Safety of ovarian preservation for premenopausal patients with FIGO stage I grade 2 and 3 endometrioid endometrial adenocarcinoma

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HIGHLIGHTS

⇒ Ovarian preservation is rarely performed for premenopausal patients with high-grade endometrioid tumors.
⇒ Ovarian preservation is not associated with worse overall survival.
⇒ Presence of ovarian metastases is associated with positive peritoneal cytology, large tumor size, and lymph node metastases.

ABSTRACT

Objective To investigate the utilization and outcomes of ovarian preservation for premenopausal patients with International Federation of Gynecology and Obstetrics (FIGO) stage I grade 2 and 3 endometrioid endometrial carcinoma undergoing hysterectomy.

Methods The National Cancer Database was accessed; patients aged ≤45 years diagnosed between January 2004 and December 2015 with FIGO stage I grade 2 or 3 endometrioid endometrial carcinoma, who underwent hysterectomy with or without bilateral salpingo-oophorectomy and had at least 1 month of follow-up, were identified. Overall survival was assessed following generation of Kaplan-Meier curves and compared with the log-rank test. A Cox model was constructed to control for a priori selected variables.

Results A total of 2941 patients who met the inclusion criteria were identified; 200 (6.8%) patients did not undergo bilateral salpingo-oophorectomy. Rate of ovarian preservation was comparable between patients with grade 2 (n=163, 6.6%) and grade 3 (n=37, 7.7%) tumors (p=0.38). Patients who did not undergo bilateral salpingo-oophorectomy were younger (median 39 vs 41 years, p<0.001) and less likely to undergo surgical lymph node assessment (52% vs 76.2%, p<0.001). There was no difference in overall survival between patients who did and did not undergo bilateral salpingo-oophorectomy (p=0.94); 5 year overall survival rates were 96.6% and 97%, respectively. After controlling for confounders, including tumor grade, ovarian preservation was not associated with worse overall survival (HR 0.92, 95% CI 0.47 to 1.84).

Conclusions For patients with grade 2 and 3 FIGO stage I endometrioid carcinoma undergoing hysterectomy, ovarian preservation is rarely performed while no clear detrimental effect on overall survival was found.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ For premenopausal patients with endometrial cancer, ovarian preservation is not associated with worse oncologic outcomes for those with grade 1 tumors. However, safety of ovarian preservation for grade 2 or 3 tumors is not established.

WHAT THIS STUDY ADDS

⇒ Ovarian preservation was not associated with worse overall survival for patients with grade 2 or 3 endometrioid tumors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Ovarian preservation may be considered for carefully selected patients with grade 2 tumors.

INTRODUCTION

Endometrial cancer is the most prevalent malignancy of the female reproductive tract in the USA, with an increasing incidence especially among premenopausal women secondary to the obesity pandemic.[1] Standard surgical management of apparent early-stage disease includes hysterectomy, bilateral salpingo-oophorectomy, and lymph node staging.[2] Performance of bilateral salpingo-oophorectomy aims to remove occult ovarian metastases and decrease estrogen production since endometrial cancer is typically estrogen-responsive.[3] Nevertheless, surgical menopause has significant consequences for the long-term health of cancer survivors.[4] Several retrospective studies have investigated the oncologic outcomes of ovarian preservation in premenopausal patients.[5–7] A recent meta-analysis of seven cohort studies found no overall survival difference

among premenopausal women who did and did not undergo bilateral salpingo-oophorectomy.[8] Similarly, an analysis of a large population-based database demonstrated that cancer-specific and overall survival is not impacted by ovarian preservation.[9] The current National Comprehensive Cancer Network guidelines state that, for premenopausal women with stage IA or IB endometrial cancer, ovarian preservation may be safe and not associated with an increased cancer-related mortality.[2] However, evidence on the safety of ovarian preservation in patients with grade 2 or grade 3 tumors is limited given the small number of patients included in the aforementioned retrospective studies.[5–8] Given the theoretically higher risk of occult ovarian metastases, and the increased risk of recurrence, certain surgeons are hesitant to offer ovarian preservation in this subgroup. In fact, the recently updated European Society of Gynaecological Oncology-European Society of Medical Oncology (ESGO-ESMO) guidelines are more conservative and suggest that ovarian preservation can be considered for premenopausal patients aged <45 years with no evidence of extra-uterine disease, and a low-grade endometrioid tumor that invades <50% of myometrium.[10]

