RESEARCH ARTICLE

Incidence and Clinical Outcomes of Non-endometrioid Carcinoma of Endometrium: Siriraj Hospital Experience

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Abstract

Background: To study the incidence of non-endometrioid carcinoma of endometrium and compare the clinical characteristics and treatment outcomes with endometrioid carcinoma patients. Materials and Methods: This study included 236 patients with endometrial carcinoma at Siriraj Hospital whom were diagnosed and treated from 2003 through 2006. The clinical characteristics, pathological features, treatment and clinical outcomes were collected from the medical records. The 5-year survival was calculated according to 2009 FIGO staging. Results: Non-endometrioid carcinoma of endometrium accounted for 10.2% of all endometrial carcinomas (24/236 patients). The 5 -year survival rate was significantly lower in the non-endometrioid group compared to the endometrioid group (77.3% *vs* 96%, p<0.001) and clinical data pointed to greater malignancy. Conclusions: Non-endometrioid carcinoma of endometrium is relative rare but is more aggressive, has more distant metastasis at diagnosis with a worse survival rate than endometrioid carcinoma. Only patients in stage IA with no residual disease on a hysterectomy specimen may not need adjuvant treatment.

Keywords: Endometrial carcinoma - non-endometrioid - survival outcome - distant metastasis

Asian Pac J Cancer Prev, **15 (6)**, 2905-2909

Introduction

Endometrial cancer is the most common malignancy in the female genital system in the developed countries including the United States(Ferlay et al., 2008). In Thailand, endometrial cancer is the second most common gynecologic cancer after the cervical cancer. In 2004-6, its incidence was 3.6/100000 of Thai female population(Khunhaprema et al., 2012). Endometrial cancer has a good prognosis because most of patients are diagnosed in the early stage of disease. The 5-year overall survival rate after treatments is 83-87% (Siegel et al., 2013). The most common histologic subtype is endometrioid carcinoma, which occults 87.4% of the endometrial cancer, followed by papillary serous carcinoma (2.9%), clear cell carcinoma (2.2%), mucinous carcinoma (0.6%), squamous cell carcinoma (0.2%) and others (6.7%). Non-endometrioid endometrial carcinoma has lower incidence but poorer prognosis than the endometrioid endometrial carcinoma when compared in each stage. Papillary-serous cell type, one of non-endometrioid group, had only 53% in 5-year survival rate, compared to 83% in the endometrioid group (Creasman et al., 2006; Hamilton et al., 2006).

The objective of this study is to evaluate the incidence and clinical outcomes of non-endometrioid endometrial carcinoma in Siriraj Hospital and to compare these with the incidence and clinical outcomes of the endometrioid endometrial carcinoma.

Materials and Methods

The medical records of all endometrial carcinoma patients treated at Siriraj Hospital between January 2003 and December 2006 were reviewed retrospectively under an Institutional Review Board approved protocol. This study included all 265 patients who had a pathologically confirmed diagnosis of primary endometrial carcinoma. The patients who did not undergo surgery (5 patients), received preoperative radiation therapy (6 patients), were denied adjuvant treatment (6 patients), or did not complete adjuvant treatment (5 patients) were excluded. Therefore, 236 patients remained for analysis. The patients' clinical characteristics, treatments and clinical outcomes were analyzed by stratifying the patients into 2 groups: non-endometrioid and endometrioid.

Statistical methods

The clinical outcome will be reported as 5-year overall survival (OS) and 5-year disease free survival (DFS). The details of each non-endometrioid patient were analyzed. Fisher's exact test and Chi square were used for statistical analysis of categorical data. Student t-test and Mann-Whitney U test were used for continuous data. The

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survival curves were calculated according to the Kaplan-Meier method with the log-rank test. PASW statistics 18 was used for statistical analysis. p value less than 0.05 was considered to be of statistical significance.

