

Nonsurgical management of early-stage endometrial cancer due to obesity: a survey of the practice patterns of current Society of Gynecologic Oncology members

Aparna Kailasam^{*}, Giuseppe Cucinella¹, Angela J Fought, William Cliby, Andrea Mariani, Gretchen Glaser, Carrie Langstraat

Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States

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ABSTRACT

Objective: Nonsurgical management for endometrial cancer in patients with class 3 obesity ($\text{BMI} \geq 40 \text{ kg/m}^2$) is a challenging scenario given lack of consensus on patient selection and treatment options. Our objective was to evaluate trends in practice patterns and physician opinions in the Society of Gynecologic Oncology (SGO) on nonsurgical management of endometrial cancer and complex atypical hyperplasia due to obesity.

Methods: An online survey was sent to all gynecologic oncologist members of the SGO with questions centered on decision-making for nonsurgical approaches for patients with class 3 obesity patients. Fisher's exact tests were used to assess the associations between offering nonsurgical management and geographic region, practice type, and time in practice.

Results: 255 (19.8 %) members from 6 geographic regions responded, of which 183 (71.8 %) offered primary nonsurgical management of endometrial cancer to patients with class 3 obesity and 72 (28.2 %) do not. The choice to offer initial nonsurgical management did not vary based on geographic region, time in practice or practice type. When asked to select BMI cutoff, the majority (65.2 %) started to offer nonsurgical management was BMI 60–64 kg/m^2 . Progesterone intrauterine device was the preferred treatment (68.3 %, 125/183). Of those who offered nonsurgical management, 97.3 % (178/183) recommended resampling in 3–6 months.

Conclusion: Primary nonsurgical management of endometrial cancer in patients with class 3 obesity is offered by most gynecologic oncologists in SGO. However, almost one-third of gynecologic oncologists indicated they do not offer nonsurgical management for endometrial cancer for obesity alone. Additional data are needed to determine the safety of both approaches in these complex patients.

1. Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States with approximately 61,000 cases treated every year (SEER, 2022). With most cases being early stage, the standard of care for treatment as determined by the National Comprehensive Cancer Network (NCCN), involves surgical staging with a cure rate of 95 % (National Cancer Center Network, 2022). The precursor to endometrial cancer, complex atypical hyperplasia (CAH)/ endometrial intraepithelial neoplasia (EIN), carries a 40 % risk of coexisting endometrial cancer at the time of diagnosis and up to 29 % risk of progression to

carcinoma if left untreated (Vetter et al., 2020). Unfortunately, not all patients are candidates for surgical management. Several reasons may preclude a patient from undergoing surgical treatment, including medical comorbidities, a desire to maintain fertility, and an increasing incidence of class 3 obesity (body mass index [BMI] $\geq 40 \text{ kg/m}^2$), the subject of the present study (Vetter et al., 2020; Baker et al., 2012).

In considering patients for nonsurgical management of endometrial cancer, NCCN offers guidelines only for patients desiring fertility preservation. Based on NCCN guidelines, most evidence suggests nonsurgical management of early-stage endometrial cancer is safe, if all of the following criteria are met: well-differentiated (grade 1) endometrioid

^{*} Corresponding author.

E-mail addresses: Kailasam.Aparna@mayo.edu (A. Kailasam), giusepppecucinella@outlook.com (G. Cucinella), Fought.Angela@mayo.edu (A.J. Fought), Cliby.William@mayo.edu (W. Cliby), Mariani.Andrea@mayo.edu (A. Mariani), Glaser.Gretchen@mayo.edu (G. Glaser), Langstraat.Carrie@mayo.edu (C. Langstraat).

¹ Present address and affiliation: Department of Surgical, Oncological and Oral Sciences (Di.Chir.On.S.), University of Palermo, Palermo, Italy.

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adenocarcinoma confirmed by expert pathology review, disease limited to endometrium on MRI (preferred) or transvaginal ultrasound, absence of suspicious or metastatic disease on imaging, no contraindications to medical therapy or pregnancy, and counseling that fertility-sparing option is not the standard of care for the treatment of endometrial cancer (National Cancer Center Network, 2022). While this approach is well established for fertility sparing treatment, similar criteria do not exist specifically relating to patients with comorbidities or class 3 obesity.

For patients with class 3 obesity there are safety concerns related to surgical management and an increased need for conversion from minimally invasive to open procedures (Bernardini et al., 2012; Blikkendaal et al., 2015; Al Sawah et al., 2018). The adequacy of staging is also likely compromised for these patients (Bernardini et al., 2012; Blikkendaal et al., 2015; Al Sawah et al., 2018). Although nonsurgical management represents an alternative for patients with class 3 obesity, there is considerable heterogeneity in treatment options (i.e. oral hormone therapy, intrauterine devices, radiation). Retrospective studies as well as phase II clinical trials have demonstrated that 47–75 % of cases of endometrial cancer and CAH/EIN will have complete regression with progesterone therapy alone with factors such as grade and myometrial invasion being known to affect response (Baker et al., 2012; Janda et al., 2021; Pal et al., 2018; Levine et al., 2013). While this is certainly not as high as the disease control rates seen in surgery, it is a reasonable alternative when surgery presents substantial risks. The objective for this study is to identify specific criteria that most gynecologic oncologists use when deciding to offer a patient nonsurgical management and to determine whether this varies between academic and non-academic institutions or by geographic location.

