

The effect of cell type on surgico-pathologic risk factors in endometrial cancer

Endometrium kanserinde hücre tipinin cerrahi-patolojik risk faktörlerine etkisi

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Abstract

Objective: In this study the effect of histologic subtype as a surgico-pathologic risk factor in endometrial cancer is evaluated.

Material and Methods: We evaluated 182 patients who underwent systematic lymphadenectomy up to the level of the renal vessels and at least 15 lymph nodes were dissected from the pelvic area and 10 lymph nodes from the para-aortic area. Investigation of whether endometrioid and aggressive cell types (serous papillary cell and clear cell) affect the distribution of surgicopathologic risk factors among endometrial cancer cases was carried out.

Results: Patients in the aggressive cell type group were older and the tumor size was significantly smaller. There was no difference between the two groups for the total number of dissected lymph nodes except for the external iliac area. Although the difference is not statistically significant, the total number of lymph nodes dissected in the aggressive group was less (54.3 vs 62.9, $p=0.067$) than that of the endometrioid cell type group. While the incidence of pelvic lymph node metastasis in the aggressive group was 59.1% the incidence was 15.6% in the endometrioid cell type group ($p>0.001$). The possibility of lymph node metastasis for aggressive cell type endometrial carcinoma in the para-aortic area was twice the endometrioid cell type group. It was found that the presence and type (stromal/glandular) of cervical invasion, depth of myometrial invasion and presence of lymphovascular space invasion were not affected by cell type.

Conclusion: Aggressive cell types significantly increase the adnexial and lymph node metastasis in endometrial cancer.

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Key words: Endometrial carcinoma, cell type

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Introduction

Endometrial cancer is the fourth most common cancer among women worldwide (1). More than 80% of the cases are endometrioid type histologically and are associated with a good prognosis (2). Clear cell and serous papillary cell carcinoma, which are the aggressive ones, are quite rare, with an incidence of 1-6% and 1-10%, respectively (3-6).

Serous papillary cell carcinoma of the uterus resembles epithelial ovarian cancer with its aggressive clinical course (7, 8).

Özet

Amaç: Bu çalışmada endometrium kanserinde hücre tipinin cerrahi-patolojik risk faktörleri üzerine olan etkisi araştırıldı.

Gereç ve Yöntemler: Endometrium kanseri nedeniyle renal damarlar seviyesine kadar sistematik lenf nodu diseksiyonu yapılan 182 hasta retrospektif olarak değerlendirildi. Lenf nodu diseksiyonu yapılan olgularda pelvik bölgeden en az 15 adet, para-aortic bölgeden de en az 10 adet lenf nodu çıkarılmıştır. Hastalar yapılan histolojik değerlendirme sonucuna göre hücre tipine göre endometrioid hücre tipi ve agresif hücre tipi (seröz papiller ve berrak hücreli) olmak üzere 2 gruba ayrıldı. Bu iki grup cerrahi-patolojik risk faktörlerinin dağılımı açısından karşılaştırıldı.

Bulgular: Agresif hücre tipi grubunda yer alan hastaların yaş ortalaması daha yüksekti ve tümör boyutu daha küçüktü. İki grup arasında eksternal iliac bölge dışında diseke edilen lenf nodu sayısı açısından fark olmadığı bulundu. Agresif hücre tipi grubunda çıkarılan toplam lenf nodu sayısı endometrioid hücre tipi grubundan daha azdı fakat fark istatistiksel olarak anlamlı değildi (54.3 vs 62.9, $p=0.067$). Agresif hücre tipi grubunda pelvik lenf nodu metastazı insidansı %59.1 iken endometrioid hücre tipi grubunda insidans %15.6 olarak bulundu ($p>0.001$). Agresif hücre tipi grubunda para-aortic lenf nodu metastazı olasılığının diğer grubun 2 katı olduğu görüldü. Servikal invazyon ve invazyonun tipinin (stromal/glandüler), miyometrial invazyonun derinliğinin ve lenfovasküler alan invazyonunun hücre tipinden etkilenmediği görüldü.

