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Parametrial Invasion in Early-Stage Cervical Cancer

Swita Luengyosluechakul, M.D.*,
Amornrat Temtanakitpaisan, M.D.*,
Chumnan Kietpeerakool, M.D.*,
Bandit Chumworathayi, M.D.*,
Pilaiwan Kleebkaow, M.D.*,
Apiwat Aue-aungkul, M.D.*,
Nampet Jampathong.*

** Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Khon Kean, Thailand*

ABSTRACT

Objectives: To determine the rate of parametrial involvement and associated factors among patients who underwent radical hysterectomy and pelvic lymphadenectomy for early-stage cervical cancer.

Materials and Methods: Medical records of 165 patients who had complete data were reviewed. Early stage cervical cancer was defined as cervical cancer stage IA2 to IIA. We excluded patients who presented with neuroendocrine tumors or sarcoma. The lesion size was measured clinically during pelvic examination preceding surgery.

Results: The majority of patients (87.39%) were in stage IB1. One hundred twenty-five (75.8%) patients had tumors smaller than 2 cm in diameter. Pelvic lymph node metastases were noted in twelve (7.3%) patients. Parametrial invasion was noted in six (3.6%) patients. The rate of parametrial invasion was 10% among patients with tumors larger than 2 cm in diameter compared to 1.6% among those with smaller lesions. The rate of parametrial invasion was higher among patients who had deep stromal invasion (13.5% vs 0.9%) and pelvic node metastasis (41.7% vs 0.7%) compared to those without these two pathological factors.

Conclusion: The overall rate of parametrial invasion in patients with early stage cervical cancer in this study was 3.6%. The one significant preoperative predictor for parametrial invasion was tumor size. Significant pathological factors for predicting an increased risk of parametrial invasion included the presence of deep stromal invasion and pelvic lymph node metastasis.

Keywords: cervical cancer, parametrial invasion, radical hysterectomy.

Correspondence to: *Amornrat Temtanakitpaisan, M.D., Department of Obstetrics and Gynaecology, Faculty of Medicine, KhonKaen University, Khon Kean, Thailand, Email: kunglekmed@hotmail.com*

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การลุกลามเนื้อเยื่อข้างมดลูกในมะเร็งปากมดลูกระยะต้น

ศวิตา เลื่องยศลือชากุล, อมรรัตน์ เต็มธนะกิจไพศาล, ชำนาญ เกียรติพีรกุล, บัณฑิต ชุมวรฐายี, พิไลวรรณ กลีบแก้ว, อภิวัฒน์ เอื้ออังกูร, น้ำเพชร จำปาทอง

บทคัดย่อ

วัตถุประสงค์: *เพื่อประเมินอัตราการลุกลามเนื้อเยื่อข้างมดลูกและปัจจัยที่เกี่ยวข้องในผู้ป่วยมะเร็งปากมดลูกระยะต้นที่ได้รับการผ่าตัดมดลูกแบบกว้างร่วมกับการเลาะต่อมน้ำเหลืองในอุ้งเชิงกราน*

วัสดุและวิธีการ: *ทำการเก็บรวบรวมข้อมูลประวัติการรักษาจากเวชระเบียนของผู้ป่วยมะเร็งปากมดลูกระยะต้น (มะเร็งปากมดลูกตั้งแต่ระยะ 1A2 ถึง 2A) จำนวน 165 ราย ยกเว้นผู้ป่วยมะเร็งปากมดลูกระยะต้นชนิด neuroendocrine หรือ sarcoma นอกจากนี้มีการวัดขนาดของรอยโรคก่อนผ่าตัดจากการตรวจภายในทางช่องคลอด*

