Original Article

Rate of Recurrent and Clinicopathologic Features in Cervical Cancer Stage IA2-IB1 after Radical Hysterectomy and Pelvic Lymphadenectomy

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Objective: To determine the rate of recurrent cervical cancer stage IA2-IB1 after radical hysterectomy and pelvic lymphadenectomy [RHPL], and to explore its clinicopathologic features in association with recurrent rates.

Materials and Methods: A retrospective descriptive study was conducted on patients diagnosed with cervical cancer stages IA2-IB1 after RHPL in Songklanagarind Hospital between January 1, 2004 and December 31, 2012. The demographic data, clinical outcomes, and pathological factors were collected. The rate of recurrence was calculated in percentage. The exploration of clinicopathologic features associated with the recurrence was performed by univariate and multivariate analyses.

Results: One hundred thirty-one patients were included in the present study. The recurrence rate was 7.6% without mortality after two years of follow-ups. The 5-year disease free survival rate was 91.6%. Histology was the significant factor for predicting recurrence of the disease ($p = 0.02$).

Conclusion: There was still recurrence of the disease in the low-risk group of stage IA2-IB1 cervical cancer even after RHPL. The histology was the significant risk factor associated with recurrent disease.

Keywords: Cervical cancer, Clinicopathologic features, Early stage, Radical hysterectomy, Recurrent disease

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Cervical cancer is the second most common cancer in women worldwide in 2013 as well as in Thailand[1,2]. Radical hysterectomy and pelvic lymphadenectomy [RHPL] is the standard treatment of cervical cancer as recommended by the International Federation of Gynecology and Obstetrics [FIGO] for stage IA2-IB1[3]. Adjuvant treatments after surgery depend on the pathological factors on the risk of recurrence to improve survival outcomes[3]. Patients who had pelvic lymph node metastasis, parametrium involvement, or positive surgical margin were categorized into the high-risk group. They were treated with concurrent chemoradiation [CCRT][4] and had 5-year disease free survival [DFS] rates of 56%[5]. Patients who had two or more pathological factors (tumor size greater than 4 cm, lymphovascular space invasion [LVSI], or deep stromal invasion) were grouped into the intermediate-risk group and conservatively treated with radiation therapy [RT] or CCRT[4] and had 5-year DFS rates of 82%[5].

Patients who had no or one pathological factor of the intermediate-risk or no pathological factor of the high-risk were classified into the low-risk group without adjuvant treatment[4] and had 5-year DFS rates of 93%[5]. However, recurrence of disease in this group was in the range of 10% to 18%[5-8]. The median time to recurrence from the primary surgery was 28.4 months (range 1.2 to 129.9 months). Recurrence was detected in 20.4%, 53.7%, and 77% within one, three, and five years, respectively[6]. The aim of the present study was to assess the rate of recurrence and explore the clinicopathologic features of cervical cancer stage IA2-IB1 after RHPL to predict the recurrence of disease.

Materials and Methods

A retrospective study was conducted at Songklanagarind Hospital between September 2014 and August 2015. The present study was approved

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by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University (EC 57-0161-12-4; August 21, 2014). The guideline for cervical cancer after radical surgery without adjuvant treatment was to undergo follow-up every three months for two years, four to six months for four years, and then every year. Clinical and complete physical examinations were performed during each visit. A Papanicolaou [PAP] smear was done annually if there was no recurrence or symptoms were not suspicious.

The medical records of patients diagnosed as cervical cancer, FIGO stage IA2-IB1 and treated with RHPL without adjuvant treatment in Songklanagarind Hospital between January 1, 2004 and December 31, 2012 were reviewed. Patients who received no adjuvant therapy before surgery or had synchronous disease with other carcinoma or histological type of neuroendocrine tumor cell or cervical sarcoma or a follow-up period less than two years were excluded. The sample size was calculated using the precision of proportion considering a prevalence of recurrence in 13% from a previous study[6]. Based on a 95% confidence interval and precision of 6%, at least 121 patients were required.

