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Short communication

Can we safely forgo hysterectomy in non-fertility-sparing surgery for borderline ovarian tumors?

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ABSTRACT

Forgoing hysterectomy as part of borderline ovarian tumor (BOT) staging is considered appropriate for fertility preservation. We evaluated whether forgoing hysterectomy may also be acceptable in non-fertility-sparing surgery by evaluating the frequency of uterine involvement and the rate of recurrence involving the uterus. A review of all BOTs at one institution over ten years (2009–2019) was performed. Patients with hysterectomy prior to BOT diagnosis were excluded. Data were abstracted from electronic medical records. Bivariate statistics were used to compare groups.

129 patients with BOT on final pathology were identified. 67 cases included hysterectomy. Reasons for no hysterectomy (n = 62) included fertility preservation (40), benign intraoperative frozen pathology (4), patient preference (3), comorbidities (7), and unknown (8). Four of 67 (6.0%) uterine specimens had non-invasive serosal implants, of which two had grossly visible uterine involvement and all four had grossly visible extra-uterine peritoneal disease. 12 of 129 (9.3%) patients had documented recurrence, of which all had uterine preservation at the time of initial surgery. Of the 12 recurrences with uterus in situ, none were documented to involve the uterus, and all were composed of non-invasive implants. In patients with BOT grossly confined to ovaries at the time of surgery, we found no cases of uterine involvement. We found no cases in which microscopic uterine serosal involvement changed stage and no cases of recurrence involving the uterus. Hysterectomy may be able to be safely excluded from non-fertility-sparing surgery for BOTs, particularly when disease is grossly confined to the ovaries.

1. Introduction

Borderline ovarian tumors are neoplasms of epithelial origin characterized by increased cellular proliferation and nuclear atypia, distinguished from carcinoma by lack of stromal invasion (Silverberg, 2004). The majority of borderline ovarian tumors are limited to one or both ovaries at the time of diagnosis and have a very favorable prognosis, with a 10-year survival of 97% for all stages combined (Kurman, 2000; Hauptmann, 2017). Fertility-sparing surgery is considered acceptable for borderline ovarian tumors, as is forgoing lymphadenectomy (du Bois, 2016; Matsuo, et al., 2017).

Despite their favorable prognosis, borderline ovarian tumors can recur. Rate of recurrence is higher after fertility-sparing (10 to 20%) compared to non-fertility-sparing surgery (approximately 5%) (du Bois, 2016; DM, 2002). In one study of 1,143 women with borderline ovarian tumors, fertility-sparing surgery had a hazard ratio of 3.8 for recurrence and most recurrences occurred in the remaining ovary (Karlsen, 2016). Other reported sites of recurrence for borderline ovarian tumors include peritoneum, pelvic lymph nodes, and lung/pericardium (du Bois, 2016; Park, 2009). Although fertility-sparing surgery is accepted in the management of borderline ovarian tumors, the National Comprehensive Cancer Network (NCCN) guidelines define comprehensive surgery as including hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies, and peritoneal washings. Based on these guidelines, hysterectomy is considered part of the standard primary surgical management of borderline ovarian tumors (Benedet, 2000; Trope, 2000).

The objective of this study was to determine, in a cohort of patients

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with borderline ovarian tumors, the rate of uterine involvement at the time of initial surgery and the rate of recurrence involving the uterus to evaluate whether hysterectomy might be safely excluded from the surgical management of borderline ovarian tumors in non-fertility-sparing scenarios. We hypothesized that there would be a low rate of both uterine involvement at time of initial surgery and at recurrence.

2. Methods

Women age 18 to 99 who diagnosed with a borderline ovarian tumor of any histotype and received care or had pathology records reviewed at the University of Colorado Hospital between August 1, 2009 and August 1, 2019 were included. Patients with hysterectomy prior to initial surgery (n = 18) and those with a pre-operative diagnosis of endometrial cancer (n = 2) were excluded. Institutional Review Board approval was obtained prior to data collection. Medical records, operative and pathology reports were reviewed for patient and disease characteristics. Since many cases predated the 2014 change in ovarian cancer staging, the designation IC was used to include all substages.

