

Analysis of outcome of Stage I-III endometrial cancer treated with systematic operation omitting paraaortic lymphadenectomy

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Summary

Purpose: The aim of this study was to assess the outcomes of endometrial cancer patients treated with systematic surgery omitting paraaortic lymphadenectomy.

Patients and Methods: We retrospectively analyzed a consecutive series of 84 endometrioid-type endometrial cancer patients at FIGO Stage I, II or III without grossly metastatic paraaortic lymphadenodes, who underwent surgery at our institute.

Results: Sixty-five patients (77%) underwent primary surgery with pelvic lymphadenectomy while the remaining 19 patients underwent surgery without lymphadenectomy due to severe medical complications or age greater than 70 years. The patients with high risk for recurrence were treated mainly by adjuvant irradiation therapy of the whole pelvis. The median follow-up period was 44 months. The 5-year overall survival (OS) rate was 92%, 92% and 65% for FIGO Stage I, II and III, respectively. Recurrence was detected in eight of the 82 optimally operated patients (9.8%). Out of the eight recurrent patients, five patients had a recurrent tumor at extra-pelvic sites (chest or abdomen), two patients had a recurrent tumor only in a paraaortic lymph node, and one patient had a recurrent tumor only in the vagina. Thus, the recurrence rate was relatively low, with 2.4% relapse at the paraaortic lymph nodes, and 5-year OS rate appeared to be favorable. However, all the six recurrent patients who underwent adjuvant radiation therapy had distant recurrence.

Conclusions: These findings indicate that omission of paraaortic lymphadenectomy may be acceptable for endometrial cancer patients without gross metastasis at this site. However, the high rate of distant recurrence after whole pelvic irradiation strongly indicates an urgent need to develop potent systemic adjuvant therapy, potentially by chemotherapy or chemoradiation therapy.

Key words: Endometrial cancer; Operation; Paraaortic lymphadenectomy; Recurrence; Prognosis.

Introduction

Endometrial cancer is the third most common gynecologic malignancy in Japan, and its frequency has dramatically increased in the last decade. The established therapeutic modality for this cancer includes primary surgery consisting of total abdominal hysterectomy with bilateral salpingo-oophorectomy (BSO). Retroperitoneal lymph node metastasis is one of the critical prognostic factors for recurrence and survival [1-3]. In 1988, the International Federation of Gynecologic and Obstetrics recommended that pelvic and paraaortic lymphadenectomy be included in primary surgery for this cancer [4]. However, there have been controversies regarding the value of lymphadenectomy, especially in early-stage endometrial cancer [5-8]. Since paraaortic lymphadenectomy is sometimes associated with severe postoperative complications, the issues of inclusion of paraaortic lymphadenectomy have clinical significance for most gynecologic surgeons. In our hospital, patients with endometrial cancer without grossly metastatic paraaortic lymph nodes have been treated with primary surgery consisting of total abdominal hysterectomy and BSO with pelvic lymphadenectomy

(PLAN), omitting paraaortic lymphadenectomy, irrespective of the presence of risk factors for metastasis. Therefore, a follow-up survey of these patients may provide useful information about the role of paraaortic lymphadenectomy. In the present retrospective study, we analyzed treatment outcomes in a consecutive series of 91 endometrial cancer patients surgically treated in our hospital.

Patients and Methods

The subjects comprised a consecutive series of 84 surgical Stage I to III endometrial cancer patients who underwent systematic surgery at Kanazawa University Hospital between 1995 and 2004. The surgical procedures in our hospital are defined as extended surgical staging consisting of washing peritoneal cytology, simple total hysterectomy (STH) or radical hysterectomy (RH), bilateral salpingo-oophorectomy (BSO) and PLAN. PLAN consists of removal of tissue overlying the external iliac artery and vein and tissue in the obturator fossa above the obturator nerve, and is considered adequate when at least ten lymph nodes are dissected. The patients with grossly metastatic paraaortic lymph nodes, assessed preoperatively by computed tomography (CT) or magnetic resonance imaging (MRI) or intraoperatively, underwent operations with the addition of paraaortic lymph node biopsy or paraaortic lymphadenectomy, and such patients were excluded from the analysis, since the

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purpose of this study is to demonstrate the outcome of patients who underwent systemic operations omitting paraaortic lymphadenectomy in the absence of macroscopic metastasis. Fifty-five patients (65%) underwent STH+BSO+PLAN. Patients with suspected cervical invasion underwent RH+BSO+PLAN (10 patients; 12%). All these patients underwent adequate PLAN with the average number of pelvic lymph nodes dissected being 16.4 (ranging from 11 to 32). Patients with severe medical complications and patients older than 70 years underwent STH+BSO (17 patients; 20%); this included some patients in advanced stages for whom complete resection of the lesions was impossible. Two Stage Ia patients with small endometrial lesions (2%) underwent STH alone, due to their desire for ovarian preservation.

