RESEARCH COMMUNICATION

Clinicopathologic Variables and Survival Comparison of Patients with Synchronous Endometrial and Ovarian Cancers versus Primary Endometrial Cancer with Ovarian Metastasis

Shina Oranratanaphan, Tarinee Manchana*, Nakarin Sirisabya

Abstract

Objectives: To determine the clinicopathologic variables and survival in the patients with synchronous endometrial and ovarian cancer (synchronous group) compared to the patients with primary endometrial cancer with ovarian metastasis (metastatic group). Methods: The medical records of 423 endometrial cancer patients who received primary surgery were reviewed. Fourteen patients were diagnosed as synchronous group while 49 patients were diagnosed as metastatic group. Results: The median age in synchronous group was significantly younger than metastatic group (47 versus 56 years). More nulliparous and premenopausal patients were demonstrated in synchronous group. Synchronous group had significantly higher incidence of low grade tumor and lower incidence of deep myometrial invasion. All patients in synchronous group presented in stage I endometrial cancer. Moreover, most patients (85.7%) presented in early stage ovarian cancer and only 14.3% in advanced stage ovarian cancer. Synchronous group had better disease free survival (DFS) and overall survival (OS) than metastatic group. Estimated 5 years DFS was 64.2% versus 41.5%, (P = 0.17) and 5 years OS was 92.8% versus 48.5% (P = 0.036). Conclusion: The patients in synchronous group were younger, more nulliparous and better prognosis than the patients in metastatic group.

Key Words: Clinicopathologic variables - endometrial cancer - synchronous cancers

Asian Pacific J Cancer Prev, **9**, 403-408

Introduction

Synchronous endometrial and ovarian cancer is uncommon event with the incidence ranging from 2-8.5 % (Castro et al., 2000). Presently, there was no consensus about the definite diagnostic criteria. Most authors usually diagnosed this tumor by pathologic criteria which were proposed by Ulbright and Roth (1985) or Scully et al. (1998). There is no doubt if it had different histology. In contrast, if it had the similar histology, it should be differentiated into 3 categories; 1) synchronous endometrial and ovarian cancer, 2) primary endometrial cancer with ovarian metastasis and 3) primary ovarian cancer with endometrial metastasis. The definite diagnosis is important for determining the exact stage and proper management which would affect the prognosis.

Previous studies reported the characteristics in the patients with synchronous endometrial and ovarian cancer occurred typically in young, premenopause, nulliparous and obese. In addition, they usually presented in early stage with low grade histology which influenced excellent prognosis (Sheu et al., 1995; Zaino et al., 2001; Soliman et al., 2004). Generally, it was accepted that the prognosis in these patients is more favorable than stage IIIA endometrial cancer or stage IIA ovarian cancer. The purpose of the present retrospective study was to determine clinicopathologic variables and survival in the patients with synchronous endometrial and ovarian cancer compared to the patients with primary endometrial cancer with ovarian metastasis.

Materials and Methods

The medical records of 423 patients with endometrial cancer who received primary surgical treatment at King Chulalongkorn Memorial Hospital during 1996-2005 were reviewed. Surgical interventions included total abdominal hysterectomy with bilateral salpingo-oophorectomy with or without surgical staging such as peritoneal cytology, omental biopsy, pelvic and/or paraaortic lymphadenectomy. Fourteen patients were diagnosed as synchronous endometrial and ovarian cancer (synchronous group) using pathologic criteria by Scully et al. (Table 1-3), while 49 patients were diagnosed as primary endometrial cancer with ovarian metastasis (metastatic group). All pathologic results of synchronous group were reviewed by gynecologic pathologists. Patient's characteristics such as age at diagnosis, parity,

Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand
**For correspondence: T_manchana@hotmail.com*

menopausal status, family history of cancer, body mass index (BMI) and presenting symptoms were recorded. Pathologic variables such as histology, grade, myometrial invasion, lymphovascular invasion (LVSI), lymph node involvement and extrapelvic metastasis were obtained from pathologic reports. The histological grade was classified according to WHO criteria and Eifel's classification (Eifel et al., 1982). It was graded as: grade 1 (well differentiated), grade 2 (moderately differentiated), and grade 3 (poorly differentiated including clear cell carcinoma). Surgical staging was classified according to the FIGO staging system (International Federation of Gynecology and Obstetrics, 1989).

