Preoperatively Assessable Clinical and Pathological Risk Factors for Parametrial Involvement in Surgically Treated FIGO Stage IB–IIA Cervical Cancer

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Objective: Determining the risk factors associated with parametrial involvement (PMI) is of paramount importance to decrease the multimodality treatment in early-stage cervical cancer. We investigated the preoperatively assessable clinical and pathological risk factors associated with PMI in surgically treated stage IB1–IIA2 cervical cancer.

Methods: A retrospective cohort study of women underwent Querleu-Morrow type C hysterectomy for cervical cancer stage IB1–IIA2 from 2001 to 2015. All patients underwent clinical staging examination under anesthesia by the same gynecological oncologists during the study period. Evaluated variables were age, menopausal status, body mass index, smoking status, FIGO (International Federation of Obstetrics and Gynecology) stage, clinically measured maximal tumor diameter, clinical presentation (exophytic or endophytic tumor), histological type, tumor grade, lymphovascular space invasion, clinical and pathological vaginal invasion, and uterine body involvement. Endophytic clinical presentation was defined for ulcerative tumors and barrel-shaped morphology. Two-dimensional transvaginal ultrasonography was used to measure tumor dimensions.

Results: Of 127 eligible women, 37 (29.1%) had PMI. On univariate analysis, endophytic clinical presentation ($P = 0.01$), larger tumor size ($P < 0.001$), lymphovascular space invasion ($P < 0.001$), pathological vaginal invasion ($P = 0.001$), and uterine body involvement ($P < 0.001$) were significantly different among the groups with and without PMI. In multivariate analysis endophytic clinical presentation (odds ratio, 11.34; 95% confidence interval, 1.34–95.85; $P = 0.02$) and larger tumor size (odds ratio, 32.31; 95% confidence interval, 2.46–423.83; $P = 0.008$) were the independent risk factors for PMI. Threshold of 31 mm in tumor size predicted PMI with 71% sensitivity and 75% specificity. We identified 18 patients with tumor size of more than 30 mm and endophytic presentation; 14 (77.7%) of these had PMI.

Conclusions: Endophytic clinical presentation and larger clinical tumor size (>3 cm) are independent risk factors for PMI in stage IB–IIA cervical cancer. Approximately 78% of the patients with a tumor size of more than 3 cm and endophytic presentation will require adjuvant chemoradiation for PMI following radical surgery. Considering clinical tumor presentation along with tumor size can enhance the physician's prediction of PMI in early-stage cervical cancer.

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Querleu-Morrow type C hysterectomy with pelvic lymphadenectomy and adjuvant therapy according to individual risk factors or concurrent chemoradiotherapy are acknowledged as standard treatment methods in International Federation of Obstetrics and Gynecology (FIGO) stage IB to IIA cervical cancer.[1] Parametrial involvement (PMI), lymph node metastasis, and positive surgical margins are prognostic factors associated with recurrence and established indications for adjuvant chemotherapy and pelvic radiotherapy following surgery.[2] If PMI is suspected before the treatment, only the Japanese guideline and some centers from Germany recommend surgery, whereas guidelines from the United States and European countries other than Germany recommend concurrent chemoradiation instead of surgery.[3–6] In a landmark phase 3 clinical study by Landoni et al,[7] survival outcomes of radical surgery and adjuvant radiotherapy in the presence of poor prognostic factors were found to be similar with those of primary radiotherapy. However, postoperative irradiation as a part of multimodality treatment can increase the morbidity associated with radical hysterectomy such as prolonged colorectal and bladder dysfunction and urinary fistulas. Grade 3 to 4 morbidity can be expected in 10% to 30% of patients receiving combined treatment.[8–11] Moreover, multimodality treatment can considerably affect the quality of life of the women.[12] According to a cost-utility analysis, additional treatment modalities after radical surgery, with radiotherapy alone or with concurrent chemotherapy, result in higher treatment costs.[13] Hence, regarding both the treatment morbidity and efficient use of health care resources, it is reasonable to save the surgery option for patients who have a low probability of requiring adjuvant therapy.

