Gynecologic Oncology 153 (2019) 230–237

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Mucinous borderline ovarian tumor *versus* invasive well-differentiated mucinous ovarian cancer: Difference in characteristics and outcomes

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HIGHLIGHTS

- Mucinous borderline ovarian tumors (BOT) and invasive well-differentiated ovarian cancer (OC) were compared
- Clinical demographics between mucinous-BOT and mucinous-OC are largely different
- Mucinous-OC is more likely to present with stage T1c disease whereas mucinous-BOT is more likely to have large tumor size
- Mucinous-OC had worse prognosis compared to mucinous-BOT

ARTICLE INFO

Article history:
Received 17 December 2018
Received in revised form 29 January 2019
Accepted 4 February 2019
Available online 20 February 2019

Keywords:
Ovarian cancer
Borderline ovarian tumor
Low malignant potential
Mucinous ovarian cancer
Survival

ABSTRACT

Objective. Mucinous borderline ovarian tumor (mucinous-BOT) and invasive well-differentiated mucinous ovarian cancer (mucinous-OC) are often histopathologically misclassified. The objective of this study was to examine differences in clinico-pathological characteristics and outcomes of these two entities.

Methods. This is a retrospective population-based study examining the Surveillance, Epidemiology, and End Results Program from 1988 to 2000. Stage I mucinous-BOTs and stage I well-differentiated mucinous-OC were compared for patient demographics, tumor characteristics, and outcomes. Propensity score matching and multivariable analysis were used to assess cause-specific survival (CSS).

Results. A total of 2130 mucinous-BOT and 581 mucinous-OC cases were examined for analysis. On multivariable analysis, women with mucinous-OC were more likely to be older, Eastern U.S. residents, and have undergone hysterectomy or lymphadenectomy compared to those with mucinous-BOT, and the number of women diagnosed with mucinous-OC decreased over time (all, $P < 0.05$). Mucinous-OCs were more likely to be stage T1c and have a smaller tumor size as compared to mucinous-BOT (both, adjusted-$P < 0.05$). After propensity score matching, women with mucinous-OC had significantly poorer CSS compared to those with mucinous-BOT on multivariable analysis (10-year rates: 92.7% *versus* 97.5%, adjusted-hazard ratio [HR] 2.03, $P = 0.007$). Similar results were observed among subgroups for reproductive age, stage T1a disease, large tumor, and unstaged cases (all, $P < 0.05$).

Conclusion. Stage I mucinous-BOT and stage I invasive well-differentiated mucinous-OC have distinct differences in clinical characteristics and patient survival. The inability to conduct centralized pathology review in our study limits our conclusions given the recognized issue of misclassification of mucinous-BOT and mucinous-OC, but further highlights the importance of making the proper histopathological diagnosis for invasive cancer when the ovarian tumor is of mucinous histology.

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1. Introduction

Borderline ovarian tumors (BOTs) have histopathologic characteristics and clinical behavior between benign ovarian tumors and invasive epithelial ovarian cancers (OCs) [1]. For this reason, histological

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https://doi.org/10.1016/j.ygyno.2019.02.003
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misclassification of BOT as OC or OC as BOT is not uncommon [2–5]. Nearly 10% of BOTs diagnosed *via* intraoperative frozen evaluation are upgraded to the diagnosis of invasive OC on permanent histology evaluation [2,6,7]. A re-evaluation of permanent histology slides for central pathology review by expert pathologists identified that approximately 5% of BOTs were under-diagnosed and reclassified as OC [6]. This is particularly common with mucinous type tumors [2–5].

One important concern regarding the misdiagnosis of OC as BOT is the impact on survival. In cases of OC misdiagnosed as BOT, patients would most likely receive under-treatment resulting in compromised survival. Conversely, when BOT is over-diagnosed as OC, patients may receive additional unnecessary treatments that can result in significant side effects. A prior large-scale retrospective study has shown that women with BOT which was reclassified to OC following central pathology review have poorer survival compared to those without [6].

This evidence highlights the importance of making a proper diagnosis between the two entities as it ultimately impacts survival. Yet, population-based statistics are lacking to date regarding the comparison of survival outcome of women with BOT to those with OC. As (*i*) distinguishing mucinous-BOT and mucinous-OC is particularly challenging, even by experienced pathologists when mucinous-OC is well-differentiated, and (*ii*) under-diagnosed BOT are commonly reclassified as well-differentiated OC [7,8], this study compared clinical characteristics and outcomes of women with stage I mucinous-BOT and stage I mucinous-OC with well-differentiated tumors through an examination of a population-based tumor registry.

2. Materials and methods

2.1. Source

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program was utilized for this retrospective observational cohort study [9]. The SEER program is the largest population-based tumor registry in the United States. Launched in 1973, the SEER database has more than a four-decade history of operations and covers approximately 34.6% of the U.S. population in the most recent registry areas. It is considered a powerful tool for identification of population characteristics and the study of long-term outcomes for rare tumors. The deidentified data in the SEER database is publicly available, and thus its use is exempt from review by the University of Southern California Institutional Review Board.

