

# Is there a difference between synchronous multiple primary cancer and metastasis cancer?

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## Summary

The purpose of this study was to evaluate synchronous multiple primary neoplasms of gynecologic origin in terms of clinical features, diagnosis, treatment, and relapse. Seven patients treated from 2012 to 2017 were studied; five of whom had synchronous multiple primary neoplasms associated with endometrial cancer. Two patients recurred and additional chemotherapy was performed. Synchronous multiple primary neoplasms have a better prognosis than single metastatic tumors, but they should be followed up carefully, as they tend to recur in the latter half of treatment. The authors herein report these seven cases along with a brief review of the literature.

**Key words:** Synchronous multiple primary neoplasms; Endometrial neoplasm; Ovarian neoplasm; Uterine cervical neoplasm.

## Introduction

Coexistence of carcinoma in the uterus, ovaries, and other organs is a somewhat uncommon, but not a rare, event, occurring in about 10% of patients with ovarian carcinoma and in slightly more than 5% of those with endometrial carcinoma [1]. The etiology and pathogenesis of these tumors remain unclear; however, it has been proposed that embryologically similar tissues may develop a synchronous neoplasm when simultaneously subjected to either hormones or carcinogens [2, 3]. The most common site of this neoplasm is thought to be the hormone-producing reproductive organs, arising from the same germ layer. The aim of this study is to present seven cases of synchronous primary cancer, and to compare the clinical characteristics, treatment, and prognoses between multiple primary cancers and metastatic cancer.

## Case Report

### Case 1

A 74-year-old woman [height: 152 cm, weight: 56 kg, BMI: 23.2 kg/m<sup>2</sup>, gravida 3] was admitted to the Obstetrics and Gynecology (OB/GYN) hospital, because a high-grade squamous intraepithelial lesion (HSIL) was detected on cervical cytology. Her chief complaint was vaginal spotting, commencing about one month previously. The loop electrical excision procedure (LEEP) pathology result was of poorly differentiated endocervical squamous cell carcinoma (SCC), and the deep margin was positive. Positron emission tomography-computed tomography revealed diffuse and mild hyper-metabolism in the uterine cervix, and a large intra-pelvic mass with severe hyper-metabolism. She underwent a laparoscopic radical hysterectomy with bilateral salpingo-oophorectomy (BSO), pelvic lymphadenec-

tomy (PLA), and omentectomy. The pathological report noted invasive non-keratinizing SCC in the uterine cervix, with an invasion depth of 10 mm and no parametrial invasion. The right ovary was also affected by SCC, moderately differentiated into a cystic teratoma (Figure 1). The patient was treated with concurrent chemoradiation therapy (CCRT) and has been disease-free for two years.

### Case 2

A 56-year-old menopausal woman (height: 157 cm, weight: 52 kg, BMI: 21.1 kg/m<sup>2</sup>, gravida 2) was admitted to the OB/GYN hospital due to an increase in vaginal discharge and a bad odor persisting for one month. At the time of admission, a hysteroscopy was performed (Figure 2) as the ultrasound findings revealed an endometrial thickness of 20.18 mm and a right adnexa mass. Histology revealed endometrioid adenocarcinoma (FIGO grade 2). Her cancer antigen (CA) level had increased to 114.3 U/mL. Radiology revealed cancer in the endometrium and ovary (Figure 2). The final histological exam confirmed endometrial carcinoma (grade 2) of the endomyometrium, and endometrioid carcinoma of the right ovary with capsular involvement. The patient was diagnosed with double primary endometrioid carcinomas of the endometrium and ovary. She underwent radiotherapy (RT) postoperatively and had no recurrence at the three-year follow-up. She is currently being followed-up and has no apparent specific signs, excluding a treatment history of lymphedema of the right lower limb.

### Case 3

A 39-year-old unmarried woman (height: 154 cm, weight: 59 kg, BMI: 21.1 kg/m<sup>2</sup>, gravida 0) visited the hospital due to a left ovarian mass detected in a private clinic. Radiological examination revealed mixed cystic and solid tumors in the endometrium and ovary. Her CA-125 level was elevated to 359.7 U/mL. The patient underwent

Table 1. — Summary of cancer patient characteristics.

