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Implication of genomic characterization in synchronous endometrial and ovarian cancers of endometrioid histology

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HIGHLIGHTS

- The majority of SEOCs with endometrioid histology were single primary tumors with metastatic disease.
- Clinicopathological criteria used to determine SEOCs must be adjusted.
- Testing of copy number alterations on SEOCs may help determining the need of adjuvant therapy.

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ABSTRACT

Objectives. Synchronous endometrial and ovarian carcinomas (SEOCs) present gynecologic oncologists with a challenging diagnostic puzzle: discriminating between double primary cancers and single primary cancer with metastasis. We aimed to determine the clonal relationship between simultaneously diagnosed endometrial and ovarian carcinomas.

Methods. Fourteen pairs of SEOCs of endometrioid type and two pairs of SEOCs with disparate histologic types (control for dual primary tumors) were subjected to massively parallel sequencing (MPS) and molecular inversion probe microarrays.

Results. Thirteen of the 14 pairs of SEOCs harbored somatic mutations shared by both uterine and ovarian lesions, indicative of clonality. High degree of chromosomal instability in the tumors from 10 patients who received adjuvant chemotherapy, of whom 9 had synchronous carcinomas with significantly overlapping copy number alterations (CNAs), suggestive of single primary tumors with metastasis. The clonal relationship determined by genomic analyses did not agree with clinicopathological criteria in 11 of 14 cases. Minimal CNAs were identified in both ovarian and endometrial carcinomas in 4 patients, who did not receive adjuvant chemotherapy and experienced no recurrent diseases. In contrast, two of the 10 patients with chromosomally unstable cancers developed recurrent tumors.

Conclusion. Our findings support a recent paradigm-shifting concept that most SEOCs originate from a single tumor. It also casts doubt on the clinicopathological criteria used to distinguish between dual primary tumors and single primary tumor with metastasis. Testing of CNAs on SEOCs may help determining the need of adjuvant therapy.

1. Introduction

Synchronous endometrial and ovarian carcinomas (SEOCs) are not uncommonly encountered in clinical practice, occurring in 3.1 to 10% of patients with endometrial cancers [1,2]. SEOCs could represent either dual primary tumors with independent origins, or clonally related metastatic tumors of either endometrial or ovarian origin [3,4]. This

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presents a challenging task for clinicians because the prognosis and management of independent or metastatic malignancies can be very different. Thus distinguishing between dual primary tumors and metastatic disease is usually a subjective process requiring integrative evaluation of multiple clinicopathological factors, including the histologic similarity of synchronous tumors, laterality of the ovarian tumors, depth of myometrial invasion, presence of vascular invasion, presence of atypical endometrial hyperplasia, and presence of ovarian endometriosis, etc [5].

To solve this conundrum, a plethora of molecular features have been evaluated in SEOCs, including ploidy analysis, loss of heterozygosity, microsatellite instability, or mutational analyses of single or small sets of genes frequently mutated in endometrial cancers [6–12]. The majority of these molecular studies have failed to identify shared molecular alterations in the bulk of the SEOCs studied. This, together with the generally favorable prognosis of SEOCs, has led to the common belief that most SEOCs were clonally unrelated, dual primary tumors. This common belief has recently been challenged by two independent studies, which investigated the clonal relationship between synchronously diagnosed ovarian and endometrial carcinomas with massively parallel sequencing and found that the majority of the SEOCs studied (39/41, 95%) represent single primary tumors with metastasis [13,14]. This finding is potentially paradigm shifting and demands more independent corroboration with additional cases as well as different methodologies.

We herein sought to examine the clonality of 16 pairs of SEOCs with two different high-throughput approaches, including mutational analysis with targeted massively parallel sequencing of a panel of 409 cancer-related genes, and copy number analysis with molecular inversion probe (MIP) microarrays.

2. Material and methods

2.1. Patients

Sixteen patients diagnosed with SEOCs receiving primary surgery between 2000 and 2014 were retrospectively retrieved from the database of tissue bank [15] (Table 1). All tumors were newly diagnosed and have not been treated before undergoing definitive surgeries. Two

Table 1
Sixteen patients with synchronous tumors of uterus and ovary.