Cervical cancer staging is based on clinical discretion with examination of the anatomical compartments by vaginal inspection and bimanual palpation. Cystoscopy, proctoscopy, pyelography, and barium enema can be performed if needed.[14] However, clinical staging even under anesthesia does not correlate with surgical staging in up to 32% of stage IB and 50% of stage II patients with cervical cancer.[15] Further imaging based on magnetic resonance imaging (MRI) or computed tomography is recommended but usually not necessarily performed. Nevertheless, information about PMI cannot always be provided definitely before surgery. Therefore, 5% to 30% of patients who have stage IB1 and 32% to 63% of patients who have stage IB2 and IIA cervical disease have PMI and receive adjuvant chemoradiation after radical hysterectomy.[16–21]

With the purpose of minimizing the multimodality treatment-related morbidity and high cost, determining the preoperative risk factors associated with PMI is of paramount importance. The objective of the current study was to evaluate the preoperatively assessable clinical and pathological risk factors that can help the clinician to predict the PMI in stage IB–IIA cervical cancer before radical surgery.

PATIENTS AND METHODS

We retrospectively reviewed the records of patients who underwent Querleu-Morrow type C hysterectomy and pelvic ± para-aortic lymphadenectomy for FIGO stage IB1–IIA2 cervical cancer after approval by institutional review board (approval no. 15928). Demographic, clinical, and pathologic data were extracted from prospectively recorded tumor registry of gynecological oncology department and institutional medical records. Between 2001 and 2015, a total of 129 patients with stage IB1–IIA2 cervical cancer underwent type C hysterectomy and lymphadenectomy without receiving any neoadjuvant therapy. Patients who were incidentally diagnosed as having cervical cancer after simple hysterectomy were not eligible for the study. All of the patients underwent clinical staging examination by at least 1 of the 3 attending gynecological oncologists during the study period. Clinical examination included speculum inspection and parametrial assessment by rectovaginal palpation under general anesthesia, 2-dimensional (2D) transvaginal ultrasonography (TVUS), and chest radiography in all of the patients; cystoscopy, proctoscopy, and MRI were performed if needed. A 5- to 8-MHz microconvex probe was used to measure the clinical tumor size transvaginally by gynecological oncologists following speculum inspection and bimanual palpation under general anesthesia. Vertical and horizontal tumor dimensions were measured and preoperatively recorded in patients' charts. Patients postoperatively diagnosed as having endometrial cancer with cervical involvement (n = 2) were excluded from the study. Consequently, 127 patients were eligible for study analysis.

We reviewed preoperatively recorded characteristics and postoperative pathological data available for preoperative investigation. Variables analyzed to predict PMI were age, menopausal status, body mass index (BMI), smoking, FIGO stage, clinically measured maximal tumor diameter, clinical presentation (exophytic or endophytic tumor), histological type, tumor grade, lymphovascular space invasion (LVSI), clinical and pathological vaginal invasion (VI), and uterine body involvement. Tumors were classified according to the dominant morphology for clinical presentation. Ulcerative tumors and tumors with barrel-shaped morphology were referred to as endophytic tumors. Fungating tumors with or without small superficial ulcerations were referred to as

TABLE 1. Clinical and pathologic characteristics of the patients

Variables	PMI Negative (n = 90)	PMI Positive (n = 37)	*P*
Age, mean, y	47.0 ± 1.03	50.5 ± 1.9	0.09
BMI, mean, kg/m^2	26.9 ± 5.06	27.0 ± 5.68	0.88
Menopausal status			0.054
Premenopausal	58 (64.4%)	17 (45.9%)	
Postmenopausal	32 (35.6%)	20 (54.1%)	
Stage			0.59
1B1	75 (83.3%)	27 (73%)	
1B2	5 (5.6%)	3 (8.1%)	
2A1	8 (8.9%)	6 (16.2%)	
2A2	2 (2.2%)	1 (2.7%)	
Histologic classification			0.89
Squamous	77 (85.6%)	32 (86.4%)	
Nonsquamous	13 (14.4%)	5 (13.5%)	
Adenocarcinoma	10 (11.1%)	4 (10.8%)	
Adenosquamous	3 (3.3%)	1 (2.7%)	
Clinical presentation			**0.01**
Exophytic	42 (46.7%)	12 (32.4%)	
Endophytic	31 (34.4%)	24 (64.9%)	
Prior conization	15 (16.7%)	—	
Unknown	2 (2.2%)	1 (2.7%)	
Tumor size, mean (range), mm			**<0.001**
Clinic (TVUS)	25.7 ± 1.19 (8–50)	34.2 ± 1.53 (10–55)	**<0.001**
Pathologic	25.6 ± 1.45 (8–75)	36.0 ± 1.56 (20–65)	**<0.001**
Tumor grade			0.56
1	15 (16.7%)	4 (10.8%)	
2	52 (57.8%)	21 (56.8%)	
3	12 (13.3%)	7 (18.9%)	
Not specified	11 (12.2%)	5 (13.5%)	
LVSI			**<0.001**
Positive	33 (36.7%)	28 (75.7%)	
Negative	41 (45.6%)	1 (2.7%)	
Not specified	16 (17.7%)	8 (21.6%)	
Clinical vaginal involvement			**0.24**
Yes	10 (11.1%)	7 (19%)	
No	80 (88.9%)	30 (81%)	
Pathological vaginal involvement			**0.001**
Yes	4 (4.4%)	9 (24.3%)	
No	86 (95.6%)	27 (73%)	
Not specified		1 (2.7%)	
Uterine body involvement			**<0.001**
Yes	5 (5.6%)	11 (29.7%)	
No	64 (71.1%)	15 (40.6%)	
Not specified	21 (23.3%)	11 (29.7%)	

