Title page

EPITHELIAL OVARIAN CANCERS AND ENDOMETRIOSIS

Running title: Ovarian carcinomas and endometriosis

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Endometriosis-associated ovarian carcinoma, atypical endometriosis, epithelial ovarian cancer, endometrioid, clear cell, endometrial carcinoma.

Abstract

Aims: To determine the prevalence of endometriosis in epithelial ovarian cancers (EOC) and the association among their histological subtypes and with endometrial carcinoma.

Methods: An observational cohort study performed in 192 patients operated on for EOC, 30 women with atypical endometriosis and 17 with p53 positive endometriosis. Data on associated endometriosis and endometrial carcinomas, histological subtypes, tumor stage, clinical and pathological characteristics and survival were analyzed.

Results: Twenty cases of EOC (10.4%) had also endometriosis (12.7% in borderline and 9.3% in invasive cases), being a synchronous finding in most cases. Endometriosis associated with serous or mucinous EOC was observed in 2.2 and 2.7% of cases respectively. However, this association was observed in 50% of endometrioid and 23% of clear cell EOC. Age, parity and tumor stage were lower in endometriosis-associated EOC patients; and all associated cases were type I (Kurman and Shih's classification) and showed better results in survival rate. Endometrial carcinoma was more frequently associated with endometrioid EOC (25%).

Conclusions: There is a significant association between endometriosis, including atypical forms, and endometrioid and clear cell carcinomas, but not with other EOC histotypes. The presence of endometriosis in EOC suggests a better prognosis and an intermediate stage within the progression endometriosis-carcinoma.

Text

Introduction

Sampson [1] first described the association between endometriosis and ovarian cancer, and his criteria are still used to identify malignant tumors that arise from endometriosis. Scott [2] further defined the diagnosis of an endometriosis-associated ovarian carcinoma stating that benign endometriosis should be contiguous with malignant tissue. This association has later been reported in several studies [3-7], particularly for endometriosis with ovarian endometrioid and clear cells carcinomas, suggesting that concurrent endometriosis is generally associated with a better prognosis for these specific subtypes of EOC [8-10]. Moreover, atypical endometriosis has been described as a precursor lesion that can lead to certain types of ovarian cancer [12-16]. Other authors have also suggested a hormonal dependence or a relationship with other hormone-dependent pathologies in this type of association [17-18]. Endometriosis-induced inflammation and the auto- and paracrine production of sex steroid hormones could contribute to ovarian tumor genesis because these changes provide a microenvironment that favors the accumulation of sufficient genetic alterations and endometriosis-associated malignant transformation [16]. So, Wei et al. [16] have suggested that this pathophysiological progression begins with atypical epithelial proliferation (atypical endometriosis and metaplasia), followed by well-defined borderline tumors and culminating in malignant ovarian cancer. However, although some cases of endometriosis-associated ovarian carcinomas appear to be the final consequence of this pathological progression, the development and neoplastic transformation is usually controversial, and the epidemiological findings on the association are still elusive [6,19]. The aims of this study were to determine the prevalence of endometriosis in all cases of histopathologically confirmed EOC (both invasive and borderline) operated on by our group within the last 20 years, and to analyze the relation with different histological subtypes of EOC and endometriosis, evaluating a possible pathological progression in our patients. The relationship between these pathologies and endometrial carcinoma was also considered.

Materials and Methods

We reviewed the medical charts of 192 patients with EOC (borderline and malignant carcinomas) who were operated on in our service from 1993 to 2013. Patient clinical

characteristics, tumor markers, tumor histology and staging, associated pathology, surgery performed, postoperative clinical course and data for survival analysis were collected. It was also collected the presence and type of endometriosis when it was associated with an EOC, as well as the association with other malignant tumors especially endometrial carcinoma and breast cancer.