Results

The incidence of non-endometrioid endometrial carcinoma was 10.2% (24 patients), of the endometrial carcinoma patients. The pathological subtypes of non-endometrioid carcinoma were clear cell carcinoma (5.5%, 13 patients, 8/13 patients mixed with endometrioid carcinoma), papillary-serous carcinoma (3%, 7 patients, 4/7 patients mixed with endometrioid carcinoma), undifferentiated carcinoma (1.3%, 3 patients) and mucinous carcinoma (0.4%, 1 patient, mixed with endometrioid carcinoma). The clinical characteristics were shown in Table 1. Most of patients in both groups were in post-menopausal status. The mean age of the patients and mean body mass index were not different between the two groups. Most of the patients were multiparous. We found less abnormal uterine bleeding in the non-endometrioid group. However, the presenting symptom with abdominal/pelvic mass was more common in the non-endometrioid group (25.0% *vs* 7.1%, p=0.01). The majority of patients in both groups were in stage I (FIGO, 2009). All patients underwent surgical staging. Adjuvant treatments consisted of radiation therapy, chemotherapy and/or hormonal therapy. The adjuvant treatments were given based on operative findings, histologic features, stages of disease and underlying conditions of each patient.

The clinical outcomes were shown in Table 2. Median follow up times were similar in both groups (60.5 months *vs* 64.5 months, p=0.197). The 5-year OS in the non-

Table 1. Clinical Characteristics

	Non-endometrioid (n=24)	Endometrioid (n=212)	p-value
Mean age±SD (years)	57.0±10.1	56.6±11.8	0.86
Menopausal status			0.75
Premenopause	6 (25.0%)	60 (28.3%)	
Postmenopause	18 (75.0%)	152 (71.7%)	
Mean BMI±SD (kg/m^2)	25.1±4.9	26.5±5.4	0.23
Parity			0.37
Nulliparity	5 (20.8%)	63 (29.7%)	
Multiparity	19 (79.2%)	149 (70.3%)	
Presenting symptoms			
Bleeding	16 (66.7%)	199 (93.9%)	<0.001
Mass	6 (25.0%)	15 (7.1%)	0.01
Others*	5 (20.8 %)	19 (8.9%)	0.08
Stage (FIGO 2009)			0.106
Stage I	17 (70.8%)	156 (73.6%)	
Stage II	1 (4.2%)	10 (4.7%)	
Stage III	3 (12.5%)	40 (18.9%)	
Stage IV	3 (12.5%)	6 (2.8%)	
Received adjuvant treatment	19/24 (79.2%)	127/210 (59.9%)	0.066

*Others; abdominal or pelvic pain, abnormal Pap smear, leukorrhea

Table 2. Clinical Outcomes and Survival Rate

	Non-endometrioid (n=24)	Endometrioid (n=212)	p-value
Median follow up time in months (range)	60.5 (2-101)	64.5 (0.2-99)	0.197*
5-year overall survival rate	77.30%	96.00%	<0.001†
5-year disease free survival	75.60%	81.70%	0.623†
-Local recurrence free survival	80.40%	91.30%	0.150†
-Distant recurrence free survival	79.80%	88.00%	0.368†

