RESEARCH ARTICLE

Predicting Factors for Positive Vaginal Surgical Margin Following Radical Hysterectomy for Stage IB1 Carcinoma of the Cervix

Sethawat Sethasathien[1], Kittipat Charoenkwan[1]*, Jongkolnee Settakorn[2], Jatupol Srisomboon[1]

Abstract

Background: To examine the incidence of positive vaginal surgical margins and determine the predicting factors following radical hysterectomy for stage IB1 carcinoma of the cervix. Materials and Methods: The clinical and histological data of 656 FIGO stage IB1 cervical cancer patients who had radical hysterectomy with bilateral pelvic lymphadenectomy (RHPL) from January 2003 to December 2012 were retrospectively reviewed and were analyzed for their association with a positive vaginal surgical margin. A p-value of < 0.05 was considered significant. Results: Thirty-five patients (5.3%) had positive vaginal surgical margins following RHPL; 24 (3.7%) for intraepithelial lesions and 11 (1.7%) for carcinoma. On multivariate analysis, microscopic vaginal involvement by high-grade squamous intraepithelial lesion and/or carcinoma (adjusted odd ratio (OR) 186.8; 95% confidence interval (CI) 48.5-718.5) and squamous histology (OR 8.7; 95% CI 1.7-44.0), were significantly associated with positive vaginal surgical margin. Conclusions: Microscopic vaginal involvement by HSIL and/or carcinoma are strong predictors for positive vaginal surgical margins for stage IB1 cervical cancer patients undergoing radical hysterectomy. Preoperative 'mapping' colposcopy or other strategies should be considered to ensure optimal vaginal resection.

Keywords: Cervical cancer - positive vaginal margin - radical hysterectomy - vaginal involvement - vaginal metastasis

Asian Pac J Cancer Prev, **15 (5)**, 2211-2215

Introduction

For early-stage carcinoma of the cervix, radical hysterectomy and pelvic lymphadenectomy (RHPL) is an effective treatment with a 5-year disease-free survival rate of approximately 75% (Landoni et al., 1997). However, certain pathological characteristics have been regarded as high-risk factors for recurrence and decreased survival. These include pelvic node metastasis, parametrial extension, and positive or close surgical margins (Delgado et al., 1989; Randall et al., 2013). It has been generally recommended that adjuvant pelvic radiation with or without concurrent chemotherapy be given to the patients with any of these high-risk pathological factors. Of the three high-risk factors, only the positive vaginal surgical margin could be associated with preoperative planning and surgical technique and is potentially modifiable if its predicting factors are known. While data on risk factors for pelvic node metastasis and parametrial invasion are extensive, the data on predicting factors for positive or close vaginal surgical margin in the literature is lacking.

The objectives of this study were to examine the incidence of and determine the predicting factors for positive vaginal surgical margin following radical hysterectomy for stage IB1 carcinoma of the cervix.

Materials and Methods

After ethical approval, the clinical and histological data of all FIGO stage IB1 cervical cancer patients who had radical hysterectomy with bilateral pelvic lymphadenectomy (RHPL) from January 2003 to December 2012 were retrospectively reviewed. The information about age, parity, menopausal status, underlying disease, previous abdominal surgery, prior conization, cone margin status, preoperative chemotherapy, operative data, tumor appearance, tumor size, histology, grade, depth of stromal invasion, lymph-vascular space invasion (LVSI), and detail of local spread and metastasis were collected from patients' medical records and pathological reports. These data were analyzed for their association with positive vaginal surgical margin.

After initial clinical staging examination, all patients were re-evaluated one day before surgery to ensure that the disease stage was unchanged from that previously assigned. All of the pathology materials

*[1]Department of Obstetrics and Gynecology, [2]Department of Pathology Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand *For correspondence: kittipat.c@cmu.ac.th, charoenkwan@live.com*

were examined by gynecologic pathologists. The tumors were classified histologically as squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and others. Squamous cell carcinomas were graded as well differentiated (grade 1), moderately differentiated (grade 2), and poorly differentiated (grade 3) by using a modified Broders' method. The depth of tumor invasion was categorized by the proportion of the cervical wall invaded by tumor as inner third, middle third, and outer third. LVSI was defined as the presence of neoplastic cells within endothelium-lined spaces. Total number of LVSI in the uterine cervix specimens was reviewed. The extent of LVSI was defined as follow: negative (no LVSI identified), few (less than 10 lymph-vascular spaces involved by tumor cells), and extensive (10 or more lymph-vascular spaces involved by tumor cells).Tumor spread to the uterine cavity, adnexa, parametrium, vaginal margin, and pelvic lymph nodes were determined.

