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Case series

The role of endometrial sampling for surveillance of recurrence in postmenopausal patients with medically inoperable stage I endometrial cancer

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ABSTRACT

It is unclear if surveillance for postmenopausal women with medically inoperable stage 1 endometrial cancer (EC) should differ depending on their management strategy. Thus, we investigated the utility of surveillance endometrial sampling among 53 postmenopausal women with medically inoperable, clinical stage I, grade 1 endometrioid EC who received either progestin therapy or radiation between 2009 and 2018, at a single academic institution. Frequency and results of endometrial sampling, as well as recurrence and survival rates were studied. Of 53 patients, 18 (34.0%) received progestin therapy and 35 (66.0%) radiation. Medically managed patients were treated with megestrol acetate (27.7%), a levonorgestrel intrauterine device (27.7%), or both (44.4%). Radiated patients were mostly treated with high-dose rate brachytherapy only (77.1%). Surveillance endometrial sampling (median procedures = 4, range 1–10) was strictly adhered to among all patients who received progestin therapy, but infrequently (6/35, 17.1%) performed among radiated patients, yielding no positive results. Three recurrences occurred over the median follow-up of 38 months. Two (11%) women in the progestin therapy group recurred locally and were diagnosed by endometrial sampling. One (3%) patient in the radiation group recurred distally in the lung 25.3 months after completing brachytherapy. We conclude that appropriate surveillance for women with medically inoperable, clinical stage I, grade 1 EC depends on the management strategy. For those treated with progestins, surveillance with endometrial sampling every 3–6 months can reveal local recurrence. However, given the excellent local control after radiation, endometrial sampling may not be warranted for women treated with definitive radiation.

1. Introduction

While incidence rates for many cancers are decreasing, endometrial cancer (EC) has risen over 1% each year resulting in 11,000 deaths annually (National Cancer Institute, 2018). The current standard of care for early stage EC is hysterectomy with surgical staging. However, 10% of patients with newly diagnosed EC are not surgical candidates (Network NCC, 2018). Medical management with progestin therapy and definitive radiation therapy (RT) have been validated as nonsurgical treatment options for medically inoperable patients, but risks for recurrence, cancer-specific mortality, and overall mortality are poorly understood, leaving clinicians with little evidence to guide surveillance in this patient population (Network NCC, 2018).

The goal of surveillance is to identify recurrence before symptoms occur, when interventions may improve quality or duration of life. Thus, the disparate recurrence rates that clinical stage I EC patients face based

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on their treatment(s) (progestin therapy – 20%; RT – 18% vs. hysterectomy – 5%) (Baker et al., 2012; Podzielinski et al., 2012; Sasada et al., 2018; Acharya et al., 2016) suggests that endometrial sampling should be tailored to their management strategy. Unfortunately, there is limited published data to support development of evidence-based guidelines on the role of endometrial sampling during surveillance exams for postmenopausal women with medically inoperable, clinical stage I EC. Recommendations for this vulnerable population were not included in the Society of Gynecologic Oncology (SGO) position statement on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies (Salani et al., 2017). The National Comprehensive Cancer Network provides general guidance for surveillance for all EC survivors without distinguishing differences based on recurrence risk or patterns of recurrence (Network NCC, 2018). The one exception is the algorithm on women who meet criteria for fertility-sparing management of their EC. Though one may extrapolate and apply these recommendations to postmenopausal, medically inoperable women who undergo progestin therapy or RT, the role of surveillance endometrial sampling in this population is unclear.

Our objectives were two-fold. First, we set out to describe how endometrial sampling is utilized by gynecologic oncologists during surveillance for postmenopausal, medically inoperable stage I grade 1 EC patients. Second, we aimed to describe recurrence patterns among those who responded to initial treatment with progestin therapy or definitive RT.

2. Methods

We conducted a single institution case series of our experience with endometrial sampling for surveillance of recurrence in patients with medically inoperable, clinical stage I grade 1 endometrioid EC. All surveillance exams were performed by faculty or fellows within the Division of Gynecologic Oncology at Washington University School of Medicine. Individualized risk assessments for perioperative morbidity and mortality were performed by the treating gynecologic oncologist and patients were deemed medically inoperable if these risks outweighed the benefit of surgical staging. Before initiation of our study, all investigations were reviewed and approved by Washington University's Human Research Protection Office (IRB #201903117).