2.2. Eligibility

Women with stage I mucinous-BOT who were diagnosed between 1988 and 2000 were eligible for the mucinous-BOT cohort. This time period was chosen as the data for BOT were first recorded in the SEER program in 1988 [10]. The study endpoint was chosen as 2000 due to the infrequent number of BOT diagnoses after this time point. Women with stage I invasive well-differentiated mucinous-OC who were diagnosed between 1988 and 2000 were eligible for the mucinous-OC cohort. This period was chosen to match the study period of the mucinous-BOT group. Stage I disease was chosen because the vast majority of mucinous-BOT are stage I tumors [11].

Women who had stage II-IV or unknown stage were excluded. In the mucinous-OC cohort, those with moderately-/poorly-differentiated tumors or unknown tumor differentiation were also excluded from this study, as were secondary entries to the database.

2.3. Data extraction

SEER*Stat 8.3.2. (IMS Inc., Calverton, MD, USA) was used to extract the dataset. The International Classification of Disease for Oncology third edition site/histology validation list and World Health Organization (WHO) histological classification were used for histologic coding to identify cases with mucinous-BOT and mucinous-OC as described previously [10,12–15]. The American Joint Committee on Cancer 3rd staging classification schema that was performed between 1988 and 2003 in the SEER database was then used to identify the cases for stage I disease [16].

2.4. Clinical information

Variables abstracted from the SEER database were patient demographics, tumor characteristics, treatment type, and survival outcome. Patient demographics included age at diagnosis, calendar year at diagnosis (trisected as 1988–1991, 1992–1996, and 1997–2000), race/ethnicity (white, black, Hispanic, Asian, and others), marital status (single, married, and others), and registered area (West, Central, and East; Table S1). Tumor characteristics included cancer sub-stage (T1a, T1b, T1c, and T1NOS) and tumor size (≤4, 4.1–6, 6.1–8, 8.1–10 and ≥10 cm).

Treatment types included use of hysterectomy (yes *versus* no), and lymphadenectomy for regional lymph node chains (examined *versus* not examined). Performance of lymphadectomy with sampled lymph nodes among staged cases was also ascertained. For survival outcome, follow-up time after the diagnosis, vital status, and cause of death were collected from the database to assess cause-specific survival (CSS) and overall survival (OS).

2.5. Study definition

Age cutoff was based on the minimum *P*-value method that is widely used to determine thresholds of dichotomous outcomes [17]. The current study assessed the age cutoff *via* an unadjusted binary logistic regression model (mucinous-OC *versus* mucinous-BOT). The *P*-value results with corresponding odds ratio (OR) and 95% confidence interval (CI) were plotted for every one increment of year between age 20–80 (Fig. 1A), and the age exhibiting the smallest *P*-value was chosen for the further analysis. We identified 61 years as the age with the minimum *P*-value (6.9×10^{-7}).

T1a stage refers to the tumor limited to one ovary, capsule intact, and no tumor on the ovarian surface; T1b refers to the tumor limited to both ovaries, capsules intact, and no tumor on the ovarian surface; and T1c refers to the tumor limited to one or both ovaries with any of the following three (ruptured capsule, ovarian surface tumor involvement, malignant cells in peritoneal washing or ascites) [18].

Lymphadenectomy performance was based on the coding for the Regional Nodes that was introduced in 1988 in the SEER database, grouped as 1–7 *versus* ≥8 based on the Gynecologic Oncology Group adequate lymphadenectomy definition [19]. CSS was defined as the time interval between the diagnosis and the date of death due to corresponding malignancy in each cohort (mucinous-BOT or mucinous-OC). OS was defined as the time interval between the diagnosis and the death from any cause. Patients who were alive at the last follow-up were censored.

2.6. Study objective

The primary objective of the analysis was to compare survival between stage I mucinous-BOT and well-differentiated stage I mucinous-OC. The secondary objective was to identify the characteristic demographics associated with mucinous-OC *versus* mucinous-BOT.

2.7. Statistical approach

A binary logistic regression model was used to identify the independent characteristics for mucinous-OC over mucinous-BOT. The Kaplan-Meier method was used to construct the survival curves, and the difference between the curves was assessed with the log-rank test [20]. A Cox proportional hazard regression model was used to examine

