

## Clinical-pathologic factors, as predictor of lymph nodes metastasis in cervical cancer stage IB and IIA

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### Abstrak

Tujuan penelitian ini adalah untuk mengidentifikasi faktor prediktor metastasis kelenjar getah bening (KGB) pada pasien dengan kanker serviks stadium IB dan IIA. Penelitian dilakukan dari bulan Mei 1996 sampai bulan Desember 2001. Ada 183 pasien kanker serviks dengan stadium menurut FIGO IB dan IIA menjalani operasi histerektomi radikal dan limfadenektomi. Dari pasien tersebut 158 pasien yang dapat dinilai, terdiri dari 43 pasien dengan metastasis KGB dan 115 tanpa metastasis KGB. Rancangan penelitian adalah kasus-kontrol. Kasus adalah pasien dengan metastasis KGB dan kontrol pasien tanpa metastasis KGB. Analisis multivariat dilakukan setelah analisis bivariat. Pada analisis bivariat umur < 39 tahun, diameter lesi >4 cm, stadium IIA > 4 cm, histopatologi dengan diferensiasi sedang dan buruk, invasi ke pembuluh darah dan limfa merupakan variabel yang independen terjadinya metastasis KGB dengan nilai  $p \leq 0,05$ . Tetapi pada analisis multivariat yang muncul sebagai variabel independen adalah umur muda, paritas > 4, diameter lesi, histopatologi adenoskuamosa, dan invasi limfo-vaskular dengan nilai  $p \leq 0,05$ . Kesimpulan: Usia muda, paritas > 4, stadium IIA > 4 cm, diameter lesi, histopatologi adenoskuamosa, invasi limfa-vaskular merupakan faktor risiko terjadinya metastasis dan dapat dipergunakan sebagai faktor prediktor metastasis KGB. (*Med J Indones 2004; 13: 113-8*)

### Abstract

The aim of this study was to identify possible predictor factors of lymph node metastases in patients with cervical cancer stage IB and IIA. Study was conducted between May 1996 and December 2001. There were 183 patients of cervical cancer with FIGO Stage IB and IIA who were underwent radical hysterectomy and lymphadenectomy. From those 158 patients could be evaluated, consisting 43 patients with node metastases 115 patients without metastases. Research design was case control study. Case was patients with node metastases and control was those without node metastases. Multivariate analysis was made after bivariate analysis. On bivariate analysis age < 39 years, diameter of lesion > 4 cm, stage IIA > 4 cm, histopathology moderate and poor differentiation, blood and lymphatic vessel invasion were independent variables for node metastases with  $p$  value  $\leq 0.05$ . However, on multivariate analysis younger age, parity  $\geq 4$ , diameter of lesion, histopathology adenosquamous, and lymph vascular invasion (+) as independent factors for node metastases with  $p$  value  $\leq 0.05$ . Conclusion: Younger age, parity  $\geq 4$ , stage IIA > 4 cm, diameter of lesion, histopathology adenosquamous, and lymph vascular invasion (+) were risk factors for node metastases and can be used as predictors. (*Med J Indones 2004; 13: 113-8*)

**Keywords:** cervical cancer, radical hysterectomy, node metastases, case control study, predictor

The presence of lymph node metastasis is considered as the most important prognostic factor for cervical cancer stage IB and IIA.<sup>1,2</sup> Of 100 stage IB patients, 15 are likely to be node-positive and 45% of these patients would be cured. The majority of patients is

node-negative (85%), and of these 90% is cured.<sup>3</sup> Five year disease free interval decrease significantly from 95% with node-negative patients to 76% with node-positive ( $p < 0.002$ ). Therefore, the presence of nodal-positivity defines the high-risk group and nodal-negativity the low-risk group.

Detection node metastasis with CT-scan, MRI have high false negative especially for nodes seizing less than 2 cm,<sup>4</sup> in fact 80% node metastases were less than 10 cm.<sup>5</sup>

Although many authors have reported risk factors to node metastasis, this study try to identify risk factors

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to node metastasis and then make a formula that can predict probability of node metastasis.