Adjuvant radiation therapy of the whole pelvis with an external beam was administered at a total dose of 50.4 Gy in 22 patients with risk factors for recurrence; i.e., deep myometrial invasion (> 1/2), grade 3 tumor, cervical extension, or extrauterine disease. Patients with positive peritoneal cytology or with lesions that extended outside the pelvis were administered adjuvant chemotherapy in combination with cisplatin (75 mg/m²), doxorubicin (50 mg/m²) and cyclophosphamide (500 mg/m²) in four cycles from 1995 to 2000, and in combination with paclitaxel (180 mg/m²) and carboplatin (AUC = 5) in four to six cycles since 2001. Since 2004, patients in FIGO Stage III have been routinely administered adjuvant chemotherapy in combination with paclitaxel (180 mg/m²) and carboplatin (AUC = 5) in four to six cycles.

All patients were followed after therapy for recurrence by vaginal ultrasonography and tumor marker tests every one to three months depending on the time after therapy as well as by CT every six months. Time-on-study or time-to recurrence was calculated from the date of surgery to the follow-up cutoff date or to recurrence. Survival curves were estimated using the Kaplan-Meier product limit method. Statistical significance was determined using the log-rank test and the chi-square test, and a p value of < 0.05 was considered to indicate statistical significance.

Results

The mean age of all patients was 57.9 years, with a range of 26 to 76 years. The median follow-up was 44 months, with a range of one to 131 months. Tables 1 and 2 show the clinicopathological characteristics of the patients. Pelvic lymph node metastasis was found in eight (15%) of the 55 patients who underwent PLAN. Eighty of the 84 patients (95%) survived, and nine patients (11%) died (6 died of endometrial cancer and 3 died of other causes). Recurrence was detected in eight (9.8%) of the 82 optimally operated patients: 0 (0%) of the 17 Stage Ia patients, one (2.9%) of the 34 Stage Ib patients, two (20%) of the ten Stage Ic patients, two (25%) of the eight Stage IIa patients, one (25.0%) of the four Stage IIb patients, 0 (0%) of the three Stage IIIa patients, and two (33%) of the six Stage IIIc patients. Table 2 shows the data for all eight patients with recurrence. Of the eight recurrent patients, four patients (50%) had extrapelvic recurrence at the chest or abdomen, including one patient who also had recurrence at the vagina. Two patients had recurrence only at the paraaortic lymph nodes and two patients had pelvic recurrence at the vagina or at the pelvic mesentery. No patient had recurrence at the pelvic

Table 1. — Surgical stage and histological grade.

Grade	(n)	FIGO Stage								
		Ia	Ib	Ic	IIa	IIb	IIc	IIIa	IIIb	IIIc
G1	(55)	15	22	4	7	2	0	2	0	3
G2	(17)	1	8	3	0	1	0	0	0	4
G3	(12)	1	4	3	1	1	0	1	0	1
Total	(84)	17	34	10	8	4	0	3	0	8

Table 2. — Depth of myometrial invasion and histological grade.

Grade	(n)	Depth of myometrial invasion		
		none	1-50%	50% <
G1	(55)	21	27	7
G2	(17)	1	11	7
G3	(12)	2	3	7
Total	(84)	24	41	21

Table 3. — Characteristics of patients with recurrence.

Patient	Age	Stage	Grade (Histology)	Myometrial invasion	Site	Time therapy	Adjuvant
1	68	Ib	1	< 50%	Pelvic mesentery	8	none
2	64	Ic	2	> 50%	Lung	30	Radiation (WP)
3	72	Ic	3	> 50%	Lung, liver	6	Radiation (WP)
4	68	IIa	1	none	Vagina	5	none
5	68	IIa	3	> 50%	Vagina, lung	6	Radiation (WP)
6	76	IIb	3	> 50%	Lung	2	Radiation (WP)
7	58	IIIc	1	< 50%	PAN	23	Radiation (WP)
8	69	IIIc	2	< 50%	PAN	17	Radiation (WP)

Stage FIGO 1988 surgical stage; Grade, final grade; Site, site of recurrence; Time, time to recurrence in months; WP, Whole pelvis; PAN, paraaortic lymph node.

lymph nodes. Both of the two patients with vaginal recurrence were classified as FIGO Stage IIa. Figures 1 to 3 show the Kaplan-Meier survival curves. The 5-year overall survival (OS) rate was 92%, 92% and 65% for FIGO Stage I, II and III, respectively. Patients with grade 3 tumors had a lower survival rate (63%) than patients with grade 1 or 2 tumors (87%) (p = 0.005). Patients with > 50% myometrial invasion had a significantly lower survival rate (67%) than patients with < 50% myometrial invasion or no invasion (88%) (p = 0.002).