Descriptive statistics were used to report the rate of uterine involvement on final pathology. Patients with hysterectomy were compared to those without hysterectomy using chi-square for categorical variables and Student's *t*-test for continuous variables that were normally distributed or nonparametric tests for continuous variables not normally distributed. A p-value ≤ 0.05 was considered statistically significant.

3. Results

A total of 129 patients met inclusion criteria. Of those, 67 had hysterectomy at the time of surgery. Reasons for not performing hysterectomy included fertility preservation (n = 40), benign intraoperative pathology (n = 4), patient preference (n = 3), being considered a poor surgical candidate (included refusal of blood products, uncontrolled hypertension, obesity, etc., n = 7), and unknown or undocumented reason (n = 8).

Included patients had a median age of 43 years and the majority were white (n = 90) and premenopausal (n = 85). Compared to patients who did not have hysterectomy at the time of surgery, those who did were more likely to be older, multiparous, and post-menopausal [Table 1].

Most patients had stage I disease (74%) with serous histology (61%). Compared to patients who did not have hysterectomy at the time of surgery, those who did were more likely to: have an open surgery, have both ovaries removed, have an intraoperative (frozen section) specimen evaluated, have peritoneal biopsies, have a lymph node dissection and omentectomy, and have a higher estimated blood loss [Table 2].

Four of the 67 (6.0%) uterine specimens had non-invasive serosal implants. Two of these four cases had grossly visible uterine serosal disease. Because all four also had grossly visible and pathology-confirmed extrauterine peritoneal disease, uterine involvement did not upstage any cases. The histology in all four cases of uterine involvement was serous.

Two uterine specimens were notable for clinically significant endometrial pathology: one had endometrial intraepithelial carcinoma and the other had a minute focus of endometrioid adenocarcinoma. Neither of these had serosal implants on the uterus. On review of the pre-operative documentation for these patients, in both cases the indication for surgery was adnexal mass and it was unclear whether there was any pre-operative concern about endometrial pathology.

Of the 129 patients included in our analysis, 12 (9.3%) had documented recurrence. Ten of the 12 patients had serous histology (83.3%), one had mucinous histology (8.3%), and one had endometrioid histology (8.3%). All 12 had non-invasive recurrences and had the uterus left in-situ at time of initial surgery (11 for fertility preservation, one for patient preference). Of these 12 patients, all uteri were grossly examined at time of initial surgery with no mention of gross uterine disease. Seven of these 12 patients (58.3%) had a hysterectomy performed at the time of surgery for recurrence, and none had recurrent disease in the uterine specimen. In the 11 patients who had originally kept their uteri for fertility preservation, ten (90.9%) had a recurrence in the remaining ovary and one (9.1%) recurred in the diaphragm and omentum. The patient who kept her uterus per patient preference recurred at the uterosacral ligament. In the four patients with uterine serosal disease at time of initial surgery, none had a documented recurrence [Fig. 1].

4. Discussion

In our retrospective cohort of 129 patients, we found no cases of uterine involvement on final pathology when disease was grossly confined to the ovaries. In four cases with non-invasive uterine implants at initial surgery, all had grossly visible extrauterine disease and none experienced a documented recurrence. None of the 12 documented recurrences involved the uterus.

Two prior studies have shown that serosal uterine involvement is rare in borderline ovarian tumors, occurring in 1.3–7.8% of patients (Kennedy, 1996; Fotopoulou, 2009), which is consistent with our findings. Our study is the first to evaluate and conclude that uterine involvement alone did not alter the stage of disease since all cases of

Table 1
Patient Characteristics.

