Int J Gynecol Obstet, 1993, 43: 305–312
International Federation of Gynecology and Obstetrics

Synchronous dual primary ovarian and endometrial carcinomas*

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(Received May 31st, 1993)
(Revised and accepted July 29th, 1993)

Abstract

OBJECTIVES: The synchronous occurrence of carcinoma confined to the ovary and endometrium presents a diagnostic and therapeutic dilemma. These tumors have been variously staged as FIGO Stage IIA ovarian carcinoma, Stage III endometrial carcinoma, or synchronous dual primary carcinomas. Accumulating evidence suggests such patients have a favorable outcome. This retrospective study was undertaken to review our experience with these fascinating tumors. METHODS: The clinical records and the pathologic findings of 16 patients with synchronous dual primary ovarian and endometrial carcinomas were reviewed. RESULTS: The median age was 51 years. Abnormal uterine bleeding was the most common presenting symptom (70%). All patients had Stage I ovarian and endometrial carcinomas. Fourteen patients (88%) had endometrioid carcinoma in both sites, while two patients (12%) had dissimilar histology. For 15 patients (94%), the grade of both tumors was identical. Only three (19%) patients had myometrial invasion, with less than 50% involvement in each case. All patients underwent surgical staging, 11 (70%) of whom received adjuvant radiation or chemotherapy. The five patients treated with surgery alone had Grade 1 endometrioid tumors. The only relapse occurred in a patient with a clear cell component in both sites. No patient has died of disease. CONCLUSIONS: Patients with synchronous dual primary carcinomas appear to have a more favorable prognosis than that expected with Stage IIA ovarian or Stage III endometrial carcinoma (100% vs. 63% or 42% survival at 3 years, respectively). The excellent survival for patients with Grade 1 dual endometrioid tumors treated with surgery alone suggests that adjuvant therapy may not be necessary for this sub-group.

Keywords: Ovarian; Endometrial; Malignancy; Synchronous.

Introduction

The synchronous occurrence of carcinoma in the ovary and the endometrium is uncommon. The incidence of endometrial carcinoma in women with ovarian carcinoma ranges from 4.5 to 30%, with the highest frequency occurring with endometrioid ovarian carcinoma [1–4]. Conversely, the incidence of ovarian carcinoma in women with endometrial carcinoma ranges from 2 to 8.5% [1–5].

*Presented at the 41st Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, Washington, D.C.

**Recipient of American Cancer Society Clinical Oncology Fellowship 92-101-1.

0020-7293/93/$06.00

The appropriate staging of these cases is controversial. Various authors have suggested staging such lesions as FIGO Stage IIA ovarian carcinoma, Stage III endometrial carcinoma, or synchronous primary carcinomas [6–11]. Classification of these tumors as dual primary carcinomas is relatively straightforward when the histology is dissimilar. However, such a designation is more difficult when the histology is similar or identical.

Evidence is accumulating that suggests women with dual primary carcinomas have a favorable outcome. The survival for women with dual endometrioid carcinomas has been reported as 66–100% [6,8]. In contrast, the 5-year survival is 45% for women with Stage II ovarian carcinoma [12], and 33–36% for women with Stage III endometrial carcinoma [13,14].

The therapeutic approach to these patients varies. Some authors suggest that surgical management alone may be adequate for selected patients [6,8,9], while others believe that adjuvant therapy is indicated [10]. A wide variety of adjuvant therapies has been utilized, including radiation therapy, both external beam and brachytherapy, as well as a multitude of chemotherapy regimens.

The purpose of this study was to review our experience with synchronous dual primary carcinomas of the ovary and endometrium.

Materials and methods

Twenty patients with the diagnosis of synchronous dual primary ovarian and endometrial carcinomas were treated by the Gynecologic Oncology Service at the University of Michigan Medical Center from 1980–1991. Four patients were excluded from analysis on review: three had intra-abdominal spread of tumor precluding accurate classification as dual primary tumors, and one was lost to follow-up 1 month after initial surgery. The clinical records of the remaining 16 patients were abstracted to obtain information regarding their age, gravity, menopausal status, hormonal replacement therapy, presentation, treatment and follow-up. The pathologic findings were reviewed with regard to histology, depth of invasion, grade and stage.

