

Pretreatment risk factors for parametrial involvement in FIGO stage IB1 cervical cancer

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See accompanying editorial by Bouchard-Fortier and Covens on page 243.

Objective: All patients with stage IB1 cervical cancer do not need to undergo parametrectomy. Some low-risk criteria for parametrial involvement (PI) have been proposed based on pathological findings. The aim of this study was to determine pretreatment risk factors for PI in stage IB1 cervical cancer.

Methods: We retrospectively reviewed 115 patients with stage IB1 cervical cancer who underwent radical hysterectomy or radical trachelectomy. Magnetic resonance imaging (MRI) was performed and serum concentrations of squamous cell carcinoma antigen (SCC-Ag) and cancer antigen 125 (CA-125) were determined in all patients before initial treatment. The following pretreatment factors were investigated: histological variant, maximum tumor diameter, tumor volume (volume index), pelvic lymph node enlargement, and serum tumor markers. Logistic regression analysis was used to select the independent risk factors for PI.

Results: Eighteen of the 115 patients (15.7%) were pathologically diagnosed with PI. Multivariate analysis confirmed the following independent risk factors for PI: MRI-based tumor diameter ≥ 25 mm (odds ratio [OR], 9.9; 95% confidence interval [CI], 2.1 to 48.1), MRI-based volume index $\geq 5,000$ mm³ (OR, 13.3; 95% CI, 1.4 to 125.0), and positive serum tumor markers SCC-Ag ≥ 1.5 ng/mL or CA-125 ≥ 35 U/mL (OR, 5.7; 95% CI, 1.3 to 25.1). Of 53 patients with no risk factors for PI, none had PI.

Conclusion: Less radical surgery may become one of the treatment options for stage IB1 cervical cancer patients with MRI-based tumor diameter < 25 mm, MRI-based volume index $< 5,000$ mm³, and negativity for SCC-Ag and CA-125.

Keywords: Hysterectomy; Magnetic Resonance Imaging; Risk Factors; Tumor Burden; Tumor Markers, Biological; Uterine Cervical Neoplasms

INTRODUCTION

Standard treatment for International Federation of Gynecology and Obstetrics (FIGO) stage IB1 cervical cancer includes radical hysterectomy [1,2]. Radical trachelectomy is also a treatment option for women who wish to undergo

fertility-sparing treatment in accordance with the National Comprehensive Cancer Network clinical guidelines [2]. Both surgical procedures include parametrectomy as part of the whole procedure. The parametrium is rich in vasculature and autonomic nerve fibers; therefore, resection of parametrial tissue needs a longer operating time, and increases the need for blood transfusion and postoperative complications, particularly bladder dysfunction [3]. In addition, parametrectomy may enhance unsatisfactory obstetrical outcomes in radical trachelectomy [4]. According to previous reports, the incidence of parametrial involvement (PI) is not high: $< 10\%$ (range, 5.4% to 30.6%) in stage IB1 cervical cancer [5-16] and

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<4% (range, 0% to 4.5%) in small-sized (<20 mm) cervical cancer [14-18]. Some patients with stage IB1 cervical cancer may not need to undergo parametrectomy. It has been reported that less radical surgery including conization, simple trachelectomy, or simple hysterectomy leads to satisfactory oncological outcomes in small-volume stage IB1 cervical cancer [19-21]. Low-risk group criteria for PI have been proposed. These studies produced excellent prediction models with risk of PI of <2% [11-14,18,22,23]. However, these criteria included pathological findings of the resected specimen; namely, they were postoperative risk assessments. Practically, preoperative risk assessment is needed for surgical decision making. We aimed to determine candidates preoperatively who can safely undergo less radical surgery among patients with stage IB1 cervical cancer.

MATERIALS AND METHODS

1. Patients

The present study was carried out using data of patients with FIGO stage IB1 cervical cancer for whom tumor diameter/volume were preoperatively confirmed by magnetic resonance imaging (MRI), and radical hysterectomy or radical trachelectomy was performed. Eligible patients underwent resection of bilateral parametrial tissues. A total of 421 patients with invasive cervical cancer were treated in the National Hospital Organization Hokkaido Cancer Center from January 2008 to June 2014 (Table 1). Of 140 patients who had FIGO stage IB1 disease, eight were treated with radiotherapy. One patient refused to receive any treatment. Of 131 patients who underwent surgical treatment, nine underwent conization or simple hysterectomy instead of radical surgery. Two patients received systemic chemotherapy before surgical treatment. Pretreatment images were not obtained in five patients. These patients were excluded from the present study. Finally, we

carried out this study with data from 115 patients with stage IB1 cervical cancer. Approval of the Institutional Review Board was obtained from the hospitals' ethics boards.

