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Utero-ovarian preservation and overall survival of young women with early-stage borderline ovarian tumors

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Abstract

Purpose To examine survival of women who had uterine and ovarian preservation during surgical treatment for early-stage borderline ovarian tumors (BOTs).

Methods The Surveillance, Epidemiology, and End Results Program was used to identify women aged < 50 years with stage I BOTs who underwent ovarian conservation at surgical treatment between 1988 and 2003. Survival outcomes were examined based on the use of concurrent hysterectomy at surgery.

Results Among 6379 cases of BOT, there were 1065 women who had utero-ovarian preservation at surgery, and there were 52 women who had hysterectomy with ovarian preservation alone. Women who had uterine preservation were more likely to be single and diagnosed in recent years (both, $P<0.05$). On univariable analysis, women who had utero-ovarian preservation had cause-specific survival similar to those who had ovarian preservation alone without uterine preservation (10-year rates: 99.2% versus 98.1%, $P=0.42$); however, overall survival was higher in the utero-ovarian preservation group compared to the hysterectomy group (95.8% versus 87.6%, $P<0.001$). On multivariable analysis, utero-ovarian preservation remained an independent prognostic factor for improved overall survival (adjusted hazard ratio 0.35, 95% confidence interval 0.15–0.79, $P=0.012$). Cardiovascular disease mortality was lower in the utero-ovarian preservation group compared to the hysterectomy group, but it did not reach statistical significance (20-year cumulative rate, 0.8% versus 3.0%, $P=0.29$).

Conclusion Our study suggests that utero-ovarian preservation for young women with early-stage BOTs may be associated with improved overall survival compared to ovarian preservation alone without affecting BOT-related survival outcome.

Keywords Borderline ovarian tumor · Fertility-sparing surgery · Ovarian preservation · Survival · Hysterectomy

Introduction

Borderline ovarian tumors (BOTs), also known as tumors of low malignant potential or atypical proliferative tumors, have histologic features and biological behavior on the spectrum between benign and frankly malignant epithelial ovarian neoplasms [1]. These tumors have generated considerable debate for decades, not only regarding terminology, but also surrounding histopathologic diagnosis and appropriate treatment algorithms. The International Federation of Gynecology and Obstetrics (FIGO) classified them as a separate entity of epithelial ovarian tumors with a distinct staging system in early 1970s [2]. Compared to invasive ovarian malignancy, BOTs usually affect women at a younger age, with approximately one-third of patients diagnosed before the age of 40 years [3]. In the majority of women with BOTs, disease is diagnosed at an early stage

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and confined to a single ovary. Five- and ten-year survival rates of 97% and 96% have been reported for early-stage serous tumors while these rates are 96% and 90% for early-stage mucinous tumors [4, 5]. Due to the excellent prognosis of these tumors, fertility-sparing surgery is of particular interest in young women with early-stage disease.

Surgery remains the mainstay of management for BOTs, but the extent of surgical management has been extensively debated because of comparable survival outcomes between conservative and radical approaches [6–11]. Historically, the same radical surgical staging procedures for invasive epithelial ovarian cancer have been applied to BOTs, including bilateral salpingo-oophorectomy, hysterectomy, pelvic and para-aortic lymphadenectomy, omentectomy, peritoneal washings and biopsies, and appendectomy for those with mucinous histology [12, 13]. The recommendation to perform these procedures as part of surgical staging is based on the treatment rationale used in invasive ovarian cancer. Hysterectomy allows for the diagnosis and removal of possible tumor implants on the uterine serosa, while lymphadenectomy is used to identify potential nodal metastases. In BOTs, the probability of either uterine or nodal metastases is extremely low, while the morbidity associated with these procedures can be substantial [6–15].

Recurrence rates following conservative surgical management are higher, with one systematic review reporting a pooled estimate of 13% compared to 0–5% following radical surgery [14, 15]. Thus, radical surgery is often still recommended for older women for whom fertility or ovarian preservation are not of major concern. In young women, however, recurrences are often surgically salvageable with a good prognosis, and higher recurrence rates have not translated into higher mortality, a key difference from invasive disease [14]. Thus, given the lack of impact on survival, recent studies have not supported the performance of routine stating surgery, namely hysterectomy and lymphadenectomy, for stage I BOTs [7, 8, 16, 17].