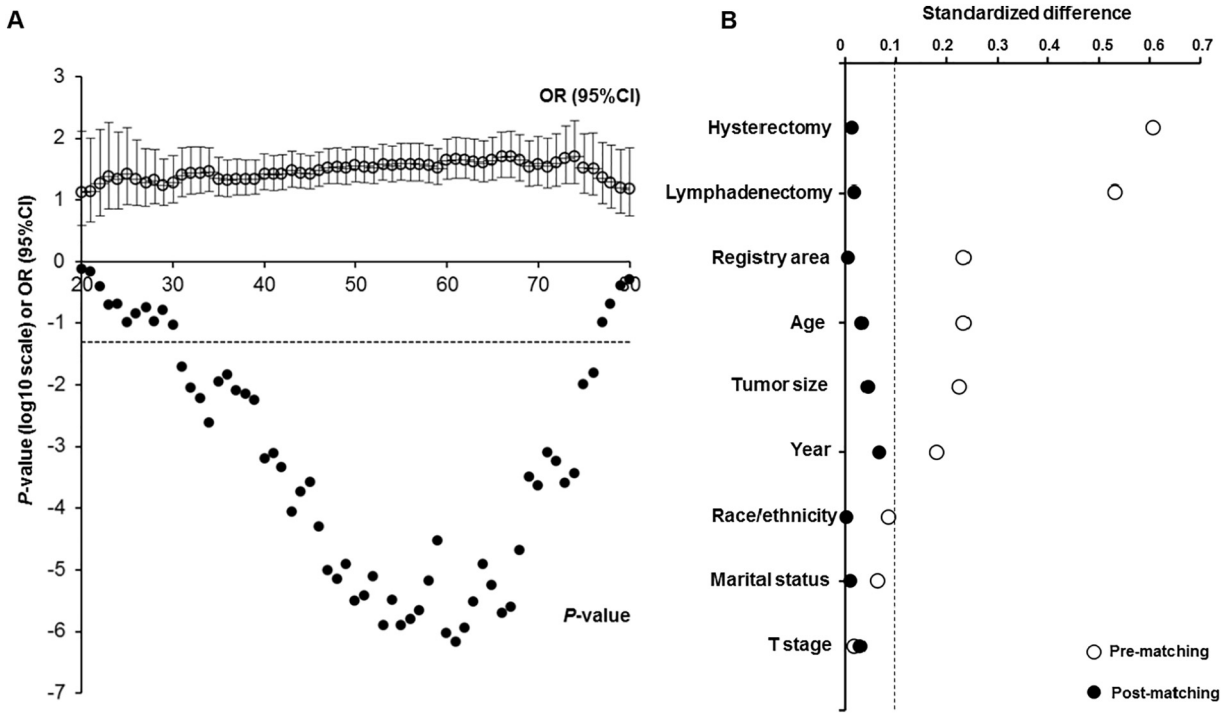

Fig. 1. Results of age cutoff analysis and propensity score matching. A) *P*-values with corresponding ORs are shown for mucinous invasive well-differentiated ovarian cancer versus mucinous borderline ovarian tumor per age at diagnosis. Y-axis represents *P*-values with log10 scale (black circles) or OR (white circle). Bars represent 95%CI. Dash line represents $P = 0.05$. B) Standardized differences before and after the propensity score matching. Abbreviations: OR, odds ratio; and CI confidence interval.

independent prognostic factors for survival [21]. Proportional hazard assumption was satisfied without interaction to time. For all of the multivariable models, all covariates with $P < 0.10$ on univariable analysis were entered in the initial model, and a conditional backward method was used to retain only the covariates with $P < 0.05$ in the final model. This liberal cutoff value for selection of covariates was used due to the relatively small sample/event size in our study.

Propensity score matching was used to adjust for background differences between the two groups [22]. All the covariates ascertained in the study were entered for matching. The propensity score was computed by multivariable logistic regression analysis, and all the aforementioned covariates were entered in the propensity score model. An automated algorithm was used for 1-to-1 propensity score matching between the two groups. The optimal caliper width for estimating differences was equal to 0.2 of the standard deviation for the logit of the propensity score, resulting in a propensity score difference cutoff of 0.033 in this study [23]. The standardized difference was examined to assess the post-matching frequency distributions between the two groups, and a value ≤0.10 was considered to indicate a good balance [24].

Various sensitivity analyses were performed to assess the robustness of the study. The association between tumor type and CSS was examined in women of reproductive age (<50 years per the WHO definition), those with stage T1a disease, those in whom the tumor size was large (≥10 cm), and those who were unstaged by lymphadenectomy. These groups are based on the rationale that BOTs are commonly confined to one ovary with large tumor size and that women with BOT are less likely to undergo lymphadenectomy [11].

The ratio of events of interest per the entered covariates was assessed for over-adjustment (cutoff level < 10) [25], and the variance inflation factor was determined among covariates with a value of ≥2.0 being interpreted as multicollinearity in multivariable analysis [26]. All statistical analyses were based on a two-tailed hypothesis, and a $P < 0.05$ was considered statistically significant. Statistical Package for Social Sciences (SPSS, version 24.0, IBM Corp, Armonk, NY, USA) was used for the analysis. The STROBE guidelines were consulted to outline this observational study [27].

3. Results

The CONSORT diagram for the study selection schema is shown in Supplemental Fig. S1: 581 cases of stage I well-differentiated mucinous-OC were compared to 2130 cases of stage I mucinous-BOT in the study.