The patients were divided into three groups according to the histology of the ovarian and endometrial tumors [6]. Group A consisted of patients with similar endometrioid ovarian and endometrial histology (Fig. 1a and b). Group B consisted of patients with non-endometrioid but similar ovarian and endometrial histology. Group C consisted of patients with dissimilar ovarian and endometrial histology (Fig. 2a and b).

All patients were re-staged according to surgical findings utilizing current FIGO criteria [15,16]. Staging was performed assuming the presence of synchronously occurring dual primary carcinomas.

Statistical analysis was by chi-square test of homogeneity, with $P < 0.05$ considered significant.

Results

The median age at presentation was 51 years (range: 39–65 yrs). Ten (63%) patients were post-menopausal, of which only two were on hormonal replacement therapy. There were 3 (19%) nulligravid women; the median gravity was 2.5 (range: 0–6). The presenting complaint was abnormal bleeding in 10 (63%) patients, while 6 (37%) had a palpable adnexal mass.

A total of 127 ovarian and 353 endometrial carcinomas were treated by our division during the study period. Synchronous occurrence of dual primary tumors occurred in 12.6% of the ovarian carcinoma patients and 4.5% of the endometrial carcinoma patients.

All sixteen patients had Stage I ovarian carcinoma: eight (50%) were Stage IA, two were Stage IB (12%), and six were Stage IC (38%) (Table 1). Both patients with Stage IB tumors had identical histology in both ovaries. Five of the Stage IC patients had carcinoma arising in a focus of surface endometriosis, while two, including one with

