Clinical Outcomes and Prognostic Factors of Node - Negative Cervical Cancer Patients with Deep Stromal Invasion or Lymphovascular Space Involvement Following Radical Hysterectomy

Prapaporn Suprasert MD*,
Jatupol Srisomboon MD*, Sumalee Siriaunkgul MD**,
Surapan Khunamornpong MD**, Chailert Phongnarisorn MD*,
Sitthicha Siriaree MD*, Kittipat Charoenkwan MD*,
Chalong Cheewakriangkrai MD*, Chumnarn Kietpeerakool MD*

** Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai*
*** Division of Gynecologic Pathology, Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai*

Objective: *To evaluate the clinical outcomes and prognostic factors of node-negative cervical cancer patients who had deep stromal invasion (DSI) and/or lymphovascular space invasion (LVSI) following radical hysterectomy and pelvic lymphadenectomy (RHPL).*
Material and Method: *The medical records of 150 node-negative stage IA2-IIA cervical cancer patients who had DSI and/or LVSI after RHPL from 1999 to 2004 were reviewed.*
Results: *Eighty-eight (58.4%) patients were treated with RHPL alone. Twenty-eight (18.7%), 23 (15.4%), eight (5.3%), and three (2%) patients received postoperative chemotherapy, chemoradiation, radiotherapy, and brachytherapy, respectively. Overall, 11 (7.3%) patients developed recurrence. The estimated 5- year disease-free survival of the patients was 90.9%. By multivariate analysis, two factors, age of less than 35 years old and a non squamous histology, were significantly independent prognostic. Eight (5.3%) patients experienced treatment-related complications.*
Conclusion: *Node-negative cervical cancer patients with DSI and/or LVSI had excellent clinical outcomes. Young age and non-squamous histology are significant independent prognostic factors.*

Keywords: *Cervical cancer, Deep stromal invasion, Lymph vascular space invasion*

J Med Assoc Thai 2006; 89 (9): 1368-75
Full text. e-Journal: *http://www.medassocthai.org/journal*

The standard treatment for patients with early-stage cervical cancer is either radical surgery or radiation therapy[1]. Adjuvant radiation is usually recommended for those who are at high risk of recurrence, i.e. lymph node metastases, parametrial involvement, and positive surgical margins[2]. However, approximately half of the recurrences in patients with early-stage occur in those with negative nodes[3]. The independent risk factors in this group were large tumor size, deep stromal invasion (DSI) and lymphovascular space invasion (LVSI)[4-9]. The Gynecologic Oncolgy Group Study (GOG) has conducted a prospective randomized study of adjuvant pelvic radiation for patients with these intracervical risk factors. The study showed the benefit of postoperative radiation in these patients by reducing the recurrence from 28% in patients who underwent surgery alone to 15% in patients who received adjuvant radiation[10]. An improvement of disease-free

Correspondence to : Suprasert P, Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. Fax: 0-5394-6112, E-mail: psuprase@mail.med.cmu.ac.th

survival was also noted for those with adjuvant radiation[10]. However, some authors suggested that these patients may be treated with radical surgery alone without affecting the survival outcomes[11,12]. In addition, the risk of severe complications from combined surgery and adjuvant radiation is also considerably increased.

This retrospective study was undertaken to evaluate the clinical outcomes and prognostic factors of node-negative cervical patients who had deep stromal invasion and/or lymphovascular space invasion.

Material and Method

Following the Research Ethics Committee approval, the medical records of node-negative cervical cancer patients, who had high-risk intracervical factors, defined as deep stromal invasion (DSI) and/or lymphovascular space invasion (LVSI) after radical hysterectomy and pelvic lymphadenectomy (RHPL) at Chiang Mai University Hospital between January 1999 and January 2004, were reviewed. Gross appearance of the tumor, pathologic tumor size, histological cell type, tumor grade, the presence of LVSI, and depth of stromal invasion were analyzed. Deep stromal invasion was defined as outer third cervical stromal invasion. LVSI was defined as the presence of tumor cells in the luminal spaces lined by endothelial cells within an area of cervical stroma.