The aim of this study was to investigate the utilization and outcomes of ovarian preservation for patients with International Federation of Gynecology and Obstetrics (FIGO) stage I grade 2 and 3 endometrioid endometrial carcinoma using a large hospital-based database. In addition, we aimed to evaluate the incidence of isolated adnexal metastases among patients with clinical stage I disease.

METHODS

The National Cancer Database was accessed, and patients aged ≤45 years diagnosed between January 2004 and December 2015 with FIGO stage I endometrioid endometrial adenocarcinoma of the uterus (International Classification of Disease-O-3 histology codes 8380/3, 8382/3 and 8383/3) were identified. Patients with grade 2 or grade 3 tumors, who did not have a history of another tumor, underwent hysterectomy (with or without lymphadenectomy), and had at least 1 month of follow-up, were selected for further analysis. Based on site-specific surgery codes, performance of bilateral salpingo-oophorectomy was assessed and patients who had ovarian preservation were identified. Patients with unknown data on the performance of bilateral salpingo-oophorectomy as well as those who received neo-adjuvant radiotherapy were excluded.

The National Cancer Database is a hospital-based database capturing approximately 70% of all malignancies diagnosed in the USA. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytical or statistical methodology employed, or the conclusions drawn from these data. The present study was deemed exempt from Institutional Board Review from Penn Medicine (Protocol #829268).

De-identified patient information was extracted from the dataset. Insurance status was recoded into private, government (including Medicaid and Medicare,) and uninsured/unknown, while tumor size was classified into <2 cm, 2–4 cm, >4 cm, and unknown. The presence of comorbidities was evaluated from the Charlson-Deyo Comorbidity Index as provided by the National Cancer Database and further classified as absent (if score 0) or present (if score ≥1). Performance of lymph node sampling/dissection was abstracted from the pathology report. The status of peritoneal cytology and lymph-vascular invasion variables were introduced into the database after 2010, and were missing for the majority of cases, so were not included in the survival analysis.

For categorical variables the frequency of distribution was compared with the χ^2 test while continuous variables were compared with the Mann-Whitney U test. Overall survival was assessed following generation of Kaplan-Meier curves and compared with the log-rank test. A Cox model was constructed to control for a priori selected confounders known to be associated with overall survival for patients with endometrial cancer.

In addition, we identified in the National Cancer Database patients diagnosed between 2010–2015 with clinical stage I grade 2 or grade 3 endometrioid endometrial adenocarcinoma, no history of another tumor, who underwent hysterectomy with lymphadenectomy and bilateral salpingo-oophorectomy, did not receive neoadjuvant radiotherapy, and had available pathological data on tumor grade, size, peritoneal cytology, presence of lymph-vascular invasion, and intra-abdominal disease extent. The incidence of isolated ovarian metastases was calculated, and independent predictors were investigated with binary logistic regression. Secondary to the coding classification schema of disease extent, depth of myometrial invasion was not provided for cases with ovarian metastases as such could not be utilized in this analysis.

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) v.27 (International Business Machines Corp (IBM), Armonk, NY) and the α level of statistical significance was set at 0.05.

