

Search for conditions to avoid parametrectomy during radical hysterectomy for cervical cancer

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Abstract

Aim: This study aimed to assess adequate conditions for omitting parametrectomy for stage IB1–IIA2 cervical cancer with the aim of reducing postoperative complications during Type III radical hysterectomy (RH).

Methods: We investigated factors associated with parametrial invasion (PMI) in patients who underwent Type III RH for stage IB1, IB2, IIA1, IIA2 and IIB cervical cancer at two tertiary institutions from November 2006 to February 2018. Both clinicopathological and preoperatively estimated factors were assessed.

Results: One hundred fifty-six patients were preoperatively diagnosed with stage IB1 to IIB disease. Thirty-four patients (21.8%) showed PMI on histological analyses. In the multivariate analysis, an age older than 50 years, tumor size larger than 40 mm, common iliac lymph node metastasis and lymphovascular space invasion were identified as significant risk factors for PMI (P -values = 0.008, 0.003, 0.004 and 0.004, respectively). The preoperatively estimated risk factors for PMI were an older age, larger tumor size, and common iliac lymph node metastasis (P -values = 0.007, 0.002 and 0.001, respectively). A combination of these three factors was sufficient to estimate PMI with a high specificity (100%) and positive predictive value (100%) in patients with stage IB1 to IIA2 disease.

Conclusion: During RH, resecting the posterior layer of the vesicouterine ligament and the paracolpium without removing the cardinal ligament (avoiding parametrectomy) might be feasible for stage IB1–IIA2 cervical cancer in patients younger than 50 years presenting with smaller tumors (<40 mm) and no common iliac lymph node metastasis.

Key words: cervical cancer, parametrectomy, parametrial invasion, radical hysterectomy, urinary dysfunction.

Introduction

Cervical cancer is one of the most common gynecological malignancies worldwide. Nearly 530 000 women are diagnosed with cervical cancer every year.¹ Furthermore, women who achieve a cure via treatment often experience complications such as leg lymphedema, urinary dysfunction and bowel dysfunction. In particular, surgically induced urinary dysfunction can drastically reduce the patient's quality of life.

According to the National Comprehensive Cancer Network guidelines, radical hysterectomy (RH) and pelvic lymph node dissection are recommended by the Federation of Gynecology and Obstetrics (FIGO) only for stage IB1, IB2, IIA1 and IIA2 cases. Concurrent chemoradiotherapy (CCRT) is recommended for stage IIB cases.² However, pathological confirmation of parametrial invasion (PMI) after surgery is not rare, and such cases are diagnosed as pathological T2b, stage IB1–IIA2. Moreover, in Japan, surgery is often

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selected for stage IIB disease to avoid severe complications due to CCRT, as indicated by the Japan Society of Gynecologic Oncology guideline.^{3,4}

The European Organization of Research and Treatment of Cancer Gynecological Cancer Group (EORTC-GCG) criteria mainly classify RH as Type II or Type III. In Type III RH, the parametrium is resected as near as possible to the pelvic wall, in contrast to Type II RH.^{5,6} Thus, Type III RH more frequently causes urinary dysfunction. Despite the common use of the term RH, the selection of Type II or III RH according to the EORTC-GCG classification remains particularly controversial between countries and facilities.^{5,6} In Japan, Type III RH is commonly used; this method of uterine parametrial dissection originated with the Okabayashi surgery and is often applied to stage IIB cases. However, radical surgery is frequently accompanied by urinary complications, even in nerve-sparing procedures. To minimize complications, it is important to avoid radical surgery if conditions allow.

PMI is known as a strong prognostic factor. Conversely, the absence of PMI implies a good prognosis and indicates that dissection of the parametrium is unnecessary. To determine the presence of PMI and the FIGO stage before surgery, an internal clinical examination and magnetic resonance imaging (MRI) can be performed. However, the final pathological diagnosis does not always confirm the preoperative determination.

Unnecessary type III RH must be avoided to reduce postoperative complications. Therefore, our study aimed to determine the conditions that could adequately avoid resection of the parametrium in cases of stage IB1–IIA2 cervical cancer.