Statistical analysis was performed by using Stata® program version 12 (StataCorp LP, College Station, Texas, USA). The chi-square or Fisher's exact test, as appropriate, was used for an analysis of association with positive vaginal surgical margin of all categorical variables. The logistic regression model was applied in a multivariate analysis to determine the independent predicting factors for positive vaginal surgical margin. The p-value of <0.05 was considered significant.

Results

Data of 656 FIGO stage IB1 cervical cancer patients who underwent RHPL between January 2003 and December 2012 were included in this study. The clinical, operative, and pathological data are summarized in Table 1.

The median age was 45 years old (24-85). Most of the patients were 50 years old or younger and premenopausal. The median parity was 2 (0-13). Approximately 12% of the patients had previous abdominal surgery. Thirty-five percent of the patients had cervical conization before undergoing radical surgery. Of these, the cone margins were found to be positive in more than 90%. Due to the occasionally long interval between diagnosis and surgery, one-fifth of the patients received preoperative chemotherapy to prevent tumor spread during the waiting time. Almost 98% of the patients had type 3 radical hysterectomy. The median operative time was 222.5 minutes (130-620). The median operative blood loss was 500 ml (50-4,000).

The median tumor size was 1.8 cm. The majority of patients had squamous histology, moderately differentiated tumor, with tumor invasion to the outer third of cervical stroma. Some degrees of LVSI were identified in more than half of the patients. Metastasis to pelvic nodes and parametria were documented in approximately 18% and 9%, respectively. Vaginal involvement was found in 67 patients (10%), 30 patients (4.6%) by high-grade squamous intraepithelial lesion (HSIL) and 37 patients (5.6%) by carcinoma.

Thirty-five patients (5.3%) had positive vaginal surgical margin, 24 patients (3.7%) for intraepithelial lesion and 11 patients (1.7%) for carcinoma. Twenty-four patients (3.7%) had positive vaginal surgical margin without the other two high-risk pathological factors; pelvic node metastasis and parametrial metastasis. Of these, 21 patients (3.2%) had positive margin for intraepithelial lesion and 3 patients (0.5%) had positive

Table 1. Association between Clinico-Pathological Factors and Positive Vaginal Surgical Margin

