Parametrial spread is a prognostic factor in endometrial carcinoma

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Summary

Objective: Parametrial spread of endometrial carcinoma, including the histopathological pattern of the spread and its significance as a prognostic factor, as well as its correlation with other prognostic factors are not well understood.

Methods: We reviewed histopathologically the resected parametria from 269 patients with endometrial carcinoma who underwent radical or modified radical hysterectomy with pelvic lymphadenectomy. The relationship between parametrial spread and other histopathological features, including histological type, tumor grade, depth of myometrial invasion, lymph vascular space invasion (LVSI) of the myometrium, cervical invasion, adnexal metastasis, lymph node metastasis and peritoneal cytology was studied. Clinical outcomes of the patients with parametrial spread were also evaluated.

Results: Parametrial spread was demonstrated in 16 patients (5.9%). Direct invasion of cancer cells to connective tissue, LVSI and lymph-node metastasis in the parametrium were seen in 13, seven and three cases, respectively. Three patients had all three spread patterns. According to the FIGO surgical stage, parametrial spread was found in none of the 164 patients in Stage I, two (6.3%) of 32 in Stage II, 12 (16.9%) of 71 in Stage III, and two (100%) of two in Stage IV. The presence of parametrial involvement was significantly correlated with depth of myometrial invasion, cervical involvement, lymph-node metastasis, adnexal metastasis, LVSI in the myometrium and peritoneal cytology (each, $p < 0.01$). With a median follow-up of 68.3 months, six (37.5%) of 16 patients with parametrial involvement developed recurrence and died.

Conclusion: Direct parametrial extension or lymphatic involvement within the parametrium can occur in endometrial carcinoma. Patients with parametrial spread have a poor prognosis.

Key words: Parametrial spread; Endometrial carcinoma; Prognostic factors; Multivariate analysis.

Introduction

Current FIGO criteria for the staging of endometrial cancer [1] are based on the findings at surgery and histopathological evaluation of the surgical specimen, including peritoneal cytology. However, the FIGO criteria do not consider parametrial involvement of endometrial carcinoma, because simple total hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy may be recognized as the cornerstone of the staging and treatment method for endometrial carcinoma [2-8]. Therefore, it is unclear how often endometrial carcinoma spreads to the parametrial tissue, unlike primary cervical cancer, and large series of studies on parametrial involvement of endometrial carcinoma are rare. Yura *et. al.* [9] reported parametrial involvement was histologically demonstrated in 12 (13.2%) of the 91 cases. Tamussino *et al.* [10] examined 24 patients with endometrial carcinoma treated with radical hysterectomy and found that two of 16 patients with cervical involvement had developed parametrial spread. However, they did not mention the prognostic significance of parametrial spread.

In this paper, we aimed to clarify the significance of parametrial spread on survival rate, as well as the incidence and spread pattern of parametrial involvement, and the correlation of parametrial spread with other prognostic factors.

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Patients and Methods

A total of 269 patients (mean age 53 years, range 28-78) with endometrial carcinoma were treated consecutively with radical or modified radical hysterectomy with pelvic lymphadenectomy at Kitasato University Hospital between July 1971 and December 1995. None of the patients had received preoperative radiation or chemotherapy. Preoperatively, all patients were staged based on the FIGO criteria (1971) [11]. Radical hysterectomy was performed for 133 patients with positive endocervical curettage (clinical Stage II) and six cases with parametrial induration or palpable adnexal tumors (clinical Stage III). Modified radical hysterectomy was performed for 130 patients with negative endocervical curettage (clinical Stage I). Ascitic cytology or peritoneal washing cytology was collected at laparotomy. Surgical staging was determined by the FIGO surgical staging system for corpus cancer [12]. The uterus, cervix, and bilateral parametria were processed for step serial sections. The number of parametrial tissue specimens ranged from two to 21 (mean ± SD, 7.4 ± 3.3), including four to 21 (9.1 ± 3.3) in cases with radical hysterectomy and two to 15 (5.6 ± 2.2) in those with modified radical hysterectomy. Special attention was paid to histological involvement of the carcinoma in the cervix and parametrial tissue, including histological type, tumor grade, depth of myometrial invasion, lymph-vascular space invasion (LVSI) in the myometrium, adnexal involvement, and pelvic lymph-node metastasis. The tumor grade of endometrioid adenocarcinoma was assessed according to the FIGO criteria [1]. Parametrial spread was analysed histologically, including the involvement of parametrial connective tissue and regional lymph-node and lymph-vascular space (LVS). All patients were followed until December 2000 or death.

