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Differences in tumor behavior between serous and non-serous ovarian carcinoma, focus on distribution of stage, laterality and survival

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Summary

Purpose: To determine the differences in tumor behavior between ovarian serous and non-serous carcinoma. *Materials and Methods:* We retrospectively collected the medical records of patients with epithelial ovarian cancer at our hospital from January 2010 to December 2015. We compared the clinicopathological behavior and survival between serous and non-serous carcinoma. Kaplan-Meier and Cox regression methods were used to analyze risk factors on survival. *Results:* A total of 268 patients were included, of whom 38.1% had serous carcinoma. The patients with serous carcinoma had significantly more advanced disease including extra-ovarian disease (89.2% *vs.* 34.3%), abdominal disease (69.6% *vs.* 22.9%), lymph node metastasis (39.2% *vs.* 14.4%), para-aortic lymph node involvement (17.7% *vs.* 5.4%), and FIGO Stage III/IV disease (78.4% *vs.* 28.3%). In addition, serous carcinoma tended to involve bilateral ovaries (65.7% *vs.* 22.3%). However, in FIGO Stage III/IV disease, serous carcinoma had a better overall survival than non-serous type (HR 0.469, 95% CI = 0.268-0.882, $p = 0.008$). *Conclusions:* Although serous carcinoma presented more metastasis, it appeared to have better survival when compared to non-serous type in advanced stage disease.

Key words: Ovarian cancer; Tumor behavior; Serous carcinoma.

Introduction

Ovarian cancer is a common malignant disease in women. According to the Taiwan Cancer Registry, it was the seventh most common malignant disease and the eighth leading cause of malignancy-related deaths in 2014 [1]. Primary ovarian cancer can be divided into three categories: epithelial ovarian cancer, malignant germ cell tumors, and malignant sex cord stromal cell tumors, according to the origin of the malignant cells. Epithelial ovarian cancer accounts for about 70-75% of cases of ovarian cancer, and it can be further divided into histologic types included serous, mucinous, endometrioid, clear cell, and other types such as transition cell and squamous cell [2].

Several studies have demonstrated different carcinogenesis pathways and etiologies among the different histologic types [3, 4]. However, few studies have focused on differences in tumor behavior such as laterality, staging distribution, and pattern of tumor spread. The present authors supposed that the percentage of advanced mucinous or endometrioid and early stage serous carcinoma would be very low. Thus, we conducted this retrospective study to clarify whether any differences in tumor behavior exist among different types of epithelial ovarian cancer, especially between serous and non-serous carcinoma.

Materials and Methods

We retrospectively collected the medical records of patients with ovarian cancer at our hospital from January 2010 to December 2015. We excluded patients with ovarian cancer other than the epithelial type. In addition, we also excluded patients with double cancer and those with a mixed histology. The stage and disease burden were determined according to pathology reports after primary cytoreductive surgery. For those who did not receive primary cytoreductive surgery, the authors used pelvic and abdominal CT to determine the extent of the disease. We analyzed the tumor behavior, including the location of pelvic and abdominal metastasis, site of metastatic retroperitoneal lymph nodes, and laterality of ovarian tumors. In addition, we also compared the oncological outcomes of the different histology types.

The chi-square test was used to analyze the distribution of categorical variables, and continuous variables such as age and tumor markers level were dichotomized using median values as cut-off points. Kaplan-Meier and Cox regression methods were used to analyze survival outcomes. All analyses were conducted with SPSS statistical software.

The Ethics Institutional Review Board of Chang Gung Memorial Hospital approved this study, and the need for informed consent was waived. All methods were performed in accordance with the relevant guidelines and regulations.