2. Image analysis

MRI was performed on all 115 patients before initial treatment. Images were judged by at least two physicians without knowledge of the clinical findings and survival outcomes. The parameters obtained from MRI were tumor size and pelvic lymph node size. Tumor diameter was measured three dimensionally (anteroposterior, craniocaudal, and horizontal diameters) in either T2-weighted images or gadolinium-enhanced T1-weighted images, which show tumor lesions more clearly. Maximal tumor diameter was used for the present analysis.

Volume index was evaluated in T2- or gadolinium-enhanced T1-weighted images, which show tumor lesions clearly. Volume index was defined as the product of the maximum longitudinal diameter (mm) along the uterine axis; the maximum anteroposterior diameter (mm), namely the thickness, on a sagittal section image; and the maximum horizontal diameter (mm) on a horizontal section image. Lymph node enlargement was defined as a minimal diameter >10 mm, as determined radiologically, according to published recommended guidelines [24].

3. Tumor markers

The serum concentration of squamous cell carcinoma antigen (SCC-Ag) was determined by radioimmunoassay. The cut-off value of 1.5 ng/mL was adopted to determine an abnormally increased serum level of SCC-Ag. The serum cancer antigen 125 (CA-125) level was also determined by radioimmunoassay. The cut-off value of 35 U/mL was adopted to determine abnormally increased serum level of CA-125. Patients were classified into two categories: negative (SCC-Ag <1.5 ng/mL and CA-125 <35 U/mL) and positive (SCC-Ag ≥1.5 ng/mL or CA-125 ≥35 U/mL).

Table 1. Distribution of initial treatment for 421 patients with cervical cancer at the Hokkaido Cancer Center between January 2008 and June 2014

Initial treatment	No.	FIGO stage					
		IA	IB1	IB2	II	III	IV
Surgery (including NAC→surgery)	292	44	131	24	69	11	13
Radiation (including NAC→radiation)							
Concurrent chemoradiotherapy	69	0	2	1	20	33	13
Radiotherapy alone	41	1	6	1	9	17	7
Others/not done	19	0	1	1	2	3	12
Total	421	45	140	27	100	64	45

FIGO, International Federation of Gynecology and Obstetrics; NAC, neoadjuvant chemotherapy.

4. Statistical analysis

The primary outcome measure was PI, which was confirmed by pathological examination. First, the chi-square test was performed to determine the relationship between parametrial invasion and each of the following pretreatment factors: (1) histological variant (SCC vs. non-SCC); (2) maximum tumor diameter (<25 mm vs. ≥25 mm); (3) pelvic lymph node

Table 2. Clinical characteristics of 115 patients with cervical cancer treated with radical hysterectomy/trachelectomy with pelvic lymphadenectomy

Characteristic	No. (%)
Age (yr), median (range)	41 (27–77)
Tumor histology	
SCC	65 (56.5)
NSCC	50 (43.5)
Vaginal involvement	
Negative	98 (85.2)
Positive	17 (14.3)
Endometrial involvement	
Negative	99 (86.1)
Positive	13 (11.3)
Not assessed	3 (2.6)
Parametrial involvement	
Negative	97 (84.3)
Positive	18 (15.7)
Lymphovascular space invasion	
Negative	62 (53.9)
Positive	53 (46.1)
Lymph node metastasis	
Negative	98 (85.2)
Positive	17 (14.8)
Serum tumor markers	
Negative	44 (38.3)
Positive	71 (61.7)
Serum SCC-Ag level (ng/mL)	
SCC-Ag <1.5	72 (62.6)
SCC-Ag ≥1.5	43 (37.4)
Serum CA-125 level (U/mL)	
CA-125 <35	106 (92.2)
CA-125 ≥35	9 (7.8)
Adjuvant treatment	
No	67 (58.3)
Chemotherapy	45 (39.1)
Radiation therapy including CCRT	3 (2.6)

CA-125, cancer antigen 125; CCRT, concurrent chemoradiotherapy; NSCC, non-squamous cell carcinoma; SCC, squamous cell carcinoma.

enlargement (no vs. yes); (4) volume index (<5,000 mm³ vs. ≥5,000 mm³); and (5) tumor marker (negative vs. positive). Factors that achieved statistical significance in univariate analysis were subsequently included in multivariate analysis. Logistic regression analysis was used to select the independent risk factors for parametrial invasion. The statistical significance level was set at 0.05. Statistical analyses were performed with R version 3.2.0: A Language and Environment for Statistical Computing (R Core Team 2015).