2. Methods

After receiving IRB approval, an anonymous, non-validated, online electronic survey was sent to all gynecologic oncologist members of the Society of Gynecologic Oncology (SGO) in 2022. A preliminary survey was conducted initially among program directors in SGO, where program directors were asked to respond on behalf of their group. These survey responses helped to direct the final survey that was sent to all SGO members. This final survey was not sent to the initial group of program directors. The list of email addresses of member gynecologic oncologists was obtained with permission directly from SGO. The survey was adaptive based on responses and contained up to 21 questions (Table 1). Three emails were sent over the span of a month for recruitment in May 2022. Study data were collected and managed using REDCap electronic data capture tools hosted at Mayo Clinic (made available by funding from grant UL1TR002377). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies.

Respondents were asked to categorize themselves based on geographic region, practice type (academic, private-rural, private urban and academic-affiliate) and time in practice. Participants were also asked a series of questions focused on the non-surgical management of patients with class 3 obesity. The terms “morbid obesity” and “morbidly obese” were used in the survey, but class 3 obesity will be used for the purpose of this manuscript as this is the latest definition used by the Centers for Disease Control and Prevention (CDC – National Center for Health, 2023). Survey respondents were asked questions in the following categories: amount of experience in nonsurgical management of endometrial cancer/CAH/EIN, reasons for opting against surgical management, specific BMI cutoff ranges that were used, pretreatment procedures (imaging, biopsies), preferred nonsurgical management therapy, and follow up practices (length of follow for biopsies, imaging obtained). Sixteen questions allowed selection of only one answer, while eight questions allowed participants to select multiple answer choices. The survey questions are included in Table 1. When given increments of 5 for BMI starting at 40 kg/m², respondents were advised to select the

cutoff at which they would offer nonsurgical management primarily.

Statistical analysis was performed using the SAS version 9.4 software package. Survey responses were summarized using frequency and percentage for surgeon and practice characteristic. Responses were summarized overall and stratified by if the surgeon provides nonsurgical management. Fisher’s exact tests were performed to test if there was any difference in the relationships between if the surgeon provided nonsurgical management and time in practice, geographic region for the practice, and practice type. All tests were two-sided and considered statistically significant if less than 0.05.

3. Results

A total of 255 (19.8 %) out of the 1288 gynecologic oncologist members of SGO from 6 geographic regions responded. Respondents also spanned all four types of institutions, with 58.4 % (149/255) comprising academic centers. For the entire cohort, 183 (71.8 %) respondents offered primary nonsurgical management of endometrial cancer to patients due to class 3 obesity and 72 (28.2 %) did not. Demographics and reason for not offering nonsurgical management were the only data collected from participants who did not offer nonsurgical management of endometrial cancer. Six participants did not answer all questions. The baseline demographics of the respondents are shown in Table 2. For those who did not offer nonsurgical management, 55.6 % (40/72) were concerned about persistent disease without definitive surgical management. Of those who do offer nonsurgical management, 47 % (86/183) stated that they do so for about 1–3 cases of endometrial cancer annually with 32.2 % (59/183) stating that they offer nonsurgical management for 4–6 cases annually. Most respondents (55.7 %, 102/183) who offered nonsurgical management, reported that they treated less than 100 cases of endometrial cancer annually. When considering a “cutoff” for which the respondent would consider offering nonsurgical management, approximately 30 % started to offer nonsurgical management at BMI 60–64 kg/m² (Fig. 1). Cumulatively, two-thirds of respondents offered nonsurgical management at BMI 60–64 kg/m² or below (Fig. 1).

Table 3 outlines pretreatment factors that were considered when selecting candidates for nonsurgical management. The majority 54.6 % (100/183) performed hysteroscopy, dilation and curettage prior to initiating treatment. The vast majority also obtained a pelvic MRI to assess for depth of myometrial invasion prior to starting treatment 85.8 % (157/183). This is consistent with recommendations by the NCCN for fertility management. Most respondents offered nonsurgical management for grade 1 endometrioid endometrial cancer with less than or equal to 50 % myometrial invasion. A small subset of respondents offered nonsurgical management for high grade cancers as well. However, this was not the focus of this survey and we did not ask about management options for high grade. Further, when asked to select which molecular markers were used to determine if patients may undergo nonsurgical management, the majority 57.1 % (104/182) of respondents did not use molecular markers, while 25.8 % (47/182) used mismatch repair/microsatellite instability (MMR/MSI), 4.4 % (8/182) used POLE, and 15.4 % (28/182) used p53. Hormonal markers such as estrogen receptor (ER) and progesterone receptor (PR) were used to determine candidacy for nonsurgical management by 29.7 % (54/182) of respondents.