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Table 1. — *Clinicopathologic characteristics of the study patients (n=268).*

Parameter	
Age, median (range), (years)	51 (13-83)
Pretreatment tumor markers	
CEA, median (range),	1.42 (0.5-725.84)
CA-125 median (range)	288.2 (0.7-15950)
Treatment, n (%)	
Neoadjuvant chemotherapy then interval debulking surgery	29 (10.8)
Surgery then adjuvant chemotherapy	239 (89.2)
Retroperitoneal lymphadenectomy, n (%)	
Yes	233 (86.9)
No	35 (13.1)
Histology, n (%)	
Serous	
High-grade	99 (36.9)
Low-grade	3 (1.1)
Endometrioid	55 (20.5)
Mucinous	38 (14.2)
Clear cell	52 (19.4)
Other types	21(7.8)
FIGO stage, n (%)	
I	113 (42.2)
II	28 (10.4)
III	104 (38.8)
IV	23 (8.6)
Follow up, mean (range), months	37.12 (0-84)
Overall Survival mean (range), months	37.12 (0-84)
Progression free survival mean (range), months	31.62 (0-84)

FIGO: International Federation of Gynecology and Obstetrics, CEA: carcinoembryonic antigen.

Table 2. — *Distribution of tumor behavior in serous and non-serous carcinoma (n=268).*

	Serous, n=102	Non-serous, n=166	*p*-value
Extra-ovarian disease, n (%)			
Yes	11 (10.8)	109 (65.7)	<0.001
No	91 (89.2)	57 (34.3)	
Abdominal disease, n (%)			
Yes	71 (69.6)	38 (22.9)	<0.001
No	31 (30.4)	128 (77.1)	
Overall lymph node involvement, n (%)			
Yes	40 (39.2)	24 (14.4)	<0.001*
No	52 (51.0)	117 (70.5)	
Pelvic lymph node involvement, n (%)			
Yes	33 (35.9)	19 (13.5)	<0.001*
No	59 (64.1)	122 (86.5)	
Para-aortic lymph node involvement, n (%)			
Yes	18 (17.7)	9 (5.4)	0.004*
No	74 (72.5)	132 (79.5)	
Distant metastasis, n (%)			
Yes	17 (16.7)	6 (3.6)	<0.001
No	85 (83.3)	160 (96.4)	
FIGO Stage, n (%)			
I/II	22 (21.6)	119 (71.7)	<0.001
III/IV	80 (78.4)	47 (28.3)	
Laterality, n (%)			
Bilateral	67 (65.7)	37 (22.3)	<0.001
Unilateral	35 (34.3)	129 (77.7)	

**Only the patients who received lymphadenectomy were analyzed (n=233) .FIGO: International Federation of Gynecology and Obstetrics.*

Table 3. — *Relationships between lymph node status and T stage (n=233).*

	Pelvic LN (%)			Para-aortic LN (%)			All (%)		
	Serous	Non-serous	All	Serous	Non-serous	All	Serous	Non-serous	All
T1	0.0	6.7	5.9	0.0	0.0	0.0	0.0	6.7	5.9
T2	20.0	11.1	15.8	20.0	0.0	10.5*	35.0	11.1	23.7
T3	47.5	42.4	45.7	22.9	27.3	24.5*	54.1	48.5	52.1
All	35.9	15.6	22.3	19.6	6.4	11.6	43.5	17.0	27.5

*LN: lymph node. *Isolated PA LN: 3/38 (7.9%) in T2 Stage, 6/94 (6.4%) in T3 Stage.*

Results

During the study period, 390 patients with ovarian cancer received treatment at the present hospital. We excluded the patients who did not have the epithelial type and those with synchronous ovarian and endometrial cancer or a mixed histology. The remaining 268 patients were included for analysis. The general clinicopathological characteristics of the study cohort are shown in Table 1. Twenty-nine patients (10.8%) received neoadjuvant chemo-therapy followed by interval debulking surgery, and 35 (13.1%) patients did not receive retroperitoneal lymphadenectomy during the initial surgery because of disseminated intra-abdominal disease. Overall, 102 (38.1%) patients had serous carcinoma, of whom only three patients were low grade differentiation.