ผลการศึกษา: *ผู้ป่วยส่วนใหญ่เป็นมะเร็งปากมดลูกระยะ 1B1 (ร้อยละ 87.39) และมีขนาดเส้นผ่าศูนย์กลางของรอยโรคน้อยกว่า 2 เซนติเมตร (ร้อยละ 75.8) มีการกระจายของมะเร็งไปต่อมน้ำเหลืองในอุ้งเชิงกรานจำนวน 12 ราย (ร้อยละ 7.3) มีการลุกลามไปเนื้อเยื่อข้างมดลูกจำนวน 6 ราย (ร้อยละ 3.6) โดยอัตราของการลุกลามเนื้อเยื่อข้างเคียงในกลุ่มที่มีขนาดเส้นผ่าศูนย์กลางของรอยโรคมากกว่า 2 เซนติเมตร (ร้อยละ10) มากกว่ากลุ่มที่มีขนาดรอยโรคน้อยกว่า 2 เซนติเมตร (ร้อยละ 1.6) นอกจากนี้พบว่า อัตราการลุกลามเนื้อเยื่อข้างมดลูกสัมพันธ์กับการลุกลามสโตรม่าชั้นลึก และการกระจายของมะเร็งไปต่อมน้ำเหลืองในอุ้งเชิงกราน โดยพบว่าอัตราการลุกลามเนื้อเยื่อข้างมดลูกในกลุ่มที่มีการลุกลามสโตรม่าชั้นลึก (ร้อยละ 13.5) จะสูงกว่ากลุ่มที่ไม่มีการลุกลามสโตรม่าชั้นลึก (ร้อยละ 0.9) และพบอัตราการลุกลามเนื้อเยื่อข้างมดลูกในกลุ่มที่มีการกระจายของมะเร็งไปต่อมน้ำเหลืองในอุ้งเชิงกราน (ร้อยละ 41.7) สูงกว่ากลุ่มที่ไม่มีการกระจายของมะเร็งไปต่อมน้ำเหลืองในอุ้งเชิงกราน (ร้อยละ 0.7)*

สรุป: *อัตราการลุกลามเนื้อเยื่อข้างมดลูกในผู้ป่วยมะเร็งปากมดลูกระยะต้นของการศึกษานี้เท่ากับร้อยละ 3.6 ปัจจัยสำคัญก่อนการผ่าตัดที่ช่วยทำนายการลุกลามเนื้อเยื่อข้างมดลูกคือขนาดของรอยโรคและปัจจัยสำคัญทางพยาธิวิทยาที่ช่วยทำนายการลุกลามเนื้อเยื่อข้างมดลูกคือการลุกลามสโตรม่าชั้นลึกและการกระจายของมะเร็งไปต่อมน้ำเหลืองในอุ้งเชิงกราน*

คำสำคัญ: *มะเร็งปากมดลูก, การลุกลามเนื้อเยื่อข้างปากมดลูก, การผ่าตัดมดลูกแบบกว้าง*

Introduction

Cervical cancer is a major health burden in less economically developed countries. Approximately 90% of cervical cancer-related deaths are in developing countries due to a lack of effective organized prevention programs[1]. Treatment of cervical cancer depends on the clinical stage of the disease. Clinical staging procedures in cervical cancer include detailed physical examination and diagnostic investigations to assess the size of the primary tumor and the extent to which it has spread to the surrounding tissues, retroperitoneal lymph nodes, and distant organs[2].

Radical hysterectomy is the surgical procedure performed to remove the uterus, cervix, upper vagina and parametria[3]. This procedure aims to ensure complete resection of the tumor[3]. Radical hysterectomy in conjunction with bilateral pelvic lymphadenectomy is the standard surgical treatment for stage IA2-IIA cervical cancer, when preservation of fertility is not necessary[4]. Radical hysterectomy results in treatment outcomes similar to those who receive pelvic radiation[4]. Radical hysterectomy, however, may be preferable to pelvic radiation among premenopausal women in order to preserve ovarian function and minimize sexual dysfunction[5].

One of the most distressing morbidities following radical hysterectomy is bladder dysfunction. Bladder dysfunction, caused by injury to the pelvic autonomic nerves during resection of the parametria (parametrectomy), may occur in up to 70% of women following radical hysterectomy[6, 7]. Other morbidities secondary to parametrectomy include ureteric damage, significant blood loss, fistula formation, and bowel denervation[8-10]. To prevent these potential complications, omitting parametrectomy during radical hysterectomy in women with an early stage cervical cancer might be reasonable if the risk of parametrial involvement is very low[2]. The purpose of this study was to determine the rate of parametrial involvement and associated factors among patients who underwent radical hysterectomy and pelvic lymphadenectomy for early stage cervical cancer.

Materials and Methods

After receiving approval from the Research Ethics Committee, we reviewed medical records of women with cervical cancer stages IA2-IIA who underwent radical hysterectomy from January 2005 to December 2016. In all cases, bilateral pelvic lymphadenectomy had been performed. Abstracted data included baseline characteristics, clinical stage, perioperative complications, and detailed pathological findings. Early stage cervical cancer was defined as cervical cancer stages IA2 to IIA. We excluded patients who received preoperative neoadjuvant chemotherapy or radiation therapy and those who presented with unusual histology such as neuroendocrine tumors or sarcoma.

