

Endometriosis-associated Ovarian Cancer: A Distinct Clinical Entity?

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Abstract. *Aim: The aim of the study was to evaluate the incidence of endometriosis-associated ovarian cancer (EAOC) and compare clinicopathological characteristics and overall survival (OS) between patients with EAOC and those with ovarian cancer not associated with endometriosis. Patients and Methods: We identified EAOC among 203 patients with invasive epithelial ovarian cancer who underwent complete surgery at our Institution from January 2004 to March 2014. Results: EAOC was present in 45 patients. EAOC was significantly more frequently diagnosed at an earlier stage of disease ($p=0.038$). At a median follow-up time of 32 months, OS among patients with EAOC was significantly longer ($p=0.039$). However, stratifying by stage, the OS advantage of EAOC was not significant. At multivariate analysis, only stage was an independent prognostic factor for OS (hazard ratio=5.7; 95% confidence interval=1.8-18.6; $p=0.003$). Conclusion: EAOC incidence was 22.2%. EAOC appears to be diagnosed at an earlier stage and confers a better OS. However, stratifying by stage, the advantage in survival of EAOC disappears.*

Endometriosis is an oestrogen-dependent benign disease that shares many features with ovarian cancer, such as the invasive growth, hormone dependency and recurrence (1). Epidemiological, histopathological and molecular data suggest a possible malignant potential of endometriosis. In particular, oxidative stress and chronic inflammation may play a key role

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in neoplastic transformation of endometriosis (1, 2). Atypical endometriosis is, therefore, considered an intermediate lesion between endometriosis and ovarian cancer (1).

The malignant transformation of endometriosis is a rare event, mostly involving the ovary; however, malignant transformation of endometriosis has also been observed in extra-ovarian endometriosis (1, 3, 4).

Many studies report an increased risk of ovarian cancer in women with endometriosis, especially in those with a long-standing history of endometriosis (>10 years) and with endometriosis diagnosed at a young age (<30 years) (5). In particular, endometriosis-associated ovarian cancer (EAOC) is predominantly of clear-cell and endometrioid histology and often diagnosed at a younger age, at an earlier stage, and with a lower grade, and has a better outcome (2).

In the present study, we evaluated the incidence of EAOC in a series of cases with invasive epithelial ovarian cancer treated at our Institution, as well as clinicopathological characteristics, personal history and outcome, in terms of overall survival (OS) compared to ovarian cancer not associated with endometriosis (non-EAOC).

Patients and Methods

In this retrospective study, by reviewing the medical charts, we identified EAOC among patients with invasive epithelial ovarian cancer who underwent complete surgery at the Department of Gynecology and Obstetrics, Umberto I Hospital, University of Turin, Italy, from January 2004 to March 2014.

In all cases in which concurrent endometriosis was described in the final pathological report, a review of the pathological specimen was carried out by an expert pathologist in Gynaecological Oncology at the Department of Pathology of the same Hospital in order to confirm the concurrent presence of endometriosis, the site of occurrence of endometriosis and to define endometriosis as typical or atypical. We defined EAOC according to the Van Gorp classification (1), including all three categories: endometriosis concurrent with ovarian cancer in the same ovary with histological proof of transition from endometriosis to cancer (category A), as previously described by Sampson and Scott (6, 7); ovarian cancer with endometriosis in the

Table I. Classification of endometriosis-associated ovarian cancer (EAOC) according to Van Gorp categories in this study.

Van Gorp category	Definition of EAOC	Patients with EAOC (n=45)
A	Endometriosis in the same ovary affected by cancer with histological proof of transition from endometriosis to cancer	1 (2.2%)
B	Endometriosis in the same ovary affected by cancer without histological proof of transition from endometriosis to cancer	7 (15.6%)
C	Endometriosis in the contralateral ovary	2
	Endometriosis in both ovaries	1
	Extragenital endometriosis (uterus, fallopian tube, parametrium, bowel, peritoneum, omentum, appendix, utero-sacral ligaments)	34

same ovary but without histological proof of transition (category B); ovarian cancer with concomitant endometriosis at any other location in the pelvis (endometriosis in the contralateral ovary), in both ovaries or extra-gonadal endometriosis (category C). According to the pathological criteria listed above, we divided all patients with invasive epithelial ovarian cancer into those with and those with non-EAOC.