EOC patients were grouped by histological types: 1) Serous, 91 cases [32 low grade serous papillar or borderline, and 59 invasive high grade serous carcinomas]; 2) Mucinous, 37 cases [22 mucinous borderline, and 15 mucinous invasive]; 3) Endometrioid, 28 cases [7 pure endometrioid: 3 borderline and 4 invasive; 21 mixed with endometrioid: 3 borderline and 18 invasive]; 4) Clear cells carcinoma, 13 cases [9 pure clear cells: 2 borderline and 7 invasive; 4 mixed of clear cells and endometrioid: 1 borderline and 3 invasive]; and 5) Other mixed and undifferentiated carcinomas (20 cases) and 3 cases of ovarian carcinosarcomas.

In this study, endometriosis-associated ovarian carcinoma was defined by the presence of ovarian cancer and endometriosis in the same or contralateral ovary or extraovarian pelvic endometriosis. So, endometriosis was identified when the tissue resembling endometrial stroma surrounding epithelial glands was present in ovaries or peritoneum. Besides, atypical endometriosis was considered according to the criteria from Thomas and Campbell [20] based on the features that were identified in histological examinations (i.e., large hyperchromatic or pale nuclei with moderate-to-marked pleomorphism, increased nuclear-to-cytoplasmic ratio, cellular crowding and stratification) and p53 positive expression. According to these criteria, we identified 20 of the 192 patients as having endometriosis, which was diagnosed as atypical in 5 cases.

With the intention to analyze the significance of the atypical endometriosis associated or not to EOC, we also reviewed the medical charts of other 47 patients operated on for endometriosis of which 30 were diagnosed as atypical endometriosis and 17 as typical endometriosis but p53 positive. These 47 cases reported by the Pathology Service within the period of study were all operated on after 1999.

Based on a dualistic model of carcinogenesis and Kurman and Shih´s classification [21-22], we divided our EOC cases into two groups: 1) Type I tumors comprising borderline and low grade serous carcinomas, mucinous, endometrioid, clear cells and transitional cell carcinomas. 2) Type II tumors comprising high grade serous cancer, malignant mixed mesodermal tumors and undifferentiated carcinomas. The clinical and

pathological characteristics as well as the actuarial survival of the different subtypes, with or without associated endometriosis, were compared.

Statistical analysis was performed using SPSS-15 and 21 (IBM, Spain), RSigma (Systat Software, San Jose, California, USA) and PEDro (Physiotherapy Evidence Database, Sidney, Australia) software. Comparison of independent means (Student's T-test), comparison of two proportions (relative risk –RR-), a 95% confidence interval (CI) and the chi-squared test were used to compare the groups. Data are expressed as percentages, mean ± standard deviation, mean standard error (mse) and minimum and maximum values. The actuarial survival was analyzed to all EOC groups after 2, 5 and 10 years of follow-up according to the Kaplan-Meier method of estimated survival. All *p* values reported are 2-tailed and $p < 0.05$ was considered significant.

Results

Twenty cases of EOC (10.4%) were associated with endometriosis, 5 of which involved atypical endometriosis. As shown in Table 1, synchronous endometriosis was found in 8 of 63 patients with borderline or low grade tumors (12.7%) and in 12 of 129 invasive cases (9.3%), but difference was not significant. Atypical endometriosis was more frequent in the cases of endometrioid invasive cancer. Synchronous endometrial carcinoma was also observed in 5 (7.9%) of the borderline tumors and in 7 (5.4%) of the invasive cases, without significant differences.

Table 2 shows the distribution of endometriosis and endometrial carcinoma among the different histological subtypes of EOC. Association of endometriosis with serous or mucinous EOC was observed in 2.2% and 2.7% respectively, and only in borderline or low grade tumors. However, most of the EOC with subtype endometrioid (71%) or mixed with predominant endometrioid component (43%) showed associated endometriosis, mainly in the borderline cases. In the clear cell carcinomas, associated endometriosis was observed only in the invasive cases (43%); it was not present in the mixed endometrioid+clear cell or mixed clear cell carcinomas. Nor endometriosis was observed in the other mixed subtypes, high grade invasive, carcinosarcomas and undifferentiated carcinomas. The association of endometriosis with endometrioid, mix-endometrioid and clear cells invasive cases was clearly significant (RR=20.9; CI= 5.08-86.0) compared to serous EOC. Respect to the association of endometrial carcinoma with EOC, the result was also significant for the endometrioid and mix-endometrioid subtypes (25%).

