# Role of Adjuvant Radiotherapy after Radical Hysterectomy in Node-Negative Stage IB-IIA Cervical Cancer with Intermediate Risk Factors

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***Objective:*** *To assess the benefit of adjuvant radiotherapy after radical hysterectomy in node-negative FIGO stage IB-IIA cervical cancer patients with intermediate risk factors.*
***Material and Method:*** *Medical records of FIGO stage IB-IIA cervical cancer patients who underwent radical hysterectomy at Rajavithi Hospital between January 2000 and December 2007 with negative pelvic node were reviewed. Of the 573 node-negative stage IB-IIA cervical cancer patients, 115 had at least one of the intermediate risk factors; 18 cases received adjuvant radiotherapy (RT group) while 97 patients did not receive (non RT group). Recurrence-free survival and complications of combined treatment of each group were investigated.*
***Results:*** *The median follow-up period was 62.5 months (range 5-119 months). Of the 115 patients with any of the intermediate risk factors, 56 (48.7%) had single intermediate risk factor and 59 (51.3%) had two or more intermediate risk factors. Sixteen patients (13.9%) developed recurrence, 6 at the locoregional site, 5 at the distant sites and 5 at synchronous sites. Eleven patients (18.6%) who had two or more intermediate risk factors developed recurrences. In the RT group, 3 patients (20.0%) developed recurrences whereas 8 patients (18.2%) in the non RT group developed recurrences ($p = 0.574$). The 5-year recurrence free survival rates in patients with two or more risk factors received adjuvant radiotherapy and those without adjuvant radiotherapy were 77.8% and 83.0%, respectively ($p = 0.904$). No locoregional recurrence occurred in patients who received adjuvant radiotherapy. Three patients had treatment related complications (2 with leg lymphedema and 1 with radiation proctitis).*
***Conclusion:*** *Postoperative radiotherapy in node-negative stage IB-IIA cervical cancer patients with intermediate risk factors reduced only the incidence of locoregional recurrence. Distant recurrence was the major pattern of treatment failure after adjuvant radiotherapy.*

***Keywords:*** *Cervical cancer, Radical hysterectomy, Negative lymph node, Intermediate risks, Adjuvant radiotherapy*

***J Med Assoc Thai 2012; 95 (Suppl. 3): S117-S124***
***Full text. e-Journal:*** *http://www.jmat.mat.or.th*

Cervical cancer is the second most common cancer among women in Thailand[1]. Radical hysterectomy and pelvic lymphadenectomy is the optional effective treatment of early stage cervical cancer (FIGO IB-IIA). The 5-year disease-free survival rates range from 80 to 92%[2,3]. However, recurrence of disease will develop in 10-20% of patients with poor clinicopathologic risk factors[4]. Adjuvant concurrent chemoradiation is usually recommended in patients who had high risk factors for recurrence, *i.e.* lymph node metastases, parametrial involvement, and positive surgical margins[5].

Some investigators proposed to use adjuvant radiotherapy(RT) in patients who had intermediate risk factors for recurrence; *i.e.* large tumor size (TS), lymphovascular space invasion (LVSI) and deep cervical stromal invasion (DSI)[6-10]. Most of these studies showed that adjuvant radiotherapy significantly reduced local relapse[10,11], but its impact on survival improvement was controversial and depended on selection criteria used in each study[10-13]. However, patients treated with combined modalities may be more likely to develop serious complications[13], identification of those patients most

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likely to benefit is essential.

The main objective of this retrospective study was to evaluate the benefit of adjuvant radiotherapy in node-negative stage IB-IIA cervical cancer with intermediate risk factors.

**Material and Method**

Between January 2000 and December 2007, 685 FIGO stage IB-IIA cervical cancer patients were treated by radical hysterectomy with lymphadenectomy at Rajavithi Hospital, 112 had pelvic and/or paraaortic lymph nodes metastases and underwent adjuvant postoperative radiotherapy. Medical records of 573 node-negative cervical cancer patients were retrospectively reviewed. The present study protocol was approved by the Ethical Committee of Rajavithi Hospital. Patients with any of the following conditions such as (1) unusual histologic types (*e.g.*, neuro-endocrine carcinoma, lymphoma and sarcoma (n = 52)), (2) history of pre-operative radiotherapy and chemotherapy (n = 83), (3) positive for high risk of recurrence (parametrial involvement and positive surgical margins (n = 125)), (4) no any intermediate risk factor (n = 175) and (5) patients had no pathological reviewed (n = 23) were excluded. The remaining 115 patients with any intermediate risk factors were analyzed.