For statistical analysis, the χ^2 test and Fisher's exact probability test were used to determine the significance of parametrial involvement with each surgical and pathologic variable. Survival curves were illustrated by the Kaplan-Meier method. The log-rank test was used for the analysis of survival curves and univariate analysis to assess the significance of parametrial spread. Cox's proportional hazards regression model (statistical analysis system: SAS) was used to determine which variables were independent prognostic factors. In all analyses, the significance level was set at 0.05.

Results

Parametrial spread of endometrial carcinoma was demonstrated histologically in 16 (5.9%) of 269 patients including 14 (10.1%) of 139 patients who underwent radical hysterectomy and two (1.5%) of 130 with modified radical hysterectomy.

Incidencies of parametrial spread in relation to clinicopathological features are shown in Table 1. Parametrial spread tended to increase with progress according to the clinical stage, although there was no statistical significance. According to the FIGO surgical stage, parametrial spread was not seen in any of the 164 patients with Stage I. The incidence of parametrial spread increased significantly with advances in surgical stage of the disease ($p < 0.01$). Incidence (55.6%) of parametrial involvement in carcinosarcoma was significantly higher than that (4.3%) in endometrioid adenocarcinoma. Histological differentiation of endometrioid adenocarcinoma was not correlated with parametrial involvement, although the incidence in G3 cases tended to be high. Parametrial involvement was significantly correlated with myometrial invasion ($p < 0.01$), LVSI in the myometrium ($p < 0.01$), cervical invasion ($p < 0.01$), adnexal metastasis ($p < 0.01$), lymph-node metastasis ($p < 0.01$) and peritoneal cytology ($p < 0.01$) by univariate analysis (Table 1).

Three patterns of parametrial spread were identified histologically (Table 2). The tumor invaded parametrial connective tissue (Figure 1) in 13 patients (81.3%), whereas spread in lymph-vascular space (LVS) (Figure 2) and lymph-nodes (Figure 3) was identified in seven patients (43.8%) and three patients (18.4%), respectively.

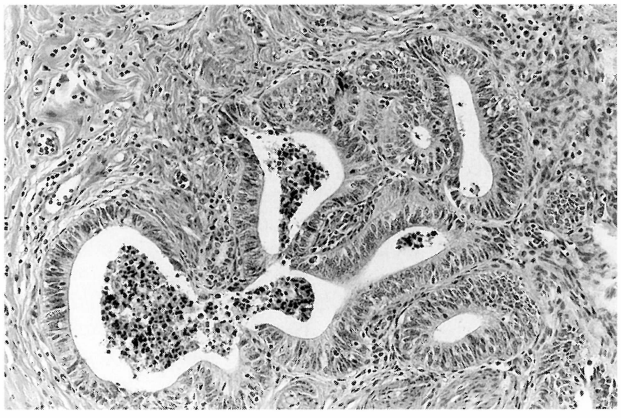

Figure 1. — Tumor cells invading the parametrial connective tissue. (Magnification x 50).

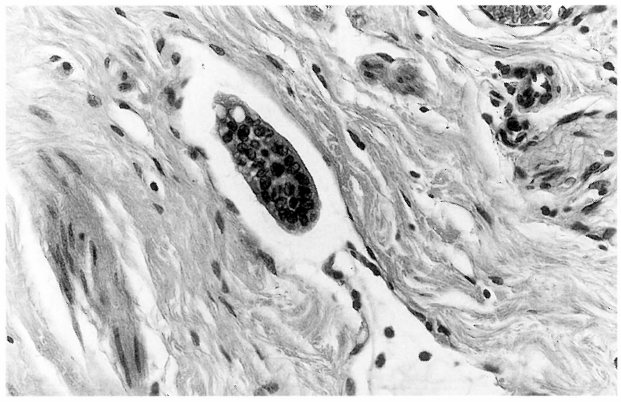

Figure 2. — Tumor cells present within the lymphatic space. (Magnification x 100).