Table 3 shows the clinical and pathologic characteristics of the EOC with or without associated endometriosis. Endometriosis-associated patients were significantly younger (48.8 versus 56.1 years old) and had lower parity. In these patients, there was a tendency to be premenopausal at the time of diagnosis, to have a lower-grade tumor according to FIGO classification and more borderline cases, and to have synchronous endometrial carcinoma. Moreover, they showed lower CA-125 values, although differences were not significant. In this sense, all endometriosis-associated EOC cases were type I according to the Kurman and Shih classification, and showed the best results in survival rates at 5 and 10 years (Kaplan-Meier method) (Figure 1) .

When the 192 cases of EOC were reclassified according to Kurman and Shih´s classification, 109 were type I and 83 were type II tumors (Table 4). Comparing both groups, we observed clear significant differences: patients with type II EOC were older and had higher parity, were more frequently postmenopausal, showed higher CA-125 levels and more advanced FIGO stages, and showed lower survival rates at 2, 5 and 10 years (Figure 2). Moreover, there was a higher frequency (not significant) of breast cancer in this group, although a lower frequency of endometrial carcinoma.

In table 4, the type I EOC are separated into: 1) low grade and borderline serous and all mucinous tumors, 2) endometrioid, and 3) clear cells carcinomas. No differences were observed between the subgroups 2 and 3 (which had more frequently associated endometriosis) respect to age, parity and FIGO stage. Blood sedimentation rate (BSR) values were significantly higher in clear cells carcinomas, whereas CA-125 and CA-19-9 levels were higher in endometrioid EOC. As mentioned, these tumors showed a clear association with endometriosis and endometrial carcinoma and perhaps for this reason the survival rate was worse at 5 and 10 years.

In order to analyze the possible pathologic progression among the subtypes of endometriosis and the endometrioid and clear cell EOC subtypes, Table 5 shows the clinical and pathologic characteristics of typical p53+ endometriosis, atypical endometriosis, endometrioid and clear cells (E/CC) carcinomas with atypical or typical endometriosis, and E/CC carcinomas without associated endometriosis. Although there were no significant differences among groups because of the low number of cases in each one, the results showed that typical or atypical endometriosis were similar in all variables, but, when they were associated with an E/CC carcinoma, there was an increase in age, parity, BSR and tumor marker values. Moreover, the E/CC carcinomas without associated endometriosis had higher age, parity and tumor staging, and a lower

survival rate at 10 years. Therefore, it seems that the malignant transformation and progression evolved the next pathological order: 1. Endometriosis typical or atypical, 2. E/CC carcinomas with associated endometriosis and 3. Endometrioid or clear cell carcinomas.

Discussion

In this study, the percentage of patients with endometriosis-associated EOC among the total of EOC observed (20/192, 10.4%) was similar or superior that other recent publications: 10.9% (23/210) in Dzatic-Smiljkovic et al. [23]; 9.8% in Pearce et al. [24] (a pooled analysis of 13 case-control studies); or 7.5% (17/209) in Wang et al. [11]. But it was lower than other previous reports (11.2 to 29%) [14, 15, 25-27]. This variability may be the result of an under detection or missing reports of endometriosis in some centers, but a recent systematic review by Heidemann et al. [28] shows that some studies include all type of EOC and others only determined subtypes as endometrioid, clear cell, I-stage cases [29] (52.6%), or early stages [30] (23.7%). In fact, the association of endometriosis with EOC is more frequent in early stages and in determined histological types, mainly endometrioid and clear cell carcinomas, although there is also variability in results on the latter. Some studies report a predominant association with clear cell carcinomas [31]: 47% vs. 35% in endometrioid. Others [32] describe a higher association with endometrioid types, as observed in our results: 50% in endometrioid and mixed endometrioid, 23% in clear cells and mixed clear cells, versus 2.2-2.7% in serous or mucinous subtypes, or 0% in the type II tumors according to the Kurman and Shih's classification [22]. Somigliana et al. [6] reviewed 11 studies about the frequency of endometriosis in ovarian cancer patients based on the histological type; the endometriosis-associated carcinoma was most commonly seen in clear cell carcinoma (35% of 390 cases), followed by endometrioid (27% of 648 cases), serous (5% of 1372 cases) and mucinous carcinoma (4% of 614 cases). These differences may be due to the group in which mixed tumors (endometrioid or clear cells) are included, because they are the most commonly associated with endometriosis. Furthermore, Song et al.[33] performed a retrospective review of 203 patients comparing endocervical-like versus intestinal-type mucinous borderline ovarían tumors and pointed that the first type had higher CA-125 and CA-19-9 levels and less relation to endometriosis (1.4%).

