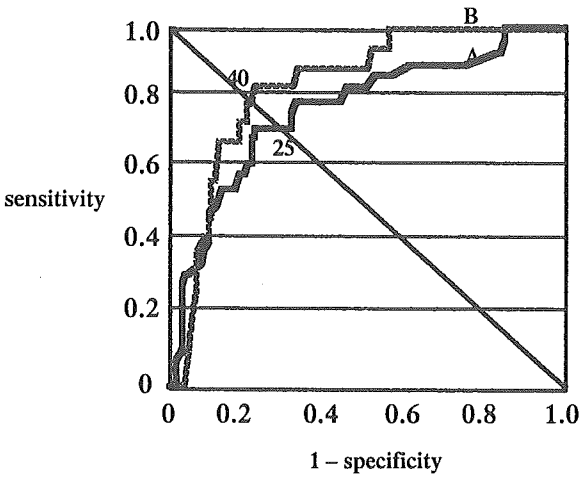

Fig 2. Receiver operating characteristic curves were obtained from relationships between volume index and lymph node metastasis. *A*, Pelvic lymph node metastasis. *B*, Para-aortic lymph node metastasis.

hysterectomy, and 16% of G2 cases in preoperative settings were upgraded to G3 adenocarcinoma after hysterectomy. In histologic type evaluation, there was no difference between preoperative biopsy specimens and specimens that were obtained from hysterectomy.

Table IV shows the results of logistic regression analysis in which volume index, MRI myometrial invasion, serum CA 125 level, histologic type, and histologic grade in preoperative settings were used as independent variables and pelvic lymph node metastasis was used as a dependent variable. Univariate analyses revealed that a volume index of ≥25, MRI myometrial invasion of more than or equal to one half, high serum CA 125 level, serous adenocarcinoma, and histologic grade of G2 and G3 were risk factors. Multivariate analysis indicated that serous adenocarcinoma, a volume index of ≥25, a preoperative histologic grade of G3, and a high serum CA125 level were independent risk factors for pelvic lymph node metastasis (Table V).

Table VI shows results of logistic regression analysis in which para-aortic lymph node metastasis was used as a dependent variable. Univariate analyses revealed that a volume index of ≥40, an MRI myometrial invasion of more than or equal to one half, a high serum CA 125 level, and a histologic grade of G3 were risk factors. Multivariate analysis indicated that a high serum CA 125 level and a volume index of ≥40 were independent risk factors (Table VII).

Table VIII shows actual metastasis frequencies by risk factors for lymph node metastasis. Of 110 cases with no risk factors for pelvic lymph node metastasis, 4 cases (3.6%), in fact, had pelvic lymph node metastasis, in only one pelvic lymph node in each case. On the other hand, there was only 1 patient with para-aortic lymph node metastasis in 128 patients with no risk factors for para-aortic lymph node metastasis. This patient had serous adenocarcinoma. Of those 128 cases, 125 cases (which exclude cases of serous adenocarcinoma) had no actual para-aortic lymph node metastasis.

Comment

It is known that lymph node metastasis is a critical prognostic factor in endometrial carcinoma[1] and that histologic grade and myometrial invasion are correlated strongly with lymph node metastasis.[2,3] On the basis of these facts, we may be able to stratify patients before operation into those who must be treated with lymphadenectomy and those who do not need to undergo lymphadenectomy by determining the grade and depth of myometrial invasion of the tumor. However, there is no preoperative method for determining the presence of localized invasion in endometrial carcinoma accurately. In many institutions, it seems that the necessity for lymphadenectomy is determined by an indirect evaluation of myometrial invasion with the use of MRI or by the consideration of histologic grade in biopsy specimens. However, it is questionable whether the indirect determination of myometrial invasion with the use of MRI can provide adequate evidence for the indication of lymphadenectomy.

MRI can provide multisectional images and depict clearly uterine zonal anatomy. The junctional zone just beneath the endometrium in a T2-weighted image is an excellent indicator for the determination of myometrial invasion. In 1987, Hricak et al[9] reported criteria for determining clinical stages of endometrial carcinoma by MRI. The diagnosis of deep invasion (invasion of more than one half of the myometrium) in clinical stage I carcinoma that was treated in their institution had a high sensitivity and specificity: 100% and 97%, respectively. However, their multi-institutional cooperative study in 1991 showed that the diagnosis of deep invasion had a low sensitivity and specificity (54% and 89%, respectively), which indicated that their previous single institutional study might have been biased.[10] Scoutt et al,[11] who investigated causes of misdiagnosis of myometrial invasion, reported that polypoid tumor and age are significant factors in misdiagnosis. In cases of polypoid tumor, the normal myometrium is stretched and thinned; myometrial invasion therefore tends to be misdiagnosed as deep invasion. Junctional zones are usually not found in elderly women,[12] and it is difficult to determine myometrial invasion on the basis of findings of the status of the junctional zone. In the 1990s, many studies demonstrated the usefulness of gadolinium-enhanced T_1-weighted MRI. The rate of correct diagnosis of deep invasion with the use of this technique was improved from 85.7% to 92.8% in a study by Sironi et al[13] in 1992 and from 85.0% to 92.5% in a study by Yamashita et al[14] in 1993. The rate