The patients with serous carcinoma had more advanced disease including extra-ovarian disease (89.2% *vs.* 34.3%, $p < 0.001$), abdominal disease (69.6% *vs.* 22.9%, $p < 0.001$), overall lymph node metastasis (39.2% *vs.* 14.4%, $p < 0.001$), pelvic lymph node involvement (35.9% *vs.* 13.5%, $p < 0.001$), para-aortic lymph node involvement (17.7% *vs.* 5.4%, $p < 0.001$), and FIGO Stage III and IV disease (78.4% *vs.* 28.3%, $p < 0.001$) (Table 2). Of the patients with T2 and T3 disease, 10.5% and 24.5% had para-aortic lymph node metastasis, respectively. In addition, three of 38 (7.9%) patients with T2 disease and six of 94 (6.4%) patients with T3 disease had isolated para-aortic lymph node

Table 4. — *Univariate and multivariate analyses for factors predicting survival (n=268).*

Parameter	Number	5-year overall survival, %	*p*-value
Age at diagnosis			
< 51 years	131	77.7	0.061
≥ 51 years	137	63.9	
Histology			
Serous	102	64.4	0.197
Non-serous	166	75.0	
FIGO Stage			
I/II	141	90.2	<0.001
III/IV	127	50.3	
CEA			
< 1.4	106	69.7	0.074
≥ 1.4	109	67.5	
Not checked	53		
CA-125			
< 288	131	75.9	0.250
≥ 288	132	65.3	
Not checked	5		

Parameter	HR (95% CI)	*p*-value
FIGO Stage I/II *vs.* III/IV	0.178 (0.094-0.334)	<0.001

FIGO: International Federation of Gynecology and Obstetrics, CEA: carcinoembryonic antigen, HR: hazard ratio, CI: confidence interval.

involvement. The details of nodal metastasis according to different T stage in terms of the serous and non-serous type are shown in Table 3.

Overall, serous carcinoma tended to involve bilateral ovaries (65.7% *vs.* 22.3%, $p < 0.001$) regardless of the FIGO Stage (Table 2). It was more significant in the patients with FIGO Stage I and II disease (31.8% *vs.* 7.6%, $p = 0.001$). However, asymmetric distribution was less significant in the patients with FIGO Stage III and IV disease (75.0% *vs.* 59.6%, $p = 0.069$).

Although more of the patients with serous carcinoma presented with advanced disease, overall survival was similar to those with non-serous carcinoma (five-year overall survival 64.4% *vs.* 75.0%, $p = 0.197$) (Table 4). The sole independent factor for a better survival was an early stage (HR 0.178, 95% CI = 0.094-0.334, $p < 0.001$) (Table 3). Another interesting finding was that the patients with serous carcinoma and an advanced stage had better overall survival (HR 0.469, 95% CI = 0.268-0.882, $p = 0.008$), and especially those with Stage III disease (HR 0.409, 95% CI = 0.217-0.771, $p = 0.006$) (Table 5), compared to those with the non-serous type. The survival curves for the patients with an advanced stage, Stage III and IV are shown in Figure 1.

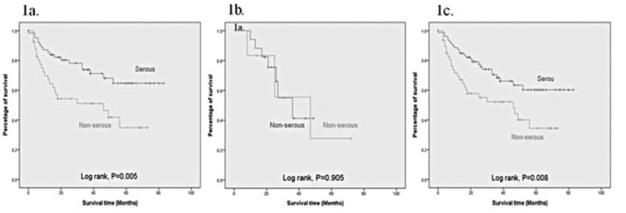

Figure 1. — Survival curves in terms of the serous and non-serous type. 1a) FIGO Stage III disease, 1b) FIGO Stage IV disease, and 1c) advanced stage (FIGO Stages III and IV).

Discussion

Previous studies have reported rates of serous, endometrioid, clear cell, and mucinous type epithelial ovarian cancer of around 75%, 10%, 10%, and 5%, respectively [5], which is very different compared to the present cohort, in whom only 38% had serous carcinoma. This is consistent with a national population-based, long-term follow-up study in Taiwan in which around 40% of the patients had serous carcinoma [6], and a worldwide analysis which reported that serous carcinoma accounted for about 40% of cases of epithelial ovarian cancer in most Asian countries [7]. Thus, the distribution of the histological types of ovarian cancer may be different in different areas.