We identified postmenopausal women diagnosed with clinical stage I grade 1 endometrioid EC between 2009 and 2018, and did not undergo primary surgery for treatment of their cancer. Patients were identified by ICD-9 or ICD-10 procedure code(s) for endometrial biopsy and/or dilation and curettage. Endometrial sampling method (eg, number of passes or sample amount) was not standardized. Central pathology was performed by subspecialized gynecologic pathologist. Patients with grade 2 or 3 endometrioid EC or mixed malignancy were excluded. We also excluded patients who were deemed medically inoperable at time of their cancer diagnosis, but whose perioperative risk factors improved and they ultimately underwent hysterectomy. All patients in our case series underwent either progestin therapy or received RT at the Radiation Oncology Center Mallinckrodt Institute of Radiology at Washington University. Patients referred for definitive RT underwent axial imaging with pelvic magnetic resonance imaging (MRI) or computed tomography (CT) and were treated with high-dose rate (HDR) brachytherapy ± pelvic external beam RT for those with evidence of deep myometrial invasion. Patients (n = 2) who initially received progestin therapy for their EC and then underwent salvage RT for either refractory or recurrent carcinoma were classified under the progestin therapy group.

Records were reviewed for demographic information, medical comorbidities, pathology, number and results of surveillance endometrial biopsies, as well as recurrence and survival rates. Recurrence was based on pathologic diagnosis of endometrial adenocarcinoma or imaging. Patients were followed from time of diagnosis until loss to follow-up, death, or time of analysis. The primary outcome was number of surveillance endometrial sampling and the incidence of positive results. Secondary outcomes included recurrence patterns and survival outcomes. Differences between treatment groups were compared using χ^2 test, Fisher's exact tests or Student's *t* test as appropriate. A p-value of <0.05 was considered statistically significant.

3. Results

We identified 53 postmenopausal women with clinical stage I grade 1 endometrioid EC between 2009 and 2018, who had a documented evaluation by their treating gynecologic oncologist stating that they were medically unfit to undergo surgical staging. Eighteen (34.0%) of these women received progestin therapy and the remaining thirty-five (66.0%) inoperable patients received definitive RT. There were no differences in patient demographics based on treatment group (Table 1). Median body mass index was 54.1 kg/m^2 (IQR 41.4–63.4) and most had obesity-related comorbidities such as diabetes mellitus (58.5%) and hypertension (86.8%). Reasons for not being surgical candidates included obesity (73.5%) or a cardiopulmonary diagnosis (62.2%) followed by poor performance status (22.6%) or a recent cerebrovascular accident (7.5%). Fifty-one (96.2%) patients had imaging prior to treatment to confirm their clinical stage—most frequently this was either by MRI (66.0%) or CT scan (30.2%).

3.1. Utilization of endometrial sampling

All patients who underwent progestin therapy had surveillance endometrial sampling (median procedures = 4, range 1–10). Two women (11.1%) were refractory to medical management, including one

Table 1
Patient Demographics and Clinical Characteristics.

Variable	Progestin Therapy (N = 18) n (%)	Radiation Therapy (N = 35) n (%)	P-value
Age (median, IQR)	61.2 (56.0, 72.1)	62.5 (57.8–70.1)	0.56
Race			0.89
White	15 (83.3)	28 (84.8)	
Black	3 (16.7)	5 (15.2)	
Ethnicity			0.64
Hispanic	1 (6.2)	1 (3.3)	
Non-Hispanic	15 (93.8)	29 (96.7)	
Diabetes	10 (55.6)	21 (60.0)	0.39
Hypertension	17 (94.4)	29 (82.9)	0.23
BMI (kg/m^2) (median, IQR)	58.5 (38.9, 62.6)	53.8 (41.4–63.4)	0.462
Tobacco			0.44
Never	10 (55.6)	11 (31.4)	
Former	8 (44.4)	22 (62.9)	
Current	0	2 (5.7)	
Alcohol user	4 (66.7)	6 (17.1)	0.81
Hormones			N/A
LNG-IUD	5 (27.7)		
Megestrol Acetate	5 (27.7)		
LNG-IUD/Megestrol Acetate	8 (44.4)		
*			
Radiation			N/A
HDR Brachytherapy + EBRT		7 (20.0)	
HDR Brachytherapy Only		28 (80.0)	
Brachytherapy			N/A
Tandem and Ovoid (T&O)		3 (8.6)	
Simon-Heyman Capsules &		29 (82.9)	
T&O		3 (8.6)	
Y-Applicator			

IQR, interquartile range; BMI, body mass index; kg, kilogram; m, meters; LNG, levonorgestrel; IUD, intrauterine device; HDR, high-dose rate; EBRT, external beam radiotherapy.
Listed as Median and interquartile ranges
Missing values were excluded from the denominator of the percentages.
* One patient also received concomitant letrozole.

