Taiwanese Journal of Obstetrics & Gynecology 54 (2015) 398–402

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Differentiating between borderline and invasive malignancies in ovarian tumors using a multivariate logistic regression model

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ARTICLE INFO

Article history:
Accepted 19 February 2014

Keywords:
borderline ovarian tumor
cancer antigen 125
invasive ovarian tumor
logistic regression

ABSTRACT

Objective: The objective of this study was to build a model to differentiate between borderline and invasive ovarian tumors.
Materials and Methods: We performed a retrospective study involving 148 patients with borderline or invasive ovarian tumors in our institute between 1997 and 2012. Clinical and pathologic data were collected. Logistic regression was used to build the model.
Results: The model was created based on the following variables ($p < 0.05$): menopausal status; preoperative serum level of cancer antigen 125; the greatest diameter of the tumor; and the presence of solid parts on ultrasound imaging. The sensitivity and specificity of the model were 94.6% [95% confidence interval (CI), 0.887–1] and 78.3% (95% CI, 0.614–0.952) for patients aged $\geq$ 50 years, and 76.0% (95% CI, 0.622–0.903) and 60.0% (95% CI, 0.438–0.762) for those aged < 50 years, respectively. The performance of the model was tested using cross-validation.
Conclusion: Differentiation between borderline and invasive ovarian tumors can be achieved using a model based on the following criteria: menopausal status; cancer antigen 125 level; and ultrasound parameters. The model is helpful to oncologists and patients in the initial evaluation phase of ovarian tumors.

Introduction

Ovarian cancer is the second leading cause of death in women's gynecological cancers worldwide, and the leading cause to death in developed countries [1]. Women with an ovarian mass often present a diagnostic challenge to physicians because benign, invasive, and low malignant potential tumors (borderline ovarian tumor: BOT) require different surgical interventions. Many attempts have been made to distinguish malignant tumors from benign tumors [2–5], however, little effort has been focused on differentiating BOTs from invasive tumors.

It is often difficult for gynecologic oncologists to establish a diagnosis of a BOT prior to surgery. Many patients with BOTs present characteristics similar to invasive tumors, such as the presence of solid components and ascites on ultrasound imaging, and elevated serum levels of tumor markers, such as cancer antigen (CA)125 [6]. However, unlike invasive tumors, BOTs typically occur in young women with an intention to preserve fertility, and they have a favorable prognosis, even after conservative treatment [7,8]. Therefore, it is desirable to differentiate BOTs from invasive tumors preoperatively to avoid unnecessary procedures. A risk calculator with a good predictive value before surgery would be of great help to oncologists and patients.

The standard diagnostic procedures for patients with ovarian masses include ultrasound imaging and blood tests of tumor

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http://dx.doi.org/10.1016/j.tjog.2014.02.004

markers, such as CA125, carcinoembryonic antigen, and CA19-9. There have also been reports on adjunctive examinations, such as positron emission tomography, computed tomography, magnetic resonance imaging, and new tumor markers, such as calprotectin, oviduct-specific glycoprotein 1, growth differentiation factor 15, human epididymis protein 4, and a new diagnostic multivariate index assay, the OVA1 test [6,9,10]. Although these tests may help detect invasive tumors, they have not been shown to play a significant role in diagnosing BOTs. In addition, in many parts of the world where medical costs are a major concern, adjunctive tests are only performed when malignancy is suspected after initial testing, or not performed at all due to high medical costs or limited medical resources. We therefore developed a model based on the results of initial testing (ultrasonographic findings and tumor markers) to evaluate the probability of a BOT versus an invasive ovarian tumor.

Materials and methods

This retrospective study was conducted at the Kaohsiung Veterans' General Hospital (KSVGH), a public teaching medical center in south Taiwan. All patient information was retrieved from the hospital records, including electronic and chart data. The acquisition of data was approved by the institutional review board of KSVGH. Information was retrieved from 148 patients, who had pathologic reports of epithelial borderline or invasive ovarian tumors between May 1997 and January 2012 at KSVGH. Of the 148 patients, 58 had BOTs. Two senior pathologists were consulted on the cases and reviewed the pathology slides following the World Health Organization criteria for the diagnosis of BOTs [11]. It was agreed that all 58 patients had BOTs. The ultrasound reports of all the patients were reviewed by three physicians from the KSVGH Department of Obstetrics and Gynecology to ensure accuracy.

All statistical analyses were conducted using the statistical computing and graphic drawing language, R [12]. Patients who were aged < 50 years and those who were aged ≥ 50 years were divided into two separate regression curves. The patients were grouped according to age because not all of them reported their menopause status. We chose 50 years of age to represent the menopause because the median age of menopause amongst Chinese women in Taiwan is 50 years [13] and 50–51.4 years for women in Europe and North America [14].