The size of each tumor was clinically measured during pelvic examination preceding surgery. Parametrial invasion was defined as metastasis in either the parametrial tissue or parametrial lymph node. Deep stromal invasion was defined as a tumor invading cervical stroma to a depth of ≥ 10 mm. Lymphovascular space invasion (LVSI) was defined as the presence of neoplastic cells within vascular or lymphatic spaces lined by flattened endothelial cells.

Descriptive statistics were used to analyze patient characteristics. A 95% confidence interval (CI) of the rate of parametrial invasion was calculated to determine the precision of the data. A chi-square test or Fisher's exact test was used to univariately identify factors associated with parametrial invasion. A multivariate analysis using a logistic model was used to determine the independent effects of factors of interest. An adjusted odds ratio (aORs) with a 95%CI that did not include unity was considered statistically significant.

Results

This study reviewed medical records of 165 patients, all of whom had complete records. The mean age ± standard deviation (SD) of the patients was 45.7±7.9 years. Table 1. shows the patients' clinical and pathological characteristics. The majority

of patients (144 patients, 87.39%) were in stage IB1. Nine (5.5%) had tumors larger than 4 cm in diameter, and 125 (75.8%) had tumors smaller than 2 cm. Pelvic lymph node metastases were reported in 12 (7.3%) patients. Parametrial invasion was noted in six (3.6%) patients (95% CI 1.3-7.7%).

Table 1. Clinical and pathological characteristics of the patients.

Characteristics	Number (%)
Age	
< 40 years	47 (28.5)
≥ 40 years	118 (71.5)
Parity	
Nulliparous	10 (6.1)
Multiparous	155 (93.9)
Stage	
IA2	8 (4.8)
IB1	144 (87.3)
IB2	9 (5.5)
IIA1	4 (2.4)
Histology	
Squamous cell carcinoma	98 (59.4)
Adenocarcinoma	66 (40.0)
Adenosquamous carcinoma	1 (0.6)
Tumor size (largest diameter)	
≤ 2 cm	125 (75.8)
> 2 cm	40 (24.2)
Lymphovascular space invasion	
Presence	64 (38.8)
Absent	73 (44.2)
Not recorded	28 (17.0)
Deep stromal invasion	
Presence	37 (22.4)
Absent	113 (68.5)
Not recorded	15 (9.1)
Parametrial invasion	
Presence	6 (3.6)
Absent	159 (92.7)
Pelvic lymph node metastasis	
Presence	12 (7.3)
Absent	153 (92.7)

Table 2 displays the clinical and pathological factors for predicting parametrial invasion. Four clinical factors were analyzed; including the size of tumor, histological type, patient's age, and parity status, of which only tumor size was significantly associated with parametrial invasion. The rate of parametrial invasion was 10% among patients with tumors larger than 2 cm in diameter compared to 1.6% among those with smaller lesions. After adjusting by patient age and histological type, patients who had tumors larger than 2 cm in diameter were approximately seven times more likely to have parametrial invasion (aORs 7.24; 95%CI 1.24-42.17).

Three pathological factors were also examined; the presence of LVSI, deep stromal invasion (DSI), and pelvic lymph node metastasis, all of which were confirmed after pathological examination of surgical specimens. Patients found to have DSI or pelvic lymph node metastasis carried a higher risk of parametrial invasion (Table 2).

Table 2. Clinical and pathological factors predicting parametrial invasion.

Variable	Parametrial invasion		p value
	Presence	Absent	
Tumor size (n = 165)			
≤ 2 cm (n = 125)	2 (1.6)	123 (98.4)	0.031
> 2 cm (n = 40)	4 (10.0)	36 (90.0)	
Histology (n = 165)			
Squamous cell carcinoma (n = 98)	5 (5.1)	93 (94.9)	0.476
Others (n = 67)	1 (1.5)	65 (98.5)	
Age (n = 165)			
≥ 40 years (n = 118)	5 (4.2)	113 (95.7)	0.676
< 40 years (n = 47)	1 (2.1)	46 (97.9)	
Parity status (n = 165)			
Nulliparous (n = 10)	0 (0)	10 (100.0)	1.00
Multiparous (n = 155)	6 (3.9)	149 (96.1)	
Lymphovascular space invasion (n = 137)			
Presence (n = 64)	4 (6.3)	60 (93.7)	0.111
Absent (n = 73)	0 (0)	73 (100.0)	
Deep stromal invasion (n = 150)			
Presence (n = 37)	5 (13.5)	32 (86.5)	0.004
Absent (n = 113)	1 (0.9)	112 (99.1)	
Pelvic lymph node metastasis (n = 165)			
Presence (n = 12)	5 (41.7)	7 (58.3)	< 0.001
Absent (n = 153)	1 (0.7)	152 (99.3)	

Data presented as number (percentage)

Of the six patients with parametrial invasion, five (83.3%) had deep stromal invasion. The rate of parametrial invasion among patients without DSI was 0.9% (one of 113 patients). In addition, five of these

patients (83.3%) had pelvic lymph node metastasis. On the other hand, only one of the 153 patients without pelvic lymph node metastasis had parametrial invasion, a rate of 0.7%.