All patients underwent clinical staging with pelvic examination preoperatively under anesthesia (EUA). Tumors were staged according to the International Federations of Gynecology and Obstetrics (FIGO) staging system of the uterine cervix 1994. The clinical tumor diameter was assessed by inspection and palpation. Large tumor size was considered $\geq$ 4 cm. Pathologic slides were reviewed by only one of the authors (YM) and histologic variables were confirmed. Depth of cervical stromal invasion was measured from the base of the surface epithelium to the deepest malignant cells. Stromal invasion was divided into superficial (inner third), mid (middle third) and deep (outer third) levels. LVSI was considered to be present only if viable tumor cells were present inside an endothelium-lined space within an area of stroma of the uterine cervix. Presence of uterine corpus invasion was defined pathologically as a tumor extending over the histologic internal os and invading the endometrium and/or myometrium of the uterine corpus. Patients with 2 or more intermediate risk factors for recurrence; according to the first pathological report, received adjuvant radiotherapy. Patients with evidence of only uterine corpus invasion was not considered for adjuvant treatment.

The whole pelvis radiotherapy consisting of external-beam irradiation of 50 Gy was 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, 5 fractions per week. High-dose rate brachytherapy using vaginal colpostat or cylinder with Iridium-192 source was also given for all patients. The usual dose per fraction prescribed at 0.5 cm depth from vaginal stump was 6 Gy given in 3 fractions.

All patients were scheduled for follow-up after complete treatments by physical examination and conventional Papanicolaou smear every 3 months for the first year, every 4 months for the second year, every 6 months until the fifth year and then every year thereafter. Chest radiography were per-formed annually. Recurrence was defined either by pathological proof of recurrence or by imaging study showing regrowth of the tumor or enlargement of lymph nodes. Recurrences were classified as locoregional group (vagina and pelvis) and distant group (extrapelvic lymph node and non-node metastases (*e.g.* lung, bone, brain or liver)).

Recurrence-free survival was calculated from the date of surgical treatment to the date of recurrence or the date of last follow-up. Overall survival was calculated from the date of surgical treatment until death or the date of last contact.

Statistical analysis of the data was carried out by SPSS for windows program (version 11.5). Clinical variables were compared using the Chi-square and Fisher's exact test. The differences were judged significant at p-value of $< 0.05$. Association was expressed in term of odds ratio and 95% confidence intervals. The recurrence-free survival and overall survival distributions were calculated by the Kaplan-Meier method. The significance of survival was compared by log-rank test. Multivariable analysis was performed using the Cox proportional hazards regression model. The stability of the model was certified by using the likelihood ratio step-forward and step-backward selection methods.

**Results**

The characteristics of 115 node-negative FIGO stage IB-IIA cervical cancer with intermediate risk factors patients are summarized in Table 1. The mean age of the patients at diagnosis was 45.45 years (SD 7.83). The median parity was 3 times (range 1-7 times). The mean body mass index was 24.2 kg/m$^2$ (SD 3.96).

Most patients had stage IB1 disease (76.5%) and squamous cell carcinoma histologic type (67.8%). All 115 patients underwent radical hysterectomy and pelvic lymphadenectomy. The median number of removed pelvic lymph nodes was 20 nodes (range 7-48 nodes). The median follow-up period of surviving patients was 62.5 months (range 5-119 months). The 5-year recurrence-free survival and overall survival rates for all patients were 87.8% and 86.1%, respectively.

Fifty-six patients (48.7%) had single intermediate risk factor, 43 patients (37.4%) had two factors and 16 patients (13.9%) had all three factors. The most frequent single intermediate-risk factor was positive LVSI (44.6%), whereas as positive LVSI and DSI (74.4%) are the most frequent combination. Fifteen patients with two or more risk factors (25.4%) received radiotherapy while 44 patients (74.6%) did not receive (Table 2).