RESULTS

A total of 2941 patients who met the inclusion criteria were identified; 200 (6.8%) patients had ovarian preservation (online supplemental Figure 1 depicts the patient selection flowchart). Figure 1 depicts the temporal trends in ovarian preservation, demonstrating an overall decrease in its utilization. Patients who had ovarian preservation were younger (median 39 vs 41 years, p<0.001) compared with those who had bilateral salpingo-oophorectomy. The rate of ovarian preservation for patients aged <35, 35–40, and 41–45 years was 11.1% (52/468), 6.8% (65/951), and 5.5% (83/1522),

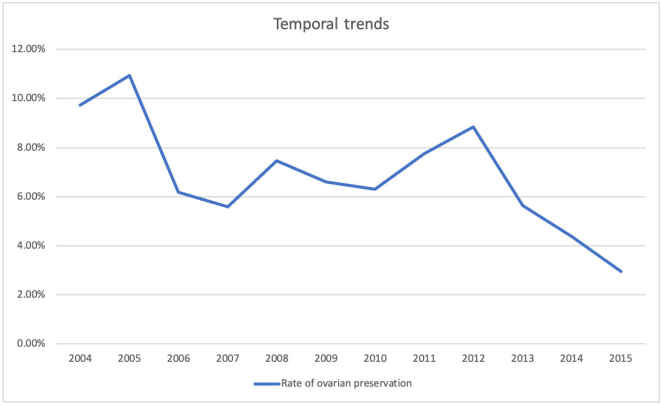

Figure 1 Temporal trends of ovarian preservation among premenopausal patients with stage I grade 2/3 endometrioid adenocarcinoma.

respectively. There was no difference between the two groups in terms of demographic characteristics such as race, insurance status, and presence of comorbidities or pathological characteristics such as tumor grade, size, and depth of myometrial invasion. However, patients who had ovarian preservation were less likely to undergo lymphadenectomy (52% vs 76.2%, p<0.001). The rate of ovarian preservation was comparable between patients with grade 2 (n=163, 6.6%) and grade 3 (n=37, 7.7%) tumors (p=0.38), while the rate of adjuvant radiation therapy was 16.9% and 17% for those patients who did and did not undergo bilateral salpingo-oophorectomy, respectively (p=0.97). Overall, most patients receiving radiation therapy underwent brachytherapy (70% (n=348)), while 20% (n=94) underwent external beam radiation, and 10% (n=54) a combination of both. Among patients receiving radiation therapy, utilization of external beam radiation (with or without vaginal brachytherapy) was comparable between patients who did and did not undergo bilateral salpingo-oophorectomy (38.2% vs 29.2%, p=0.27). Table 1 depicts demographic and clinico-pathological characteristics of patients who did and did not undergo bilateral salpingo-oophorectomy. Online supplemental file 2 summarizes the distribution of pathologic characteristics, based on tumor grade and performance of bilateral oophorectomy.

Based on the reverse Kaplan-Meier method, the median follow-up of patients who did and did not undergo bilateral salpingo-oophorectomy was 61.7 (95% CI 66.17 to 78.50) months and 68.3 (95% CI 61.33 to 75.35) months, respectively. There was no difference in overall survival between patients who did and did not undergo bilateral salpingo-oophorectomy (p=0.94); 5 year rates were 96.6% and 97%, respectively (Figure 2). After controlling for patient insurance, presence of comorbidities, performance of lymphadenectomy, disease substage, tumor size and grade, ovarian preservation was not associated with worse survival (hazard ratio (HR) 0.92, 95% CI 0.47 to 1.84). After excluding patients who received adjuvant radiation, again there was no overall survival difference between those who did and did not undergo bilateral salpingo-oophorectomy (p=0.33); 5 year overall survival rates were 97.1% and 100%, respectively. There was no difference in overall survival between patients who did and did not undergo bilateral salpingo-oophorectomy for patients with grade 2 (p=0.75; 5 year overall survival rates were 97.7% and 99.2%, respectively) or grade 3 tumors (p=0.73; 5 year overall survival rates were 90.6% and 88.2%, respectively). Following stratification by depth of myometrial invasion, overall survival was comparable between patients who did and did not undergo bilateral salpingo-oophorectomy for those with <50% myometrial invasion (p=0.71; 5 year overall survival rates 96.7% and 97.2%, respectively) or those with >50% myometrial invasion (p=0.27; 5 year overall survival rates 96.2% and 100%, respectively)