The lists of all patients diagnosed as cervical cancer FIGO stage IA2-IB1 were obtained from the hospital information system and their medical records were reviewed based on inclusion and exclusion criteria for eligible patients. The main outcome in the present study was a recurrence, which was defined as confirmation of a positive pathology for the same type of original cervical cancer. Independent variables were the patients' demographic and clinical data and the pathological characteristics of suspected tissue. The demographic data included age, menarche, age at first sexual intercourse, menstrual status, number of partners, parity, and smoking status. Patients in the high-risk group had pelvic lymph node metastasis, parametrium involvement or positive surgical margin. Patients in the intermediate-risk group had two or more pathological risk factors that included tumor size greater than 4 cm, LVSI, or deep stromal invasion. Patients in the low-risk group had one pathological risk factor of the intermediate-risk group and no pathological risk factors of the high-risk group. All of the pathological characteristics were reviewed by a pathologist of which the maximum tumor size, histological type, differentiation grading, margin, parametrium involvement, LVSI, deep stromal invasion, tumor depth invasion, total cervical stromal length, remaining muscular layer, vaginal margin, myometrial and endometrial involvement, lymph node status, and the number of lymph node dissections, and the number of positive lymph node[3] were recorded. The clinical data consisted of the FIGO stage, risk group classification (no, low, intermediate, high), time to follow-up, site of recurrent, and clinical outcome.

All data were entered into the EpiData 3.1 program and analyzed by R software version 3.0.1 (The R Foundation for Statistical Computing 2008, Austria). The rate of recurrence was calculated in percentage. All independent variables were analyzed descriptively in mean (standard deviation), median (interquartile range), and range as appropriated. The exploration of clinicopathologic features associated with the recurrence was performed by univariate and multivariate analyses. The significant features associated with recurrence were also explored using DFS shown by Kaplan-Meier curves and compared using the log-rank test. A *p*-value less than 0.05 was considered as statistically significant.

Results

One hundred forty-six patients diagnosed as cervical cancer FIGO stage IA2-IB1 were found

Table 1. Patient demographic data

Demographic data	n (%)
Age group	
≤40 years	33 (25.2)
41 to 60 years	93 (71.0)
>60 years	5 (3.8)
Menarche	
≤14 years	48 (36.6)
>14 years	36 (27.5)
Unknown	47 (35.9)
Age at first sexual intercourse	
≤16 years	13 (9.9)
>16 years	89 (67.9)
Unknown	29 (22.1)
Menstrual stage	
Reproductive	102 (77.9)
Menopause	29 (22.1)
Number of partners	
Single partner	80 (61.1)
Multi-partner	38 (29.0)
Unknown	13 (9.9)
Parity	
Nulliparity	2 (1.5)
Multiparity	124 (94.7)
Unknown	5 (3.8)
Smoking	
Never	97 (74.0)
Active	7 (5.3)
Passive	24 (18.3)
Unknown	3 (2.3)

in the present study period. Fifteen patients were excluded due to loss to follow-up, resulted in 131 eligible patients for the present study. The patients' demographic data are described in Table 1. The mean age at diagnosis was 46 years old (range 28 to 78years) and most patients were between 41 and 60 years. For most of the patients, the age at menarche was less than 14 years and the age at first sexual intercourse was more than 16 years. Most patients were in reproductive status, single partner, multiparity, and non-smoker.

Table 2 shows the pathological characteristics. A quarter of the patients had carcinoma cells in the PAP smear. The patients were diagnosed by small biopsy in 87% and the results were 60% squamous cell carcinoma, 35.9% adenocarcinoma, and 3.8% adenosquamous. The times between biopsy and surgery were one month for 6.9%, one to two months for 26.0%, two to three months for 35.9%, and more than three months for 31.3%. There was no lymph node metastasis or positive margin in any of the patients. Table 3 shows the patients' clinical data. Most patients had FIGO stage IB1 (93.9%) and were in the no risk group. The median time to follow-up was 49.1 months (range 24.7 to 125.6 months). Ten cases (7.6%) had recurrent disease after surgical treatment, seven patients had central recurrence, two patients had regional recurrence, and one patient had distance recurrence. Four of the 10 patients were treated after recurrence of disease. One hundred twenty-five patients were alive, without disease, and six patients were alive with disease. The median time of recurrence was 29.1 months (range 1.7 to 69.0 months). The 5-year DFS rate was 91.6%. Of all patients, no mortality case was detected.