## METHODS

This study was conducted at Dr. Cipto Mangunkusumo Hospital Jakarta from May 1996 until December 2001. There were 183 patients with cervical cancer stage IB and IIA who fulfill inclusion criteria underwent radical hysterectomy and lymphadenectomy. Of those only 158 cases could be evaluated due to incompleteness of surgical procedure, lost of specimens, down stage, paraffin block damage. Stages were determined by physical, gynecological examination, chest x-rays, IVP, cystoscopy, rectoscopy. Ultrasonography, CT-scan or MRI was optional. Peripheral blood test, blood chemistry and ECG was done prior surgery. The surgery was hysterectomy with or without removing one or both ovary and lymphadenectomy. All the specimens were processed and examined at the Department of Pathological Anatomy University of Indonesia.

Study design was a case-control study, patient with node metastasis as a case and who without node metastasis as a control. All clinical and pathological features were evaluated against node metastasis. A model of multivariate was made after bivariate analysis, and then develops a model to predict probability of node metastasis. Statistical program used was Stata Version 6 up-grade.

## RESULTS

There were 43 patients of 158 with node metastasis. The mean age of the study population was 42.19 years with SD  $\pm 7.78$  years, ranging between 20-63 years. The education range was 0-18 years, mean education 8.13 years with SD  $\pm 3.88$  years. The parity range was 0-10, mean parity 4.02 with SD  $\pm 2.23$  (Table 1). The diameter of the lesion ranging 10-70 mm, mean 33.84 mm with SD  $\pm 13.37$  mm. Most of the patients were stage IB  $\leq 4$  cm (50.63%) followed by IB  $> 4$  cm (21.52%) IIA  $\leq 4$  cm and IIA  $> 4$  cm (Table 2).

Bivariate analysis identified risk factors to node metastasis age  $< 39$  years ( $p = 0.013$ ) (Table 3), diameter of the lesion  $> 4$  cm ( $p = 0.005$ ), stage IIA

$> 4$  cm ( $p = 0.000$ ) (Table 4), moderate ( $p = 0.008$ ) and poor differentiation ( $p = 0.020$ ), vascular invasion ( $p = 0.001$ ), lymphatic invasion ( $p = 0.002$ ), lymph-vascular invasion ( $p = 0.009$ ) (Table 5). Multivariate analysis revealed that age ( $p = 0.024$ ), parity  $\geq 4$  ( $p = 0.001$ ), diameter of lesion ( $p = 0.000$ ), histological type adenosquamous ( $p = 0.010$ ), are independent factors for risk of node metastasis in cervical cancer (Table 6).

## DISCUSSION

Lymph node metastasis can affect 5-year survival in patients with cervical cancer. FIGO in 1998 reported 5-year survival was 57.1% on patients with lymph node metastasis and 88.4% without lymph node metastasis.<sup>6</sup> Patients with lymph node metastasis found after radical hysterectomy should have adjuvant radiation, chemotherapy or combination of both. However radiation and surgery as a primary treatment yield the same result as shown by Landoni et al<sup>7</sup> in their randomized study. Complication will increase if radiation or chemo radiation administered post radical surgery.<sup>8,9</sup> If lymph node metastasis can be predicted prior surgery the treatment can be well planned and the complication can be avoided. The patient can choose that is suite for her condition. Currently morphological pathology used to predict lymph node metastasis.<sup>10</sup> Sevin et al in univariate analysis found deep of invasion, diameter of lesion, lymph-vascular infiltration, volume of the tumor were significant predictor lymph node metastasis. Benedetti-Panici et al<sup>11</sup> revealed pelvic lymph node metastasis 21% the lesion  $< 4$  cm and 23% if the lesion  $> 4$  cm.

Our study in multivariate analysis revealed younger age, parity  $\geq 4$ , diameter of lesion, histopathology adenosquamous, and lymph vascular invasion as independent factors for lymph node metastasis with  $p$  value  $\leq 0.05$ . Based on this multivariate model and equation we can predict the probability lymph node metastasis (Form 1).

Form 1 showing the way to predict probability lymph node metastasis. Conclusion: Younger age, parity  $\geq 4$ , stage IIA  $> 4$  cm, diameter of lesion, histopathology adenosquamous, and lymph vascular invasion (+) were risk factors for node metastases and can be used as predictors.