A total of 9407 patients with grade 2 (72.8%) or grade 3 (27.2%) endometrioid tumors and clinical stage I disease who underwent hysterectomy with bilateral salpingo-oophorectomy, and available data on the presence of lymph-vascular invasion, lymph node status, tumor size, presence of positive cytology, and disease extent in final pathology, were identified. In the present cohort, 23.6% had lymph-vascular invasion, while the rate of lymph node metastases and positive peritoneal cytology was 5.8% and 7%, respectively. On final pathology, 9113 (96.9%) patients had disease confined to the uterus while a total of 108 (1.1%) patients had isolated adnexal metastases. In addition, 52 patients had disease extending to the uterine serosa without involvement of the adnexa, 33 had stage IIIA not otherwise specified, and 81 patients had disease extending to the parametria (stage IIIB) or other intra-abdominal organs (stage IVA). These cases were excluded from the binary logistic regression. Presence of lymph-vascular invasion (odds ratio (OR) 2.70, 95% CI 1.77 to 4.13), positive peritoneal cytology (OR 4.29, 95% CI 2.74 to 6.72), premenopausal age (OR 3.13, 95% CI 1.95 to 5.02), lymph node metastases (OR 2.74, 95% CI 1.68 to 4.46), and tumor size >4 cm (OR 2.63, 95% CI 1.13 to 6.13), but not tumor grade, were associated with the presence of isolated adnexal metastases.

Table 1 Clinico-pathological and demographic characteristics of the patient population

	BSO (n=2741)	OP (n=200)	P value
Age (median)	41 years	37 years	<0.001
Race			0.75
White	2209 (80.6%)	157 (78.5%)	
Black	274 (10%)	23 (11.5%)	
Other/unknown	258 (9.4%)	20 (10%)	
Comorbidities			
No	2110 (77%)	164 (82%)	0.10
Yes	631 (23%)	36 (18%)	
Insurance			0.61
Private	1987 (72.5%)	139 (69.5%)	
Government	489 (17.8%)	41 (20.5%)	
Uninsured/unknown	265 (9.7%)	20 (10%)	
LND			<0.001
Yes	2079 (76.2%)	103 (52%)	
No	648 (23.8%)	95 (48%)	
Tumor size			0.079
<2 cm	382 (13.9%)	26 (13%)	
2–4 cm	580 (21.2%)	43 (21.5%)	
>4 cm	967 (35.3%)	56 (28%)	
Unknown	812 (29.6%)	75 (37.5%)	
Grade			0.38
Grade 2	2299 (83.9%)	163 (81.5%)	
Grade 3	442 (16.1%)	37 (18.5%)	
Stage			0.73
IA	2340 (85.4%)	173 (86.5%)	
IB	319 (11.6%)	20 (10%)	
INOS	82 (3%)	n<10	
Radiation therapy			0.97
Yes	463 (16.9%)	34 (17%)	
No	2278 (83.1%)	166 (83%)	

BSO, bilateral salpingo-oophorectomy; INOS, stage I not otherwise specified; LND, lymphadenectomy; OP, ovarian preservation.