Methods

The relationship between pathological PMI and other factors was retrospectively investigated in patients who underwent type III RH for stage IB1–IIB cervical cancer at two tertiary institutions, from November 2006 to February 2018. All procedures were performed via the abdominal approach. This study was approved by the institutional review boards of the participating institutions.

The FIGO stage was determined via clinical internal examinations performed by practiced oncologists with reference to preoperative MRI findings. The surgical team included at least one gynecological cancer

specialist certified by Japan Society of Gynecologic Oncology. We searched for identifying factors of PMI in patients with stage IB1, IB2, IIA1, IIA2 and IIB cervical cancers who underwent type III RH. This search included all clinicopathological and preoperatively estimated factors including age (cut off: 50 years old), tumor size (cut off: 40 mm), pelvic lymph node metastasis, common iliac lymph node metastasis, vaginal invasion, lymphovascular space invasion, histology (SCC or non-SCC), the values of SCC-Ag, CEA and CA125. Next, we applied the preoperatively evaluated factors to IB1, IB2, IIA1 and IIA2 samples (excluding IIB samples) using the frozen section procedure and rapid pathological examination-which has a specificity and positive predictive value of metastasis that is similar to final pathological diagnosis-and estimated the accuracy of the pathological PMI designations.

Statistical analysis

To extract the factors predictive of PMI, the chi-square test was used in the univariate analysis, and multiple logistic regression was used in the multivariate analysis. Differences in variables with *P*-values of <0.05 were considered statistically significant. When selecting factors from the univariate analysis for the multivariate analysis, those with *P*-values of <0.10 were considered significant. All statistical analyses were conducted using SPSS software, version 22 (SPSS Inc.).

Results

One hundred fifty-six cases were eligible for study inclusion; of these, 61 cases were stage IB1, 35 were stage IB2, nine were stage IIA1, 12 were stage IIA2 and 39 were stage IIB. In 34 cases (21.8%), histology revealed PMI (Table 1); of these, four cases were stage IB1, four were stage IB2, one was stage IIA1, three were stage IIA2 and 22 were stage IIB.

The clinicopathological factors associated with PMI in the univariate analysis included an age older than 50 years, tumor size larger than 40 mm, common iliac lymph node metastasis, lymphovascular space invasion, and serum squamous cell carcinoma antigen (SCC-Ag) level > 1.5 ng/mL. The multivariate analysis revealed age, tumor size, common iliac lymph node metastasis and lymphovascular space invasion as factors significantly associated with PMI, with *P*-values of 0.008, 0.003 0.004, and 0.044, respectively (Table 2).

Table 1 Patient characteristics

Variables		n (%)
Parametrial invasion	Positive	34 (21.8)
	Negative	122 (78.2)
FIGO stage	IB1	61
	IB2	35
	IIA1	9
	IIA2	12
	IIB	39
Histology	SCC	107 (68.6)
	non-SCC	49 (31.4)
Pelvic LN metastasis	Positive	48 (30.8)
	Negative	108 (69.2)
Common iliac LN metastasis	Positive	15 (9.6)
	Negative	141 (90.4)
LVSI	Positive	123 (78.8)
	Negative	33 (21.2)
VI	Positive	47 (30.1)
	Negative	109 (69.9)
Age (years)		55 (30–79)
Tumor size (mm)		41 (6–100)
Serum SCC-Ag level (ng/mL)		1.8 (0–104)
Serum CEA level (ng/mL)		2.7 (0.2–87.3)
Serum CA125 level (U/mL)		14.0 (3.0–1860)

FIGO, International Federation of Gynecology and Obstetrics; PMI, parametrial invasion; LN, lymph node; LVSI, lymphovascular space invasion; VI, vaginal invasion; SCC, squamous cell carcinoma; Ag, antigen; CEA, carcinoembryonic antigen; CA125, cancer antigen 125.

A multivariate analysis was also used to identify factors that could be evaluated preoperatively and identified age, tumor size, and common iliac lymph node metastasis as significant, with *P*-values of 0.007, 0.002 and 0.001, respectively (Table 3). When all three factors surpassed the cut-off threshold (age > 50 years and tumor size >40 mm) or were positive (common iliac lymph node metastasis present), the sample was declared positive for PMI. The sensitivity, specificity,

positive predictive value and negative predictive value of this combination for detecting PMI in the 117 samples of stage IB1–IIA2 cervical cancer were 22.9%, 100%, 100% and 12.9%, respectively (Table 4).