Clinicopathologic variables as categorical data were analyzed by Chi-square or Fisher exact test and continuous data by Student t-test. Kaplan- Meier method was used to generate the survival curve and compared using log lank test. A probability value of less than 0.05 was defined as statistically significant.

Results

Patient's characteristics were demonstrated in Table 4. The median age at diagnosis in synchronous group was significantly younger than metastatic group (47 versus 56 years, $P < 0.05$). More nulliparous and premenopausal patients were also demonstrated in synchronous group (92.9% versus 34.7% and 92.9% versus 34.7%, $P < 0.05$). The incidence of obesity which was defined as BMI more than 30 kg/m2 was lower in synchronous group than metastatic group without significant difference (0% and 22.4%, P =0.22) None of these patients had family history of cancer such as colorectal cancer, gynecologic cancer and breast cancer. The most common presenting symptom in synchronous group was abnormal uterine bleeding (8 in 14 patients; 57.1%). The other symptoms were pelvic mass with pelvic pain or abdominal distension in 6/14 patients (42.9%).

Primary surgical treatment included total abdominal hysterectomy with bilateral salpingo-oophorectomy. Surgical staging such as peritoneal cytology, omental biopsy and pelvic with or without paraaortic lymphadenectomy was performed in 10/14 patients (71.4%) in synchronous group and 34/49 patients (69.4%) in metastatic group. Pathologic variables were shown in Table 5. For the details of endometrial cancer component, all patients in synchronous group had endometrioid cell type and low grade histology; grade 1 (92.9%) and grade 2 (7.1%). According to FIGO surgical staging, all patients presented in stage I; IA (57.1%), IB (42.9%). No patient in synchronous group had deep myometrial invasion (myometrial invasion more than 50%), while metastatic group had significantly higher incidence of deep myometrial invasion (0% versus 69.4%, $P < 0.05$). Extrauterine metastasis such as lymph node metastasis, omental metastasis and positive peritoneal cytology was found only in metastatic group.

The pathologic variables of ovarian cancer component in synchronous group, 12 patients (85.7%) had concordant endometrioid adenocarcinoma and 2 patients (14.3%) had disconcordant histology (1 patient with mixed clear cell and endometrioid adenocarcinoma and 1 patient with mucinous adenocarcinoma). Nine patients (64.3%) presented in stage I, 3 patients (21.4%) in stage II, 1 patient (7.1%) in stage III and 1 patient (7.1%) in stage IV.

All patients in synchronous group received adjuvant treatment with platinum based chemotherapy; single agent

Table 1. Pathologic Criteria for Primary Endometrial Cancer with Ovarian Metastasis

1. Histologic similarity of the tumors
2. Large endometrial tumor - small ovarian tumor(s)
3. Atypical endometrial hyperplasia additionally present
4. Deep myometrial invasion
a. Direct extension into the adnexa
b. Vascular space invasion in myometrium
5. Spread elsewhere in typical pattern of endometrial carcinoma
6. Ovarian tumor bilateral and/or multinodular
7. Hilar location, vascular space invasion, surface implants, or combination in ovary
8. Ovarian endometriosis absent
9. Aneuploidy with similar DNA indices or diploidy of both tumors*
10. Similar molecular genetic or karyotypic abnormalities in both tumors

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

Table 2. Pathologic Criteria for Primary Ovarian cancer with endometrial metastasis

1. Histologic similarity of the tumors
2. Large ovarian tumor– small endometrial tumor
3. Ovarian endometriosis present
4. Location in ovarian parenchyma
5. Direct extension from ovary predominantly into outer wall of uterus
6. Spread elsewhere in typical pattern of ovarian carcinoma
7. Ovarian tumor unilateral (80–90% of cases) and forming single mass
8. No atypical hyperplasia in endometrium
9. Aneuploidy with similar DNA indices or diploidy of both tumors*
10. Similar molecular genetic or karyotypic abnormalities in both tumors