who reported vaginal spotting, but otherwise was asymptomatic. Pelvic ultrasound was not utilized in either case and both underwent endometrial biopsy which confirmed persistent grade 1 disease after 6 and 12 months respectively. Both were salvaged with definitive HDR brachytherapy. With regards to the radiated cohort, only 6 (17.1%) patients underwent surveillance endometrial sampling (median procedures = 1, range 1–4). Of these 6 patients, 5 had endometrial samples that were evaluable. One patient was not able to be sampled, even under anesthesia with ultrasound guidance due to significant vaginal synechiae. Of the 5 patients who had evaluable pathology, 3 had documentation of fibrinous or necrotic tissue, consistent with prior radiation.

3.2. Recurrence and follow-up

Median follow-up was 29.0 ± 26.0 months for those receiving progestin therapy compared to 28.7 ± 25.0 months after RT (P = 0.48). Table 2 provides a clinical summary of the 3 medically inoperable EC patients who recurred – 2 (11%) were treated with progestin and 1 (3%) with definitive RT (P = 0.22). All women who experienced recurrence in the progestin therapy group were asymptomatic, recurred locally, and were diagnosed by surveillance endometrial sampling by pipelle. The first patient achieved a complete response after 14 months of the levonorgestrel intrauterine device (LNG-IUD), but recurrence was detected 3 months later. Her IUD was continued and her cancer resolved 3 months later and she remains without evidence of disease. The other patient who failed progestin therapy had an endometrial biopsy that showed rare microscopic foci of endometrioid adenocarcinoma after 12 months of LNG-IUD and megestrol acetate, and ultimately had complete resolution after 24 months. One year later, endometrial pipelle diagnosed local recurrence and she underwent salvage RT and is alive without disease. The one patient who recurred after definitive RT had lung metastasis 25.3 months after completing HDR brachytherapy. She received hormonal therapy for her recurrence and ultimately died of disease 4.2 years from her initial diagnosis. The overall mortality rate was 5.7% – 1 patient (1.9%) in the RT group was dead of disease and the remaining (N = 2, 3.8%) died due to cardiopulmonary comorbidities.

4. Discussion

In this study, endometrial sampling during post-treatment surveillance of medically inoperable clinical staged I grade 1 EC patients is inconsistently utilized by gynecologic oncologists. Albeit a small case series, our results add value to a growing literature on medically inoperable patients by comparing clinical outcomes of postmenopausal women who received either progestin therapy or RT. Our data supports that appropriate surveillance for women with medically inoperable, clinical stage I, grade 1 EC depends on the management strategy given differences in local control. Given the excellent local control after RT, endometrial sampling may be omitted for asymptomatic women treated with definitive RT. However, for those treated with progestins, surveillance with endometrial sampling every 3–6 months is appropriate. In our study, all recurrences in the progestin group were diagnosed in asymptomatic women and detected through surveillance endometrial sampling with pipelle. Whether endometrial sampling changes disease-specific survival, or just adds lead-time bias in this highly-comorbid population is an important question that remains to be addressed in a larger prospective trial.

Though treatment of EC by progestin therapy is largely based on studies of younger women desiring future fertility, our study, along with others, suggests there may also be a role for progestin therapy to treat postmenopausal women if RT is not feasible or desired (Baker et al., 2012; Staples et al., 2018). Macchia and colleagues reported on 9 women aged ≥65 years treated with LNG-IUD followed by palliative radiation (30 Gy) and showed a high bleeding remission rate of 88.8% (Macchia et al., 2016). Median follow-up was 20 months, but they did not report recurrence or survival data. Baker et al showed complete response rates of 50% attained by women with either atypical endometrial hyperplasia (n = 20) or grade 1 EC (n = 16) treated with LNG-IUD (Baker et al., 2012); yet, 4 of the 18 women who achieved a complete response later relapsed. Based on their experience of few women (n = 1) developing bleeding with recurrence, they favored surveillance biopsies following response to LNG-IUD; the exception being those women whose goals were palliation of symptoms.

Furthermore, Staples et al reported on 51 obese patients with stage I-II EC, all grades, with mean age of 66 and mean BMI of 49.0 kg/m^2 (Staples et al., 2018). Though likely underpowered, their response rates were notably lower for women treated with hormonal therapy compared to RT (38.1% vs. 63.6%, p = 0.063). This mirrors our study results, though we admittedly have a lower risk population. Nevertheless, both our study and theirs lack consistent endometrial sampling. Staples and colleagues disclosed that of the 25 patients who responded to initial treatment, 15 (60%) were deemed to have complete responses based on documented exams though not confirmed by biopsy.