As conservative or fertility-sparing surgery becomes more widely accepted in the treatment of BOTs, tailored discussions with young women with BOTs regarding reproductive life planning, postoperative morbidity, and long-term survival data can help dictate the best surgical approach for patients on an individual basis. When considering conservative surgical management, future fertility is an obvious indication for uterine and ovarian preservation, however, survival outcomes following utero-ovarian preservation and ovarian preservation alone have not yet been studied. The objective of the study was to examine the survival impact of utero-ovarian preservation compared to ovarian preservation with hysterectomy in the surgical treatment of early-stage BOTs.

Materials and methods

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute is the largest population-based tumor registry in the United States, capturing around 400,000 cancer cases annually and accounting for approximately 34% of the US population [18]. It includes patient demographics, clinical tumor data, treatment information, as well as long-term follow-up to assess survival outcomes, and allows for high-quality population-level estimates of cancer incidence and mortality.

This database is both publicly available and deidentified, making it exempt from review by the University of Southern California Institutional Review Board. The STROBE guidelines were applied for study design and planning [19]. SEER*Stat 8.3.2. (IMS Inc., Calverton, MD, USA) was used to extract the dataset Cases of BOTs between 1988, when they were first recorded in SEER, and 2003 were extracted using corresponding histopathology codes (serous 8442-1, 8451-1, and 8462-1; and mucinous 8472-1, 8473-1) [5, 20]. Statistical Package for Social Sciences (version 12.0, Chicago, IL, USA) was then used for analyses.

Within the extracted dataset, women aged < 50 years with stage T1 BOTs with known hysterectomy and oophorectomy status were included. An age cutoff of < 50 years was chosen due to a general consensus that the reproductive age limit is 50 years of age per the World Health Organization (WHO) definition [21]. Exclusion criteria included stage T2–3 or unknown stage, metastatic disease, prior radiotherapy, or unknown hysterectomy or oophorectomy status. Information regarding patient demographics, tumor characteristics, treatment modality and surgeries performed, and survival during the follow-up period were extracted from the database and used in analyses.

Patient demographics included age at diagnosis (grouped as age < 30, 30–39, and ≥ 40 years), calendar year at diagnosis (1995 or earlier versus later than 1995), race/ethnicity (White, Black, Hispanic, Asian, and others), marital status (single, married, and others), and registered area (West, Central, and East). Tumor information included histology (serous versus mucinous), cancer stage [T1a, T1b, T1c, and T1 not otherwise specified (NOS)], and tumor size (≤5.0 cm, 5.1–10 cm, and >10 cm) Surgical treatment patterns were analyzed by performance of oophorectomy, hysterectomy, and/or lymphadenectomy. Cause-specific survival (CSS) and overall survival (OS) were calculated based on mortality information during the follow-up period.

The American Joint Committee on Cancer (AJCC) 3rd staging classification, which is reported in the SEER database during the study time period, was recoded for T stage

[22, 23]. Histology of BOTs was categorized based on the WHO classification system and ascertained using the published International Classification of Disease for Oncology 3rd edition (ICD-O-3) SEER site/histology validation list [24]. Lymphadenectomy performance was based on the coding for the Regional Nodes that was introduced into the database in 1988, and number of nodes removed at time of lymphadenectomy was documented and grouped (1–9, 10–19, and ≥ 20).

The ICD-9 procedure codes were used to identify surgical operations performed, principally hysterectomy and oophorectomy. If the surgical coding for either procedure was absent, it was interpreted as that it was not performed, thus absence of oophorectomy codes was used as a surrogate for ovarian conservation. Cause-specific survival was defined as the time interval between the BOT diagnosis and death due to BOT. Overall survival was defined as the time interval between the BOT diagnosis and death from any cause (all-cause). Patients without survival event at the last follow-up were censored.

Primary outcome for analysis was survival of women < 50 years of age with stage T1 BOTs who underwent ovarian preservation, stratified by utilization of concurrent hysterectomy.