Table 1. — *Frequency of parametrial spread in 269 patients with endometrial carcinoma.*

Clinical stage	No.	Positive (%)	p value
I	131 (48.7%)	2 (1.5)	n.s.
II	132 (49.1%)	13 (9.8)	
III	6 (2.2%)	1 (16.7)	
Surgical stage	**No.**	**Positive (%)**	**p value**
I	164 (61.0%)	0 (0.0)	$p < 0.01$
II	32 (11.9%)	2 (6.3)	
III	71 (26.4%)	12 (16.9)	
IV	2 (0.7%)	2 (100.0)	
Histological type	**No.**	**Positive (%)**	**p value**
Em. adenoca.	235 (87.4%)	10 (4.3)	*
(squamous different.)	23 (8.6%)	4 (17.4)	
Adenosquamous ca.	6 (2.2%)	1 (16.7)	
Serous adenoca.	7 (2.6%)	0 (0.0)	
Mucinous adenoca.	7 (2.6%)	0 (0.0)	
Clear cell adenoca.	5 (1.9%)	0 (0.0)	
Carcinosarcoma	9 (3.3%)	5 (55.6)	*
Histological grade (n = 235)	**No.**	**Positive (%)**	**p value**
Em-G1	100 (42.6%)	2 (2.0)	n.s.
Em-G2	109 (46.4%)	5 (4.6)	
Em-G3	26 (11.0%)	3 (11.5)	
Myometrial invasion	**No.**	**Positive (%)**	**p value**
Intra-endometrial	50 (18.6%)	0 (0.0)	$p < 0.01$
Inner 1/3	114 (42.3%)	3 (2.6)	
Middle 1/3	53 (19.7%)	2 (3.8)	
Outer 1/3	44 (16.4%)	8 (18.2)	
Serosa	8 (3.0%)	3 (37.5)	
LVSI	**No.**	**Positive (%)**	**p value**
Positive	89 (33.1%)	10 (11.2)	$p < 0.01$
Negative	180 (66.9%)	6 (3.3)	
Cervical invasion	**No.**	**Positive (%)**	**p value**
Positive	72 (26.8%)	10 (13.9)	$p < 0.01$
Negative	197 (73.2%)	6 (3.0)	
Adnexa meta.	**No.**	**Positive (%)**	**p value**
Positive	14 (5.2%)	4 (28.6)	$p < 0.01$
Negative	255 (94.8%)	12 (4.7)	
Lymph-node meta.	**No.**	**Positive (%)**	**p value**
Positive	43 (16.0%)	12 (27.9)	$p < 0.01$
Negative	226 (84.0%)	4 (1.8)	
Peritoneal cytology (n = 179)	**No.**	**Positive (%)**	**p value**
Positive	27 (15.1%)	5 (18.5)	$p < 0.01$
Negative	152 (84.9%)	7 (4.6)	

*$p < 0.01$: significant; n.s.: not significant. Em. adenoca.: endometrioid adenocarcinoma including 23 with squamous differentiation. Em-G1: endometrioid adenocarcinoma (grade 1). Em-G2: endometrioid adenocarcinoma (grade 2). Em-G3: endometrioid adenocarcinoma (grade 3). LVSI: lymph-vascular space invasion in the myometrium. meta: metastasis.

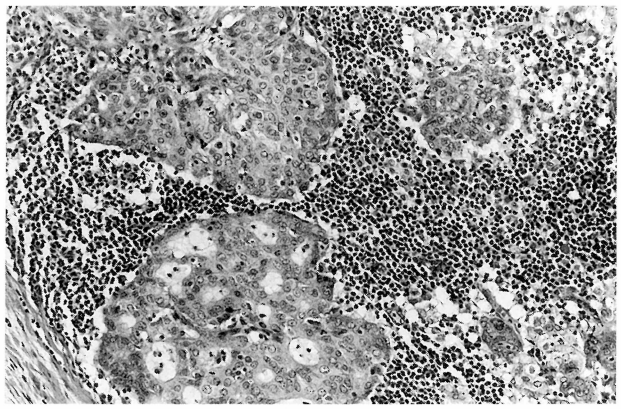

Figure 3. — Metastasis in a parametrial lymph node. (Magnification x 50).

