Arch Gynecol Obstet (2012) 286:1241–1245
DOI 10.1007/s00404-012-2402-7

GYNECOLOGIC ONCOLOGY

Coexisting ovarian malignancy in patients with clinical stage I endometrial carcinoma

Ozgur Akbayır · Oguzhan Kuru · Pınar Goksedef · Ceyhun Numanoglu · Aytul Corbacıoglu · Ahmet Cetin

Received: 24 January 2012 / Accepted: 29 May 2012 / Published online: 12 June 2012

Abstract
Aim To evaluate the feasibility of ovarian preservation at the time of operation in patients with clinical stage I endometrial carcinoma.
Materials and methods The data of 499 consecutive patients with clinical stage 1 endometrial cancer operated between January 2001 and December 2011 were retrospectively reviewed. Clinical and pathologic information and the intraoperative inspection findings of ovaries were evaluated to find the factors associated with the coexisting ovarian malignancy.
Results The mean age of patients was 56.8 ± 9.8 years. Coexisting ovarian tumors were detected in 38 patients (7.6 %), and 28 (5.6 %) of them were malignant (12 metastatic and 16 synchronous primaries). Most of the patients were postmenopausal ($n = 371$, 74.3 %) and 60 (12 %) of the patients were at the age of 45 years or less. Coexisting malignancy was detected in 9 % ($n = 11$) of the premenopausal patients and in 5 % ($n = 3$) of the patients aged 45 years or less. Multivariate analysis revealed that serosal invasion, tubal involvement, and positive abdominal cytology were independent risk factors for coexisting ovarian malignancy. The sensitivity, specificity, positive predictive value and negative predictive value of the intraoperative examination for the diagnosis of benign/normal ovary was 99.6, 78.8, 98.5 and 92.9 %, respectively.
Conclusion The incidence of coexisting ovarian malignancy in clinical stage I endometrial carcinoma is low. Although occult metastasis cannot be excluded at all, careful intraoperative inspection of ovaries seems valuable for the prediction of co-existing ovarian malignancy.

Keywords Endometrial carcinoma · Synchronous ovarian cancer · Ovarian metastasis · Stage I

Introduction

Endometrial cancer is the most common cancer of the female genital tract in developed countries [1]. Although it is thought to be a disease of postmenopausal women, one-fourth of the cases occur in women who are premenopausal, and 5 % occur in women under the age of 40 years [2]. The standard treatment of endometrial carcinoma is surgical staging, including total hysterectomy and bilateral salpingo-ooforectomy (BSO) that would destroy the reproductive function of women. However, the removal of ovaries at the time of operation remains controversial as the incidence of ovarian metastasis or synchronous ovarian tumor in clinical stage I endometrial carcinoma is only 1.7–11 % [3, 4].

The preservation of ovaries in early stage endometrial carcinoma is a choice; especially, for young women after careful preoperative and intraoperative assesment, but occult ovarian malignancy cannot be excluded at all. In contrast, unnecessary removal of ovaries may produce some serious problems associated with the loss of estrogen.

In this retrospective study, we aimed to determine the frequency of synchronous/metastatic ovarian malignancy

O. Akbayır · O. Kuru (✉) · C. Numanoglu · A. Corbacıoglu
Department of Obstetrics and Gynecology, Kanuni Sultan Suleyman Research and Training Hospital, Seyidomer mah. Kopruluzade sok. no:5/4 Fatih, 34098 Istanbul, Turkey
e-mail: drokuru@yahoo.com

P. Goksedef · A. Cetin
Department of Obstetrics and Gynecology, Haseki Research and Training Hospital, Istanbul, Turkey

and analyze the clinical and pathological features of coexisting ovarian malignancy in clinical stage I endometrial carcinoma to evaluate the feasibility of ovarian preservation at the time of operation.

Materials and methods

In this study approved by the institutional review board, the data of 499 consecutive patients with clinical stage 1 endometrial cancer operated in Kanuni Sultan Suleyman Research and Training Hospital and Haseki Research and Training Hospital between January 2001 and December 2011 were reviewed. In these tertiary centers, all patients underwent total abdominal hysterectomy, bilateral salpingo-ooforectomy, pelvic ± paraaortic lymphadenectomy, and none of them received neo-adjuvant therapy.