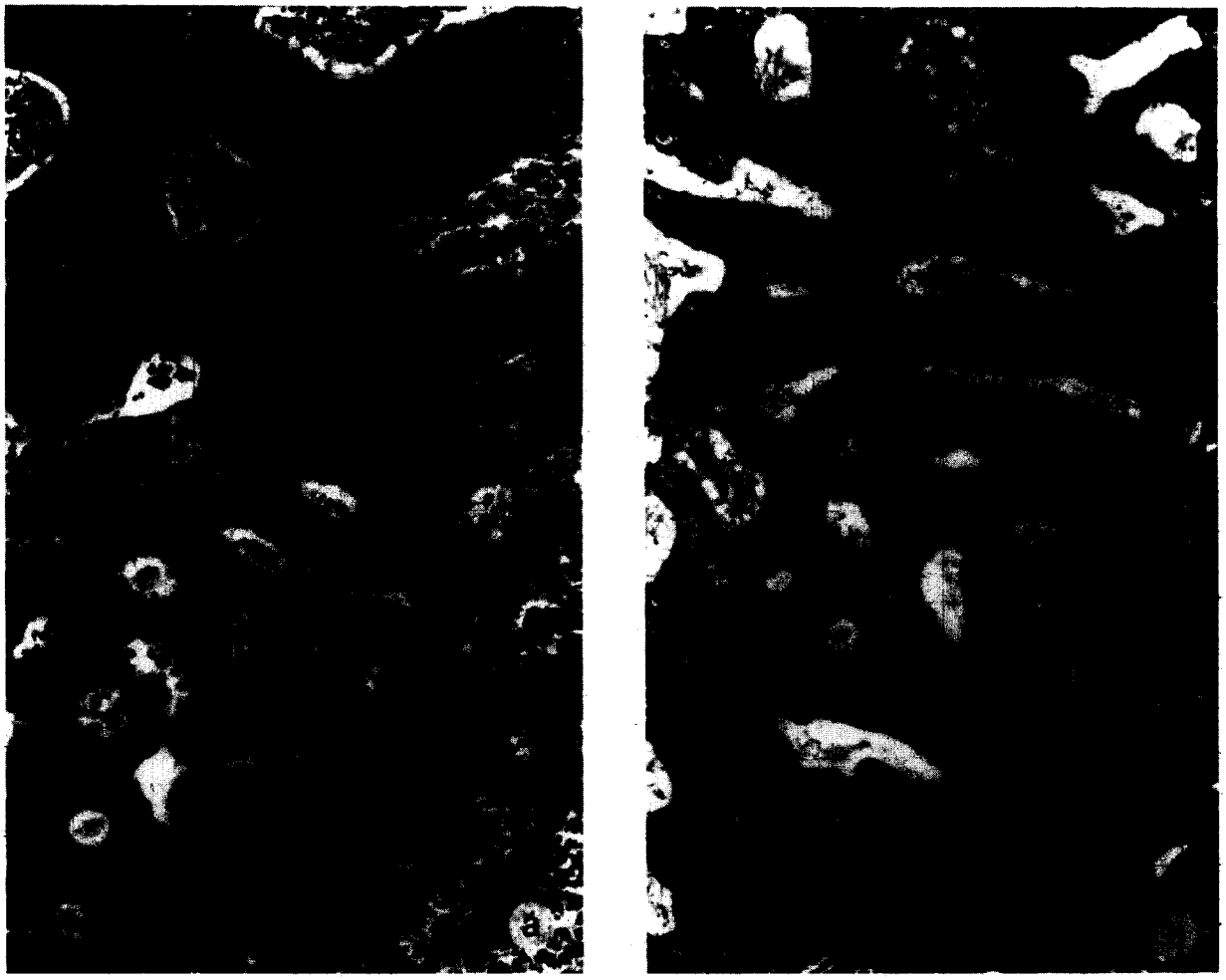

Fig. 1. Simultaneous ovarian and endometrial carcinomas of similiar histology. Both the ovarian (a) and endometrial neoplasms (b) have an endometrioid histology, characterized by prominent glands lined by columnar cells with clear cytoplasm and stratifying, round to oval nuclei (magnification ×330).

surface endometriosis, had intra-operative rupture of the ovarian cyst. The histology of the ovarian carcinoma was endometrioid in fifteen (94%) patients, two of which contained either a clear cell or adenosquamous component. The histology of the remaining carcinoma was transitional cell carcinoma. Twelve lesions were Grade 1 (75%), three were Grade 2 (19%), and one was Grade 3 (6%).

All sixteen patients had Stage I endometrial carcinoma: 13 (81%) were Stage IA and 3 (19%) were Stage IB (Table 1). The histology of the endometrial carcinoma was endometrioid in 15 (94%) patients, one of which contained a clear cell component. The histology of the remaining carcinoma was mucinous. Thirteen lesions were Grade 1 (81%), and three were Grade 2 (19%). In 15 patients (94%), the endometrial tumor was the same grade as the ovarian tumor. Each patient with myometrial involvement had less than 50% invasion into the myometrium.

Twelve (75%) patients had endometrioid ovarian and endometrial carcinomas and were

