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Original Research

Clinicopathological features and prognostic factors for survival and lymph node metastases in stage IB adenocarcinoma of the cervix

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Purpose: To compare the clinicopathological characteristics of patients with stage IB adenocarcinoma (AC) of the cervix and to determine the risk factors for survival and lymph node metastasis. *Methods*: We retrospectively analyzed 83 patients with stage IB cervical AC treated between 2011 and 2018. The Silva Classification was used to classify all specimens. Kaplan-Meier method was used for survival analysis and Cox regression model used for univariate and multivariate analysis of prognostic factors for survival. A binary logistic regression model was used for the univariate and multivariable analysis of the risk factors for lymph node metastasis. *Results*: The median follow-up was 45 months (range from 9 to 95 months). A total of 64 (77.12%) patients had stage IB1 and 19 (22.89%) stage IB2. Six patients had recurrence, out of which, 5 died. Univariate analysis revealed that only LVSI ($P = 0.001$) was a significant prognostic factor. Multivariate analysis showed that LVSI ($P = 0.037$) was also the only independent significant prognostic factor. By univariate analysis, grade 3 ($P = 0.04$), LVSI ($P < 0.001$), depth of stromal invasion $\geq$10 mm ($P = 0.049$), Silva C ($P < 0.001$) were significant risk factors for lymph node metastasis. Multivariate analysis showed that LVSI ($P = 0.03$) and Silva C ($P = 0.023$) were the independent risk factors for lymph node metastasis. *Conclusions*: For stage IB AC, LVSI was the only independent prognostic factor for survival. LVSI and Silva C were the independent risk factors for lymph node metastasis.

Keywords

Prognostic factor; Adenocarcinoma of the uterine cervix; Lymph node metastasis; Silva classification

1. Introduction

In the past 40 years, the incidence of cervical cancer in developed countries has shown a marked decline [1–3]. Over the years, effective screening has led to a downward trend of squamous cell carcinoma (SCC) [1]. In the past three decades, it has been noted that cervical adenocarcinoma (AC) has been on the rise [1–4], which can be explained by the fact that cervical cytological screening is not effective enough for AC [5–8]. AC comprises more than 20% of cervical cancers in USA [4]. It seems that AC and SCC of the cervix are different in incidence rate, prognostic factors and response to treatment [3]. The majority of the studies have shown that the 5-year overall survival rates of AC is lower than SCC by 10%–20% [9–13]. The prognostic factors for cervical AC are controversial. In our department, stage IB is the most common stage of cervical AC. There are few studies about the prognostic factors of stage IB cervical AC. All the patients with stage IB cervical AC in our department underwent radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node dissection. The postoperative radiotherapy or chemoradiotherapy was dependent on the pathological results.

In this article, we compare the clinicopathological features of IB1 and IB2 AC. We also determine the prognostic factors for survival and lymph node metastasis of stage IB cervical AC.

2. Material and methods

2.1 Patient selection

We collected clinical and pathological data of 83 patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB AC treated in Jiangsu Cancer Hospital affiliated to Nanjing Medical University between 2010 and 2018. To compare the clinicopathological characteristics and prognosis between patients with tumor size >4 cm and tumor size $\leq$4 cm, we used the 2014 version of the FIGO classification, instead of the latest version. The inclusion criteria were as follows: according to International Endocervical Adenocarcinoma Criteria and Classification [14], HPV-associated AC (mucinous and usual-type endocervical carcinoma) and endometrioid (although non-HPV-associated AC, but accounts for approximately 20% of all AC); FIGO stage IB; patients who underwent primary surgery consisting of radical hysterectomy and pelvic lymphadenectomy with bilateral salpingo-oophorectomy; and patients who received preoperative chemotherapy, radiotherapy or chemoradiotherapy. The exclusion criteria were as follows: Non-HPV-associated adenocarcinoma AC (intestinal type, clear cell, serous, or mesonephric AC). The following data were collected: age, FIGO stage, tumor grade, surgical margin, depth of stromal invasion, parametrial invasion, lymph vascular space invasion (LVSI), pelvic node status, tumor size, ovarian metastasis, radiotherapy or chemoradiotherapy.