All pathologic specimens were reviewed by the senior gyneco-pathologists in these centers. Histo-pathologic criteria for synchronous primary tumors included either the detection of different histological types or the same histology with the following minor criteria: no direct extension between the tumors, different immunohistochemical staining, no lymphovascular tumor emboli, no or superficial tumor invasion and no distant metastases [5, 6]. Ovarian metastasis was differentiated from synchronous ovarian primary cancer either by a multinodular ovarian pattern or two or more of the following criteria: size of ovary(ies) <5 cm, bilateral ovarian involvement, more than 50 % of depth of myometrial invasion, vascular invasion, and tubal lumen involvement [6].

Demographic data, including age at diagnosis, menopausal status, parity, body mass index (BMI), tobacco use, hormone use, history of diabetes, hypertension, ovulation induction, and personal history of breast cancer were obtained from medical records. Pathologic information, such as histology, grade, depth of myometrial invasion, lymphovascular space invasion, diameter of the endometrial tumor, lymph node metastasis, serosal invasion, cervical involvement, abdominal cytology, and tubal involvement was collected from surgical pathology reports. In addition, the intraoperative inspection findings of the ovaries were obtained from the surgical reports.

Statistical analyses were performed using SPSS 16.0 version (SPSS, Chicago, IL, USA). Clinicopathologic parameters were analyzed by χ^2, Fisher's exact test, and Student's t test. Multivariate logistic regression was performed to identify independent risk factors associated with coexisting ovarian cancer. $p < 0.05$ was defined as statistically significant.

Results

A total of 499 patients with clinical stage I endometrial cancer were analyzed for this study. Coexisting ovarian tumors were detected in 38 patients (7.6 %) and 28 (5.6 %) of them were malignant (12 metastatic and 16 synchronous primaries; 2.4 and 3.2 %, respectively). Table 1 summarizes the histologic features of malignant and benign ovarian tumors in patients with clinical stage I endometrial cancer.

The mean age of the cohort was 56.8 ± 9.8 years. Most of the patients were postmenopausal ($n = 371$, 74.3 %) and 60 (12 %) patients were at the age of 45 years or less. Coexisting ovarian malignancy was detected in 9 % ($n = 11$) of the premenopausal patients and in 5 % ($n = 3$) of the patients aged 45 years or less. Table 2 summarizes the demographic characteristics of the patients according to the coexisting malignant ovarian tumor. There were no statistical differences in demographic data between the groups ($p > 0.05$).

The clinical and pathologic features of the patients according to coexisting ovarian malignancy are summarized in Table 3. The distribution of features was similar between the two groups, including the histology and diameter of endometrial tumor. However, the two groups' distribution of grade, the degree of myometrial involvement, the presence of lymphovascular invasion, cervical involvement, serosal invasion, tubal involvement, lymph node metastasis and positive abdominal cytology demonstrated significant differences.

Multivariate analysis identified that serosal invasion (OR 12.51; 95 % CI 1.14–136.48, $p = 0.03$), tubal involvement (OR 15.53; 95 % CI 2.59–93.06, $p = 0.003$)

Table 1 Histologic features of coexisting ovarian tumors in patients with endometrial cancer

	n	(%)
Malignant histology	28	5.6
Primary ovarian malignancy	16	3.2
Endometrioid cancer	6	1.2
Mucinous cancer	5	1.09
Serous cancer	2	0.4
Granulosa cell tumor	2	0.4
Undifferentiated tumor	1	0.2
Metastatic ovarian malignancy	12	2.4
Benign histology	10	2.0
Fibrothecoma	5	1.0
Brenner tumor	2	0.4
Benign teratoma	2	0.4
Endometrioma	1	0.2

Table 2 Demographic characteristics of the patients according to coexisting ovarian malignancy

	No coexisting malignancy $n = 471$ (%)	Coexisting malignancy $n = 28$ (%)	Total $n = 499$ (%)	p
Age (mean ± SD)	56.8 ± 9.9	57.3 ± 9.8	56.8 ± 9.8	0.66†
BMI (mean ± SD)	31.1 ± 5.5	28.3 ± 4.2	31.02 ± 5.5	0.57†
Age ≤45	57 (12.1)	3 (10.7)	60 (12)	0.55*
Nulliparous	39 (8.3)	2 (7.1)	41 (8.2)	0.83*
Premenopause	117 (24.8)	11 (39.3)	122 (25.7)	0.89‡
HRT use	3 (0.6)	0 (0)	3 (0.6)	0.84*
OI	18 (3.8)	1 (3.6)	19 (3.8)	0.71‡
Breast cancer	7 (1.5)	0 (0)	7 (1.4)	0.66*
Currently smoker	63 (13.4)	4 (14.3)	67 (13.4)	0.89‡
HT	214 (45.4)	9 (32.1)	223 (44.7)	0.11*
DM	106 (22.5)	5 (19.7)	111 (22.2)	0.38*

