GYNAECOLOGY

Risk Factors Associated with Parametrial Involvement in Early-stage Cervical Cancer

Atiwat Techapalokun, M.D.*,
Yuthana Khongthip, M.D.**

Department of Obstetrics and Gynecology, Faculty of Medicine, Chonburi Hospital, Chonburi, Thailand

ABSTRACT

Objectives: The study aimed to identify the risk factors affecting parametrial involvement in patients with early-stage cervical cancer.

Materials and Methods: The sample participated in the study was the patients with stage IA2 to IIA1 cervical cancer according to 2018 International Federation of Gynecology and Obstetrics (FIGO), who had been treated with radical hysterectomy and pelvic lymphadenectomy during April 2011 to April 2020. In term of methodology, the retrospective cross-sectional analysis was to determine the factors including tumor size, deep stromal invasion (DSI), lymphovascular space invasion (LVSI), pelvic node status, FIGO staging, age and histology (squamous cell carcinoma, adenocarcinoma and adenosquamous cell carcinoma), associated with parametrial involvement (PI).

Results: Overall, 19 of the 206 patients (9.22%) had PI. Patients with PI were more likely to have larger tumor size (> 4 cm: 15%, 2-4 cm: 10%, < 2 cm: 2%, p = 0.02), DSI (deep 1/3: 19%, middle 1/3: 2%, superficial 1/3: 0%, p = 0.01), LVSI (positive: 17%, negative: 3%, p < 0.01), metastasis to pelvic lymph nodes (positive: 50%, negative: 4%, p < 0.01), and higher FIGO stage (IB3: 16%, IB2: 10%, IB1: 3%, IA2: 0%, p = 0.02). Multivariate analysis showed that only deep stromal invasion (p = 0.02) and pelvic lymph node metastasis (p < 0.01) were independent risk factors for PI.

Conclusion: The deep stromal invasion and pelvic lymph node involvement were significantly associated with PI in multivariate analysis. Cervical cancer with superficial 1/3 stromal invasion and no pelvic lymph node metastasis seldom had PI.

Keywords: early-stage cervical cancer, parametrectomy, parametrial invasion.

ปัจจัยเสี่ยงที่เกี่ยวข้องกับการลุกลามเข้าเนื้อเยื่อข้างปากมดลูกในโรคมะเร็งปากมดลูกระยะต้น

อธิวัฒน์ เตชะพะโลกุล, ยุทธนา ของทิพย์

บทคัดย่อ

วัตถุประสงค์: เพื่อระบุปัจจัยเสี่ยงของการลุกลามของมะเร็งปากมดลูกเข้าสู่เนื้อเยื่อข้างปากมดลูก

วัสดุและวิธีการ: ศึกษาโดยสืบค้นข้อมูลของผู้ป่วยมะเร็งปากมดลูกระยะ IA2 ถึง IIA1 *(International Federation of Gynecology and Obstetrics 2018 หรือ FIGO 2018)* ที่ได้รับการผ่าตัดมดลูกแบบกว้างและผ่าตัดต่อมน้ำเหลืองอุ้ง เชิงกรานตั้งแต่เดือนเมษายน พ.ศ. 2554 ถึง เดือนเมษายน พ.ศ. 2563 เป็นการศึกษาย้อนหลังแบบตัดขวางเพื่อระบุว่าขนาด ของเนื้องอก ความลึกของการลุกลาม การกระจายของเซลล์มะเร็งไปในหลอดเลือดหรือน้ำเหลือง การกระจายไปที่ต่อมน้ำ เหลืองอุ้งเชิงกราน ระยะโรค อายุ และจุลกายวิภาคศาสตร์เนื้อเยื่อ *(squamous cell carcinoma, adenocarcinoma and adenosquamous cell carcinoma)* มีปัจจัยใดที่มีความสัมพันธ์กับการลุกลามเข้าเนื้อเยื่อข้างปากมดลูก