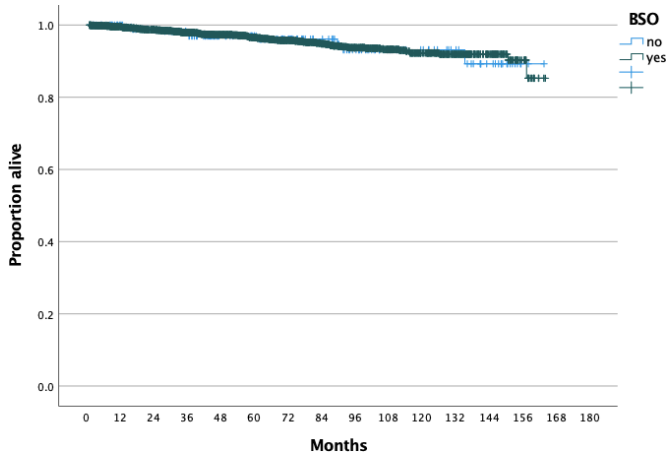

Figure 2 Overall survival of premenopausal patients with stage I grade 2/3 endometrioid adenocarcinoma stratified by performance of bilateral salpingo-oophorectomy.

DISCUSSION

Summary of Main Results

In a large cohort of premenopausal patients with FIGO stage I grade 2 or grade 3 endometrioid endometrial carcinoma, the rate of ovarian preservation was low (6.8%). No detrimental effect on overall survival after a follow-up of approximately 5 years was found. In addition, based on a large cohort of patients with clinical stage I disease who underwent bilateral salpingo-oophorectomy, the incidence of isolated ovarian metastases was low (1.1%) and by binary logistic regression was associated with the presence of other risk factors such as positive lymph nodes, lymph-vascular invasion, and peritoneal cytology, but not tumor grade.

Results in the Context of Published Literature

Several retrospective studies have previously investigated the oncologic safety of ovarian preservation for premenopausal patients with endometrial cancer. An analysis of the Surveillance Epidemiology and End Results population-based database identified 3269 patients aged ≤45 years with stage I endometrial cancer; 402 (12%) had ovarian preservation.[9] By multivariate analysis, lower tumor grade was associated with higher likelihood of ovarian preservation, while compared with patients who had bilateral salpingo-oophorectomy, they did not have worse overall survival (HR 0.68, 95% CI 0.34 to 1.35) or cancer-specific survival (HR 0.58, 95% CI 0.14 to 2.44).[9] However, that study included only 58 and 11 patients with grade 2 or grade 3 tumors, respectively, who underwent ovarian preservation.[9] On the other hand, in a cohort of 495 premenopausal patients from Japan with stage I grade 1 or 2 endometrioid carcinoma, ovarian conservation was associated with decreased disease-free survival (HR 5.2, 95% CI 1.56 to 17.46, p=0.007), but again it was not associated with decreased overall survival (p=0.99) since relapses were highly salvageable.[11]

In another large multi-institutional study, Lee et al analyzed 495 patients with clinical early-stage endometrioid endometrial cancer; 176 had ovarian preservation (including 40 patients with grade 2 and three patients with grade 3 tumors).[6] Authors found no difference in overall or recurrence-free survival after adjusting for confounders.[6] In the ovarian preservation group, four patients experienced a relapse and two of them had grade 2 tumors; however, both had stage II disease and lymph-vascular invasion.[6] A recent meta-analysis of data from four retrospective studies that included premenopausal patients who had ovarian preservation did not reveal any detrimental impact on overall or progression-free survival.[8] Based on data from four studies including 57 premenopausal patients with grade 2 endometrial cancer who had ovarian conservation, only two experienced a relapse.[6 12–14] We observed a decrease in the utilization of ovarian preservation during the study period. It is unclear whether this is related to a practice change or increased use of hormone replacement therapy for these patients.