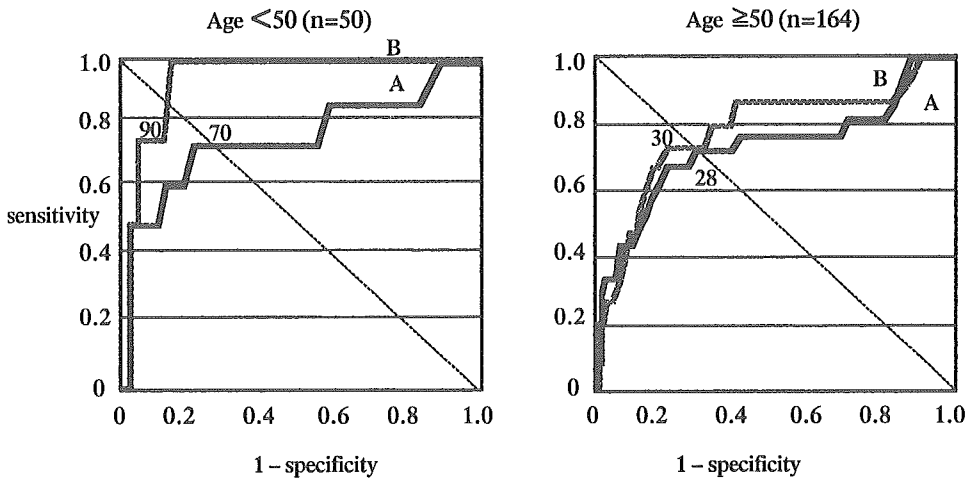

Fig 3. Receiver operating characteristic curves were obtained from relationships between serum CA 125 level and lymph node metastasis. *A,* Pelvic lymph node metastasis. *B,* Para-aortic lymph node metastasis.

Table IV. Factors that can be evaluated before operation and pelvic lymph node metastasis

Factor	*Pelvic lymph node metastasis (n/N)*	*Univariate analysis, P value*
Volume index		
<25	8/144 (5.6%)	
>25	21/70 (30.0%)	<.0001
Myoinvasion (MRI)		
<½	8/119 (6.7%)	
≥½	21/95 (22.1%)	<.005
CA 125 level		
Low*	8/147 (5.4%)	
High†	21/67 (31.3%)	<.0001
Histologic type		
Nonserous	25/207 (12.1%)	
Serous	4/7 (57.1%)	<.005
Histologic grade (before operation)		
G1	10/136 (7.3%)	
G2	11/58 (19.0%)	<.05 (Gl vs G2)
G3	8/20 (40.0%)	<.0005 (G2 vs G3)

*Level, <70 (age,<50 years); level, <28 (age, ≥50 years).
†Level, ≥70 (age, <50 years); level, ≥28 (age, ≥50 years).

Table V. Factors that can be evaluated before operation and pelvic lymph node metastasis

Factor	β	*SE*	*Odds ratio (95% CI)*	*P value*
Histologic type (nonserous, serous)	2.4	1.01	11.4 (1.6-83.3)	<.05
CA 125 level (low,* high†)	1.5	0.50	4.3 (1.6-11.6)	<.005
Volume index (<25, ≥25)	1.5	0.58	4.3 (1.4-13.3)	<.05
Histologic grade				
G2 0.9	0.9	0.53	2.6 (0.9-7.3)	NS
G3 1.3	1.3	0.66	3.7 (1.0-13.7)	<.05
Myoinvasion (MRI, <½, ≥½)	0.2	0.54	1.3 (0.4-3.6)	NS

NS, Not significant.
*Level, <70 (age,<50 years); level, <28 (age, ≥50 years).
†Level, ≥70 (age, <50 years); level, ≥28 (age, ≥50 years).

of correct diagnosis by the use of this technique has also increased in postmenopausal women and in cases in which no junctional zone is observed, as was demonstrated in a study by Lee et al[15] in 1999 in which the rates of correct diagnosis of deep invasion in postmenopausal women were 52% with the use of T_2-weighted imaging and 86% with the use of gadolinium-enhanced T_1-weighted imaging. In 1999, Kinkel et al[16] demonstrated by meta-analysis that gadolinium-enhanced T_1-weighted imaging is a superior diagnostic method to T_2-weighted

Table VI. Factors that can be evaluated before operation and para-aortic lymph node metastasis

Factor	*Para-aortic lymph node metastasis (n/N)*	*Univariate analysis P value*
Volume index		
<40	3/156 (1.9%)	
≥40	16/56 (28.6%)	<.0001
Myoinvasion (MRI)		
<½	3/118 (2.5%)	
≥½	16/94 (17.0%)	<.005
CA 125 level		
Low*	5/156 (3.2%)	
High†	14/56 (25.0%)	<.001
Histologic type		
Nonserous	17/206 (8.3%)	
Serous	2/6 (33.3%)	NS
Histologic grade (before operation)		
G1	7/135 (5.2%)	
G2	5/57 (88%)	NS (G1 vs G2)
G3	7/20 (35.0%)	<.01 (G2 vs G3)

NS, Not significant.
*Level, <70 (age,<50 years); level, <28 (age, ≥50 years); logistic regression analysis.
†Level, ≥70 (age, <50 years); level, ≥28 (age, ≥50 years); logistic regression analysis.

Table VII. Factors that can be evaluated before operation and para-aortic lymph node metastasis

Factor	β	*SE*	*Odds ratio (95% CI)*	*P value*
Volume index (<40, ≥40)	2.1	0.71	8.2 (2.0-32.6)	<.005
CA 125 level (low,* high†)	1.6	0.60	5.0 (1.5-16.2)	<.01
Myoinvasion (MRI, <½, ≥½)	1.0	0.72	2.8 (0.7-11.6)	NS
Histologic grade (G1/G2, G3)	1.0	0.65	2.7 (0.7-9.6)	NS

NS, Not significant.
*Level, <70 (age,<50 years); level, <28 (age, ≥50 years); logistic regression analysis.
†Level, ≥70 (age, <50 years); level, ≥28 (age, ≥50 years); logistic regression analysis.