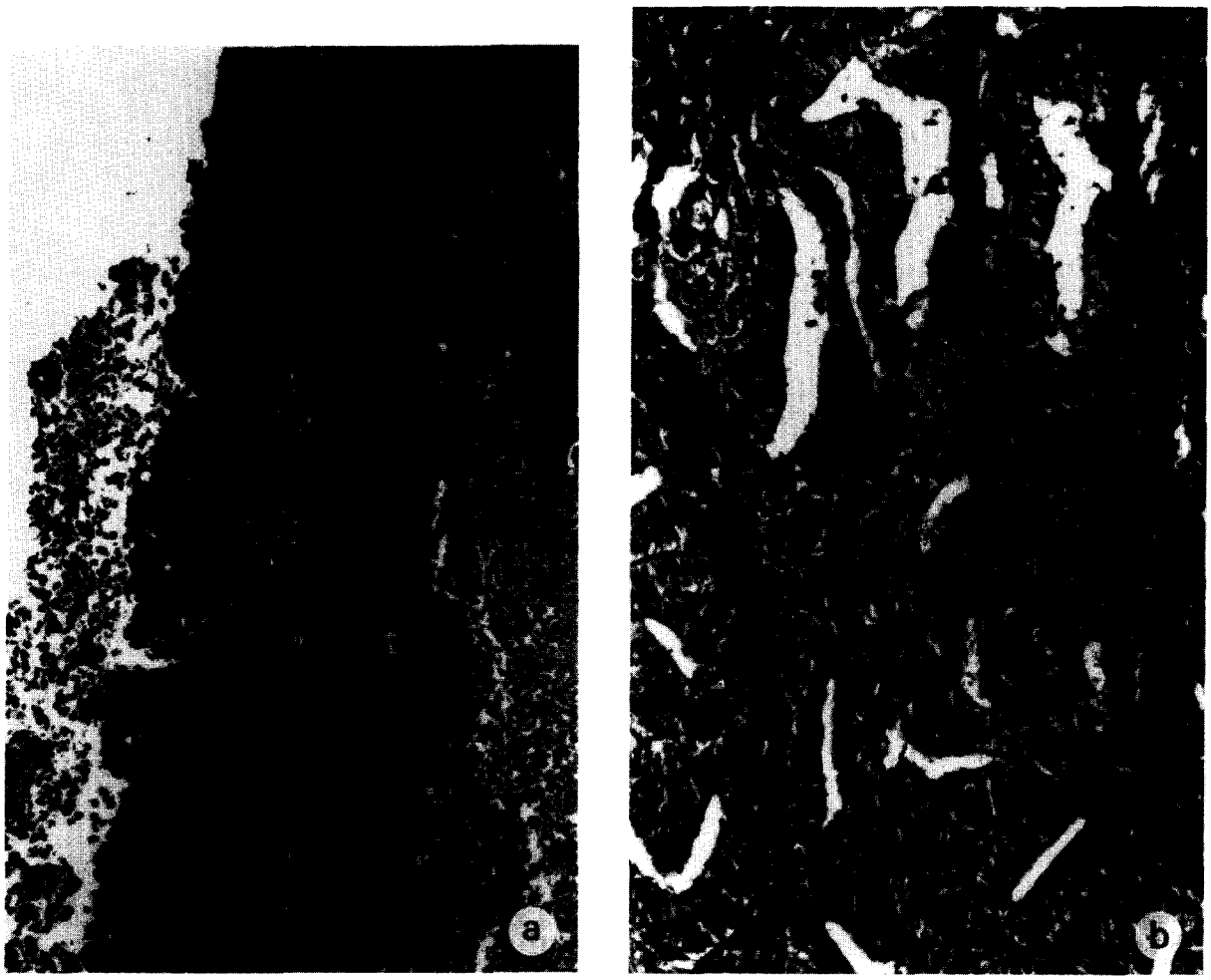

Fig. 2. Simultaneous ovarian and endometrial carcinomas of divergent histology. The ovarian carcinoma (a) is of a transitional type in which spindled cells surround a central fibrovascular core without prominent gland formation. In contrast, the endometrial carcinoma (b) is comprised of glands lined by cells with uniform, rounded nuclei similar to Fig. 1 (magnification ×330).

classified as Group A. One (6%) patient had identical endometrioid ovarian and endometrial carcinomas containing a clear cell component and was classified as Group B. The remaining two (12%) patients had dissimilar ovarian and endometrial carcinomas: a transitional cell carcinoma and an endometrioid ovarian carcinoma with an adenosquamous component, both in conjunction with endometrioid endometrial carcinoma. These patients were classified as Group C.

All patients underwent surgical staging, consisting of cytologic washings, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and pelvic lymphadenectomy. Five (31%) patients were treated with surgery alone. One (6%) patient received a preoperative cesium implant. Three (19%) patients were treated with post-operative intra-peritoneal ^{32}P. Four (25%) patients received post-operative external beam radiation therapy, either whole abdomen [3] or whole abdomen and whole pelvis [1]. Five (31%) patients were treated with various post-

operative chemotherapy regimens: carboplatin; cisplatin/cyclophosphamide; melphalan/medroxyprogesterone acetate; 5-flurouracil/vinblastine/medroxyprogesterone acetate.