Of the 115 patients, 16 (13.9%) developed recurrence, 6 at locoregional sites, 5 at the distant sites and 5 at synchronous sites. Five patients (8.9%) who had single intermediate risk factor developed recurrence. In the patients who had two or more risk factors, 3 of 15 patients (20.0%) in the RT group developed recurrence whereas 8 of 44 patients (18.2%) in non RT group had recurrence. Association between adjuvant radiotherapy and recurrence of stage IB-IIA cervical cancer with two or more intermediate risk factors is summarized in Table 2.

Six patients (6.2%) in the non RT group developed locoregional recurrence, 4 died from the disease. The patients in the RT group had no incidence of local failure. Ten patients who had distant $\pm$ locoregional recurrence were treated by radiotherapy (n = 4), combined modalities (chemotherapy and radiotherapy) (n = 5) and palliative treatment (n = 1), but 7 patients died from the disease. Three patients in the RT group had treatment related complication (2 lymphedema of leg and 1 radiation proctitis). The 5-year recurrence free survival rates in patients with two or more two risk factors who received adjuvant radiotherapy and who did not receive were 77.8% and 83.0%, respectively (p = 0.904) (Fig. 1). Characteristics of all patients with cancer recurrence are shown in Table 3.

## Discussion

Most of patients with early stage cervical cancer are treated with radical hysterectomy and systematic lymphadenectomy[2-4]. Surgico-pathological information helps guide adjuvant treatment. Delgado et al[9] proposed separate intermediate and high risk factors for recurrence based on a Gynecologic Oncology Group (GOG) clinico-pathological study. These definitions had become generally accepted and incorporated into the design of both prospective trials and retrospective reports, but strictly indications for adjuvant radiotherapy in node-negative group that outweigh hazard of therapy are not defined.

In the present study, of 115 patients, 56 (48.7%) had single pathological intermediate risk factor while 59 (51.5%) had two or more risk factors. Sixteen (13.9%) of the 115 patients with any risk factors developed recurrences (single risk factor (n = 5), two or more risk factors (n = 11)). Five of these patients who had single risk factor died from locoregional recurrence (n = 2) and synchronous locoregional and distant recurrence (n = 3). It is postulated that these recurrence were the result of subclinical locoregional disease or pelvic node positive (inadequate number of lymph node obtained from pelvic lymphadenectomy). In order to evaluate benefit of adjuvant radiotherapy in patients with two or more intermediate risk factors , these patients were divided into 2 groups. The first group (15 patients) received adjuvant RT and the second group (44 patients) no adjuvant RT.

Recurrence occurred in the RT and NRT group in the present study was not significant difference (20% and 18.2%, respectively) (p = 0.574). But those in RT and NRT group in Sedlis et al's study[10] was significant difference (15% and 28%, respectively) (p = 0.008). However, more complications were reported in the RT group compared with NRT group in their study such as grade 3-4 urologic complications (3.1%: 1.4%),

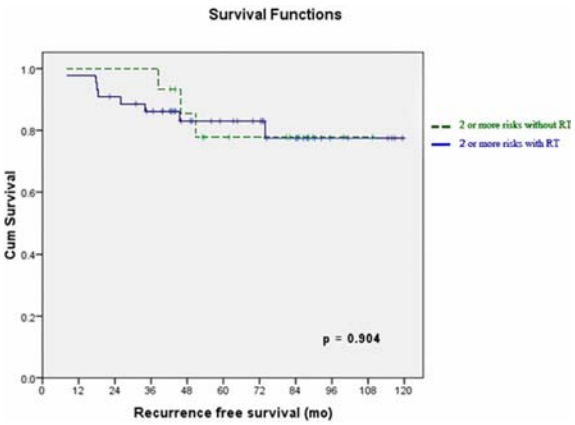


**Fig. 1** Recurrence-free survival curve of node-negative stage IB-IIA cervical cancer patients with 2 or more intermediate risk factors interval by adjuvant radiotherapy