With regards to the relationship between nodal status and histology, Takeshima *et al.* studied 208 patients with epithelial ovarian cancer, and reported that the patients with the serous type had a higher rate of para-aortic but a similar rate of pelvic lymph node metastasis to those with the non-serous type [8]. Roger *et al.* also reported a higher rate of lymph node metastasis in the patients with serous carcinoma, although the distribution of the location of the involved nodes was similar between the two groups [9]. In the present study, the patients with serous carcinoma had more lymph node involvement in both para-aortic and pelvic lymph node areas.

With regards to correlations between pathological T stage and lymph node metastasis in this study, 10.5% and 24.5% of the patients with T2 and T3 had para-aortic lymph node involvement, respectively. In addition, three of 38 (7.9%) patients with T2 disease and six of 94 (6.4%) patients with T3 disease had isolated para-aortic lymph node involvement. Thus, the need of systemic retroperitoneal lym-

Table 5. — *Multivariate analysis for factors predicting survival, in advanced disease (n=127) and FIGO Stage III disease (n=104).*

	Advanced stage (Stage III/IV)		Stage III	
Parameter	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Serous *vs.* non-serous	0.469 (0.268-0.882)	0.008	0.409 (0.217-0.771)	0.006

FIGO: International Federation of Gynecology and Obstetrics, HR: hazard ratio, CI: confidence interval.

phadenectomy including para-aortic lymph node dissection should be re-evaluated, although FIGO reports suggest selective lymphadenectomy in the early stage ovarian cancer [10].

Previous studies have reported that patients with serous carcinoma tend to have a higher stage than those with non-serous carcinoma. In 2003, Kaku *et al.* reported that patients with serous carcinoma predominantly had an advanced stage, whereas those with clear cell and endometrioid carcinomas tended to have tumors confined to the ovaries [11]. Kobel *et al.* also found that more patients with serous carcinomas had Stage III/IV disease than those with other histologic types [12]. A more recent study by Bergamini *et al.* described a more disseminated tumor spreading in advanced-stage high-grade endometrioid and serous types carcinoma [13]. We found similar results, and also that serous carcinoma tended to involve bilateral ovaries. An analysis of the SEER program found that 57.5% of cases of serous carcinoma involved bilateral ovaries, and that this rate was higher than for other histologic subtypes [14]. The uneven distribution of laterality was observed at all stages, although it was less significant in the late stage in this cohort.

Many previous studies have demonstrated that patients with serous carcinoma have a similar [15] or worse prognosis than those with the non-serous types [16, 17]. However, the present authors found that the patients with an advanced FIGO Stage and serous carcinoma had better outcomes than those with the non-serous type and an advanced FIGO Stage. Low grade histology only accounted for 2.9% of all of the patients with serous carcinoma in this study. Therefore, there may be other reasons for the better survival outcomes. An in vitro study demonstrated that serous and endometrioid carcinomas are more sensitive to platinum and taxane regimens compared to mucinous and clear cell carcinomas [18]. Since the main adjuvant therapy for advanced ovarian cancer is a combination of carboplatin and paclitaxel, it is possible that the patients with advanced serous carcinoma had a better survival than those with the non-serous type due to better chemosensitivity.

Conclusions

In this study, we attempted to clarify differences in tumor behavior between serous and non-serous ovarian carcinoma. The patients with serous ovarian carcinoma presented with more advanced disease, and had a higher rate of bilateral ovary involvement. In addition, the patients with more advanced serous carcinoma tended to have better outcomes compared to those with more advanced non-serous carcinoma. The mechanisms underlying these differences in tumor behavior are still unknown, and further investigations are warranted to clarify this issue and potentially improve the management of this disease.

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References

[1] Taiwan Cancer Registry [database online]: "Health Promotion Administration, Ministry of Health and Welfare", 2017, updated May 8, 2017. Available at: http://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=269&pid=7330

[2] Chen V.W., Ruiz B., Killeen J.L., Coté T.R., Wu X.C., Correa C.N.: "Pathology and classification of ovarian tumors". *Cancer,* 2003, *97*, 2631.