As mentioned above, the frequency in the association endometriosis-EOC also depends to the tumor staging. In our study, 50% of endometriosis-associated EOC cases were FIGO I-stage, and was also more common in low grade or borderline tumors. Several studies have reported a more benign character of the tumor when endometriosis is present [8-11, 29, 34, 35] with better survival rates (as shown in figure 1). Moreover, patients with endometriosis-associated EOC are younger, premenopausal, and have lower parity than those without endometriosis, so perhaps they are an intermediate stage in the pathological progression. Some authors [36, 37] have suggested that patients with a previous history of endometriosis should be followed up more closely, and then incidentally finding of early ovarian cancers would be more possible. However, the appearance is synchronous in most cases. Wang et al. [31] noted that only one of their patients had history of surgically identified endometriosis and, among our cases, only 2 patients had previous surgically identified endometriosis. They are described in another article.

On the other hand, atypical endometriosis is considered to be precancerous and strongly associated with endometriosis-associated ovarian cancer [16], although recognition of this form of endometriosis as a diagnostic criterion for pathological and clinical management remains controversial. Czernobilsky and Morris [12] first described atypical endometriosis, and Thomas and Campbell [20] further classified it based on the features that were identified in histological examinations. However, frequency of atypical endometriosis that is observed in EOC patients with associated endometriosis varies greatly between different series, from 3 to 12% [5] or up to 34% in EOC FIGO-I stage [15], with both types of endometriosis present in most of the same EOC cases (37 of 127 EOC -29%-, having 33 typical and 29 atypical endometriosis). In this last study, the transition from typical to atypical endometriosis was observed in 22 cases, and the transition from atypical endometriosis to carcinoma was also observed in 23 cases, but a direct transition from typical endometriosis to carcinoma was observed in only 1 case [6, 15]. Besides, Ogawa et al. [15] described 43 patients who had clear cell carcinoma and only 7 cases of endometrioid carcinoma, which confirms the great variability that is found in the histological classifications, both in the subtype of carcinoma and the subtype of endometriosis. But it has to be taken into account that the prevalence of clear cell EOC in Japan [34] seems to be much higher than that in western countries for unknown reasons. In our study, the few cases of atypical endometriosis that were associated with EOC were observed in endometrioid carcinomas, but no differences

were observed between typical (with or without p53 expression) and atypical endometriosis in the clinical variables analyzed.

Ness [38] also reviewed the concept of endometriosis as a precursor lesion for ovarian cancer and proposed both inflammatory and hormonal pathways for this process. Estrogens seem to be a mitogen for both endometriosis and ovarian cancer [16] since most endometriotic tissues and several endometrioid carcinomas have a functional stroma and in situ estrogen production [39-41]. So, although there is evidence supporting a role for estrogens in the etiology of endometriosis and the enhancement of inflammation [42, 43], a plausible mechanism that links estrogens to ovarian carcinogenesis, as well as the steps for malignant transformation in ectopic endometrium has not yet been established.