Patient demographics are shown in Table 1. Women with mucinous-OC were older compared to those with mucinous-BOT (mean, 51.9 *versus* 48.0, $P < 0.001$). On univariable analysis, women with mucinous-OC were more likely to reside in the Eastern U.S. (22.0% *versus* 13.6%) and to have undergone hysterectomy (64.4% *versus* 35.8%) and lymphadenectomy (47.0% *versus* 23.2%) at the time of surgery (all, $P < 0.001$). They were less likely to be single (20.0% *versus* 24.7%) compared to those with mucinous-BOT ($P = 0.001$). The number of women with mucinous-OC decreased from 34.7% in the period of 1988–1991 to 22.0% in 1997–2000 ($P < 0.001$).

Mucinous-OCs were more likely to be stage T1c disease (15.7% *versus* 7.3%) and have a smaller tumor size (<4 cm: 12.9% *versus* 8.9%) compared to mucinous-BOT (both, $P < 0.05$). Among those who underwent pelvic lymphadenectomy at the time of surgery, the number of sampled lymph nodes was similar between the mucinous-OC and mucinous-BOT groups (median, 8 for both, $P = 0.73$).

On multivariable analysis (Table 1), older age (≥61 *versus* < 61 years, OR 1.55, 95%CI 1.25–1.93), Eastern U.S. residence (OR 1.98 compared to Western U.S. residence, 95%CI 1.52–2.58; and OR 2.05 compared to Central U.S. residence, 95%CI 1.51–2.80), stage T1c disease (OR 2.25 compared to T1a disease, 95%CI 1.65–3.05), smaller tumor size (OR for the interaction, from 1.36 to 0.71 for 4-10 cm), and the use of hysterectomy (OR 3.25, 95%CI 2.59–4.07) and lymphadenectomy (OR 2.77, 95%CI 2.24–3.43) at the time of surgery remained independent characteristics associated with mucinous-OC as compared to mucinous-BOT (all,

Table 1
Patient demographics.

Characteristic	Mucinous-BOT	Mucinous-OC	*P*-value	OR (95%CI)	*P*-value[§]
Number	$n = 2130$	$n = 581$			
Age (y)	48.0 (±16.7)	51.9 (±17.4)	<**0.001**		
<61	1616 (75.9%)	381 (65.6%)		1	
≥61	514 (24.1%)	200 (34.4%)		1.55 (1.25–1.93)	<**0.001**
Race/ethnicity			0.09		
White	1604 (75.3%)	462 (79.5%)			
Black	89 (4.2%)	23 (4.0%)			
Hispanic	199 (9.3%)	42 (7.2%)			
Asian	187 (8.8%)	36 (6.2%)			
Others	51 (2.4%)	18 (3.1%)			
Marital status			**0.001**		
Single	526 (24.7%)	116 (20.0%)			
Married	1091 (51.2%)	310 (53.4%)			
Others	425 (20.0%)	145 (25.0%)			
Unknown	88 (4.1%)	10 (1.7%)			
Registry area			<**0.001**		<**0.001**[*]
West	1338 (62.8%)	313 (53.9%)		1	
Central	502 (23.6%)	140 (24.1%)		0.97 (0.75–1.24)	0.78
East	290 (13.6%)	128 (22.0%)		1.98 (1.52–2.58)	<**0.001**
Year at diagnosis			<**0.001**	0.97 (0.94–0.99)	**0.031**[b]
1988–1991	380 (17.8%)	132 (22.7%)			
1992–1996	831 (39.0%)	247 (42.5%)			
1997–2000	919 (43.1%)	202 (34.8%)			
T stage			<**0.001**		<**0.001**[*]
T1a	1790 (84.0%)	464 (79.9%)		1	
T1b	65 (3.1%)	26 (4.5%)		1.41 (0.84–2.34)	0.19
T1c	156 (7.3%)	91 (15.7%)		2.25 (1.65–3.05)	<**0.001**
T1 NOS	119 (5.6%)	0		na	0.99
Tumor size (cm)			<**0.001**		<**0.001**[*]
≤4.0	189 (8.9%)	75 (12.9%)		1	
4.1–6.0	37 (1.7%)	17 (2.9%)		1.36 (0.68–2.72)	0.38
6.1–8.0	41 (1.9%)	19 (3.3%)		1.20 (0.62–2.33)	0.59
8.1–10.0	53 (2.5%)	19 (3.3%)		0.96 (0.50–1.83)	0.90
>10	426 (20.0%)	144 (24.8%)		0.71 (0.49–1.02)	0.06
Unknown	1384 (65.0%)	307 (52.8%)		0.54 (0.39–0.75)	<**0.001**
Hysterectomy			<**0.001**		<**0.001**[*]
No	1278 (60.0%)	165 (28.4%)		1	
Yes	763 (35.8%)	374 (64.4%)		3.25 (2.59–4.07)	<**0.001**
Unknown	89 (4.2%)	42 (7.2%)		2.52 (1.64–3.87)	<**0.001**
Lymphadenectomy			<**0.001**		<**0.001**[*]
No	1629 (76.5%)	306 (52.7%)		1	
Yes	494 (23.2%)	273 (47.0%)		2.77 (2.24–3.43)	<**0.001**
Unknown	7 (0.3%)	2 (0.3%)		1.83 (0.33–10.2)	0.49
Sampled pelvic nodes[a]	8 (IQR 4–14)	8 (IQR 4–14)	0.73		
1–7	205 (48.6%)	113 (48.5%)			
≥8	217 (51.4%)	120 (51.5%)			