Sonuç: Endometrium kanserinde agresif hücre tipi adneksiyal alan ve lenf nodu metastazını istatistiksel olarak anlamlı ölçüde artırmaktadır. (J Turkish-German Gynecol Assoc 2011; 12: 9-14)

Anahtar kelimeler: Endometrium kanseri, hücre tipi

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Clear cell carcinoma of the uterus is another aggressive type of endometrial cancer, which has a similar relapse pattern to uterine serous papillary cell carcinoma and a 5 year survival less than 50% (3, 9). In addition to serous papillary cell and clear cell carcinoma, there is another group with aggressive characteristics called mixed type and is histologically composed of more than 75% serous papillary or clear cells (9). Even if the tumor is only confined to the uterus in the case of an aggressive cell type, adjuvant therapies following surgery are generally recommended (10-13). Because of their aggress-

sive clinical course radical surgical procedures are suggested, and to prevent and control the potential pelvic and extrapelvic disease, radiotherapy and/or systemic chemotherapy are recommended as adjuvant therapies.

Carighead et al. analyzed 103 patients whose histopathologic diagnosis was one of the aggressive variants of endometrial cancer and showed that pelvic radiotherapy reduces pelvic recurrence significantly and increases the overall survival in stage IB, IC, II and III cases (14).

However, in view of the fact that studies on this subject and the number of subjects included in those studies are not sufficient, the most appropriate treatment regimen for clear cell and serous papillary cell carcinoma is still controversial. For this reason, further prospective randomized trials are required to determine the most appropriate treatment method (15, 16). In addition, it is not clearly known that there is a relationship between the aggressive clinical course of the serous papillary and the clear cell carcinoma and the surgico-pathologic risk factors associated with those cell types. However, it is known that extra uterine spread is common among aggressive cell types (7, 13, 14, 17, 18).

In this study we evaluated whether there is an association between the surgico-pathologic risk factors and cell type in endometrial cancer.

Material and Methods

Between 1993 and 2009, a total of 182 patients who had open systematic pelvic and para-aortic lymphadenectomy surgery extending to the renal vessels for endometrial cancer at the gynecologic oncology department were studied retrospectively. Patients who had no other malignancies diagnosed within two years before or after their diagnosis and who had had at least 15 lymph nodes removed from pelvic region and at least 10 lymph nodes removed from para-aortic region were included. All surgical procedures were performed by experienced gynecologic oncologists and frozen sections were studied routinely for all cases, providing information on the grade of neoplasia, histology, depth of myometrial invasion, tumor diameter, sites of extrauterine spread and lymphovascular invasion.

Patients were staged according to FIGO 1988 criteria. In addition to total abdominal hysterectomy and bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymph node dissections were performed when one of the following criteria was determined by frozen section examination; (1) Grade 2-3, (2) $\geq 1/2$ myometrial invasion, (3) tumor size > 2 cm, (4) adnexial metastasis, (5) cervical involvement and (6) aggressive cell types (clear cell, adenosquamous or serous papillary).

The variations in distribution of surgico-pathologic risk factors according to endometrioid cell type and other aggressive cell types were investigated.

Statistical analyses were performed using 17.0 SPSS programme. χ^2 test and Anova Table tests are used, and $p < 0.05$ value is accepted as statistically significant. The study was approved by the Ethical committee in our hospital.

Results

In this study 182 patients with stage IA-IVB endometrial cancer were evaluated. The mean age was 57.3 (35-92). The mean tumor size was 40.6mm with a maximum of 130 mm. There was no tumor in nine patients. The histological subtype was endometrioid in 87.9% of patients. Grade 1 tumor was detected in 61 patients, grade 2 in 68 and grade 3 in 53. There was no myometrial invasion in 14 patients, $< 1/2$ myometrial invasion in 68, $\geq 1/2$ myometrial invasion in 93 and serosal infiltration was present in 11. Ovarian involvement was detected in 22 patients and tubal involvement in 13 patients. In 139 patients the information about lymphovascular space invasion (LVSI) was indicated by the histopathological examination and LVSI was determined in 57 of these patients (Table 1).

The mean of the total number of lymph nodes removed was 61.9 and 42.3 of those were dissected from the pelvic area while 19.6 were from the para-aortic area.