BMI body mass index, *OI* ovulation induction, *HRT* hormone replacement therapy, *SD* standard deviation

† p value for t test

* p value for Fisher's exact test

‡ p value for χ^2 test

and positive abdominal cytology (OR 3.92; 95 % CI 1.24–12.31, $p = 0.01$) were independent risk factors for coexisting ovarian malignancy (Table 4).

Intraoperative inspections of the ovaries were benign/normal in 466 of the patients, and 464 (99.6 %) of them were benign/normal after pathologic examination. Our results showed that the rate of occult ovarian malignancy was 0.4 % ($n = 2$). Intraoperative gross examination of the ovaries indicated coexisting malignancy in 33 of the patients. 26 of them (78.8 %) were malignant and 7 (21.2 %) of them were benign/normal after pathologic examination. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the intraoperative examination for the diagnosis of benign/normal ovary was 99.6, 78.8, 98.5 and 92.9 %, respectively.

Discussion

Our study showed that the incidence of coexisting ovarian malignancy in clinical stage I endometrial carcinoma was 5.6 %; of those 3.2 % was synchronous primary cancer and 2.4 % was ovarian metastasis. In the literature, the incidence of ovarian metastasis or synchronous ovarian tumor in clinical stage I endometrial carcinoma is approximately 1.7–11 % [3, 4]. Pan et al. [7] found 20 (2.05 %) coexisting ovarian malignancies in 976 patients with clinical stage I endometrial carcinoma; of those, 1.74 % was ovarian metastasis and 0.31 % was synchronous primary cancer. However, Walsh et al. in their study of 102 women (aged 24–45 years), who underwent hysterectomy for endometrial cancer, reported that 26 (25 %) women were found to have coexisting ovarian cancer; 23 (22 %) were classified as synchronous primaries and 3 (3 %) as metastases [8]. The inconsistency of these results depends on the reported sample size, patients' characteristics, and the criteria differentiating between ovarian metastasis and synchronous primaries. Although a variety of pathological criteria have been identified for the determination of the origin of such malignancies, it is not certain whether these features are always able to distinguish primary from metastatic tumors [5, 6, 9]. In the future, it seems that molecular analysis and genetic alterations will aid in differentiating synchronous primaries from ovarian metastasis [10, 11].

In our study, we analyzed the parameters for predicting coexisting ovarian malignancy in clinical stage I endometrial carcinoma and found that grade, the degree of myometrial involvement, the presence of lymphovascular invasion, cervical involvement, serosal invasion, tubal involvement, lymph node metastasis and positive abdominal cytology were associated with ovarian involvement in the univariate analysis. In the multivariate analysis, serosal invasion, tubal involvement, and positive abdominal cytology were appeared to be independent risk factors for ovarian malignancy. Pan et al. showed that cervical invasion, uterine serosal extension, and tubal involvement were independent high-risk factors for coexisting ovarian cancer [7]. On the other hand, Li et al. found that lymph node metastasis, positive peritoneal washing, and grade were independent risk factors [12]. As the findings of the studies regarding the risk factors are inconsistent, the preservation of ovaries should be discussed without the high-risk factors mentioned above.

Of the 41,200 newly diagnosed cases of endometrial carcinoma in the US, an estimated 5–10 % will occur in women younger than 40 years of age [13]. Similarly, in our cohort 60 (12 %) of the patients were at the age of 45 years or less. The majority of these cases tend to be early stage and low-grade tumors. The standard therapy remains total hysterectomy and BSO. However, in selected cases, medical therapy, such as high dose progestins, conservative

Table 3 Clinicopathologic features of the patients according to coexisting ovarian malignancy