Table VIII. Rates of lymph node metastasis by risk factor for lymph node metastasis

	*Pelvic lymph node metastasis (n/N)**					
	Volume index <25‡		*Volume index ≥25‡*		*Para-aortic lymph node metastasis (n/N)†*	
CA 125 level	*G1/G2*	*G3/Serous*	*G1/G2*	*G3/Serous*	*Volume index <40§*	*Volume index ≥40§*
Low	4/110 (3.6%)	1/7 (14%)	2/25 (8%)	1/5 (20%)	1/128 (0.8%)	4/28 (14%)
High	1/23 (4.3%)	2/4 (50%)	12/31 (39%)	6/9 (67%)	2/28 (7%)	12/28 (43%)

*N = 214.
†N = 212.
‡Low: <70 (age, <50 years); <28 (age, ≥50 years); high: ≥70 (age, <50 years); ≥28 (age, ≥50 years).
§Low: <90 (age, <50 years); <30 (age, ≥50 years); high: ≥90 (age, <50 years); ≥30 (age, ≥50 years).

imaging or sonography. In the current study, the diagnosis of deep invasion with the use of gadolinium-enhanced MRI had a sensitivity of 79.2%, a specificity of 74.4%, and an accuracy of 76.1%, less than those in above-mentioned studies. In regard to the assessment of depth of myometrial invasion with MRI, equivocal cases are encountered often. We used the volume index as a new MRI-related factor in this study. It was shown that MRI-based evaluation of myometrial invasion is a confounding factor of the volume index and that the latter is more useful than the former for the prediction of lymph node metastasis. We also believe that it is easier to identify a risk for lymph node metastasis by the use of volume index than by the use of MRI-based evaluation of myometrial invasion, because this index is a continuous variable.

With regard to histologic grade of the tumor, the fact that there is a difference between the grade that is determined by examination of a curettage biopsy specimen and that is determined by examination of a specimen that was obtained from hysterectomy must be taken into ac-

count. Obermair et al[17] investigated 137 cases of G1 adenocarcinoma that were diagnosed by the results of examination of curettage biopsy specimens and reported that 20% of those cases were upgraded to G2 adenocarcinoma after an examination of the specimens that were obtained from hysterectomy. In the current study, we found that postoperative histologic grade 2 was not a risk factor for pelvic lymph node metastasis but that preoperative histologic grade 2 was a risk factor for pelvic lymph node metastasis in univariate analysis. Preoperative histologic grade 2 cases include postoperative histologic grade 3 cases to some extent. We found that 16% of G2 cases in preoperative settings were upgraded to G3 adenocarcinoma after an examination of specimens that were obtained from hysterectomy.

Serous adenocarcinoma and clear cell adenocarcinoma of the endometrium have been shown to be associated with poor survival.[18-20] We demonstrated that the prognostic significance of these specific cell types of tumor is independent of lymph node metastasis and other histopathologic prognostic factors.[21] Lampe et al[22] reported that lymph node metastasis occurs more easily in cases of serous adenocarcinoma than in other histologic types of tumor. Goff et al[23] reported that metastasis occurred in 22 of 50 cases (42%) of serous adenocarcinoma. However, it is not clear whether the rate of lymph node metastasis in clear cell adenocarcinoma is high. Because previous studies have suggested that serous adenocarcinoma has a marked impact on lymph node metastasis, we took histologic type into consideration and divided our patient population into 2 groups: a serous adenocarcinoma group and a nonserous adenocarcinoma group.

No specific serum tumor markers have been established for endometrial carcinoma. However, it has been reported that the elevation of CA 125 level is associated with an increase in the incidence of extrauterine disease[24] and that high CA 125 values are related strongly to advanced surgical stage,[4] lymph node metastasis,[4] and poor prognosis.[5] The results of the present study suggested that serum CA 125 level may be more useful than the depth of myometrial invasion and histologic grade for the prediction of lymph node metastasis.

Finally, individualization of treatment should be considered. Of the 110 cases with no risk factors for pelvic lymph node metastasis, metastasis was actually found in 4 cases (3.6%). In these 4 cases, metastasis to only one pelvic lymph node and lymph–vascular space invasion was observed, but neither cervical invasion nor adnexal metastasis was observed. The prediction of lymph node metastasis was very difficult in these cases, because lymph–vascular space invasion cannot be detected before the operation. Careful consideration of the possibility of the elimination of the requirement of pelvic lymphadenectomy is needed in cases with no risk factors for pelvic lymph node metastasis. On the other hand, only 1 case (0.7%) of our 128 cases with no risk factors for para-aortic lymph node metastasis actually had metastasis. The histologic type in this case was serous adenocarcinoma. With the exclusion of cases with serous adenocarcinoma, none of the 125 cases with no risk factors for para-aortic lymph node metastasis had metastasis. In this study, we were not able to determine whether serous adenocarcinoma is an independent factor for para-aortic lymph node metastasis because the number of patients with serous adenocarcinoma was not sufficient for statistical analysis. We believe that para-aortic lymphadenectomy should not be eliminated, at present, for cases of serous adenocarcinoma.

