Lymph node pathway in the spread of endometrial carcinoma

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Summary

Objective: To elucidate the sentinel nodes of endometrial carcinoma, the spread pathway was clarified. The correlation between lymph node spread and other clinicopathological variables was also analyzed.

Methods: Dissected lymph node samples in 342 patients who underwent pelvic and selective paraaortic lymphadenectomy were reviewed. Pelvic and paraaortic node (PLN and PAN) status was compared with clinicopathological parameters.

Results: Lymph node metastasis was demonstrated in 52 patients, including 46 cases with PLN metastasis and six patients with independent PAN metastasis. The metastatic sites were most frequent in the obturator and internal iliac nodes. Eleven of 49 patients who underwent PAN dissection were positive for metastasis. Sixteen of 23 cases with parametrial metastasis also metastasized in the retroperitoneal lymph node.

Conclusion: The lymph node spread pathway in endometrial carcinoma consists of a major route via the obturator node or internal iliac node with or without parametrial involvement, and rarely a direct PAN pathway.

Key words: Endometrial carcinoma; Lymph node metastasis; Spread pattern; Prognostic factor; Staging laparotomy.

Introduction

The International Federation of Gynecology and Obstetrics (FIGO) has adopted surgical and pathological staging of endometrial carcinoma since 1988 [1]. In this classification, metastasis to the pelvic or paraaortic lymph node (PLN or PAN) should be staged as IIIc. This is based on the results of the Gynecologic Oncology Group (GOG) study, which reported PLN and PAN involvement in endometrial carcinoma in 9% and 5%, respectively [2]. Therefore, it is necessary to investigate lymph node status. Metastasis in PAN in endometrial carcinoma is reportedly more frequent than that in cervical carcinoma [2-5]. Recently, McMeekin *et al.* [6, 7] reported retroperitoneal lymph node metastasis, including PLN and PAN, in 8% of 607 patients of which 17% showed metastasis in PAN only, whereas Mariani *et al.* [8] reported that it accounted for 17.4% in 65 patients of which 7.7% was in PAN only. Many investigators have reported that patients with endometrial carcinoma had a poor prognosis if they revealed metastasis on PLN [9]. It is not, however, a reasonable method to dissect both PLN and PAN in all patients with endometrial carcinoma. Patients who should undergo lymphadenectomy of either PLN or PAN can be identified if spread patterns and pathways of lymph node metastasis in endometrial carcinoma are clarified. Holub *et al.* [10] tried to identify the sentinel node in endometrial carcinoma by using pre- or intraoperative dye and/or lymphoscintigraphy.

In this paper, we aimed to clarify the spread patterns of lymph node metastasis in endometrial carcinoma and analyze the correlation of lymph node metastasis with clinicopathological prognostic factors in a series of cases at Kitasato University Hospital.

Revised manuscript accepted for publication November 18, 2005

Patients and Methods

There were 342 patients with endometrial carcinoma who underwent complete surgical therapy, including systemic lymphadenectomy, treated during the period between 1971 and 1998. Radical hysterectomy in addition to bilateral salpingo-oophorectomy was basically performed for patients with clinical Stage II and III, and modified radical hysterectomy was done for those with Stage I. Pelvic lymphadenectomy was performed in all cases and PAN dissection was selectively performed for those who met the criteria such as enlarged PLN and PAN, myometrial invasion of more than one-third in the excised uterine specimen, adnexal metastasis, specific histological types including serous adenocarcinoma and clear cell adenocarcinoma, and positive peritoneal cytology.

Lymph node metastasis was carefully investigated and multiple metastatic lesions found in the same node region were classed as one metastasis. To investigate the spread pathway, the left or right pelvic nodes in each case were separately analyzed and expressed as a region calculated as a side. PAN was defined as one node. Metastasized nodes were mapped and the relationship among individual positive nodes was analyzed. In addition, relationships among lymph node status and various clinicopathological variables, including clinical stage, histopathological findings, myometrial invasion, lymphovascular space invasion (LVSI), cervical invasion, adnexal metastasis, parametrial involvement and peritoneal cytology were evaluated.

Statistical analysis was performed using the chi-square test and $p < 0.05$ was considered statistically significant.

Results

Incidence of lymph node metastasis

Among the 342 patients, 165 and 177 cases underwent modified radical hysterectomy and radical hysterectomy, respectively, and 46 were positive for PLN metastasis; Eleven of 49 who underwent both PLN and PAN dissection appeared positive, including six cases with positive PAN metastasis independently, without PLN metastasis. Consequently, 52 (15.2%) of 342 patients showed positive lymph node metastasis in PLN and/or PAN.