The presence of co-existing primary ovarian cancer or ovarian metastases is another concern for patients interested in ovarian preservation. A retrospective study that included 102 patients <45 years of age who underwent hysterectomy for endometrial cancer, Walsh et al reported a relatively high (25%, n=26) incidence of co-existing ovarian pathology; three cases classified as metastases and 23 as synchronous primary ovarian malignancy.[15] Interestingly four (15%) patients had normal pre-operative imaging while another four (15%) patients had normal appearing ovaries on intra-operative assessment.[15] On the other hand, in another retrospective study, coexisting ovarian malignancy was found in 19 (7.3%) of 260 patients; 12 cases were deemed metastatic and seven as synchronous primaries.[12] Only two (0.97%) of these patients had normal intra-operative findings.[12] Recent molecular data suggest that the majority of synchronous ovarian tumors are in fact indolent disseminated cells from a uterine primary.[16]

In our study, among patients with clinical stage I disease, the incidence of isolated ovarian metastases was approximately 1%, lower than previously reported. Unfortunately, while the National Cancer Database does not collect imaging data as such and we could hypothesize that only patients without any suspicious findings on pre-operative imaging are categorized as clinical stage I. In a recent retrospective study that included 802 patients with endometrial cancer, 49 patients (6.2%) had adnexal involvement; of these, 12 patients had suspicious pre-operative imaging and two had suspicious intra-operative findings.[17] Similar to our study, lymph-vascular invasion (OR 3.24, p=0.005) and lymph node metastases (OR 3.41, p=0.004) as well as non-endometrioid histology (OR 2.66, p=0.017) were associated with adnexal involvement.[17] It should be noted that the incidence of adnexal involvement among patients with endometrioid tumors of any grade was significantly lower (3.1%, 21/656) compared with those with non-endometrioid tumors.[17]

In another retrospective study that included 759 patients diagnosed with endometrioid tumors, without gross pelvic disease on intra-operative examination or pre-operative imaging, ovarian pathology was found in 38 patients (2% had ovarian metastases and 3% had synchronous ovarian carcinoma). However, only six patients (0.8%) had microscopic ovarian disease.[18] In two studies focusing exclusively on premenopausal patients, the authors reported low rates of ovarian involvement (4.2% and 4.5%, respectively); in both studies deep myometrial invasion was associated with the presence of ovarian pathology.[19 20] Recently, Chen et al analyzed data from 511 premenopausal patients with clinical stage I endometrioid carcinoma undergoing hysterectomy with bilateral salpingo-oophorectomy, and reported a comparable incidence of ovarian involvement (4.5%).[21] Authors identified the depth of myometrial invasion on pre-operative imaging and elevated cancer antigen

Table 2 Incidence of adnexal involvement for patients with grade 2 or 3 endometrial cancer reported in the literature

Study	Grade 2		Grade 3		
	N	Patients with adnexal involvement	N	Patients with adnexal involvement	
Ignatov et al 2018[22]	948	40	460	71	Pre/post menopausal
Pan et al 2011[25]	n/a	n/a	256	8	Pre/post menopausal
Gilani et al 2011[24]	95	12	31	5	Pre/post menopausal
Takeshima et al 1998[28]	122	6	64	3	Pre/post menopausal
Kinjyo et al 2015[19]	12	3	7	1	Premenopausal only
Chen et al 2021[21]	n/a	n/a	28	3	Premenopausal only
Baiocchi et al 2021[17]	n/a	n/a	256	24	Pre/post menopausal
Juhasz-Böss et al 2012[23]	159	17	48	13	Pre/post menopausal
Gemer et al 2004	11	0	5	1	Pre/post menopausal
Lee et al 2007[12]	63	5	22	2	Pre/post menopausal
Akbayir et al 2012	218	10	87	11	Pre/post menopausal
Walsh et al[15]	31	5	7	2	Premenopausal only
Kuwabara et al 2004[27]	n/a	n/a	74	16	Pre/post menopausal
Sun et al 2013[5]	37	1	3	19	Premenopausal only
Total	1696	99 (5.8%)	1348	179 (13.3%)	

n/a, not available.

125 (CA125) as an independent predictor of ovarian involvement.[21] Table 2 summarizes the incidence of adnexal involvement reported in the literature for patients with grade 2 or grade 3 endometrial carcinoma.[5 12 17 19 21–28] For patients with grade 2 tumors (n=1696) adnexal involvement was found in 5.8%; however, for those with grade 3 tumors (n=1348) the incidence of adnexal involvement was higher (13.3%).