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2.2 Pathological analyses

The tumor maximum diameter was measured before fixed in formalin and embedded in paraffin. In order to identify LVSI, double staining of cytokeratin and CD10 was been performed. The definition of LVSI is the finding of the tumour cells in a luminal space lined by endothelial cells. Every specimen was cut into 4 parallel sections and stained with hematoxylin-eosin (HE). The specimens were evaluated by 2–4 experienced pathologists, and the kappa ratio between the pathologists was greater than 0.8. Specimens were classified as Silva A, B or C. Silva A tumours consist of well-demarcated glands with rounded contours, frequently forming groups. Pattern A was not impacted by the presence of single cells or desmoplastic stromal reaction, LVSI, large cervical vessels or depth of the tumour. In addition, complex intraglandular growth is allowed. Silva B is characterized by early destructive stromal invasion arising from well-demarcated glands (Pattern A-like glands). LVSI is allowed in pattern B. Silva C consists of diffuse destructive invasion [15].

2.3 Surgery and adjuvant radiotherapy

All the patients underwent radical hysterectomy (type C1, QM type) [16], bilateral salpingo-oophorectomy and pelvic lymph node dissection. The criteria for postoperative radiotherapy included pelvic lymph node metastasis, positive surgical margin, parametrial involvement, or 2 of the following risk factors: deep stromal invasion, LVSI and bulky tumour (>4 cm).

2.4 Study end points

We compared the clinicopathological features between stage IB1 and IB2 cervical AC. The primary end point was to determine the risk factors of the 5-year survival rate of stage IB cervical AC. The second end point was to determine the risk factors for lymph node metastasis.

2.5 Follow-up and statistical method

SPSS software (version 22.0, IBM, Armonk, NY, USA) was used for statistical analysis. Continuous variables, expressed as median, were assessed using independent sample *t* test as necessary. Chi-squared test was used to assess the categorical variables. Fisher's exact test was used where the expected frequency was <5. To determine the risk factors for survival outcome, univariate and multivariable analyses were performed using Cox regression analysis. A binary logistic regression model was used for univariate and multivariable analysis to determine the risk factors for lymph node metastasis.

3. Results

3.1 Differences in clinicopathological features between IB1 and IB2

A total of 64 (77.12%) patients had stage IB1, and 19 (22.89%) stage IB2. Table 1 showed the comparison of the clinicopathological characteristics of cervical AC between stage IB1 and IB2.

The median age of 83 patients was 45 years, ranging from 29 to 68 years. The median age of stage IB1 patients was 45 years, and the median age of stage IB2 patient was 46 years. Patients with stage IB1 over 45 years old accounted for 53.13%, while those with stage IB2 accounted for 63.16%. The difference was not significant (P = 0.600).

Grade 3 was found in 45.31% of stage IB1 patients, while grade 1 and 2 accounted for 54.69%. In stage IB2, Grade 3 was found in 31.58% of the patients, while 68.42% were grade 1 and 2. The difference between IB1 and IB2 in term of grade was not statistically significant (P = 0.287).

All IB1 and IB2 patients had negative margins. There was only one case with parametrial invasion in stage IB2, with no such case in stage IB1. LVSI was present in 17.19% of IB1 patients and 31.58% of IB2 patients. The difference was not significant (P = 0.172).

In stage IB, 66 cases were negative for LVSI and we recorded 1 death, while 17 cases were positive, out of which 4 died. For the cases without LVSI, the 5-year overall survival rate was 98.48%, whereas it was 76.47% in patients with LVSI. The difference was significant (P = 0.001).

The percentage of IB1 patients with depth of stromal invasion ≥10 mm was 43.75%, and 68.42% of IB2 patients had depth of stromal invasion ≥10 mm. The difference was not significant (P = 0.059).

Among patients with stage IB AC, the 5-year survival rate of cases with depth of stromal invasion <10 mm and those with stromal depth invasion ≥10 mm was 97.87% and 88.89%, respectively. The difference was not significant (P = 0.088).

