European Journal of Gynaecological Oncology

Original Research

Clinical and demographic factors in endometrial and ovary carcinoma: synchronous carcinoma vs stage IIIA endometrial carcinoma

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DOI:10.31083/j.ejgo4204099

Submitted: 20 Janurary 2021 Revised: 10 March 2021 Accepted: 18 March 2021 Published: 15 August 2021

Objective: To compare pre-surgical demographic and clinical factors and preoperative serum tumor marker values of patients with endometrial and ovarian synchronous carcinoma with those diagnosed with endometrial carcinoma with metastatic ovarian involvement (FIGO stage IIIA). *Methods*: A retrospective observational study including patients with endometrial and ovarian malignant tumors that were treated at Miguel Servet University Hospital, Zaragoza, Spain, since January 2000 to June 2020. All pathologic specimens were reviewed by two pathologists specialized in gynecological oncology. *Results*: Overall, 51 patients were included. 24 cases of them, were endometrial and ovarian synchronous primary carcinomas and the remaining 27 cases were endometrial tumors with adnexa. Parity, personal and family oncological history, arterial hypertension, diabetes, dyslipidemia, obesity and the prior use of hormone replacement therapy did not show significant differences between both groups. Age (p = 0.002), menopausal status (p = 0.029), abnormal uterine bleeding (p = 0.001), Ca 12.5 preoperative serum level (p = 0.038) and Ca 19.9 preoperative serum level (0.028) were factors with significant differences between both groups. In multivariate analysis, only abnormal uterine bleeding and Ca 19.9 values were independents factors. *Conclusions*: The presence of abnormal uterine bleeding and Ca 19.9 preoperative serum level could guide the clinician in the preoperative differential diagnosis between endometrial cancer with ovarian involvement and endometrial and ovarian synchronous carcinoma.

Keywords

Endometrial and ovarian synchronous tumors; Endometrial cancer; Synchronous tumors; Ca 19.9 tumor marker

1. Introduction

The coexistence of endometrial and ovarian synchronous malignancies is a relatively uncommon event, accounting for 10% of all females with ovarian cancer and 5% of all females with endometrial cancer [1]. Simultaneously multiple primary neoplasms is clinically very important due to prognostic and therapeutic considerations [2].

Patients with disease of both the endometrium and the ovary can be classified into three groups: endometrial and ovarian synchronous primary cancers, endometrial cancer with adnexal metastasis, and ovarian cancer with metastasis to the endometrium [3, 4]. Ulbright and Roth proposed in 1985 a set of histological criteria to distinguish the first two groups [5]. Scully *et al.* [6] described a similar but more extensive list of clinical pathologic features used to differentiate all the three groups. However, there are still no absolute surgical or histological criteria. Moreover, there are no pre-surgical criteria able to distinguish both entities and to guide the surgical management

The aim of this study is to compare the pre-surgical clinical and demographic factors and the preoperative value of tumor markers of patients with endometrial and ovarian synchronous carcinoma with those diagnosed with endometrial carcinoma with metastatic ovarian involvement (FIGO stage IIIA). If distinctive features are found between both groups, they could be used to support the differential diagnosis of both pathologies and to implement he most optimal surgical management.

2. Methods

A single-institution retrospective observational study was performed at the Gynecology Department of a tertiary referral center of gynecological oncology (Miguel Servet University Hospital, Zaragoza, Spain). 780 patients with primary endometrial cancer were treated in our center since January 2000 to June 2020. Patients diagnosed and treated for endometrial cancer with ovarian involvement who gave their consent were included in the study. Patients who received preoperative radiation therapy or did not undergo a surgery approach were excluded. There were 51 cases of primary endometrial cancer coexisting with adnexal malignancies: among them, 24 cases were endometrial and ovarian synchronous primary carcinomas, and 27 cases were endometrial tumors with adnexal involvement.