The age at menarche and histology were shown to be significant in univariate analysis, but only histology was significantly associated with recurrence (Table 4). Figure 1 shows the DFS on recurrence. Adenosquamous histological type had poorer prognosis with more rapid recurrence compared to other types ($p = 0.02$).

Table 2. Pathological characteristics

Feature	n (%)
PAP group	
Non-carcinoma	66 (50.4)
Carcinoma	36 (27.5)
Unknown	29 (22.1)
Histological type	
Squamous	79 (60.3)
Adenocarcinoma	47 (35.9)
Adenosquamous	5 (3.8)
Grading	
Well differentiated	35 (26.7)
Moderately differentiated	16 (12.2)
Poorly differentiated	19 (14.5)
Undetermined differentiation	61 (46.6)
Tumor size	
≤2 cm	100 (76.3)
2 to 4 cm	30 (22.9)
>4 cm	1 (0.8)
Parametrium involvement	
Free	130 (99.2)
Not free	1 (0.8)
Lymphovascular space invasion	
No	115 (87.8)
Yes	16 (12.2)
Tumor stromal invasion	
≤10 mm	110 (84.0)
>10 mm	11 (8.4)
No data	10 (7.6)
Ratio of stromal invasion	
≤½	88 (67.2)
>½	33 (25.2)
No data	10 (7.6)
Residual stromal length	
≤5 mm	46 (35.1)
5 to 10 mm	60 (45.8)
>10 mm	15 (11.5)
No data	10 (7.6)
Ratio of residual stroma	
≤½	88 (67.2)
>½	33 (25.2)
No data	10 (7.6)
Uterine invasion	
No	127 (96.9)
Yes	4 (3.1)

PAP = Papanicolaou

Table 3. Clinical data

	n (%)
FIGO stage	
IA2	8 (6.1)
IB1	123 (93.9)
Risk group	
No	73 (55.7)
Low	45 (34.4)
Intermediate	12 (9.2)
High	1 (0.8)
Site of recurrent	
Central	7 (5.3)
Region	2 (1.5)
Distance	1 (0.8)
No recurrent	121 (92.4)
Clinical outcome	
AWD	6 (4.6)
ANED	125 (95.4)

FIGO = International Federation of Gynecology and Obstetrics; AWD = alive with disease; ANED = alive with no evidence of disease

Table 4. Clinicopathologic features associated with recurrent disease

Factor	Recurrence		Univariate *p*-value	Multivariate	
	No, n (%)	Yes, n (%)		Adjusted OR (95% CI)	*p*-value
Menarche			0.004		0.99
≤14 years	40 (33.1)	8 (80.0)		1	
>14 years	34 (28.1)	2 (20.0)		0.33 (0.06 to 1.72)	
No data	47 (38.8)	0 (0.0)		-	
Histology			0.04		0.04
Squamous	75 (62.0)	4 (40.0)		1	
Adenocarcinoma	43 (35.5)	4 (40.0)		1.74 (0.42 to 7.33)	
Adenosquamous	3 (2.5)	2 (20.0)		12.5 (1.61 to 97.34)	