[3] Bell D.A.: "Origins and molecular pathology of ovarian cancer": *Modern. Pathol.,* 2005; *18*, S19.

[4] Kurian A.W., Balise R.R., McGuire V., Whittemore A.S.: "Histologic types of epithelial ovarian cancer: have they different risk factors?" *Gynecol. Oncol.,* 2005, *96*, 520.

[5] Prat J.: "New insights into ovarian cancer pathology". *Ann. Oncol.,* 2012; *23*, 111.

[6] Chiang Y.C., Chen C.A., Chiang C.J., Hsu T.H., Lin M.C., You S.L., *et al.*: "Trends in incidence and survival outcome of epithelial ovarian cancer: 30-year national population-based registry in Taiwan". *J. Gynecol. Oncol.,* 2013, *24*, 342.

[7] Sung P.L., Chang Y.H., Chao K.C., Chuang C.M., Task Force on Systematic Review and Meta-analysis of Ovarian Cancer: "Global distribution pattern of histological subtypes of epithelial ovarian cancer: A database analysis and systematic review". *Gynecol. Oncol*., 2014; *133*, 147.

[8] Takeshima N., Hirai Y., Umayahara K., Fujiwara K., Takizawa K., Hasumi K.: "Lymph node metastasis in ovarian cancer: difference between serous and non-serous primary tumors". *Gynecol. Oncol*., 2005, *99*, 427.

[9] Roger N., Zafrani Y., Uzan C., Gouy S., Rey A., Pautier P., et al.: "Should Pelvic and Para-aortic Lymphadenectomy Be Different Depending on Histological Subtype in Epithelial Ovarian Cancer?' *Ann. Surg. Oncol.*, 2008, *15*, 333.

[10] Berek J.S., Crum C. & Friedlander M.: "FIGO cancer reports 2015: Cancer of the ovary, fallopian tube, and peritoneum". *Int.J. Gynecol. Obstet.,* 2015, *131*, S111.

[11] Kaku T., Ogawa S., Kawano Y., Ohishi Y., Kobayashi H., Hirakawa T., Nakano H.: "Histological classification of ovarian cancer". *Med. Electron. Microsc.*, 2003, *36*, 9.

[12] Köbel M., Kalloger S.E., Huntsman D.G., Santos J.L., Swenerton K.D., Seidman J.D., Gilks C.B.: "Differences in tumor type in low-stage versus high-stage ovarian carcinomas". *Int. J. Gynecol. Pathol.,* 2010, *29*, 203.

[13] Bergamini A., Candiani M., Taccagni G., Rabaiotti E., Viganò R., De Marzi P., *et al.*: "Different patterns of disease spread between advanced-stage type I and II epithelial ovarian cancer". *Gynecol. Obstet. Invest.*, 2016, *81,* 10.

[14] Boger-Megiddo I., Weiss N.S.: "Histologic subtypes and laterality of primary epithelial ovarian tumors". *Gynecol. Oncol.* 2005, *97*, 80.

[15] Malkasian G.D. Jr., Melton L.J. 3rd., O'Brien P.C., Greene M.H.: "Prognostic significance of histologic classification and grading of epithelial malignancies of the ovary". *Am. J. Obstet. Gynecol.*, 1984, *149*, 274.

[16] Makar A.P., Baekelandt M., Tropé C.G., Kristensen G.B.: "The Prognostic Significance of Residual Disease, FIGO Substage, Tumor Histology, and Grade in Patients with FIGO Stage III Ovarian Cancer". *Gynecol. Oncol.*, 1995, *56*, 175.

[17] Brun J.L., Feyler A., Chêne G., Saurel J., Brun G., Hocké C.: "Long-Term Results and Prognostic Factors in Patients with Epithelial Ovarian Cancer". *Gynecol. Oncol.*, 2000, *78*, 21.

[18] Cloven N.G., Kyshtoobayeva A., Burger R.A., Yu I.R., Fruehauf J.P.:

"In vitro chemoresistance and biomarker profiles are unique for histologic subtypes of epithelial ovarian cancer". *Gynecol. Oncol.*, 2004, *92*, 160.

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