Data in bold means statistically significant.

exophytic tumors. Data regarding morphology were retrieved from preoperative examination records and pathology reports. Because tumor grade, LVSI, and uterine body involvement can be regarded as preoperatively assessable variables with additional investigations such as loop electrosurgical excision procedure biopsy and MRI, these data were included in the analysis to clarify their predictive value and the need of preoperative investigation in predicting PMI and were based on postoperative pathology records. We analyzed clinical vaginal involvement and pathological vaginal involvement as separate variables. Because clinical staging can overestimate the vaginal involvement in comparison with the pathological examination particularly in bulky tumors, to eliminate the interobserver variability, discrimination errors, and doubts and to discover the necessity for further preoperative investigations of vaginal involvement in predicting PMI, pathologically defined VI was also assessed as a separate variable.

Clinically estimated tumor size was compared with tumor size measured at pathological specimen to check out the accuracy of size estimation with TVUS during the staging examination. Finally, to identify the diagnostic performance of clinical examination under general anesthesia, we calculated the negative predictive value for PMI.

Statistical Analysis

Patients were assigned to dichotomous groups on the basis of PMI according to the postoperative pathological results. Pearson χ^2 test and Fisher exact test were used for categorical data, and the Student *t* test or Mann-Whitney *U* statistic for continuous data according to normality. Univariate analysis of various clinical and pathologic characteristics was performed to identify the prominent risk factors posing difference between the 2 groups. Risk factors that achieved statistical significance with univariate comparison were included in binary logistic regression analysis to define the

TABLE 2. Multivariate analysis of risk factors for PMI

	OR (95% CI)	*P*
Endophytic clinical presentation	11.34 (1.34–95.85)	**0.02**
Tumor size >30 mm	32.31 (2.46–423.83)	**0.008**
Positive LVSI	—	0.99
Pathological vaginal involvement	—	0.10
Uterine body involvement	—	0.08

independent factors. Receiver operating characteristic analysis of the significant quantitative factors were made to define threshold values. Statistical analyses were done by using IBM SPSS Statistics for Windows version 22.0 (IBM Corp, Armonk, NY). $P < 0.05$ was considered statistically significant for both univariate and multivariate analyses. Data are presented as mean ± SEM.

RESULTS

Clinical and pathologic characteristics of the patients with and without PMI are presented in Table 1. The mean age of the cohort was 48.0 years (range, 25–72 years). Overall, 75 patients (59.1%) were premenopausal; 52 patients (40.9%) were postmenopausal. Mean BMI was 26.9 kg/m^2 (range, 16.3–43.0 kg/m^2). Histological diagnosis was squamous cell carcinoma in 109 patients (85.8%) and nonsquamous cell carcinoma in 18 patients (14.1%) (adenocarcinoma in 14 patients [11%] and adenosquamous in 4 patients (3.1%]).

The distribution of the patients according to FIGO staging was IB1 in 102 patients (80.3%), IB2 in 8 patients (6.3%), IIA1 in 14 patients (11%), and IIA2 in 3 patients (2.4%). Clinical presentation of the tumor was exophytic in 54 patients (42.5%), and endophytic (ulcerative or barrel shaped) in 55 patients (43.3%). Tumor morphology was not assessed in 15 patients (11.8%) because of prior conization procedure, and it was unmentioned in 3 patients (2.3%). Grade was defined as 1 in 19 patients (15%), 2 in 73 patients (57.5%), 3 in 19 patients (15%), and unspecified in 16 patients (12.6 %). Vaginal invasion was confirmed in 13 cases in pathologic assessment; however, the number of patients considered as having stage IIA disease in preoperative examination was 17.