Number (%) per column, mean (±standard deviation), or median (IQR) are shown. Student *t*-test, Mann-Whitney *U* test, or chi-square test for *P*-values (univariable analysis).
Abbreviations: IQR, interquartile range; BOT, borderline ovarian tumor; OC, invasive well-differentiated ovarian cancer; NOS, not otherwise specified; OR, odds ratio; and CI, confidence interval.

[§] P-value for multivariable analysis with a binary logistic regression model. Conditional backward methods to retain covariates with $P < 0.05$ (all the covariates with $P < 0.10$ on univariable analysis were entered in the initial model). Significant *P*-values are emboldened.

[*] *P*-values for interaction.

[a] Among staged cases.

[b] Entered as a continuous variable.

adjusted-$P < 0.05$). The number of mucinous-OC diagnoses decreased by 3% every year on multivariable analysis (adjusted-OR 0.97, 95%CI 0.94–0.99, $P = 0.031$).

After propensity score matching, 1098 cases were assessed for survival analysis (mucinous-BOT group, $n = 549$; and mucinous-OC group, $n = 549$). The demographics between the two groups were well-balanced (all, standardized difference ≤ 0.10; Table 2 and Fig. 1B). The median follow-up time of censored cases was similar between the two groups: 18.0 (IQR 15.4–20.8) years for the mucinous-BOT group *versus* 17.6 (IQR 15.0–20.6) years for mucinous-BOT ($P = 0.53$). There were 44 deaths from mucinous-OC and 22 deaths from mucinous-BOT. There were 209 all-cause deaths in the mucinous-OC group and 173 all-cause deaths in the mucinous-BOT group.

Women with mucinous-OC had significantly poorer CSS compared to those with mucinous-BOT (10-year rates: 92.7% *versus* 97.5%, net difference 4.8%, $P = 0.003$; Fig. 2A). On multivariable analysis (Table 3), this association remained independent, and mucinous-OC was associated with a nearly two-fold increased risk of death from ovarian neoplasm compared to mucinous-BOT (adjusted-HR 2.03, 95%CI 1.21–3.38, $P = 0.007$). Older age (≥61 *versus* <61 years, adjusted-HR 2.03, 95%CI 1.24–3.32, $P = 0.005$) and higher tumor stage (T1c *versus* T1a, adjusted-HR 2.38, 95%CI 1.36–4.16, $P = 0.002$) also remained independent prognostic factors.

Women with mucinous-OC had significantly poorer OS compared to those with mucinous-BOT (10-year rates: 76.1% *versus* 83.6%, net difference 7.5%, $P = 0.008$; Fig. 2B). On multivariable analysis (Table 3), mucinous-OC remained an independent prognostic factor

Table 2
Patient demographics after propensity score matching.

Characteristic	Mucinous-BOT	Mucinous-OC	*SD*
Number	$n = 549$	$n = 549$	
Age (y)	51.4 (±15.4)	51.9 (±17.5)	0.030
Race/ethnicity			0.003
White	434 (79.1%)	436 (79.4%)	
Black	27 (4.9%)	23 (4.2%)	
Hispanic	40 (7.3%)	39 (7.1%)	
Asian	31 (5.6%)	35 (6.4%)	
Others	17 (3.1%)	16 (2.9%)	
Marital status			0.010
Single	113 (20.6%)	109 (19.9%)	
Married	292 (53.2%)	297 (54.1%)	
Others	135 (24.6%)	133 (24.2%)	
Unknown	9 (1.6%)	10 (1.8%)	
Registry Area			0.005
West	302 (55.0%)	301 (54.8%)	
Central	130 (23.7%)	134 (24.4%)	
East	117 (21.3%)	114 (20.8%)	
Year at diagnosis			0.065
1988–1991	123 (22.4%)	123 (22.4%)	
1992–1996	262 (47.7%)	236 (43.0%)	
1997–2000	164 (29.9%)	190 (34.6%)	
T stage			0.029
T1a	456 (83.1%)	451 (82.1%)	
T1b	21 (3.8%)	20 (3.6%)	
T1c	72 (13.1%)	78 (14.2%)	
Tumor size (cm)			0.043
≤4.0	63 (11.5%)	69 (12.6%)	
4.1–6.0	12 (2.2%)	16 (2.9%)	
6.1–8.0	19 (3.5%)	14 (2.6%)	
8.1–10.0	17 (3.1%)	17 (3.1%)	
>10	128 (23.3%)	137 (25.0%)	
Unknown	310 (56.5%)	296 (53.9%)	
Hysterectomy			0.013
No	167 (30.4%)	165 (30.1%)	
Yes	345 (62.8%)	345 (62.8%)	
Unknown	37 (6.7%)	39 (7.1%)	
Lymphadenectomy			0.018
No	300 (54.6%)	304 (55.4%)	
Yes	246 (44.8%)	243 (44.3%)	
Unknown	3 (0.5%)	2 (0.4%)	