Cross-validation was performed to check the performance of the model. The data were randomly partitioned into two sets in each age group, with one set comprised of only one patient. The model was trained based on the larger data set, and it was then applied to the single-patient set to test whether or not malignancy was correctly predicted. The same procedure was performed in rotations for all of the patients, and the results were averaged out over all of the rounds.

Results

The current study included 148 patients; 58 patients had BOTs and 90 patients had invasive cancer. Most patients with BOTs were aged < 50 years (60.3%) and had mucinous histology (65.5%). The majority of the patients with invasive cancer were aged ≥ 50 years (62.2%), and serous histology was most common (31.1%). The majority of patients underwent intraoperative frozen section analysis (94.8% for BOTs and 92.2% for invasive tumors). The demographics of the patients are shown in Table 1.

To identify the factors that differentiate BOTs from invasive tumors, we first performed univariate analysis with logistic regression to test a series of parameters, including body mass index, gravida, preoperative serum levels of CA125, carcinoembryonic antigen and CA19-9, the greatest tumor diameter, and the presence of ascites, solid parts, and septa on preoperative ultrasound imaging (Table 2). We then performed multivariate analysis on those factors with $p < 0.05$ (Table 3). The preoperative serum level of CA125, the greatest tumor diameter, and the presence of solid parts were significant factors ($p < 0.05$) based on multivariate analysis (Tables 2 and 3). The factors were then used to derive the following formulas:

Aged < 50 years:

$$R = -1.23 + 1.57 \times [CA125(80)] - 0.004 \times size + 0.57 \times [solid\ part]$$

Table 1
Distribution of patients' surgical and pathological information.

	Borderline	Invasive
Age (y), median (range)	46.5 (14–85)	52.0 (26–77)
Number of patients		
< 50 y	35 (60.3)	34 (37.8)
≥ 50 y	23 (39.7)	56 (62.2)
Histological type		
Serous	16 (27.6)	28 (31.1)
Mucinous	38 (65.5)	7 (7.8)
Endometrioid	1 (1.7)	26 (28.9)
Mixed	1 (1.7)	8 (8.9)
Clear cell	0	15 (16.7)
Other [a]	2 (3.5)	6 (6.6)
FIGO Stage		
IA	51 (88)	9 (10.0)
IB		2 (2.2)
IC		15 (16.8)
IIB	0	2 (2.2)
IIC	3 (5.2)	8 (8.9)
IIIA	2 (3.4)	3 (3.3)
IIIB	0	2 (2.2)
IIIC	2 (3.4)	37 (41.1)
IV	0	10 (11.1)
Unknown	0	2 (2.2)
Frozen section analysis		
Benign	2 (3.4)	0
Borderline	53 (91.4)	2 (2.2)
Invasive	0	81 (90)
Not performed	3 (5.2) [b]	7 (7.8) [c]
Overall		
148	58	90

Data are presented as *n* (%) unless otherwise indicated.
FIGO = International Federation of Gynecology and Obstetrics.
[a] Brenner tumor, undifferentiated, and unknown types.
[b] Frozen section analysis was not performed due to seemingly benign tumors in surgery.
[c] Frozen section analysis was not performed because these patients were admitted to our institute for restaging surgery based on their pathology reports from their local hospitals.

Table 2
Univariate analysis of patients' characteristics.

	p	Standard error
Body mass index	0.63	0.04
Gravida	0.82	0.09
CEA	0.48	0.41
CA19-9	0.11	0.54
CA125	<0.001	0.39
Tumor size	0.001	0.03
Solid parts	0.03	0.34
Ascites	0.01	0.38
Septa	0.003	0.36

The cut off values of CEA, CA199, and CA125 are 5.0 ng/mL, 37.0 U/mL, and 80 U/mL, respectively. The tumor size denotes the longest tumor diameter in preoperative ultrasound imaging. The presence of solid parts, ascites, and septa was based on findings in the preoperative ultrasound imaging.
CA = cancer antigen; CEA = carcinoembryonic antigen.

Table 3
Multivariate analysis of patients' characteristics.

	p	Standard error
CA125	<0.001	0.70
Tumor size	0.03	0.05
Solid parts	0.002	0.64
Ascites	0.18	0.64
Septa	0.43	0.64

The cut off value of CA125 is 80 U/mL. The tumor size denotes the longest tumor diameter in preoperative ultrasound imaging. The presence of solid parts, ascites, and septa was based on findings in the preoperative ultrasound imaging.
CA = cancer antigen.

Aged $\geq$ 50 years:
$R = 0.54 + 4.53 \times [CA125(80)] - 0.25 \times size + 2.69 \times [solid\ part]$

Pre- and postmenopausal patients were fitted into two separate regression curves because the same factor may have different weights according to menopausal status [2–4].