Patients, with DSI less than 3 mm from the outermost stroma of the cervix and LVSI more than 10 spaces per case, received treatment with adjuvant cisplatin-based chemoradiation. Weekly cisplatin at a dosage of 40 mg/m^2 was administered for six courses during the radiation. Radiation alone was given in patients who refused chemotherapy or had poor performance status. Radiation therapy consisted of external beam irradiation 40-50 Gy delivered to the whole pelvis with a 10-MV X-ray by parallel opposed anteroposterior fields or four-field box technique. The daily fraction was 2.0 Gy, five fractions per week. Patients, who had only LVSI more than 10 spaces per case, received adjuvant cisplatin chemotherapy at a dosage of 75 mg/m^2 triweekly for four courses. Patients who had only DSI and/or LVSI $\leq$ 10 spaces per case received no treatment after the operation. After completion of treatment, all patients were followed every 3 months in year 1, every 4 months in year 2, and every 6 months thereafter. Treatment failure was defined either by pathological proof of recurrence or by image studies showing recurrence or enlargement of lymph nodes. Treatment-related complications were recorded.

Statistical analysis of the data was carried out by the SPSS for window program (version 10.0). Disease free survival was estimated by the Kaplan-Meier method and compared with Log rank test. Clinical variables were compared using the chi-square, Fisher's exact, and Pearson's correlation coefficient. The differences were judged significant at p value of < 0.05. Multivariate analysis was performed using a Cox proportional hazards regression model.

Results

During the study period, 150 node-negative cervical cancer patients had high-risk intracervical factors including DSI and/or LVSI after undergoing

Table 1. The clinical characteristics (n = 150)

Characteristic	Number (%)
Gross appearance	
Exophytic	59 (39.3)
Endophytic	66 (44.0)
Ulcerative	1 (0.7)
No gross lesion	24 (16.0)
Stage	
IA2	3 (2.0)
IB1	118 (78.7)
IB2	13 (8.7)
IIA	16 (10.7)
Histology	
SCCA	106 (70.7)
AdenoCA	28 (18.7)
Adenosquamous cell CA	16 (10.7)
Grade	
I	42 (28.0)
II	81 (54.0)
III	26 (17.3)
Unknown*	1 (0.7)
LVSI	
Negative	45 (30.0)
$\leq$ 10 spaces/case	64 (42.7)
$>$ 10 spaces/case	41 (27.3)
Stromal invasion	
Outer third	93 (62.0)
Middle third	5 (3.3)
Inner third	52 (34.7)

RHPL = radical hysterectomy with pelvic lymphadenectomy, RT = radiation therapy

* unknown grade : 1 case could not find a slide to identify the grade, in cases of adenosquamous cell CA, the grading were according to adenoCA

SCCA = squamous cell carcinoma, AdenoCA = adenocarcinoma, CA = carcinoma, LVSI = lymphovascular space invasion

radical hysterectomy and pelvic lymphadenectomy. The mean age was 43 years with a range of 28-67 years. The mean number of lymph nodes removed was 28 (range 11-70). The mean tumor size was 2.7 cm (range 1-8 cm). The clinico-pathological features of the patients are shown in Table 1. Infiltrative tumor appeared to be the most common in these patients who had DSI and/or LVSI. No LVSI was present in 45 (30%) patients with DSI, while 52 (34.7%) patients with inner third and 5 (3.3%) patients with middle third stromal invasion had LVSI.

Eighty-eight (58.4%) patients were treated with surgery alone. Twenty-eight (18.7%), 23 (15.4%), and eight (5.3%) patients received postoperative chemotherapy, chemoradiation, and radiation therapy, respectively. With a median follow-up of 37 months (range 1-81 months), 11 (7.3%) patients developed recurrent disease 8-37 months after treatment. Seven patients had pelvic recurrence, four after surgery alone, two after adjuvant chemotherapy, and one after adjuvant chemoradiation. Three patients had pulmonary recurrence: two after surgery alone, and one after adjuvant chemoradiation. The remaining one patient had liver metastases after adjuvant chemotherapy. The estimated 5-year disease-free survival (DFS) of the patients who had DSI and/or LVSI was 90.9% as shown in Fig. 1.