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

Table 3. Synchronous Primary Endometrial Cancer and Primary Ovarian Cancer

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 findings

Table 4. Patient Characteristics in the Synchronous and Metastatic Groups

Factor	Synchronous (n = 14)	Metastatic (n = 49)	p value
Median age (range)	47 (29-58)	56 (34-77)	0.001
Age – n (%)			
Less than 40 years	3 (21.4)	4 (8.1)	0.005
41-50 years	10 (71.4)	13 (26.5)	
51-60 years	1 (7.1)	16 (32.7)	
More than 60 years	0 (0.0)	16 (32.7)	
Median BMI*	22.5 (19-30)	24.7 (17-37)	0.12
BMI – n (%)			
Less than 30 kg/m^2	14 (100)	38 (77.6)	0.22
More than 30 kg/m^2	0 (0.0)	11 (22.4)	
Parity – n (%)			
Nulliparous	13 (92.9)	17 (34.7)	0.001
Multiparous	1 (7.1)	32 (65.3)	
Menopausal status – n (%)			
Premenopausal	13 (92.9)	17 (34.7)	0.001
Postmenopausal	1 (7.1)	32 (65.3)	

* kg/m2 (range)

Table 5. Pathologic Variables in the Synchronous and Metastatic Groups

Variable	Synchronous	Metastatic	p value
Histology – n (%)			
Endometrioid	14 (100)	47 (95.9)	0.62
Non-endometrioid	0 (71.4)	2 (4.1)	
Grade – n (%)			
1	13 (92.9)	30 (61.2)	0.07
2	1 (7.1)	9 (18.4)	
3	0 (0.0)	19 (20.4)	
Myometrial invasion – n (%)			
None	8 (57.1)	3 (6.1)	0.001
< 50%	6 (42.9)	12 (24.5)	
> 50%	0 (0.0)	34 (69.4)	
LVSI – n (%)	0 (0.0)	10 (20.4)	0.07
Metastasis – n (%)			
Pelvic node	0/10 (0)	8/34 (23.5)	0.17
Paraaortic node	0/5 (0)	3/21 (14.3)	1.00
Omental	0 (0)	9 (18.4)	0.19
Positive peritoneal cytology – n (%)			
	0 (0)	3 (6.1)	0.62

carboplatin (78.6%), single agent cisplatin (7.1%) and combination carboplatin and paclitaxel (14.3%). No patient was given adjuvant radiotherapy. In contrast to the metastatic group, they received various adjuvant treatments; adjuvant radiotherapy (30.6%), adjuvant chemotherapy (40.8%), hormonal treatment (24.5%), combined chemotherapy and radiotherapy (2.0%) and no adjuvant treatment (2.0%). Median time to follow up was 45 months (range 3-113 months). Five patients (35.7%) in synchronous group and 24 patients (49.0%) in metastatic group had recurrent disease. Cancer related death was occurred in 3 patients (21.4%) in synchronous group and 24 patients (49.0%) in metastatic group. Synchronous group had higher disease free survival (DFS) and overall survival (OS) than metastatic group. Mean DFS in synchronous group was 81 months and metastatic group was 68 months, while mean OS was 99 months and 73 months, respectively. Estimated 5 years DFS in synchronous group was 64.2% versus 41.5% in metastatic

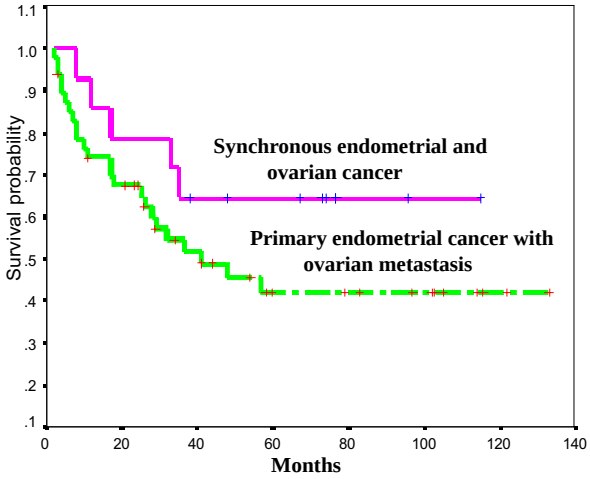

Figure 1. Disease Free Survival Analysis of the Synchronous and Metastatic Groups