Characteristics		Number	Positive vaginal margin	p value
		n (%)	n (%)	
Age	<50	451 (68.8)	18 (4.0)	0.02*
	≥50	205 (31.2)	17 (8.3)	
Parity	≤2	516 (78.7)	25 (4.8)	0.28
	≥3	140 (21.3)	10 (7.1)	
Menopause	No	507 (77.3)	25 (4.9)	0.4
	Yes	149 (22.7)	10 (6.7)	
Underlying disease	No	477 (72.8)	25 (5.2)	0.85
	Yes	178 (27.2)	10 (5.6)	
Previous abdominal surgery	No	579 (88.3)	34 (5.9)	0.09
	Yes	77 (11.7)	1 (1.3)	
Prior conization	No	425 (64.9)	22 (5.2)	0.8
	Yes	230 (35.1)	13 (5.7)	
Cone margin status	Negative	19 (8.6)	0 (0)	0.61
	Positive	203 (91.4)	12 (5.9)	
Preoperative chemotherapy	No	513 (78.4)	28 (5.5)	0.57
	Yes	141 (21.6)	6 (4.3)	
Type of hysterectomy	II	15 (2.3)	2 (13.3)	0.19
	III	637 (97.7)	33 (5.2)	
Incidental appendectomy	No	374 (57.4)	20 (5.3)	0.86
	Yes	278 (42.6)	14 (5.0)	
Operation time (min)	<220	304 (47.9)	13 (4.3)	0.4
	≥220	330 (52.1)	19 (5.8)	
Blood loss (ml)	<500	256 (40.3)	9 (3.5)	0.15
	≥500	380 (59.7)	23 (6.1)	
Intraoperative complication	No	531 (83.5)	26 (4.9)	0.73
	Yes	105 (16.5)	6 (5.7)	
Tumor appearance	Microscopic	226 (34.6)	15 (6.6)	0.23
	Gross	427 (65.4)	19 (4.4)	
Tumor size (cm)	<2	319 (50.6)	14 (4.4)	0.26
	≥2	312 (49.4)	20 (6.4)	
Histology	Squamous	426 (64.9)	31 (7.3)	0.04*
	Adeno	154 (23.5)	3 (1.9)	
	Adenosquamous	49 (7.5)	0 (0.0)	
	Neuroendocrine	18 (2.7)	1 (5.6)	
	Others	9 (1.4)	0 (0.0)	
Histology grouping	Squamous	426 (64.9)	31 (7.3)	<0.01*
	Non-squamous	230 (35.1)	4 (1.7)	
Tumor grade	1	146 (30.2)	7 (4.8)	0.66
	2	261 (53.9)	18 (6.9)	
	3	77 (15.9)	4 (5.2)	
Depth of stromal invasion	Inner third	123 (23.3)	6 (4.9)	0.75
	Middle third	123 (23.3)	7 (5.7)	
	Outer third	281 (53.3)	19 (6.8)	
Lymph-vascular space invasion				
	No	247 (44.0)	11 (4.5)	0.34
	1-9 spaces	164 (29.2)	10 (6.1)	
	≥10 spaces	150 (26.7)	12 (8.0)	
Adnexal metastasis	No	648 (99.1)	34 (5.2)	0.28
	Yes	6 (0.9)	1 (16.7)	
Pelvic node metastasis	No	536 (82.2)	25 (4.7)	0.09
	Yes	116 (17.8)	10 (8.6)	
Parametrial metastasis	No	598 (91.2)	30 (5.0)	0.24
	Yes	58 (8.8)	5 (8.6)	
Parametrial margin	Negative	654 (99.7)	33 (5.0)	<0.01*
	Positive	2 (0.3)	2 (100.0)	
Uterine involvement	No	607 (92.5)	30 (4.9)	0.12
	HSIL/CA*	49 (7.5)	5 (10.2)	
Vaginal involvement	No	589 (89.8)	3 (0.5)	<0.01*
	HSIL/CA*	67 (10.2)	32 (47.8)	

*HSIL: High-Grade Squamous Intraepithelial Lesion; CA: Carcinoma

Table 2. Association between Different Categories of Vaginal Involvement and Vaginal Margin Status

Vaginal involvement	Number	Positive vaginal margin		p value
	n (%)	HSIL n (%)	CA n (%)	
No	589 (89.8)	3 (0.5)	0 (0.0)	< 0.01
HSIL[a]	30 (4.6)	19 (63.3)	0 (0.0)	
CA[b]	37 (5.6)	2 (5.4)	11 (29.7)	

[a]HSIL: High-Grade Squamous Intraepithelial Lesion; [b]CA: Carcinoma

Table 3. Association between Histology and Vaginal Margin Status

Histology	Number	Positive vaginal margin		p value
	n (%)	HSIL[a] n (%)	CA[b] n (%)	
Squamous	426 (64.9)	24 (5.6)	7 (1.6)	0.04
Adeno	154 (23.5)	0 (0.0)	3 (1.9)	
Adenosquamous	49 (7.5)	0 (0.0)	0 (0.0)	
Neuroendocrine	18 (2.7)	0 (0.0)	1 (5.6)	
Others	9 (1.4)	0 (0.0)	0 (0.0)	

[a]HSIL: High-Grade Squamous Intraepithelial Lesion; [b]CA: Carcinoma

Table 4. Association between Clinico-Pathological Factors that Can be known Preoperatively and Vaginal Involvement by HSIL and/or CA[a]

