DOI:10.31557/APJCC.2022.7.2.201

RESEARCH ARTICLE

Comparison Clinicopathologic Characteristics of Primary and Secondary Ovarian Cancers

Kamonchanok Choosak[1], Thitirath Thantiprechapong[1,2]

[1]Department of Obstetrics and Gynecology, Rajavithi Hospital, Bangkok, Thailand. [2]College of Medicine, Rangsit University, Bangkok, Thailand.

Abstract

Objective: Due to primary and secondary ovarian cancer have different management, preoperative assessment is important. We endeavor to identify the different preoperative clinical characteristics. **Methods:** We performed a retrospective case-control study that included 31 patients with secondary ovarian cancer (SOC) and 301 controls with primary ovarian cancer (POC) diagnosed between 2007 and 2018. The demographic parameters, signs, symptoms, preoperative tumor marker levels, and imaging findings were reviewed. **Results:** The incidence of SOC was 2.5% (66/2605) of all ovarian malignancies. The most common site of origin was the colon (58.1%). Thirty-five percent of the patients with SOC had a history of previous malignancy and 80.8% of them were multiparous. Abdominal mass and bladder symptoms were significantly higher in patients with POC than those with SOC ($p < 0.001$, $p = 0.04$, respectively). The preoperative imaging showed that SOC was more often bilateralism ($p < 0.001$) and more presence of ascites ($p = 0.004$). The consistency of SOC was cystic-solid (50%). From the multivariate analysis, the risk of SOC was significantly increased in patients who developed previous malignancy, CEA level (>5 ng/mL), and CA 125/CEA ratio (≤25) with the odds ratios (95%CI) of 5.07 (1.52, 16.96), 6.17 (1.68, 22.59) and 12.12 (3.91, 37.59), respectively. **Conclusions:** The preoperative distinction between POC and SOC is difficult. A history of malignancy, an elevated serum CEA, and CA 125/CEA ratio, can provide a useful clue for diagnosis and proper management in these patients.

Keywords: Primary ovarian cancers- Secondary ovarian cancers- Metastatic ovarian cancers- Clinicopathologic Characteristics

Asian Pac J Cancer Care, **7 (2)**, 201-205

Submission Date: 11/10/2020 Acceptance Date: 07/25/2021

Introduction

Ovarian cancer is the second most common gynecologic cancer in the United States. It also accounts for a very high mortality rate. The rate of new cases of ovarian cancer was 11.2 per 100,000 women per year. The death rate was 6.7 per 100,000 women per year. Ovarian cancer ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system. Approximately 5-6% of ovarian tumors are metastatic from other organs, most frequently from the female genital tract, the breast, or the gastrointestinal tract. The incidence rate of metastatic ovarian cancer appears to be higher in Asia compared to Western countries [1].

The preoperative distinction between primary ovarian cancers (POC) and secondary ovarian cancers (SOC) is very important since the correct diagnosis can prevent inappropriate management and suboptimal treatment [2]. In the POC, surgery remains the preferred treatment method if feasible. But in the SOC, the treatment of choice depending on the primary origin [3, 4]. The differentiation between primary and secondary ovarian cancers is difficult and the gold standard investigation is not available [5-10].

We evaluated the proportion of secondary ovarian cancers among primary ovarian cancers and preoperative characteristics to compare clinicopathologically characteristics of both ovarian cancer groups to explore some keys to aid in differentiation.

Corresponding Author:
Dr. Thitirath Thantiprechapong
Department of Obstetrics and Gynecology, Rajavithi Hospital, Bangkok, Thailand.
Email: naungsung@gmail.com

Materials and Methods

A retrospective case-control study was performed. We enrolled the patients who underwent the operation at Rajavithi Hospital from 2007 to 2018. The exclusion criteria were secondary ovarian metastasis from genital tract origin, no pathologic official result, and loss of medical record papers. Thirty-one patients with SOC and 301 cases with POC were matching by time in the rate of 1 to 10 cases.