Clinical information regarding to age at diagnosis, parity, menopausal status, family or personal history of cancer, body mass index (BMI), dyslipidemia, high blood pressure, diabetes, use of hormone replacement therapy and presenting symptoms were recorded. Postmenopausal women were considered to be those with more than one year since the last period or those undergoing hysterectomy with double adnexectomy or only double adnexectomy. According to the World Health Organization (WHO) international BMI classification, patients were stratified as follows: normal weight (BMI 18.5 kg/m^2 to $<$25 kg/m^2), overweight (BMI 25 kg/m^2 to $<$30 kg/m^2), and obese (BMI $\geq$30 kg/m^2). There were no underweight patients (BMI $<$18.5 kg/m^2). Data on tumor marker serum values were collected in the month before surgery in the same laboratory: Ca 12.5 (mU/mL) and Ca 19.9 (mU/mL).

All patients underwent a hysterectomy, salpingoophorectomy and peritoneal cytology. Pelvic, or pelvic and para-aortic lymphadenectomy were performed following guidelines of the European Society of Gynecological Oncology [9, 10]. The most relevant histological data and pathological factors of the surgical specimen were collected. Thus, peritoneal cytology, final histology, tumor grade, myometrial invasion, lymphovascular space invasion (LVSI), lymph node involvement, presence of hyperplasia with atypia (EIN), bilateral or non-ovarian involvement and FIGO (International Federation of Gynecology and Obstetrics) stage were recorded [7, 8].

All pathologic specimens were reviewed by two pathologists specialized in gynecological oncology, according to the criteria described by Scully *et al.* [6] (Table 1). If there were doubts, a third pathologist studied the sample. According to the histological findings, the recruited patients were grouped into two cohorts for comparison: those with Endometrial and ovarian synchronous primary carcinomas (synchronous group) and those with endometrial cancer with ovarian metastasis (metastasis group).

The research was conducted in accordance with Good Clinical Practice standards and the current revision of the Declaration of Helsinki. There was no financial compensation for the participants or funding for the research team. The study was approved by the Research Ethics Committees of Aragon, Spain (CEICA) with the study reference code PI16/0252. All subjects gave their informed consent for inclusion before they participated in the study.

Data was collected in accordance to privacy policies. Statistics Process Social Sciences (SPSS) 22.0 (IBM Corp., Armonk, NY, USA) for Windows (Copyright© Inc., 2013) was used for further statistical analysis.

For the descriptive analysis, the categorical variables were expressed with their frequencies and percentages. The quantitative variables that did not follow a normal distribution were expressed as median and interquartile range (p25–75) and those that presented a normal distribution were expressed as mean and standard deviation (SD). The parametric distribution of quantitative variables was studied using the Kolmogorov-Smirnov test. Student's *t* test and the Mann–Whitney U test were used for comparisons between the two histological groups in the case of normally and not normally distributed variables, respectively. The χ^2 or Fisher's exact test were used as appropriate for comparisons between both groups in the case of nominal variables. Then, a linear regression model was performed to assess the association between the statistically significant preoperative variables by univariate analysis and the type of tumor involvement. In all statistical tests, $p < 0.05$ was considered as the reference value of significance.

Table 1. Endometrial and ovarian synchronous primary carcinoma [6].

1. Histologic dissimilarity of the tumors
2. No or only superficial myometrial invasion of endometrial tumor
3. No vascular space invasion of endometrial tumor
4. Atypical endometrial hyperplasia additionally present
5. Absence of other evidence of spread of endometrial tumor
6. Ovarian tumor unilateral (80–90% of cases)
7. Ovarian tumor located in parenchyma
8. No vascular space invasion, surface implants, or predominant hilar location in ovary
9. Absence of other evidence of spread of ovarian tumor
10. Ovarian endometriosis present
11. Different ploidy of DNA indices, if aneuploid, of the tumors*
12. Dissimilar molecular genetic or karyotypic abnormalities in the tumors

*The possibility of tumor heterogeneity must be taken into account in the evaluation of ploidy finding.