Parametrial Involvement

Overall, 37 women (29.1%) had PMI; 27 (26.5%) of IB1, 3 (37.5%) of IB2, 6 (42.9%) of IIA1, and 1 (33.3%) of IIA2, respectively. On univariate analysis, endophytic presentation ($P = 0.01$), larger clinical tumor size ($P < 0.001$), LVSI ($P < 0.001$), pathological VI ($P = 0.001$), and uterine body involvement ($P < 0.001$) were significantly different among the groups with and without PMI. There was no difference with regard to age ($P = 0.09$), BMI ($P = 0.88$), smoking ($P = 0.32$), menopausal status ($P = 0.054$) of the patients and clinical stage ($P = 0.59$), clinical vaginal involvement ($P = 0.24$), and histological type ($P = 0.89$) or grade ($P = 0.56$) of the disease.

The multivariate logistic regression model had a predictive value of 86% and Nagelkerke constant value of 0.69. This analysis concluded that endophytic presentation (odds ratio [OR], 11.34; 95% confidence interval [CI], 1.34–95.85; $P = 0.02$) and larger clinical tumor size (odds ratio, 32.31; 95% CI, 2.46–423.83; $P = 0.008$) were independent risk factors for PMI (Table 2). A threshold of 31 mm in tumor size predicted PMI with a 71% sensitivity and 75% specificity (receiver operating characteristic analysis, area under the curve of tumor size = 0.778) (Fig. 1).

We found that 14 (15.5%) of 90 patients with clinical tumor size of 30 mm or less had PMI, and if endophytic tumors are excluded, only 5 (9.4%) of 53 patients were found to have PMI. However, 22 (59.5%) of 37 patients with a clinical tumor size of more than 30 mm had PMI. We identified 18 patients with tumor size of more than 30 mm and endophytic presentation, and 14 (77.7%) of these had PMI.

Tumor Size

The mean pathologically measured maximal tumor diameter (30.1 ± 1.2 mm; range, 8–75 mm) was slightly larger than the clinically estimated maximal tumor diameter (28.1 ± 1 mm; range, 8–55 mm) ($P = 0.016$). After exclusion of the patients who previously underwent conization procedure, 84 (75%) of 112 patients had consistency between size measurement by TVUS and pathological examination within the limits of ±5 mm, and in 102 patients (91%), size difference was less than 10 mm.

Magnetic Resonance Imaging

In this study population, 76 patients (59.8%) had preoperative MRI assessment; however, MRI results did not

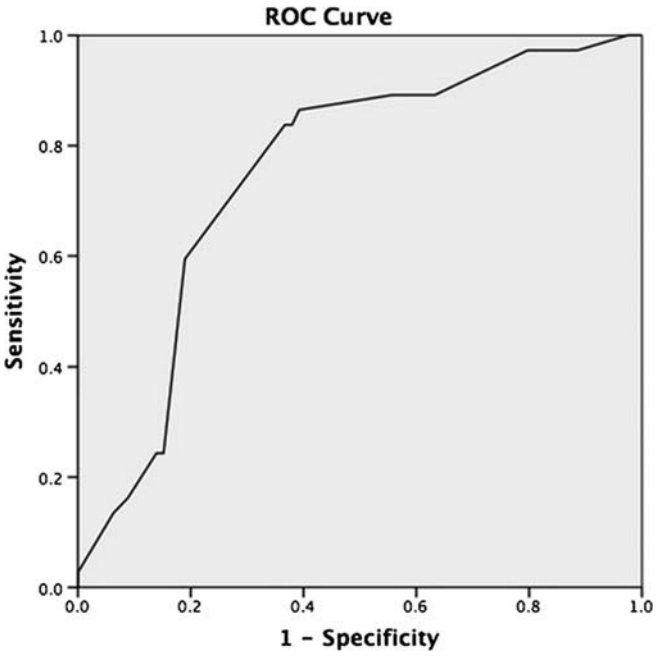

FIGURE 1. Receiver operating characteristic analysis, area under the curve of tumor size = 0.778. A threshold of a 31 mm in tumor size predicted PMI with a 71% sensitivity and 75% specificity.