Lymph node metastasis was found in 43 patients (23.6%). Tumor spread to the pelvic lymph nodes in 38 patients (20.9%) and to the para-aortic lymph nodes in 24 patients (13.2%). Obturator lymph nodes were the most commonly involved area. Details of the surgico-pathologic factors of the patients are shown in Table 1.

The patients in the aggressive cell type group were older and the tumor size in this group was significantly smaller (Table 2). There was no difference between the two groups with regard to the total number of removed lymph nodes except for the external iliac area (Table 2). In the aggressive cell type group, lymph nodes dissected from the external iliac area were significantly fewer in number. Although the difference is not significant statistically, the total number of lymph nodes removed in the aggressive cell type group was also fewer (54.3 vs 62.9, $p = 0.067$). However in the aggressive cell type group, pelvic lymph node involvement was greater (59.1% vs 15.6%, $p < 0.001$) (Table 3). The possibility of para-aortic lymph node involvement in the aggressive cell type group was twice that in the endometrioid cell type group (22.7% vs 11.9%, $p = 0.158$) (Table 3).

Spread of disease to the tuba uterina and ovaries was more common in the aggressive cell type group (Table 3). While the ovarian metastasis was found in 27.3% of patients in the aggressive cell type group, the rate of ovarian metastasis was 10% in the endometrioid cell type group. The rate of tubal involvement was 18.2% and 5.6%, respectively.

It was found that the presence and type of cervical invasion either stromal or glandular, and depth of myometrial invasion and presence of LVSI were not affected by cell type (Table 4).

Discussion

The term clear cell carcinoma of mesonephric origin was first described by Schiller et al. in 1939 to describe clear cell carcinoma of ovarian cancer resembling renal cell carcinoma histologically (19). The descriptive term clear cell carcinoma for tumors originating from the Müllerian duct was first introduced in 1967 by Scully and Barlow (20). The prognostic significance of clear cell histology was recognized in 1970s. Scully and

Table 1. General parameters

Parameter		Mean / n	Range / %
Age (years)		57.3	35-92
Tumor size (mm)		40.6	0-130
Stage	IA	12	6.6
	IB	48	26.4
	IC	49	26.9
	IIA	4	2.2
	IIB	11	6
	IIIA	9	4.9
	IIIB	2	1.1
	IIIC	45	24.7
	IVA	1	0.5
Cell type	IVB	1	0.5
	Endometrioid	160	87.9
	Clear	11	6
Grade	Serous papillary	11	6
	1	61	33.5
	2	68	37.4
Depth of myometrial invasion	3	53	29.1
	Only endometrium	14	7.7
	< ½	68	37.4
	≥ ½	93	51.1
Peritoneal cytology	Serosal infiltration	7	3.8
	Negative	171	94
Ovarian metastasis	Positive	11	6
	Negative	160	87.9
Tuba uterina metastasis	Positive	22	12.1
	Negative	169	92.9
Cervical invasion	Positive	13	7.1
	Negative	141	77.5
	Glandular	8	4.4
Lymphovascular space invasion	Stromal	33	18.1
	Negative	82	45.1
	Positive	57	31.3
Total number of removed lymph nodes	Not reported	43	23.6
Number of lymph nodes removed from pelvic area		61.9	27-122
Number of lymph nodes removed from para-aortic area		42.3	16-81
Lymph node status	Negative	139	76.4
	Pelvic lymph node metastasis	43	23.6
	Para-aortic lymph node metastasis	27	13.2
Pelvic lymph node area	Common iliac lymph node	16	8.8
	External iliac lymph node	19	10.4
	Internal iliac lymph node	16	8.8
	Obturator lymph node	20	11
	Presacral lymph node node	1	0.5