3. Results

Patient's characteristics are shown in Table 2. The mean age at diagnosis in synchronous group was significantly lower than in metastatic group, 54.8 $\pm$ 13.5 years vs 69.8 $\pm$ 10.7 years (p = 0.002). There was significant difference between the groups according to menopausal status: 58.3% of the women in the synchronous group were menopausal versus 96.3% in the metastatic group (p = 0.029). Women with ovarian metastasis had a higher proportion of abnormal uterine bleeding (85.2% versus 29.2%; p = 0.001). The rest of the clinical and demographic studied variables did not show significant differences between groups. Preoperative values of tumor markers showed significant differences between both groups (Table 2).

The histological data and pathological factors in the surgical specimen are shown in Table 3. Except for the presence of EIN and para-aortic lymph node involvement, the pathological variables analyzed showed statistically significant differences between the groups. The sites of other metastasis in the patients with metastatic endometrial cancer were: nodes (81.5%; n = 22), omentum (11.1%; n = 3) vagina (7.4%; n = 2) and intestinal serous (7.4%; n = 2).

Multivariate analysis revealed that the presence of abnormal uterine bleeding (p = 0.005) was an independent fac-

Table 2. Patient's demographics, clinical characteristics, preoperative value of tumor markers and statistical analysis of the relationship of them between the groups.

		Synchronous group (n = 24)	Metastatic group (n = 27)	*p* value*
		n (%)	n (%)	
Age (years)	Mean (SD)	58.4 (13.5)	69.8 (10.7)	0.002
Parity	None	11 (45.8)	9 (33.3)	0.582
	1	3 (12.5)	6 (22.3)	
	2 or more	10 (41.7)	12 (44.4)	
Personal oncological history	Yes	12 (50)	18 (66.7)	0.277
	No	12 (50)	9 (33.3)	
Family oncological history	Yes	4 (16.7)	3 (11.1)	0.742
	No	20 (83.3)	24 (88.9)	
Arterial hypertension	Yes	11 (45.8)	13 (48.1)	0.767
	No	13 (54.2)	14 (51.9)	
Diabetes	Yes	7 (29.2)	2 (7.4)	0.074
	No	17 (70.8)	25 (92.6)	
Dyslipidemia	Yes	3 (12.5)	6 (22.6)	0.599
	No	21 (87.5)	21 (77.4)	
Obesity†	No	14 (58.4)	11 (40.7)	0.522
	Overweight	8 (33.3)	11(40.7)	
	Obese	2 (8.3)	5 (18.6)	
Menopause	Yes	14 (58.3)	26 (96.3)	0.029
	No	10 (41.7)	1 (3.7)	
MHT[§]	Yes	1 (4.2)	1 (3.7)	0.464
	No	23 (95.8)	26 (96.3)	
Abnormal uterine bleeding	Yes	7 (29.2)	23 (85.2)	0.001[¥]
	No	17 (70.8)	4 (14.8)	
Ca 12.5 serum level at diagnosis (U/mL)	Median (p25–75)	147 (40–880)	54 (28–109)	0.038
Ca 19.9 serum level at diagnosis (U/mL)	Median (p25–75)	571 (110–773)	6.2 (0.8–343)	0.028[¥]

* *p* significant <0.05; [§]MHT: menopause hormone therapy.

[¥]Independent differential factors between groups in the multivariate analysis ($p = 0.035$ for age and $p = 0.020$ for abnormal uterine bleeding).

†According to WHO criteria.

tor mostly associated with endometrial cancer with ovarian metastasis and Ca 19.9 preoperative serum level ($p = 0.018$) was an independent factor associated with synchronous tumors.

4. Discussion

Age, presence of abnormal uterine bleeding and menopausal status were significantly more associated to endometrial cancer and adnexal involvement than to synchronous tumors in our cohort. Conversely, preoperative values of tumor markers were significantly higher in patients with synchronous tumors. Moreover, in the multivariate study, only abnormal uterine bleeding and Ca 19.9 preoperative serum level were independent factors, so they could be considered to accomplish the differential diagnosis between both categories.