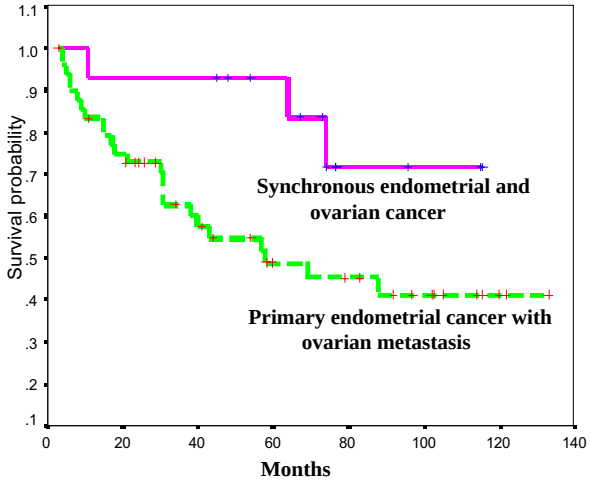

Figure 2. Overall Survival Analysis of the Synchronous and Metastatic Groups

group (P = 0.18) and estimated 5 years OS was 92.8% versus 48.5%, respectively (P = 0.04) (Figures 1, 2).

Discussion

Synchronous endometrial and ovarian cancer is an uncommon event; the incidence in this study was about 3.3% (14 in 423 patients) which was comparable to the previous study (Chiang et al., 2008). Presently, there is no consensus about the most accurate method for diagnosis. If the tumors had dissimilar histology, it can diagnose definitely as synchronous primary cancers. But if the tumors had similar histology, it should be differentiated with primary endometrial cancer with ovarian metastasis and primary ovarian cancer with endometrial metastasis. Several molecular studies such as DNA flow cytometry, loss of heterozygosity on chromosome, X-chromosome inactivation, mutation in PTEN/MMAC1, p53 or K-ras genes, alteration in beta-catenin pathway and microsatellite instability (Fujita et al., 1996; Lin et al., 1998; Fujii et al., 2002; Irving et al., 2005) were proposed aiming to differentiate synchronous cancer with similar histology from metastatic disease. Due to limitation in the number of the patients, molecular studies could not be recommended as worldwide use. In

the moment that the best molecular method is unavailable, pathologic criteria has still been used for diagnosis the synchronous primary cancers.

Synchronous endometrial and ovarian cancer typically occurred in young, nulliparous, premenopause and obesity (Eifel et al., 1982; Sheu et al., 1995; Zaino et al., 2001; Soliman et al., 2004;). In contrast, the patients with metastatic disease were predominantly old and postmenopause. The results from this study were also comparable to the previous studies except the incidence of obesity was not different between both groups. The ethnic difference might be an explanation. The median age of endometrial cancer patients from our previous study was 55 years, while the median age of ovarian cancer patients was 51 years (Worasethsin et al., 2000; Manipalviratn et al., 2002). The median age of synchronous primary cancer patients in this study was 47 years which was younger than primary endometrial cancer and primary ovarian cancer patients. This result was similar to the study of Chiang et al. (Chiang et al., 2008). However, it was slightly younger than the results from the large trial of Soliman et al. and GOG that reported the median age was about 50 years (Zaino et al, 2001; Soliman et al., 2004). Previous studies reported the incidence of synchronous cancer in young patients about 7-29% depended on the definition of young patients ranging from less than 40 years to less than 50 years (Soliman et al., 2005). In this study, we defined young patients as less than 40 years; therefore the incidence was 21.4% which was significantly higher than the patients with primary endometrial cancer with ovarian metastasis (8.2%). In young patients who present with multiple sites of primary cancers, genetic predisposition should be considered. The two most common hereditary cancers which include gynecologic cancer are hereditary non-polyposis colorectal cancer (HNPCC) and hereditary breast ovarian cancer syndrome (HBOC). However, no patient had family history of cancer in this study. Furthermore, Soliman et al. reported that only 1 in 84 patients met criteria for HNPCC and 1 patient had family history of HBOC, they concluded that it was unlikely that the patients with synchronous primary cancers had hereditary cancer syndrome (Soliman et al., 2004).