Table 2. Age, tumor size and dissected lymph nodes according to cell types

Cell type		Age	Tumor size (mm)	Total LN	PA LN	Total pelvic LN	CI LN	EI LN	II LN	PS LN	O LN
Endometrioid	Mean	56.7	41.9	62.9	20	43.1	9.71	11.6	5.2	1.74	14.9
	Minimum	35	0	27	10	16	2	2	0	0	0
	Maximum	92	130	122	49	81	26	28	20	8	41
	Median	56	40	58.5	18	40	9	11	6	1	15
Clear cell and serous type	Mean	62.3	31.7	54.3	17.4	37	8.1	9	6.5	1.23	12.2
	Minimum	48	5	32	9	18	2	4	1	0	3
	Maximum	76	60	87	33	59	20	14	15	7	26
	Median	62.5	32.5	50.5	15.5	34.5	8	9	6	0	11
p		0.009	0.029	0.067	0.167	0.068	0.142	0.030	0.119	0.291	0.085
LN: Lymph node, PA: Para-aortic, CI: Common iliac, EI: External iliac, II: Internal iliac, PS: Presacral, O: Obturator											

Table 3. Lymph node, ovarian and tubal involvement according to cell type (%)

Cell type	PA LN	Total pelvic LN	CI LN	EI LN	II LN	PS LN	O LN	Ovarian involvement	Tubal involvement
Endometrioid	11.9	15.6	6.9	7.5	4.4	0	8.8	10	5.9
Clear cell and serous type	22.7	59.1	22.7	31.8	40.9	4.5	27.3	27.3	18.2
p	0.158	<0.001	0.014	<0.001	<0.001	0.007	0.009	0.020	0.032
LN: Lymph node, PA: Para-aortic, CI: Common iliac, EI: External iliac, II: Internal iliac, PS: Presacral, O: Obturator									

Table 4. Presence of cervical invasion, depth of myometrial invasion and lymphovascular space invasion according to cell type (%)

Cell type	Cervical invasion			Depth of myometrial invasion				LVSI	
	Absent	Glandular	Stromal	Endometrial	<1/2	≥1/2	Serozal	Negative	Positive
Endometrioid	79.4	4.4	16.3	6.9	37.5	52.5	3.1	79.4	20.6
Clear cell and serous type	63.6	4.5	31.8	13.6	36.4	40.9	9.1	63.6	36.4
p	0.201			0.327				0.098	
LVSI: Lymphovascular space invasion									

Kurman reported a series of 21 cases of clear cell carcinoma with an unfavorable clinical course (21).

The concept of uterine serous papillary carcinoma was first brought out by Hendrichson and described as a rare aggressive subtype of endometrioid adenocarcinoma (22). The main histological property of serous papillary carcinoma is the psammoma bodies and the distinct papillary microarchitecture. The serous papillary carcinoma of the uterus, which is a very different clinicopathological entity from endometrioid adenocarcinoma, also differs from the carcinogenesis point of view. The major role in the molecular pathogenesis of uterine serous papillary carcinoma is p53 inactivation (23-25). Overexpression of the p53 gene is observed in 80% of all uterine serous papillary carcinoma cases, while this rate is only 10-25% among all high grade endometrioid adenocarcinoma cases.

The biological behavior of serous papillary malignancies of other tissues, such as the ovaries and the peritoneum, resembles that of uterine serous papillary carcinoma. The reason for this is that the p53 gene inactivation is common in all types of

serous papillary malignancies and all of them have the capability to develop aggressively and rapidly instead of undergoing some slow processes of tumor development depending on hormone related mechanisms (23, 25).

In this study it is found that the aggressive cell type significantly increases the pelvic lymph node involvement. Pelvic lymph node metastasis was present in 16% of the endometrioid cell type group, while this ratio was 59% among the aggressive cell type group. When the cases were investigated in detail, it was observed that lymph node involvement in all areas of the pelvis was significantly higher among clear cell and serous papillary cell types. In contrast, lymph node involvement in the para-aortic area was found to be independent of cell type.

Typically, uterine serous papillary cell carcinoma differs from the endometrioid adenocarcinoma with its aggressive clinical course associated, with diffuse peritoneal involvement resembling that of ovarian cancer, and it is also associated with deep myometrial invasion and lymphatic involvement (17).

In a study investigating the pattern of metastasis and prognosis among clear cell carcinoma cases; Abeler et al. found that the 5 year survival decreases with myometrial invasion, which is one of the surgicopathologic risk factors. Five year survival was 90% for intramural tumor, while it was 15% in cases with deep myometrial invasion (3).