Number (%) per column or mean (±standard deviation) are shown. SD ≤0.10 indicates good balance between the two groups. Abbreviations: BOT, borderline ovarian tumor; OC, invasive well-differentiated ovarian cancer; and SD, standardized difference.

associated with decreased OS compared to mucinous-BOT (adjusted-HR 1.23, 95%CI 1.01–1.51, $P = 0.045$). Age and marital status also remained as independent prognostic factors for OS (all, adjusted-$P < 0.05$).

Sensitivity analyses were performed (Table 4). On multivariable analysis, mucinous-OC was significantly associated with poorer CSS compared to mucinous-BOT among women of reproductive-age ($n = 1478$), those in whom the tumor was stage T1a ($n = 2254$), those with a large tumor size ($n = 570$), and those who did not undergo a staging procedure at the time of surgery ($n = 767$), (all, $P < 0.05$).

4. Discussion

Key findings of the current study are that mucinous-BOT and mucinous-OC have distinct differences in characteristics with regards to epidemiology, highlighted by a geographic disparity and diagnostic shift over time. Moreover, tumor characteristics are also distinct between the two entities, with mucinous-OC having more stage T1c disease and smaller tumor size. Most importantly, survival of these two diseases is completely different.

The probable common reason for misclassification between mucinous-BOT and mucinous-OC is that mucinous ovarian tumors are heterogeneous entities, and benign-appearing, borderline patterns and invasive tumors may co-exist within one neoplasm site [8,28]. The continuum of these findings supports the concept of tumor progression from mucinous-BOT to mucinous-OC, triggered by certain oncogenic mutations such as K-ras [8,28–30]. As mucinous ovarian tumors are often large, sampling error may occur during histopathologic evaluation, resulting in the misclassification between intraoperative frozen evaluation and permanent evaluation [11]. Some studies are indeed suggestive that large tumor size is a risk factor for misclassification between intraoperative and postoperative evaluations in BOT [2].

Our study showed that the women in the more recent years of the study were less likely to be diagnosed with mucinous-OC. This decreasing trend of mucinous-OC diagnoses has also been observed in another population [8]. These authors speculate that over time, practices in the diagnosis of mucinous ovarian tumors may possibly have changed, and improving diagnostic accuracy for distinguishing primary mucinous-OC from mucinous-BOT, as well as from metastatic mucinous tumors arising from other organ sites has contributed to this decreasing trend [8].

This study showed that women with Eastern U.S. residence are more likely to have mucinous-OC compared to those with Western U.S. residence. The exact reason underlying this association is unknown, but certain unmeasured factors in the study may be associated with this finding. For example, tobacco smoking is associated with the development of mucinous ovarian tumors, and there is a geographic disparity in current cigarette users across the United States, with a higher prevalence of tobacco use in the East and Central U.S. as compared to the West [11,31].

This study adds new insights regarding age, in that our analysis found that the age of 61 years was useful to distinguish mucinous-OC from mucinous-BOT (Fig. 1A). In a post-hoc analysis examining the risk of mucinous-OC over mucinous-BOT among the independent demographic factors (age, registry area, year of diagnosis, and stage; Table 1), an age cutoff of 61 years was found to be the second strongest factor following stage at diagnosis for distinguishing between mucinous-OC over mucinous-BOT (Fig. S2). Even in stage T1a tumor, when a woman is ≥61 years and was diagnosed earlier than 1998, the risk of mucinous-OC is comparable to those with stage T1b-c disease (31.6% *versus* 34.6%, $P = 0.35$). Integrating this age cutoff in the management algorithm of mucinous ovarian tumors could potentially be of value.

Survival of women with stage I well-differentiated mucinous-OC was significantly worse compared to those with stage I mucinous-BOT. This is based on sophisticated background adjustment and multivariable modeling in our analysis. Therefore, although this seems an intuitive finding, our work functions as a proof-of-concept study by providing reassuring information to clinicians.

The subgroup of reproductive-age women demonstrated a larger magnitude of statistical difference in CSS compared to the other subgroups (Table 4), However the significance of this should be interpreted with caution given the quite wide range of confidence interval. Similar to the entire cohort, reproductive-age women in the mucinous-OC group had higher chance of hysterectomy and lymphadenectomy compared to the mucinous-BOT group (Table S2). Reproductive-age women often undergo conservative surgery for fertility-sparing purposes, so thorough preoperative, intraoperative, and postoperative evaluations are highly recommended.