Characteristics		Number	Vaginal involvement	p value
		n (%)	n (%)	
Age	<50	451 (68.8)	36 (8.0)	<0.01*
	≥50	205 (31.2)	31 (15.1)	
Parity	≤2	516 (78.7)	45 (8.7)	0.02*
	≥3	140 (21.3)	22 (15.7)	
Menopause	No	507 (77.3)	49 (9.7)	0.39
	Yes	149 (22.7)	18 (12.1)	
Underlying disease	No	477 (72.8)	48 (10.1)	0.82
	Yes	178 (27.2)	19 (10.7)	
Previous abdominal surgery	No	579 (88.3)	62 (10.7)	0.25
	Yes	77 (11.7)	5 (6.5)	
Prior conization	No	425 (64.9)	46 (10.8)	0.5
	Yes	230 (35.1)	21 (9.1)	
Cone margin status	Negative	19 (8.6)	0 (0)	0.38
	Positive	203 (91.4)	19 (9.4)	
Preoperative chemotherapy	No	513 (78.4)	54 (10.5)	0.48
	Yes	141 (21.6)	12 (8.5)	
Tumor appearance	Microscopic	226 (34.6)	23 (10.2)	0.97
	Gross	427 (65.4)	43 (10.1)	
Tumor size (cm)	<2	319 (50.6)	19 (6.0)	<0.01*
	≥2	312 (49.4)	46 (14.7)	
Histology	Squamous	426 (64.9)	51 (12.0)	0.3
	Adeno	154 (23.5)	9 (5.8)	
	Adenosquamous	49 (7.5)	4 (8.2)	
	Neuroendocrine	18 (2.7)	2 (11.1)	
	Others	9 (1.4)	1 (11.1)	
Histology grouping	Squamous	426 (64.9)	51 (12.0)	0.04*
	Non-squamous	230 (35.1)	16 (7.0)	
Tumor grade	1	146 (30.2)	16 (11.0)	0.39
	2	261 (53.9)	30 (11.5)	
	3	77 (15.9)	13 (16.9)	
Depth of stromal invasion				
	Inner third	123 (23.3)	7 (5.7)	<0.01*
	Middle third	123 (23.3)	8 (6.5)	
	Outer third	281 (53.3)	47 (16.7)	
Lymph-vascular space invasion				
	No	247 (44.0)	17 (6.9)	<0.01*
	1-9 spaces	164 (29.2)	17 (10.4)	
	≥10 spaces	150 (26.7)	30 (20.0)	

[a]HSIL: High-Grade Squamous Intraepithelial Lesion; CA: Carcinoma

margin for carcinoma. Vaginal involvement by HSIL and/or carcinoma, squamous histology, positive parametrial margin, and age 50 or older, were associated with positive vaginal surgical margin in univariate analysis. (Table 1) The rates of positive vaginal margin were comparable among surgeons. In multivariate analysis, the factors significantly associated with positive vaginal surgical margin included vaginal involvement by HSIL and/or carcinoma (adjusted odd ratio (OR) 186.8; 95% confidence interval (CI) 48.5-718.5) and squamous histology (OR 8.7; 95% CI 1.7-44.0).

Association between different categories of vaginal involvement and vaginal margin status and association between histology and vaginal margin status were further explored and are illustrated in Table 2 and Table 3, respectively. Regarding the effect of histology, the rate of positive vaginal margin for HSIL and/or CA was significantly higher in those with squamous cell carcinoma compared to adenocarcinoma (7.2% *vs* 1.9%; p=0.02). However, the difference in the rates of positive vaginal margin could not be demonstrated between squamous cell carcinoma and neuroendocrine carcinoma (p=1.00) and between adenocarcinoma and neuroendocrine carcinoma (p=0.36). (Table 3)

Table 4 demonstrates the association between clinico-pathological factors that can be known preoperatively and vaginal involvement by HSIL and/or CA. In univariate analysis, age ≥50, parity ≥3, tumor size ≥2 cm, squamous histology, outer third cervical stromal invasion, and extensive LVSI (≥10 spaces) were significantly associated with microscopic vaginal involvement.