**Table 1.** Clinical characteristics of intermediate risk factors (n=115)

| Characteristics | Total | NRT | RT | p-value |
|---|---|---|---|---|
| Patient (n) | 115 | 97 | 18 | |
| Age | | | | 0.433 |
| < 50 years | 79 | 68 | 11 | |
| ≥ 50 years | 36 | 29 | 7 | |
| FIGO stage | | | | < 0.001 |
| IB1 | 88 | 82 | 6 | |
| IB2 | 22 | 12 | 10 | |
| IIA | 5 | 3 | 2 | |
| Histology | | | | 0.839 |
| Squamous cell carcinoma | 78 | 65 | 13 | |
| Adenocarcinoma | 32 | 28 | 4 | |
| Adenosquamous carcinoma | 5 | 4 | 1 | |
| Grade | | | | 0.965 |
| Well differentiated | 33 | 28 | 5 | |
| Moderate differentiated | 74 | 62 | 12 | |
| Poorly differentiated | 8 | 7 | 1 | |
| Tumor size | | | | 0.003 |
| < 4 cm | 80 | 73 | 7 | |
| ≥ 4 cm | 35 | 24 | 11 | |
| Depth of cervical stromal invasion | | | | 0.103 |
| < 10 mm | 30 | 28 | 2 | |
| ≥ 10 mm | 85 | 69 | 16 | |
| Level of cervical stromal invasion | | | | 0.158 |
| Superficial | 14 | 13 | 1 | |
| Mid | 20 | 19 | 1 | |
| Deep | 81 | 65 | 16 | |
| Lymphovascular invasion | | | | 0.003 |
| Negative | 41 | 40 | 1 | |
| Positive | 74 | 57 | 17 | |
| Uterine corpus invasion | | | | 0.002 |
| Negative | 98 | 87 | 11 | |
| Positive | 17 | 10 | 7 | |
| Risk factors | | | | |
| One risk | 56 | 54 | 2 | < 0.001 |
| DSI | 23 | 23 | 0 | |
| TS | 8 | 8 | 0 | |
| LVSI | 25 | 23 | 2 | |
| Two risks | 43 | 38 | 5 | < 0.001 |
| LVSI + TS | 1 | 1 | 0 | |
| LVSI + DSI | 32 | 28 | 4 | |
| DSI + TS | 10 | 9 | 1 | |
| Three risks | 16 | 6 | 10 | < 0.001 |

NRT = No adjuvant radiotherapy, RT= Adjuvant radiotherapy, DSI = Deep cervical stromal invasion, TS = Large tumor size, LVSI = Lymph-vascular space invasion

gastrointestinal complication (3.1%: 0.8%) and myelosuppression (2.3%: 0.7%), respectively, while only 3 cases in RT group had complication (2 lymphedema of leg and 1 radiation proctitis).

Ryu et al[14] also reported the significant difference of 3 year recurrence- free survival rate among no further treatment, RT and chemoradiation (CRT) group (67.5%, 90% and 97.5%, respectively) ($p < 0.05$) in cervical cancer patients with intermediate risk factors. But their complications were not significantly different between RT and CRT groups (6.1% and 13.4%, respectively) ($p > 0.05$)

**Table 2.** Cervical cancer recurrence and survival (n = 115)

| Characteristics | Total | NRT | RT | p-value |
|---|---|---|---|---|
| Patient (n) | 115 | 97 | 18 | |
| Recurrence (n, (%)) | 16 (13.9) | 12 (12.4) | 4 (22.2) | 0.222* |
| Locoregional | 6 (37.5) | 6 (50.0) | 0 | |
| Vagina | 3 (18.8) | 3 (25.0) | 0 | |
| Pelvis | 3 (18.8) | 3 (25.0) | 0 | |
| Distant | 5 (31.3) | 2 (16.7) | 3 (75.0) | |
| Para-aortic lymph node | 2 (12.5) | 1 (6.3) | 1 (25.0) | |
| Non-lymph node | 3 (18.8) | 1 (6.3) | 2 (50.0) | |
| Combined distant +locoregional | 5 (31.3) | 4 (33.3) | 1 (25.0) | |
| Pelvis+ non-LN extrapelvis | 2 (12.5) | 2 (16.7) | 1 (25.0) | |
| Pelvis+vagina+para-aortic LN | 3 (18.8) | 2 (16.7) | 0 | |
| Two or more intermediate risk factors (n) | 59 | 44 | 15 | |
| Recurrence found in 2 or more intermediate risk factors (n, (%)) | 11 (18.6) | 8 (18.2) | 3 (20.0) | 0.574** |
| Locoregional | 3 (27.3) | 3 (37.5) | 0 | |
| Vagina | 2 (18.2) | 2 (25.0) | 0 | |
| Pelvis | 1 (9.1) | 1 (12.5) | 0 | |
| Distant | 5 (45.5) | 2 (25.0) | 3 (100) | |
| Para-aortic lymph node | 2 (18.2) | 1 (12.5) | 1 (33.3) | |
| Non-lymph node | 3 (27.3) | 1 (12.5) | 2 (66.7) | |
| Combined distant +locoregional | 3 (27.3) | 3 (37.5) | 0 | |
| Pelvis+non LN extrapelvis | 1 (9.1) | 1 (12.5) | 0 | |
| Pelvis+vagina+para-aortic LN. | 2 (18.2) | 2 (25.0) | 0 | |
| Survival (%) | | | | |
| 5-yr OS in 1 risk | | 88.2 | 85.6 | 0.235 |
| 5-yr OS in $\geq$ 2 risks | | 85.7 | 93.8 | 0.632 |
| 5-yr RFS in 1 risk | | 88.4 | 83.9 | 0.347 |
| 5-yr RFS in $\geq$ 2 risks | | 88.3 | 77.8 | 0.904 |