All patients signed a written informed consent allowing that their blinded clinical data and biological material could be used for research purposes.

The patients in both groups were treated according to the same protocol and operated on the same surgical team specialized in Gynecological Oncology. Patients with early-stage disease [International Federation of Gynecology and Obstetrics (FIGO) I-IIa] underwent complete staging surgery followed by adjuvant chemotherapy with carboplatin and paclitaxel with the exception of those with IA and IB grade 1 and 2. Patients with advanced disease (FIGO IIB-IV) underwent cytoreductive surgery, followed by first-line chemotherapy with carboplatin and paclitaxel. The patients unsuitable for upfront cytoreductive surgery received neoadjuvant chemotherapy with carboplatin and paclitaxel, followed by interval debulking surgery. Since September 2013 (bevacizumab approval in Italy), patients with disease from FIGO stage IIIb on received bevacizumab in addition to standard first-line carboplatin-paclitaxel chemotherapy, followed by bevacizumab-only maintenance therapy up to 12 months (8). Residual disease at the end of the main surgical procedure was defined as: no residual tumour (TR) (optimal cytoreduction; TR=0) or residual disease ≥ 1 mm (TR ≥ 1).

Patients typically underwent clinical follow-up examination (clinical examination and cancer antigen 125 (CA125) biomarker) every 3 months in the first two years, every 6 months afterwards until the fifth year after diagnosis, and every year subsequently. Abdomino-pelvic computed tomographic scan was prescribed in cases with symptoms, clinical findings or CA125 elevation *etc.*

Statistical analysis. Statistical analysis was performed using the SPSS software for Windows 17 (SPSS Inc., Chicago, IL, USA). The date of primary treatment was used as the date of diagnosis. OS was calculated according to the date of death or date lost to follow-up.

Categorical variables were compared by the Pearson's chi square test or by Fisher's exact test. Numerical variables were compared by the variance analysis (ANOVA) or with independent-samples *t*-test. Normality of the variables distribution was tested by the Kolmogorov-Smirnov test. Survival curves were estimated using the Kaplan-Meier method and compared by the log-rank test. Cox proportional hazards regression was used for multivariate analysis.

Variables included in the multivariate analysis were those found to be statistically significant in the univariate analyses. Hazards ratios (HR) and 95% confidence intervals (95% CI) were used to calculate the relative risk of death or relapse for each variable of interest while adjusting for other covariates.

All *p*-values are two-tailed and a *p*-value of less than 0.05 was considered statistically significant.

Results

Patients. In the study period, we identified 203 patients treated with complete surgery at our Institution for invasive epithelial ovarian cancer. According to the pathological criteria described above, we identified 45 (22.2%) patients with EAOC and 158 with non-EAOC (77.8%).

In two cases of EAOC, atypical endometriosis was found: in one case it was located in the same ovary affected by cancer with histological proof of transition from endometriosis to cancer; in the second case, concurrent endometriosis was found in the bowel wall. In the other 43 cases of EAOC, concurrent endometriosis was typical.

According to the Van Gorp classification (1), concurrent endometriosis was found in the same ovary affected by cancer in eight patients, among them, one category A; in the other seven, only typical endometriosis was present (category B). In two patients, endometriosis was found in the contralateral ovary, and in one patient, endometriosis was present in both ovaries; in the remaining 34 women concurrent endometriosis was present outside the ovaries (category C) (Table I).

Comparison of clinicopathological characteristics between EAOC and non-EAOC. The clinicopathological data were compared between the two groups as shown in Table II.