Discussion

Positive or close vaginal surgical margin has been regarded as one of high-risk pathological factors associated with increased recurrence and decreased survival in early-stage cervical cancer following radical surgery (Delgado et al., 1989; Randall et al., 2013). In the recent study by McCann et al. (2013), although not an independent predicting factor for recurrence, close vaginal margin of ≤5 mm was associated with other high or intermediate-risk pathological factors including nodal metastasis, parametrial involvement, larger tumor, deeper cervical stromal invasion, and LVSI. At our institution, patients with positive vaginal surgical margin are generally offered postoperative adjuvant radiotherapy; vaginal brachytherapy for patients with positive margin for intraepithelial lesion and pelvic radiation with concurrent chemotherapy for those with positive margin for carcinoma. Knowledge of the predicting factors for positive vaginal margin is important in that if the risks are modifiable, the rate of positive vaginal margin and the need for postoperative treatment could be lowered.

In the present study, the rate of positive vaginal surgical margin was low, approximately 5% overall and less than 2% if only positive vaginal surgical margin for carcinoma is considered. This is in line with the rate of close (≤5 mm) vaginal margin of approximately 4.2% in Estape et al study (Estape et al., 1998) and the rate of

surgical margin involvement of 8.3% in Chittithaworn et al study (Chittithaworn et al., 2007) in similar study population. It should be noted that two-third of those who had positive vaginal surgical margin had no other high-risk factors such as pelvic node metastasis and parametrial metastasis. This finding has suggested that other factors probably play a more important role than tumor biology in determining vaginal margin status. Multivariate analysis showing that vaginal involvement by HSIL and/or carcinoma and squamous histology were independent predicting factors for positive vaginal surgical margin in this study supports this assumption.

For the patients with stage IB1 cervical cancer in this study, vaginal involvement by HSIL and/or carcinoma was the strongest predicting factor associated with positive vaginal surgical margin with a very high odd ratio. More detailed consideration on this issue is essential. It should be noted from our findings that if the vagina was involved by HSIL, the rate of positive vaginal surgical margin for HSIL increased from 0.5% (in those with no vaginal involvement) to 60% but the rate of positive surgical margin for carcinoma remained the same. If the vagina was involved by carcinoma, the rate of both positive margins for HSIL and for carcinoma increased, from 0.5% to 5% and from 0% to 30%, respectively. (Table 2) One would assume that for a patient with cervical cancer to be classified as stage IB1, there would be no gross vaginal involvement by tumor. The 10% rate of vaginal involvement by HSIL and/or cancer found in this study is significant and would be solely microscopic. Kim et al reported that vaginal cuff length is not associated with the rates of three-year vaginal and pelvic recurrence following radical hysterectomy for cervical cancer (Kim et al., 2011). Therefore, accurate preoperative information about the presence, the location, and the extent of microscopic vaginal involvement is important to ensure adequate, tumor-free resection of the upper vagina. The vaginal resection can then be conformed to that information rather than merely to an arbitrary length of the vaginal cuff. In order to obtain this information, preoperative 'mapping' colposcopy would be beneficial, especially in those with increased risk of microscopic vaginal involvement by HSIL or CA including age ≥50, parity ≥3, tumor size ≥2 cm, squamous histology, outer third cervical stromal invasion, and extensive LVSI (≥10 spaces). (Table 4)