Discussion

The overall rate of parametrial invasion in early stage cervical cancer in this study was 3.6% (95%CI 1.3-7.7%). The one significant preoperative factor was the size of the cervical lesion. Significant pathological factors for predicting the risk of parametrial invasion included the presence of DSI and pelvic lymph node metastasis. Histological type and presence of LVSI were not significantly associated with the risk of parametrial invasion.

The rate of parametrial invasion in our study was in line with previously reported findings. In the present study, the rate of parametrial invasion was 3.6%. The rate of parametrial invasion in early stage cervical cancer found in previous reports varied from less than 1% to up to 10%[11-17].

The size of cervical lesions was the preoperative factor most strongly associated with the risk of parametrial invasion. Previous studies have found parametrial involvement to occur in less than 1% to 1.9% of women with cervical lesions 2 cm in diameter or smaller. In the present study, only 1.6% of patients whose largest tumor was smaller than 2 cm in diameter were found to have parametrial invasion, which significantly differed from the rate of 10% found among those with tumors larger than 2 cm (Table 2). After adjustment for patient age and histological tumor type, patients with tumors larger than 2 cm in diameter carried an approximately seven times higher risk of suffering from parametrial invasion (aORs 7.24; 95%CI 1.24-42.17). Tumor size therefore may be a potential indicator that can be used to tailor the radicality of a hysterectomy to minimize surgical morbidity associated with parametrectomy. However, effectiveness of simple hysterectomy for early stage cervical cancer needs to be critically evaluated in a randomized controlled trial before its relevance to patient care can be considered. In our analysis, we found status of the pelvic lymph node to be the pathological factor with the strongest association with parametrial invasion. The rate of parametrial invasion was approximately 42% in patients with pelvic lymph node metastasis compared to only 0.7% among patients without pelvic node metastasis. After adjustment for patient age and histological type, the presence of tumors larger than 2 cm in diameter was a significant independent factor associated with an increased risk of parametrial invasion (aORs 7.24; 95%CI 1.24-42.17). In addition, most patients who had parametrial invasion (83.3%) were also found to have pelvic lymph node metastasis (Table 2). These findings were similar to those of previous studies[12, 15, 16, 18], which have found the rates of parametrial involvement among patients with pelvic lymph node metastasis from 26.3% to 80% compared to 3.6% to 10% among those without pelvic lymph node metastasis[12, 15, 16, 18].

In this study, we defined lesions with DSI as tumors invading cervical stroma to a depth of ≥ 10 mm. Our study found a higher rate of parametrial invasion among patients who had DSI. The rates of parametrial invasion were 13.5% and 0.9% among patients with DSI and those without deep invasion, respectively (Table 2). Similarly, Vanichtantikul et al[18] reported rates of parametrial involvement among patients who had stromal invasion deeper than10 mm and those with more superficial invasions of 14.3% and 1.2%, respectively.

There are differences in the characteristics of patients with adenocarcinoma and those adenosquamous carcinoma, as well as differences in the natural course of disease between these two squamous cell carcinoma subtypes. This may raise questions regarding whether different histological subtypes of cervical cancer pose different levels of risk of parametrial invasion. In our study, histological type of cancer was not associated with risk of parametrial involvement. Our finding reaffirmed previously reported results which indicate a lack of significant impact of histological subtype on the risk of parametrial invasion in cases of early stage cervical cancer[12, 15-18].

Some limitations of this study are worthy of note. First, the lesion size measures in this study were solely based on physical examination or the so-called 'the clinical tumor size'. Different techniques in tumor size

measurement (i.e. pathological examination or radiologic imaging) may not yield a similar result. Second, a relative small sample size in this study resulted in a wide confidence interval of estimate measures.

Conclusion

In conclusion, the overall rate of parametrial invasion in stage IA2-IIA cervical cancer in this study was 3.6%. The one significant preoperative factor associated with the risk of parametrial invasion was clinical tumor size. Significant pathological factors for predicting the risk of parametrial invasion included the presence of DSI and pelvic lymph node metastasis.

Potential conflicts of interest

The authors declare no conflict of interest.

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