Moreover, many of the same genes, such as ß catenin and PTEN, have been shown to be mutated in both endometrial and endometrioid ovarian cancers, suggesting a shared molecular pathogenesis [36]. However, clear cell carcinomas do not express estrogen or progesterone receptors [444] and therefore endometriosis, that can transform into clear-cell ovarian cancer, could became hormone independent during the transformation process [24, 45]. Therefore, an interesting dualistic model for the development of endometriosis-associated endometrioid EOC (with E and P receptor positive, and associated with hyperplastic aspects of the ectopic endometrium) and for endometriosis-associated clear cell EOC (E and P receptor negative, and associated with iron-mediated oxidative stress) could be suggested [46, 47]. Synchronous endometrial-ovarian carcinomas are expected to be endometrioid hystotype, thus confirming the hormone-dependent pathway. The clear cell ovarian histotype could arise from “atrophic” ectopic endometrium, similarly to the eutopic counterpart, not due to hyperplastic changes but rather repetitive DNA damage caused by iron-generated reactive oxygen species (the hormone-independent pathway) [48, 49]. Gounaris et al. [50] have questioned whether clear cell EOC is induced by “bad endometriosis” or “bad endometrium”.

Molecular similarities between synchronous endometriosis and ovarian cancer at the time of diagnosis have been also described [38], but Pearce et al. [24] have pointed that would be also interesting to compare endometriotic lesion samples collected years ago to those obtained at the time of cancer diagnosis, because it might provide a basis for identification of women with endometriosis who are at highest risk of ovarian cancer, not forgetting that most of these patients do not develop EOC [24]. Although there is no evidence that surgery for endometriosis can reduce the risk of endometriosis-associated

EOC (clear cell/endometrioid/LG serous), various authors have reported this reduction observed in women with endometriosis-associated E/CC ovarian tumors [51] or among patients with endometriosis [52] who underwent ovarian surgery and radical extirpation of all visible endometriosis, suggesting therefore a preventive effect of this type of intervention.

Respect to the endometrial-ovarian carcinoma synchrony, there are studies that have found no association between endometrial carcinoma and overall EOC or/and endometriosis [53, 54]. However, an interesting finding in our material was that 25% of endometrioid EOC were associated with a synchronous endometrial carcinoma, being in agree with other reports [55] which describe that approximately 90% of synchronous tumors that were identified in the ovary and in the endometrium were endometrioid cell type [56]. Two of our cases which associated endometriosis and borderline or malignant ovarian cancers had: endometrial carcinoma + ovarian endometrioid carcinoma + endometriosis, which was atypical in one of them. Similarly, Mangili et al [36] have found endometrial carcinoma in 33% of 21 cases of EOC with endometriosis, and in 11% of 44 cases with EOC without endometriosis. This aspect has been indeed mentioned in the literature to describe clinical and pathological features of synchronous tumors, but there are few studies describing endometrial carcinoma and EOC with associated endometriosis [36, 56, 57]. These authors suggest the existence of a molecular, histological and clinical parallelism between endometrial carcinoma and endometrioid ovarian cancer that would be interesting in terms of prevention measures for ovarian cancers of endometrioid histotype.

Summarizing, according to our results and the reviewed literature, it seems that, in certain endometriosis patients, the progression and pathological transformation to EOC may occur in the following order: 1. Endometriosis atypical or typical, 2. EOC (endometrioid/clear cell ovarian carcinoma) with associated endometriosis, and 3. Complete transformation into endometrioid (by hormonal and inflammatory effects due to recurrent episodes as hemorrhagic cysts) or clear cell carcinoma (by menses and acute inflammatory effects due to oxidative stress). Recently, Taniguchi et al. [34] have analysed the clinical characteristics of 33 patients diagnosed with ovarian cancer presumably arising from ovarian endometrioma. The diameter of the endometrioma and the preoperative CA-125 value did not significantly correlate. However, the authors concluded that to detect malignant transformation of ovarian endometrioma early and

precisely, the clinician should determine the existence of mural nodules and assess the rapid growth of the endometrioma.

Conflict of Interest Statement: We declare that we have no conflict of interest

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TABLES

Table 1. Epithelial ovarian cancers (EOC) with synchronous endometriosis and/or endometrial carcinoma.