	All patients (N = 129)	No hysterectomy performed (n = 62; 48.0%)	Hysterectomy performed (n = 67; 52.0%)	P value
Age (years)	43 (15–79)	34 (15–61)	52 (21–79)	<0.001
BMI (kg/m^2)	29 (15–54)	28 (15–54)	29 (19–46)	0.08
Race				
African American	2 (1.6%)	1 (1.6%)	1 (1.5%)	0.35
American Indian	2 (1.6%)	0 (0%)	2 (3.0%)	
Asian	3 (2.3%)	1 (1.6%)	2 (3.0%)	
Hispanic	8 (6.2%)	6 (9.7%)	2 (3.0%)	
Other	6 (4.7%)	4 (6.5%)	2 (3.0%)	
Unknown	18 (14.0%)	10 (16.1%)	8 (11.9%)	
White	90 (69.8%)	40 (64.5%)	50 (74.6%)	
Parity				
0	42 (32.6%)	28 (45.2%)	14 (20.9%)	<0.001
1	19 (14.7%)	14 (22.6%)	5 (7.5%)	
2	30 (23.3%)	9 (7.1%)	21 (31.3%)	
3 or more	20 (15.5%)	4 (6.5%)	16 (23.9%)	
Unknown	18 (14.0%)	7 (11.3%)	11 (16.4%)	
Menopausal Status				
Pre-menopausal	85 (65.9%)	54 (87.1%)	31 (46.2%)	<0.001
Post-menopausal	42 (32.6%)	8 (12.9%)	34 (50.7%)	
Unknown	2 (1.6%)	0 (0%)	2 (3.0%)	

Table 2
Surgical and Histologic Characteristics.

	All patients (N = 129)	No hysterectomy performed (n = 62)	Hysterectomy performed (n = 67)	P value
Stage Disease				
IA	71 (55.0%)	36 (58.0%)	35 (52.2%)	0.35
IB	9 (7.0%)	3 (4.8%)	6 (9.0%)	
IC	16 (12.4%)	11 (17.7%)	5 (7.5%)	
IIA	4 (3.1%)	2 (3.2%)	2 (3.0%)	
IIB	3 (2.3%)	1 (1.6%)	2 (3.0%)	
IIC	3 (2.3%)	2 (3.2%)	1 (1.5%)	
IIIA	6 (4.7%)	1 (1.6%)	5 (7.5%)	
IIIB	5 (3.9%)	2 (3.2%)	3 (4.5%)	
IIIC	12 (9.3%)	4 (6.5%)	8 (11.9%)	
CA-125				
<35	48 (37.2%)	24 (38.7%)	24 (35.8%)	0.33
>35	36 (27.9%)	13 (21.0%)	23 (34.3%)	
Not measured/ unknown	45 (34.9%)	25 (40.3%)	20 (29.9%)	
Route of surgery				
Open	83 (64.3%)	30 (48.4%)	53 (79.1%)	0.001
Laparoscopic	28 (21.7%)	23 (37.1%)	5 (7.5%)	
Robotic	7 (5.4%)	4 (6.5%)	3 (4.5%)	
Unknown	11 (8.5%)	5 (8.1%)	6 (9.0%)	
Number ovaries removed				
0	9 (7.0%)	8 (12.9%)	1 (1.5%)	<0.001
1	59 (45.7%)	47 (75.8%)	12 (17.9%)	
2	61 (47.3%)	7 (11.3%)	54 (80.6%)	
Frozen section sent				
Yes	71 (55.0%)	28 (45.2%)	43 (64.2%)	0.01
No	20 (15.5%)	16 (25.8%)	4 (6.0%)	
Unknown	38 (29.5%)	18 (29.0%)	20 (29.9%)	
Pelvic washings				
Yes	90 (69.8%)	40 (64.5%)	50 (74.6%)	0.29
No	39 (30.2%)	22 (35.5%)	17 (25.4%)	
Peritoneal biopsies				
Yes	66 (51.2%)	22 (35.5%)	44 (65.7%)	0.01
No	61 (47.3%)	38 (61.3%)	23 (34.3%)	
Unknown	2 (1.6%)	2 (3.2%)	0 (0%)	
Lymph node dissection				
Yes	57 (44.2%)	16 (25.8%)	41 (61.2%)	<0.001
No	72 (55.8%)	46 (74.2%)	26 (38.8%)	
Omentectomy				
Yes	69 (53.5%)	20 (32.3%)	49 (73.1%)	<0.001
No	60 (46.5%)	42 (67.7%)	18 (26.9%)	
Surgical complication				
None	89 (69.0%)	42 (67.7%)	47 (70.1%)	0.40
Hemorrhage	1 (0.8%)	0 (0%)	1 (1.5%)	
Convert to laparotomy	3 (2.3%)	1 (1.6%)	2 (3.0%)	
Unknown	36 (27.9%)	19 (30.6%)	17 (25.4%)	
BOT Histotype				
Serous	78 (60.5%)	42 (67.7%)	36 (53.7%)	0.57
Mucinous	40 (31.0%)	15 (24.2%)	25 (37.3%)	
Mixed epithelial	2 (1.6%)	1 (1.6%)	1 (1.5%)	
Endometrioid	3 (2.3%)	1 (1.6%)	2 (3.0%)	
Brenner	1 (0.8%)	0 (0%)	1 (1.5%)	
Seromucinous	5 (3.9%)	3 (4.8%)	2 (3.0%)	
Uterine Pathology				
Normal	21 (16.3%)	–	21 (31.3%)	—
Benign (adenomyosis, leiomyoma)	40 (31.0%)	–	40 (59.7%)	
Noninvasive serosal implant	4 (3.1%)	–	4 (6.0%)	
Endometrioid intraepithelial carcinoma (EIC)	1 (0.8%)	–	1 (1.5%)	
Endometrioid adenocarcinoma	1 (0.8%)	–	1 (1.5%)	
Not applicable	62 (48.8%)	62 (100%)	–	