Analysis of positive node lesions

Ninety-nine nodes were positive in 52 patients, including 11 in PAN, 13 in the common iliac node, 19 in the external iliac node, 29 in the internal iliac node, 22 in the obturator node, four in the suprainguinal node and one in the sacral node. Single metastasis in unilateral PLN or PAN regions was found in 47 patients (55 sides), of which nine cases developed multiple node metastasis in the contralateral node regions. Multiple metastases were found in the bilateral sides in four cases and in the unilateral side in one case. As a result, multiple node metastasis was found in 14 cases (18 sides).

In 55 sides with single metastasis in unilateral PLN or PAN, lymph node metastasis was most frequent in the internal iliac and obturator nodes revealing 30.9%, followed by the external iliac node in 18.2% (Table 1).

Table 1. — *Single lymph node metastasis in 55 sides (47 cases) with endometrial carcinoma.*

	Metastatic nodes (%)
Paraaortic*	6 (10.9)
Common iliac	2 (3.6)
External iliac	10 (18.2)
Internal iliac	17 (30.9)
Suprainguinal	2 (3.6)
Obturator	17 (30.9)
Sacral	1 (1.8)
Total (sides)	55 (100.0)

*: without distinction of the side.

Forty-four nodes were positive in 14 cases that suffered multiple metastases in 18 sides of PLN and PAN. Metastasis in the internal iliac node and/or obturator node was found in 16 sides (88.9%). Metastasis in the internal iliac node was found on 12 sides, of which five and seven cases were also metastasized in the external and common iliac nodes, respectively. Of these, four cases metastasized into PAN with or without common iliac node metastasis. Metastasis in the obturator node, where single metastasis was frequently found, occurred on five sides, of which additional metastases were found in one of the internal iliac nodes and two in PAN. Additional metastasis, both in the external and the common iliac nodes was seen on two sides, one of which also metastasized in to PAN. Five (22.7%) of 22 sides with positive obturator nodes, 11 of 29 with positive internal iliac nodes and six of 19 with positive external iliac nodes had more metastasis in the distant cranial nodes, whereas only two with both negative obturator or internal iliac nodes were positive in the external iliac and/or suprainguinal node.

In 49 patients who underwent PLN and PAN dissection, 11 were positive for PAN metastasis. Thirteen cases were found to have metastasis in PLN, whereas 36 were not. The incidence of metastasis in PAN was 38.5% and 16.7%, respectively. Six cases that developed PAN metastasis without metastasis in PLN are listed in Table 2. Cancer lesions occupied the whole endometrium; there was also deeper myometrial invasion and frequent LVSI. No additional adnexal metastasis nor positive peritoneal cytology was determined.

Table 2. — *Cases with paraaortic node metastasis and without pelvic node metastasis.*

Case	Clin. Stage	Histology	Myometrial invasion	Cervical involvement	LVSI	Peritoneal cytology	Adnexal metastasis	Pm. metastasis
1	III	adenosq	outer 1/3	+	+	negative	–	–
2	II	clear cell	inner 1/3	+	–	negative	–	–
3	II	clear cell	middle 1/3	+	–	negative	–	–
4	II	G2 em	outer 1/3	+	+	negative	–	–
5	II	carcinoma	serosa	–	+	negative	–	+
6	III	G3 em	serosa	+	+	negative	–	–

Clin: clinical; LVSI: lymph vascular space invasion in the myometrium; Pm: parametrium; adenosq: adenosquamous cell carcinoma; clear cell: clear cell carcinoma; em: endometrioid adenocarcinoma; carcinosa: carcinosarcoma.

Parametrial metastasis was found in 23 of 342 cases (29 sides). Metastasis both in the parametrium and the lymph nodes was found in 16 cases (Table 3) and one of those 16 cases had a single metastasis in PAN. Ipsilateral PLN involvement was found in 13 cases or in 17 of 28 sides and contralateral node metastasis was also found in five sides. In two cases (2 sides), metastasis was found in only the contralateral lymph node. Among 17 sides with ipsilateral involvement, 14 were found to have metastasis either in the internal iliac node or obturator node. Single metastasis in PLN was recorded in nine sides with ipsilateral parametrial involvement, and seven were involved either in the internal iliac node or obturator node.

Table 3. — *Lymph node state of 15 patients with both parametrial and pelvic lymph node metastasis.*

	Number	Sacral	Suprainguinal	Obturator	Internal iliac	External iliac	Common iliac
Ipsilateral	17 sides*	1	2	3 (2)	11 (5)	4 (1)	6 (1)
Contralateral	7 sides**	–	1	2 (2)	4 (2)	3	2

( ): case number with single node metastasis; *: three sides had both pelvic and paraaortic node metastasis; **: one side had both pelvic and paraaortic node metastasis.