Discussion

Cervical cancer is a common gynecologic cancer that is often cured by radical surgery. However, surgical treatment is often accompanied by severe postoperative complications that reduce the patient’s quality of life, and this problem has persisted despite the introduction of laparoscopic or robotic surgical options. Originally, the EORTC-GCG criteria mainly classified RH as Type II or Type III. In Type III RH, in contrast to Type II RH, the parametrium is resected as near as possible to the pelvic wall, and removal as far as possible from the uterosacral ligament and ligation at the origin of uterine vessels are necessary.^{5,6} Thus, Type III RH more frequently causes urinary dysfunction. Therefore, in this study, we retrospectively examined the possibility that factors could adequately predict the absence of PMI before surgery and thus allow the avoidance of parametrectomy for stage IB1–IIA2 cervical cancer.

We extracted the clinicopathological factors – namely age, tumor size and common iliac lymph node metastasis – that could be evaluated preoperatively through a multivariate analysis. We applied these extracted factors only to stage IB1, IB2, IIA1 and IIA2 cases and excluded IIB, as clinical T2b cervical cancer requires an adaptation of complete Type III RH or CCRT. When all three factors exceeded the identified thresholds (age > 50 years and tumor size >40 mm) or were positive (common lymph node

Table 2 Analysis of all clinicopathological factors affecting PMI

Variables	Univariate analysis	Multivariate analysis		
	<i>P</i> value	Odds ratio	95% CI	<i>P</i> value
Age > 50 years	0.051	3.876	1.423–10.552	0.008
Tumor size > 40 mm	0.001	4.210	1.618–10.954	0.003
Pelvic LN metastasis	<0.001			
Common iliac LNM	<0.001	6.223	1.797–21.550	0.004
VI	0.112			
LVSI	0.003	8.368	1.054–66.458	0.044
Non-SCC histology	0.581			
SCC-Ag > 1.5 ng/mL	0.068	—	—	0.131
CEA > 5 ng/mL	0.439			
CA125 > 35 U/mL	0.199			

PMI, parametrial invasion; LNM, lymph node metastasis; VI, vaginal invasion; LVSI, lymphovascular space invasion; SCC, squamous cell carcinoma; Ag, antigen; CEA, carcinoembryonic antigen; CA125, cancer antigen 125; CI, confidence interval.

Table 3 Analysis of preoperatively estimated factors affecting PMI

Variables	Multivariate analysis		
	Odds ratio	95% CI	P value
Age > 50 years	3.915	1.451–10.563	0.007
Tumor size > 40 mm	4.588	1.791–11.757	0.002
Common iliac LNM	8.124	2.357–27.999	0.001
SCC-Ag > 1.5 ng/mL	—	—	0.158

PMI, parametrial invasion; LNM, lymph node metastasis; SCC, squamous cell carcinoma; Ag, antigen; CI, confidence interval.

metastasis), the absence of PMI could be estimated with a very high specificity (100%) and positive predictive value (100%). Combined with a sensitivity of 22.9% and a negative predictive value of 12.9%, we determined that no risk of pathological PMI existed in 24 of 117 stage IB1–IIA2 cervical cancer cases (20.5%), in which parametrectomy could be allowed to achieve curative results.

In a previous report, Canaz *et al.*⁷ identified two predictive factors for PMI: endophytic presentation and a tumor size larger than 3 cm. However, in that study, PMI occurred in 29.1% of subjects with stage IB–IIA disease, a higher rate than that in our study or other reports. This discrepancy may have been caused by differences in the accuracies of preoperative diagnoses. Xie *et al.*⁸ reported that patients with inner-third stromal invasion, no lymphovascular space invasion, and a squamous histological type may be candidates for less radical surgery but were unable to make a preoperative determination. Baiocchi *et al.*⁹ analyzed 345 patients with stage IA2–IB2 cervical cancer and concluded that parametrectomy was not

Table 4 Accuracy of PMI prediction using a combination of three factors

	PMI		
	No	Yes	
Age 50 years, Tumor size ≤40 mm, and No metastasis to common iliac LN	24	0	24
Factors others than the above	81	12	93
	105	12	117

PPV = 24/24 = 100%; NPV = 12/93 = 12.9%; Sensitivity = 24/105 = 22.9%; Specificity = 12/12 = 100%. PMI, parametrial invasion; LN, lymph node; PPV, positive predictive value; NPV, negative predictive value.

necessary for patients with tumors with a size of 20 mm or smaller and no lymphovascular space invasion, unless lymph node metastasis or deep stromal invasion was present. However, the subjects in that study had a very low risk of PMI, and therefore it may have been difficult to identify risk factors in that patient group.