necessarily change the clinicians' judgment. In the parametrial invasion group, 78.3% of the patients underwent MRI assessment preoperatively, whereas 52.2% of the patients in negative parametrium had preoperative MRI. In the group with MRI scan, only 6 (20.7%) of 29 patients with parametrial invasion were preoperatively identified in MRI. However, among the 10 patients who had MRI results suggestive of PMI, 4 had negative parametrium on pathologic examination. In the group with MRI scan, diagnostic accuracy of MRI in terms of PMI was 65.2%. The positive and negative predictive values were 60% and 65.2%, respectively. The negative predictive value of clinical staging examination under anesthesia for parametrial infiltration was 70.8% in our study population.

DISCUSSION

Cervical cancer staging is based on clinical examination performed according to the FIGO guidelines. Stage IA cancers are treated well alone by surgery with an excellent survival. Stage IB and IIA cervical cancers can be treated by surgery or chemoradiation. However, only 30% of patients with a tumor diameter larger than 4 cm are cured by surgery alone; others will require adjuvant radiation, and 50% will require adjuvant chemoradiation for high-risk features.[22,23] Thus, FIGO staging in this group does not yield to select the patients who can be treated by surgery alone. In this study group, 29.1% of patients with stage IB–IIA cervical cancer required adjuvant chemoradiation for PMI. We evaluated preoperatively assessable clinic and pathologic characteristics to determine the high-risk factors for PMI before surgery. On univariate analysis, endophytic tumor presentation, clinical tumor size of more than 30 mm, LVSI, and infiltration of the vagina and uterine body were found to be significantly different in patients with and without PMI. Multivariate analysis showed that only endophytic presentation and a clinical tumor size of more than 30 mm were independent risk factors for PMI. Our results are in accordance with previous studies that reported that up to 30% of patients in stage IB1 disease, 63% in stage IB2, and 58% in stage IIA disease had PMI on histopathologic examination.[17,21] These studies concluded that age, tumor size, LVSI, deep stromal invasion, and lymph node metastasis were closely associated with PMI. In addition, with the aim of emphasizing the preoperatively assessable risk factors, the current study showed considering the endophytic clinical presentation along with tumor size can enhance the physician's prediction of PMI. Approximately 78% of patients with a tumor size of more than 3 cm and endophytic presentation were shown to have PMI in this study. Interestingly, clinical stage was not found as a risk factor possibly because the numbers of patients treated surgically in stage IB2 and IIA2 disease were small.

Tumor morphology is considered as a prognostic variable in various human cancers. Trimbos and colleagues[24] showed both lymph node metastasis and deep stromal invasion were more frequent in barrel-shaped bulky cervical tumors compared with their exophytic counterparts. Moreover, they concluded that bulky barrel-shaped tumor geography was an independent prognostic factor along with lymph node involvement, PMI, and affected surgical margins in multivariate analysis. This can be attributed to the aggressive tumor biology of endophytic-growing tumors. For example, in a recent study, expression of the parvin-β (*PARVB*) gene that increases the cell migration capability was reported to be significantly up-regulated in the endophytic subtype of squamous cell carcinoma of tongue, which is the subtype known to be associated with worse prognosis and metastatic disease.[25] Similarly, Paley et al[26] found residual disease in 61% of hysterectomy specimens following radiation therapy in women with bulky barrel-shaped cervical carcinoma; and they emphasized the need for more efficacious therapies in these patients and not to attenuate the radiation dose even postradiation hysterectomy to be scheduled. Several authors have reported that cervical tumors in elderly women are prone to grow endophytically because the squamocolumnar junction is within the canal, and they have a higher incidence of PMI even when their tumors are 2 to 3 cm or less in size.[20,27,28] Kong et al[29] have reported that postmenopausal women had smaller tumor volumes (10.1 cm^3 in the premenopausal group vs 7.8 cm^3 in the postmenopausal group, $P = 0.017$) and lower FIGO stage compared with those in premenopausal women. However, the current study emphasizes that independently of menopausal status, endophytic growth is one of the most important preoperative features reflecting deep infiltration and PMI, which might be unrecognized in pelvic examination.