As for lymph nodes involvement, 15.63% of stage IB1 patients and 15.79% of stage IB2 patients were positive. The difference was not significant (P = 0.989). The 5-year survival rate of lymph node negative patients and lymph node positive patients with stage IB was 95.71% and 84.62%, respectively. The difference was not significant (P = 0.122).

The median tumor size for IB1 and IB2 was 2 cm and 4.5 cm, respectively. The median tumor size for the entire cohort of stage IB was 2.5 cm. Only one patient with stage IB2 disease had right ovarian metastases, with no metastasis noted to the left ovary, fallopian tubes or parametrium.

According to our adjuvant therapy criteria, 26.56% of stage IB1 patients needed postoperative radiotherapy or chemoradiotherapy. Of stage IB2 patients 42.11% needed postoperative radiotherapy or chemoradiotherapy. The difference of the 5-year survival between them was not significant (P = 0.195).

Of IB1 tumours 40.63% (26/64) were classified as Silva A, with 40.63% (26/64) cases Silva B and 18.75% (12/64) cases Silva C. Of IB2 tumours 15.79% (3/19) were classified as Silva A, 52.63% (10/19) cases Silva B and 31.58% (6/19) cases Silva C.

The median depth of stromal invasion for tumour Silva A, B and C was 6, 9 and 12 mm, respectively. The median tumour size of Silva A, B and C was 2, 3 and 3 cm, repectively. Of Silva C and B tumours, 47.37% and 11.11% (4/36)

Table 1. Comparison of demographic and clinicopathological characteristics in IB1 and IB2 adenocarcinoma.

		IB1 n (%)	IB2 n (%)	*P* value
Age (year)		44.11 ± 9.16	45.68 ± 7.54	*P* = 0.203
Age				
	<45	30 (46.88%)	7 (36.84%)	
	≥45	34 (53.13%)	12 (63.16%)	*P* = 0.600
Grade				
	Grade 1&2	35 (54.69%)	13 (68.42%)	
	Grade 3	29 (45.31%)	6 (31.58%)	*P* = 0.287
Surgical margin				
	Negative	64 (100%)	19 (100%)	
	Positive	0	0	Not significant
Parametrial invasion				
	Negative	64 (100%)	18 (94.74%)	
	Positive	0 (0%)	1 (5.26%)	*P* = 0.229
Lymph vascular space invasion				
	Negative	53 (82.81%)	13 (68.42%)	
	Positive	11 (17.19%)	6 (31.58%)	*P* = 0.172
Deepth of invasion				
	<10 mm	36 (56.25%)	6 (31.58%)	
	≥10 mm	28 (43.75%)	13 (68.42%)	*P* = 0.059
Pelvic node status				
	Negative	54 (84.38%)	16 (84.21%)	
	Positive	10 (15.63%)	3 (15.79%)	*P* = 1.000
Tumour size				
	≤4 cm	83 (100%)	0 (0%)	
	≥4 cm	0 (0%)	19 (100%)	*P* < 0.001
Ovarian metastasis				
	Negative	64 (100%)	18 (94.74%)	
	Positive	0 (0%)	1 (5.26%)	*P* = 0.229
Radiotherapy or chemoradiotherapy				
	Negative	47 (73.44%)	11 (57.89%)	
	Positive	17 (26.56%)	8 (42.11%)	*P* = 0.195
Silva pattern				
	Pattern A	26 (40.63)	3 (15.79)	
	Pattern B	26 (40.63)	10 (52.63)	
	Pattern C	1 (18.75)	6 (31.58)	*P* = 0.123

had lymph node metastasis. As for Silva A tumours, no lymph node metastasis was identified. Of Silva C tumours 72.22% had LVSI, which is much higher than Silva B (8.33%) and Silva A (3.45%). The recurrence and death rate of patients with Silva C was much higher than patients with Silva B and A (21.05% vs 5.56% vs 0%; 15.79% vs 5.56% vs 0%) (Table 2).