Given the finding of ovarian involvement in a patient diagnosed with endometrial carcinoma, we must make a differential diagnosis between a stage IIIA endometrial carcinoma and a synchronous tumor. It is essential to distinguish between these two entities due to the different impact they have on the prognosis [2].

The criteria described by Ulbright and Roth [5] and Scully [6] are based on the pathological study, so it is necessary to obtain the complete surgical specimen in order to accomplish the definitive differential diagnosis. However, being able to distinguish between both entities preoperatively is really interesting in order to be able to perform an optimal surgical approach from the beginning, as the staging surgery for ovarian and endometrial cancer differs in some aspects and for the need to perform omentectomy or debulking surgery in patients with ovarian cancer [9, 10].

The mean age of appearance of both entities has been studied. In several studies, in agreement with the findings of our sample, women with endometrial and ovarian synchronous tumors are younger than those with endometrial carcinoma with ovarian involvement [2, 3]. Previous studies reported the incidence of cancer incidence in young patients about 7–29% depending on the definition of young patients ranging from less than 40 years to less than 50 years [11].

In young patients who present with multiple sites of primary cancers, genetic predisposition should be considered. Nevertheless, Soliman *et al.* [12] reported that only 2 in 84 patients met criteria for hereditary cancers and they concluded

Table 3. Pathological characteristics in the surgical specimen in both groups.

		Synchronous group (n = 24)	Metastatic group (n = 27)	*p* value*
		n (%)	n (%)	
Peritoneal cytology	Positive	0	13 (48.1)	0.002
	Negative	24 (100)	14 (51.9)	
Endometrial histology	Endometrioid	19 (79.2)	11 (40.7)	0.022
	Non endometrioid	5 (20.8)	16 (59.3)	
Endometrial tumor grade	G1, 2	23 (95.8)	6 (22.2)	<0.001
	G3	1 (4.2)	21 (77.8)	
Myometrial invasion	<50%	19 (79.2)	8 (29.6)	0.002
	>50%	5 (20.8)	19 (70.4)	
Ovary involvement	Unilateral	17 (70.8)	2 (7.4)	<0.001
	Bilateral	7 (29.2)	25 (92.6)	
Lymphovascular space invasion	Yes	3 (12.5)	17 (62.9)	<0.001
	No	21 (87.5)	10 (37.1)	
Pelvic lymph nodes	Positive	3 (12.5)	13 (48.1)	0.014
	Negative	21 (87.5)	14 (51.9)	
Para-aortic lymph nodes	Positive	1 (4.2)	6 (22.2)	0.118
	Negative	23 (95.8)	21 (77.8)	
Hiperplasia with atypia	Positive	5 (20.8)	2 (7.4)	0.395
	Negative	19 (79.2)	25 (92.6)	
FIGO stage of endometrial cancer	I	20 (83.3)	0	<0.001
	II	1 (4.2)	0	
	III	3 (12.5)	24 (88.8)	
	IV	0	3 (11.1)	
Ovarian cancer histology	Endometrioid	13 (54.2)	-	-
	Serous	3 (12.5)	-	
	Clear-cell	1 (4.2)	-	
	Mucinous	5 (20.8)	-	
	Mixed	2 (8.3)	-	
	Other	1 (4.2)	-	
Ovarian tumor grade	G1, 2	20 (83.3)	-	
	G3	4 (16.7)	-	
FIGO stage of ovarian cancer	I	13 (54.2)	-	-
	II	4 (16.7)	-	
	III	5 (20.8)	-	
	IV		-	

* *p* significant <0.05.

that it was unlikely that the patients with synchronous primary cancers had a hereditary cancer syndrome. The women in our study had a low and similar percentage of first-degree oncological antecedents in both groups and no case with genetic mutation were identified.