Univariated analysis showed that both age and histology significantly affected the prognosis of patients with node-negative cervical cancer who had high-risk intracervical factors. Patients aged less than 35 years old or had nonsquamous histology developed a higher recurrence than those aged older than 35 years or those who had squamous histology as shown in Table 2. Cox regression analysis for disease-free survival was carried out incorporating all the prognostic variables listed in Table 2. Age below 35 years old ($p = 0.02$) and a nonsquamous histology ($p = 0.01$) were significantly independent factors that predicted recurrence as shown in Table 3. Patients younger than 35 years old had an estimated 5.9 times higher hazard than patients who were older. For histology, the hazard ratio was 5.6 when the histology was non-squamous cell carcinoma compared with squamous cell carcinoma. Based on the hazard ratios, young age and non-squamous cell carcinoma were defined as risk factors. The estimated 5-year DFS for patients without any risk factor was 97%, whereas for patients with one and two risk factors, the DFS was 85% and 75%, respectively as shown in Fig. 2. Two of 88 patients (2.3%) who did not have any risk factors developed recurrence, while seven of 58 (12.1%) patients with one risk factor and two of four (50%) patients with two risk factors developed recurrence.

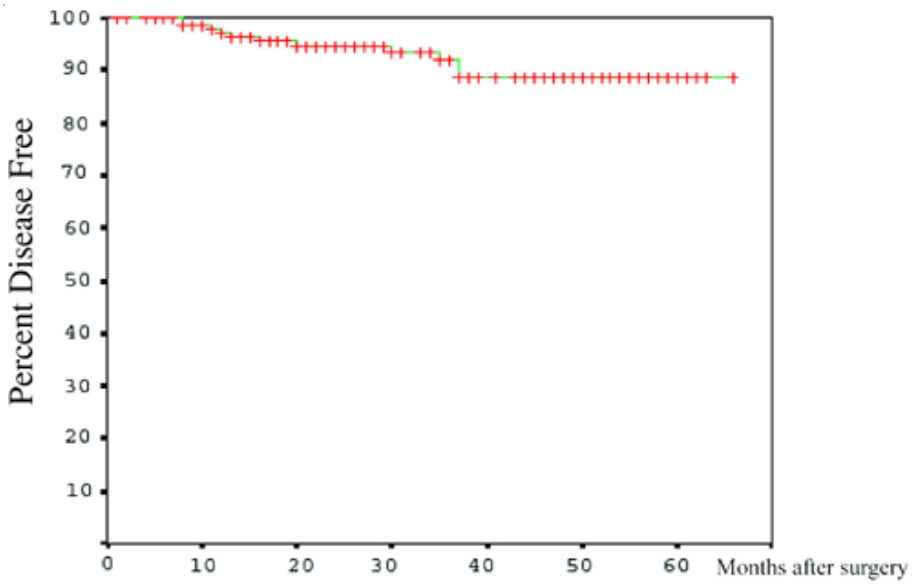


Fig. 1 Disease free survival rate of the early stage cervical stage patients with deep stromal invasion and /or lymphovascular space invasion

Table 2. Univariate analysis of the prognostic variables

Factor	No. of patients	No. of recurrence (%)	Odd ratio	95%CI	p-value
Age					
> 35	128	7 (5.5)			
≤ 35	22	4 (18.2)	3.84	1.02-14.44	0.05
Stage					
IA2 & IB1	121	8 (6.6)			
IB2 & IIA	29	3 (10.3)	1.63	0.40-6.57	0.45
Histology					
SCCA	106	4 (3.8)			
Non-SCCA	44	7 (15.9)	4.82	1.33-17.43	0.01
Grade					
I & II	123	8 (6.5)			
III	26	3 (11.5)	1.87	0.46-7.60	0.41
Size					
≤ 4 cm	140	9 (6.4)			
> 4 cm	10	2 (20.0)	3.63	0.67-19.73	0.16
Treatment					
RHPL	88	6 (6.8)			
RHPL & adjuvant Rx	62	5 (8.1)	1.20	0.35-4.11	0.76
LVSI					
Negative	45	2 (4.4)			
Positive	105	9 (8.6)	2.02	0.42-9.72	0.51
Stromal invasion					
Inner & Middle third	57	5 (8.8)			
Outer third	93	6 (6.4)	0.72	0.21-2.47	0.75