Xiaohai et al. investigated 310 patients retrospectively to determine the clinicopathological factors other than cell type affecting lymph node involvement (26). As a result of this study, it was found that the presence of LVSI, deep myometrial invasion and cervical invasion were determinants of lymph node involvement. This result is also supported by the results of another study. Fotopoulou et al. found that the presence of LVSI, grade, serous cell type and incomplete resection of the tumor were also associated with lymph node involvement (18). However, in our study there was no significant difference in depth of myometrial invasion, presence of LVSI and cervical metastasis between the aggressive cell type group and endometrioid cell type group. This means that aggressive cell type increases pelvic lymph node involvement independent of depth of myometrial invasion, presence of LVSI and cervical metastasis. Similarly, Goff et al. found in their study that extrauterine disease in uterine serous papillary carcinoma was not associated with depth of myometrial invasion and grade (7). Goff et al. investigated 50 cases of surgically staged uterine serous papillary carcinoma, and lymph node metastasis was observed in 36% of patients without myometrial invasion and 40% of patients with outer one-half myometrial invasion. Among 14 cases in which the tumor was limited to the endometrium, there was lymph node metastasis in 36% and extrauterine disease was present in 43%. In addition, Goff et al. found that the incidence of extrauterine disease was increased with the presence of LVSI (85% of patients), but even if LVSI is not present in these patients, the incidence of extrauterine disease was still found to be high (58% of patients). There are other studies which also reported that myometrial invasion had no prognostic value in uterine serous papillary carcinoma (5, 7, 8).

In this study, ovarian and tubal involvement was found to be higher among the aggressive cell type group. This may explain the higher incidence of pelvic lymph node involvement in the presence of aggressive cell type. In contrast to this, although the adnexial involvement was increased with aggressive cell type, the para-aortic lymph node involvement was not increased with adnexial involvement with the aggressive cell type. Mariani et al. reported that one of the possible ways for para-aortic lymph node involvement in endometrial cancer was the peduncle of ovarian vessels. In their study, there was metastasis in the gonadal vein and surrounding soft tissue in 28% of patients with para-aortic lymph node involvement (27). Mc Meekin et al. also reported similar results and they found that the para-aortic lymph node involvement was present in 11 of 12 patients who have adnexial metastasis and/or positive peritoneal cytology (28). 240 cases of stage I-III endometrial cancer were surgically treated by total abdominal hysterectomy, bilateral salpingo-oophorectomy and retroperitoneal lymph node dissection. They investigated the histopathological factors from the prog-

nostic aspect and found that the incidence of deep myometrial invasion, high nucleolar grade (G3), LVSI and pelvic lymph node involvement were higher among the serous papillary and clear cell carcinoma group compared to the endometrioid cell type group (29). In accordance with that study, we also found that pelvic lymph node involvement and adnexial metastasis was significantly higher among aggressive cell type cases.

For all stages in uterine serous papillary carcinoma, 5-year survival is found to be 30% (6, 30). While 5-year survival for stage I-II cases is 54% and 27% respectively, 5-year survival cannot be predicted in stage III-IV cases (31). Also, unfortunately disseminated disease and death is possible in the case of uterine serous papillary carcinoma even if the tumor is confined to the endometrium (8, 30, 32).

As a result, in this retrospective study we found that the prognostic factors which determine the survival in the aggressive cell type group were poorer. Tubal and adnexial involvement in the aggressive cell type group were significantly higher. However, this situation was independent of depth of myometrial invasion, presence of cervical involvement and LVSI. Also, although it is not statistically significant, para-aortic lymph node involvement in the aggressive cell type group was approximately twice that in the endometrioid cell type group, and adnexial involvement was thought to be responsible for this. In the aggressive cell type group, the treatment plan should be as aggressive as the clinical course.

Since the number of patients included in this study was limited and the study was designed retrospectively, conclusions are restricted. In addition to this, the patients included in our study group were at high risk for lymph node metastasis. For that reason, well designed more prospective studies including all endometrial cancer patients are required for understanding of effect of cell type on variations in surgico-pathologic risk factors.

Conflict of interest

None declared.

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