Table 1. Distribution of patients with cervical cancer stage IB and IIA who underwent radical hysterectomy by demographic profile

Demographic profile	N=158	
	n	(%)
<b>Age (year)</b>		
20-29	9	5.70
30-39	49	31.01
40-49	71	44.94
50-59	26	16.46
≥ 60	3	1.90
Range	20—63	
Standard Deviation (SD)	42.19	7.78
<b>Education (year)</b>		
0	10	6.33
1—6	57	36.08
7—9	38	24.05
10—12	47	29.75
13—15	3	1.90
≥ 16	3	11.90
Range	0—18	
Standard Deviation (SD)	8.13	(3.88)
<b>Parity</b>		
0	6	3.80
1—3	67	42.41
4—5	48	30.38
≥ 6	37	23.42
Range	0—10	
Standard Deviation (SD)	4.02	(2.23)

Table 2. Distribution of patients with cervical cancer stage IB and IIA who underwent radical hysterectomy by clinical characteristic

Clinical characteristic	N=158	
	n	(%)
<b>Diameter of lesion</b>		
10—20 mm	35	22.15
21—30 mm	56	35.44
31—40 mm	35	22.15
41—50 mm	19	12.03
51—60 mm	9	5.70
≥ 61 mm	4	2.53
Range	10--70	
Standard Deviation (SD)	33.84	(13.37)
<b>Stage</b>		
Stage IB ≤ 4 cm	80	50.63
Stage IB > 4 cm	34	21.52
Stage IIA ≤ 4 cm	34	21.52
Stage IIA > 4 cm	10	6.33

Table 3. Odds ratio (OR) node metastasis of patients with cervical cancer stage IB and IIA by demographic profile (bivariate analysis)

Demographic profile	Metastasis				OR	(95% CI)	P Value
	Negative		Positive				
	n	%	n	%			
<b>Age(year)</b>							
< 39	32	27.83	21	48.84	1		
≥ 39	83	27.17	22	51.11	0.40	(0.19;0.84)	<b>0.013</b>
Test for trend (Chi2, P Value)	6.16	0.013					
<b>Education (year)</b>							
≤ 9	42	36.52	11	25.58	1		
> 9	73	63.48	32	74.42	1.67	(0.76;3.69)	0.196
Test for trend (Chi2, P Value)	1.67	0.196					
<b>Parity</b>							
≤ 4	76	66.09	23	53.49	1		
> 4	39	33.91	20	46.51	1.69	(0.82;3.48)	0.146
Test for trend (Chi2, P Value)	2.11	0.146					

Table 4. Odds ratio (OR) node metastasis of patients with cervical cancer stage IB and IIA by clinical characteristic (bivariate analysis)

Clinical characteristic	Metastasis				OR (95% CI)	P value
	Negative		Positive			
	n	%	n	%		
<b>Diameter of lesion</b>						
≤ 40 mm	98	85.22	28	65.12	1	
> 40 mm	17	14.78	15	34.88	3.09 (1.34;7.12)	<b>0.005</b>
<i>Test for trend (Chi2, P Value)</i>	7.78	0.005				
<b>Stage</b>						
Stage Ib ≤ 4 cm	64	55.64	16	37.21	1	
Stage Ib > 4 cm	22	19.33	12	27.91	2.18 (0.88;5.41)	0.840
Stage IIA ≤ 4 cm	27	23.48	7	16.28	1.04 (0.38;2.82)	0.943
Stage IIA > 4 cm	2	1.74	8	18.60	16.0 (2.57;99.45)	<b>0.000</b>
<i>Test for trend (Chi2, P Value)</i>	6.64	0.010				

Table 5 Odds ratio (OR) node metastasis of patients with cervical cancer stage IB and IIA by pathological characteristic