uterine involvement also had extrauterine disease.

Other studies have investigated the role of comprehensive surgical staging in the management of borderline ovarian tumors. Mandelbaum et al. (Mandelbaum, 2019) identified 1,065 women with borderline ovarian tumors with utero-ovarian preservation at surgery and 52 women who had hysterectomy with ovarian preservation alone. They found that borderline ovarian tumor-related survival outcomes were not impacted by whether uterus and ovaries versus ovaries alone were preserved. Overall survival was higher in the utero-ovarian preservation group. Possible reasons for this difference were not speculated upon. Matsuo et al. investigated the role of hysterectomy and lymphadenectomy in borderline ovarian tumors (Matsuo, et al., 2017). They found that cause-specific survival was no different between patients receiving hysterectomy and lymphadenectomy, hysterectomy alone, lymphadenectomy alone, or neither for treatment of stage I borderline ovarian tumors. They suggested that both hysterectomy and lymphadenectomy may be omitted in the surgical management of women with stage I borderline ovarian tumors. Our study supports their conclusion that hysterectomy may be able to be excluded and adds the evaluation of all stages of borderline ovarian disease, quantification of rates of uterine involvement at time of initial surgery, and of rate of recurrence involving the uterus.

We did find two cases where hysterectomy identified malignant or pre-malignant lesions of the endometrium. The patient with endometrioid adenocarcinoma had her surgery at an outside hospital and transferred her care post-operatively. Documentation was unclear regarding whether there was pre-operative concern for endometrial pathology. The patient with endometrial intraepithelial carcinoma also had risk factors for cancer and had documented post-menopausal bleeding prior to surgery. Given the limitations of available pre-operative documentation, we were unable to assess whether these were truly incidental discoveries or whether there was clinical suspicion for endometrial pathology prior to surgery.