Mean age at diagnosis was similar for the two groups and as was the number of pregnancies. In the EAOC group, only six women (13.3%) reported a personal history of endometriosis. Around half of the non-EAOC tumours were serous, compared to 37.8% in the EAOC group (*p*=0.13). Among EAOCs, around one-third were endometrioid and

Table II. Clinicopathological characteristics of patients with invasive epithelial ovarian cancer compared according to the concurrent presence (EAOC) or absence of endometriosis (non-EAOC).

		EAOC (n=45)	Non-EAOC (n=158)	p-Value
Mean (\pm SD) age at diagnosis, years		59 (\pm 9.6)	60.4 (\pm 11)	0.47
Number of pregnancies	None	12 (26.7%)	54 (34.2%)	0.343
	≥ 1	33 (73.3%)	104 (65.8%)	
Histotype	Serous	17 (37.8%)	82 (51.9%)	0.13
	Endometrioid	13 (28.9%)	36 (22.8%)	0.461
	Clear cell	5 (11.1%)	10 (6.3%)	0.29
	Mucinous	4 (8.9%)	9 (5.7%)	0.461
	Undifferentiated	6 (13.3%)	21 (13.3%)	0.461
Grading	G1	2 (4.4%)	10 (6.3%)	0.313
	G2	8 (17.8%)	14 (8.9%)	0.313
	G3	33 (73.3%)	130 (82.3%)	0.260
	Gx	2 (4.4%)	4 (2.5%)	0.313
Kurman and Shih category (9)	Type I (low-grade serous, endometrioid, mucinous, clear cell)	23 (51.1%)	64 (40.5%)	0.205
	Type II (high-grade serous and undifferentiated)	22 (48.9%)	94 (59.5%)	
FIGO stage	I	13 (28.9%)	34 (21.5%)	0.734
	II	3 (6.7%)	9 (5.7%)	
	III	25 (55.6%)	97 (61.4%)	
	IV	4 (8.9%)	18 (11.4%)	
Early-stage disease	FIGO stage I-IIa	15 (33.3%)	35 (22.2%)	0.038
Advanced-stage disease	FIGO stage IIb-IV	30 (66.7%)	123 (77.8%)	
Surgery	Upfront surgery	28 (62.2%)	105 (66.5%)	0.598
	Interval debulking surgery	17 (37.8%)	53 (33.5%)	
Residual disease	0	37 (82.2%)	109 (69%)	0.090
	≥ 1 mm	8 (17.8%)	49 (31%)	0.081

11.1% were clear cell (*versus* 22.8% and the 6.3% among non-EAOCs, respectively). EAOC tumours were significantly more frequently diagnosed at an earlier stage of disease compared to non-EAOC ($p=0.038$). According to Kurman and Shih categories (9), type I ovarian cancer was more frequent in the EAOC group (51.1% *versus* 40.5%, respectively); on the contrary, type II ovarian cancer was more represented in the non-EAOC group (59.5% *versus* 48.9% of the EAOC group). However, these differences were not significant ($p=0.205$).

Stratifying the whole series by stage, 50 patients had early-stage disease (FIGO stage I-IIa; 24.6%) and 153 advanced-stage (FIGO stage IIB-IV; 75.4%).

Among the 50 patients with early-stage disease, 15 had EAOC. Comparing EAOC to non-EAOC, the mean age at diagnosis was 57 years for both groups. We found a non-significant difference in the histotype distribution in those with early-stage disease: in the EAOC group, we found fewer serous, no undifferentiated and more clear-cell and mucinous tumours; the most frequent histotype in both groups was endometrioid.