Pathological characteristic	Metastasis				OR (95% CI)	P value
	Negative		Positive			
	n	%	n	%		
<b>Histopathology</b>						
Squamous	75	65.22	27	62.79	1	
Adenocarcinoma	29	25.22	6	16.95	0.57 (0.21;1.55)	0,267
Adenosquamous	10	8.70	8	18.60	2.22 (0.78;6.31)	0,124
Others	11	0.87	2	4.65	5.56 (0.47;66.35)	0,127
<i>Test for trend (Chi2, P Value)</i>	2.08	0.149				
<b>Differentiation</b>						
Good	30	26.09	3	6.98	1	
Moderate	36	31.30	19	44.19	5.28 (1.33;20.87)	<b>0.008</b>
Poor	49	42.61	21	48.84	4.29 (1.13;16.28)	<b>0.020</b>
<i>Test for trend (Chi2, P Value)</i>	3.34	0.067				
<b>Lymphocyte infiltration</b>						
Dense	9	7.83	6	13.95	1	
Moderate	38	33.04	15	34.88	0.59 (0.18;1.98)	0.390
Mild	68	59.13	22	51.16	0.49 (0.15;1.54)	0.209
<i>Test for trend (Chi2, P Value)</i>	1.41	0.236				
<b>Necrosis</b>						
Mild	44	38.26	17	39.53	1	
Moderate	44	38.26	12	27.91	0.71 (0.30;1.66)	0.422
Severe	27	23.48	14	32.56	1.34 (0.57;3.17)	0.501
<i>Test for trend (Chi2, P Value)</i>	0.30	0.583				
<b>Vascular invasion</b>						
Negative	65	56.52	12	27.91	1	
Positive	50	43.48	31	72.09	3.36 (1.52;7.40)	<b>0.001</b>
<i>Test for trend (Chi2, P Value)</i>	10.19	0.001				
<b>Lymphatic invasion</b>						
Negative	64	55.65	12	27.91	1	
Positive	51	44.35	31	72.09	3.24 (1.47;7.13)	<b>0.002</b>
<i>Test for trend (Chi2, P Value)</i>	9.59	0.002				
<b>Lymph vascular invasion</b>						
Negative	50	43.48	9	20.93	1	
Positive	65	56.52	34	79.07	2.91 (1.25;6.75)	<b>0.009</b>
<i>Test for trend (Chi2, P Value)</i>	6.76	0.009				

Table 6 Multivariate analysis Odds ratio (OR) node metastasis of patients with cervical cancer stage IB and IIA

Variable	Coef.	OR	95% CI	P value
Lymph vascular (positive)	1.125	3.08	1.16 ; 8.18	0.024
Diameter of lesion ( mm)	0.080	1.08	1.04 ; 1.13	0.000
Age (year)	-0.087	0.92	0.86 ; 0.98	0.012
Parity (≥ 4)	1.851	6.37	2.10 ; 19.26	0.001
Adenocarcinoma	0.315	1.37	0.43 ; 4.37	0.594
Adenosquamous	1.726	5.62	1.50 ; 20.99	0.010
Others	2.625	13.80	0.80 ; 236.78	0.070
Constanta	-2.124			

Form 1 Probability node metastasis in patient with cervical cancer stage IB and IIA

Variable	Individual characteristic	Index	Score)
	(IC)	(I)	(IC x I)
Lymph-vascular invasion Negative Positive (Negative=0; positive=1)		0 1,125	
Diameter of lesion ( mm)		0,080	
Age (year)		-0,087	
Histopathology Squamous Adenocarcinoma Adenosquamous Others (squamous=0;adenoca=0;adenosq=1;others=1)		0 0,315 1,726 2,625	
Constanta		-2,124	
<b>Total score</b>			
$Pr_{(node-metastasis)} = \frac{1}{1 + e} total - score$			

**CONCLUSION**

On bivariate analysis of patients with cervical cancer stage IB and IIA who underwent radical hysterectomy, age < 39 years, diameter of the lesion > 4 cm, stage II > 4 cm, histopathology moderate and poor differentiation,

blood and lymphatic vessel invasion were independent variables for lymph node metastasis with p value ≤ 0.05.

However, on multivariate analysis younger age, parity ≥ 4, diameter of lesion, histopathology adenosquamous,

and lymph vascular invasion (+) as independent factors for node metastases with p value  $\leq 0.05$ . Model to predict the probability of lymph node metastasis can be made.

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