Limitations of our study include the retrospective nature and the fact that not all data were available from initial surgeries. Given that a large, randomized control trial assessing the role of hysterectomy in surgical management of borderline ovarian tumors is unlikely to occur, we will likely need to rely on results of retrospective studies to inform pre-surgical counseling. Strengths of our study include inclusion of

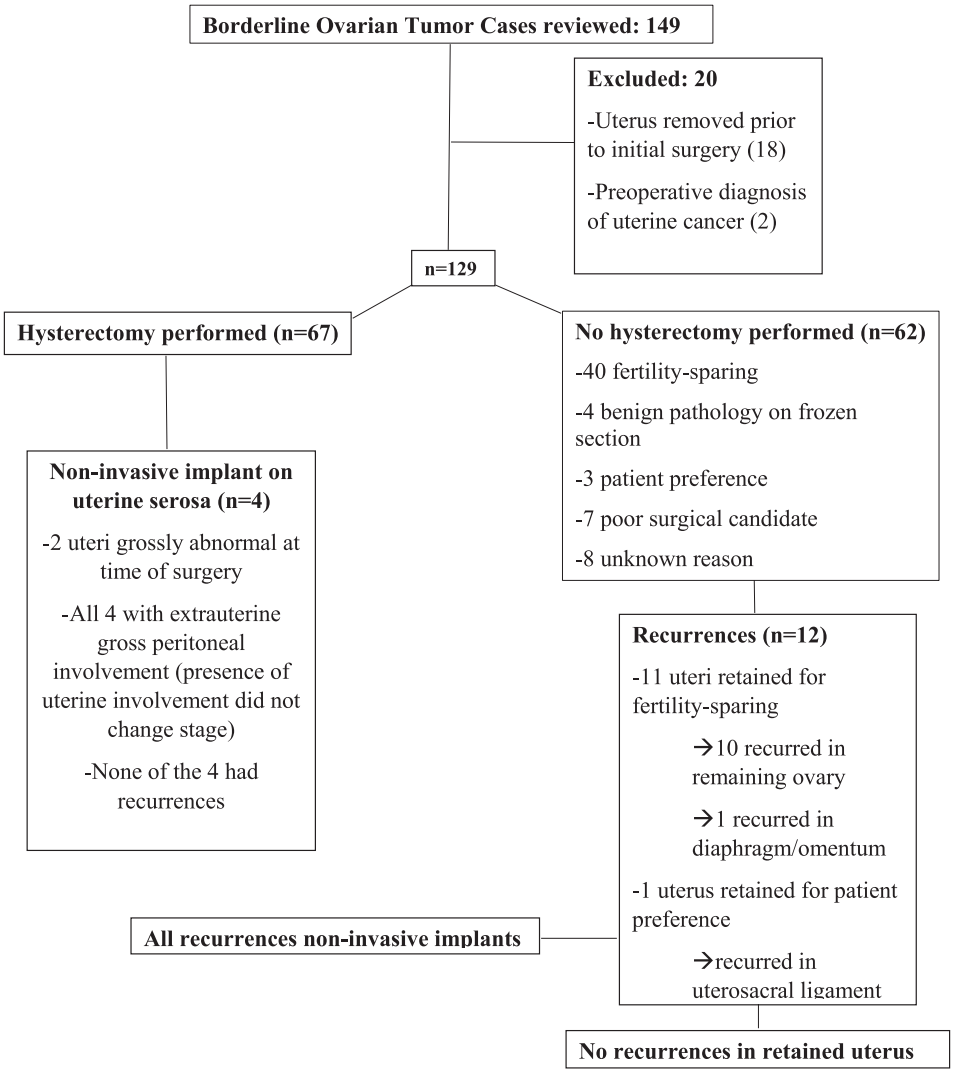

Fig. 1. Charts reviewed (separate file).

borderline ovarian tumors of all stages, evaluation of all sites of recurrence and cohort not limited to a fertility-sparing population.