For univariable analysis, the Student *t* test or Mann–Whitney *U* test was used for continuous variables, and the Chi-square test or Fisher exact test for ordinal or categorical variables. The Kaplan–Meier estimator with the log-rank test was used to produce and analyze the difference in survival curves in BOTs [25]. Cox proportional hazard regression models were performed to identify independent prognostic factors in multivariable analysis [26]. All covariates in the univariable analysis with $P < 0.10$ were entered in the initial model. The ratio of death as the event of interest per prognostic variable was compared across variables to assess for over-adjustment (cutoff level < 10) [27, 28]. A variance inflation factor value of ≥ 2.0 was interpreted as multicollinearity in this study [29]. Finally, the conditional backward method was used to retain only the significant covariates, using a cutoff of $P < 0.05$ in the final model. All statistical analyses were two-tailed, and a $P < 0.05$ was considered statistical significant. The magnitude of statistical significance was expressed with hazard ratios [HR] and 95% confidence intervals [CI].

Results

Patient selection schema is shown in Fig. 1. Of 6379 total BOTs identified in the SEER database between 1988 and 2003, 2890 were diagnosed in women less than 50 years of age and stage I. Of the women for whom data regarding ovarian status was available, 1117 (59.8%) underwent

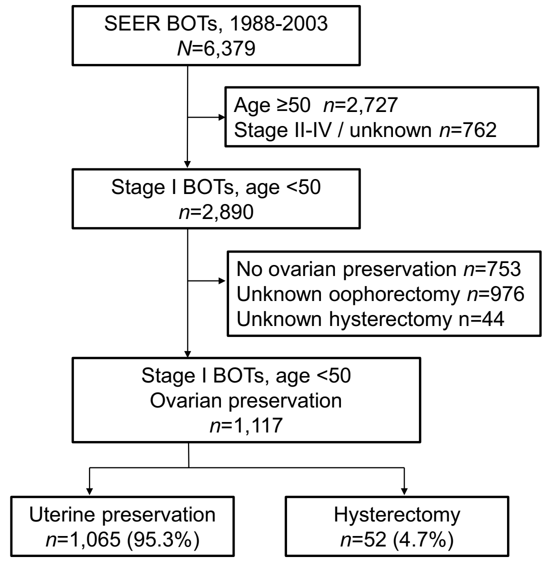

Fig. 1 Selection schema. *Among available information for surgical staging. *SEER* Surveillance, Epidemiology, and End Results program, *BOTs* borderline ovarian tumors

ovarian-preserving surgery with known hysterectomy status, and of these women, 1065 (95.3%) had uterine preservation while 52 (4.7%) underwent hysterectomy.

Patient characteristics based on hysterectomy status are shown in Table 1. Women who underwent hysterectomy were significantly older than those who had uterine preservation (mean age, 39.2 versus 31.4 years, $P < 0.001$). Single women were more likely to undergo uterine preservation compared to married women (97.4% versus 94.6%, $P = 0.005$). A more recent year of diagnosis was significantly associated with increased uterine preservation (≥ 1995 versus < 1995, 96.9% versus 93.8%, $P = 0.015$). There was no difference observed between those who underwent hysterectomy and those in whom the uterus was preserved in terms of race/ethnicity, registry area, T stage, histology subtype, tumor size, performance of lymphadenectomy, or number of lymph nodes sampled if lymphadenectomy was performed.

Survival analysis was performed for both cause-specific and overall survivals. The median follow-up time of censored cases was 17 years (interquartile range, 6.3 years). There were 10 (0.9%) women who died as a result of BOTs, and there were 48 (4.3%) all-cause deaths. On univariable analysis, women who had utero-ovarian preservation had BOT-related survival similar to those who had ovarian preservation at the time of hysterectomy (20-year CSS rates 99.2% versus 98.1%, $P = 0.42$; Fig. 2a). Overall survival was improved in women who had utero-ovarian preservation compared to those who underwent hysterectomy (20-year OS rates: 95.8% versus 87.6%, $P < 0.001$; Fig. 2b).

On univariable analysis, age and stage were significantly associated with overall survival (both, $P < 0.05$; Table 2).