CA125 is assigned 1 if the level is ≥80 U/mL, and 0 if <80 U/mL. An abnormal level of CA125 is >35 U/mL [15], however, different cut-off values, ranging from 10 U/mL to 200 U/mL, have been used in managing ovarian tumors [2,16]. In our work, we found that a CA125 cut-off level of 80 U/mL was most powerful in discriminating BOTs from invasive ovarian tumors. Size (in cm) refers to the greatest tumor diameter on ultrasound imaging. Solid parts is assigned 1 if present on ultrasound imaging, and 0 if not present. A positive result or zero ($R \geq 0$) predicted an invasive tumor, and a negative R predicted a BOT.

The preoperative CA125 level had a profound effect on the prediction. For patients aged < 50 years, if the CA125 level was >80 U/mL, the hazard ratio of an invasive tumor versus a BOT was 4.78; for patients aged ≥ 50 years, the hazard ratio was 92. The presence of solid parts increased the odds of getting an invasive tumor by 77% for the younger group (aged < 50 years), and 13 times for older patients (aged ≥ 50 years). By contrast, tumor size slightly decreased the probability of an invasive tumor. For every 1 cm increase in tumor diameter, the probability of an invasive ovarian tumor decreased by 0.4% for patients aged < 50 years and 28% for those who were aged ≥ 50 years.

The model we created had a sensitivity of 94.6% [95% confidence interval (CI), 0.887–1; 53/56 tumors were correctly predicted as invasive] and a specificity of 78.3% (95% CI, 0.614–0.952, 18/21 were correctly predicted as BOTs) for patients who were aged ≥ 50 years. The positive and negative predictive values for this group were 91.0% and 85.7%, respectively. For patients aged < 50 years, the sensitivity was 76.0% (95% CI, 0.622–0.903, 26/34 were correctly predicted as invasive), and the specificity was 60.0% (95% CI–0.438–0.762, 21/35 were correctly predicted as BOTs). The positive and negative predictive values were 65.0% and 72.4%, respectively. These results are summarized in Table 4, and the receiver operating characteristic curve analysis is shown in Figure 1.

To further test the value of the model, cross-validation was performed. Cross-validation is a rotation process to assess how a statistical model generalizes to apply to independent data [17]. The sensitivity was 94.6% (95% CI, 0.887–1) and the specificity was 69.6% (95% CI, 0.508–0.884) for the group aged ≥ 50 years, and the sensitivity was 74.4% (95% CI, 0.622–0.907) and the specificity was 60.0% (95% CI, 0.438–0.762) for the other group (Table 4). Compared with the sensitivities and specificities before cross-validation, the sensitivities and specificities were the same or slightly lower, which suggests that the model is reliable in distinguishing BOTs from invasive ovarian tumors and can be applied to independent data.

Discussion

BOTs have long been a diagnostic challenge to gynecologic oncologists because they often exhibit similar behaviors to invasive carcinomas [18]. In contrast to invasive carcinomas, BOTs usually have an excellent prognosis. In addition, a significant percentage of patients are still of reproductive age, and conservative treatment, including a unilateral salpingo-oophorectomy or a cystectomy for Stage I BOTs, is often preferred to preserve future fertility [7,19]. Radical surgery, which consists of peritoneal washings, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, complete peritoneal resection of macroscopic lesions, or multiple peritoneal biopsies, is recommended for patients at advanced stage or those who are finished with reproduction [20]. It is therefore important to prepare patients and oncologists for the tumor type with reasonable certainty before surgery. Indeed, the risk model we developed will contribute significantly to the preoperative diagnosis.

Only a few previous studies have focused on differentiating BOTs from invasive tumors. Zanetta et al [21] proposed a model in 1995 to differentiate BOTs based on complex sonographic intracystic features, and reported a 91% accuracy. Similarly, a recent study by Sobiczewski et al [16] developed a scoring system that included six ultrasonographic parameters (e.g., echogenicity) to distinguish BOTs from invasive cancers, and they had a sensitivity of 90.2%. Compared with these studies, our model considered a much larger patient pool; specifically, we had 148 patients, including 58 BOTs, whereas in the aforementioned studies, only 20 BOTs and 16 BOTs were enrolled, respectively. Our model is also simpler and based on fewer parameters with a similar sensitivity.

A noteworthy feature of our study was that we tested the model performance using cross-validation, which assesses how accurate a model is when applied to independent data [17]. A good model

Table 4
Model performance in predicting invasive tumors from borderline ovarian tumors (BOTs).