EOC	**N**	**With associated endometriosis N (%), CI**	**B vs. I cases RR, CI, P**	**With endometrial carcinoma N (%), C.I.**	**End vs. EC RR, CI, *P***
Borderline	63	8 (12.7)* (0.066-0.231)	-	5 (7.9) (0.034-0.172)	RR 1.60 (CI:0.55-4.62), NS
Invasive	129	12 (9.3)** (0.054-0.156)	RR 0.73 (0.31-1.70), NS	7 (5.4) (0.026-0.108)	-
Total	192	20 (10.4) (0.073-0.184)	-	12 (6.25) (0.036-0.106)	RR 1.66 (CI:0.83-3.31), NS

N= number of cases; RR: relative risk; CI: confidence interval; B vs. I= borderline vs. invasive; EOC = end vs. EC (endometriosis vs. endometrial carcinoma). * 1 case and ** 4 cases of atypical endometriosis. NS: not significant.

Table 2. Association between the histological type of epithelial ovarian cancer (EOC) and endometriosis, and with endometrial carcinoma.

EOC	**n**	**Associated endometriosis**		**Endometrial carcinoma, n (%)**
		n (%)	**RR and CI**	
Serous:	**91**	**2 (2.2)**	(C)	3 (3.2)
LG/borderline	32	2 (6.25)	-	
HG/Invasive	59	0	-	
Mucinous:	**37**	**1 (2.7)**	-	1 (2.7)
Borderline	22	1 (4.5	-	
Invasive	15	0	-	
Endometrioid	**7**	**5 (71.4)**	RR:32.5	2 (28.6)
Borderline	3	3* (100)	(CI:7.6-138.3)	
Invasive	4	2** (50)	-	
Mix with Endometrioid	**21**	**9 (42.8)**	RR:19.5	5 (23.8)
Borderline	3	2 (66.6)	(CI:4.5-83.7)	
Invasive	18	7* (38.9)	-	
Clear cells	**9**	**3 (33.3)**	RR:17.1	0
Borderline	2 (1 mix)	0	(CI:3.3-87.7)	
Invasive	7	3* (42.8)	-	
Mix, End+CC	**4**	**0**	-	1 (25)
Borderline	1	0		
Invasive	3	0		
All clear cell EOC: 3/13 (23.1%)			RR 10.5 (CI:1.93-57.02)	
Endometrioid and clear cell EOC: 17/37 (46%)			RR: 20.9 (CI: 5.08-86.0)	
Other mix and undifferenciated	23 (3 carcinosarcomas)	0		0

(C) = considered as control group to statistical comparison; n= number of cases; CI= confidence interval; LG= low grade; HG= high grade; Mix, End+CC= mixed, endometrioid + clear cells; RR= relative risk compared with (C). * 1 and ** 2 atypical endometriosis.

Table 3. Clinical and pathologic characteristics of the epithelial ovarian cancer (EOC) with or without associated endometriosis.

Variable	**EOC with endometriosis**	**EOC without endometriosis**	**RR(CI), p**
No. of cases	20	172	-
Age, mean ± SD (range)	48.8 ± 11.6 (32-74)	56.1 ± 14.9 (21-88)	<0.017
Parity, % Null ≥1	 10 (50) 10 (50)	 46 (26.7) 123 (71.5)	 0.53(0.32-0.88)
Age of menopause, years	49.0 ± 5.01	49.1 ± 3.8	-
Premenopause at the time of diagnosis, %	11 (55)	65 (37.8)	0.68 (0.44-1.07), NS
Age ≥50 years at the time of diagnosis, %	9 (45)	116 (67.4)	1.49 (0.41-2.46), NS
BSR	52.3 ± 39.7 [15]	31.8 ± 21.4 [79]	<0.071
CA-125	325.6 ± 376.2 [14]	533.6 ± 1081.7 [82]	NS
CA-19-9	275.6 ± 500.3 [13]	229.4 ± 851.7 [79]	NS
FIGO Stage, % I II III/IV	 10 (50) 3 (15) 7 (35)	 67 (39) 19 (11) 86 (50)	 NS
Ovarian carcinoma, % Borderline Invasive	 8 (40) 12 (60)	 55 (32) 117 (68)	 NS
Type (Kurman and Shih), % Type I Type II	 20 (100) 0	 90 (52.3) 82 (47.7)	 0.52(0.45-0.60)
With synchronous endometrial carcinoma, %	3 (15)	9 (5.2)	NS
Survival (Kaplan-Meier) at, % 2 years 5 years 10 years	[20] 58 58 34.7	[172] 53 31 17.2	 NS 0.53(0.35-0.83) 0.49(0.25-0.98)

BSR = blood sedimentation rate; [ ] = number of cases analyzed for these variables.