In the SOC group, we identified 179 patients from the records of the Department of Pathology, Rajavithi Hospital. We excluded 113 patients with SOC originated from gynecologic malignancies and 35 patients due to loss of medical record paper from the medical informatics gynecologic cancer. Matching by time with the same year was done in the POC group. The medical records were reviewed for the demographic parameters, signs and symptoms, preoperative tumor marker level, and imaging findings.

Statistical analyses were performed using either the Chi-square test, the Mann-Whitney U test, the Fisher's exact test, and Logistic regression analysis. A two-tailed P-value lower than 0.05 was considered statistically significant. The calculations were performed with SPSS program version 20.

Results

From 2007 to 2018, all ovarian cancer 2,605 cases were diagnosed. The incidence of primary epithelial ovarian cancer was 24.4 percent (636/2605) and the incidence of SOC was 6.8% (179/2605). The total of non-genital tract origin were 66 cases (2.5%). The most common sites of non-genital tract origin were the colon (58.1%), stomach (22.6%), and appendix (9.7%), respectively.

Table 1 shows the demographic and clinical characteristics of patients with SOC and POC. The POC and SOC groups could not be distinguished by age, BMI, or underlying diseases.

However, Thirty-five percent of the patients with SOC had a history of previous malignancy and 80.8% of them were multiparous. Abdominal mass and bladder symptoms were significantly higher in patients with POC than those with SOC ($p < 0.001$, $p = 0.004$, respectively).

Of the serum tumor markers, serum CA 125, CEA, and CA125/CEA ratios were significantly different between the two groups. The preoperative level of serum CA 125 (median 318 vs. 91.9) was higher in the POC group. On the other hand, the preoperative level of serum CEA (median 25.0 vs. 1.9) was higher in the SOC group as shown in Table 2.

Table 3 shows the results of preoperative imaging. The preoperative size of tumors, as measured by imaging were not different between the two groups (p 0.054). The preoperative imaging showed that SOC was more often bilateralism ($p <0.001$) and more presence of ascites ($p = 0.004$). The consistency of SOC was cystic-solid (50%). Carcinomatosis did not differ between the two groups.

From the multivariate analysis, the risk of SOC was significantly increased in patients who developed previous malignancy, CEA level (>5 ng/mL), and CA 125/CEA ratio (≤25) with the odds ratios (95%CI) of 5.07 (1.52, 16.96), 6.17 (1.68, 22.59) and 12.12 (3.91, 37.59), respectively as described in Table 4.

Table 1. Demographic and Clinical Characteristics

	SOC n = 31	POC n = 301	p-value
Age (year), mean (SD)	50.5 (11.5)	54.0 (10.5)	0.083 [d]
BMI[e] (kg/m^2), mean (SD)	24.3 (5.0)	24.2 (4.9)	0.957 [d]
Previous CA (%)	11 (35.5)	15 (5)	<0.001 [b]
Parity (%)			0.004 [b]
Nulliparous	5 (19.2)	144 (48.3)	
Multiparous	21 (80.8)	154 (51.7)	
Underlying diseases	11 (35.5)	141 (46.8)	0.227 [b]
Presentation symptoms			
Abdominal mass (%)	14 (45.2)	224 (74.4)	<0.001 [b]
Abdominal distention (%)	14 (45.2)	149 (49.5)	0.645 [b]
Abnormal uterine bleeding (%)	5 (16.1)	32 (10.6)	0.354 [b]
Pelvic pain (%)	6 (19.4)	108 (35.9)	0.065 [b]
Weight loss (%)	14 (45.2)	120 (39.9)	0.567 [b]
Loss of appetite (%)	11 (35.5)	70 (23.3)	0.131 [b]
Bladder symptoms (%)	2 (6.5)	70 (23.3)	0.037 [c]
Bowel symptoms (%)	5 (16.1)	22 (7.3)	0.087 [b]

a, Mann-Whitney U test; b, Chi-square test; c, Fisher's exact test; d, Student T test; e, Body mass index

