RESEARCH COMMUNICATION

Clinicopathologic Analysis of Women with Synchronous Primary Carcinomas of the Endometrium and Ovary: 10- Year Experience from Chiang Mai University Hospital

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Abstract

The aim of this study was to analyze the clinicopathologic features and survival outcomes of women with synchronous primary carcinomas of the endometrium and ovary that were treated at Chiang Mai University Hospital between January 1995 and December 2004. During the study period, 43 women with such tumors were identified. These carcinomas accounted for 0.58% (95%CI=0.42-0.79%) of all gynecologic malignancies. Median age at diagnosis was 49 years (range: 34-60 years). Median body mass index (BMI) was 21.6 kg/m2(range: 15.5-27.7 kg/m2). The majority of women (65%) were premenopausal. The most common presenting symptom was abnormal uterine bleeding (42%), followed by a pelvic mass (30%). Twenty-seven (62.8%, 95%CI= 46.7-77.0%) women had concordant endometrioid carcinomas of the endometrium and ovary. Five (11.6%) women experienced tumor recurrence with median follow up 39 months (range: 1-85 months). The overall 5-year survival was 85.2%. There was no significant difference in survival outcomes among the women who had endometrioid/endometrioid histology and those who had other histological subtypes (P=0.674). In conclusion, synchronous primary carcinomas of the endometrium and ovary, although uncommon, should be considered in differential diagnosis in premenopausal women presenting with abnormal uterine bleeding and ovarian tumors. The prognosis of patients with these tumors appears excellent.

Key Words: Synchronous tumors - endometrial carcinoma - ovarian carcinoma - clinicopathologic characteristics

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Introduction

The term synchronous tumors is applied when two or more tumors occur in a patient simultaneously. Among women with gynecologic cancer, the simultaneous presence of primary carcinomas of endometrium and ovary is relatively uncommon, but not rare event, being reported in about 10% of patients with ovarian carcinoma and in slightly more than 5% of patients with endometrial carcinoma (Zaino et al., 2001). The etiology of synchronous primary endometrial and ovarian carcinomas remains unknown. Some factors have been postulated to increase the risk of these carcinomas including endometriosis, low past use of combined oral contraception, low parity, and ovulation induction (Choo et al., 1982, Herrinton et al., 2001, Ghourab et al., 2001). Recently, Soliman et al (2005) observed that 7% of women with synchronous primary carcinomas of the endometrium and ovary met either clinical or molecular criteria for Lynch syndrome or hereditary nonpolyposis colorectal cancer (HNPCC).

However, cancer developing concomitantly in both locations may indicate either independent or metastatic neoplasms. The clinical implications and prognosis are quite different. Nevertheless, the discrimination between these two possibilities is difficult because these carcinomas may have similar histopathologic features. Although there are various molecular techniques developed for identifying the independent or metastatic characteristics (Jaime et al., 1991, Shenson et al., 1995, Fujita et al., 1996, Julie et al., 2005), routine laboratory performance of these procedures is generally not available. Therefore, differential diagnosis using clinicopathologic findings is still the principal method. The identification of specific clinicopathologic findings of women with synchronous primary carcinomas of the endometrium and ovary would provide the clinician with baseline information for decision making and further research planning on cancer prevention, early detection, and treatment strategy. The present study was undertaken

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accordingly to evaluate the clinicopathology and treatment outcomes of women diagnosed with synchronous primary carcinomas of the endometrium and ovary in a single institute experience.

Materials and Methods

After approval of the Research Ethics Committee, the medical records of women diagnosed with synchronous primary carcinomas of the endometrium and ovary at Chiang Mai University Hospital between January 1995 and December 2004 were reviewed. All enrolled women had their histological materials initially reported or reviewed by gynecologic pathologist at our institute at the time of treatment. The age at diagnosis, body mass index (BMI), parity, menopausal status, presenting sign and symptom, preoperative diagnosis, stage of each location, and postoperative histological features were analyzed. The histological classification and grading were determined using the criteria of World Health Organization (WHO). Surgical staging was assessed using the criteria of the International Federation of Gynecology and Obstetrics (FIGO).The diagnosis of synchronous primary carcinomas of the endometrium and ovary was made according to the Scully criteria (Scully et al., 1998).

In the statistical analysis, frequency distributions were calculated for each variable. Student's t test, Mann-Whitney U test, chi-square, or Fisher's exact test was used whenever appropriate to compare the two groups. Kaplan-Meier survival analyses were generated using the log-rank test. Value of P less then 0.05 were considered statistically significant. All tests were two sided.