As our population ages and the obesity epidemic continues,

Table 2
Summary of medically inoperable clinical stage I grade 1 endometrial cancer patients who recurred.

Age *	Contra-indication for surgical staging	Clinical Stage	Treatment	Endometrial sampling every 3 months?	# of endometrial sampling before negative result/Total # of sampling	How recurrence was detected	Time to recurrence after negative biopsy (months)	Site of recurrence	Treatment of recurrence	Follow-up from diagnosis (y)	Status
58	Obesity, Cardio-pulmonary, Poor PS	IA	LNG-IUD	Yes	2/8	Endometrial Biopsy	9.0	Uterus	Hormonal therapy	1.8	Alive
57	Obesity, Cardio-pulmonary	IA	LNG-IUD + Megestrol Acetate	No	4/6	Endometrial Biopsy	6.2	Uterus	Radiation	4.9	Alive
71	Cardio-pulmonary, Poor PS	IB	36 Gy HDR brachy only¥	N/A	N/A	CT scan	25.3 (from date of brachy completion)	Right lung†	Hormonal therapy	4.2	Dead of disease

PS = performance status; LNG-IUD = Levonorgestrel intrauterine device; HDR = high-dose rate; brachy = brachytherapy.
* Age at diagnosis.
¥ Simon-Heyman capsules and tandem and ovoid.
† This was suspected based on interval increase in size of pulmonary nodules visualized on CT scan of the chest taken 8.2 months apart. Not amenable to CT-guided biopsy and patient too unhealthy to undergo a video-assisted thoracoscopic surgery.

examining survival and recurrence outcomes among postmenopausal women treated with progestin therapy versus definitive RT is important. The median BMI of 54.1 kg/m^2 in our cohort is an alarming reminder that effective and accessible weight management strategies for inoperable EC patients are likely underutilized. Progestin therapy may effectively stabilize EC, but is associated with weight gain (Cholakian et al., 2016). As obesity remains an independent predictor of mortality for women with EC (Calle et al., 2003) and weight loss can reverse endometrial pathology (Argenta et al., 2013), further study of how to treat obesity while managing EC is needed.

We acknowledge other limitations in our study related to its retrospective study design and small sample size. Though all patients were evaluated by a gynecologic oncologist and felt that perioperative risks outweighed the benefits of surgical staging, there remained heterogeneity in the definition of medically inoperable, as well as pre-treatment diagnostic imaging and management strategy. Consistent with other observational studies on medically inoperable EC patients, we confirmed the practical challenges of inconsistent endometrial sampling during surveillance visits, as well as possible sample error. Given our small case series, it was not feasible to match based on propensity score to reduce selection bias for treatment modality. Nevertheless, our data lend support for providers to consider patient adherence to cancer care follow-up when recommending treatment for medically inoperable EC patients. Although RT provides excellent local control, this treatment may be considered less feasible due to financial, social, or even physical constraints, not to mention patients' emotional stress, including issues related to sexual health. The unique considerations to each management strategy must be individualized to patients' goals of care and level of comfort.

5. Conclusions

Appropriate surveillance for women with clinical stage I grade 1, medically inoperable EC depends on the management strategy. RT provides such excellent local control that post-treatment endometrial sampling may be safely omitted in asymptomatic women after definitive RT. Secondly, patients undergoing progestin therapy were more likely to recur locally and should undergo surveillance with endometrial sampling according to the schedule recommended by the NCCN guidelines. Given overall poor compliance with endometrial sampling, adherence to follow-up should be considered when determining initial treatment for patients with medically inoperable EC. A multi-centered trial is warranted to assess generalizability of our findings to improve outcomes for this vulnerable population.

Author contributions

1. Angelina Carey-Love, M.D.: Lead author who performed the data collection and entry, IRB submission, project design, and manuscript writing.
2. Mary Mullen, M.D.: Performed the data collection and entry, IRB submission, project design, and manuscript writing.
3. Abigail Zamorano, MD, MPH: Assisted with manuscript revisions and approval of final submitted version.
4. Stephanie Markovina, M.D., PhD: Assisted with manuscript revisions and approval of final submitted version.
5. Andrea Hagemann, M.D.: Assisted with project conception, manuscript revisions, and approval of final submitted version.
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8. Matthew Powell, M.D.: Assisted with manuscript revisions and approval of final submitted version.
9. David Mutch, M.D.: Assisted with manuscript revisions and approval of final submitted version.
10. Lindsay Kuroki, M.D., M.S.C.I: Senior author involved with study design, manuscript writing and revisions, and approval of final submitted version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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