RESULTS

Table 2 shows the clinicopathological characteristics of the 115 patients included in this study. Their median age was 41 years (range, 27 to 77 years). Sixty-five patients (57%) had SCC and 50 (43%) had non-SCC. The breakdown of non-SCC was: adenocarcinoma, 37; adenosquamous carcinoma, 9; and other types of carcinoma, 4. Eighteen patients (16%) were

Table 3. A relationship between pretreatment variables and parametrial involvement

Pretreatment factor	Parametrial involvement		p-value
	Negative	Positive	
MRI-based factor			
Maximal tumor diameter (mm)			<0.001
0 to 20	64 (98.5)	1 (1.5)	
20 to 25	20 (91.3)	2 (8.7)	
25 to 30	8 (72.7)	3 (27.3)	
30 to 35	4 (33.3)	8 (66.7)	
35 to 40	1 (20.0)	4 (80.0)	
Pelvic LN enlargement			0.11
No	95 (85.6)	16 (14.4)	
Yes	2 (50.0)	2 (50.0)	
Volume index (mm ³)			<0.001
0 to 5,000	73 (98.6)	1 (1.4)	
5,000 to 10,000	15 (88.2)	2 (11.8)	
10,000 to 20,000	5 (50.0)	5 (50.0)	
20,000 to 30,000	3 (30.0)	7 (70.0)	
Greater than 30,000	1 (25.0)	3 (75.0)	
Serum tumor marker			<0.001
Negative*	67 (94.4)	4 (5.6)	
Positive†	30 (68.2)	14 (31.8)	

Values are presented as number (%).

CA-125, cancer antigen 125; LN, lymph node; MRI, magnetic resonance imaging; SCC, squamous cell carcinoma.

*SCC-Ag <1.5 ng/mL and CA-125 <35 U/mL. †SCC-Ag ≥1.5 ng/mL or CA-125 ≥35 U/mL.

pathologically diagnosed with PI. Seventeen patients (15%) had lymph node metastasis (LNM). Seventy-one patients (62%) showed positive serum tumor markers before surgery. Sixty-seven patients (58%) received no adjuvant treatment and 45 patients (39%) received adjuvant platinum-based chemotherapy.

Table 3 shows the relationship between pretreatment variables and PI. The percentage of patients with PI significantly increased as the MRI-based tumor diameter increased ($p < 0.001$); 1.5% (tumor diameter, < 20 mm), 8.7% (tumor diameter, 20 to 25 mm), 27.3% (tumor diameter, 25 to 30 mm), 66.7% (tumor diameter, 30 to 35 mm), and 80.0% (tumor diameter, 35 to 40 mm). The percentage of patients with PI significantly increased as volume index increased

($p < 0.001$); 1.4% (tumor volume, $< 5,000$ mm³), 11.8% (tumor volume, 5,000 to 10,000 mm³), 50.0% (tumor volume, 10,000 to 20,000 mm³), 70.0% (tumor volume, 20,000 to 30,000 mm³), and 75.0% (tumor volume, $\geq 30,000$ mm³). The rate of PI was significantly higher in patients with positive results for serum tumor marker than in those with negative results (31.8% vs. 5.6%, $p < 0.001$).

Table 4 shows the result of logistic regression analysis of pretreatment factors relating to PI. Multivariate analysis confirmed that MRI-based tumor diameter (odds ratio [OR], 9.9; 95% confidence interval [CI], 2.1 to 48.1), volume index (OR, 13.3; 95% CI, 1.4 to 125.0), and serum tumor marker (OR, 5.7; 95% CI, 1.3 to 25.1) were independent risk factors for PI. Receiver operating characteristic curves were constructed

Table 4. Logistic regression analysis of pretreatment factors relating to parametrial involvement

Pretreatment factor	Parametrial involvement	Univariate analysis		Multivariate analysis	
		Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
MRI-based tumor diameter (mm)					
<25	3/87 (3.4)	1		1	
≥ 25	15/28 (53.6)	32.3 (8.21–127.2)	<0.001	9.9 (2.05–48.1)	<0.001
MRI-based volume index (mm ³)					
<5,000	1/74 (1.4)	1		1	
$\geq 5,000$	17/41 (41.5)	51.7 (6.53–409.4)	<0.001	13.3 (1.41–125.0)	0.024
Serum tumor marker					
Negative*	4/71 (5.6)	1		1	
Positive [†]	14/44 (31.8)	7.8 (2.37–25.7)	<0.001	5.7 (1.29–25.1)	0.022

Values are presented as number/total number (%).