Furthermore, Kong *et al.*¹⁰ reported the utility of the SCC-Ag and Cyfra levels for predicting PMI in stage IB, while Chang *et al.*¹¹ reported the utility of the SCC-Ag level for stage IB1 disease. Yamazaki *et al.*¹² suggested the possibility of less radical surgery for stage IB1 cases that were negative for SCC-Ag and cancer antigen 125. In our study, however, we did not find a correlation between PMI and tumor markers, possibly because our subjects included higher risky patients with stage IB2, IIA and IIB cervical cancer.

Klat *et al.*¹³ demonstrated the absence of PMI in patients with tumor sizes smaller than 20 mm and no sentinel lymph node metastasis. Although sentinel lymph node detection appears promising, it is not yet well established and its use is not currently widespread in many hospitals and countries. Therefore, we considered the detection of common iliac lymph node metastasis because it is relatively easy to examine intraoperatively via rapid pathologic diagnosis. The performance of this additional diagnostic procedure during surgery, in combination with the patient's age and tumor size, may help to determine whether parametrectomy is required.

Our study is highly distinct from previously reported studies as the prognostic factors were extracted from samples that included cases of clinical T2b cervical cancer. This was possible because clinical T2b disease has long been treated surgically in Japan. To our knowledge, no previous report has described an analysis of subjects including those with clinical T2b disease; previous studies have included subjects up to stage IIA.

Moreover, common iliac lymph node metastasis is distinct. We focused on this factor because it is relatively easy to examine intraoperatively via rapid pathologic diagnosis. In this study, common iliac node metastasis was revealed to be a significant predictor of PMI; however, types of pelvic lymph node metastasis other than common iliac lymph node metastasis are also of great clinical importance and should be examined in future studies.

The National Comprehensive Cancer Network guidelines recommend radical surgery for stage IB–IIA disease, with the addition of CCRT in stage IIB.²

However, pathological PMI is not infrequently determined postoperatively in patients with stage IB–IIA disease. Xie *et al.*⁸ reported a PMI rate of 9.1% (46/507) among stage IB–IIA cases, while Kong *et al.*¹⁴ reported a rate of $\geq 20\%$. Recent studies revealed that preoperative PMI identified via MRI had a negative predictive value of approximately 90% among stage IB–IIA cases.^{15,16} This value is similar to our results (9.4% of PMI). Together, these results indicate that preoperative MRI contributes to the precise clinical diagnosis of PMI, in addition to clinical inspection.

In our study, as many as 56.4% (22/39) of clinical T2b cases correlated with pathological T2b. Therefore, in our practice in Japan, where the accuracy of clinical staging is guaranteed by practiced vaginal inspection and preoperative MRI, we should select CCRT or Type III RH for stage IIB cases. Therefore, we applied the predictive factors derived from stage IB–IIB disease to stage IB–IIA cases while excluding stage IIB.

Our study had several limitations. First, the subjective period was substantially extended, and consistent conditions at the times of preoperative diagnosis and surgery may not have been maintained, which might have reduced the accuracy of our procedure. Second, our study was limited to two facilities, and the number of samples was relatively low.

We conclude that during RH, resecting the posterior layer of the vesicouterine ligament and the paracolpium without removing the cardinal ligament (avoiding parametrectomy) might be feasible for one in five patients with stage IB1–IIA2 disease who meet the following clinicopathological characteristics indicative of a lack of pathological PMI risk: age younger than 50 years, tumor size smaller than 40 mm and no common iliac lymph node metastasis as determined by intraoperative rapid pathological diagnosis.

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Disclosure

The authors have no interests to disclose.

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