Table 1 Patient demographics

Characteristic	Uterine preservation	Hysterectomy	*P* value
Number	1065 (95.3%)	52 (4.7%)	
Age (y)	31.4 (±7.7)	39.2 (±7.1)	**< 0.001**
<30	435 (99.3%)	3 (0.7%)	
30–39	459 (95.8%)	20 (4.2%)	
40–49	171 (85.5%)	29 (14.5%)	
Race/ethnicity			0.11
White	670 (94.5%)	39 (5.5%)	
Black	66 (93.0%)	5 (7.0%)	
Hispanic	190 (97.4%)	5 (2.6%)	
Asian	107 (99.1%)	1 (0.9%)	
Others	32 (94.1%)	2 (5.9%)	
Marital status			**0.005**
Single	445 (97.4%)	12 (2.6%)	
Married	512 (94.6%)	29 (5.4%)	
Others	108 (90.8%)	11 (9.2%)	
Registry area			0.06
West	737 (96.2%)	29 (3.8%)	
Central	179 (94.7%)	10 (5.3%)	
East	149 (92.0%)	13 (8.0%)	
Year at diagnosis			**0.015**
1995 or earlier	510 (93.8%)	34 (6.3%)	
After 1995	555 (96.9%)	18 (3.1%)	
AJCC stage			0.59
T1a	898 (95.0%)	47 (5.0%)	
T1b	23 (100%)	0	
T1c	91 (96.8%)	3 (3.2%)	
T1 NOS	52 (96.3%)	2 (3.7%)	
Histology			0.20
Serous	555 (94.5%)	32 (5.5%)	
Mucinous	510 (96.2%)	20 (3.8%)	
Tumor size			0.12
≤5.0 cm	150 (94.4%)	4 (2.6%)	
5.1–0 cm	99 (96.1%)	4 (3.9%)	
>10 cm	120 (98.4%)	2 (1.6%)	
Unknown	696 (94.3%)	42 (5.7%)	
Lymphadenectomy			0.11
No	980 (95.6%)	45 (4.4%)	
Yes	77 (91.7%)	7 (8.3%)	
Sampled pelvic nodes[a]			0.38
1–9	42 (93.3%)	3 (6.7%)	
10–19	13 (81.3%)	3 (18.8%)	
≥20	7 (87.5%)	1 (10.1%)	

Significant *P* values are emboldened

Number (%), mean (±SD), or median (range) is shown

y years, *AJCC* American Joint Commission on Cancer, *NOS* not otherwise specified

[a]Among 69 cases with available sampled node number

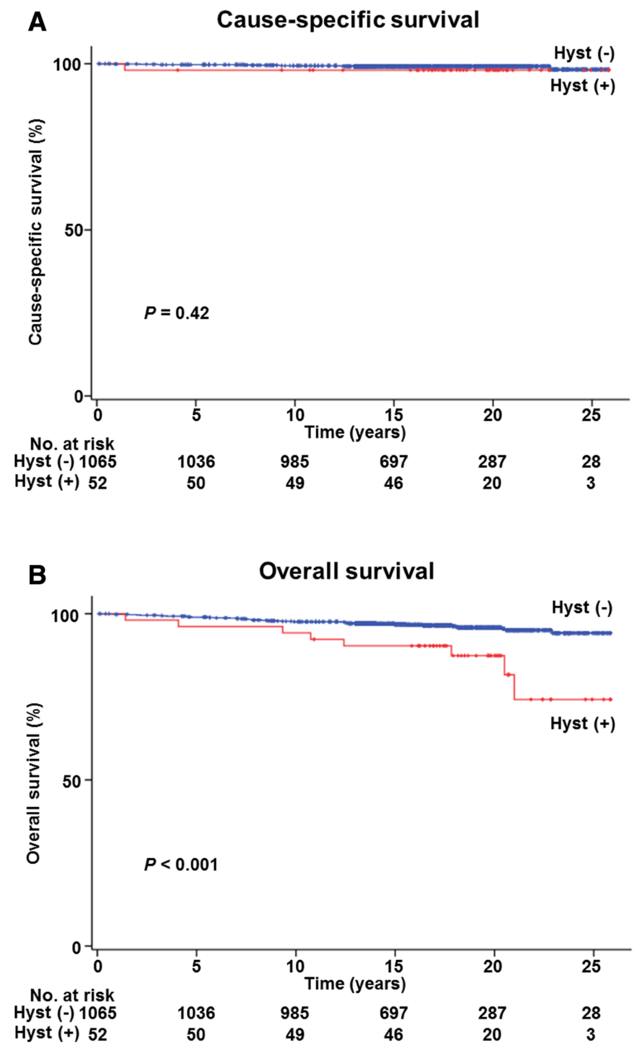

Fig. 2 Survival curves based on hysterectomy status. Log-rank test for *P* values. Survival curves based on hysterectomy status are shown for **a** cause-specific survival and **b** overall survival. *hyst* hysterectomy