	No coexisting malignancy $n = 471$ (%)	Coexisting malignancy $n = 28$ (%)	Total $n = 499$ (%)	p
Endometrial histology				0.52*
Endometrioid	421 (89.4)	24 (85.7)	445 (89.2)	
Non-endometrioid	50 (10.4)	4 (14.3)	54 (10.8)	
Grade				0.02†
1	176 (37.4)	7 (25)	183 (36.7)	
2	208 (44.2)	10 (35.7)	218 (43.7)	
3	87 (18.5)	11(39.3)	98 (19.6)	
Myometrial involvement				0.01‡
<1/2	322 (68.4)	13 (46.4)	335 (67.1)	
≥1/2	149 (31.6)	15 (53.7)	164 (32.9)	
Diameter of endometrial tumor (mm)				0.68*
<20	179 (38)	9 (32.1)	188 (37.7)	
≥20	292 (62)	19 (67.9)	311 (62.3)	
LVSI	123 (26.1)	12 (49.2)	135 (27.1)	0.05‡
Cervical involvement	29 (6.2)	5 (17.9)	34 (6.8)	0.01‡
Serosal invasion	3 (0.6)	8 (28.6)	11 (2.2)	0.0001‡
Lymph node involvement	45 (9.6)	7 (25)	52 (10.5)	0.009‡
Abdominal cytology				0.0001‡
Negative	416 (88.3)	15 (53.6)	431 (86.4)	
Positive	55 (11.7)	13 (46.4)	68 (13.6)	
Tubal involvement	3 (0.6)	10 (35.7)	13 (2.6)	0.0001‡

LVSI lymphovascular space invasion

* p value for Fisher's exact test

† p value for linear trend

‡ p value for χ^2 test

surgical approach (limited resection of the tumor) or the preservation of ovaries could be offered for the impact of infertility and premature ovarian failure. As a variety of fertility preservation techniques (embryo, oocyte, and ovarian cryopreservation) have been developed and yielded pregnancies, ovarian preservation at the time of operation has great importance in young patients with early stage, low risk endometrial carcinoma [14, 15]. Premature loss of ovarian function is associated with significant increase in the prevalence of coronary heart disease and osteoporosis which are the two major causes of morbidity and mortality in women [16, 17]. On the other hand, due to the fact that estrogen replacement therapy does not increase the risk of recurrence of endometrial cancer, ovarian preservation may be an option for the surgeon and the patients [18, 19]. However, there is controversy regarding the removal of ovaries in young patients with the early stage disease. Richter et al. [20] reported BSO leads better disease-free survival in young endometrial cancer patients, especially with stage I disease and they strongly suggest BSO as a part of the surgical treatment [20]. In contrast, in the study of Wright et al. [21] with the largest series in the literature, 402 patients in whom the ovaries were preserved in stage I endometrial cancer were retrospectively analyzed and it was suggested that ovarian conservation had no effect on either the cancer specific or overall survival [21]. Similarly, Lee et al. [22] suggest that ovarian preservation does not adversely affect the recurrence of early stage endometrial cancer [22].

Careful intraoperative inspection of the ovaries is mandatory before ovarian preservation in the clinical stage I endometrial carcinoma [8, 23]. The present study showed that sensitivity of the intraoperative inspection for diagnosis of benign/normal ovary was 99.6 %; specificity was 78.8 %, PPV and NPV were 98.5 and 92.9 %, respectively. Despite the risk for occult ovarian tumor in patients undergoing ovarian preservation, macroscopic appearance of the ovaries seems valuable in early stage endometrial carcinoma.

Our study has some limitations. The specimens were examined by different pathologists in two centers. Because of the ethical issues and current treatment guidelines, the feasibility of ovarian preservation in clinical stage I endometrial carcinoma was retrospectively and indirectly evaluated by determining the frequency of coexisting ovarian malignancy.

In conclusion, the incidence of coexisting ovarian malignancy in clinical stage I endometrial carcinoma is low. Although occult metastasis cannot be excluded at all, careful intraoperative inspection of the ovaries seems valuable for the prediction of co-existing ovarian malignancy.