Table 2. Tumor Markers

Tumor markers	SOC (median), (min-max)	POC (median), (min-max)	p-value	
CA 125 (median)	91.9 (7.82-1141) (n=27)	318.0 (8-25000) (n=243)	0.042	0.04
CA 19-9 (median)	26.1 (0.6-9347) (n=24)	24.0 (0.6-10000) (n=165)	0.849	0.85
CEA (median)	25.0 (1.26-3841) (n=25)	1.9 (0.2-3566) (n=128)	<0.001	<0.001
CA125-CEA ratio	2.9 (n=25)	145.3 (n=128)	<0.001	<0.001

Table 3. Preoperative Imaging Findings

Imaging findings	SOC n=28	POC n=299	p-value
Tumor size (cm), mean (SD)	12.6 (6.5)	15.1 (6.5)	0.054 [d]
Side			<0.001 [b]
Bilateral (%)	12 (42.9)	44[e] (15.3)	
Consistency			<0.001 [b]
Cystic (%)	6 (21.4)	13 (4.3)	
Solid (%)	8 (28.6)	24 (8)	
Cystic-solid (%)	14 (50)	262 (87.6)	
Ascites (%)	19 (67.9)	119 (39.8)	0.004 [b]
Carcinomatosis (%)	5[f] (26.3)	37[g] (24.3)	0.851 [b]

a, Mann-Whitney U test; b, Chi-square test; c, Fisher's exact test; d, Student T test; e, Data on 287 patients; f, Data on 19 patients; g, Data on 152 patients.

Discussion

In the present study, the proportion of non-genital tract origin SOC of all ovarian malignancies was 2.5% close to the result in a study by Skirnisdottir et al. [11] that the detected proportion was 2.3%. While the other study in Thailand at Chiang Mai University, Khunamornpong et al. [12] found non-genital tract metastatic tumors accounted for 20.6% of malignant ovarian tumors. More than 90% of the SOC were metastases from the gastrointestinal tract. Colorectal cancer was the most common primary tumor followed by stomach cancer. This is in good agreement with the previously reported studies [1, 12-15].

The POC and SOC groups could not be distinguished by age, body mass index, or underlying diseases. It has been reported that patients with metastatic ovarian cancers had a high percentage of the history of malignant disease [13]. Our results confirm this, thirty-five percent of the patients with SOC had a history of previous malignancy. The most common origin is the gastrointestinal tract. Abdominal mass and bladder

Table 4. The Association between Clinicopathologic Factors and SOC

Parameter		Univariate			Multivariate		
		OR	95%CI	P-value	OR	95%CI	P-value
Age	(≥ 50 vs >50)	0.6	0.29, 1.27	0.186	-	-	-
BMI	(≥ 25 vs <25)	1.04	0.48, 2.21	0.927	-	-	-
Previous CA	(yes vs no)	10.48	4.26, 25.80	<0.001	5.07	1.52, 16.96	0.008
Parity	(multi- vs nulli-)	1.05	0.53, 2.07	0.888	-	-	-
Abdominal mass	(yes vs no)	0.28	0.13, 0.60	0.001	0.22	0.08, 0.58	0.002
Bladder symptoms	(yes vs no)	0.23	0.05, 0.98	0.047	0.22	0.04, 1.12	0.068
Bowel symptoms	(yes vs no)	2.44	0.85, 6.97	0.096	-	-	-
CA 125	(> 35 vs ≤35 U/ml)	1.23	0.74, 2.04	0.431	-	-	-
CA 19-9	(> 39 vs ≤39 U/ml)	2.86	1.04, 7.83	0.041	2.56	0.72, 9.10	0.148
CEA	(> 5 vs ≤5 ng/ml)	2.78	1.04, 7.47	0.042	6.17	1.68, 22.59	0.006
CA125/CEA	(≤25 vs >25)	10	4.49, 22.30	<0.001	12.12	3.91, 37.59	<0.001
Carcinomatosis	(yes vs no)	1.76	0.86, 3.60	0.118	-	-	-
Tumor size	(> 10 vs ≤10 cm)	1.37	0.63, 3.00	0.431	-	-	-
Ascites	(yes vs no)	1.08	0.53, 2.20	0.833	-	-	-
Bilateral	(yes vs no)	1.26	0.57, 2.80	0.573	-	-	-
Solid	(yes vs no)	0.35	0.09, 1.40	0.138	-	-	-
Mixed	(yes vs no)	0.67	0.31, 1.44	0.31	-	-	-