Menopausal status	Disease	Predicted BOT	Predicted invasive	Total	Sensitivity	Specificity	PPV	NPV
Combined	BOT	39	19	58	87.8%	67.2%	80.6%	78.0%
	Invasive	11	79	90				
	Total	50	98	148				
Aged < 50 y	BOT	21	14	35	76.5%	60.0%	65.0%	72.4%
	Invasive	8	26	34				
	Total	29	40	69				
	CV				76.5%	60.0%		
Aged ≥ 50 y	BOT	18	5	23	94.6%	78.3%	91.0%	85.7%
	Invasive	3	53	56				
	Total	21	58	78				
	CV				94.6%	69.6%		

CV = cross validation; NPV = negative predictive value; PPV = positive predictive value.

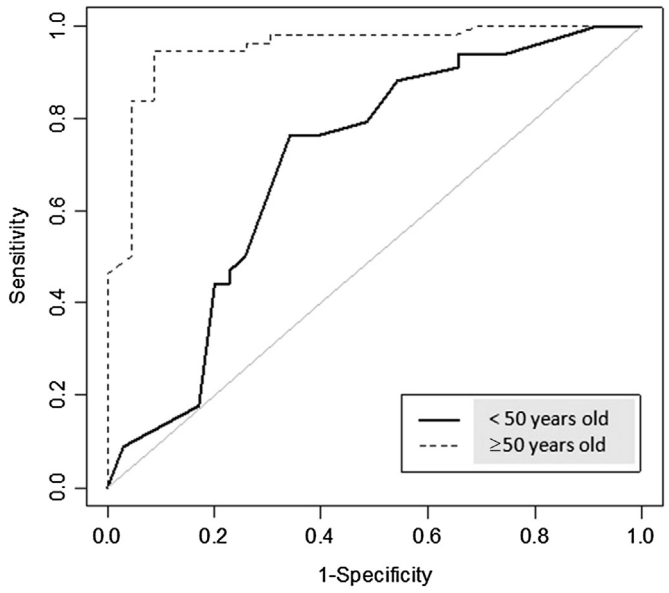

Figure 1. Receiver operating characteristic curve analysis of risk prediction in assessment of borderline and invasive ovarian tumors. The area under the curve was 0.667 for patients aged < 50 years and 0.953 for patients aged ≥ 50 years.

should withstand cross-validation with no significant loss of sensitivity or specificity, which was achieved in our study (Table 3), suggesting that our model had stable performance and may work well with independent data. It would be of great interest to test it with a large sample of external data which relies on patient information from other institutions.

Ultrasonography is currently the most popular imaging approach in clinical practice to evaluate ovarian masses, due to its wide accessibility and low cost. Detailed sonographic findings, such as wall and septal thicknesses, and Doppler parameters, such as pulsatility index (PI) and resistive index (RI) values and velocimetry flow evaluation, have been reported in patients with BOTs [22–24]. According to these studies, no specific parameters could typically differentiate BOTs from invasive tumors. Aside from the diagnostic limitations, medical costs are also a concern. State-of-the-art imaging techniques are more costly, and they are usually ordered after an ultrasound image suggestive of malignancy. In areas with limited medical resources, new technical advances may not be widely accessible in the near future. We therefore based our study on grayscale sonographic parameters, hoping to provide a risk model in the very early stage of evaluation without referring to complex tests.

It should be noted that the majority of the BOT patients in this study had a mucinous tumor (65.5%). Mucinous BOTs have been reported to be predominant in Asia, whereas serous BOTs are predominant in the USA and Europe [25]. This may partially explain why a larger tumor size lowered the risk of an invasive tumor in the model we developed, because mucinous tumors are usually bigger. Another possible reason is that most BOTs are diagnosed at an early stage, whereas most invasive tumors are diagnosed at a late stage. A recent study hypothesized that early-stage tumors grow locally and advanced-stage tumors disseminate while still small [26]. If this holds true, early-stage BOTs may grow to a large size before detection.

It should also be noted that we achieved very high sensitivity and specificity in the older group (aged ≥ 50 years). It seems more complicated and difficult to differentiate BOTs and invasive tumors in women at a childbearing age, and more advanced diagnostic procedures may have to be used to improve detection of BOTs.

In conclusion, we have developed a model to predict the risk of BOTs or invasive ovarian tumors early during the preoperative evaluation. The model has a potential wide application, particularly in areas with limited medical resources and in areas with a predominance of mucinous BOTs, such as Asia. Further studies should be directed to validate our model prospectively in an external and heterogeneous population.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

We thank Mr Wei-Wen Wu for assistance with data collection, Drs Chia-Jung Chen and Pei Pei Kao for reviewing the pathology reports of the BOT patients, and the reviewers for their constructive suggestions. The study was supported in part by a grant from KSVGH (VGHKS 101-120) and a grant from the National Science Council of Taiwan (NSC 100-2118-M-110-004).

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