Table 4. Clinical and pathologic characteristics of the EOC, type I tumors (separating endometrioid and clear cells) versus type II tumors [22].

Variable	EOC, type I			EOC, type II	RR(CI), p (type II vs. type I)
	LG and borderline serous and mucinous	pure and mixed endometrioid	Pure and mixed clear cells		
No. of cases	68	28	13	83	
Age, mean ± SD (MSE)	50.3 ± 16.8 (2.04)	53.9 ± 12.7 (2.4)	53.8 ± 15.3 (4.2)	60.1 ± 11.8 (1.3)	<0.001
Parity (64/57), %					
Null	25 (37.3)	8 (28.6)	5 (38.5)	18 (21.7)	
>1	42 (62.7)	20 (71.4)	8 (61.5)	65 (78.3)	0.62 (0.38-1.01)
Menopause at the time of diagnosis, %					
Premenopause	38 (55.9)	11 (39.3)	5 (38.5)	22 (26.5)	
Postmenopause	30 (44.1)	17 (60.7)	8 (61.5)	61 (73.5)	0.53 (0.35-0.80)
BSR	24.6 ± 18.1 (2.7) * [43]	47.2 ± 30.7 (7.4) [17]	80.4 ± 27.5 (12.3)* [5]	38.2 ± 23.3 (3.9) [35]	NS
CA-125	148.1 ± 376.1 (58) [42]	886.9 ± 1494.7 (362) [17]	228.6 ± 159.1 (71.2) [5]	803.8 ± 1201 (192) [39]	<0.045
CA-19-9	281.8 ± 1070 (165) [42]	356.3 ± 625 (156) [16]	63.7 ± 58.3 (26) [5]	[36] 166.6 ± 517.4 (86.2)	NS
Stage, %					
I/II	57 (83.8)	16 (57.1)	9 (69.2)	17 (20.5)	
III/IV	11 (16.2)	12 (42.8)	4 (30.8)	66 (79.5)	0.27(0.17-0.42)
Endometriosis, %					
Typical	3 (4.4) (in BL)	10 (35.7)	2 (15.4) **	0	15.2(2.08-111.2)
Atypical	0	4 (14.3)	1 (7.7)	0	
Endometrial carcinoma, %	2 (2.9)	7 (25)	1 (7.7)	2 (2.4)	NS
Breast carcinoma, %	3 (4.4)	1 (3.6)	0	7 (8.4)	NS
Survival (Kaplan-Meier) at					
2 years	78.8	64.3	57.2	36.6	0.51(0.38-0.69)
5 years	65.7	42.9	57.2	12.8	0.22(0.12-0.40)
10 years	65.7	10.7	57.2 +	6.9	0.21(0.09-0.47)

[ ]: number of cases analysed in this variable; BSR= blood sedimentation rate; * significant differences CC vs. S/M. ** significant differences E/CC versus S/M; + significant differences CC vs. endometrioid.

Table 5. Clinical and pathologic characteristics of atypical and typical endometriosis with p53+, associated or not with endometrioid and clear cell carcinomas