Patients interested in ovarian preservation should also be carefully counseled on the risks of synchronous and metachronous ovarian cancer.[11 29] In a recent analysis of the Surveillance Epidemiology and End Results database, that included 1322 patients younger than 50 years who had stage I endometrioid endometrial carcinoma and underwent hysterectomy with ovarian preservation, 16 (1.2%) patients developed a subsequent ovarian cancer with a cumulative 5 and 10 year incidence of 1% and 1.3%, respectively.[29] It should be noted that 75% of the cases were stage I and, after a follow-up of 11 years, no ovarian cancer deaths were reported. In another study from Japan, patients who had ovarian preservation had an increased risk of a metachronous ovarian cancer (OR 7.2, 95% CI 1.35 to 37.55, p=0.021).[11] Performance of genetic testing and identification of individuals at higher risk for a metachronous ovarian carcinoma, as well as removal of ovaries following menopause, could potentially mitigate this risk.

Strengths and Weaknesses

A major strength of our study was the large number of patients identified that was derived from a hospital-based database covering 70% of all newly diagnosed cancer cases in the USA, thus reflecting real-world practice. In addition, median follow-up was adequate to capture relapses that would impact overall survival.

Several limitations of the study should be noted. Given the absence of central pathology review, possible tumor and stage misclassifications cannot be excluded. Also, the National Cancer Database does not collect details on tumor relapse, precluding us from analyzing differences in progression-free survival and patterns of recurrence. Moreover, results from the pre-operative imaging performed and individual genetic data were not available. In addition, we could not verify if any patients who did not undergo oophorectomy simultaneously had ovarian transposition. Similarly, no data were available on the hormonal function of these patients. For patients who had surgical lymph node assessment we could not identify those who underwent sentinel lymph node mapping or full lymphadenectomy. Lastly, depth of myometrial invasion and presence of cervical involvement could not be extracted when evaluating factors associated with the presence of adnexal involvement.

Implications for Practice and Further research

Our study demonstrated that ovarian preservation is rarely offered to premenopausal women with grade 2 or 3 endometrioid tumors, while there was no evidence of a detrimental impact of ovarian preservation on their overall survival. However, results should be interpreted with caution for patients with grade 3 tumors or those with >50% myometrial invasion, given the small number of patients who had ovarian preservation. The incidence of ovarian metastases among patients with grade 2 or 3 tumors is low and correlates with the presence of additional risk factors such as lymph node metastases, lymph-vascular invasion, and positive peritoneal cytology. Ovarian preservation could potentially be offered to carefully selected and motivated patients, following extensive counseling on the risk of occult synchronous/metachronous ovarian carcinoma.

Genetic testing and careful pre-operative imaging, focusing on the depth of myometrial invasion, can additionally aid in selecting appropriate candidates for ovarian preservation. In addition, a thorough intra-operative evaluation to exclude presence of extra-uterine disease and abnormal appearing ovaries, and a frozen pathologic examination to evaluate the uterine specimen for depth of myometrial invasion and cervical involvement, as well as an intra-operative examination of peritoneal cytology for malignant cells, could further identify patients at high risk for ovarian metastases and prompt removal of the ovaries at the time of hysterectomy.

CONCLUSIONS

In the USA ovarian preservation is rarely offered to patients with grade 2 or 3 endometrioid endometrial carcinoma. No clear negative impact on overall survival was found, especially for patients with grade 2 tumors. For patients with grade 3 tumors evidence to support ovarian preservation is weak.