Performance of lymphadenectomy (yes versus no, HR 1.99, 95% CI 0.84–4.69, $P=0.11$), and histology type (mucinous versus serous, HR 0.86, 95% CI 0.49–1.52, $P=0.60$) did not impact overall survival outcomes in this study population. Upon multivariable analysis for overall survival, controlling for age and cancer stage, utero-ovarian preservation remained a significant prognostic factor associated with improved overall survival compared to ovarian preservation alone, reducing all-cause mortality risk by 65% (adjusted HR 0.35, 95% CI 0.15–0.79, $P=0.012$).

Cause of death was examined between the two groups, and there were 7 (0.6%) women who died of cardiovascular disease. On univariable analysis, mortality due to cardiovascular disease was lower in the utero-ovarian preservation group compared to the hysterectomy group. Uterine preservation in addition to ovarian preservation reduced the

Table 2 Univariable and multivariable analysis for overall survival

Characteristic	No.	20 years (%)	Univariable		Multivariable	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (y)				**0.003**		**0.046**
< 30	438	97.1%	1		1	
30–39	479	95.3%	1.55 (0.76–3.16)		1.46 (0.71–3.00)	0.31
40–49	200	91.6%	3.36 (1.58–7.13)		2.70 (1.21–6.01)	**0.015**
Ethnicity				0.11		
White	709	95.6%	1			
Black	71	87.2%	2.46 (1.08–5.58)			
Hispanic	195	98.3%	0.56 (0.20–1.58)			
Asian	108	95.1%	0.93 (0.33–2.63)			
Others	34	94.1%	1.42 (0.34–5.93)			
Marital status				0.06		
Single	457	96.9%	1			
Married	541	95.1%	1.31 (0.68–2.50)			
Others	119	90.7%	2.54 (1.14–5.66)			
Registry area				0.49		
West	766	96.0%	1			
Central	189	94.6%	1.41 (0.70–2.84)			
East	162	93.2%	1.43 (0.67–3.04)			
Year at diagnosis				0.70		
1995 or earlier	544	95.1%	1			
After 1995	573	96.3%	0.89 (0.47–1.67)			
AJCC T stage				**0.032**		**0.025**
T1a	945	95.7%	1		1	
T1b	23	90.6%	2.68 (0.64–11.1)		3.46 (0.82–14.6)	0.09
T1c	94	96.2%	0.85 (0.26–2.75)		0.95 (0.29–3.0)	0.93
T1 NOS	54	90.7%	3.02 (1.27–7.15)		3.22 (1.35–7.68)	**0.008**
Histology				0.60		
Serous	587	94.5%	1			
Mucinous	530	96.3%	0.86 (0.49–1.52)			
Tumor size				0.09		
≤ 5.0 cm	154	94.0%	1			
5.1–10 cm	103	92.2%	1.24 (0.49–3.13)			
> 10 cm	122	97.4%	0.41 (0.11–1.49)			
Unknown	738	95.8%	0.56 (0.27–1.15)			
Uterine preservation				**< 0.001**		
No	52	87.6%	1		1	
Yes	1065	95.8%	0.26 (0.12–0.56)		0.35 (0.15–0.79)	**0.012**
Lymphadenectomy				0.11		
No	1025	95.6%	1			
Yes	84	93.9%	1.99 (0.84–4.69)			

A Cox proportional hazard regression model for multivariable analysis. All the covariates in the univariable analysis with cutoff of $P < 0.10$ were entered in the initial model. Conditional backward method was used to retain only the significant covariates with cutoff of $P < 0.05$ in the final model. Significant *P* values are emboldened. Variance inflation factor < 2.0 for procedure type and nodal metastasis with absence of multicollinearity

y years, *AJCC* American Joint Commission on Cancer, *NOS* not otherwise specified, *hyst* hysterectomy, *LND* lymphadenectomy, *HR* hazard ratio, *CI* confidence interval cardiovascular mortality risk by 66%, however, it did not reach statistical significance (20-year cumulative rate, 0.8% versus 3.0%, HR 0.34, 95% CI 0.04–2.80, $P = 0.29$).