Table 4 lists treatment preferences for respondents. Intrauterine device was the preferred treatment option (68.3 %, 125/183). Respondents who selected oral progesterone were asked to select preferred progesterone, with most indicating that they would opt for megestrol acetate. Of those who offer hormonal management, 97.3 % (178/183) stated that they would resample again in 3–6 months. Regarding weight loss strategies, most respondents (82 %) indicated that they would recommend bariatrics referral for these patients (Table 4). Other options listed for respondents to select on the survey included informal counseling, nutritionist referral, endocrine referral, and weight loss

Table 1

Survey Questions.

The goal of this survey is to understand how morbid obesity impacts your primary management options for presumed stage 1 EC and CAH/EIN.

In particular, we are interested if you use nonsurgical initial strategies with simultaneous efforts at weight loss to reduce surgical morbidity.

Note:

EC = endometrial cancer

CAH = complex atypical hyperplasia

EIN = endometrial intraepithelial neoplasia

Thank you!

-
- 1 Do you offer initial nonsurgical management to patients with presumed stage 1 endometrioid EC or CAH/EIN due to morbid obesity?
- 1a If you answered no, what is your primary concern with proceeding with initial nonsurgical management?
- 1b If you selected other, please explain.
- 2 Approximately how many patients with EC or CAH/EIN do you offer initial nonsurgical management due to morbid obesity per year?
- 3 Approximately how many total patients with EC or CAH/EIN do you treat per year?
- 4 Please select the BMI range threshold at which you are more likely to offer initial nonsurgical management, while working on weight loss strategies.
- Yes
 - No
 - Progression of EC if left untreated in obese patients
 - Presence of micrometastasis
 - Other
 - None
 - 1 to 3
 - 4 to 6
 - 7 to 10
 - More than 10
 - < 100
 - 101–200
 - 201–300
 - 301–400
 - >400
 - 40–44
 - 45–49
 - 50–54
 - 55–59
 - 60–64
 - 65–69
 - 70–74
 - 75–79
 - 80+
-

5. Please rank in order (from most important to least important) your perioperative concerns for patients above your selected BMI range.

Anesthesia Concerns

Safety and feasibility in completing surgery minimally invasively

Risk of postoperative surgical complications

6 Please indicate which diagnostic procedure you perform prior to initiating nonsurgical management.

7 If considering initial nonsurgical management for patients with endometrioid EC or CAH/EIN and morbid obesity, what type of imaging do you prefer before MRI pelvis beginning therapy? (Please select all that apply)

7a If you selected other imaging, please specify

8 Which of the following molecular markers do you use in determining whether a patient may undergo initial nonsurgical management?

8a If you answered other markers, which markers do you use?

9 For which of the following histology types are you comfortable opting for initial nonsurgical management (choose all that apply)?

[Assume stage 1 and morbid obesity]

10 In stage I endometrioid EC patients, up to what % of myometrial invasion by imaging are you comfortable treating with initial hormonal therapy for morbid obesity?

11 In addition to weight loss, what is your preferred method of initial nonsurgical management for morbidly obese patients with stage I endometrioid EC or CAH/EIN?

11a Please indicate which oral progesterone you prefer to use.

11b If you indicated other management, please specify.

Hysteroscopy + Dilation and curettage

Dilation and curettage only

Endometrial biopsy only

CT abdomen/pelvis

PET/CT

Transvaginal USN

Other

MMR / MSI testing

POLE

p53

ER/PR

None

Other

Complex atypical hyperplasia/Endometrial intraepithelial neoplasia

Grade 1 endometrioid carcinoma

Grade 2 endometrioid carcinoma

Grade 3 endometrioid carcinoma

Clear cell carcinoma

Papillary serous carcinoma

Carcinosarcoma

Precancer only (CAH/EIN)

No myometrial invasion

Up to 25 % invasion

26–50 % invasion

51–75 % invasion

76–100 % invasion

Oral progesterone

Intrauterine progesterone

Both oral and intrauterine progesterone

Other

Megace (megestrol acetate)

Prometrium (micronized progesterone)

Provera (medroxyprogesterone)

12. What is your approximate conversion rate from MIS to open surgery when performing surgical staging for each of the following BMI ranges?