We previously reported that the prognostic significance of para-aortic lymph node metastasis is much greater than that of pelvic lymph node metastasis.[25] We believe that we have a responsibility to try to improve the prognosis of patients with para-aortic lymph node metastasis and that elimination of para-aortic lymphadenectomy should therefore be given careful consideration. However, our result suggests that para-aortic lymphadenectomy may be eliminated in cases with no risk factor for para-aortic lymph node metastasis.

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Lymph-vascular space invasion and number of positive para-aortic node groups predict survival in node-positive patients with endometrial cancer☆

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Abstract

Objective. The aim of this study was to determine pathologic variables associated with disease-specific survival of node-positive patients with endometrial carcinoma treated with combination of surgery including pelvic and para-aortic lymphadenectomy and adjuvant chemotherapy.

Methods. Survival of 55 node-positive endometrial carcinoma patients prospectively treated with surgery and adjuvant chemotherapy between 1982 and 2002 at Hokkaido University Hospital was compared to various histopathologic variables. All patients underwent primary surgical treatment including pelvic and para-aortic lymphadenectomy followed by adjuvant chemotherapy consisting of intravenous cisplatin, doxorubicin, and cyclophosphamide. Survival analyses were performed by the Kaplan–Meier curves and the log-rank test. Independent prognostic factors were determined by multivariate Cox regression analysis using a forward stepwise selection.

Results. Among 303 consecutive endometrial cancer patients treated during the period of this study, 55 patients (18.2%), including 44 without peritoneal metastasis (FIGO stage IIIc) and 11 with peritoneal metastasis (FIGO stage IV), were found to have retroperitoneal lymph node metastasis. Multivariate Cox regression analysis revealed that peritoneal metastasis and lymph-vascular space invasion (LVSI) were independently related to poor survival in node-positive endometrial carcinoma. The estimated 5-year survival rate of stage IIIc patients with or without moderate/prominent LVSI was 50.9% and 93.3%, respectively with statistically significant difference ($P = 0.0024$). The estimated 5-year survival rate of stage IV patients was 20.0%. Prognosis of stage IIIc patients could be stratified into three groups by the number of positive para-aortic node (PAN) with an estimated 5-year survival rate of 86.4% for no positive PAN ($n = 23$), 60.4% for one positive PAN ($n = 13$), and 20.0% for ≥ 2 positive PAN ($n = 8$). The difference of survival rate between no or one positive PAN and ≥ 2 positive PAN was statistically significant ($P = 0.0007$ for no positive PAN vs. ≥ 2 positive PAN, $P = 0.0319$ for one positive PAN vs. ≥ 2 positive PAN). Multivariate analysis including number of positive PAN groups showed that LVSI, number of positive PAN groups were independent prognostic factors for survival. Survival of patients with stage IIIc disease could be stratified into three groups by combination of LVSI and number of positive PAN groups with an estimated 5-year survival rate of 93.3% for no or one positive PAN group with nil or minimal LVSI, 62.6% for no or one positive PAN group with intermediate or prominent LVSI, and 20.0% for ≥ 2 positive PAN groups irrespective of LVSI ($P = 0.0002$ for no or one positive PAN group with nil or minimal LVSI vs. ≥ 2 positive PAN groups, $P = 0.0223$ for no or one positive PAN group with nil or minimal LVSI vs. no or one positive PAN group with intermediate or prominent LVSI, $P = 0.0388$ for no or one positive PAN group with intermediate or prominent LVSI vs. ≥ 2 positive PAN groups).

Conclusions. LVSI and number of positive PAN groups were independent prognostic factors for stage IIIc endometrial cancer patients. Postoperative therapy and follow-up modality need to be individualized according to LVSI and the number of positive PAN for stage IIIc patients. New molecular markers to predict the prognosis of endometrial cancer patients preoperatively should be found for individualization

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of treatment. New chemotherapy regimen including taxane needs to be considered as an adjuvant therapy for patients with node-positive endometrial cancer.

Keywords: Endometrial carcinoma; Prognostic factor; Stage IIIc; Para-aortic lymph node metastasis; Lymph-vascular space invasion

Introduction

The incidence of endometrial carcinoma is rapidly increasing in Japan, with an estimated 4800 new cases in the year 2000; this number is still much lower than that in the United States, which was 40,100 in the year 2003 [1].

A majority of patients are diagnosed as being without clinical evidence of extrauterine spread, the International Federation of Gynecology and Obstetrics (FIGO) stages I and II, and have a 5-year survival of approximately 90%. Involvement of pelvic and para-aortic lymph nodes has been recognized as a poor prognostic factor in endometrial carcinoma. The new FIGO surgical staging system classifies endometrial carcinoma with metastasis to the pelvic and/or para-aortic lymph nodes as stage IIIc. The overall 5-year survival for patients with stage IIIc disease varies considerably, depending on the presence of various risk factors, extent of lymphadenectomy, and postoperative adjuvant therapy. Data on surgically staged endometrial cancer patients with nodal involvement have been limited [2–5]. The distribution of nodal disease and its importance in predicting survival are largely unknown, since various procedures have been used to assess para-aortic and pelvic nodes in endometrial cancer, that is, biopsies from enlarged nodes only, selective nodal sampling from multiple sites, pelvic lymphadenectomy, and para-aortic and pelvic lymphadenectomy. It is obvious that para-aortic and pelvic lymphadenectomy is most accurate of these methods. However, para-aortic and pelvic lymphadenectomy is not regarded as the standard surgical procedure for endometrial cancer because the therapeutic significance of the procedure has not yet been sufficiently demonstrated [6,7]. We have routinely performed complete lymphadenectomy in all patients with endometrial cancer because (i) nodal status is the most important prognosticator [2], (ii) results of lymphadenectomy allow tailoring of postoperative adjuvant treatment, (iii) there is an apparent small survival advantage after lymphadenectomy [8], and (iv) there is no increased morbidity with lymphadenectomy [9].