3.2 Prognostic factors for survival

In the COX regression model, we included 8 risk factors. Because we considered tumour size ≤4 or >4 cm, stage IB1 and IB2 were not included. In univariate analysis, only LVSI ($P = 0.001$) was a statistically significant prognostic factor for 5-year survival. In multivariate analysis, the only statistically significant risk factor for 5-year survival rate was also LVSI ($P = 0.037$) (Table 3).

3.3 Risk factors for lymph node metastasis

By univariate analysis, grade 1 ($P = 0.04$), LVSI ($P < 0.0001$), depth of stromal invasion ≥10 mm ($P = 0.049$) and Silva C ($P < 0.001$) were statistically significant risk factors for lymph node metastasis for stage IB cervix AC. In multivariate analysis, LVSI ($P = 0.03$) and Silva C ($P = 0.023$) were independent risk factors for lymph node metastasis (Table 4).

3.4 Death and relapse cases

There were 6 patients with recurrence, 5 of which died. The patients who died had a median tumor size of 3 cm. The median age was 39 years. The median depth of stromal invasion was 12 mm. Of the 5 patients who died, all received radiotherapy after surgery, 4 patients had LVSI, and 2 had lymph node metastases.

Of the 6 relapsed cases, 2 were found to have abdominal recurrence, 2 lung metastases, 1 bone metastases, and 1 with both lung and bone metastases. Four tumours were classified as Silva C and 2 were classified as Silva B (Table 5).

Table 2. Clinicopathological characteristics for Silva Classification.

Silva pattern	N	LMN	DSI (mean in mm)	Tumour size (mean in cm)	Tumour grade III	LVSI	Recurrences	DOD
Standard	83	13 (15.66%)	9	2.5	35	17	6	5
Silv A	29	0 (0%)	6	2	11 (37.93%)	1 (3.45%)	0	0
Silv B	36	4 (11.11%)	9	3	10 (27.78%)	3 (8.33%)	2 (5.56%)	2 (5.56%)
Silv C	19	9 (47.37%)	12	3	14 (73.68%)	13 (68.42%)	4 (21.05%)	3 (15.79%)

LMN, lymph node metastasis; LVSI, Lymph vascular space invasion; DSI, Deepth of stromal invasion; DOD, died of disease.

Table 3. Univariable and multivariate analysis of risk factors on 5-year survival.

Variable	n (%)	5-year survival	*P* value	*P* value
			Univariate	Multivariate
Age				
<45 years	37 (44.58)	89.19%		
≥45 years	46 (55.42)	97.83%	0.1	0.113
Grade				
Grade 1&2	48 (57.83)	93.75%		
Grade 3	35 (42.17)	94.29%	0.919	0.205
Parametrial invasion				
Negative	82 (98.80)	98.78%		
Positive	1 (1.20)	100%	0.122	0.995
Lymph vascular space invasion				
Negative	66 (79.52)	98.48%		
Positive	17 (20.48)	76.47%	0.001	0.037
Deepth of invasion				
<10 mm	42 (50.60)	97.87%		
≥10 mm	41 (49.40)	88.89%	0.088	0.859
Pelvic node status				
Negative	70 (84.34)	95.71%		
Positive	13 (15.66)	84.62%	0.122	0.457
Tumour size				
≤4 cm	64 (77.11)	95.31%		
≥4 cm	19 (22.89)	89.47%	0.348	0.228
Silva pattern				
A + B	65 (78.31)	96.92%		
C	18 (21.69)	83.33%	0.054	0.837

4. Discussion

This study reported our experience in handling AC over the past 8 years. Stage IB AC is the most common stage of cervical AC in our department of gynecological oncology surgery.

In this study, the 5-year survival rate of stage IB AC was 94%. In 2000, Takeda *et al.* [13] reported a 5-year survival rate of stage IB AC was 95.8% in Japan. In 2014, Min-Hyun Baek *et al.* [17] reported a 5-year survival rate of stage IB AC of 93% in South Korea. Our results are consistent with existing studies on the 5-year survival rate of stage IB AC of in Asia.