	0–25%	26–50%	51–75%	76–100%	Unsure	Don't operate on this range
BMI < 50	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
BMI 51–60	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
BMI 61–70	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
BMI 71–80	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
BMI > 80	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

13 What weight loss management strategies do you use for this group of patients?

- Informal counseling on nutrition and exercise
- Nutritionist consultation
- Endocrine referral
- Bariatric referral
- Weight loss medication
- Other

13a If you selected other weight loss management, please explain.

14 When would you first resample a patient after hormone treatment initiation?

- Less than a month
- 1–2 months
- 3–6 months
- 7–12 months
- 1 year

15 What would you obtain at the first follow up in addition to endometrial sampling (select all that apply)?

- Imaging
- Labs
- Other

15a What type of imaging?

- CT abdomen/pelvis
- Transvaginal USN
- Pelvic MRI
- PET/CT

15b Which labs would you obtain?

- CBC
- BMP
- Ca-125

15c If you selected other above, please specify

Demographics

16 To which gender identity do you most identify?

- Male
- Female
- Transgender female
- Transgender male
- Gender variant/non-conforming
- Other
- Prefer not to answer

17 How would you define your racial identity? (Select all that apply)

- White or Caucasian
- Black or African American
- Asian
- Native American
- Native Hawaiian or Pacific Islander
- Other/Unknown
- Prefer not to say

18 What is your ethnicity?

- Hispanic
- Non-Hispanic
- Prefer not to say

19 How long have you been practicing?

- Less than 5 years
- 5 to 10 years
- 11 to 15 years
- 16 to 20 years
- More than 20 years

20 In which region do you practice?

- Northeast U.S. (MD, PA, NJ, NY, CT, MA, RI, VT, NH, ME)
- Southeast U.S. (FL, GA, AL, MS, AR, LA, TN, KY, SC, NC, VA, WV, DC, DE)
- Midwest U.S. (OH, MI, IN, IL, WI, MN, NE, MO, KS, IA, ND, SD)
- Southwest U.S. (AZ, TX, NM, OK)
- Western U.S. (CO, WY, MT, ID, UT, NV, CA, OR, WA)
- Alaska or Hawaii
- Canada
- Europe
- Australia
- Asia
- Africa
- Central/South America

21 How would you describe your practice setting?

- Private-Rural
- Private-Urban
- Academic Medical Center
- Private-Academic Affiliate

Table 2
Demographics of Survey Respondents.

Characteristics of SGO Members who Responded	Overall n = 255(% of each column)	Offer Primary Nonsurgical Management due to Class 3 Obesity, n = 183 (% of each row)	Do Not Offer Primary Nonsurgical Management due to Class 3 Obesity, n = 72(% of each row))
Gender Identity, n (%)			
Male	94 (36.9)	68 (72.3)	26 (27.7)
Female	153 (60.0)	108 (70.6)	45 (29.4)
Prefer Not to Say	8 (3.1)	7 (87.5)	1 (12.5)
Race			
White or Caucasian	202 (79.2)	148 (80.9)	54 (75.0)
Black or African American	3 (1.2)	2 (1.1)	1 (1.4)
Asian	26 (10.2)	15 (8.2)	11 (15.3)
Native American	2 (0.8)	1 (0.6)	1 (1.4)
Other/Unknown	7 (2.7)	5 (2.7)	2 (2.8)
Mixed	3 (1.2)	2 (1.1)	1 (1.4)
Prefer not to say	7 (2.7)	5 (2.7)	2 (2.8)
Missing	5 (2.0)	5 (2.7)	0
Geographic region, n (%)			
Northeast US	45 (17.6)	26 (57.8)	19 (42.2)
Southeast US	58 (22.7)	45 (77.6)	13 (22.4)
Midwest US	60 (23.5)	46 (75.0)	14 (23.7)
Southwest US	26 (10.2)	19 (73.1)	7 (26.9)
Western US	38 (14.5)	27 (73.0)	11 (28.9)
International	26 (10.2)	18 (69.2)	8 (30.8)
Missing	2 (0.8)	2 (1.1)	0
Time in Practice, n (%)			
< 5 years	74 (29.0)	47 (63.5)	27 (36.5)
5–10 years	61 (23.9)	47 (63.5)	14 (23.0)
11–15 years	36 (14.1)	28 (77.8)	8 (22.2)
16–20 years	27 (10.6)	17 (63.0)	10 (37.0)
More than 20 years	56 (22.0)	43 (76.8)	13 (23.2)
Missing	1 (0.4)	1 (0.6)	0
Practice Type, n (%)			
Private-Rural	9 (3.6)	6 (66.7)	3 (33.3)
Private-Urban	41 (16.2)	28 (68.3)	13 (31.7)
Academic Medical Center	149 (58.9)	110 (73.8)	39 (26.2)
Private-Academic Affiliate	54 (21.3)	37 (68.5)	17 (31.5)
Missing	2 (0.8)	2 (1.1)	0
Number of Endometrial Cancer Cases Managed with Nonsurgical Management Every Year			
None			3 (1.6)
1 to 3			86 (47.0)
4 to 6			59 (32.2)
7 to 10			20 (10.9)
More than 10			14 (7.7)
Missing			1 (0.6)
Total number of Endometrial Cancer Cases Treated per Year			
< 100			102 (55.7)
101 to 200			63 (34.4)
201 to 300			14 (7.7)
301 to 400			0 (0)
More than 400			1 (0.5)
Missing			3 (1.6)

medication.