We have previously reported that para-aortic lymph node metastasis is an independent prognostic factor for endometrial cancer patients as well as cell type, grade and LVSI [10,11]. However, the fact that patients with para-aortic lymph node metastasis sometimes have shown long survival suggest that specific prognostic factors may exist for node-positive endometrial carcinoma.

In this study, we tried to identify the independent histopathologic prognostic factors for endometrial carcinoma patients with lymph node metastasis, who were uniformly treated with extensive surgical staging that includes modified radical hysterectomy and systematic pelvic and para-aortic lymphadenectomy followed by adjuvant chemotherapy. We also described the distribution of nodal disease in FIGO stage IIIc endometrial cancer and evaluated whether nodal distribution is related to survival.

Materials and methods

Patients

A total of 303 patients with endometrial carcinoma underwent primary radical surgical treatment from 1982 to 2002 at the Department of Obstetrics and Gynecology, Hokkaido University Hospital. Among 303 patients, 55 patients showed positive retroperitoneal lymph nodes. All subjects underwent modified radical hysterectomy, bilateral salpingo-oophorectomy, and systematic retroperitoneal lymphadenectomy which consisted of complete dissection of pelvic and para-aortic lymph nodes from the femoral ring to the level of the renal vein. All lymphatic tissues that surrounded the arteries and veins were completely removed. The FIGO (1988) stage of the patients was as follows: 44 (80%) stage IIIc and 11 (20%) stage IV. Stage IV disease with distant metastasis (liver or lung metastasis) was excluded from this analysis. We, therefore, defined stage IV patients as node-positive patients with peritoneal metastasis. Median follow-up period was 43 months (1–200 months). The patients' characteristics are shown in Table 1. All patients were treated with an adjuvant chemotherapy of CAP (cyclophosphamide: 350 mg/m^2, adriamycin: 40 mg/m^2 and cisplatin: 50–70 mg/m^2) every 3 weeks.

The following histopathologic prognostic factors were included in the survival analyses: FIGO (1988) stage, histologic subtype, depth of myometrial invasion, architectural grade (AG), nuclear grade (NG), LVSI, ovarian metastasis, PAN metastasis, and number of positive PAN group. All risk factors except number of positive PAN were determined as previously described [10,11]. We defined a node group by its laterality and location. Pelvic node groups include common iliac nodes, external iliac nodes, internal iliac nodes, obturator nodes, median deep inguinal nodesal deep inguinal nodes, parametrial nodes, and sacral nodes. PAN metastasis was investigated by dividing the metastatic group according to the sites above and below the inferior mesenteric artery and left and right sections bordering on the midline of the aorta as previously described [3]. In this analysis, caval (pre-, peri-, retro-) and aortocaval nodes were

Table 1
Clinicopathologic characteristics of 55 patients with lymph node metastasis

	No.	%
FIGO stage (1988)		
IIIc	44	80.0
IV	11	20.0
Histologic subtype		
Endometrioid	43	78.2
Serous/Clear	12	21.8
Architectural grade		
1	16	29.1
2	27	49.1
3	12	21.8
Nuclear grade		
1	14	25.4
2	25	45.5
3	16	29.1
Depth of myometrial invasion		
< = 1/2	15	27.3
> 1/2	40	72.7
Lymph-vascular space invasion		
Nil/minimal	20	36.4
Moderate/prominent	35	63.6
Cervical invasion		
Negative	28	50.9
Positive	27	49.1
Ovarian metastasis		
Negative	37	67.3
Positive	18	32.7
Para-aortic lymph node metastasis		
Negative	26	47.3
Positive	29	52.7

included in right para-aortic nodes. PAN groups, therefore, consists of four groups.

Statistics

Correlation between the variables was analyzed using chi^2 test. Patients survival was calculated using Kaplan–Meier method. The significance of the survival difference was examined by the log-rank test. Univariate and multivariate survival analyses were performed using the Cox regression model with disease-specific overall survival as the outcome measure. Forward stepwise procedure was used to select the independent variable in multivariate analysis. $P < 0.05$ was considered statistically significant. Statistical analyses were performed with the Statview software package (SAS Institute, Inc, Cary, NC).

Results

Univariate and multivariate survival analysis for all node-positive patients

Age of patients ranged from 40 to 75 (median 58) years. The univariate analysis revealed that the FIGO (1988) stage (IIIc vs. IV, $P < 0.0001$), the histologic subtype (endometrioid vs. serous/clear, $P = 0.0216$), architectural grade (G1/2 vs. G3, $P = 0.0024$), nuclear grade (G1 vs. G2/3, $P = 0.0201$), depth of myometrial invasion (absence or presence of serosal invasion, $P < 0.0001$), LVSI (none/minimal vs. moderate/prominent, $P = 0.0026$), cervical invasion ($P = 0.0159$), and PAN metastasis ($P = 0.0078$) were shown to be related to poor survival. Ovarian metastasis was not related to survival ($P = 0.3306$) (Table 2).