Results

During the study period, 7,363 malignancies of the female genital tract were diagnosed including 43 women with synchronous primary carcinomas of the endometrium and ovary which accounted for 0.58% (95% confidence interval [CI] = 0.42- 0.79). In the same period, 970 and 644 women diagnosed with ovarian and endometrial cancer, respectively, were identified, therefore, synchronous primary carcinomas of the endometrium and ovary occurred in 4.4% (95% CI= 3.2-5.9) of all women with ovarian cancer and 6.7% (95% CI= 4.9-8.9) of all women with endometrial cancer. Histopathology of the endometrial and ovarian carcinomas in 43 women with synchronous primary carcinomas of the endometrium and ovary is shown in Table1. Twenty-seven (62.8%, 95% CI= 46.7-77.0) women had both endometrioid carcinoma of the endometrium and ovary which were determined to have independent nature according to the Scully criteria.

Table 1. Histopathology of the Ovarian and Endometrial Carcinomas (N = 43)

	Ovary						
Endometrium	End	EC	Clear	Serous	EM	ES	Total
End	27	3	2	2	1	1	36
EC	1	0	1	1	0	0	3
EM	1	1	0	0	1	1	4
Total	29	4	3	3	2	2	43

End: Endometrioid, EC : Endometrioid and clear cell adenocarcinoma, EM : Endometrioid and mucinous adenocarcinoma, ES : Endometrioid and serous adenocarcinoma

Table 2. Demographic Characteristics

	All (N = 43)	End* (N = 27)	Others (N = 16)	P - value
Median age (yrs)	49 (34-60)	46 (34-56)	50.5 (34-60)	0.171
Median BMI (kg/m2)	21.6 (15.5-27.7)	21.9 (15.5-27.7)	21.5 (17.7-25.8)	0.837
Nulliparous	22 (51.2)**	16 (59.2)	6 (37.5)	0.215
Premenopausal	28 (65.1)	20 (74.1)	8 (50.0)	0.185
Symptoms				0.339
Bleeding	18 (41.9)	9 (33.3)	9 (56.2)	
Pelvic pain	13 (30.2)	8 (29.7)	5 (31.3)	
Pelvic mass	11 (25.6)	9 (33.3)	2 (12.5)	
Pap abnormal	1 (2.3)	1 (3.7)	0 (0)	
Preoperative tumor diagnosis				0.021
Ovarian	26 (60.5)	19 (70.4)	7 (43.8)	
Endometrial	17 (39.5)	8 (29.6)	13 (56.2)	

*End, endometrioid/endometrioid **Values: numbers (percentages)

Demographic characteristics of the 43 women are presented in Table 2. The median age at the time of diagnosis was 49 years (range: 34-60 years). The median BMI was 21.6 kg/m2 (range: 15.5-27.7 kg/m2). The majority of enrolled women (65.1%) were premenopausal. Most of the women presented with abnormal vaginal bleeding, followed by pelvic pain, pelvic mass, and abnormal cervical cytology. There were no statistically significant difference in age at diagnosis, BMI, nulliparity, menopausal status, and presenting symptoms among women in the endometrioid/endometrioid group and women with other histological subtypes. Twenty six (60.5%) of the 43 women had preoperative diagnosis of ovarian tumor. However, significant higher proportion of women with endometrioid/endometrioid subtypes were diagnosed with ovarian tumor compared to those with other histological subtypes (70.4% versus 43.8%, P=0.021).

The characteristics of ovarian carcinoma in 43 women are provided in Table 3. Slightly more than 50% of women had tumor size between 4.0-9.9 cm in largest diameter. Bilateral ovarian involvement was noted in only 8 (18.6%) women. There were no statistically significant difference in tumor size and bilateral ovarian involvement between women in the endometrioid/endometrioid group and women with other histological subtypes. Among 43 women, the most common histological grading was well differentiated which was noted in 17 (39.5%). Women in endometrioid/endometrioid group had significantly higher proportion of well-differentiated tumors than those with other histological subtypes (51.9% versus 18.8%, P=0.014). Overall, only 11

Table 3. Characteristics of the Ovarian Tumors

	All (N = 43)	End (N = 27)	Others (N =16)	P - value
Tumor size(cm)				0.433
< 4.0	3 (7.0)*	2 (7.4)	1 (6.2)	
4.0-9.9	23 (53.5)	12 (44.4)	11 (68.8)	
> 10	16 (37.2)	12 (44.4)	4 (25.0)	
unknown	1 (2.3)	1 (3.8)	0 (0)	
Cytological grading				0.014
1	17 (39.5)	14 (51.9)	3 (18.8)	
2	13 (30.2)	7 (25.9)	6 (37.5)	
3	7 (16.3)	2 (7.4)	5 (31.2)	
unknown	6 (14.0)	4 (14.8)	2 (12.5)	
Bilateral involvement				0.101
Yes	8 (18.6)	3 (11.1)	5 (31.2)	
No	35 (81.4)	24 (88.9)	11 (68.8)	
FIGO stage				0.006
I	27 (62.8)	21 (77.8)	6 (37.5)	
II	5 (11.6)	4 (14.8)	1 (6.2)	
III	11 (25.6)	2 (7.4)	9 (56.3)	