There was no statistically significant relationship observed between geographic region ($p = 0.31$), length of time in practice ($p = 0.24$), practice type ($p = 0.78$) and whether the physician offered nonsurgical management (Table 2).

4. Discussion

This study summarizes practice patterns of members of the SGO. Primary nonsurgical management of endometrial cancer in patients with class 3 obesity was offered by most gynecologic oncologists in SGO. This finding did not vary based on practice location, practice type and length of time in practice. The respondents to this survey indicated that when considering nonsurgical management for patients with class 3 obesity, most followed the same guidelines recommended by NCCN for patients choosing to maintain fertility (such as obtaining a pretreatment MRI and resampling in 3–6 months). Intrauterine device as the preferred treatment option. We observed a threshold BMI of 60–64 kg/m², at which two-thirds of gynecologic oncologists offered nonsurgical management over surgery, with most also recommending weight-loss strategies.

While several studies have looked at fertility preservation, there is a dearth of guidance in nonsurgical approaches of endometrial cancer in patients with class 3 obesity specifically. Since our study was started, a similar investigation was published in Europe surveying respondents in the European Network of Young Gynaecological Oncologists (ENYGO) database with the goal of addressing similar issues (La Russa et al., 2018). The preferred treatment in this setting was intrauterine device according to SGO respondents compared to preferred use of oral progesterone in the La Russa study (La Russa et al., 2018). Of note, we did not include an option for respondents to indicate hysteroscopic resection prior to IUD placement, noted to be the recommended approach by the 2022 ESGO/ESHRE/ESGE guidelines for fertility sparing treatment of patients with endometrial cancer (Rodolakis et al., 2023). These guidelines were released after this survey was sent. Another important difference is that the European study did not specifically have questions centered around BMI and obesity, whereas the main purpose of our study was to look at those patients with early-stage endometrial cancer and class 3 obesity (La Russa et al., 2018).

A natural corollary to nonsurgical management in patients with class 3 obesity is attempted weight loss to improve the risk:benefit ratio for a future surgical approach or improve response to progesterone. A prospective study coupling progesterone use with weight loss interventions in patients who have endometrial cancer/CAH/EIN as well as BMI ≥ 35 kg/m² found that patients achieving weight loss of 10 % of their body weight were more likely to have response at 12 months than those who did not (Barr et al., 2021). Given that obesity is a multifactorial problem, this survey certainly emphasizes the importance of a multidisciplinary approach. A previous quality improvement study at Mayo Clinic showed that a multidisciplinary team is helpful in increasing discussion about obesity as well as referral to appropriate weight loss clinics in patients with low-risk endometrial cancer (Torres et al., 2019). Given how many respondents indicated that they would recommend bariatric referral, there may be a role for a specific gynecologic oncology clinic that partners with bariatric surgeons for this group of patients. Further research in combining weight loss strategies and bariatrics may clarify the role of these approaches in treating patients with endometrial cancer and CAH/EIN who are not initially surgical candidates.

Another area of interest for this study was to explore the utility of biomarkers as well as the new endometrial cancer molecular classification (i.e. POLE, mismatch repair, p53) in driving decision making for patients with endometrial cancer and CAH/EIN to undergo nonsurgical management. Interestingly, most respondents indicated that molecular biomarkers do not play a role in their decision for offering nonsurgical management, particularly with POLE only being used by 8 (4.4 %) respondents. Several studies have attempted to evaluate the role of molecular subclassification of endometrial cancer and the response rate to intrauterine device, and so far, studies have had too few samples to demonstrate a difference in response rate (Pal et al., 2018; Westin et al., 2021). However, Westin et al. did demonstrate that progesterone decidualization effect was positively associated with complete response to IUD (Westin et al., 2021). This may push for obtaining ER/PR testing prior to offering nonsurgical management. Notably, our study was