Multivariate analysis, which included the prognostic factors determined by univariate analysis to have statistical significance, was performed using a forward stepwise procedure (Table 3). It was shown that FIGO (1988) stage ($P < 0.0001$) and LVSI ($P = 0.0002$) were independent prognostic factors. We could stratify the patients into three prognostic risk-groups by integrating those two histopathologic risk factors, that is, low risk group (group A: stage IIIc with nil/minimal LVSI, $n = 19$), intermediate risk group (group B: stage IIIc with moderate/prominent LVSI, $n = 25$) and high risk group (group C: stage IV with any LVSI, $n = 11$) with an estimated 5-year survival rate of 93.3%, 50.9%, and 20.0%, respectively (Fig. 1). There was statistically significant difference of survival rate between each group (A vs. B: $P = 0.0024$, B vs. C: $P < 0.0001$, A vs. C: $P < 0.0001$). Because prognostic impact of FIGO (1988) stage was extremely strong for the survival of node-positive patients, we performed further analysis on stage IIIc patients alone ($n = 44$).

Lymph node metastasis in stage IIIc patients

Incidences of pelvic lymph node (PLN) metastasis alone, PAN metastasis alone, and both PLN and PAN metastasis were 52.3% (23/44), 4.5% (2/44), and 43.2% (19/44),

Table 2
Univariate and multivariate Cox regression analysis of prognostic factors of node positive endometrial carcinoma

Univariate		Multivariate		
Prognostic factor	P value	Risk ratio	95% CI	P value
FIGO (1988) stage	< 0.0001	11.2	4.0–31.3	< 0.0001
Histologic subtype	0.0216	–	–	NS
Architectural grade	0.0024	–	–	NS
Nuclear grade	0.0201	–	–	NS
Lymph-vascular space invasion	0.0026	9.3	2.1–41.7	0.0033
Myometrial invasion	< 0.0001	–	–	NS
Cervical invasion	0.0159	–	–	NS
Ovarian metastasis	0.3306	–	–	S
Para-aortic node metastasis	0.0078	–	–	NS

NS: not significant.
FIGO (1988) stage: stage IIIc vs stage IV determined by the presence of peritoneal metastasis.
Tumor cell type: endometrioid vs serous/clear cell.
Architectural grade: G1/2 vs G3.
Nuclear grade: G1 vs G2/3.
Lymph-vascular space invasion: (−)/(+) vs (++)/(+++).
Myometrial invasion: serosal invasion (−) vs (+).
Cervical in vs. ion: (−) vs (+).
Ovarian metastasis: (−) vs (+).
Para-aortic lymph node metastasis: (−) vs (+).

Table 3
Univariate and multivariate Cox regression analysis of prognostic factors of stage IIIc endometrial carcinoma

Univariate		Multivariate		
Prognostic factor	*P* value	Risk ratio	95% CI	*P* value
Histologic subtype	0.7226	—	—	NS
Architectural grade	0.3911	—	—	NS
Nuclear grade	0.0605	—	—	NS
Lymph-vascular space invasion	0.0173	8.8	1.1–71.4	0.0413
Myometrial invasion	0.6036	—	—	NS
Cervical invasion	0.4577	—	—	NS
Ovarian metastasis	0.1815	—	—	NS
Number of positive PAN	0.0016	3.9	1.2–13.0	0.0260

NS: not significant.
Tumor cell type: endometrioid vs serous/clear cell.
Architectural grade: G1/2 vs G3.
Nuclear grade: G1 vs G2/3.
Lymph-vascular space invasion: (−)/(+) vs (++)/(+++).
Myometrial invasion: serosal invasion (−) vs (+).
Cervical invasion: (−) vs (+).
Ovarian metastasis: (−) vs (+).
Number of positive PAN: 0, 1 vs ≥ 2.

respectively. The estimated 5-year survival rate of patients without or with PAN metastasis was 86.4%, 48.1%, respectively (Fig. 2). The difference was statistically significant ($P = 0.0108$).

Prognostic impact of the number of positive PLN groups in stage IIIc patients

The estimated 5-year survival rate for patients with one positive PLN group was 79.3% and that for patients with ≥ 2 positive PLN groups was 60.8%. The difference of survival was not statistically significant. However, 21 of 22 patients (95.5%) with no or one positive PLN group had no or one positive PAN group and only one of 22 patients (4.5%) had two positive PAN groups, while 15 of 22 patients (68.2%) with ≥ 2 positive PLN groups had no or one positive PAN group and 7 of 22 patients (31.8%) had ≥

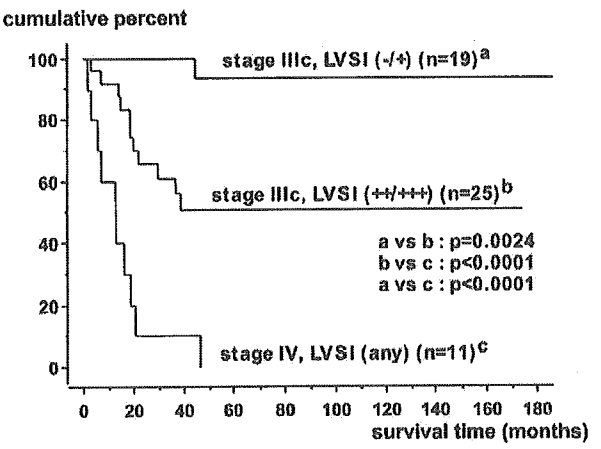

Fig. 1. Survival of node-positive patients with endometrial carcinoma by combination of FIGO (1988) stage and LVSI.