ผลการศึกษา: ผู้ป่วย 19 คน จาก 206 คน (ร้อยละ 9.22) พบมีการลุกลามเข้าเนื้อเยื่อข้างปากมดลูก ผู้ป่วยที่มีการลุก ลามเข้าเนื้อเยื่อข้างปากมดลูกมักจะมีขนาดของเนื้องอกใหญ่กว่า (> 4 เซนติเมตร: ร้อยละ 15, 2-4 เซนติเมตร: ร้อยละ 10, < 2 เซนติเมตร: ร้อยละ 2, p =0.02), ความลึกของการลุกลามมากกว่า (deep 1/3: ร้อยละ 19, middle 1/3: ร้อยละ 2, superficial 1/3: ร้อยละ 0, p = 0.01), พบการกระจายของเซลล์มะเร็งไปในหลอดเลือดหรือน้ำเหลืองบ่อยกว่า (positive: ร้อยละ 17, negative: ร้อยละ 3, p < 0.01), พบการกระจายไปที่ต่อมน้ำเหลืองอุ้งเชิงกรานบ่อยกว่า (positive: ร้อยละ 50, negative: ร้อยละ 4, p < 0.01) และระยะของโรค (FIGO stage) สูงกว่า (IB3: ร้อยละ 16, IB2: ร้อยละ 10, IB1: ร้อยละ 3, IA2: ร้อยละ 0, p = 0.02) การวิเคราะห์แบบหลายตัวแปรพบว่าความลึกของการลุกลาม (p = 0.02) และการลุกลามเข้า ต่อมน้ำเหลืองอุ้งเชิงกราน (p < 0.01) เป็นปัจจัยเสี่ยงอิสระของการลุกลามเข้าเนื้อเยื่อข้างปากมดลูก

สรุป: ความลึกของการลุกลาม และการลุกลามเข้าต่อมน้ำเหลืองอุ้งเชิงกรานมีความสัมพันธ์กับการลุกลามเข้าเนื้อเยื่อข้าง ปากมดลูกอย่างมีนัยสำคัญทางสถิติ ผู้ป่วยโรคมะเร็งปากมดลูกที่มีความลึกของการลุกลามน้อยกว่า 1/3 ของความหนา เนื้อเยื่อปากมดลูกและไม่พบการกระจายไปที่ต่อมน้ำเหลืองอุ้งเชิงกรานแทบจะไม่พบการลุกลามเข้าเนื้อเยื่อข้างปากมดลูก

คำสำคัญ: มะเร็งปากมดลูกระยะต้น, การตัดเนื้อเยื่อข้างปากมดลูก, การลุกลามเข้าเนื้อเยื่อข้างปากมดลูก

Introduction

Cervical cancer is the fourth most common malignancy in females worldwide[1] and the second most common malignancy among Thai women[2]. The current standard surgical treatment of early-stage cervical cancer (stages IA2, IB, and IIA) is radical hysterectomy with pelvic lymphadenectomy[3].

Radical hysterectomy is associated with postoperative morbidity including lymphedema (3.6%), bladder atony (3.6%), bowel ileus (2.9%), sexual dysfunction (2.2%), ureterovaginal fistula (0.8%), and vesicovaginal fistula (0.4%). More importantly, it reduces the patient's quality of life[4]. Parametrectomy is the main cause of postoperative complication due to denervation of the autonomic nerve supply to the pelvic organs during the procedure[3]. At present, several studies aim to reduce this complication by omitting parametrectomy in patients who may benefit from less radical surgery without a negative impact on survival. Previous studies have shown that there are some pathologic factors associated with parametrial involvement (PI) and for some low-risk patients, resection of the parametrium may be spared[3, 5-7]. Patients with tumor size of < 2 cm in diameter, no deep stromal invasion (DSI), no lymphovascular space invasion (LVSI), and no lymph node involvement have been found to have less than 1% risk of PI. However, there have been inconsistent results among these studies and some of them have not been analyzed by multivariate analysis.

The main objective of this study was to identify the risk factors independently associated with PI in patients with early-stage cervical cancer.

Materials and Methods

This retrospective cross-sectional study reviewed medical records of all patients, diagnosed with stage IA2 to IIA1 cervical cancer, who had undergone radical hysterectomy and pelvic lymphadenectomy from April 2011 to April 2020. The study was approved by the Institutional Review Board of Chonburi Hospital.