The median age of our 83 cervical AC patients was 45 years. The median age of cervical AC reported in the existing articles ranged from 39.5 to 50 years [17–22].

Baalbergen *et al.* [1] found that age <35 years was an important prognostic factor. In his study, the 5-year survival rate for those aged <35 years, 35–65 years and those aged >65 years was 83%, 69%, and 46%, respectively. Chargui *et al.* [2] found that age >50 years was a poor prognostic factor. The 5-year survival rate for those age <50 years and those age >50 years was 81% and 54%. Khalil *et al.* [18] found that age was a significant prognostic factor by univariate analysis. However, in our study, age was not a prognostic factor in univariate or multivariate analysis. The median age of patients who died was 39 years.

Another important prognostic factor is tumor stage, as described by Baalbergen *et al.* [1] in. The 5-year survival rates of stage I and II were 79% and 37%, respectively, and it was less than 9% for stage III and IV. Chargui *et al.* [2] found the 5-year survival rate for stage I, II, III and IV AC was 79%, 64%, 22% and 11%, respectively. In our study, we included only stage I cervical AC. Stage (IB1 versus IB2) were not identified to be a statistically significant prognostic factor.

LVSI is also known to be a prognostic factor for cervical AC. Murakami *et al.* and Baalbergen *et al.* [1, 19] found that LVSI was a prognostic factor for early invasive cervical

Table 4. Univariable and multivariate analysis of risk factors on lymph node metastasis.

Variable	n (%)	*P* value	*P* value
		Univariate	Multivariate
Age			
<45 years	37 (44.58)		
≥45 years	46 (55.42)	0.901	0.147
Grade			
Grade 1&2	48 (57.83)		
Grade 3	35 (42.17)	0.04	0.241
Parametrial invasion			
Negative	82 (98.80)		
Positive	1 (1.20)	1	1
Lymph vascular space invasion			
Negative	66 (79.52)		
Positive	17 (20.48)	0.000395	0.030
Deepth of invasion			
<10 mm	42 (50.60)		
≥10 mm	41 (49.40)	0.049	0.496
Tumour size			
≤4 cm	64 (77.11)		
>4 cm	19 (22.89)	0.986	0.493
Silva pattern			
A + B	65 (78.31)		
C	18 (21.69)	0.000097	0.023

Table 5. Death and relapse cases.

Case	Age	FIGO stage	Grade	Metastases site	PMI	LVSI	DSI (/)	Pelvic node status	Ovarian metastasis	Tumour size	Adjuvant radiotherapy	Overall survival time	Silva pattern
1	32	IB1	II	Bone	N	P	1	P	N	3 cm	P	31	C
2	39	IB1	III	Lung	N	P	1	N	N	3 cm	P	34	C
3	39	IB1	I	Lung	N	P	1	P	P	3 cm	P	31	C
4	34	IB2	I	Abdominal cavity	N	N	>4/5	N	N	4.5 cm	P	20	B
5	50	IB2	II	Abdominal cavity	N	P	>2/3	N	N	4.5 cm	P	14	B
6	34	IB1	III	Lung bone	N	P	>1/2	N	N	3.5 cm	P	34	C

PMI, Parametrial invasion; LVSI, Lymph vascular space invasion; DSI, Deepth of stromal invasion; P, positive; N, negative.
Case1–5 have been died. Case 6 is still alive.

AC. In advanced cervical AC, Shikawa *et al.* [20] also found that LVSI is an important prognostic factor. In our study, LVSI was a statistically significant prognostic factor for stage IB cervical AC, both in univariate and multivariate analysis.

Lymph node metastases is also believed to be an important prognostic factor for cervical AC. Baalbergen *et al.* [1] found lymph node metastases was a prognostic factor in AC. Khalil *et al.* [18] found that 5-year survival rate was significantly worse in patients with lymph node metastasis (81% vs 20%). But in our study, lymph node metastasis was not a prognostic factor for stage IB cervical AC.