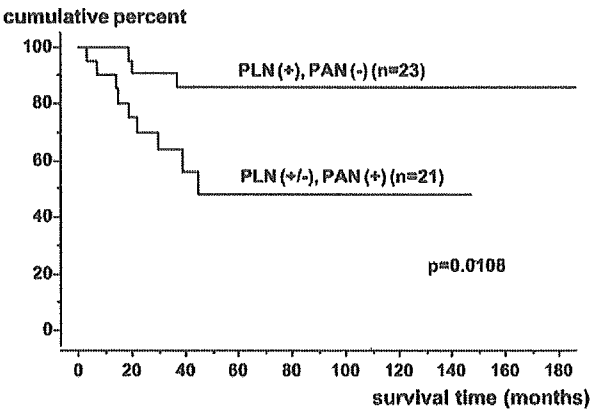

Fig. 2. Survival of patients with stage IIIc endometrial carcinoma by PAN metastasis.

2 positive PAN groups. There was a statistically significant difference in incidence of ≥ 2 positive PAN groups between patients who had no or one positive PLN group and those who had ≥ 2 positive PLN groups ($P = 0.023$). (Table 4).

Prognostic impact of the number of positive PAN groups in stage IIIc patients

Fig. 3 shows the survival of stage IIIc patients according to the number of positive PAN groups. The estimated 5-year survival rate was 86.4% for patients without positive PAN group ($n = 23$), 60.4% for those with one positive PAN group ($n = 13$), and 20.0% for those with ≥ 2 positive PAN groups ($n = 8$). There was statistically significant difference between no positive PAN group and ≥ 2 positive PAN groups ($P < 0.0007$), between one positive PAN group and ≥ 2 positive PAN groups ($P = 0.0319$). There was no statistically significant difference between no positive PAN group and one positive PAN group ($P = 0.1354$).

Univariate and multivariate survival analysis for stage IIIc patients

Since the number of positive PAN group was shown to have significant impact on the survival of stage IIIc patients,

Table 4
Incidence of para-aortic lymph node metastasis according to number of positive pelvic lymph node groups in stage IIIc endometrial cancer patients

	Positive PAN group		Total
	0, 1	≥ 2	
positive PLN group			
0, 1	21	1	22
> 2	15	7	22
Total	36	8	44
			$P = 0.0023$

PLN: pelvic lymph node, PAN: para-aortic lymph node.
There was a statistically significant difference in incidence of ≥ 2 positive PAN groups between patients who had no or one positive PLN group and those who had ≥ 2 positive PLN groups ($P = 0.023$).

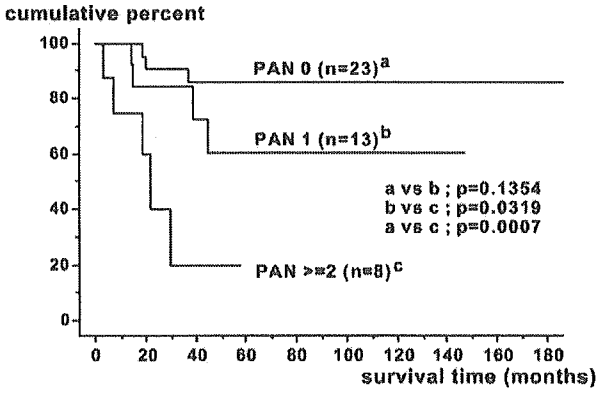

Fig. 3. Survival of patients with stage IIIc endometrial carcinoma by the number of positive PAN group.

we included number of positive PAN groups in the univariate analysis instead of presence or absence of PAN metastasis. The univariate analysis revealed that the LVSI ($P = 0.0173$), number of positive PAN groups ($P = 0.0016$) were shown to be related to poor survival. Histologic subtype ($P = 0.7226$), architectural grade ($P = 0.3911$), nuclear grade ($P = 0.0605$), depth of myometrial invasion ($P = 0.6036$), cervical invasion ($P = 0.4577$), ovarian metastasis ($P = 0.1815$) were not related to poor survival (Table 3, Fig. 4).

Multivariate analysis revealed that both LVSI ($P = 0.0413$) and number of positive PAN groups ($P = 0.026$) were independent prognostic factors. Survival of patients with stage IIIc disease could be stratified into three groups by combination of LVSI and number of positive PAN group with an estimated 5-year survival rate of 93.3% for no or one positive PAN group with nil or minimal LVSI (group D), 62.6% for no or one positive PAN group with intermediate or prominent LVSI (group E), and 20.0% for ≥ 2 positive PAN groups irrespective of LVSI (group F). The difference of survival rate between each group was statistically significant ($P = 0.0002$ for group D vs. group F, $P = 0.023$ for group D vs. group E, $P = 0.0388$ for group E vs. group F.

Discussion

Stages I and II endometrial carcinomas have shown a favorable prognosis by combination of surgery, radiotherapy, and/or chemotherapy. Some histopathologic factors have been found to be related to prognosis of endometrial carcinoma. Lymph node metastasis is one of the most important prognostic factors of endometrial carcinoma and advanced endometrial carcinoma with lymph node metastasis (IIIc/IV) has been shown to have poorer prognosis. In our series of patients treated in the same manner, the prognosis for patients with stage IIIa endometrial carcinoma was excellent with an estimated 5-year survival of over 90% (patients with stage IIIb disease were not found in our series). However, the prognosis for patients with stage IIIc endometrial carcinoma with an estimated 5-year survival rate of 79.6% was poorer than that of stage IIIa in spite of intensive treatment consisting of extended surgery including pelvic and para-aortic lymphadenectomy and systemic adjuvant chemotherapy. We, therefore, performed retrospective analysis on the prognostic factors for node-positive patients to determine appropriate therapeutic and follow-up modality to achieve their favorable prognosis.