Regarding the sample participated in the study; the patients whose radical hysterectomy were abandoned, had endometrial cancer, non-squamous cell, or non-adenocarcinoma cell type on the final pathology reports, or had inadequate medical record were excluded. The study started by obtaining the clinicopathological variables including age, International Federation of Gynecology and Obstetrics (FIGO) stage, tumor size, histology, DSI, LVSI, PI, and the status of pelvic lymph node. All the slides were reviewed by our pathologists at Chonburi Hospital. Additionally, the cancer staging was based on the criteria established by FIGO 2018[1]. Besides, histology was divided into squamous cell carcinoma, adenocarcinoma and adenosquamous cell carcinoma. With regard to tumor diameter which was obtained from the measurement of the hysterectomy specimen, we categorized into 3 groups: < 2 cm, 2-4 cm, and ≥ 4 cm according to tumor size cut-off of FIGO stage IB1, IB2 and IB3, respectively. In addition, the depth of invasion was categorized into 3 groups according to the proportion between the depth of the lesion and entire cervical thickness: superficial 1/3, middle 1/3, and deep 1/3 invasion. Also, PI was defined as a malignant cell in either parametrial tissue or parametrial lymph node.
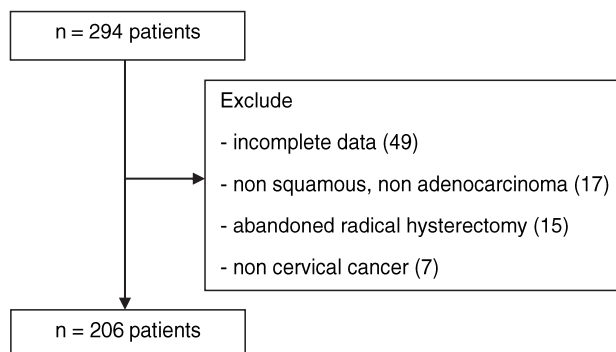
SPSS for Windows, version 26.0. Chicago: SPSS Inc; 2019, was employed to discover statistical data. The sample size was calculated by using the Jacob Cohen's sample size calculating table[8]. It was met the medium population effect size with alpha error = 0.05 and 80% of the power in which the independent variables of 8 were equal to 107 patients. The baseline characteristic of the patients and the pathology results were described by the mean and standard deviation for continuous data, and number with percentage for nominal data. The associations between clinicopathologic factors and parametrial involvement were evaluated by binary logistic regression in both univariate and multivariate analysis. Probability values of < 0.05 were considered to be statistically significant.

Results

From April 2011 to April 2020, 294 patients underwent radical hysterectomy with pelvic lymphadenectomy. However, 88 patients were excluded from the analysis as shown in Fig. 1. The final study group comprised of 206 patients with a mean age of

47 ± 10.7 years. FIGO stage IA2, IB1, IB2, IB3, and IIA1 were found in 18 (8.74%), 38 (18.45%), 90 (43.69%), 58 (28.16%) and 2 patients (0.97%), respectively. Histopathology confirmed 131 (63.59%) squamous cell carcinomas, 55 (26.70%) adenocarcinomas, and 20 (9.71%) adenosquamous cell carcinomas. The clinicopathologic characteristics of the 206 patients are summarized in Table 1.

```
        ┌─────────────────────────┐
        │   n = 294 patients      │
        └─────────────────────────┘
                    │
                    │        ┌──────────────────────────────────────────────┐
                    ├───────▶│ Exclude                                      │
                    │        │ - incomplete data (49)                       │
                    │        │ - non squamous, non adenocarcinoma (17)      │
                    │        │ - abandoned radical hysterectomy (15)        │
                    │        │ - non cervical cancer (7)                    │
                    │        └──────────────────────────────────────────────┘
                    ▼
        ┌─────────────────────────┐
        │   n = 206 patients      │
        └─────────────────────────┘
```

Fig. 1. Patient flow chart.

Table 1. Clinicopathologic characteristics of patients with cervical cancer who were treated with radical hysterectomy.

Characteristics	n
Age (years), mean ± SD	47 ± 10.7
Stage	
IA2	18 (8.7%)
IB1	38 (18.5%)
IB2	90 (43.6%)
IB3	58 (28.2%)
IIA1	2 (1.0%)
Histology	
Squamous cell carcinoma	131 (63.6%)
Adenocarcinoma	55 (26.7%)
Adenosquamous cell carcinoma	20 (9.7%)
Stromal invasion	
Superficial 1/3	64 (31.1%)
Middle 1/3	48 (23.3%)
Deep 1/3	94 (45.6%)
Tumor size	
< 2 cm	57 (27.7%)
2-4 cm	90 (43.7%)
≥ 4 cm	59 (28.6%)
Lymphovascular space invasion	
No	114 (55.3%)
Yes	92 (44.7%)
Parametrial involvement	
No	187 (90.8%)
Yes	19 (9.2%)
Pelvic lymph node involvement	
No	184 (89.3%)
Yes	22 (10.7%)

SD: standard deviation

Of the 206 patients, PI was found in 19 patients (9.22%). There was no PI found in any of the 18 patients with stage IA2. Twenty-two patients had pelvic lymph node metastasis and 50% of them had PI, while only 8 of the 184 patients (4.35%) with no pelvic lymph node involvement had PI. Table 2 demonstrates the univariate analysis of the potential risk factors for PI. Patients with PI were more likely to have higher disease stage (p = 0.02), larger tumor size (p = 0.01), deep stromal invasion (p = 0.02), presence of LVSI (p < 0.01), and pelvic node involvement (p < 0.01). However, when multivariate binary logistic regression was performed, only DSI (odds rartio (OR) 10.08; 95% confidence interval (CI) 1.35 - 75.14, p = 0.02) and pelvic lymph node involvement (OR 10.63; 95%CI 3.21 - 35.17, P < 0.01) were independently associated with PI (Table 3).