Table 4 Multivariate analysis for factors that can be related with coexisting malignancy

	OR	95 % CI	*p*
Grades			
1	–		
2	1.192	0.31–4.58	0.79
3	0.795	0.23–2.65	0.70
Myometrial invasion			
<1/2	–		
≥1/2	1.41	0.46–4.32	0.54
LVSI			
Absent	–		
Present	0.46	0.12–1.72	0.25
Cervical involvement			
Absent	–		
Present	1.05	0.49–2.25	0.89
Serosal invasion			
Absent	–		
Present	12.51	1.14–136.48	0.03
Abdominal cytology			
Negative	–		
Positive	3.92	1.24–12.31	0.01
Lymph node involvement			
Absent	–		
Present	1.24	0.29–5.24	0.76
Tubal involvement			
Absent	–		
Present	15.53	2.59–93.06	0.003

Conflict of interest We declare that we have no conflict of interest.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55(2):74–108
2. Wang CB, Wang CJ et al (2002) Fertility-preserving treatment in young patients with endometrial adenocarcinoma. Cancer 94:2192–2198
3. Sakurai N, Takura T et al (1991) Extracorporeal spread and its prognostic impact in stages 1 and 2 (FIGO) endometrial carcinoma. Asia Oceana Obstet J Gynaecol 17:193–201
4. Takesima N, Hirai Y et al (1998) Ovarian metastasis in endometrial carcinoma. Gynecol Oncol 70:183–187
5. Eifel P, Hendrickson M et al (1982) Simultaneously presentation of carcinoma involving the ovary and the uterine corpus. Cancer 50:163–170
6. Ulbright TM, Roth LM (1985) Metastatic and independent cancers of the endometrium and ovary: a clinicopathological study of 34 cases. Hum Pathol 16:28–34
7. Pan Z, Wang X et al (2011) Retrospective analysis on coexisting ovarian cancer in 976 patients with clinical stage I endometrial carcinoma. J Obstet Gynaecol Res 37(4):352–358
8. Walsh C, Holschneider C et al (2005) Coexisting ovarian malignancy in young women with endometrial cancer. Obstet Gynecol 106:693–699
9. Scully RE, Young RH, Clement PB (1998) Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of tumor pathology. Armed Forces Institute of Pathology, Bethesda
10. Irving JA, Catasus L et al (2005) Synchronous endometrioid carcinoma of the uterine corpus and ovary: alterations in the beta-catenin (CTNNB1) pathway are associated with independent primary tumors and favorable prognosis. Hum Pathol 36(6):605–619
11. Matias-Guiu X, Lagarda H, Catasus L et al (2002) Clonality analysis in synchronous or metachronous tumors of the female genital tract. Int J Gynecol Pathol 21(3):205–211
12. Li LY, Zeng SY, Wan L, Ao MH (2008) Study of the risk factors for ovarian metastasis in patients with endometrial carcinoma. Zhong Hua Fu Chan Ke Za Zhi 43:352–355
13. Jemal A, Siegel R et al (2006) Cancer statistics, 2006. CA Cancer J Clin 56:106–130
14. Oktay K, Sonmezer M (2007) Fertility preservation in gynecologic cancers. Curr Opin Oncol 19:506–511
15. Seli E, Tangir J (2005) Fertility preservation options for female patients with malignancies. Curr Opin Obstet Gynecol 17:299–308
16. Cummings SR, Browner WS, Bauer D et al (1998) Endogenous hormones and the risk of hip and vertebral fractures among older women: Study of Osteoporotic Fractures Research Group. N Engl J Med 339:733–738
17. Stevenson JC (2011) A woman's journey through the reproductive, transitional and postmenopausal periods of life: impact on cardiovascular and musculo-skeletal risk and the role of estrogen replacement. Maturitas 70(2):197–205
18. Creasman WT, Henderson T et al (1986) Estrogen replacement therapy in the patient treated for endometrial cancer. Obstet Gynecol 67:326–330
19. Chapman JA, DiSaia PJ et al (1996) Estrogen replacement in surgical stage I and II endometrial cancer survivors. Am J Obstet Gynecol 175:1195–1200
20. Richter CE, Qian B et al (2009) Ovarian preservation and staging in reproductive-age endometrial cancer patients. Gynecol Oncol 114(1):99–104
21. Wright JD, Buck AM et al (2009) Safety of ovarian preservation in premenopausal women with endometrial cancer. J Clin Oncol 27:1214–1219
22. Lee TS, Kim JW et al (2009) Ovarian preservation during the surgical treatment of early stage endometrial cancer: a nationwide study conducted by the Korean Gynecologic Oncology Group. Gynecol Oncol 115:26–31
23. Chen L, Zhao Q, Lv X (2011) Characteristics and prognosis of coexisting adnexa malignancy with endometrial cancer: a single institution review of 51 cases. Arch Gynecol Obstet 283:1133–1137