CA-125, cancer antigen 125; CI, confidence interval; MRI, magnetic resonance imaging; SCC, squamous cell carcinoma.

*SCC-Ag < 1.5 ng/mL and CA-125 < 35 U/mL. [†]SCC-Ag ≥ 1.5 ng/mL or CA-125 ≥ 35 U/mL.

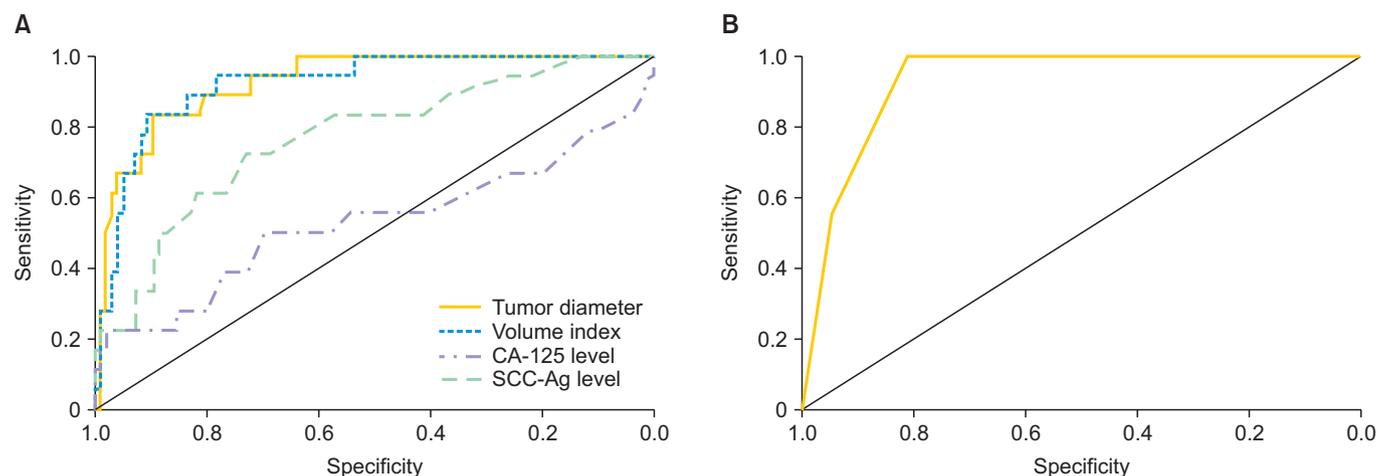


Fig. 1. (A) Receiver operating characteristic (ROC) curves of tumor diameter, volume index, and serum tumor markers (SCC-Ag and CA-125) for predicting parametrial involvement (PI). (B) ROC curve of combination of tumor diameter, volume index, and serum tumor markers for predicting PI.

Table 5. Rates of parametrial involvement by pretreatment risk factors for parametrial involvement

Tumor marker	MRI-based tumor diameter <25 mm		MRI-based tumor diameter ≥25 mm	
	VI <5,000 mm ³	VI ≥5,000 mm ³	VI <5,000 mm ³	VI ≥5,000 mm ³
Negative*	0 (0/53)	0 (0/7)	0 (0/1)	40.0 (4/10)
Positive [†]	0 (0/18)	30.0 (3/10)	50.0 (1/2)	71.4 (10/14)

Values are presented as percentage (number/total number).

MRI, magnetic resonance imaging; SCC, squamous cell carcinoma; VI, volume index.

*SCC-Ag <1.5 ng/mL and CA-125 <35 U/mL. [†]SCC-Ag ≥1.5 ng/mL or CA-125 ≥35 U/mL.

to evaluate the performance of MRI-based tumor diameter, volume index, serum level of SCC-Ag and serum level of CA-125 for predicting PI (**Fig. 1**). Area under the curve (AUC) of tumor diameter, volume index, SCC-Ag, and CA-125 was 0.925 (95% CI, 0.869 to 0.981; $p < 0.001$), 0.921 (95% CI, 0.860 to 0.982; $p < 0.001$), 0.768 (95% CI, 0.644 to 0.892; $p < 0.001$), and 0.528 (95% CI, 0.347 to 0.709; $p = 0.764$), respectively. AUC of combination criteria consisting of tumor diameter, volume index, and serum tumor markers was 0.933 (95% CI, 0.893 to 0.974; $p < 0.001$), which indicated the best performance. **Table 5** shows actual frequencies of PI according to these risk factors. Of 53 patients with no risk factors for PI, none had PI.