Table 2. Univariate analysis of potential risk factors for parametrial involvement.

Characteristics	PI, n (%)		OR (95%CI)	p value
	negative	positive		
Age (years), mean ± SD	47.13 ± 10.37	48.37 ± 14.21	1.01 (0.97-1.06)	0.63
Stage			2.10 (1.12-3.92)	0.02
IA2	18 (8.7%)	0 (0)		
IB1	38 (18.5%)	1 (3)		
IB2	90 (43.6%)	9 (10)		
IB3	58 (28.2%)	9 (16)		
IIA1	2 (1.0%)	0 (0)		
Histology			1.03 (0.51-2.08)	0.93
Squamous cell carcinoma	131 (63.6%)	12 (9)		
Adenocarcinoma	55 (26.7%)	5 (9)		
Adenosquamous cell carcinoma	20 (9.7%)	2 (10)		
Stromal invasion			13.49 (2.06-88.20)	0.01
Superficial 1/3	64 (31.1%)	0 (0)		
Middle 1/3	48 (23.3%)	1 (2)		
Deep 1/3	94 (45.6%)	18 (19)		
Tumor size			2.39 (1.18-4.83)	0.02
< 2 cm	56 (98)	1 (2)		
2 - 4 cm	81 (90)	9 (10)		
≥ 4 cm	50 (85)	9 (15)		
Lymphovascular space invasion			7.79 (2.19-27.66)	< 0.01
No	111 (97)	3 (3)		
Yes	76 (83)	16 (17)		
Pelvic lymph node involvement			22.00 (7.36-65.81)	< 0.01
No	176 (96)	8 (4)		
Yes	11 (50)	11 (50)		

PI: parametrial involvement, OR: odds ratio, CI: confidence interval, SD: standard deviation

Table 3. Multivariate analysis of risk factors for parametrial involvement.

Characteristics	OR (95%CI)	p value
Stage	0.307 (0.00 − 101.49)	0.69
Stromal invasion	10.075 (1.35 − 75.14)	0.02
Tumor size	2.659 (0.01 − 989.49)	0.75
Lymphovascular space invasion	2.254 (0.55 − 9.28)	0.26
Pelvic lymph node involvement	10.627 (3.21 − 35.17)	<0.01

OR: odds ratio, CI: confidence interval

Discussion

In the present study, PI was found in 9.22% of patients with stage IA2-IIA1 cervical cancer. This result was comparable to previous reports in the literature with the incidences of PI ranging from 4 to 11%[5-6, 9-12]. The somewhat high incidence of PI in our study might be attributed to the larger tumor size (> 4 cm) in some of our patients. Furthermore, our series included patients with stage IIA1 disease, while the diseases higher than stage IB2 were excluded in other studies[6, 9].

Our results demonstrated that tumors size > 2 cm, DSI > 10 mm or invasion > 50% of the whole cervical thickness, positive LVSI, or pelvic lymph node involvement were associated with PI. These results were in line with those previously reported in other studies[5, 6, 9]. However, pelvic lymph node status and DSI were the only two independent factors associated with PI after adjusting the confounding factors by multivariate analysis. Notably, none of the participants with stromal invasion < 10 mm, less than one-third stromal invasion, or negative pelvic lymph node involvement had PI.