There are several compelling reasons to avoid hysterectomy if it does not change oncologic outcomes. Hysterectomy adds surgical time and increases the risks of complications (Clarke-Pearson, 2013; Pinto, et al., 2012). Our findings suggest that it may be appropriate to forgo hysterectomy in the surgical management of borderline ovarian tumors in the non-fertility-sparing setting. This information could be valuable for clinicians in an informed consent discussion for known or suspected borderline ovarian tumors.

CRediT authorship contribution statement

Breana L. Hill: Investigation, Writing - original draft. **Marisa R. Moroney:** Validation, Investigation, Writing - review & editing. **Miriam D. Post:** Investigation, Writing - review & editing. **Brandon Sawyer:** Validation, Writing - review & editing. **Jeanelle Sheeder:** Formal analysis, Data curation, Writing - review & editing. **Rebecca J. Wolsky:** Investigation, Writing - review & editing. **Carolyn Lefkowits:** Conceptualization, 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

Silverberg, S.G., B.D., Kurman, R.J., Seidman, J.D., 2004. Prat J, Ronnett BM et al., Borderline ovarian tumors: key points and workshop summary. Hum Pathol., 35, 8, 910–917.
Kurman, R.J., S.I., 2000. Ovarian serous borderline tumors: a critical review of the literature with emphasis on prognostic indicators. Hum Pathol. 31, 5, 539–557.
Hauptmann, S., et al., 2017. Ovarian borderline tumors in the 2014 WHO classification: evolving concepts and diagnostic criteria. Virchows Archiv. 470 (2), 125–142.
du Bois, A., T.F., Mahner, S., Heitz, F., Harter, P., 2016. Management of borderline ovarian tumors. Ann. Oncol. 20–22.
Matsuo, K., M.H., Takiuchi, T., et al., 2017. Role of hysterectomy and lymphadenectomy in the management of early-stage borderline ovarian tumors. Gynecologic Oncol., 144, 3, 496–502.
DM, G., 2002. Clinical management of potential tumours of low malignancy. Best Pract. Res. Clin. Obstet. Gynaecol. 16 (4), 513–527.
Karlsen, N.M.S., et al., 2016. Relapse and Disease Specific Survival in 1143 Danish Women Diagnosed with Borderline Ovarian Tumours (BOT). Gynecologic Oncol. 142 (1), 50–53.
Park, J.Y., K.D., Kim, J.H., Kim, Y.M., Kim, Y.T., Nam, J.H., 2009. Surgical management of borderline ovarian tumors: The role of fertility-sparing surgery. Gynecologic Oncol. 113, 1, 75–82.
Benedet JL, B.H., Jones H, III et al., FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet, 2000. 70(2): p. 209–262.
Trope, C.G., K.G., Makar, A., 2000. Surgery for borderline tumor of the ovary. Semin. Surg. Oncol., 19, 69–75.

Kennedy, A.W., W.R.H., Ovarian papillary serous tumors of low malignant potential (serous borderline tumors). A long-term follow-up study, including patients with microinvasion, lymph node metastasis, and transformation to invasive serous carcinoma. Cancer, 1996. 78, 2, 278–286.

Fotopoulou, C., G.S., Schefold, J.C., denkert, C., Lichtenegger, W., Sehouli, J., 2009. Systematic evaluation of the intraoperative tumor pattern in patients with borderline tumor of the ovary. Int. J. Gynecol. Cancer, 19, 9, 1550–1555.

Mandelbaum, R.S., B.E., Machida, H., Grubbs, B.H., Roman, L.D., Matsuo, K., 2019. Utero-ovarian preservation and overall survival of young women with early-stage borderline ovarian tumors. Arch. Gynecol. Obstet., 299, 6, 1651–1658.

Clarke-Pearson DL, G.E., Complications of hysterectomy. Obstet Gynecol., 2013. 121(3): p. 654-73.

Pinto, P.R., M.T., Nogueira-Silva, C., et al., 2012. Risk factors for persistent postsurgical pain in women undergoing hysterectomy due to benign causes: a prospective predictive study. J. Pain, 13, 1045–1057.