Code	Age at dx (y)	Site	Gr	MI (%)	EmH	LVSI	Cx	Ov (side)	Ov tumor size[a] (cm)	Ov emsis	Other sites	Original Stage	Primary Tx	FU time (m)	Status[b]
DP1	45	Em	1	20	SH	+	−					1B	Su + CT	94	NED
		Ov	3					R	6.2	+	−	1 A			
DP2	38	Em	1	60	−	−	−					1C	Su + CT	80	NED
		Ov	1					B		−		3C			
1	50	Em	1	5	EIN	+	−				NA	1 A	Su	56	NED
		Ov	1			−		L	5.3	–		1 A			
2	43	Em	1	0	EIN	−	−				NA	1 A	Su	171	NED
		Ov	1			−		L	3.5	+		1 A			
3	47	Em	1	10	EIN	−	−				NA	1 A	Su	55	NED
		Ov	1			−		B	12.0 (R)	–		1B			
4	42	Em	1	5	EIN	−	−				NA	1 A	Su	21	NED
		Ov	1			−		R	6.0	+		1 A			
5	27	Em	2	0	–	−	−				−	1 A	Su + CT	70	NED
		Ov	3			−		L	18.0	–		1C			
6	39	Em	1	10	EIN	−	+					1B	Su + CT	176	NED
		Ov mets	1			−		R	17.0	−	PaLN, PLN[c]	3C			
7	40	Em	3	<5	EIN	−	−					1 A	Su + CT	30	Recur
		Ov mets[d]	3					B	8.0 (L)	+	Mesenteries, omentum, paravesical nodules	3C			
8	44	Em	1	<5	–	+	−				−	1B	Su + CT	14	NED
		Ov	1			−		L	15.0	–		1C			
9	52	Em	2	45	−	+	−					1B	Su + CT	45	Recur
		Ov mets recur	2			−		R	15.0	–	Omentum Umbilicus	3C			
10	42	Em	1	0	EIN	−	−					1 A	Su + CT	3	expired[e]
		Ov mets	1			−		L	13.2	–	Pleural effusion[c]	4			
11	43	Em	2	40	EIN	−	−					1 A	Su + CT	13	NED
		Ov mets	2			−		L	11.5	−	Colon[c]	2B			
12	50	Em	1	90	–	+	+					3C	Su + CCRT	23	expired
		Ov PLN	1			−		R	23.5	–		3C			
13	58	Em	1	<5	–	+	−				−	3 A	Su + CT	121	NED
		Ov	1			−		L	2.3	–					
14	45	Em	1	0	–	−	−				−	3 A	Su + CT	148	NED
		Ov	1			−		B	1.8 (R)	–					

B, bilateral; CCRT, concurrent chemoradiation; CT, chemotherapy; Cx, cervix; D, dual; DP, dual primary; dx, diagnosis; Em, endometrium; EmH, endometrial hyperplasia; emsis, endometriosis; FU, follow-up; Gr, grade; I, indeterminate; L, left; LN, lymph node; LVSI, lymphovascular space invasion; mets, metastasis; MI, myometrial invasion; m, months; NA, not applicable; NED, no evidence of disease; Ov, ovary; PaLN, paraaortic lymph node; PLN, pelvic lymph node; R, right; R/O, ruled-out; S, single; SH, simple hyperplasia; EIN, endometrial intraepithelial neoplasia; Su, surgery; Tx, treatment; y, years old.

[a] Tumors that were not located inside the ovary are excluded from this study, size as largest diameter.

[b] Patients who received surgeries alone have undergone follow-up with magnetic resonance imaging or computed tomography within 12 months.

[c] Inadequate specimens of metastatic sites for genomic analysis.

[d] Metastatic site in paravesical space was sent for genomic testing.

[e] This patient who had positive pleural effusion died of head injury when fell down during chemotherapy.