Discussion

In young women, therapeutic decisions regarding the surgical management of BOTs are of major concern, given the potential for infertility, hormonal deprivation and sequelae of premature ovarian failure, perioperative morbidity, and long-term survival. Data regarding the safety and efficacy of conservative or fertility-sparing surgical management in BOTs in reproductive-aged women have been reassuring, and prior studies have consistently shown that there is no detrimental impact on survival [4, 15, 16, 30]. This study validates these results, with excellent cause-specific survival outcomes in those who had ovarian or utero-ovarian preservation with over 20 years of follow-up. A key new finding of this study is that overall survival was significantly improved with utero-ovarian preservation in comparison to ovarian preservation alone with hysterectomy. This has a meaningful clinical impact on treatment considerations for young women with stage I BOT.

Our previous study using the same population-based database highlighted the variety of surgical procedures performed for BOTs in young women [16]. In this series, nearly 60% of women younger than 50 underwent ovarian-conserving surgery, and among these women, the vast majority also had uterine preservation. Over 30% of women younger than 50 years of age were found to have undergone hysterectomy and 25% were found to have undergone lymphadenectomy for the treatment of stage I BOTs [16]. Clearly, management of young women with BOTs remains controversial with variable treatment patterns despite overall paradigm shift towards more conservative surgical management [16, 17]. Based on our results, when conservative surgical management is performed, uterine preservation should be considered in addition to ovarian preservation for improved overall survival in young women regardless of future childbearing goals.

One possible explanation for increased survival with utero-ovarian preservation compared to ovarian preservation alone is the effect of hysterectomy on the ovarian blood supply via disruption of the utero-ovarian vessels, resulting in diminished ovarian function. The association between hysterectomy and subsequent decreased ovarian function or early menopause has been examined in several prior studies. Farquhar et al. conducted a prospective cohort study examining serial follicle-stimulating hormone (FSH) levels for 5 years following hysterectomy and concluded that menopause occurred nearly 4 years earlier in women following hysterectomy than those with intact uteri [31]. Moorman et al. confirmed these findings, reporting an almost twofold increased risk of ovarian failure 4 years following hysterectomy [32]. The theory of compromised ovarian blood supply and function following hysterectomy was further examined by Xiangying et al. Using Doppler ultrasonography, they demonstrated a lower peak systolic flow velocity and higher pulsatility index in the ovarian artery, in addition to significantly higher levels of FSH and luteinizing hormone (LH) and significantly lower estradiol and progesterone levels, in patients undergoing hysterectomy compared to those undergoing myomectomy [33].

While the notion of premature menopause following hysterectomy has been proposed previously, our study was the first to our knowledge to show actual reductions in overall survival due to this phenomenon. Surgical or premature menopause is well known to be associated with increased mortality due to cardiovascular disease, particularly coronary artery disease [34, 35]. Our study showed increased rates of cardiovascular mortality in the group who underwent ovarian preservation with hysterectomy compared to those who had utero-ovarian preservation, however, this clinically significant finding did not reach statistical significance. This is likely due to the low number of deaths, during study follow-up in this relatively young population with an overall good prognosis. Further studies are needed to elucidate whether the decreased survival rate in those who underwent ovarian preservation with concurrent hysterectomy compared to those who had utero-ovarian preservation is due to cardiovascular mortality.

Strengths of this study include a large population-based sample with long-term follow-up of nearly 2 decades. This approach is particular useful in BOTs, given that they generally have a good prognosis with low mortality rates. Additionally, because BOTs disproportionately affect young women compared to invasive ovarian cancer, the long follow-up period allows for examination of outcomes that may impact the lives of patients several years or decades following initial treatment.