*Mann-Whitney U test, † Log-rank test

Table 3. Details of Non-endometrioid Endometrial Carcinoma Patients

No	Age	Operation (TAH BSO and)	Pathology	Stage	MI	Adjuvant Rx	F/U time (months)	Course of disease
1	67	Omy	CC	I A	-	WPRT	59	Alive well
2	73	PLND	CC	I A	<50%	WPRT, VB, CMT	34	Recur at PLN, bone, dead
3	58	PLND Omy	CC	I B	>50%	CMT	64	Alive well
4	63	PLND Omy	CC	I B	>50%	WPRT, VB	86	Alive well
5	41	Omy	CC	IV B	>50%	CMT	2	Progression of disease, dead
6	71	PLND Omy	E+CC	I A†	-	CMT	66	Alive well
7	73	PLND PAND	E+CC	I A†	-	-	65	Alive well
8	57	PLND	E+CC	I A†	-	-	101	Alive well
9	45	PLND PAND Omy	E+CC	I A	<50%	WPRT, VB	9	Loss F/U
10	56	PLND Omy	E+CC	I A	<50%	WPRT, VB	65	Alive well
11	52	PLND PAND Omy	E+CC	I B	>50%	CMT	58	Alive well
12	59	*PLND	E+CC	II	-	-	62	Alive well
13	71	PLND Omy	E+CC	III A	<50%	WPRT, VB	69	Alive well
14	65	PLND PAND Omy	UPSC	I A	-	WPRT	40	Loss F/U
15	39	PLND	UPSC	I B	>50%	WPRT, VB, CMT	68	Alive well
16	55	Omy	UPSC	III A	<50%	CMT	95	Alive well
17	67	PLND PAND Omy	E+UPSC	I A	<50%	WPRT, VB	22	Loss F/U
18	72	PLND	E+UPSC	I B	>50%	CMT	49	Recur at pelvis, liver, alive
19	69	PLND PAND Omy	E+UPSC	IV B	>50%	CMT	32	Recur at vagina, alive
20	42	Omy	E+UPSC	IV B	>50%	-	2	Progression of disease, dead
21	58	PLND PAND Omy	E+M	III A	>50%	CMT	43	Recur at liver, dead
22	70	-	Undiff	I A	<50%	-	30	Alive well
23	40	Omy	Undiff	I B	>50%	CMT	65	Alive well
24	47	-	Undiff	I B	>50%	WPRT, VB	16	Recur at vagina, peritoneum, dead

*Radical hysterectomy, TH=total hysterectomy; †No residual disease in hysterectomy specimen, BSO=bilateral salpingo-oophorectomy, Omy=omentectomy, PLND=pelvic lymph node dissection, PAND=para-aortic lymph node dissection, CC=clear cell carcinoma, E=endometrioid carcinoma, UPSC=uterine papillary serous carcinoma, Undiff=undifferentiated adenocarcinoma, M=mucinous carcinoma, MI=myometrial invasion, WPRT=whole pelvic radiation, VB=vaginal brachytherapy, CMT=chemotherapy, F/U=follow up

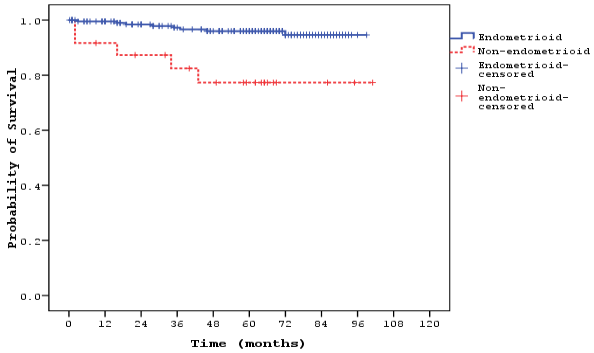

Figure 1. Overall Survival of Endometrioid and Non-Endometrioid Groups

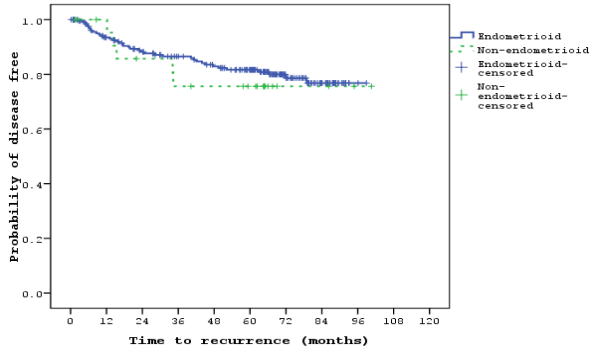

Figure 2. Disease free Survival of Endometrioid and Non-endometrioid Groups

endometrioid group was 77.3%, compared to 96% in the endometrioid group (p<0.001). The 5-year DFS rate in non-endometrioid group was 75.6%, compared to 81.7% in the endometrioid group, but not statistical significance (p=0.623). There were trends to have more distant metastases and local recurrences in the non-endometrioid group. The overall survival and disease free survival curves were shown in Figure 1 and 2.