symptoms were significantly higher in patients with POC than those with SOC ($p < 0.001$, $p = 0.004$, respectively). This may be the result of the average tumor size in POC that larger than SOC (15.1 vs. 12.6 cm, p=0.054).

From previous data reported by Antila et al. [13] in Finland which cystic-solid character and the presence of ascites were more common in cases of POC. Our pre-operative imaging showed that SOC was more often bilateralism ($p <0.001$) and more presence of ascites ($p = 0.004$). The consistency of SOC was cystic-solid (50%). The Lee et al. [1] study found ascites more than 50% and cystic-solid character up to 40% in SOC same as our study. This may be the result of advanced disease of metastatic ovarian cancer that can rise ascites and the most common primary origin in Lee et al. [1] study and our study was the same as colon cancer that ascites is a common finding in advanced GI cancer [16].

To our knowledge, CEA level > 5 ng/ml often found in GI, breast, and lung cancer and CA125/CEA ratio > 25 appeared to be excellent for differentiation between OVC and non-OVC [17]. In our study, we found that the CEA level > 5 ng/mL and CA125/CEA ratio ≤ 25 were associated to be SOC. Confirm with Sorensen et al. [17] that the sensitivity and specificity of CA125/CEA ratio ≤ 25 to diagnosed SOC was 62.6% and 73.4% respectively.

In the conclusion, there are many clues for diagnosed SOC. Clinical factors include previous cancer, no abdominal mass, and no bladder symptoms. Imaging factors include bilateralism, solid, and presence of ascites. Tumor markers include CEA>5 ng/ml and CA125/CEA ratio ≤25. All of these clues can suggest considering work up to other primary origins for the correct diagnosis and prevent inappropriate management and suboptimal treatment.

The strengths of the study, this is the first study in Thailand evaluated the association between clinicopathologic factors and SOC. The study performed in the Rajavithi Hospital, the tertiary care center that has enough cases for study in uncommon diseases. However, the problem of lost data and incomplete data in medical record papers were the common limitations in the retrospective study.

Acknowledgments

This trial was supported by Rajavithi Research Management Fund.

Conflict of interest

The authors have declared no conflict of interest.