The most common presentation in synchronous endometrial and ovarian cancer patients was abnormal uterine bleeding which bring to earlier diagnosis if compared to the patients with primary ovarian cancer. As this result, they usually presented in early stage. All patients in this study presented in stage I endometrial cancer (92.9%), while 64.3% of patients presented in stage I ovarian cancer, 21.4% in stage II and 14.2% in advanced stage (III-IV). In contrast, primary ovarian cancer is usually diagnosed in advanced stage due to asymptomatic or unspecific symptoms. The earlier detection of ovarian cancer in synchronous primary cancers might be due to abnormal uterine bleeding from concomitant endometrial cancer.

The prognosis of the patients with synchronous primary cancers was more favorable than stage IIA ovarian cancer and stage IIIA endometrial cancer. Pearl et al. reported 3 years OS was 100%, 63% and 42%, respectively (Pearl et al., 1993). In this study, mean OS in synchronous group was 99 months and metastastic group was 73 months which was comparable to the previous study (98 months and 59 months, respectively) (Ayhan et al., 2003). Estimated 5 years DFS and OS in synchronous group were 64.2% and 92.8% but in metastatic group were 41.5% and 48.5%, respectively. GOG study also reported an excellent 5 years OS (85.9%) and 10 years OS (80.3%) which was slightly lower than this study (Zaino et al., 2001). Younger patients with more patients presented in early stage and low grade tumor might be a possible explanation.

Early stage of ovarian cancer, low grade tumor in endometrial and ovarian cancer was reported as the most significant prognostic factors. However, histological cell type as a significant prognostic factor was controversy. Eifel et al. reported that non-endometrioid adenocarcinoma in ovary or uterus had worse prognosis than endometrioid adenocarcinoma (Eifel et al., 1982). Soliman et al. also reported that concordant endometrioid adenocarcinoma had more favorable prognosis (Soliman et al., 2004). However, most studies concluded that histology had less significant influence on the prognosis than the stage (Zaino et al., 2001; Chiang et al., 2008). Almost of all patients in this study had early stage of ovarian cancer (85.7%), low grade endometrial tumor (92.9%), and concordant endometrioid histology (85.7%). Due to limited number of the patients, survival analysis according to these various prognostic factors could not be evaluated.

The primary surgery is the mainstay treatment in synchronous primary cancers. However, the adjuvant treatment is still controversy and usually depends on the stage and risk factors according to the pathologic results of the individual primary cancer. Sheu et al. reported surgical treatment with or without adjuvant therapy had favorable outcome (Sheu et al., 1995). Pearl et al. suggested that adjuvant therapy may not necessary in synchronous primary cancers with grade 1 and concordant endometrioid histology (Pearl et al., 1993). No statistically significant difference on overall survival in synchronous primary cancer patients with or without adjuvant chemotherapy or radiotherapy was reported by Chiang et al. (Chiang et al., 2008). However, subgroup analysis in the patients with advanced stage of ovarian cancer suggested that adjuvant therapy should be given to improve survival (Ayhan et al., 2003). All patients in this study received adjuvant chemotherapy due to the risk factors of ovarian cancer such as advanced stage, high grade tumor or incomplete surgical staging. Therefore, we could not evaluate the prognostic significance of adjuvant treatment.

The exact etiology of synchronous primary cancers is unknown. Several investigators proposed various hypotheses. The patients with synchronous primary cancers were typical young, obese, nulliparous and premenopause. Hormonal “field effect” may be an important factor for development of synchronous primary cancers (Soliman et al., 2004). Another hypothesis was “secondary Müllerian system” that genital organs had shared molecular receptors responding to carcinogen

leading to the development of multiple primary cancers (Eifel et al., 1982). However, further studies should be evaluated to identify the exact etiology.

In conclusion, synchronous endometrial and ovarian cancer was commonly occurred in young, nulliparous and premenopausal patients. Abnormal uterine bleeding is the most common presentation influenced the early detection and treatment. It usually presented in early stage and low grade with favorable prognosis. When compared to primary endometrial cancer with ovarian metastasis, it had better disease free survival and overall survival.

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