The details of 24 patients with non-endometrioid endometrial carcinoma were shown in Table 3. Each case had different surgical approaches based on their ages, performance status and disease extent. All patients received adjuvant treatment, except for 5 patients with the following reasons. Two patients had no residual tumor on hysterectomy specimens; one stage IVB patient had disease progression and died within 2 months after the operation; one stage II patient underwent radical hysterectomy and pelvic lymphadenectomy, one stage IA patient had less than half of myometrial invasion. The latter 2 patients were alive without disease recurrence at 30 and 62 months. The local recurrence, distant metastatic and both local and distant metastatic rates were 4.2% (1 patient), 4.2% (1 patient) and 12.5% (3 patients), respectively.

Discussion

The incidence of non-endometrioid endometrial carcinoma at our institute was 10.2%, which was comparable with the previous studies (Wilson et al., 1990; Creasman et al., 2006; Kim et al., 2013). This showed its rarity and it requires more studies to explore the patients' characteristics and clinical outcomes. Wilson et al. showed that non-endometrioid carcinoma (clear cell and papillary serous carcinomas) was commonly found in the elderly (65-70 year-old), non-obese and multiparous patients (Wilson et al., 1990). In contrast, a report from the Norwegian study showed no difference in age at diagnosis (mean age 65 years in both endometrioid and non-endometrioid groups). An increased risk of both non-endometrioid and endometrioid carcinomas was associated with obesity, but was more pronounced for endometrioid carcinoma patients (Bjorge et al., 2007). Our study didn't demonstrate any significant difference in clinical characteristics of the patients (mean age, menopausal status, mean body mass index and parity) between both groups. From our study, we found that non-endometrioid patients presented with less abnormal uterine bleeding than the endometrioid group. However, the non-endometrioid patients presented with abdominal/pelvic mass in a higher proportion when compared to the endometrioid patients. Even though most of the patients in both groups were in stage I, the non-endometrioid patients developed more distant metastasis than the endometrioid patients. This may be explained by more extensive disease at presentation with abdominal/pelvic mass in the non-endometrioid group rather than with early presentation with abnormal uterine bleeding as in the endometrioid group. Non-endometrioid cancers are associated with lower Hb levels and worse prognosis (Wilairat and Benjapibal, 2012).

Siegel et al. (2013) reported the 5-year OS rate in all types of endometrial carcinoma patients at 83-87% (Siegel et al., 2013). Wilson et al. (1990) reported the 5-year OS rate of non-endometrioid endometrial carcinoma of only 33%, compared with 92% in endometrioid carcinoma (Wilson et al., 1990). From our study, the 5-year OS rate in non-endometrioid group was significantly less than in endometrioid group, but it was not as much difference as in the previous studies. This may be from small number of patients in the non-endometrioid group which did not empower us to detect the survival differences. The disease free survival was also poor in non-endometrioid group for both local and distant recurrences. Kim et al. (2013) also reported the 3-year OS rate of 81.6% in stage I non-endometrioid carcinoma, which was worse than 92.2% in grade 3 endometrioid carcinoma.

From the details of 24 non-endometrioid patients, there were varieties of surgical procedure and adjuvant treatments based upon age and disease extent of each patient. Most of the non-endometrioid patients underwent simple hysterectomy, bilateral salpingo-oophorectomy and omentectomy, given the high risk of extrauterine disease (37-63%) (Gehrig et al., 2003; Slomovitz et al., 2003). Pelvic lymph node dissection did not provide survival benefits (Benedetti Panici et al., 2008; Kitchener et al., 2009). Our study was underpowered to detect any benefits of pelvic/para-aortic lymph node dissection. We observed that 2 patients, who received pelvic lymph node dissection with negative pathology, subsequently developed pelvic recurrences. Nevertheless, Chan et al. (2006) reported the therapeutic benefit of lymphadenectomy in women with high grade endometrial