Studies indicate that the requirement for postoperative radiotherapy increases with increasing tumor size. In the Milan study, 84% of patients who had clinical tumor diameter of more than 4 cm received postoperative radiotherapy in comparison with 54% of patients with tumor size of 4 cm or less.[7] Similar to our results, Chang et al[19] identified more than 3-cm clinical tumor size along with high serum SCC-Ag level as independent preoperative risk factors for predicting PMI. Moreover, in the GOG-49 study, a cutoff value of 3 cm in clinical tumor size, LVSI, and depth of tumor invasion were shown to be independent prognostic factors.[30] In this study, tumor size was measured with 2D TVUS during preoperative pelvic examination under general anesthesia. With regard to clinical practice, there was a small (2 mm) but statistically significant difference between pathological measurement and TVUS measurement of the mean largest tumor diameter. However, after exclusion of prior conization procedures, in 75% of the patients, size difference between clinical measurement and pathologic examination was within the limits of ±5 mm, and it was smaller than 10 mm in 91% of the patients. It is known that MRI can provide a better corresponding tumor size with surgical specimen than pelvic examination in T2-weighted sections.[31–34] However, 2D TVUS and 3D TVUS were also shown to have good correlation with MRI in size estimation for cervical cancer.[35,36] The agreement between TVUS and pathological examination with regard to tumor size was also shown to be highly correlated, with a coefficient value of 0.92.[37] In a recent European multicenter trial along with high accurate preoperative assessment, it was emphasized that ultrasonography may be more accurate than MRI in detecting residual tumors and assessing parametrial invasion.[38] However, despite TVUS being a practical and easy-to-access imaging method, its value in preoperative assessment of cervical cancer needs further validation.

Presence of tumor infiltration into the uterine body is a significant finding showing that the cervix has been infiltrated by the tumor entirely. Narayan et al[39] analyzed the association of uterine body involvement in MRI with lymph node metastasis in cervical cancer and showed that in multivariate analysis uterine body involvement was the most significant and independent risk factor for lymph node metastasis. Moreover, in a recent study, they showed that uterine body involvement was also the most significant prognostic factor; in the presence of uterine isthmus invasion, neither the FIGO stage, nor the clinical diameter, had an additional prognostic value.[40] Because lymph node metastasis is strongly associated with PMI, we assessed whether uterine body involvement may also be a risk factor for PMI. Despite being significantly more common in cases with PMI, uterine body involvement was not found to be an independent risk factor in the current study.

The current study showed that vaginal involvement can be overestimated in preoperative examination, even under anesthesia, particularly in bulky tumors extending the vaginal walls. In this study 13 patients had pathologically confirmed VI; however, 17 patients were diagnosed as having stage IIA disease in preoperative examination. Use of vaginal gel may allow an accurate definition of vaginal fornices on MRI images and may be helpful in cases of suspicion.[41] In the study, despite the clinical decision of vaginal involvement not being significantly different in patients with and without parametrial metastasis, pathologically confirmed VI was a risk factor in univariate analysis. However, as in the uterine body infiltration, it was not found as an independent factor in multivariate analysis, and we do not suggest further preoperative investigation of these factors following examination under anesthesia.

There are some limitations to be mentioned. First, the study included a long retrospective study period, which may cause intraobserver and interobserver variability and selection biases. Second, tumor size was measured by TVUS during pelvic examination, not by MRI. Third, despite being considered among preoperatively identifiable features, data on uterine body involvement, pathological VI, tumor grade, and LVSI were not recorded in preoperative clinical examination but were based on pathological records. Yet, even then, in the final analysis, these factors fell short of being defined as significant independent predictors of PMI, and the authors do not recommend their preoperative investigation in predicting PMI in stage IB–IIA cervical cancer. On the other hand, preoperative examination was performed under general anesthesia in all of the patients as uniform methodology in this study. This eliminates the evaluation biases related to patient discomfort during pelvic examination regarding tumor size and clinical presentation.

We conclude that approximately 78% of the patients with cervical tumor of more than 3 cm in clinical size and endophytic morphology will require adjuvant chemoradiation for PMI following radical surgery. Along with the manual examination, these clinical features can help physicians more robustly predefine high-risk patients for PMI in stage IB–IIA cervical cancer. Based on these results, we can recommend not to operate endophytic-growing tumors larger than 3 cm. In this context, it can be expected to decrease the multimodality treatment-related morbidity and cost in well-selected cases. However, this subject can be a matter of debate when we consider the high residual tumor rates after primary radiation therapy in endophytic-growing tumors. Thus, further well-designed controlled studies are needed before reaching firm conclusion for directing these high-risk patients to primary chemoradiation instead of radical surgery.

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