Strengths of the study include that to our knowledge, this is likely the first population-based study comparing mucinous-BOT and mucinous-OC, and the almost two decades of long-term follow-up in our study give confidence to the reliability of the survival analysis. Moreover, propensity score matching enriches the quality of this analysis as the baseline characteristics between the mucinous-BOT and mucinous-OC were largely different.

There are several limitations in this study. First, this is a retrospective study and there may be missing confounders that may be important for analysis. Most importantly, central review of pathology slides is not

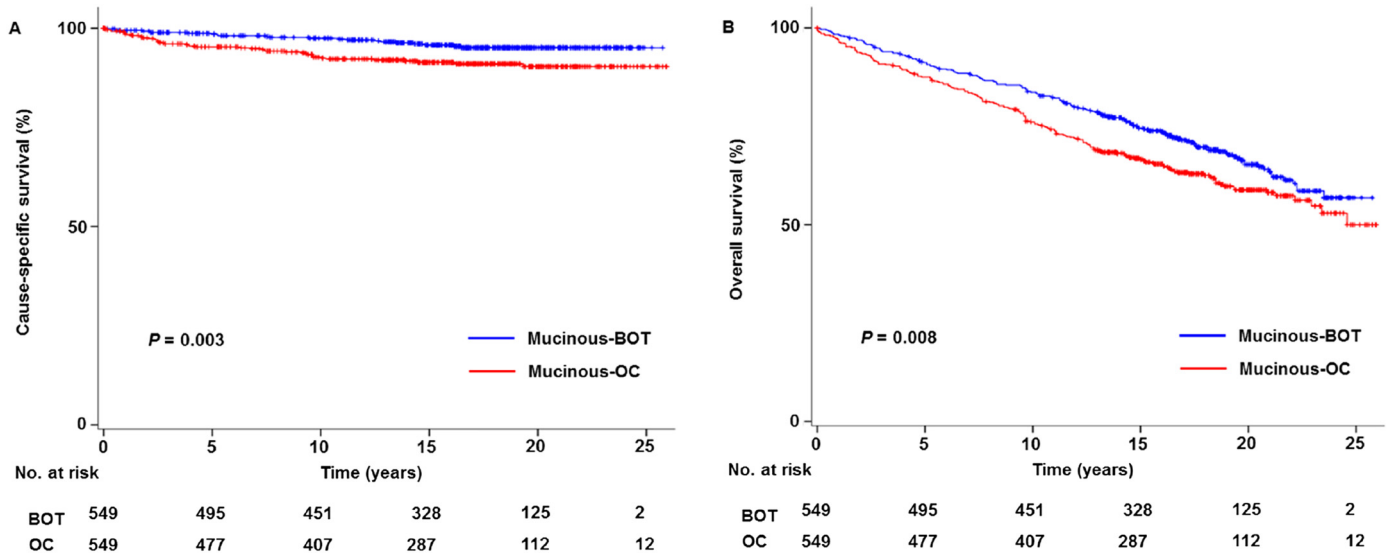

Fig. 2. Survival outcome (post-matching). A) Cause-specific survival and B) overall survival are shown based on tumor types. Log-rank test for *P*-values. Abbreviations: OC, invasive well-differentiated ovarian cancer; and BOT, borderline ovarian tumor.

available in this database, and it is unknown what proportion of tumors in the study cohort were potentially misclassified across the two groups or were of a non-ovarian origin such as gastrointestinal or pancreatic malignancy. We do not know if the ovarian tumors in this study population were universally sectioned for histopathological testing per a predetermined pathology protocol. As previously mentioned, the lack of a universal protocol for tumor sectioning may result in sampling error. Additionally, information was unavailable in the database regarding the use of intraoperative frozen section evaluation, correlation to the final pathologic diagnosis, or any additional work-up to rule out other cancer origins but these are important when applying the significant findings related to hysterectomy/lymphadenectomy rates.

Subtypes of mucinous-BOT were not available in the study. As endocervical type and intestinal type mucinous-BOT have distinct characteristics and outcomes, lack of this information could have diluted the results of this current study [28]. More detailed information regarding tumor characteristics such as lympho-vascular space invasion, substage for T1c disease, and oncogenic alteration were also not available in this study. These factors may all affect tumor progression and survival [8,32,33]. Information for chemotherapy use was not available during the study period in the SEER database. However, the effectiveness of chemotherapy for stage IC mucinous-OC is unknown. As with the other population-based data, the SEER program lacks information pertaining to disease recurrence. Thus, complete risk assessments for survival analysis were not feasible in this study.

A clinical implication of the current study is in the area of intraoperative/postoperative management. First, if intraoperative frozen section identifies mucinous-BOT, additional sectioning may be of value to detect any invasive disease given the high incidence of under-diagnosis. This is based on rationale that comprehensive surgical staging including lymphadenectomy is generally indicated for apparent early-stage invasive ovarian cancer due to high incidence of microscopic nodal metastasis, whereas peritoneal evaluation has more value in surgery for BOT [11,34]. While the prevalence of lymph node metastasis is fairly low in mucinous-OC [35], lack of lymphadenectomy in stage I mucinous-OC is associated with increased risk of ovarian cancer mortality [15].