cancer, including non-endometrioid patients. Todo et al. also reported the therapeutic benefit of pelvic and para-aortic lymphadenectomy over pelvic lymphadenectomy alone in 671 endometrial carcinoma patients (Todo et al., 2010). The Society of Gynecologic Oncology (SGO)'s recommendations regarding initial management of uterine papillary serous cancer and clear cell endometrial cancer are surgical exploration and comprehensive staging, including hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy (Boruta et al., 2009; Olawaiye and Boruta, 2009). Omentectomy is also recommended in clear cell endometrial cancer(Olawaiye and Boruta, 2009) and considered in uterine papillary serous cancer, although the necessity of omentectomy is still controversial (Boruta et al., 2009). Gehrig et al. recommended omentectomy only in patients who had extrauterine disease or gross omental metastases (Gehrig et al., 2003).

When we compare among each histologic subtype of non-endometrioid carcinoma, clear cell carcinoma appeared to be less aggressive. Most clear cell carcinoma patients (10/13 patients; 77%) were in stage I. There was only 1 stage I clear cell carcinoma patient who developed recurrence at 34 months. The other 2 clear cell carcinoma patients were in stage II and IIIA and had no disease recurrence at 62 and 69 months. Only 1 patient with clear cell carcinoma had stage IVB disease and died within 2 months during chemotherapy courses. For 7 patients with papillary serous subtypes, 4 patients (57%) were in early stage (stage I). The other 3 patients were in advanced stage (IIIA and IVB) and 2 patients died with disease progression. In our study, the 5-year DFS and OS in clear cell carcinoma are better than in uterine papillary serous carcinoma (83.9% *vs* 42.1%, p=0.396 and 83.9% *vs* 65.5%, p=0.077). Previous studies also reported the better survival in uterine clear cell carcinoma compared to papillary serous carcinoma patients (5 year OS 63-68% *vs* 53-55%) (Creasman et al., 2006; Hamilton et al., 2006).

Myometrial invasion is a relevant prognostic factor, and 4 out of 5 deaths in our study had more than 50% of myometrial invasion. Fader et al. reported higher recurrent rates in patients with myometrial invasion compared to non-myometrial invasion patients (29-80% *vs* 0-30%, respectively) (Fader et al., 2010). In general, myometrial invasion is used to determine adjuvant treatment based on its' poorer prognosis. A residual disease on hysterectomy specimens is also a prognostic factor and determines adjuvant treatments. Kelly et al reported no recurrence in 12 patients with stage IA disease (FIGO, 1988) who had no residual disease on hysterectomy specimens, regardless of adjuvant therapy. However, none of 7 stage IA patients with residual disease who received adjuvant platinum-based chemotherapy developed recurrent disease. Nevertheless, 6 of 14 (43%) stage IA patients with residual disease who did not receive adjuvant chemotherapy developed disease recurrences. In stage IB, there was no recurrence in 15 patients who received platinum-based chemotherapy. However, 10 of 13 patients (77%) who did not receive adjuvant chemotherapy had recurrence. Patients with stage IC (more than 50% myometrial invasion) had worse outcomes with 1 of 7 stage IC patients recurred; even she received adjuvant platinum-based chemotherapy. Also, 4 of 5 stage IC patients also recurred regardless of adjuvant chemotherapy (Kelly et al., 2005). However, Chang-Halpenny et al. published the different results on non-endometrioid endometrial carcinoma. They reported disease progression in 4 of 51 patients. Three of the patient who progressed had not received adjuvant treatment, as two patients had disease confined only to polyp and an additional patient had no residual disease on hysterectomy (Chang-Halpenny et al., 2013).