Concerning the distribution of lymph node metastases, 95.5% (42/44) of patients with nodal disease had pelvic node metastases and 45.2% (19/42) of patients with PLN metastases had concomitant PAN metastases. McMeekin et al. [4] analyzed nodal distribution in 47 cases of stage IIIc endometrial cancer and found that an increasing number of positive PLN was associated with PAN metastasis. Our result on nodal distribution in stage IIIc patients is similar to McMeekin et al. [4], i.e., patients with single positive PLN group rarely have multiple positive PAN groups. We also found that positive aortic nodes were associated with poorer prognosis than were positive pelvic nodes alone (estimated 5-year survival 48.1% for positive PAN vs. 86.4% for negative PAN, $P = 0.0108$), suggesting that involvement of pelvic lymph nodes alone does not necessarily carry a poor prognosis as previously reported by Onda et al [12] who performed the same operative procedure as ours. This can be explained in part due to the therapeutic significance of our operative procedure including systematic pelvic and para-aortic lymphadenectomy. Para-aortic lymphadenectomy until just below the renal vein may contribute to the favorable survival of patients with multiple positive PLN groups.

In this study, we firstly reported that the survival of patients with stage IIIc endometrial carcinoma can be stratified by the number of positive PAN groups. The survival of patients without positive PAN (PLN metastasis

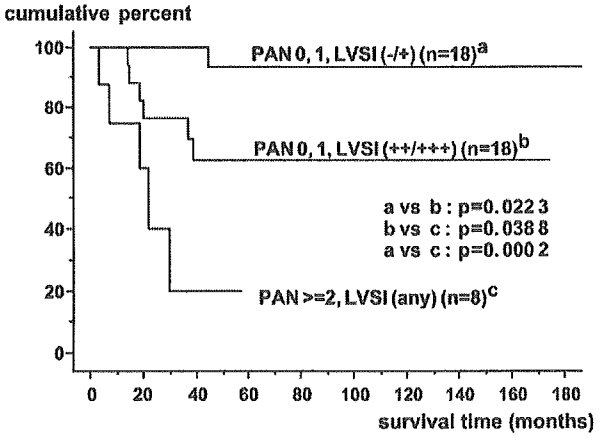

Fig. 4. Survival of patients with stage IIIc endometrial carcinoma by combination of LVSI and number of positive PAN group.

alone), with one positive PAN group, and with ≥ 2 positive PAN groups was 86.4%, 60.4%, 20.0%, respectively. The survival of patients with ≥ 2 positive PAN groups was much worse than others. Notably, there was no statistically significant difference between the patients without positive PAN group and those with one positive PAN group ($P = 0.14$), suggesting that single PAN metastasis is still a local disease that can be cured by complete lymphadenectomy and subsequent chemotherapy. When patients have multiple PAN metastasis, lymphadenectomy does not prolong survival.

Radiotherapy and chemotherapy have been employed as adjuvant therapies for endometrial cancer. Radiotherapy has been considered as a standard adjuvant therapy in Western countries. The result of GOG 122, however, clearly demonstrated that adjuvant chemotherapy (adriamycin and CDDP) significantly improved progression free survival and overall survival than adjuvant radiotherapy (whole abdominal radiotherapy) for stage III/IV patients [13], indicating that chemotherapy should be considered as a standard adjuvant therapy for endometrial cancer. Systemic chemotherapy has been widely accepted as a standard adjuvant therapy for endometrial cancer in Japan. Adriamycin has been used as a key drug for endometrial cancer. We have used CAP regimen for endometrial carcinoma with risk factors for recurrence. However, the poorer survival of stage IIIc patients with multiple positive PAN groups than single positive PAN group, who received adjuvant chemotherapy (CAP), clearly indicates that we should consider a new chemotherapeutic regimen to improve prognosis of node-positive patients. The most promising drug for endometrial cancer is taxane [14].

In this study, we found that LVSI and number of positive PAN group are independent prognostic factors by multivariate analysis, indicating that para-aortic lymphadenectomy should be routinely included in the surgical procedure for endometrial cancer to predict the survival of node-positive patients. We also conclude that we should investigate LVSI with more careful attention for node-positive patients. Careful investigation of LVSI, however, is time-consuming and it is impossible to evaluate LVSI preoperatively and during operation by frozen section. To individualize the therapeutic modality for each patient, we need to search for new molecular markers which can be easily assessed and reflect disease status in regard to LVSI preoperatively. There have been few reports on the useful molecular markers for survival of endometrial carcinoma. We reported that p53 overexpression by immunohistochemical staining was found to be an independent prognostic factor and the estimated 5-year survival rate of patients with stage III/IV disease without p53 overexpression was significantly better than that with p53 overexpression, indicating that p53 missense mutation, which is closely related to immunohistochemical p53 overexpression, have a significant prognostic impact on the survival of advanced endometrial carcinoma [15]. Kanamori et al. [16] reported that PTEN expression was found to be associated with prognosis for patients with advanced endometrial carcinoma undergoing postoperative chemotherapy. Yokoyama et al. [17] reported that high levels of immunoreactivity for vascular endothelial growth factor (VEGF)-D in stromal cells and its receptor, VEGF-R-3 in carcinoma cells were independent prognostic factors in endometrial carcinoma. We need to further investigate more useful prognostic factors for endometrial carcinoma using molecular biological techniques.

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