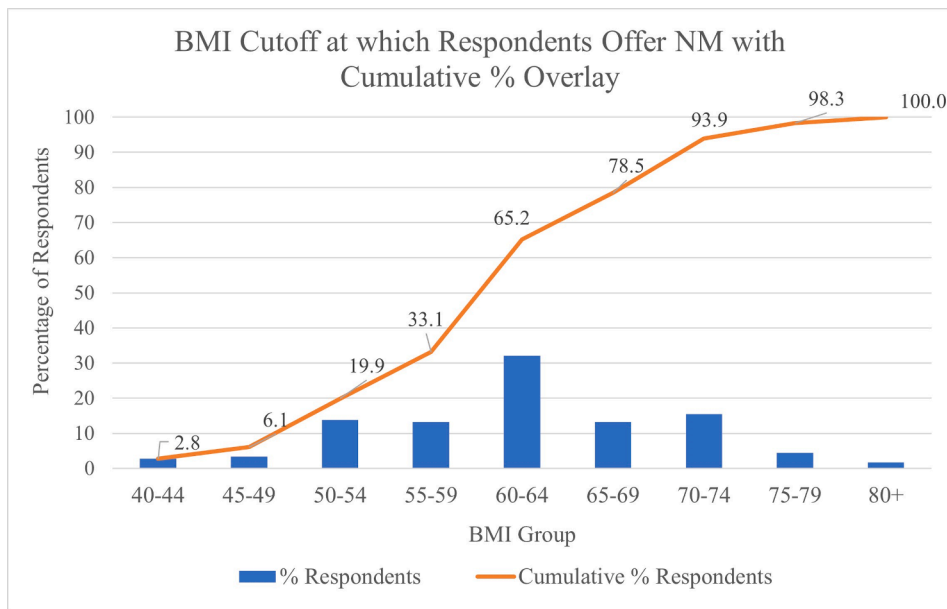


Fig. 1. Of respondents who indicated that they do offer nonsurgical management, this figure lays out the BMI cutoff at which they would first offer nonsurgical management (n = 183).

Table 3
Pretreatment Factors (n = 183 unless specified select all that apply).

Pretreatment Evaluation	Variables	Respondents (%)
Preoperative Sampling	Hysteroscopy D&C	100 (54.6)
	D&C alone	42 (23.0)
	Endometrial biopsy	38 (20.8)
	Missing	3 (1.6)
Imaging Obtained prior to Treatment (Select all that apply)	CT abdomen/pelvis	53 (29.1)
	Transvaginal ultrasound	7 (3.8)
	Pelvic MRI	157 (86.3)
	PET CT	29 (15.6)
Histologies for which respondents offer nonsurgical management (Select all that apply)	Other	6 (3.3)
	CAH/EIN	180 (98.9)
	Grade 1 EEC	178 (97.8)
	Grade 2 EEC	43 (23.6)
	Grade 3 EEC	3 (1.6)
	Clear cell carcinoma	3 (1.6)
	Papillary serous carcinoma	3 (1.6)
Nonsurgical management offered up to what % myometrial invasion? (n = 182)	Carcinosarcoma	3 (1.6)
	CAH/EIN only	0 (0)
	No myometrial invasion	109 (59.6)
	1–25 %	30 (16.4)
	26–50 %	42 (23.0)
	51–75 %	1 (0.6)
	76–100 %	0 (0)
Molecular markers used in determining whether a patient may undergo initial nonsurgical management (Select all that apply, n = 182)	Missing	1 (0.6)
	MMR/MSI	47 (25.8)
	POLE	8 (4.4)
	p53	28 (15.4)
	ER/PR	54 (29.7)
	None	104 (57.1)
	Other	4 (2.2)
Missing	1 (0.5)	

*EEC = endometrioid endometrial cancer, MMR = mismatch repair, MSI = microsatellite instability, ER = estrogen receptor, PR = progesterone receptor.

conducted in May 2022 prior to the release of the 2023 FIGO staging for endometrial cancer, which do incorporate molecular classification into staging (Berek et al., 2023). If this survey were to be repeated, we hypothesize that more respondents would indicate that they do use

Table 4
Treatment Factors (n = 183 unless specified select all that apply).

Pretreatment Evaluation	Variables	Respondents (%)
Treatment Strategy	Oral progesterone	9 (4.9)
	Intrauterine progesterone	125 (68.3)
	Both oral and intrauterine progesterone	47 (25.7)
	Other	2 (1.1)
If oral progesterone selected, preferred agent	Megestrol acetate	7 (3.8)
	Micronized progesterone	0 (0)
	Medroxyprogesterone	2 (1.1)
	Missing	174 (95.1)
Preferred Weight Loss Management Strategies (select all that apply)	Informal counseling	117 (63.9)
	Nutritionist	138 (75.4)
	Endocrine referral	30 (16.4)
	Bariatric referral	150 (82.0)
	Weight loss medication	18 (9.8)
When to first resample	Other	5 (2.7)
	Less than a month	0 (0)
	1–2 months	2 (1.1)
	3–6 months	178 (97.3)
	7–12 months	3 (1.6)
>1 year	0 (0)	

molecular classification.