In our study, there were 3 patients without residual disease on hysterectomy specimens; none of them had recurrence regardless of adjuvant chemotherapy. The other 2 patients with residual disease, but no myometrial invasion, lived well for at least 40 months after receiving whole pelvic radiation therapy. One patient with stage II disease, however, had no myometrial invasion on radical hysterectomy specimen, and was also in remission at 62 months without adjuvant treatment. One patient out of 4 stage IA patients who had less than 50% myometrial invasion, had recurrent disease and death at 34 months, even after receiving adjuvant platinum based chemotherapy. One patient with stage IA was alive without disease at 65 months. The other 2 stage IA patients were lost to follow up at 9 and 22 months.

Adjuvant vaginal brachytherapy appeared to have an important role for local control in a previous study. There was no local recurrence in 43 stage I uterine papillary serous carcinoma patients who received vaginal brachytherapy. However, 6 of 31 patients who were not treated with vaginal brachytherapy recurred at the vaginal cuffs (Kelly et al., 2005). However, Barney et al. reported the 5-year Kaplan Meier estimate of vaginal recurrence of 3% in 103 stage I non-endometrioid endometrial carcinoma patients who received postoperative high dose rate vaginal brachytherapy (Barney et al., 2013). Likewise, Desia et al. also reported the 5-year vaginal recurrence of 3% in 77 stage I-II uterine papillary serous carcinoma (Desai et al., 2013). Our study showed a minimal incidence of vaginal cuff recurrence as only 1 out of 8 stage I patients developed vaginal cuff recurrence even none of them receive any kind of adjuvant radiation therapy. In contrast, 2 out of 9 patients still developed pelvic lymph node and vaginal recurrences, even after whole pelvic radiation therapy and vaginal brachytherapy.

From this result, it may be concluded that stage IA patient with no residual disease may not need any adjuvant treatment which is similar to the SGO recommendation. For early stage uterine papillary serous carcinoma and clear cell endometrial carcinoma patients who have residual disease on the hysterectomy specimens, SGO recommended giving adjuvant platinum-based chemotherapy +/- tumor directed radiotherapy. However, our study also showed that a patient in stage IA without myometrial invasion may need only adjuvant radiation. For advanced stage, SGO recommended a cytoreductive surgery whenever feasible followed by platinum/taxane-based chemotherapy with or without tumor volume directed radiotherapy (Boruta et al., 2009; Olawaiye and Boruta, 2009). In our study, only six patients were in stage III or IV. Two of three stage IIIA patients

with less than half of myometrial invasion, were alive well after receiving adjuvant radiation (1 patient) and adjuvant chemotherapy (1 patient). Another one patient with more than half of myometrial invasion had vaginal recurrence 43 months after adjuvant chemotherapy. The other three patients were in stage IVB. All of them died even after receiving adjuvant chemotherapy. Jhingran et al. prospectively evaluated survival of FIGO 1988 stage I-IIIA papillary serous carcinoma of endometrium treated with postoperative concurrent chemoradiation and adjuvant chemotherapy. They found the favorable result with 5-year OS, DFS and local control rate of 85%, 83% and 87%, respectively (Jhingran et al., 2013).

The benefit of this study is to provide the data regarding the non-endometrioid carcinoma of the endometrium including the incidence, clinical characteristics, aggressiveness of the disease and clinical outcomes. This information could help improve the medical care of this rare group of patients. Nevertheless, our study had several limitations. Firstly, the number of non-endometrioid patients in our study was quite small. Secondly, the clinical information from a retrospective chart review was relatively limited. This could affect the accuracy of the analysis of clinical outcomes. This study should encourage more future studies in the non-endometrioid endometrial carcinoma patients, especially about suitable adjuvant treatments to improve their survival.

In conclusion, non-endometrioid carcinoma of endometrium is relatively rare. It is more aggressive, has more distant metastasis at diagnosis with worse survival rate. The patient in stage IA with no residual disease on a hysterectomy specimen may not need adjuvant treatment. Chemotherapy played a major role in all stages of non-endometrioid carcinoma.

Acknowledgements

We thank Pimrapat Tengtrakulcharoen. Unit of Clinical Epidemiology, Office for Research and Development, Siriraj Hospital Faculty of Medicine, Mahidol University.

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