OR = odds ratio; CI = confidence interval

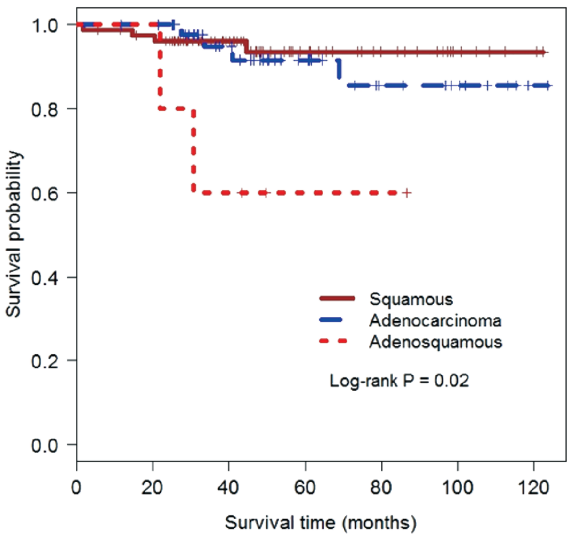

Figure 1. The disease free survival [DFS] on recurrence by histology.

Discussion

The recurrence rate in the present study was 7.6% without any mortality cases after two years of follow-up, and the 5-year DFS rate was 91.6%. The histological type was the significant factor to predict recurrence of disease.

The patients with cervical cancer stage IA2-IB1 after RHPL without adjuvant treatment had a recurrence rate of 7.6%, which was less than previous studies that reported recurrence rates of 10% to 18%[5-8]. The previous studies included patients up to stage II[5-7] and the follow-up time of at least three years, but the present study included only stage IA2-IB1 and the follow-up time was at least two years. The median time to recurrent disease in the present study was 29.1 months, which was similar to the study of Qiu et al (28.4 months)[6] and superior to the other studies (11 to 16 months)[5,7,9,10].

The present study had a good prognosis of a 5-year DFS rate of 91.6%, which was more than the present study of Chittithaworn et al (86%)[8], they included the patient with only stage IB1 and some patients had adjuvant therapy whereas the patient in the present study was stage IA2-IB1 and no adjuvant therapy. In other previous studies, early cervical cancer had a good prognosis of a 5-year DFS rate of 96% to 97%[10,11], but the 5-year DFS rate decreased to 84% to 86% when stage II patients were included[5,7]. Most of the patients with recurrent disease were in the low-risk group (9 in 10 patients) and only one patient was in the intermediate-risk group. No recurrence of disease was detected in patients in the no risk group. One patient in the high-risk group declined adjuvant treatment but had no recurrence. Local-regional recurrence occurred more often than distance recurrence, which was similar to the previous study[9].

All pathological factors were reviewed by a pathologist. There were differences from the previous reports in tumor depth invasion and cervical stromal length in three patients but no effect on the adjuvant treatment and recurrence of disease. The present study found adenosquamous type was the significant clinicopathological risk factor to predict recurrence, but histology was not the predicting factors in the other previous studies[5,6,8-11]. The study by Farley et al that included patients up to stage IB2 in early stage, which was different from the present study, found that the decrease in the median and overall survival in advanced stage of adenosquamous cervical cancer was significant but not significant in early stage[12]. The study by Baek et al[13] compared the recurrence of free survival and overall survival between the patients with adenosquamous and patients with adenocarcinoma but did not compare with squamous cell carcinoma patients, which was different from the present study. Further, LVSI and tumor size greater than 2 cm were significant factors in Baek et al's study, so the histology was possibly not a significant factor[13]. By contrast,

the pathological factors in other studies that predicted recurrent disease were pelvic node metastasis[10,13], LVSI[5,10,13], deep stromal invasion[8,13], depth of invasion more than 10 mm[10], positive human papilloma virus [HPV]-16[6], and tumor size[9]. There were the differences in the cut-point of tumor size 2 cm or more[5,6,8,9], deep of stromal invasion 1/3 or more[6-8,11], and depth of tumor invasion 10 to 13 mm[5,10]. Since the present study had no subjects with tumor size larger than 4 cm, lymph node metastasis, positive margin, parametrial involvement, LVSI, and deep stromal invasion were not found in the patients with recurrent disease. Therefore, these significant features associated with recurrence could not be analyzed.

The population in the present study did not vary in treatment method because the subjects had only surgery without adjuvant treatment. All of the pathological features were reviewed by a pathologist. Incomplete demographic data were found in the present study because it was a retrospective. Ten patients had incomplete data of grade, tumor invasion, stromal length, cervical stromal involvement, or residual stromal length due to poor quality of the pathological slides.

