled; however, removal of the device was requested by 1 patient due to pain and discomfort. The study recommended LNG-IUS treatment for surgically unfit women in accordance with our findings.

The LNG-IUS is generally well tolerated within the population of obese and medically ill post-menopausal women [19,20] and this is in line with our findings.

Regarding the effect of the intrauterine device in other forms of cancer, several studies have investigated the association between the use of progestin therapies and endometrial cancer, ovarian cancer, and breast cancer. Regarding LNG-IUS, prevention of endometrial cancer in cases of atypical endometrial hyperplasia as well as the regression of early endometrial cancer in the young population has been proven [21]. Studies have also shown a reduction in the risk of ovarian cancer in pre-menopausal [22,23] as well as post-menopausal women [24], with the effect of developing breast cancer still being controversial [24,25].

The LNG-IUS offers two main advantages over systemic administration; first, it can provide a higher dose of progestin concentration locally (intrauterine) than oral progestin.

Secondly, the LNG-IUS avoids the systemic adverse effects associated with oral administration, such as thrombophlebitis, weight gain, headaches, sleep disorders, mood and libido changes, and leg cramps, which can lead to suboptimal compliance among patients [26].

The standard treatment offered for endometrial cancer is surgery, with or without adjuvant radiation therapy, depending on the risk of recurrence. Primary radiotherapy may be considered as an alternative option in women who are unfit for surgery. In our study, primary radiotherapy was discussed with patients but was deemed unsuitable in view of morbid obesity, multiple severe co-morbidities, and increased risk of complications.

Heyman [27] described the role of primary radiotherapy in endometrial cancer in 1947. Exclusive primary radiotherapy could be in the form of brachytherapy alone or in combination with external beam radiotherapy. A review article by van der Steen-Banasik [28] stated that brachytherapy alone is considered in patients with endometrial cancer grades 1 or 2 stage 1A or 1B disease. In patients with more extensive disease (possibility of lymph node involvement, high-grade histology, and deep myometrial invasion), combined brachytherapy and external beam radiotherapy may be required. Disease-specific survival rates at 5 years have been reported to be around 75–100% with primary radiotherapy [28-31].

In clinical and medical experience, radiotherapy has more side effects when compared to LNG-IUS, though there have been no studies so far comparing these two modalities of treatment in the literature [32]. The main disadvantage of primary radiotherapy is side effects with 7% morbidity and 10% mortality in patients treated for endometrial cancer as shown in previous case series [31-33]. Mild toxicity such as diarrhea and vomiting were present in 30–35% of patients [32]. Although patients with brachytherapy may experience fewer side effects, they are not negligible, especially in this group of patients where symptom control and quality of life was the primary goal of treatment.

We have reported a small retrospective series, and a randomized controlled trial is unlikely to be performed as it would be unethical to perform surgery in patients at a high risk of surgical morbidity and mortality, or in a group with increased risk of disease progression to be left without treatment at all. Repeat histological examination was not performed in majority of the cases; therefore, histological re-

gression of the cancer was not documented for all patients in our cohort, but subjecting these women to multiple biopsies would not have changed our management plan. Extensive follow-up visits and internal examinations were undesirable in all patients due to the medically compromised status of some of the patients. The small sample of patients cannot lead us to certain conclusions, though we considered this an important contribution to the literature, because offering the LNG-IUS treatment option to such patients should be routine practice. We have also documented a long-term progression-free survival of 68 months in 1 woman treated with LNG-IUS.

Undoubtedly, larger sample studies are required. Collaboration with several cancer centers to prospectively gather data on women with endometrial cancer that are unfit for surgery would aid analysis of the tumor characteristics to determine which women are likely to respond to progesterone treatment.

In women with multiple co-morbidities who are unfit for surgery, the LNG-IUS offered an effective and safe treatment for early-stage, low-grade endometrial cancer with no significant side effects or incidences of clinical progression in our small case series. The cause of death in these women was usually the medical diseases, rather than endometrial cancer. The quality of life is of paramount importance in these women, and surgery would not offer additional long-term survival over treatment with LNG-IUS; hence, it can be considered as a reasonable treatment option.

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## Conflict of interest

No potential conflict of interest relevant to this article was reported.

## Ethical approval

This original article is a retrospective review of current clinical

hospital practice and ethical approval was not needed.

## Patient consent

The patients provided written informed consent for the publication and the use of their images.

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