Correlation with clinicopathological parameters

Lymph node metastasis was statistically higher in patients with advanced clinical stage, unusual histologic type including adenosquamous cell carcinoma, higher grade of endometrioid carcinoma, deeper myometrial invasion, LVSI, cervical invasion, adnexal metastasis, parametrial involvement and positive peritoneal cytology (Table 4).

Discussion

In this study series, 15.2% of patients with endometrial carcinoma developed retroperitoneal lymph node metastasis. The most frequent metastatic single region was the internal iliac node and obturator node in 61.8%, and multiple metastasis also involved either of these nodes in 88.9%. Frequent lymph node metastasis in the internal and external iliac nodes has been reported in the literature [11]. However, we speculate from our results that metastasis originates either in the internal iliac or obturator node region and spreads further to the cranial and distant lymph nodes (Table 2). Therefore, the internal iliac and obturator nodes could be sentinel nodes of endometrial carcinoma.

Parametrial metastasis in endometrial carcinoma has a poorer prognosis [12]. Metastasis either in the internal

Table 4. — *Frequency of lymph node metastasis in 342 patients with endometrial carcinoma.*

		Overall	Positive (%)	p value
Clinical stage	I	176	13 (7.4)	< 0.01
	II	157	33 (21.0)	
	III	9	6 (66.7)	
Histological type	Endometrioid	276	32 (11.6)	*, **
	Adenocanthoma	24	4 (16.7)	
	Adenosquamous	9	5 (55.6)	*
	Serous	9	2 (22.2)	**
	Mucinous	7	1 (14.3)	
	Clear	6	3 (50.0)	
	Carcinosarcoma	11	5 (45.4)	
Grade (Endometrioid)	G1	139	11 (7.9)	n.s.
	G2	109	17 (15.6)	
	G3	28	4 (14.3)	
Myometrial invasion	Intra-endometrial	69	0	< 0.01
	Inner 1/3	142	8 (5.6)	
	Middle 1/3	63	9 (14.3)	
	Outer 1/3	56	26 (46.4)	
	Serosa	12	9 (75.0)	
LVSI	Positive	106	42 (39.6)	< 0.01
	Negative	236	10 (4.2)	
Cervical invasion	Positive	82	30 (36.6)	< 0.01
	Negative	260	22 (8.5)	
Adnexal metastasis	Positive	19	9 (47.4)	< 0.01
	Negative	323	43 (13.3)	
Parametrial metastasis	Positive	23	16 (69.6)	< 0.01
	Negative	319	35 (11.0)	
Peritoneal cytology	Positive	45	11 (24.4)	< 0.05
	Negative	212	26 (12.3)	

LVSI: lymph vascular space invasion in the myometrium; *, **: $p < 0.01$.

iliac or obturator node was highly correlated with that in the parametrium in 61.1%. Consequently, there may be a pathway via lymphatic lesions in the parametrium in addition to direct spread to PLN.

Direct spread to PAN was observed in 16.7% as well as the pathway via the pelvic lymph node in 38.5 in this study. When 293 patients who were not indicated to undergo PAN dissection were calculated as negative, the incidence of PAN metastasis was 1.8%, similar to that reported by Mariani *et al.* [8]. The incidence of metastasis both in PLN and PAN was reported to be 3% to 16% [2, 5], and that in PAN without coexisting pelvic node metastasis was from 0% to 2% [2, 5]. Thus, there may be two spread patterns to PAN, including a major pathway via PLN, and a rare direct pathway.

Lymph node metastasis in endometrial carcinoma is correlated with clinical stage, histological type of the carcinoma, grade of endometrioid adenocarcinoma, myometrial invasion, LVSI, cervical invasion, adnexal metastasis, parametrial involvement and positive peritoneal cytology. Correlations with these clinicopathological variables have been reported in the literature [2, 5, 13, 14]. However, Creasman *et al.* [2] and Girardi *et al.* [13] reported that lymph node metastasis was not correlated with histological type. Four cases (4%) of endometrial carcinoma with pelvic lymph node metastasis and without myometrial invasion were reported by Takeshima *et al.* [15]. Boronow *et al.* [3] also denied a link between the grade of endometrioid adenocarcinoma. Creasman *et al.* [2] demonstrated that positive peritoneal cytology in endometrioid carcinoma was correlated with metastasis both at PLN and PAN, whereas in our series PAN metastasis was not correlated with positive cytology (data not shown). Lymph node metastasis was found in 69.9% of the cases with parametrial involvement in our series, which was significantly higher than the 11.0% of parametrial negative patients (Table 4). Tammusino *et al.* [16] reported supporting data with a limited number of 24 cases.

In cases of clinical Stage I, well-differentiated adenocarcinoma and shallow myometrial invasion, and sentinel node dissection of the internal iliac and obturator nodes could be substituted for total systemic PLN and PAN dissection.

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