Despite these strengths, a number of limitations exist. First, due to lack of coding information, we did not stratify by type of ovarian preservation, i.e., unilateral or bilateral cystectomy versus unilateral oophorectomy, which impacts recurrence patterns as well as future fertility [4, 36]. For instance, there were 23 cases of stage T1b tumors in this study. The absence of procedure codes for oophorectomy in these cases suggests that bilateral cystectomies were performed, but the lack of this coding information for cystectomy did not allow us to determine the exact surgical procedures performed in these cases. If this had any impact on results, the inclusion of patients who underwent only cystectomy with uterine preservation would have skewed results towards decreased survival rather than falsely elevating it given the increased rates of recurrence with cystectomy [4, 36].

Due to the nature of this retrospective study, variables contributing to the decision and indication for performance of a hysterectomy versus uterine preservation, are not obtainable, thus there may have been other contributing factors for which we were unable to account. This is particularly clinically relevant when uterine preservation is considered in young women with early-stage BOTs, and evaluation of uterine factors, including screening for cervical and endometrial pathology, should be performed preoperatively. In all studies of this type, misclassification or miscoding of cases may also be a concern. We were not able to discern temporality of surgery, i.e., whether patients had a history of hysterectomy prior to study enrollment or whether the patient underwent several separate surgical procedures for recurrent disease at different times. This database does not include information regarding subsequent staging procedures or recurrence patterns following diagnosis. Thus, a complete risk assessment was not feasible in this study.

Finally, this database does not have information regarding pregnancy outcomes following fertility-sparing surgery for BOTs. Darai et al. published a pooled estimate of spontaneous pregnancy of 54% following conservative treatment in early-stage BOTs [15]. Rates of conception are undoubtedly affected by the type of fertility-sparing surgery (cystectomy versus unilateral oophorectomy), surgical approach (laparotomy versus minimally invasive), patient age and demographics, however, they have also been shown to be affected by type of histology, and pregnancy rates have been higher in those with mucinous tumors than those with serous histology [37, 38]. Additionally, rates of infertility prior to the diagnosis of BOT were estimated at 10–35% in one published series [39]. Assisted reproductive technologies can be utilized for women with BOT-associated infertility; however, cautious use of fertility drugs for ovarian hyperstimulation is advised due to the possible risk of disease recurrence [4, 39]. Again, this database does not have this information.

Currently, there is no general consensus for follow-up after childbearing is completed, and it continues to be debated whether or not these patients should undergo reoperation to complete surgical staging. In evaluating a potential role for re-staging operations following initial incomplete surgical staging, rates of up-staging were low when examined in one retrospective multicenter study, and another study showed no difference in survival or clinical outcome among patients with complete versus incomplete surgical staging [30, 40, 41]. This is particularly relevant for two reasons. First, these data support conservative surgical approaches in young women, and it precludes the argument for a more radical initial surgical management due to the additional operative morbidity in a second staging procedure. Second, 78% of BOTs are first diagnosed by general obstetrician-gynecologists after surgery for presumed benign disease without routine staging at the time of surgery [13]. Future study should be directed towards achieving consensus on the optimal management approach for women with history of conservative surgery for BOTs once fertility goals are completed.

In conclusion, conservative surgery is safe and feasible without impact on overall survival in young reproductive-aged women with stage T1 BOTs. Regardless of future fertility goals, the improved overall survival in women who underwent utero-ovarian preservation in this study compared to ovarian preservation alone with hysterectomy can help direct surgical decision-making in young women with BOTs. Surgical management of BOTs continues to require a highly tailored and individualized approach based on the patient's age and reproductive planning goals, with discussion regarding risks and benefits of conservative versus radical procedures. These results suggest that during the preoperative consent process in women undergoing surgical management of early-stage BOT, clinicians should not only discuss issues relating to future fertility and disease recurrence but also consider incorporating discussion of long-term sequelae of treatment related to cardiovascular and bone health. Further study, including postoperative evaluation of ovarian function, is warranted to validate our results.

Author contributions R.S.M.: investigation and writing original draft. E.A.B.: visualization, review and editing manuscript, and abstract presentation. H.M.: data curation, formal analysis, visualization, review and editing manuscript. B.H.G.: supervision, review and editing manuscript. L.D.R.: funding acquisition, supervision, review and editing manuscript. K.M.: review and editing manuscript, formal analysis, funding acquisition, investigation, methodology, project administration, resource, writing original draft, review and editing manuscript.

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Compliance with ethical standards

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