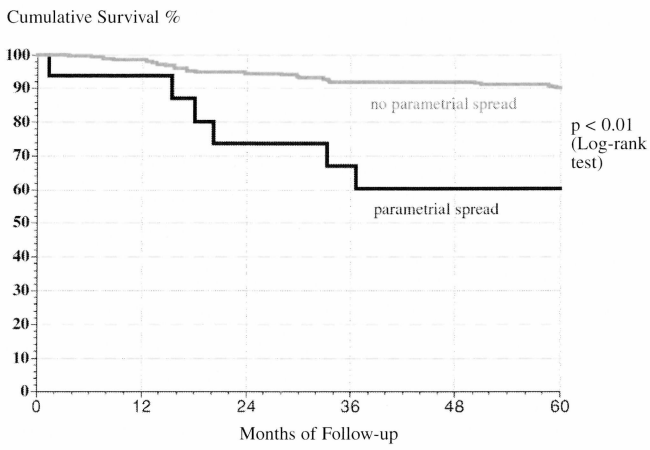

Figure 4. — Survival curves of patients with endometrial carcinoma according to the presence of parametrial spread (Kaplan-Meier's method). Patients with positive parametrial spread (n = 16) showed a significantly poorer survival curve than those without (n = 253) ($p < 0.01$).

In five patients, tumor cells were observed in both connective tissue and LVS and two of them also developed lymph-node metastasis. Pelvic lymph-node metastasis was confirmed in all three patients with parametrial lymph node metastasis and in nine of 13 cases without parametrial lymph-node metastasis. Pelvic lymph-node metastasis was observed in seven of eight cases with parametrial lymphatic spread (LVS + parametrial lymph node) and in five of eight without spread (not significant, Table 2). In six of seven patients with LVSI in the parametrium, LVSI in the myometrium of the primary lesion was observed.

The histological findings, including grading between primary and parametrial lesions, were identical in 11 cases. In two cases with G2 or G3 endometrioid adenocarcinoma, more differentiated lesions were observed in the parametrial lesions. Two of five cases with carcinosarcoma that metastasized into the parametrium revealed only adenocarcinoma in the parametrial lesion.

The median follow-up time was 68.3 months (1.4-238.9 mos.). Seven of 16 patients with parametrial spread received postoperative radiation therapy (Linac 50 Gy), six received adjuvant chemotherapy, and one received both therapies. Two patients did not receive any postoperative adjuvant therapy. Six patients (37.5%) developed recurrence, including one with a local lesion in the pelvic cavity, three with distant metastasis and two with both. Recurrence developed in five of 12 cases concomitantly with pelvic lymph-node metastasis and one of four cases without metastasis. The survival curve of the patients with parametrial spread was significantly worse than that of those without any spread ($p < 0.01$), and revealed 5-year survival rates of 60.3% and 90.1%, respectively.

Each prognostic factor, including parametrial involvement ($p < 0.01$), peritoneal cytology ($p < 0.01$), myometrial invasion ($p < 0.01$), LVSI in the myometrium ($p < 0.01$), lymph-node metastasis ($p < 0.05$) and histological