There has been no standard cut-off level for DSI. Several studies used 10 mm of DSI as their reference[7, 10, 13], However, the absolute depth of tumor invasion may be affected by the anatomical differences among the patients. The Gynecologic Oncology Group (GOG) study proposed the use of the proportion between the depth of the lesion and entire cervical thickness[14]. The invasion of more than one-third of the whole thickness, which reflected the intermediate risk for disease recurrence, was used as a cut-off level for DSI in our study which was in concordance with the GOG study. The problem of using DSI prior to the surgery to omit radical hysterectomy is that the preoperative DSI assessment is not routinely performed. Although, loop electrosurgical excision procedure (LEEP) can provide some information regarding DSI, the treatment delay makes it not suitable for most of the patients with cervical cancer. The imaging with either ultrasonography or magnetic resonance imaging (MRI) has been evaluated in some studies for preoperative DSI evaluation[15], However, the accuracy and cost-effectiveness of these techniques were still questioned. Pelvic node status was also an independent factor associated with PI in this study. Only 4% (8/184) of patients without pelvic lymph node involvement had PI, while 50% (11/22) of those with pelvic lymph node metastasis had disease involving parametrium (p < 0.01). Our findings were consistent with another previous report[7]. Pelvic lymph node involvement can be accurately evaluated prior to radical hysterectomy using intraoperative frozen section via laparoscopy or exploratory laparotomy. The pelvic lymph node status and preoperative DSI may provide information for decision making of a proper surgical procedure or choosing other treatment modalities[16].

It is advisable to identify a subgroup of patients with low-risk for PI. These patients can be offered the DSI assessment by transvaginal ultrasonography, MRI, or pathologic result from the LEEP specimen and intraoperative evaluation of pelvic lymph node status by frozen section before a definite surgical procedure was performed. Since radical hysterectomy is still the standard treatment for non-bulky early-stage cervical cancer, therefore, less radical surgery for patients who have low-risk for PI should be considered only in the setting of clinical trials. Future studies focusing on the benefit of identifying some patients with cervical cancer who are suitable for less radical surgery in term of decreasing surgical complications without compromising the oncologic outcomes is still warranted.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. Int J Gynecol Obstet 2018;143:22-36.
2. Sangariyavanich E, Buasom R. Hospital-based cancer registry. Bangkok: New Thammada Press 2018:1-4.
3. Jiamset I, Hanprasertpong J. Risk factors for parametrial involvement in early-stage cervical cancer and identification of patients suitable for less radical surgery. Oncol Res Treat 2016;39:432-8.
4. 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.

5. Wright JD, Grigsby PW, Brooks R, Powell MA, Gibb RK, Gao F, et al. Utility of parametrectomy for early-stage cervical cancer treated with radical hysterectomy. Cancer 2007;110:1281-6.

6. Frumovitz M, Sun CC, Schmeler KM, Deavers MT, Dos Reis R, Levenback CF, et al. Parametrial involvement in radical hysterectomy specimens for women with early-stage cervical cancer. Obstet Gynecol 2009;114:93-9.

7. Vanichtantikul A, Tantbirojn P, Manchana T. Parametrial involvement in women with low-risk, early-stage cervical cancer. Eur J Cancer Care 2017;26:1-5.

8. Cohen J. A power primer. Psychol bull 1992;112:155-9.

9. Kodama J, Kusumoto T, Nakamura K, Seki N, Hongo A, Hiramatsu Y. Factors associated with parametrial involvement in stage IB1 cervical cancer and identification of patients suitable for less radical surgery. Gynecol Oncol 2011;122:491-4.

10. Baiocchi G, de Brot L, Faloppa CC, Mantoan H, Duque MR, Badiglian-Filho L, et al. Is parametrectomy always necessary in early-stage cervical cancer? Gynecol Oncol 2017;146:16-9.

11. Dabi Y, Willecocq C, Ballester M, Carcopino X, Bendifallah S, Ouldamer L, et al. Identification of a low risk population for parametrial invasion in patients with early-stage cervical cancer. J Transl Med 2018;16:163-72.

12. Xie X, Song K, Cui B, Jiang J, Zhang Y, Wang B, et al. Significance of the factors associated with parametrial involvement in stage IB to IIA cervical cancer. Int J Gynecol Cancer 2016;26:939-43.

13. Lee SH, Cho KJ, Ko MH, Cho HY, Lee KB, Lim S. Factors associated with parametrial involvement in patients with stage IB1 cervical cancer: Who is suitable for less radical surgery? Obstet Gynecol Sci 2018;61:88-94.

14. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a gynecologic oncology group study. Gynecol Oncol 1999;73:177-83.

15. Epstein E, Testa A, Gaurilcikas A, Di Legge A, Ameye L, Atstupenaite V, et al. Early-stage cervical cancer: Tumor delineation by magnetic resonance imaging and ultrasound - A European multicenter trial. Gynecol Oncol 2013;128:449-53.

16. Reade CJ, Eiriksson LR, Covens A. Surgery for early stage cervical cancer: how radical should it be? Gynecol Oncol 2013;131:222-30.

Techapalokun A, et al. *Risk Factors Associated with Parametrial Involvement in Early-stage Cervical Cancer*