Comparative survival outcome data for early-stage cervical cancer patients following primary surgery between those with squamous cell carcinoma and adenocarcinoma in the literature are conflicting. Nakanishi et al reported that the survival outcome of stage IB cervical cancer patients with adenocarcinoma was worse than those with squamous cell carcinoma if there was lymph node metastasis, but the survivals were comparable if there was no node metastasis (Nakanishi et al., 2000). The Gynecologic Oncology Group study demonstrated that there was no difference in the distribution of high-risk pathological factors (pelvic node metastasis, parametrial extension, and surgical margins) and survival between cell types, but there was shorter survival in those with adenosquamous carcinoma (Look et al., 1996). Similarly, Kasamatsu et al reported that for FIGO stage I-IIB cervical cancer patients who had radical hysterectomy, the spread pattern and prognosis were comparable between those with squamous cell carcinoma and adenocarcinoma (Kasamatsu et al., 2009). Data from the previous study by our group were in accordance with these findings (Rudtanasudjatum et al., 2011). In the present study, squamous histology was strongly associated with positive vaginal surgical margin. Importantly, this was the case only if one considers the positive vaginal margin for HSIL but not the positive vaginal margin for carcinoma. (Table 3) This could be explained by the fact that HSIL is a direct precursor of and commonly found together with squamous cell carcinoma. The higher rate of positive vaginal margin for carcinoma associated with neuroendocrine carcinoma is not unexpected because of its well-known aggressive behavior.

The strength of this study included the large sample size from single institution with uniform treatment and surgical technique for all patients. In addition, all pathologic specimens were interpreted by experienced gynecologic pathologists. However, there were some limitations. The small number of patients in some categories made it impossible to determine the association between some characteristics and positive vaginal margin.

In conclusion, microscopic vaginal involvement, especially by HSIL, is a strong predictor for positive vaginal surgical margin for stage IB1 cervical cancer patients undergoing radical hysterectomy. Preoperative 'mapping' colposcopy or other strategies should be considered to ensure optimal vaginal resection especially in older, multiparous patients who have large squamous tumor with deep cervical stromal invasion and/or extensive LVSI. Such strategies may include examination of the patient under anesthesia, gross examination of the surgical specimen, and frozen section of the vaginal margin especially if there is suspicion of vaginal involvement.

Acknowledgements

Faculty of Medicine, Chiang Mai University and the National Research University Project under Thailand's Office of the Higher Education Commission provided funding support for this project.

References

Chittithaworn S, Hanprasertpong J, Tungsinmunkong K, Geater A (2007). Association between prognostic factors and disease-free survival of cervical cancer stage IB1 patients undergoing radical hysterectomy. *Asian Pac J Cancer Prev*, **8**, 530-4.

Delgado G, Bundy BN, Fowler WC, et al (1989). A prospective surgical pathological study of stage I squamous carcinoma of the cervix: a Gynecologic Oncology Group Study. *Gynecol Oncol*, **35**, 314-20.

Estape RE, Angioli R, Madrigal M, et al (1998). Close vaginal margins as a prognostic factor after radical hysterectomy. *Gynecol Oncol*, **68**, 229-32.

Kasamatsu T, Onda T, Sawada M, et al (2009). Radical hysterectomy for FIGO stage I-IIB adenocarcinoma of the uterine cervix. *Br J Cancer*, **100**, 1400-5.

Kim K, Cho SY, Park SI, et al (2011). Vaginal and pelvic

recurrence rates based on vaginal cuff length in patients with cervical cancer who underwent radical hysterectomies. *Eur J Surg Oncol*, **37**, 824-7.

Landoni F, Maneo A, Colombo A, et al (1997). Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Lancet*, **350**, 535-40.

Look KY, Brunetto VL, Clarke-Pearson DL, et al (1996). An analysis of cell type in patients with surgically staged stage IB carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol*, **63**, 304-11.

McCann GA, Taege SK, Boutsicaris CE, et al (2013). The impact of close surgical margins after radical hysterectomy for early-stage cervical cancer. *Gynecol Oncol*, **128**, 44-8.

Nakanishi T, Ishikawa H, Suzuki Y, et al (2000). A comparison of prognoses of pathologic stage Ib adenocarcinoma and squamous cell carcinoma of the uterine cervix. *Gynecol Oncol*, **79**, 289-93.

Randall ME, Fracasso PM, Toita T, et al (2013). Principles and practice of gynecologic oncology. Sixth ed. Philadelphia: Lippincott Williams & Wilkins, 598-660.

Rudtanasudjatum K, Charoenkwan K, Khunamornpong S, Siriaunkgul S (2011). Impact of histology on prognosis of patients with early-stage cervical cancer treated with radical surgery. *Int J Gynecol Obstet*, **115**, 183-7.