Among those with advanced disease, 83 patients (54.2%) underwent primary debulking surgery and 70 (45.8%) received neoadjuvant chemotherapy followed by interval debulking surgery. Comparing the 30 patients with EAOC (19.6%) with the 123 with non-EAOC (80.4%), no significant differences regarding age at diagnosis and the number of

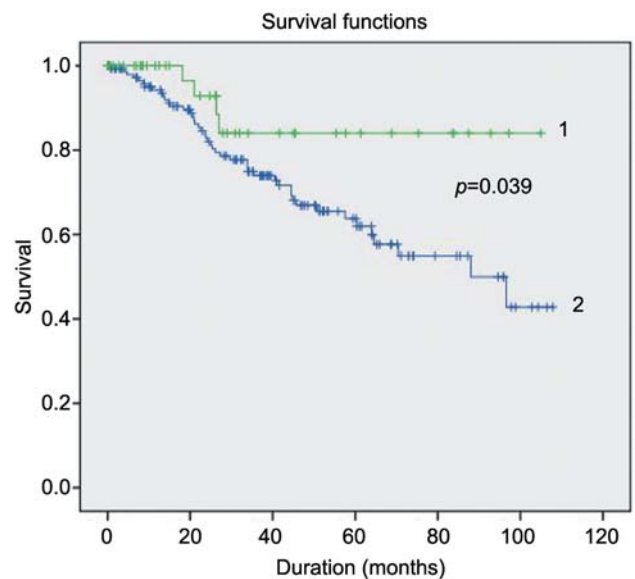


Figure 1. Overall survival (OS) of patients with ovarian cancer according to the presence (1) or absence (2) of associated endometriosis.

pregnancies were found. In both groups, mucinous and clear-cell tumours were under-represented and the main histotype was serous. Among EAOCs, 20% were endometrioid

(compared to 15.4% in the non-EAOC group) and 20% were undifferentiated (*versus* 13% in the non-EAOC group) ($p>0.05$). Around 90% of tumours in both groups were high grade. No significant difference in terms of cytoreduction were seen between the two groups.

Comparison of prognosis between EAOC and non-EAOC. At a median follow-up of 32 months (range=3-107 months), OS among those with EAOC was significantly longer ($p=0.039$), as shown in Figure 1. The median survival among non-EAOC patients was 88 months (95% CI=57.7-118.2 months), while among those with EAOC, it had not been reached (mean=91.9 months, 95% CI=80.2-103.7 months).

The difference in OS did not hold when stratification by stage was performed. Furthermore, we compared the OS according to the presence of ovarian-associated endometriosis (N=9), the presence of extra-ovarian-associated endometriosis (N=36), and the absence of concurrent endometriosis (N=158). In the follow-up period, 0, 4 and 6 deaths due to disease, respectively, were observed for these three groups. However, possibly due to the small number of events, these differences were not significant ($p=0.103$).

In order to identify the independent prognostic factors for OS, we performed univariate and multivariate analyses. At univariate analysis, advanced stage, residual disease ≥ 1 mm, the concurrent presence of endometriosis and high tumour grade were significant negative predictors for poorer OS. At multivariate analysis, only higher stage remained as an independent prognostic factor for poorer OS (HR=5.7; 95% CI=1.8-18.6; $p=0.003$).

Discussion

Endometriosis is associated with an increased risk of ovarian cancer (relative risk=1.4-8.95) and the prevalence of endometriosis in ovarian cancer ranges between 3.4 and 52.6% in the literature (5). This wide variability is due to the different definitions of EAOC adopted by authors. EAOC can be strictly defined as the presence of ovarian endometriosis in the same ovary affected by cancer with histological proof of transition from endometriosis to cancer [category A according to Van Gorp classification (1), as considered by Sainz de la Cuesta *et al.* (10), Ogawa *et al.* (11), Valenzuela *et al.* (12), Kumar *et al.* (13), or according to the less stringent criteria as endometriosis in the same ovary affected by cancer without histological proof of transition from endometriosis to cancer (category B) or even as concurrent extra-gonadal endometriosis (category C).