One of the strengths of this paper is that it surveys gynecologic oncologists from a wide variety of practices across the United States. Since criteria for guiding nonsurgical management treatment remains a gray area, this paper illuminates general trends among gynecologic oncologists in the US when selecting patients who should receive primary nonsurgical management of CAH/EIN and grade 1 endometrial cancer. A prospective study evaluating various conservative management options may further guide the ideal treatment for this group of patients.

We recognize that there are limitations to this study. The first is that this was a nonvalidated survey completed within the SGO, and may not be representative of all practices. Our response rate of 19.8 % was low with a disproportionate number of responses from individuals in academic practices, which also suggests that the observations may not be generalizable to practice patterns for all gynecologic oncologists.. Another limitation was that we did not include hysteroscopic resection followed by IUD as an option in treatment management, and if this study

were to be expanded in the future, especially internationally, we would be interested in assessing how frequently respondents offer this. This is especially true given the current ESGO/ESHRE/ESGE guidelines. In this study, we also did not seek to evaluate what other factors might impact a respondent's choice of nonsurgical management specifically regarding the role of equity. We queried respondents about their demographics, but did not ask about the impact of patient insurance status, race/ethnicity on the decision to opt for nonsurgical management.

Future directions to consider regarding nonsurgical management is a combined approach with hormonal therapy and other modalities. For example, the feMMe trial reported responses of CAH and endometrial cancer to intrauterine progesterone in addition to interventions including metformin and weight loss (Hawkes et al., 2014). Unfortunately, the study was not powered to show a difference between the arms, but all three arms demonstrated reasonable response to progesterone treatment. Other studies have demonstrated serum and molecular changes which may help to reverse carcinogenesis in endometrial cancer (Soliman et al., 2016). Even if used as a single agent, most gynecologic oncologists in SGO agree that progesterone therapy is safe in patients who have nonsurgical management and there seems to be a low risk of progression (Pal et al., 2018; Westin et al., 2021). One treatment paradigm to consider is to treat patients at least temporarily with progesterone, supportive care and to facilitate weight-loss in the hope of eventually getting to surgery (Barr et al., 2021; Barr and Crosbie, 2020).

In conclusion, nonsurgical management with hormonal therapy is offered by most members of the SGO in patients with CAH/EIN and grade 1 endometrial cancer with less than 50 % myometrial invasion. Most respondents agree on pretreatment testing. The observation that one-third of gynecologic oncologists do not offer nonsurgical management for endometrial cancer for obesity alone for low-risk women is interesting but may represent selection bias based on lower BMIs seen in those practices. Additional data are needed to determine the safety of nonsurgical management as well as surgical management in these complex patients and to further clarify standard of care.

CRedit authorship contribution statement

Aparna Kailasam: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Visualization, Writing – review & editing. **Giuseppe Cucinella:** Validation, Investigation, Data curation, Writing – review & editing. **Angela J Fought:** Formal analysis, Data curation, Visualization, Writing – review & editing. **William Cliby:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision. **Andrea Mariani:** Resources, Validation, Writing – review & editing. **Gretchen Glaser:** Validation, Writing – review & editing. **Carrie Langstraat:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision.

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.