Variable	**Endometriosis with p53+**	**Atypical endometriosis**	**E/CC with atypical endometriosis**	**E/CC with typical endometriosis**	**E/CC without endometriosis**	**RR, P**
No. of cases	17	30	5*	12	24	
Age, mean ± SD (MSE)	36.1 ± 7.24 (1.7)	35.6 ± 8.7 (1.6)	48.6 ± 13.3 (5.93)	51.5 ± 11.1 (3.2)	56.3 ± 14.4 (2.9)	NS
Parity, % Null >1	 16 (94.1) 1 (5.9)	 24 (80) 6 (20)	 2 (40) 3 (60)	 5 (41.7) 7 (58.3)	 6 (25) 18 (75)	 NS
VS	18.9 ± 11 (2.75) [16]	19.9 ± 11.7 (2.5) [22]	632 ± 65 (32.5) [4]	56.7 ± 25.6 (8.5) [9]	49 ± 218 (73) [9]	NS
CA-125	66.3 ± 79.8 (19.9) [16]	57.7 ± 28.1 (5.7) [24]	188.7 ± 219.3 (109.7) [4]	465.4 ± 431 (152) [8]	1170 ± 1899 (600) [10]	NS
CA-19-9	21.9 ± 35.8 (9.6) [14]	39.1 ± 49.1 (8.5) [24]	67.4 ± 68.1 (34.04) [4]	461.9 ± 640.5 (242.1) [7]	246.3 ± 608 (192) [10]	NS
Stage, % I/II III/IV	 -	 -	 4 (80) 1 (20)	 6 (50) 6 (50)	 15 (62.5) 9 (37.5)	 NS
Endometrial carcinoma, %	0	0	2 (40)	1 (8.3)	5 (20)	NS
Survival (Kaplan-Meier) at , % 2 years 5 years 10 years	 - 	 - 	 > 	 50 50 30	 69.3 54.5 15.6	 NS NS NS

*One case was an atypical endometrioid cystoadenoma; [ ]= number of cases analyzed in this variable; E/CC= endometrioid and clear cell carcinomas.

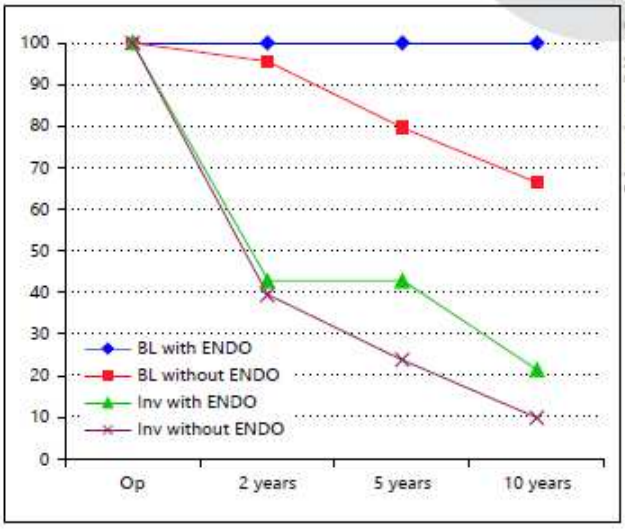

Fig. 1. Survival analysis at 2, 5 and 10 years obtained according to Kaplan-Meier method for borderline and invasive cases of EOC, with or without associated endometriosis.

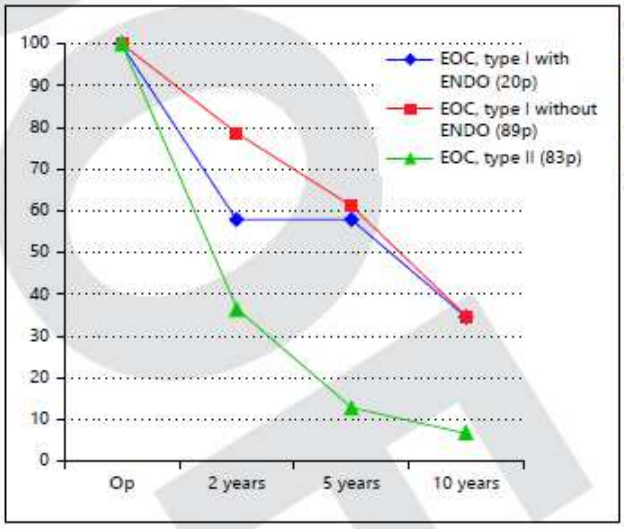

Fig. 2. Survival analysis at 2, 5 and 10 years obtained according to Kaplan-Meier method for EOC type I, with or without endometriosis, and EOC type II according to Kurman and Shih's classification.

Disclosure Statement

We declare that we have no conflict of interest.

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