	AGE	Endometrial Cancer	Ovarian cancer	Cervical cancer	Other cancer	Previous Chemotherapy	Previous RT or CCRT	Recur
1	74		•	•			•	
2	56	•	•				•	
3	39	•	•			•	•	
4	53	•			•		•	•
5	49			•	•			
6	57	•		•			•	
7	60	•	•			•		•

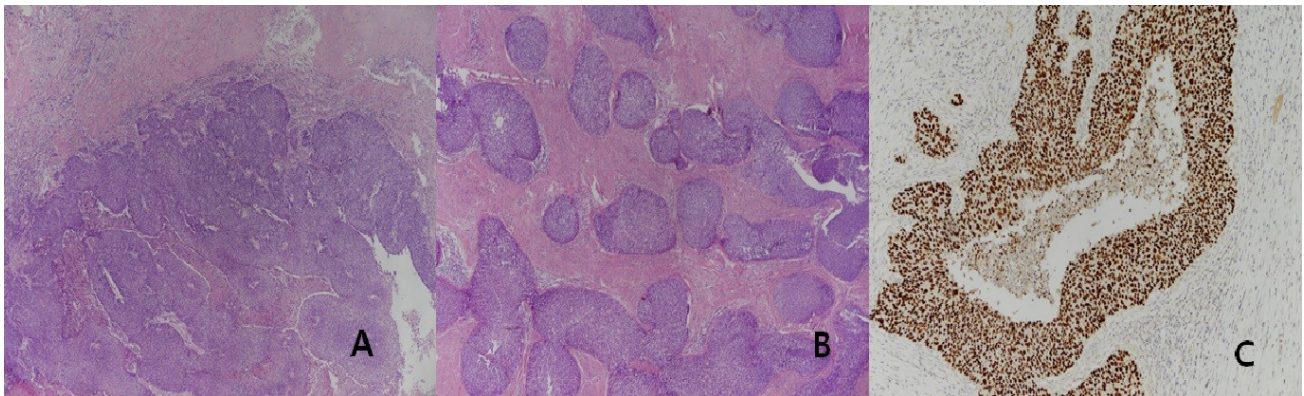


Figure 1. — A) The cervix shows invasive squamous cell carcinoma with patten of glandular involvement (H&E, × 100). B) Microscopic findings show invasive squamous cell carcinoma with papillary configuration of ovary (H&E, × 40). C) Immunohistochemical stain of p63 reveals strong positivity of ovary. It is consistent with squamous differentiation (H&E, × 100).

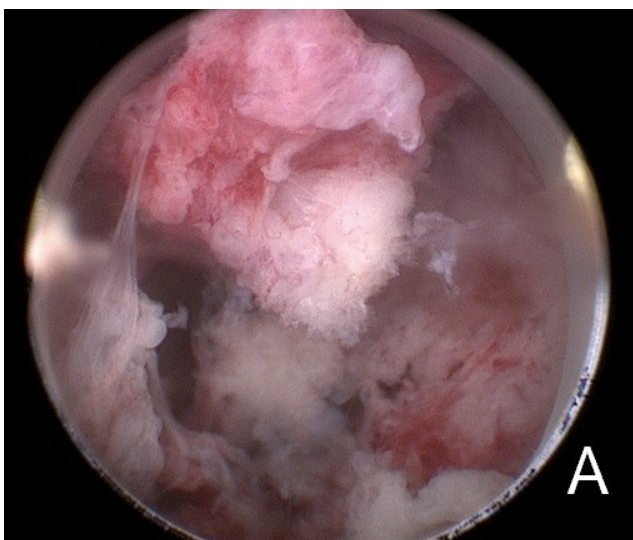


Figure 2. — A) Hysteroscopic and histologic result shows endometrioid adenocarcinoma B) PET-CT findings show large endometrial cancer (maxSUV 13.2) and right ovarian cystic mass with hypermetabolism (maxSUV 5.9), R/O malignant.

left salpingo-oophorectomy (LSO), wedge resection of the ovary, and hysteroscopic endometrial biopsy as primary surgery, and total laparoscopic hysterectomy (TLH), right salpingo-oophorectomy (RSO), and PLA as secondary surgery. The final biopsy showed endometrioid adenocarcinoma (FIGO grade 2), and endometrioid car-

cinoma favoring a primary tumor with no metastasis in either ovary. The patient underwent external beam RT (28 cycles) and paclitaxel/carboplatin combination chemotherapy (six cycles). She is currently under follow-up without recurrence for 1.5 years.