Discussion

The present study retrospectively analyzed the treatment outcome of endometrial cancer patients in FIGO Stage I, II or III, surgically treated with pelvic lymphadenectomy. Because our surgical treatment for such patients omits paraaortic lymphadenectomy, the frequency and pattern of recurrence in these patients is of particularly great concern, especially compared with patients who have undergone routine paraaortic lymphadenectomy at other institutions. We found eight (9.8%) cases of recurrence among the 82 optimally operated patients. Recurrence was detected in 5% of the FIGO Stage I patients, 25% of the Stage II patients, and 22% of the Stage III patients. There have been many reports of recurrence rates after paraaortic lymphadenectomy to treat endometrial cancer in various FIGO stages. Otsuka *et al.* reported that relapse occurred in 13% of a consecutive series comprising 105 FIGO Stage I to III patients and one Stage IV patient, in which paraaortic

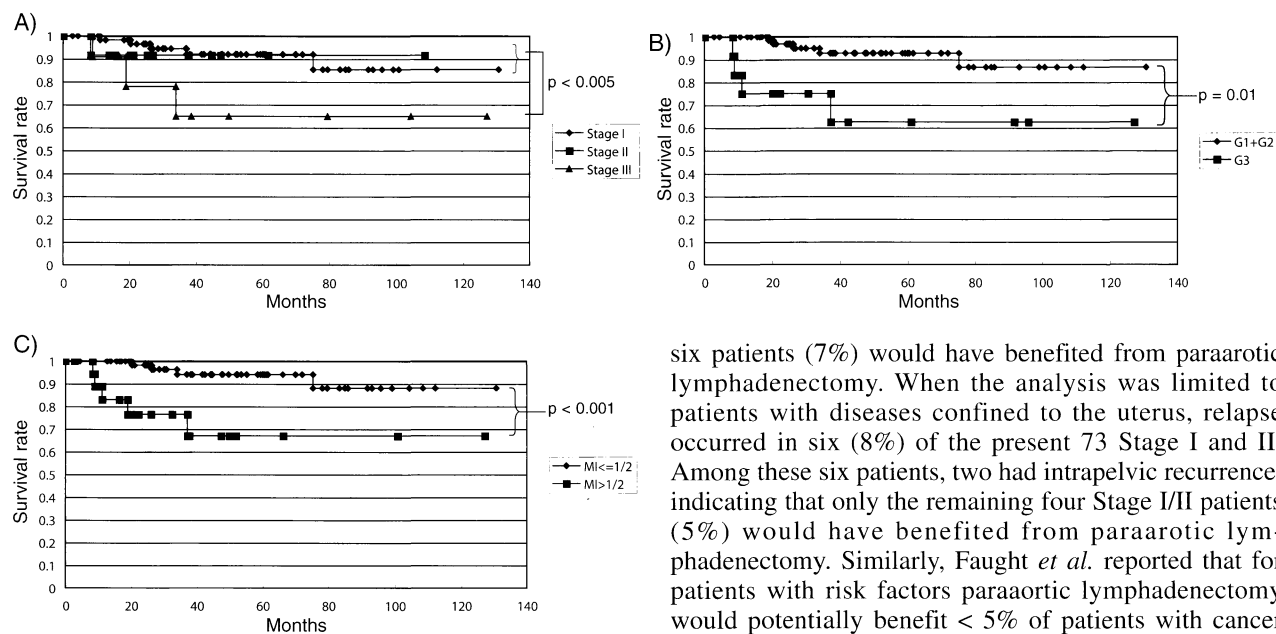


Figure 1. — The Kaplan-Meier survival curves of patients with various FIGO stages (A), tumor grades (B) and depth of myometrial invasion (MI) (C).