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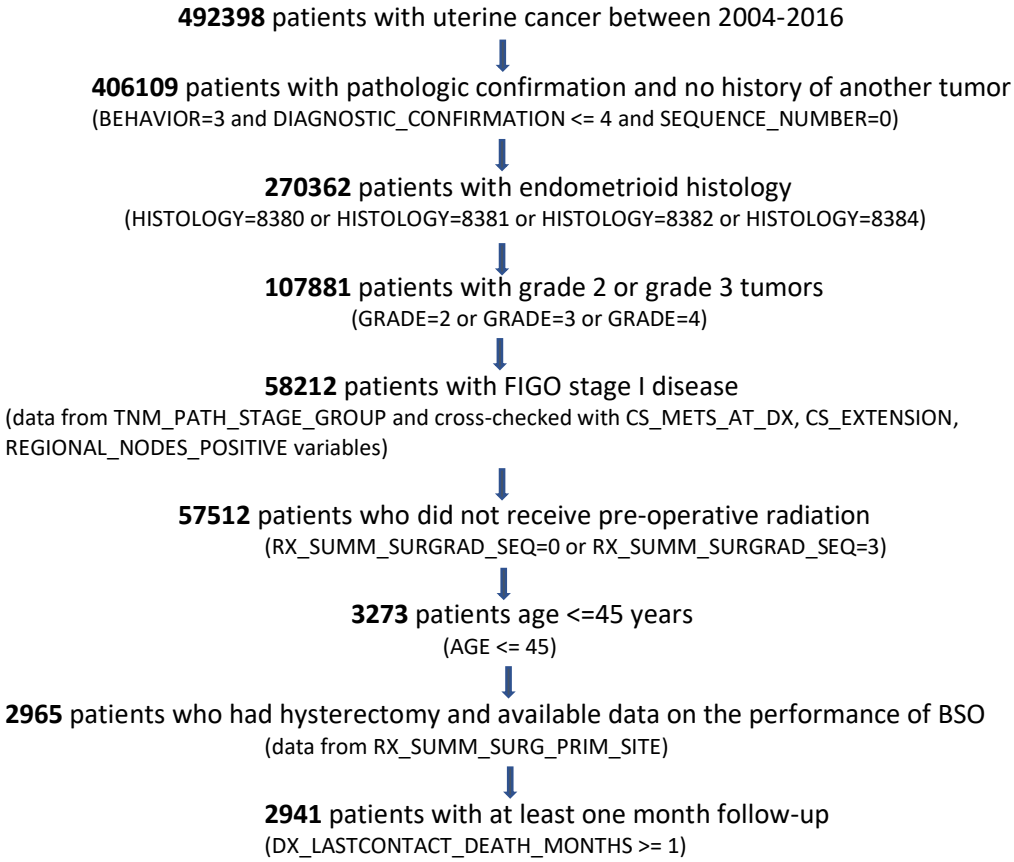
Supplemental Figure 1. Patient selection flowchart



Supplemental table 1. Distribution of pathologic characteristics based on tumor grade and performance of bilateral oophorectomy.

	Grade 2			Grade 3	
	OP	BSO		OP	BSO
Myometrial invasion					
<50%	145 (89%)	1990 (86.6%)		28 (75.7%)	350 (79.2%)
>=50%	12 (7.4%)	238 (10.4%)		n<10	81 (18.3%)
not specified	n<10	71 (3%)		n<10	11 (2.5%)
LVSI (2010-2015)					
Absent	64 (95.5%)	1040 (93.1%)		n<10 (52.9%)	168 (76.7%)
Lymphadenectomy					
Yes	75 (46.6%)	1701 (74.4%)		28 (75.7%)	378 (85.5%)
Radiation therapy					
Yes	17 (10.4%)	280 (12.2%)		17 (45.9%)	183 (41.4%)
Chemotherapy					
None	162 (99.4%)	2264 (98.5%)		30 (81.1%)	393 (88.9%)

LVSI: lymphovascular invasion available only for cases diagnosed after 2010, *n<10 and suppressed based on agreement with National Cancer Database