Conclusion

In summary, there was still recurrent disease of early stage cervical cancer in the low-risk group after RHPL. The histology was the significant risk factor associated with recurrent disease. Histology may be the significant pathological factor to consider for adjuvant treatment after RHPL in the future when there are more information and study in histology.

What is already known on this topic?

Adjuvant treatment of cervical cancer after radical hysterectomy and pelvic lymphadenectomy depended on pathological features such as tumor size, LVSI, deep stromal invasion, not free of surgical margin, parametrium, and lymph node involvement for decrease risk of recurrent.

What this study adds?

The present study explored rate and risk factor of recurrent in patients diagnosed as cervical cancer stage IA2-IB1 after RHPL without adjuvant treatment. Adenosquamous type of cervical cancer was the risk factor that significantly associated with the recurrence of the disease.

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Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Khuhaprema T, Attasara P, Sriplung H, Wiangnon S, Sangrajrang S. Cancer in Thailand Vol. VII, 2007-2009. Bangkok. Bangkok Medical Publisher; 2013.
3. Hacker NF, Vermorken JB. Cervical cancer. In: Berek JS, Hacker NF, editors. Berek & Hacker's Gynecologic oncology. 6th ed. Philadelphia: Wolters Kluwer; 2015:326-89.
4. Rogers L, Siu SS, Luesley D, Bryant A, Dickinson HO. Radiotherapy and chemoradiation after surgery for early cervical cancer. Cochrane Database Syst Rev 2012;(5):CD007583.
5. Shinohara S, Ochi T, Miyazaki T, Fujii T, Kawamura M, Mochizuki T, et al. Histopathological prognostic factors in patients with cervical cancer treated with radical hysterectomy and postoperative radiotherapy. Int J Clin Oncol 2004;9:503-9.
6. Qiu JT, Abdullah NA, Chou HH, Lin CT, Jung SM, Wang CC, et al. Outcomes and prognosis of patients with recurrent cervical cancer after radical hysterectomy. Gynecol Oncol 2012;127:472-7.
7. Samlal RA, Van Der Velden J, Van Eerden T, Schilthuis MS, Gonzalez Gonzalez D, Lammes FB. Recurrent cervical carcinoma after radical hysterectomy: an analysis of clinical aspects and prognosis. Int J Gynecol Cancer 1998;8:78-84.
8. Chittithaworn S, Hanprasertpong J, Tungsinmunkong K, Geater A. Association between prognostic factors and disease-free survival of cervical cancer stage IB1 patients undergoing radical hysterectomy. Asian Pac J Cancer Prev 2007;8:530-4.
9. Sittidilokratna K, Cheewakriangkrai C, Khunamornpong S, Siriaunkgul S. Recurrence patterns after radical hysterectomy in stage IB1-IIA cervical. Asian Pac J Cancer Prev 2010;11:499-502.
10. Grisaru DA, Covens A, Franssen E, Chapman W, Shaw P, Colgan T, et al. Histopathologic score predicts recurrence free survival after radical surgery in patients with stage IA2-IB1-2 cervical carcinoma. Cancer 2003;97:1904-8.

11. Ungár L, Pálfalvi L, Tarnai L, Nechushkina V, Lintner B, Novák Z. Surgical treatment of stage IB cervical cancer. Int J Gynecol Cancer 2012;22: 1597-603.
12. Farley JH, Hickey KW, Carlson JW, Rose GS, Kost ER, Harrison TA. Adenosquamous histology predicts a poor outcome for patients with advanced-stage, but not early-stage, cervical carcinoma. Cancer 2003;97:2196-202.
13. Baek MH, Park JY, Kim D, Suh DS, Kim JH, Kim YM, et al. Comparison of adenocarcinoma and adenosquamous carcinoma in patients with early-stage cervical cancer after radical surgery. Gynecol Oncol 2014;135:462-7.