SCCA = squamous cell carcinoma
RHPL= Radical hysterectomy and pelvic lymphadenectomy
LVSI = Lymphovascular space invasion

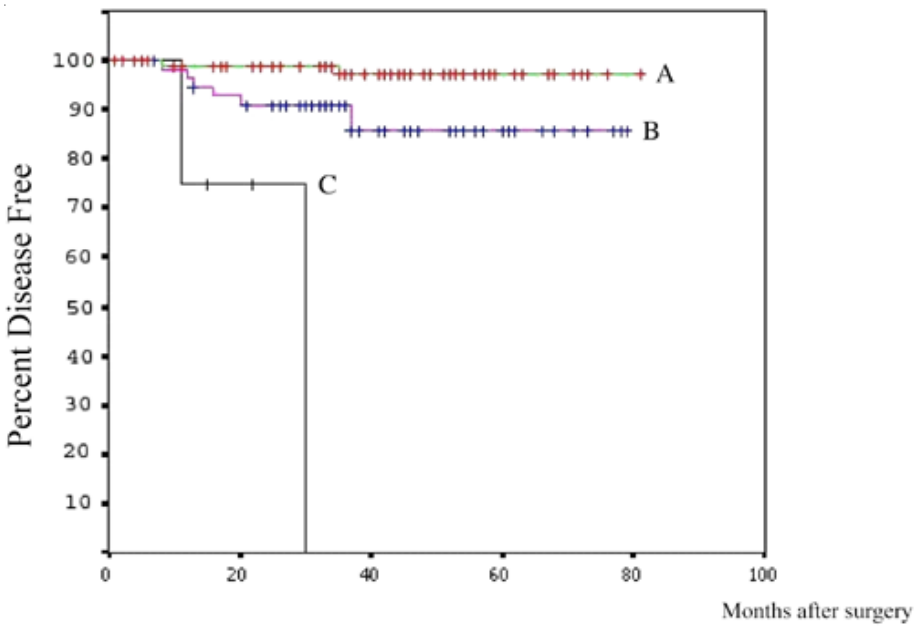
Table 3. Multivariate analysis of the prognostic factors

Factor	Hazard Ratio	95%CI	p-value
Histology (SCCA vs non SCCA)	5.65	1.43-22.29	0.01
Size (≤ 4 vs > 4 cm)	1.06	0.31-46.73	0.29
LVSI (negative vs positive LVSI)	1.58	0.25-9.92	0.63
Age (> 35 vs ≤ 35 year)	5.92	1.38-25.33	0.02
DSI (outer vs middle & inner)	1.14	0.26-4.87	0.86
Treatment (yes or no)	1.06	0.28-4.05	0.93
Stage (IA_2 & IB1 vs IB_2 & IIA)	1.06	0.13-8.77	0.96
Grade (II & I vs III)	1.26	0.29-5.32	0.75

SCCA = squamous cell carcinoma
DSI = Depth of stromal invasion, LVSI = lymphovascular space invasion

Depth of stromal invasion, the presence of LVSI, tumor size and grade, stage, and adjuvant treatment after radical surgery appeared to have no significant effect on survival in node-negative cervical cancer patients who had deep stromal invasion and/or LVSI.

Treatment-related complications occurred in eight patients (5.3%) including ureter injury (1), bladder injury (1), urinary incontinence (1), vesicovaginal fistula (1), symptomatic lymphocyst (2), lymphedema (1), and bowel obstruction (1). The patients who



A = no risk factor (5 year DFS = 97.09%)
B = 1 risk factor (5 year DFS = 85.49%)
C = 2 risk factors (2 year DFS = 75%)
Risk factors = age < 35 years old, non-squamous cell type

Fig. 2 Disease free survival interval by the number of risk factors

developed lymphedema, vesicovaginal fistula, urinary incontinence, and bowel obstruction received adjuvant radiation.