The only recurrence (6%) occurred in the woman whose endometrioid ovarian and endometrial carcinomas each contained a clear cell component. She received cisplatin/cyclophosphamide chemotherapy for pulmonary metastases 36 months after her initial surgery, followed by whole brain irradiation and leukovorin/FuDR/carboplatin chemotherapy for brain metastases 12 months later. She is currently alive with disease 62 months after presentation. With a median follow-up of 39 months, no patient has died of disease.

Discussion

The results of this study suggest that patients with synchronous dual primary ovarian and endometrial carcinomas have a favorable prognosis. The overall survival was 100%, with a median follow-up of 39 months. This is markedly better than the extrapolated 63% or 42–65% 3-year survival for patients with Stage II ovarian [17] or Stage III endometrial carcinoma, respectively [13,14].

The median age at presentation was 51 years, comparable to previous reports in which the median age ranged from 41 to 54 years [6,7,10,11]. Thus, it appears that patients with dual primary carcinoma tend to be 10–20 years younger than their counterparts with ovarian or endometrial carcinoma, in whom the median age at presentation is approximately 60 years [18,19]. As expected given the early stage of the ovarian tumor, the majority of patients presented with abnormal bleeding from the endometrial tumor.

Previous investigators have reported survival rates of 57–100% for Group A, with an average of 80% (Table 2) [6–10]. The variation in survival was attributed to variation in the depth of myometrial invasion [6–10]. Patients with deeply invasive (> 2/3) tumors appeared to have a significantly worse prognosis than did those whose tumors were less

Table 1. Clinical characteristics of patients with ovarian and endometrial carcinomas.

Patient	Ovary			Corpus				Rx	Status	Months
	Stage	Grade	Hist.	Stage	Grade	Hist.	Inv.			
L.B.	IC	1	E	IA	1	E	ϕ	S, R^1	NED	82
M.B.	IA	1	E, CC	IA	1	E, CC	ϕ	S, R^3	AWD	62
M.C.	IA	1	E	IA	1	E	ϕ	S	NED	25
U.C.	IA	1	E	IA	1	M	ϕ	S	NED	19
J.D.	IA	2	E	IA	2	E	ϕ	S, R^3	NED	3
J.G.	IB	1	E, AS	IB	1	E	< 1/3	S	NED	102
G.H.	IC	1	E	IB	1	E	< 1/2	S, C	NED	19
L.K.	IA	1	E	IA	1	E	ϕ	S, C	NED	76
J.K.	IA	1	E	IA	1	E	ϕ	S	NED	6
J.E.K.	IA	3	TC	IA	1	E	ϕ	S, C	NED	42
E.K.	IB	2	E	IB	2	E	< 1/3	R^2, S, C	NED	143
S.L.	IC	1	E	IA	1	E	ϕ	R^4	NED	82
M.E.	IC	1	E	IA	1	E	ϕ	S	NED	84
I.M.	IC	1	E	IA	1	E	ϕ	S, R^3, C	NED	144
J.M.	IC	1	E	IA	1	E	ϕ	S, R^4	NED	80
J.Z.	IA	2	E	IA	2	E	ϕ	S, R^4	NED	42

E, endometrioid; CC, clear cell; M, mucinous; AS, adenosquamous; TC, transitional cell carcinoma; S, surgery; R^1, whole abdomen and whole pelvis irradiation; R^2, preoperative cesium irradiation; R^3, whole abdomen irradiation; R^4, intraperitoneal P^{32}; C, chemotherapy; NED, no evidence of disease; AWD, alive with disease.

Table 2. Survival.

Reference	Group A		Group B		Group C	
	N	Survival (%)	*N*	Survival (%)	*N*	Survival (%)
6	16	100	11	45	2	50
7	1	100	4	25		
8	13	77	2	100	9	56
9	13	100	2	100		
10	23	57	10	50	4	50
Pearl	12	100	1	100	2	100
Total	78	83[a]	30	53	17	59

Group A: Endometrioid ovarian and endometrial histology.
Group B: Non-endometrioid but similar ovarian and endometrial histology.
Group C: Dissimilar ovarian and endometrial histology.
[a] $P < 0.05$ vs. Groups B and C.

invasive (Table 3) [6–10]. None of the patients in the present study had deeply invasive tumors, possibly contributing to the excellent survival rate.