#### Case 4

A 53-year-old menopausal woman (height: 152 cm, weight: 45 kg, BMI: 19.3 kg/m<sup>2</sup>, gravida 4) was admitted to the OB/GYN hospital due to endometrial cancer detected during dilatation and curettage performed for an increase in vaginal discharge. Radiological findings revealed FIGO Stage 1A endometrial cancer, and a tumor marker test revealed a CA-125 level of 15.4 U/mL and a carcinoembryonic antigen (CEA) of 1.61 ng/ml. Colonoscopy revealed tiny hyperplastic polyps 10 cm above the anorectal valve, confirmed as well-differentiated adenocarcinoma by histology. The patient underwent TLH, BSO, PLA, and right hemicolectomy and was diagnosed with Stage I colorectal cancer and 1AG2 endometrial cancer after external RT. The patient had no visitors for personal reasons and re-visited the hospital due to right flank pain four years after the final treatment. Recurrence of the colorectal cancer was detected at a routine follow-up, with a mass invading the right ureter and peritoneal cavity, which was treated with surgery. She is now receiving chemotherapy.

#### Case 5

A 49-year-old woman (height: 150 cm, weight: 58 kg, BMI: 25.8 kg/m<sup>2</sup>, gravida 1) was admitted to the OB/GYN hospital due to a solid mass on the left vulva, diagnosed as HSIL on a Pap smear. The antigen level of the SCC tumor marker was 1.3 ng/ml. The patient was diagnosed with well-differentiated SCC of the vulva on a histological exam, and SCC with microinvasion and glandular involvement on LEEP conization. She underwent TLH, radical left vulvectomy, left inguinal lymph node dissection (LND) and flap coverage, and was diagnosed with Stage I vulvar cancer and Stage 1A1 cervical cancer. No recurrence has been detected after three years and she is currently being followed-up without additional treatment.

#### Case 6

A 57-year-old woman (height: 154 cm, weight: 58 kg, BMI: 24.5 kg/m<sup>2</sup>, gravida 2) was admitted to the OB/GYN hospital with chief complaints of vaginal spotting, which occurred one month prior, and leg swelling on the right side. In a private clinic, the patient was diagnosed with endometrioid carcinoma grade 3 on biopsy and cervical adenocarcinoma on LEEP conization. A tumor marker test revealed a CA-125 level of 61.0 U/mL. She received laparoscopic-assisted radical hysterectomy (LRH), BSO, and pelvic lymph node dissection (PLND), and was diagnosed with endo-cervical adenocarcinoma (Stage IIIC grade 3 endometrial cancer and Stage IB1 cervical cancer). The patient underwent concurrent chemoradiotherapy after surgery. She is currently under follow-up without recurrence for two years.

#### Case 7

A 60-year-old woman (height, 162 cm, weight: 98 kg; BMI: 37.3 kg/m<sup>2</sup>, gravida 3) was admitted to the OB/GYN hospital. This patient had a history of surgery and chemotherapy (four cycles) due to endometrial cancer

(Stage I, grade 3) and ovarian cancer (Stage I), diagnosed in a hospital abroad three years ago. She underwent surgical removal of an abdominal mass in the hospital due to suspected recurrence of cancer, and was diagnosed with recurrence of endometrial cancer. She is currently undergoing chemotherapy.

### Discussion

Synchronous multiple primary cancers of the female genital tract are relatively rare, comprising only 1–6% of all genital neoplasms [4]. Of all seven cases in this report, synchronous cervical and ovarian cancers were present in one case, synchronous endometrial and ovarian cancers in three cases, synchronous endometrial and colorectal cancers in one case, synchronous cervical and vulvar cancers in one case, and synchronous cervical and endometrial cancers in one case.