*Values are numbers (percentages)

Table 4. Characteristics of the Endometrial Carcinomas

	All (N = 43)	End* (N = 27)	Others (N = 16)	P - value
Myometrial invasion				0.053
No	8 (18.6)	7 (25.9)	1 (6.2)	
Inner half	20 (46.5)	14 (51.9)	6 (37.5)	
Outer half	15 (34.9)	6 (22.2)	9 (56.3)	
LVSI**				0.089
No	33 (76.8)	23 (85.2)	10 (62.5)	
Yes	10 (23.2)	4 (14.8)	6 (37.5)	
Histological grading				0.634
1	27 (62.8)	18 (66.7)	9 (56.3)	
2	10 (23.2)	5 (18.5)	5 (31.2)	
3	6 (14.0)	4 (14.8)	2 (12.5)	
FIGO stage				0.139
I	29(67.4)	20 (74.1)	9 (56.3)	
II	12 (27.9)	5 (18.5)	7 (43.7)	
III	2 (4.7)	2 (7.4)	0 (0)	

* Endometrioid/endometrioid **LVSI :Lymphovascular space invasion

(25.6%) women were in surgically advanced stage (stage III). However, compared with the women who had endometrioid/endometrioid histology, women with other histological subtypes had a significantly higher incidence of advanced stage of ovarian carcinoma after surgical staging procedure (56.3% versus 7.4%, P=0.006).

Table 4. displays the characteristics of endometrial carcinomas in 43 women. Deep myometrial invasion was noted in 15 (34.9%) cases. Women with endometrioid/ endometrioid histological subtypes had lower incidence of deep myometrial invasion than those with other histological subtypes. However, this difference was marginally significant (P=0.053). Lymphovascular space invasion was reported in 10 (23.2%) women. The majority of women had grade 1 tumor (62.8%) and were in FIGO stage I (67.4%). There were no significant difference in the incidence of lymphovascular space invasion, cytological grading, and the distribution of FIGO stage between women in the endometrioid/endometrioid group and those who had other histological subtypes.

Five patients developed tumor recurrence at a median follow up of 39 months (range: 1-85 months). The overall 5-year survival was 82.4% and there was no statistically significant difference in survival probability according to the histological subtypes (P=0.674).

Discussion

Synchronous primary carcinomas of the endometrium and ovary are relatively uncommon in gynecologic malignancy. In series from the Gynecologic Oncology Group (GOG), these synchronous tumors occurred in 5% and 10% of women with endometrial and ovarian cancers, respectively (Zaino et al., 2001). In the present study, these carcinomas accounted for only 0.58% of all female genital cancer. Additionally, it accounted for only 6.7% and 4.4% of women with endometrial and ovarian cancers, respectively. Similar to the previous studies (Eifel et al., 1982, Zaino et al., 2001, Soliman et al., 2004), we observed that the most prevailing histological subtype was endometrioid/endometrioid adenocarcinoma (62.8%). Synchronous primary carcinomas of the endometrium and ovary are generally recognized as the disease of younger women than those who developed endometrial or ovarian carcinoma separately. The GOG reported a median age of 49 years in a prospective series of 74 women (Zaino et al., 2001). In a review of 84 women with synchronous primary carcinomas of the endometrium and ovary from M.D. Anderson Cancer Center, the median age of the patients was 50 years (Soliman et al., 2004). These observations were similar to the median age of 49 years which was noted in the present study. When divided by histological subtype, women in endometrioid/endometrioid group was slightly younger than those who had other histological subtypes. This observation was supported by Soliman et al (2004) who also noted that women who had endometrioid/endometrioid histological subtype were younger than those who had endometrioid/serous and endometrioid/clear cell histological subtypes. The authors proposed that the difference in age of patient may be due to the difference pathogenesis of each circumstance.

Obesity is closely associated with the hyperestrogenic exposure to the endometrium resulting in an increased risk of endometrial carcinoma. This correlation, however, remains inconclusive definitely in women with either ovarian carcinoma or synchronous primary carcinomas of the endometrium and ovary. Soliman et al (2004) reported the median BMI of women with synchronous primary carcinomas of the endometrium and ovary was 28 kg/m2 (range: 18-53 kg/m2). In the present series, the median BMI was only 21.6 kg/m2 (range: 15.5-27.7 kg/m2). This obvious

difference would be due to the differentiation of baseline BMI between the population in North America and Asia. However, we found that there was no statistically significant difference in median BMI among the women in the endometrioid/endometrioid group compared with those who had other histological subtypes which was similar to the findings of from Soliman et al (2004).