Another important prognostic factor for AC is tumour size. Both Ishikawa *et al.* and Eifel *et al.* [20, 21] found that tumor size >4 cm was related to the prognosis of AC. Eifel *et al.* [21] found that for stage IB cervical AC, the 5-year disease-free survival rates of tumor size <3 cm, 3–4 cm, 4–6 cm, and >6 cm were 88%, 65%, 62%, and 45%, respectively. Eifel *et al.* [22] compared the prognosis of 1538 cases of stage IB SCC with 229 cases of AC undergoing radical radiotherapy. For patients with a tumor size >4 cm, the overall survival rate of SCC was 73%, and the overall survival rate of AC was 59%. Tumour size was not a statistically significant prognostic factor in our study.

In this study, the only risk factor for survival was the presence of LVSI. Additional parameters that are well known to impact prognosis and survival, including lymph node metastases, tumor size and tumor stage were not found to be statistically significant with regards to prognosis. The reason is that we only included stage IB cervical AC, while other studies included both early and advanced cervical AC, leading to different findings. Most of the literature on the prognostic factors of cervical adenocarcinoma was published from 1995 to 2006 [1, 2, 20]. In the past 15 years, advances in radiotherapy technology had made pelvic recurrence more controllable. LVSI is closely assosiated with distant micrometastases [23]. The 6 patients who relapsed in our study all had

distant metastases, and 5 of the cases had LVSI. One of these 5 patients had an abdominal recurrence, 2 had lung metastases, 1 had bone metastases, and 1had both lung and bone metastases. It is well-known that, the most common organs for hematogenous metastasis of cervical cancer are lung, liver and bone. It is probable that the tomour in our patients migrated hematogenously. Varol Gülseren *et al.* [23] retrospectively analyzed 890 patients with cervical cancer and found that LVSI was the only pathological risk factor for isolated pulmonary metastases. Of our 6 patients with relapse, only 2 patients had lymph nodes metastasis, Margrit *et al.* [24] found 15.6% patients with negative nodes had LVSI and 75% patients with lymph nodes micrometastases had LVSI. In addition, 50% patients with lymph nodes micrometastasis had recurrent disease. Pierangelo *et al.* also found that LVSI and lymph nodes micrometastasis were more frequent in patients who recurred, compared with patients who had not recurred (77% vs 35%; 42% vs 4%, respectively). All the patients with lymph nodes micrometastasis were LVSI positive. Lymph nodes micrometastasis occurred only in LVSI positive tumors [25]. Although no enlarged lymph nodes were found during the operation, the cancer cells in the LVSI may had drifted away to distant organs. This may be the reason why the tumour recurred soon after the operation in patients without lymph node metastasis but with LVSI. Although the number of patients in this study is too small to make definitive conclusions, LVSI appears to be a significant prognostic factor for survival and lymph node metastases in stage IB adenocarcinoma of the cervix.

Both Murakami *et al.* and Baalbergen *et al.* [1, 19] found that LVSI was an independent risk factor for lymph node metastasis. We are the first to find Silva C was also a risk factors for lymph node metastasis in addition to LVSI. In our study, 47.37% (9/19) of patients with Silva C and 11.11% (4/36) with Silva B tumours had lymph node metastasis. No patients with Silva A tumours had lymph node metastasis. Of Silva C tumours 72.22% had LVSI, which is much higher than Silva B (8.33%) and Silva A (3.45%). The recurrence and death rate of patients with Silva C was much higher compared with Silva B and A. In conclusion, both LVSI and Silva C are worth our clinical attention.

Author contributions

DCW: Investigation, Formal analysis, Resources, Manuscript writing. LHZ: Data collection. YNW: Investigation, Data collection. NB: Supervision, Validation, Manuscript editing. YCW: Data analysis. JHW: Funding acquisition, Project development. PW: Investigation, Resources. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Cancer Hospital Affiliated to Nanjing Medical University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (Approval number: JSSZL2020162). Informed consent was obtained from all individual participants included in the study.

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Conflict of interest

The authors declare no conflict of interest.

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