Proper diagnosis of the two diseases also impacts postoperative management. Treatment for stage I mucinous-BOT is surgery alone [11]. For mucinous-OC, per the current guidelines, postoperative treatment for stage IA-B disease is observation whereas options for stage IC disease include observation, platinum-based chemotherapy, or even gastro-intestinal tumor chemotherapy regimens [34]. Thus, proper diagnosis is particularly important in stage IC disease, where chemotherapy may be beneficial. Our study showed that in stage IC disease, the histology was more likely to be mucinous-OC, which is especially relevant for clinicians.

The distinction between mucinous-BOT and mucinous-OC is always challenging but is essential in the management of women with mucinous ovarian tumors. Even with expert pathologists, distinguishing mucinous-BOT and well-differentiated mucinous-OC can be problematic [8]. However, given the poorer survival in mucinous-OC compared to mucinous-BOT, our study endorses the importance of making the proper diagnosis for invasive cancer when the ovarian tumor is of mucinous histology. Introduction of a standardized specimen sectioning protocol and diagnostic criteria for mucinous ovarian tumors would likely be of benefit in this regard.

Table 3
Multivariable analysis for survival outcome.

Characteristic	Cause-specific survival		Overall survival	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age (yr)				
<61	1		1	
≥61	2.03 (1.24–3.32)	**0.005**	4.52 (3.62–5.64)	<**0.001**
Marital status				<**0.001**[*]
Single			1.19 (0.87–1.61)	0.28
Married			1	
Others			1.76 (1.41–2.21)	<**0.001**
Unknown			2.04 (1.01–4.16)	**0.049**
T-stage		**0.005**[*]		
T1a	1			
T1b	2.28 (0.82–6.36)	0.11		
T1c	2.38 (1.36–4.16)	**0.002**		
Tumor type				
Mucinous-BOT	1		1	
Mucinous-OC	2.03 (1.21–3.38)	**0.007**	1.23 (1.01–1.51)	**0.045**

Cox proportional hazard regression models (conditional backward method) for *P*-values. All the listed covariates were entered in the final models. Significant *P*-values are emboldened. Abbreviations: HR, hazard ratio; CI, confidence interval; BOT, borderline ovarian tumor; and OC, invasive well-differentiated ovarian cancer.

[*] *P*-value for interaction.

Table 4
Sensitivity analysis for cause-specific survival.

Characteristic	Reproductive age		Stage T1a		Large tumor		Unstaged	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age (yr)								
<61			1		1		1	
≥61			3.13 (2.03–4.82)	<**0.001**	2.83 (1.35–5.95)	**0.006**	4.18 (2.66–6.58)	<**0.001**
T stage		**0.006**[*]				0.11[*]		**0.007**[*]
T1a	1				1		1	
T1b	na	0.98			1.84 (0.76–4.42)	0.18	2.00 (0.73–5.52)	0.18
T1c	1.28 (0.44–3.72)	0.49			5.45 (1.23–24.1)	**0.025**	2.62 (1.45–4.73)	**0.001**
T1NOS	6.22 (2.25–17.2)	<**0.001**			na	0.98	1.84 (0.73–4.64)	0.20
Tumor type								
Mucinous-BOT	1		1		1		1	
Mucinous-OC	4.44 (2.15–9.15)	<**0.001**	2.07 (1.33–3.22)	**0.001**	2.68 (1.28–5.61)	**0.009**	2.04 (1.25–3.32)	**0.004**

Reproductive age indicated age < 50 years. Large tumor indicated tumor size of ≥10 cm. Unstaged cases indicated no lymphadenectomy. Cox proportional hazard regression models for *P*-values. Significant *P*-values are emboldened. Association of tumor type and cause-specific survival was adjusted for other independent prognostic factors for cause-specific survival (Table 3). Abbreviations: NOS, not otherwise specified; BOT, borderline ovarian tumor; and OC, invasive well-differentiated ovarian cancer.

[*] *P*-values for interaction.

Disclosure statement

Scientific Advisory Board, Kiyatec (A.K.S); Share Holder, Biopath (A.K.S); Research funding, M-Trap (A.K.S.); honorarium, Chugai (K.M.); consultant, Tempus Labs (L.D.R.); none for others.

Author contributions

Conceptualization: K.M.; Data curation: H.M.; Formal analysis: K.M.; Funding acquisition: K.M., L.D.R.; Investigation: all authors; Methodology: K.M.; Project administration: K.M.; Resources: H.M.; Software: H.M.; Supervision: K.M.; Validation: K.M.; Visualization: K.M.; Writing - original draft: K.M.; Writing - review & editing: all authors.

Funding source

Ensign Endowment for Gynecologic Cancer Research (K.M.).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.02.003.

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