In contrast, survival rates of 25–100% have been reported for patients in Group B, with an average of 52% (Table 2) [6–10]. Similarly, the reported survival rates for patients in Group C are 50–100%, with an average of 53% (Table 2) [6–10]. The worse prognosis in these patients, as compared with the patients in Group A, has been attributed to greater aggressiveness of the non-endometrioid histologic types, which often present with deep myometrial or ovarian hilar invasion [6–10]. Although the results for Groups B and C from the present study are comparable to previous studies, the numbers are too small to draw any meaningful conclusions.

The etiology of these carcinomas is uncertain. Several investigators have proposed that the extended Mullerian system, comprising the ovarian epithelium, fallopian tube, uterine corpus and cervix may respond as a single morphologic unit to produce primary carcinomas in multiple sites [6,20]. Endometriosis has been considered a predisposing factor by some [11,21], but not all investigators [6,22]. Similarly, previous investigators have implicated estrogen exposure as a stimulus for malignant transformation [23], citing the well-documented association between estrogen exposure and the development of endometrial carcinoma [24].

Determining whether synchronously occurring ovarian and endometrial carcinomas represent dual primary tumors or metastatic lesions from either site remains difficult and controversial. Several investigators have classified the lesions as dual primary tumors if the endometrial lesion was minimally invasive, well-differentiated, and less than 2 cm in diameter [2,25,26]. Some authors have sug-

Table 3. Depth of invasion and survival.

Reference	Group A				Group B				Group C			
	<2/3		>2/3		<2/3		>2/3		<2/3		>2/3	
	N (%)	Survival (%)	*N* (%)	Survival (%)	*N* (%)	Survival (%)	*N* (%)	Survival (%)	*N* (%)	Survival (%)	*N* (%)	Survival (%)
6	15	100	1	100	4	25	7	57				
7	1	100			4	25						
8	9	89	4	50	2	100			4	75	5	40
9	10	100	3	100					2	100		
10	16	75	7	14	5	80	5	20	3	67	1	100
Pearl	13	100			1	100			2	100		
Total	64	92[a]	15	47	16	56	12	42	11	82	6	50

Group A: Endometrioid ovarian and endometrial histology.
Group B: Non-endometrioid but similar ovarian and endometrial histology.
Group C: Dissimilar ovarian and endometrial histology.
[a] $P < 0.05$ vs. Group A > 2/3.

gested that the presence of dissimilar histologic subtypes indicates the lesions are primary, rather than metastatic, tumors [11,27]. Still others have utilized the histologic grade, classifying Grade 1 and 2 lesions as dual primary, and Grade 3 lesions as metastatic, tumors [21]. Finally, the excellent survival for these patients has been used to support classifying these lesions as dual primary tumors [3,6,8,10]. All investigators agree that careful and extensive clinicopathologic evaluation is a prerequisite for accurate classificaton.

The treatment of these tumors varies widely. In the present study, survival was excellent following surgical therapy with or without adjuvant therapy. There were no recurrences in the patients with Grade 1 endometrioid tumors treated with surgery alone, supporting previous reports that suggest adjuvant therapy may not be necessary for patients in this subgroup [6,7,9]. In contrast, patients with higher grade ovarian tumors are usually treated with adjuvant irradiation or chemotherapy [28], and this approach should be applied to such patients with ovarian and endometrial tumors. Finally, the non-endometrioid or dissimilar histologic types may be aggressive [6,8], and should be treated with adjuvant irradiation or chemotherapy.

In conclusion, patients with synchronous dual primary ovarian and endometrial carcinomas appear to have a favorable prognosis. However, the currently available information is derived from small, retrospective studies. The definitive answer to the appropriate staging and treatment of these fascinating tumors requires a multicenter, randomized prospective trial.

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