Hypertension, diabetes, nulliparity, the prior use of hormone replacement therapy and obesity are known as risk factors for endometrial carcinoma [13–15]. Furthermore, some of these factors also increase the risk of developing ovarian cancer [16, 17]. There are no studies that assess all these factors when comparing endometrial carcinoma with ovarian involvement women with those with synchronous cancers. The most studied factor has been obesity, a clear risk marker associated with the genesis of endometrial carcinoma, which, in accordance with our results, seems to present at a similar rate in women who develop ovarian cancer in addition to endometrial cancer [3, 18]. This finding is reasonable, given that in obese patients, there is an increase in systemic exposure to estrogen stimulation, as well as a decrease in its transporter protein levels and greater insulin resistance, which may contribute to an increased risk of both endometrial and ovarian cancer [13].

Postmenopausal abnormal bleeding is the most common presentation in women with primary endometrial carcinoma, which usually leads to an earlier diagnosis compared to women with primary ovarian cancer, which is usually asymptomatic/oligo symptomatic in the early stages. 80% of women with endometrial carcinoma are menopausal and genital bleeding occurs in 90% of them [19, 20]. The cases of endometrial carcinoma in women who do not present abnormal bleeding usually correspond to earlier stages, which is consistent with our results, since abnormal bleeding was

associated in a higher proportion with women diagnosed in FIGO stage IIIA endometrial carcinoma than in the cases of synchronous tumors in which the endometrial carcinoma is in more initial stages [3, 21]. Other studies also found these differences in relation to the presence of bleeding [3, 4, 18].

Few studies have assessed the role of tumor markers in the preoperative differential diagnosis of these entities. Contrary to our study, differences between both groups were not found in any of them [4, 18]. In the work of Chen *et al.* only the value of the Ca 12.5 marker was determined, treating it categorically. Besides, most of the cases were above 35 U/mL, so it was difficult to find significant differences between the groups. In the work of Mor *et al.* the markers were evaluated as a continuous variable by carrying out the log10 transformation, with which the values were treated following a normal distribution. The means were similar, but the standard deviation values were very wide. Precisely this statistical treatment could condition the results. In our study, the preoperative value of Ca 19.9 was significantly higher in patients with synchronous tumors. Nevertheless, we should not draw definitive conclusions given our small sample size. Studies with larger sample sizes would be needed in search of a cut-off point that could guide the study of patients with endometrial cancer and concurrent adnexal masses.

Nonetheless, our findings could have some impact on clinical practice. The possibility to discriminate preoperatively between endometrial and ovarian synchronous primary carcinomas and ovarian and endometrial cáncer with adnexal metastasis could be relevant for the surgeon to counsel the patient and to plan the best surgical treatment. In this sense, the extent of the surgery could vary, something especially relevant, for example, in young women who desire to preserve fertility, or a sentinel node biopsy might even be considered for endometrial cancer.

The most important limitation of our study is the small number of cases included, as well as not having integrated others findings from the preoperative study, such as ultrasound or other imaging test, which could have provided relevant information in the preoperative differential diagnosis of both entities.

5. Conclusions

The presence of abnormal uterine bleeding and Ca 19.9 preoperative serum level could guide the clinician in the preoperative differential diagnosis between endometrial cancer with ovarian involvement and endometrial and ovarian synchronous carcinomas. Women with FIGO stage IIIA endometrial carcinoma are more likely to present abnormal uterine bleeding, while higher values of the Ca 19.9 preoperative tumor marker are more frequently associated with ovarian and endometrial synchronous tumors.

Author contributions

LBM has elaborated the research project. LBM, AER, LAS, MLB and PRC have contributed to data collection. ARP, JNS and YJG have been responsible for supervising the methodology. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The research was conducted in accordance with Good Clinical Practice standards and the current revision of the Declaration of Helsinki. There was no financial compensation for the participants or funding for the research team. The study was approved by the Research Ethics Committees of Aragon, Spain (CEICA) with the study reference code PI16/0252. All subjects gave their informed consent for inclusion before they participated in the study.

Acknowledgment

The authors thank the Pathological Service for the effort carried out.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

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