The etiology and pathogenesis of these tumors remain unclear; however, it has been proposed that embryologically similar tissues, simultaneously subjected to hormones and carcinogens, develop synchronous neoplasms [2, 3]. The most commonly affected area is thought to be the hormone-producing reproductive organs originating from the same germ layer. In fact, endometrial cancer occurring synchronously with ovarian cancer is the most frequently observed type of synchronous tumor [5]. In contrast, endometrial cancer with metastases to the ovaries accounts for approximately only 5% of all endometrial carcinomas [6]. Synchronous multiple primary tumors are diagnosed according to the stage of each of the synchronous cancers, while endometrial cancers metastasized to the ovaries are diagnosed as Stage III. The most common neoplasms of the female genital tract are endometrial cancer and synchronous multiple primary tumors. In our report, five cases had endometrial cancer occurring synchronously with other primary tumors. Excluding cases with synchronous primary cervical cancer, synchronous primary tumors seem to affect hormone-related organs without metastasis from one site to another.

Pathologically, tumors are defined as either metastatic or synchronous multiple primary cancers, based on histological features after surgery. Tumors can be diagnosed in advance via radiological assessment, but synchronous multiple primary tumors differentiated from the same histotype cannot be distinguished radiographically after surgery. In this study, cancer cells were obtained from punch biopsies of the cervix and vulva for diagnosing cervical and vulvar cancers, and were diagnosed as synchronous multiple primary tumors based on the histological test results after the final surgery.

Surgical intervention is the preferred treatment option, and additional therapies are used for patients with synchronous multiple primary tumors in advanced stages after histological diagnosis of the lesions. Brachytherapy, RT, and chemotherapy can be additionally performed in patients with endometrial cancer.

The prognosis of patients with synchronous primary cancer is better than that of patients with metastatic lesions [4, 5]. Zaino *et al.* [1] previously reported that the estimated overall probability of surviving five years was 85.9%, and that the chance of surviving for ten years was 80.3%, in women with simultaneously detected uterine and ovarian carcinomas. In this study, cancer recurred in two cases (one with endometrial and colorectal cancers and one with endometrial and ovarian cancers), and these patients are currently receiving chemotherapy. As this study had a small sample size and relatively long follow-up period of four years, the authors cannot compare these findings with those of existing studies, and no deaths occurred in this report.

Most endometrial cancers (75%) are diagnosed at an earlier stage (FIGO Stage I–II) compared to endometrial cancer originating from a single organ. The overall five-year survival rate of endometrial cancers ranges from 74% to 91%; the five-year survival for FIGO Stage III is 57–66%, and that for Stage IV disease is 20–26% [7, 8]. There is a higher probability for a better prognosis compared to that of Stage III and IV endometrial cancers, and the prognosis is comparable to the overall prognosis of all endometrial cancers. Although synchronous multiple primary neoplasms have a better prognosis than single metastatic tumors, they should be followed up carefully as they tend to recur in the latter half of treatment.

The present basic literature review suggests that a number of methods can be used to determine whether two different components of a neoplasm have independent or common origins [9–11]. Although these techniques have proven useful in some cases, surgical treatment in combination with chemotherapy, used for Stage III–IV cancer involving a single organ, is also considered to be a desirable treatment option for patients with recurrent, well-differentiated Stage I adenocarcinoma that requires additional surgical intervention and chemotherapy, even in cases of synchronous multiple Stage I primary cancers.

To conclude, synchronous multiple primary tumors of the female genital tract can be associated with tumors in the breasts, thyroid, adrenal glands, and other endocrine organs. The present authors found that patients with synchronous multiple primary tumors had a better prognosis than those with Stage III–IV carcinomas metastasized to an organ. This single-center study was limited by its small sample size and low disease prevalence; therefore, a larger multicenter study is warranted to validate the findings.

#### Author contributions

H Chung designed the manuscript and wrote the manuscript. J H Sang wrote the manuscript and revised the manuscript.

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#### Conflict of interest

The authors declare no competing interests.

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