References

1. Lee S, Bae J, Lee A, Tong S, Park Y, Park J. Clinical Characteristics of Metastatic Tumors to the Ovaries. Journal of Korean Medical Science. 2009;24(1):114. https://doi.org/10.3346/jkms.2009.24.1.114
2. de Waal YRP, Thomas CMG, Oei ALM, Sweep FCGJ, Massuger LFAG. Secondary Ovarian Malignancies. International Journal of Gynecological Cancer. 2009 Oct;19(7):1160-1165. https://doi.org/10.1111/igc.0b013e3181b33cce
3. Kubeček O, Laco J, Špaček J, Petera J, Kopecký J, Kubečková A, Filip S. The pathogenesis, diagnosis, and management of metastatic tumors to the ovary: a comprehensive review. Clinical & Experimental Metastasis. 2017 06;34(5):295-307. https://doi.org/10.1007/s10585-017-9856-8
4. Ayhan A, Guvenal T, Salman M, Ozyuncu O, Sakinci M, Basaran M. The role of cytoreductive surgery in nongenital cancers metastatic to the ovaries. Gynecologic Oncology. 2005 08;98(2):235-241. https://doi.org/10.1016/j.ygyno.2005.05.028
5. Brown DL, Zou KH, Tempany CMC, Frates MC, Silverman SG, McNeil BJ, Kurtz AB. Primary versus Secondary Ovarian Malignancy: Imaging Findings of Adnexal Masses in the Radiology Diagnostic Oncology Group Study. Radiology. 2001 04;219(1):213-218. https://doi.org/10.1148/radiology.219.1.r01ap28213
6. Bruchim I, Ben-Harim Z, Piura E, Tepper R, Fishman A. Preoperative clinical and radiological features of metastatic ovarian tumors. Archives of Gynecology and Obstetrics. 2013 03 08;288(3):615-619. https://doi.org/10.1007/s00404-013-2776-1
7. Koyama T, Mikami Y, Saga T, Tamai K, Togashi K. Secondary ovarian tumors: spectrum of CT and MR features with pathologic correlation. Abdominal Imaging. 2007 02 21;32(6):784-795. https://doi.org/10.1007/s00261-007-9186-4
8. Lewis MR, Euscher ED, Deavers MT, Silva EG, Malpica A. Metastatic colorectal adenocarcinoma involving the ovary with elevated serum CA125: A potential diagnostic pitfall. Gynecologic Oncology. 2007 05;105(2):395-398. https://doi.org/10.1016/j.ygyno.2006.12.035
9. Choi JH, Sohn GS, Chay DB, Cho HB, Kim J. Preoperative serum levels of cancer antigen 125 and carcinoembryonic antigen ratio can improve differentiation between mucinous ovarian carcinoma and other epithelial ovarian carcinomas. Obstetrics & Gynecology Science. 2018;61(3):344. https://doi.org/10.5468/ogs.2018.61.3.344
10. Moro F, Pasciuto T, Djokovic D, Di Legge A, Granato V, Moruzzi MC, Mancari R, Zannoni GF, Fischerova D, Franchi D, Scambia G, Testa AC. Role of CA125/CEA ratio and ultrasound parameters in identifying metastases to the ovaries in patients with multilocular and multilocular-solid ovarian masses. Ultrasound in Obstetrics & Gynecology. 2019 01;53(1):116-123. https://doi.org/10.1002/uog.19174
11. Skirnisdottir I, Garmo H, Holmberg L. Non-genital tract metastases to the ovaries presented as ovarian tumors in Sweden 1990–2003: Occurrence, origin and survival compared to ovarian cancer. Gynecologic Oncology. 2007 04;105(1):166-171. https://doi.org/10.1016/j.ygyno.2006.11.005
12. Khunamornpong S, Suprasert P, NA Chiangmai W, Siriaunkgul S. Metastatic tumors to the ovaries: a study of 170 cases in northern Thailand. International Journal of Gynecological Cancer. 2006 02;16(S1):132-138. https://doi.org/10.1111/j.1525-1438.2006.00302.x
13. Antila R, Jalkanen J, Heikinheimo O. Comparison of secondary and primary ovarian malignancies reveals differences in their pre- and perioperative characteristics. Gynecologic Oncology. 2006 04;101(1):97-101. https://doi.org/10.1016/j.ygyno.2005.09.046
14. Yada-Hashimoto N, Yamamoto T, Kamiura S, Seino H, Ohira H, Sawai K, Kimura T, Saji F. Metastatic ovarian tumors: a review of 64 cases. Gynecologic Oncology. 2003 05;89(2):314-317. https://doi.org/10.1016/s0090-

8258(03)00075-1
15. Moore RG, Chung M, Granai CO, Gajewski W, Steinhoff MM. Incidence of metastasis to the ovaries from nongenital tract primary tumors. Gynecologic Oncology. 2004 04;93(1):87-91. https://doi.org/10.1016/j.ygyno.2003.12.039
16. Saif MW, Siddiqui IAP, Sohail MA. Management of ascites due to gastrointestinal malignancy. Annals of Saudi Medicine. 2009 09;29(5):369-377. https://doi.org/10.4103/0256-4947.55167
17. Sorensen S, Mosgaard B. Combination of cancer antigen 125 and carcinoembryonic antigen can improve ovarian cancer diagnosis. Dan Med Bull. 2011;58(11):A4331.