lymphadenectomy was performed in patients with risk for metastasis to the paraaortic lymph nodes. In their study, 12 of the 14 recurrent patients had recurrence at distant sites, including the lungs, liver and brain [9]. Kim *et al.* reported similar findings, with a 10% recurrence rate for 103 FIGO Stage I to III patients who underwent selective paraaortic lymphadenectomy. Six of those ten recurrences were detected at distant sites, including the lungs and brain [10]. Straughn *et al.* found recurrence in 9% of 220 FIGO Stage Ic patients (6% of the radiated group, and 12% of the observation group) [11]. Ayhan *et al.* found recurrence in 17% of 48 FIGO Stage II patients [12]. Other studies have found the following recurrence rates: approximately 30 to 50% for FIGO Stage III, and 32% for Stage IIIc [13]; 41% for Stage III [14]; 42% for Stage IIIa/b, and 54% for Stage IIIc [15]. Thus, recurrence rates for patients treated with paraaortic lymphadenectomy have varied considerably among studies, probably due to a variety of factors, including differences among adjuvant settings. These recurrence rates in patients undergoing paraaortic lymphadenectomy do not appear to be significantly better than the present recurrence rates. However, since our study included only patients without grossly metastatic paraaortic lymph nodes, we cannot simply compare the recurrence rates with these previous studies. Nevertheless, based on the present recurrence rates, we can estimate what proportion of endometrial cancer patients would benefit from paraaortic lymphadenectomy. The present data indicate that relapse occurred in eight (9.8%) of the 82 optimally operated patients. Among these eight patients, two had intrapelvic recurrence, indicating that only the remaining

six patients (7%) would have benefited from paraaortic lymphadenectomy. When the analysis was limited to patients with diseases confined to the uterus, relapse occurred in six (8%) of the present 73 Stage I and II. Among these six patients, two had intrapelvic recurrence, indicating that only the remaining four Stage I/II patients (5%) would have benefited from paraaortic lymphadenectomy. Similarly, Faught *et al.* reported that for patients with risk factors paraaortic lymphadenectomy would potentially benefit $< 5\%$ of patients with cancer confined to the uterus [16]. These data may indicate the limited role of paraaortic lymphadenectomy in reducing the recurrence rate, especially among patients with cancer confined to the uterus.

Two (2.4%) of the 82 optimally operated patients had recurrence at the paraaortic lymph nodes; both patients were at FIGO Stage IIIc with pelvic lymph node metastases. It has been reported that approximately 40 to 50% of patients with pelvic lymph node metastasis have paraaortic lymph node involvement [17, 18], indicating that pelvic lymph node metastasis is the most critical risk factor for paraaortic lymph node metastasis. The two above-mentioned patients with recurrence underwent whole-pelvis adjuvant radiation therapy. It is therefore possible that micrometastatic foci developed in the paraaortic lymph nodes outside the radiation area. To minimize such treatment failure, we propose use of extended-field radiation covering the paraaortic lymph nodes or adjuvant chemotherapy in patients who undergo pelvic (but not paraaortic) lymphadenectomy, because this would apparently decrease the risk of paraaortic lymph node recurrence in Stage IIIc patients. The value of adjuvant chemotherapy has recently been recognized, given the fact that the majority of recurrences develop at distant sites. Actually, six of the eight recurrent patients in the present study underwent whole pelvic irradiation postoperatively, but all of them had relapse outside the radiation field, indicating the limitation of irradiation therapy. Based on these data, adjuvant chemotherapy has routinely been performed in our institute since 2004, in combination with paclitaxel and carboplatin, for patients with FIGO Stages Ic-III or those with G3 pathological grade, and we are currently assessing whether this treatment decreases the rate of recurrence. A recent large-scale randomized study of advanced endometrial cancer patients in FIGO Stages III and IV has shown that adjuvant chemotherapy (doxorubicin+CDDP) significantly improves survival, compared to whole-abdominal radi-

tion therapy [19]. Similarly, in a recent randomized trial targeting earlier stage patients, chemotherapy (CDDP+doxorubicin+cyclophosphamide) was found to produce a better survival rate than whole-pelvic radiation therapy in patients with high or intermediate risk of metastasis (myometrial invasion > 1/2, Stage II and IIIa) [20]. It is interesting that one study found that cisplatin-based chemotherapy followed by pelvic and extended-field periarotic irradiation produced a > 80% 5-year survival rate among FIGO Stage III node-positive endometrial cancer patients [21], indicating that chemoradiation is a useful strategy for node-positive patients.

In summary, the present data indicate the relatively favorite treatment outcome in Stage I to III endometrial cancer patients who underwent surgery with pelvic (but not paraaortic) lymphadenectomy. However, a randomized study with sufficient statistic power is required to conclude the benefit of paraaortic lymphadenectomy. Most importantly, the present study indicates an urgent need for the development of more potent systemic adjuvant therapy, possibly by chemotherapy or chemoradiation therapy, to minimize distant recurrence.

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