References

- Al Sawah, E., Salemi, J.L., Hoffman, M., Imudia, A.N., Mikhail, E., 2018. Association between Obesity, Surgical Route, and Perioperative Outcomes in Patients with Uterine Cancer. *Minimally Invasive Surgery*. 2018, 1–8.
- Baker, J., Obermair, A., GebSKI, V., Janda, M., 2012. Efficacy of oral or intrauterine device-delivered progesterin in patients with complex endometrial hyperplasia with atypia or early endometrial adenocarcinoma: a meta-analysis and systematic review of the literature. *Gynecol. Oncol.* 125 (1), 263–270.
- Barr, C.E., Crosbie, E.J., 2020. The Mirena coil is a suitable treatment of early-stage endometrial cancer in obese women: FOR: Careful selection and monitoring is key. *BJOG* 127 (8).
- Barr, C.E., Ryan, N.A.J., Derbyshire, A.E., Wan, Y.L., MacKintosh, M.L., McVey, R.J., et al., 2021. Weight loss during intrauterine progestin treatment for obesity-associated atypical hyperplasia and early-stage cancer of the endometrium. *Cancer Prev. Res.* 14 (11), 1041–1050.
- Berek, J.S., Matias-Guiu, X., Creutzberg, C., et al., 2023. FIGO staging of endometrial cancer: 2023. *Int J Gynecol Obstet.* 162, 383–394.
- Bernardini, M.Q., Gien, L.T., Tipping, H., Murphy, J., Rosen, B.P., 2012. Surgical Outcome of Robotic Surgery in Morbidly Obese Patient With Endometrial Cancer Compared to Laparotomy. *Int. J. Gynecol. Cancer* 22 (1), 76–81.
- Blikkendaal, M.D., Schepers, E.M., van Zwet, E.W., Twijnstra, A.R.H., Jansen, F.W., 2015. Hysterectomy in very obese and morbidly obese patients: a systematic review with cumulative analysis of comparative studies. *Arch. Gynecol. Obstet.* 292 (4), 723–738.
- CDC – National Center for Health, 2023. Statistics – Homepage.
- Hawkes, A.L., Quinn, M., GebSKI, V., Armes, J., Brennan, D., Janda, M., Obermair, A., 2014. Improving treatment for obese women with early stage cancer of the uterus: rationale and design of the levonorgestrel intrauterine device ± metformin ± weight loss in endometrial cancer (feMME) trial. *Contemp. Clin. Trials* 39 (1), 14–21.
- Janda, M., Robledo, K.P., GebSKI, V., Armes, J.E., Alizart, M., Cummings, M., Chen, C., Leung, Y., Sykes, P., McNally, O., Oehler, M.K., Walker, G., Garrett, A., Tang, A., Land, R., Nicklin, J.L., Chetty, N., Perrin, L.C., Hoet, G., Sowden, K., Eva, L., Tristram, A., Obermair, A., 2021. Complete pathological response following levonorgestrel intrauterine device in clinically stage 1 endometrial adenocarcinoma: Results of a randomized clinical trial. *Gynecol. Oncol.* 161 (1), 143–151.
- La Russa, M., Zapardiel, I., Halaska, M.J., Zalewski, K., Laky, R., Dursun, P., Lindquist, D., Sukhin, V., Polteraer, S., Biliasis, I., 2018. Conservative management of endometrial cancer: a survey amongst European clinicians. *Arch. Gynecol. Obstet.* 298 (2), 373–380.
- Levine, D.A., Getz, G., Gabriel, S.B., Cibulskis, K., Lander, E., Sivachenko, A., et al., 2013. Integrated genomic characterization of endometrial carcinoma. *Nature* 497 (7447), 67–73.
- National Cancer Center Network, Guidelines. Uterine Neoplasms, 2022.
- Pal, N., Broaddus, R.R., Urbauer, D.L., Balakrishnan, N., Milbourne, A., Schmeler, K.M., Meyer, L.A., Soliman, P.T., Lu, K.H., Ramirez, P.T., Ramondetta, L., Bodurka, D.C., Westin, S.N., 2018. Treatment of low-risk endometrial cancer and complex atypical hyperplasia with the levonorgestrel-releasing intrauterine device. *Obstet. Gynecol.* 131 (1), 109–116.
- Rodolakis, A., Scambia, G., Planchamp, F., Acien, M., Di Spiezio Sardo, A., Farrugia, M., Grynberg, M., Pakiz, M., Pavlakis, K., Vermeulen, N., Zannoni, G., Zapardiel, I., Tryde Macklon, K.L., 2023. ESGO/ESHRE/ESGE Guidelines for the fertility-sparing treatment of patients with endometrial carcinoma. *Facts Views vis Obgyn.* 15 (1).
- SEER. Cancer Stat Facts: Uterine Cancer: SEER. 2022.
- Soliman, P.T., Zhang, Q., Broaddus, R.R., Westin, S.N., Iglesias, D., Munsell, M.F., Schmandt, R., Yates, M., Ramondetta, L., Lu, K.H., 2016. Prospective evaluation of the molecular effects of metformin on the endometrium in women with newly diagnosed endometrial cancer: A window of opportunity study. *Gynecol. Oncol.* 143 (3), 466–471.
- Torres, D., Shafa, A., Klennert, S., Hokenstad, A., Bird, M., Weinhold, M., Mundi, M.S., Langstraat, C., Kumar, A., 2019. Using quality improvement to increase the awareness of obesity among endometrial cancer patients. *Int. J. Gynecol. Cancer* 29 (6), 1010–1015.
- Vetter, M.H., Smith, B., Benedict, J., Hade, E.M., Bixel, K., Copeland, L.J., Cohn, D.E., Fowler, J.M., O'Malley, D., Salani, R., Backes, F.J., 2020. Preoperative predictors of endometrial cancer at time of hysterectomy for endometrial intraepithelial neoplasia or complex atypical hyperplasia. *Am. J. Obstet. Gynecol.* 222 (1), 60.e1–60.e7.
- Westin, S.N., Fellman, B., Sun, C.C., Broaddus, R.R., Woodall, M.L., Pal, N., Urbauer, D. L., Ramondetta, L.M., Schmeler, K.M., Soliman, P.T., Fleming, N.D., Burzawa, J.K., Nick, A.M., Milbourne, A.M., Yuan, Y., Lu, K.H., Bodurka, D.C., Coleman, R.L., Yates, M.S., 2021. Prospective phase II trial of levonorgestrel intrauterine device: nonsurgical approach for complex atypical hyperplasia and early-stage endometrial cancer. *Am. J. Obstet. Gynecol.* 224 (2), 191.e1–191.e15.