Table 2. — *Patients with parametrial spread in endometrial carcinoma.*

No.	Age	Histology uterus	Histology (pm)	Myometrial invasion	Cervical involvement	LVSI	Pelvic lymph-node metastasis	Parametrium connec	Parametrium LVS	Parametrium lymph-node
1	58	Em-G1	(Em-G1)	outer 1/3	+ micro	+	–	+	–	–
2	43	Em-G1	(Em-G1)	serosa	+ massive	–	+	+	+	+
3	39	Em-G2	(Em-G2)	inner 1/3	+ micro	–	+	+	–	–
4	47	Em-G2	(Em-G2)	inner 1/3	+ massive	–	+	+	–	–
5	37	Em-G2	(Em-G2)	middle 1/3	+ massive	+	+	–	–	+
6	66	Em-G2	(Em-G2)	outer 1/3	–	+	+	–	+	–
7	51	Em-G2	(Em-G2)	outer 1/3	+ massive	+	+	–	+	–
8	53	Em-G3	(Em-G1)	inner 1/3	+ massive	–	–	+	–	–
9	51	Em-G3	(Em-G2)	middle 1/3	–	+	+	+	–	–
10	61	Em-G3	(Em-G3)	outer 1/3	–	+	–	+	+	–
11	59	ca.sa.	(Em-G1)	serosa	–	+	–	+	–	–
12	67	ca.sa.	(ca.sa.)	outer 1/3	+ massive	–	+	+	–	–
13	63	ca.sa.	(ca.sa.)	serosa	–	–	+	+	–	–
14	57	ca.sa.	(ca.sa.)	outer 1/3	–	+	+	+	+	–
15	74	ca.sa.	(Em-G3)	outer 1/3	+ massive	+	+	+	+	–
16	67	ad.sq.ca.	(Em-G1)	outer 1/3	+ massive	+	+	+	+	+

Em-G1: endometrioid adenocarcinoma (grade 1). Em-G2: endometrioid adenocarcinoma (grade 2). Em-G3: endometrioid adenocarcinoma (grade 3). ca.sa.: carcinosarcoma. ad.sq.ca.: adenosquamous carcinoma. LVSI: lymph-vascular space invasion in the myometrium. connec.: connective tissue. LVS: lymph-vascular space. Lymph node: lymph-node metastasis.

Table 3. — *Univariate and Cox multivariate analysis of prognostic factors for endometrial carcinoma for survival rate (using a Statistical Analysis System – stepwise included –).*

	Univariate analysis				Multivariate analysis			
	Beta	S.E.	Hazard Ratio (95% C.I.)	p	Beta	S.E.	Hazard Ratio (95% C.I.)	p
Parametrial spread	2.14	0.53	8.51 (2.99-24.29)	< 0.0001	1.37	0.58	3.95 (1.27-12.33)	0.018
Peritoneal cytology	1.54	0.49	4.66 (1.77-12.29)	0.0018	1.10	0.53	3.00 (1.06- 8.44)	0.037
Myometrial invasion	0.77	0.21	2.17 (1.44- 3.25)	0.0002			N.S.	
LVSI in the myometrium	1.56	0.51	4.76 (1.76-12.86)	0.0021	1.26	0.52	3.54 (1.27- 9.89)	0.0157
Cervical invasion	0.73	0.49	2.09 (0.79- 5.48)	0.1361			N.S.	
Adnexa metastasis	1.02	0.75	2.77 (0.63-12.13)	0.1755			N.S.	
Lymph-node metastasis	1.22	0.51	3.38 (1.25- 9.15)	0.0164			N.S.	
Histological type	1.07	0.31	2.91 (1.58- 5.36)	0.0006			N.S.	

Parametrial spread, peritoneal cytology, LVSI in the myometrium, cervical invasion, adnexal metastasis, lymph-node metastasis: negative vs positive.
Myometrial invasion: intra-endometrial vs inner 1/3 vs middle 1/3 vs outer 1/3 serosa.
Histological type: Em (G1-3) adenoca., vs adsq ca., serous adenoca., mucinous adenoca., clear cell adenoca. vs carcinosarcoma.

type ($p < 0.01$) was significant for poor survival rate according to univariate analysis, whereas cervical invasion ($p = 0.14$) and adnexal metastasis ($p = 0.18$) were not significant. On the contrary, according to multivariate analysis, independent significant factors for prognosis were parametrial involvement ($p = 0.018$), peritoneal cytology ($p = 0.037$) and LVSI in the myometrium ($p = 0.0157$) (Table 3).

Discussion

Parametrial spread in endometrial carcinoma was realized to be significantly prognostically poor both by univariate and multivariate analyses. However, parametrial involvement has not been considered in the current FIGO surgical and pathological staging system for endometrial carcinoma [1]. The results in the present series of studies may indicate that parametrial factor should be adopted into the staging system.