Discussion

The present study showed that early-stage cervical cancer patients who had negative lymph nodes after radical hysterectomy and pelvic lymphadenectomy but had DSI and/or LVSI, showed excellent outcomes with an estimated 5-year disease-free survival rate of 90%. Adjuvant treatment either chemotherapy or radiation therapy appeared to have no significant impact on survival outcomes. Both DSI and LVSI have been found to be significant prognostic factors in many studies[4-8]. The data on clinical outcomes of patients who had only these intermediate risk factors or high-risk intra-cervical factors, are limited.

Delgado et al reported that both DSI and LVSI were independent prognostic factors of cervical cancer patients undergoing radical hysterectomy. The 3-year disease free survival rate was 77% and 73% in patients who had LVSI and DSI, respectively[13]. Samlal et al reported on 196 early-stage cervical cancers that had negative pelvic node. Adenocarcinoma, DSI and extensive stromal inflammatory cell infiltrate were the independent prognostic factors. The 5-year disease free survival in patients who had these risk factors decreased when compared to the patients who had no risk factors (81% vs 97%)[14]. Ho et al reported a worse outcome of node-negative patients with both DSI and LVSI who were treated with radical surgery alone. The 5-year disease free survival rate was 43.3% in patients with both risk factors compared with 75% in those who had only LVSI[15]. In the present study, the 5-year disease free survival rate in patients who had both LVSI and DSI was as high as 87%. The difference might have resulted from the adjuvant radiation that was administered to the patients who had DSI less than 3 mm from the outermost stroma of the cervix and had LVSI of more than 10 spaces per case. Many studies recommended adjuvant radiation in patients who had both intracervical factors[10,11,15-17].

Okada et al evaluated the role of adjuvant radiation following radical surgery in stage IB-IIB cervical cancer patients who had positive nodes, compromised surgical margins, parametrial involvement and deep stromal invasion of cervix with less than 3 mm. from the outermost stroma of the cervix. Multivariate

analysis showed that only lymph node metastases and parametrial invasion were significant prognostic factors but deep stromal invasion was not[18]. Shimada et al investigated DSI as an isolated risk factor in cervical cancer patients who did not receive adjuvant radiation and noted that none of these patients experienced recurrent disease. The authors proposed that DSI can be excluded from the criteria to select patients for adjuvant radiation after radical surgery in cervical cancer[12]. In the present study, adjuvant radiation was not administered to patients who had only DSI. By multivariate analysis, the authors found that both DSI and LVSI were not the independent prognostic factors, only age of less than 35 years old and non-squamous histology were significant prognostic factors. These findings correspond with the previous reports[14,19-21]. Rutledge et al studied a match analysis comparing 250 cervical cancer patients of less than 35 years old with patients who were older than 35 years old. They found that younger age patients were less likely to survive and more likely to have recurrence[21].

Kridelka et al suggested the use of adjuvant small-field pelvic radiation in node-negative stage IB cervical cancer patients who had DSI and LVSI decreased the complications of combined treatment. The efficacy was similar to conventional radiation[22]. Since DSI and LVSI might increase the risk of local recurrence, adjuvant small-field radiation may be considered in these patients with high-risk intracervical factors to reduce severe morbidity.

The recurrence rate of 7.3% in the present study was similar to that of 7.7% in the report by Samlal et al[14]. Adjuvant chemotherapy or chemoradiation could not prevent distant recurrence. Two patients developed distant lung and liver metatastases despite receiving such adjuvant therapy in the present study.

In conclusion, node-negative cervical cancer patients who had deep stromal invasion and/or lymphovascular space involvement had excellent outcomes. This might be from the optimal selected criteria for adjuvant therapy. Those younger than 35 and with nonsquamous histology showed significant independent prognostic factors.