DISCUSSION

While radical trachelectomy has achieved satisfactory oncological outcomes in selected patients with early-stage cervical cancer, it has had unsatisfactory obstetrical outcomes [4]. Because the number of patients with invasive cervical cancer is increasing among young women who long for pregnancy and childbirth, less-invasive surgery should be considered as an alternative therapy. Previous studies have confirmed that tumor diameter [13,15,16,18,25], depth of cervical invasion [8,10,11,25,26], lymphovascular space invasion (LVSI) [7,8,10,11,15,18,25], and pelvic LNM [8,11,13,25] are pathological risk factors for PI in cervical cancer.

Some low-risk criteria for PI have been proposed by optionally combining the above-mentioned risk factors. When tumor diameter <20 mm, depth of cervical invasion <10 mm, negative LVSI, or negative LNM were considered as a component of low-risk criteria, the rate of PI was reported to be <2.0% [11,12,14,18,22]. However, surgery is necessary to identify the depth of cervical invasion or LVSI. In contrast, MRI seems to have become a reliable source of information regarding risk of PI. MRI-based tumor size can be a substitute for a histopathologically measured tumor. Kodama et al. [16] demonstrated a significant correlation between MRI-based and histopathological tumor size in stage IB1 cervical cancer

($r = 0.787$, $p < 0.001$). Although the percentage of PI is 0% to 4.5% in small (<20 mm) cervical cancer [14-18], it is 0% to 1.1% in MRI-based, small (<20 mm) cervical cancer [9,10,16]. MRI-based tumor diameter <20 mm can be a sufficient index for low-risk PI. Patients who meet these criteria might be candidates for less-invasive surgery.

We focused on patients with tumor diameter 20 to 25 mm, which accounts for 20% to 30% of all stage IB1 cervical cancer in our study. It is possible to extend the indication range for less-invasive surgery by assessing tumor volume, serum tumor marker, and tumor diameter in one direction. In our study, a low-risk of PI was confirmed as a tumor diameter <25 mm, a small volume index, and negativity for serum tumor markers (SCC-Ag and CA-125). No PI was seen in patients meeting these criteria, accounting for 47% of all stage IB1 cervical cancer in the present study.

Lee et al. [27] focused on patients with microscopic stage IB1 disease, namely, the cancer can be seen only with a microscope. They suggested a unique criterion for less radical surgery, as patients with no demonstrable lesions on post-conization MRI in microscopic stage IB1 cervical cancer [27]. The rate of PI was 1.4% (1/74) for invisible tumors on MRI and 11.8% (6/51) for MRI-visible tumors. They claimed that less radical surgery, namely, omission of parametrectomy is feasible in accordance with their criteria. In the present study, 17 patients (14.5%) were diagnosed by conization, thus the above-mentioned criteria should be applicable to such patients.

Tumor volume or serum tumor markers may play an auxiliary role for tumor diameter to confirm a low-risk group for PI. Chang et al. [13] also proposed unique low-risk criteria for PI. They showed that the percentage of PI was 1.1% in patients with tumor diameter <30 mm and negativity for serum SCC-Ag [13]. Moreover, intraoperative assessment including sentinel lymph node biopsy can be promising. Klat et al. [23] showed that no PI was identified in patients with tumor diameter <20 mm and negative sentinel LNM.

Our study had some limitations. First, the number of patients was too small to power conclusive results. Our study inevita-

bly had selection bias because of its retrospective nature and being a single-institution study. Second, reproducibility with regard to measurement of tumor diameter or tumor volume, namely interobserver variability has not yet been validated.

In conclusion, MRI-based tumor diameter ≥ 25 mm, volume index $\geq 5,000$ mm³, and positive serum tumor markers SCC-Ag ≥ 1.5 ng/mL or CA-125 ≥ 35 U/mL were independent risk factors for PI in a Japanese cohort. Less radical surgery may become one of the treatment options for patients with stage IB1 cervical cancer who do not have any of these risk factors.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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