Parametrial spread was histologically proven in 16 of 269 cases (5.9%) of patients with endometrial carcinoma in the present series. It consisted of three patterns, including involvement of connective tissue, lymph vascular space (LVS) and lymph nodes, and suggests two routes of spread: direct invasion and spread via lymphatic channels.

In earlier studies, Homesley *et al.* [13] studied 90 patients who were retrospectively assigned to Stage II by reviewing preoperative, operative and pathologic findings, and found parametrial spread in eight of 36 cases (22.2%) treated by radical hysterectomy. Mackillop *et al.* [14] stated that five of 36 cases (13.8%) with surgical Stage III had parametrial spread. Schwartz & Brunschwig reported that parametrial lymph-node metastasis in endometrial carcinoma was found in only four of 96 cases treated with radical hysterectomy [15]. Yura *et al.* [9] reviewed 91 patients who underwent radical or modified radical hysterectomy with clinical Stage I or II disease. Parametrial involvement was found in none of 48 patients with surgical Stage I disease, but in 12 of 43 (28%) with surgical Stage II or III disease, and was significantly correlated with deep myometrial involvement and LVSI in the myometrium. Tamussino *et al.* [10] reviewed 24 patients who underwent radical hysterectomy, and parametrial spread was found in six (2.5%) of 16 patients with cervical involvement of the carcinoma, but none of eight without cervical involvement.

Yura *et al.* [9] classified 12 cases with parametrial spread into two patterns. One was direct invasion of cancer cells into parametrial stroma, and the other was lymphatic involvement with or without direct invasion. Also, pelvic lymph node metastasis was observed in six of seven patients with parametrial lymphatic spread, but only in one of five cases without lymphatic spread ($p < 0.05$). However, it was not significantly different between the two patterns in our series.

The therapeutic value of radical hysterectomy for endometrial cancer patients has not been generally accepted. Rutledge [2] reviewed the role of radical hysterectomy in endometrial carcinoma in 1974, and concluded that routine use of radical hysterectomy and pelvic lymphadenectomy for endometrial cancer did not prove feasible. Irradiation adjuvantly added to conservative hysterectomy could improve the effectiveness to equal that of radical hysterectomy, and the high cure rate obtained by conservative hysterectomy does not need more hazardous surgical intervention in most patients. Kinsella *et al.* [3] reported that in 55 patients with clinical Stage II endometrial carcinoma treated by simple hysterectomy and radiation therapy, ten patients recurred and six of them (60%) had recurrent tumors at the vaginal stump or pelvic cavity. In contrast, Takeshima *et al.* [16] reported that 49 of 393 patients with clinical Stage I endometrial cancer treated by modified radical hysterectomy and pelvic lymphadenectomy recurred, but only 18 cases (25%) were found to recur in the pelvic cavity. Boente *et al.* [17] reported that the pelvic recurrence rate was only 6% in 33 patients with radical hysterectomy, although they had a high frequency of risk factors, whereas in 142 patients with simple hysterectomy with or without radiation it was 22.5%. Tamussino *et al.* [10] reported that the pelvic recurrence rate was 8% in a series of 24 patients who underwent radical hysterectomy without adjuvant radiation therapy. Eltabbakh and Moore [18] reported that sur-

vival of women with Stage II endometrial carcinoma was excellent in both groups of patients, either treated with radical hysterectomy or simple hysterectomy, followed by both pelvic and vaginal cuff radiotherapy, and morbidity secondary to both therapies was mild. On the other hand, Boothby *et al.* [4] reviewed 42 patients with surgical Stage II endometrial cancer, and concluded the majority of patients with Stage II endometrial cancer were best treated by combined therapy of radiation and simple hysterectomy. These results and our data may support the therapeutic value of parametrial resection, which is at least as effective as adjuvant radiation therapy following surgery without parametrial resection.

Conclusion

Direct parametrial extension or lymphatic involvement within the parametrium can occur in endometrial carcinoma. Patients with parametrial spread have a poor prognosis.

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