References

1. National Comprehensive Cancer Network (NCCN) guideline version 1. 2004.
2. Guttmann R. Significance of postoperative irradiation in carcinoma of the cervix: a ten year survey. Am J Roentgenol Radium Ther Nucl Med 1970; 108: 102-8.
3. Burke TW, Hoskins WJ, Heller PB, Bibro MC, Weiser EB, Park RC. Prognostic factors associated with radical hysterectomy failure. Gynecol Oncol 1987; 26: 153-9.
4. Chung CK, Nahhas WA, Stryker JA, Curry SL, Abt AB, Mortel R. Analysis of factors contributing to treatment failures in stages IB and IIA carcinoma of the cervix. Am J Obstet Gynecol 1980; 138: 550-6.
5. Boyce J, Fruchter RG, Nicastri AD, Ambiavagar PC, Reinis MS, Nelson JH Jr. Prognostic factors in stage I carcinoma of the cervix. Gynecol Oncol 1981; 12: 154-65.
6. van Nagell JR Jr, Donaldson ES, Wood EG, Parker JC Jr. The significance of vascular invasion and lymphocytic infiltration in invasive cervical cancer. Cancer 1978; 41: 228-34.
7. Abdulhayoglu G, Rich WM, Reynolds J, DiSaia PJ. Selective radiation therapy in stage IB uterine cervical carcinoma following radical pelvic surgery. Gynecol Oncol 1980; 10: 84-92.
8. Boyce JG, Fruchter RG, Nicastri AD, DeRegt RH, Ambiavagar PC, Reinis M, et al. Vascular invasion in stage I carcinoma of the cervix. Cancer 1984; 53: 1175-80.
9. Kamelle SA, Rutledge TL, Tillmanns TD, Gould NS, Cohn DE, Wright J, et al. Surgical-pathological predictors of disease-free survival and risk groupings for IB2 cervical cancer: do the traditional models still apply? Gynecol Oncol 2004; 94: 249-55.
10. 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.
11. Schorge JO, Molpus KL, Koelliker D, Nikrui N, Goodman A, Fuller AF Jr. Stage IB and IIA cervical cancer with negative lymph nodes: the role of adjuvant radiotherapy after radical hysterectomy. Gynecol Oncol 1997; 66: 31-5.
12. Shimada M, Kigawa J, Takahashi M, Minagawa Y, Okada M, Kanamori Y,et al. Stromal invasion of the cervix can be exclude from the criteria for the using adjuvant radiotherapy following radical surgery for the patients with cervical cancer. Gynecol Oncol 2004; 93: 628-31.
13. Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F. Prospective surgical-pathological study of disease-free interval in patients with stage

IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 1990 ;38:352-7.
14. Samlal RA, van der Velden J, Ten Kate FJ, Schilthuis MS, Hart AA, Lammes FB. Surgical pathologic factors that predict recurrence in stage IB and IIA cervical carcinoma patients with negative pelvic lymph nodes. Cancer 1997; 80: 1234-40.
15. Ho CM, Chien TY, Huang SH, Wu CJ, Shih BY, Chang SC. Multivariate analysis of the prognostic factors and outcomes in early cervical cancer patients undergoing radical hysterectomy. Gynecol Oncol 2004; 93: 458-64.
16. Hellebrekers BWJ, Zwinderman AH, Kenter GG, Peters AAW, Snijders-Keilholz A, Graziosi GCM, et al. Surgically-treated early cervical cancer: prognostic factors and the significance of depth of tumor invasion. Int J Gynecol Cancer 1999; 9: 212-9.
17. Uno T, Ito H, Yasuda S, Aruga T, Isobe K, Kawakami H, et al. Adjuvant pelvic irradiation in patients with node - negative carcinoma of the uterine cervix. Anticancer Res 2002; 22: 1213-6.
18. Okada M, Kigawa J, Minagawa Y, Kanamori Y, Shimada M, Takahashi M,et al. Indication and efficacy of radiation therapy following radical surgery in patients with stage IB to IIB cervical cancer. Gynecol Oncol 1998; 70: 61-4.
19. Huang HJ, Chang TC, Hong H, Tseng CJ, Chou HH, Huang KG. Prognostic value of age and histologic type in neoadjuvant chemotherapy plus radical surgery for bulky (> 4 cm) stage IB and IIA cervical carcinoma. Int J Gynecol Cancer 2003; 13: 204-11.
20. Fuller AF, Elliott N, Kosloff C, Hoskins WJ, Lewis JL. Determinants of increased risk for recurrence in patients undergoing radical hysterectomy for stage IB and IIA carcinoma of the cervix. Gynecol Oncol 1989; 33: 34-9.
21. Rutledge FN, Mitchell MF, Munsell M, Bass S, McGuffee V, Atkinson EN. Youth as a prognostic factor in carcinoma of the cervix: a matched analysis. Gynecol Oncol 1992; 44: 123-30.
22. Kridelka FJ, Berg DO, Neuman M, Edwards LS, Robertson G, Grant PT, et al. Adjuvant small field pelvic radiation for patients with high risk, stage IB lymph node negative cervix carcinoma after radical hysterectomy and pelvic lymph node dissection. Cancer 1999; 86: 2059-65.