* Odds ratio = 0.494 (95% CI = 0.139 to 1.751), Fisher's Exact Test, p = 0.222

** Odds ratio = 1.125 (95% CI = 0.256 to 4.937), Fisher's Exact Test, p = 0.574

NRT = No adjuvant radiotherapy, RT = Adjuvant radiotherapy, LN = Lymph node, OS = Overall survival, RFS = Recurrence-free survival

But Lee et al[15] and Hosaka et al[16] reported the non significant difference of disease free survival rate in early stage cervical cancer patients (FIGO IB-IIA) with immediate risk factors who received RT and chemotherapy (CT) after radical hysterectomy and pelvic lymphadenectomy. However, they had no cases of NRT in their studies[15,16].

Postoperative CRT gave higher recurrent free survival than that of postoperative RT group in cervical cancer patients with intermediate risk factors.

However, hematologic toxicities was more common in the CRT group compared with the RT group ($p < 0.01$)[17].

The strength of the present study was the single institute investigation and the pathological slides reviewed by the gynecologic pathologist. However the present results must be cautiously interpreted because of a retrospective nature and small sample size of the present study. Moreover, LVSI were reported only as positive or negative results and some of patients had an inadequate number of lymph node dissection.

In conclusion, postoperative RT reduced only the incidence of locoregional relapse in node-negative stage IB-IIA cervical cancer patients with intermediate risk factors. The distant recurrence was the major pattern of treatment failure after adjuvant radiotherapy. Prospective clinical trial of the treatment outcomes of adjuvant treatment among chemotherapy, radiotherapy and chemoradiation should be conducted in the future.

**Potential conflicts of interest**

None.

**Table 3.** Characteristics of patients with recurrence

| No. | Stage | Pathology | No. LN | Risk | RT | Sites |
|---|---|---|---|---|---|---|
| 1 | IB1 | Squamous | 7 | DSI | No | Mixed |
| 2 | I1B | Squamous | 11 | LVSI | No | Locoregional |
| 3 | I1B | Adenocarcinoma | 16 | LVSI | Yes | Mixed |
| 4 | I1B | Squamous | 27 | TS | No | Locoregional |
| 5 | I1B | Adenocarcinoma | 19 | DSI | No | Locoregional |
| 6 | I1B | Adenocarcinoma | 15 | DSI + LVSI | No | Mixed |
| 7 | I1B | Squamous | 20 | DSI + TS | No | Mixed |
| 8 | I1B | Adenocarcinoma | 22 | DSI + LVSI | No | Mixed |
| 9 | I1B | Squamous | 26 | DSI + LVSI | No | Locoregional |
| 10 | I1B | Adenocarcinoma | 16 | DSI + LVSI | No | Locoregional |
| 11 | IB2 | Squamous | 19 | DSI + TS | No | Locoregional |
| 12 | IB2 | Adenocarcinoma | 21 | DSI + LVSI | Yes | Distant |
| 13 | IB2 | Squamous | 19 | LVSI + TS | No | Distant |
| 14 | IB2 | Squamous | 23 | LVSI + TS | Yes | Distant |
| 15 | IB2 | Adenocarcinoma | 30 | LVSI + TS | No | Distant |
| 16 | IIA | Squamous | 41 | LVSI + TS | Yes | Distant |