Nulliparity is recognized as predisposing factor for endometrial and ovarian carcinomas. In the women with synchronous primary carcinomas of the endometrium and ovary, Eifel et al (1982) reported that 50% of the women in endometrioid /endometrioid group were nulliparous. Soliman et al (2004) reported 33% of women were nulliparous and there was no significant difference in the prevalence of nulliparity among women in the endometrioid/ endometrioid group and other groups. In the present series, 52.3% of women were nulliparous. We also similarly observed that there was no significant different in the proportion of nulliparity between women in the endometrioid/endometrioid group and those who had other histological subtypes.

In accordance with the previous report (Soliman et al., 2004), the most common presenting sign and symptom in the present study was abnormal vaginal bleeding (41.9%), followed by pelvic pain (30.2%). Interestingly, the majority of women (60.5%) in our study had ovarian tumor as preoperative diagnosis while the remainders had endometrial carcinoma. According to histological subtypes, the proportion of women diagnosed with ovarian tumor were significant higher in the endometrioid/endometrioid group (P=0.021). This difference might be due to the difference of initial sign and symptom at the time of diagnosis. In the endometrioid/ endometrioid group, the number of women presented with abnormal uterine bleeding was lower, while the presentation with pelvic mass was higher than those who-had other histological subtypes. Therefore, it is not surprising that most of women in the endometrioid/endometrioid group (70.4%) had preoperative diagnosis of ovarian tumor and the underlying endometrial carcinoma could be diagnosed preoperatively in only one third of the cases.

In the present study, 37.2% of women had ovarian tumor of at least 10 cm in largest diameter which was slightly lower than those reported of 40-50% (Zaino et al., 2001, Soliman et al., 2004). In addition, we also demonstrated that there was no significant difference in size of ovarian tumor between women in the endometrioid/endometrioid group and those who had other histological subtypes (P=0.433). According to the WHO histological grading, only 16.3% of women in the present study had poorly differentiated carcinoma which was consistent with the previous reported prevalence ranging from 11-23% (Zaino et al., 2001, Soliman et al., 2004). Interestingly, we also demonstrated that the proportion of poorly differentiated ovarian carcinoma was significant lower in women in the endometrioid/ endometrioid group (P=0.014). Histological grading is well recognized as predictor for tumor characteristics in which aggressiveness increase with grading. Therefore, it is not surprising that women in the endometrioid/endometrioid group in our series had lower incidence of advanced stage ovarian carcinoma (P=0.006).

In an analysis of characteristics of endometrial carcinoma in women who had synchronous primary carcinomas of the endometrium and ovary, the prevalence of poorly differentiated tumor ranged from 7-12% and lymphovascular space invasion was noted in 5-30% of women (Zaino et al., 2001, Soliman et al., 2004). In the present study, only 14% and 23% of women had poorly differentiated endometrial carcinoma and lymphovascular space invasion, respectively, which were consistent with the results of the aforementioned reports. In addition, the present study could not demonstrate any difference in the distribution of histological grading and lymphovascular space invasion among women in the endometrioid/endometrioid group and those who had other histological subtypes(P=0.634 and P=0.089, respectively). Concerning the stage of endometrial carcinoma, almost all women in the present study (95.3%) were in early stage (stage I and stage II) which was similar to the report from M.D. Anderson Cancer Center which noted that 92% of women with synchronous primary carcinomas of the endometrium and ovary were in early stage of endometrial carcinoma (Zaino et al., 2001, Soliman et al., 2004). Moreover, no difference could be identified in the distribution of FIGO stage in women who had endometrioid/ endometrioid histological subtypes and those who had other histological subtypes (P=0.139).

The overall survival of women with synchronous primary carcinomas of the endometrium and ovary was excellent. Zaino et al (2001) reported 5-year and 10-year survivals of 86% and 80%, respectively. In addition, Soliman et al (2004) noted that women with concordant endometrioid histology had significantly better survival than those who had other histological subtypes (median survival 119 versus 48 months, P=0.02). The overall 5-year survival of patients in our study was 82%. However, our study failed to demonstrated the better survival outcomes between women who had endometrioid/endometrioid histology and those who had other histological subtypes (P=0.674). The ability to demonstrate difference in survival probability based on histological subtypes in the present study might have been limited by the small sample size.

This study was hampered by a number of limitations including small sample size and a retrospective study design which may have potential limitations of some relevant data collection, i.e. tumor size and histological grading in some cases. However, to the best of our knowledge, this study is the largest series of clinicopathologic analysis in a solely Asian population. The characteristics and treatment outcomes of women in the present study are quite similar to those reported in North American population. In conclusion, synchronous primary carcinomas of the endometrium and ovary, although uncommon, should be considered in differential diagnosis in premenopausal women presenting with abnormal uterine bleeding and ovarian tumor. The prognosis of patients with these tumors appears excellent.

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