ผลการรักษาและปัจจัยพยากรณ์โรคในผู้ป่วยมะเร็งปากมดลูกที่มีการกระจายเข้าไปลึกในชั้นสโตรมาของปากมดลูก และ/หรือ กระจายเข้าทางเดินน้ำเหลืองและหลอดเลือด โดยที่ต่อมน้ำเหลืองปกติหลังการผ่าตัดมดลูกแบบแรดดิคอล

ประภาพร สู่ประเสริฐ, จตุพล ศรีสมบูรณ์, สุมาลี ศิริอังกุล, สุรพันธ์ คุณอมรพงศ์, ชัยเลิศ พงษนริศร, สิทธิชา สิริอารีย์, กิตติภัต เจริญขวัญ, ฉลอง ชีวเกรียงไกร, ชำนาญ เกียรติพีรกุล

วัตถุประสงค์: เพื่อประเมินผลการรักษาและปัจจัยพยากรณ์โรคของผู้ป่วยมะเร็งปากมดลูกระยะที่ IA2-IIA ที่มีการกระจายเข้าไปลึกในชั้นสโตรมาของปากมดลูก และ/หรือ กระจายเข้าทางเดินน้ำเหลืองและหลอดเลือดโดยที่ต่อมน้ำเหลืองปกติหลังการผ่าตัดมดลูกแบบ แรดดิคอล

วัสดุและวิธีการ: ทบทวนเวชระเบียนในผู้ป่วยที่มีการกระจายเข้าไปลึกในชั้นสโตรมาของปากมดลูก และ/หรือ กระจายเข้าทางเดินน้ำเหลืองและหลอดเลือด โดยที่ต่อมน้ำเหลืองปกติหลังการผ่าตัดมดลูกแบบ แรดดิคอล ในช่วงปี พ.ศ. 2542 - พ.ศ. 2547 จำนวน 150 ราย

ผลการศึกษา: ผู้ป่วยที่ได้รับการรักษาโดยการผ่าตัดอย่างเดียวมี 88 ราย (ร้อยละ 58.4) ผู้ป่วยที่เหลือ ได้รับการรักษาเพิ่มเติมหลังผ่าตัด ดังนี้ ได้รับยาเคมีบำบัด 28 ราย (ร้อยละ 18.7), ยาเคมีบำบัดร่วมกับการฉายรังสี 23 ราย (ร้อยละ 15.4), การฉายรังสี 8 ราย (ร้อยละ 5.3) และการใส่แร่ 3 ราย (ร้อยละ 2) ผลการรักษามีอัตราการอยู่รอด 5 ปี ร้อยละ 90.9 มีผู้ป่วย 11 ราย (ร้อยละ 7.3) เกิดการกลับเป็นซ้ำ และเมื่อวิเคราะห์ตัวแปรแบบ multivariate analysis พบการที่ผู้ป่วยมีอายุน้อยกว่า 35 ปี กับลักษณะทางพยาธิสภาพเป็นแบบ non-squamous cell carcinoma เป็นปัจจัยพยากรณ์โรคที่มีนัยสำคัญทางสถิติ

สรุป: ผู้ป่วยมะเร็งปากมดลูก ที่มีการกระจายเข้าไปลึกในชั้นสโตรมาของปากมดลูก และ/หรือ กระจายเข้าทางเดินน้ำเหลืองและหลอดเลือด โดยที่ต่อมน้ำเหลืองปกติ มีผลการรักษาที่ดี และพบว่าอายุที่น้อย และพยาธิสภาพ แบบ non-squamous cell carcinoma เป็นปัจจัยพยากรณ์โรคที่มีนัยสำคัญทางสถิติ