In our series, the proportion of EAOCs was 22.2%. Most tumors with concurrent endometriosis (82%) were in category C according to Van Gorp classification (1); 15% were in category B and only one patient was in category A. The same definition of EAOC adopted in our study has been used by others (3, 14, 15). The Sampson and Scott criteria to define

category A (1, 6, 7) are difficult to meet for different reasons. Sampling techniques cannot be extensive enough to detect all foci of endometriosis adjacent to tumours, especially, if the study is retrospective and sampling was performed with the main goal of studying tumour characteristics and not for identifying concurrent endometriosis. Furthermore, the tumour can be so aggressive that the endometriotic tissue has been destroyed or only a minor residual component, difficult or even impossible to detect, is left.

Many studies have been performed in order to understand whether EAOC is a clinically distinct entity. According to the currently accepted dualistic model of Kurman and Shih for the pathogenesis of epithelial ovarian cancer (9), type I tumours include endometrioid, clear-cell, mucinous and low-grade serous carcinoma, and usually have an indolent clinical behaviour, are often detected in early stage, rarely harbour *p53* gene mutations, are genetically stable, carry mutation of Kirsten rat sarcoma virus (*KRAS*), phosphatase and tensin homolog (*PTEN*), AT-rich interactive domain 1A (*ARID1A*) genes (1, 2), and pre-malignant lesion such as borderline tumors and endometriosis can be identified. Type II tumours include high-grade serous and undifferentiated carcinoma, have a very aggressive clinical behaviour, are usually advanced stage at presentation, often harbour *p53* gene mutations, and are genetically unstable.

EAOCs frequently exhibit the favourable features of type I tumours, often being diagnosed at an earlier stage and at a younger age, and are associated with nulliparity and infertility (2).

Wang *et al.* found that concurrent endometriosis was significantly more frequent among those with type I tumours (14). In our series, the same trend was observed: type I tumors were more frequent among those with EAOC; on the contrary, type II tumors were more frequent in the non-EAOC group. However, the difference was not statistically significant.

In our series, EAOCs were significantly more frequently diagnosed at an early stage, consistent with previous findings (2, 13, 16, 17). The earlier diagnosis of EAOC may be due to the symptoms associated with endometriosis (pelvic pain or adnexal mass) or to the concurrent presence of endometrial lesions (polyps, hyperplasia and endometrial carcinoma) (1).

In our study, early-stage EAOCs were 46.7% endometrioid, 26.7% clear-cell, 20% mucinous, 6.7% serous and none was of undifferentiated histotype. The high prevalence among early-stage EAOCs of endometrioid and clear-cell tumours, the absence of undifferentiated tumours and the small number of serous tumours is consistent with the literature (2-4).

In the literature, a younger age at diagnosis is reported for those with EAOC (2, 14, 17-20). In our series, we found no differences in the mean age at diagnosis between those with EAOC and those with non-EAOC.

In our study, only 13.3% of patients with EAOC reported a personal history of endometriosis. Most women did not know

they had endometriosis, as also reported in other studies (14). If these data are confirmed, many doubts will be raised as to the feasibility of preventing EAOC with a strict follow-up of women with endometriosis.

We would have expected a higher proportion of nulliparous women among those with EAOC (2, 20) due to the close relationship between endometriosis and infertility; in our series, no significant difference was observed between the two groups as to parity.

As described in the meta-analysis by Kim *et al.* (2), we also found no significant difference in optimal cytoreduction between the two groups.

In patients with EAOCs, a significantly longer OS was recorded, both in our and in other studies (2, 13, 16). Other authors, instead, saw no benefit in OS, but only a longer disease-free interval (17, 19). Stratifying our series by stage, no significant difference was observed in OS between those with EAOC and those with non-EAOC. Similar findings were reported by others who evaluated the OS of patients with EAOC according to FIGO stage (13, 17, 20). At multivariate analysis, only higher stage of disease was a significant independent predictor of poorer OS (HR=5.7; 95% CI=1.8-18.6; $p=0.003$).

In conclusion, the association of endometriosis with ovarian cancer is relevant. The advantage in survival associated with EAOC seems more related to its favourable features, disappearing after stratifying by stage, thus suggesting a role of endometriosis as a precursor of cancer and not as a promoter of cancer after its onset (2).

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