No. LN = Number of pelvic lymph nodes, RT = Adjuvant radiotherapy, DSI = Deep cervical stromal invasion, TS = Large tumor size, LVSI = Lymph-vascular space invasion

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## บทบาทของรังสีรักษาหลังผ่าตัดมดลูกแบบถอนรากถอนโคนในผู้ป่วยมะเร็งปากมดลูกระยะ IB–IIA ที่ไม่มีการกระจายไปต่อมน้ำเหลือง ซึ่งมีปัจจัยเสี่ยงปานกลางต่อการเกิดการกลับเป็นซ้ำ

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***วัตถุประสงค์**: เพื่อประเมินผลของการให้รังสีรักษาหลังผ่าตัดมดลูกแบบถอนรากถอนโคน ในผู้ป่วยมะเร็งปากมดลูกระยะ IB-IIA ที่ไม่มีการกระจายไปต่อมน้ำเหลือง ที่มีปัจจัยเสี่ยงปานกลางต่อการกลับเป็นซ้ำ*

***วัสดุและวิธีการ**: ทบทวนเวชระเบียนของผู้ป่วยมะเร็งปากมดลูกระยะ IB-IIA ที่ได้รับการผ่าตัดมดลูกแบบถอนรากถอนโคนและไม่พบการกระจายไปต่อมน้ำเหลืองระหว่างปี พ.ศ. 2543-2550 ในโรงพยาบาลราชวิถี จำนวนทั้งหมด 573 ราย พบผู้ป่วยที่มีปัจจัยเสี่ยงปานกลางต่อการกลับเป็นซ้ำอย่างน้อย 1 ชนิด จำนวน 115 ราย โดยผู้ป่วยจำนวน 18 ราย ได้รับรังสีรักษาหลังการผ่าตัด ขณะที่ 97 ราย ไม่ได้รับรังสีรักษา ทำการวิเคราะห์อัตราการปลอดโรค ที่ระยะ 5 ปีและภาวะแทรกซ้อนที่เกิดขึ้นหลังการรักษา*

***ผลการศึกษา**: ระยะเวลาในการติดตามผลโดยเฉลี่ย 62.5 เดือน (ช่วงเวลา 5-119 เดือน). ในผู้ป่วยจำนวน 115 รายที่มีปัจจัยเสี่ยงปานกลางต่อการกลับเป็นซ้ำ พบว่า 56 ราย(ร้อยละ 48.7) มีปัจจัยเสี่ยง 1 ชนิด และ 59 ราย(ร้อยละ 51.3) มีปัจจัยเสี่ยง 2ชนิดขึ้นไป ผู้ป่วยจำนวน 16 ราย(ร้อยละ 13.9) มีการกลับเป็นซ้ำของโรค โดยที่ 6 ราย เกิดขึ้นในช่องเชิงกราน 5 ราย เกิดขึ้นนอกช่องเชิงกราน และ 5 ราย เกิดการกลับเป็นซ้ำทั้งในช่องเชิงกรานและนอกช่องเชิงกราน ผู้ป่วย 11 ราย ร้อยละ 18.6 ซึ่งมีปัจจัยเสี่ยงปานกลางตั้งแต่ 2 ปัจจัยขึ้นไป มีการกลับเป็นซ้ำของโรค โดยที่ 3 ราย เกิดในกลุ่มที่ได้รับรังสีหลังการผ่าตัด ในขณะที่ 8 ราย เกิดในกลุ่มที่ไม่ได้รับรังสีรักษาหลังการผ่าตัด พบว่าบทบาทรังสีรักษาในการลดการกลับเป็นซ้ำในทั้ง 2 กลุ่มไม่แตกต่างกัน ($p = 0.904$ ) อัตราการปลอดโรคที่ระยะ 5 ปี ในผู้ป่วยที่มีปัจจัยเสี่ยงปานกลางตั้งแต่ 2 ปัจจัยขึ้นไปที่ได้รับรังสีรักษา และที่ไม่ได้รับรังสีรักษาหลังการผ่าตัด เท่ากับ ร้อยละ 77.8 และ ร้อยละ 83.0 ตามลำดับ และพบว่าไม่มีการกลับเป็นซ้ำเฉพาะที่ (ในช่องเชิงกราน)เลยในผู้ป่วยที่ได้รับรังสีหลังการผ่าตัด*

***สรุป**: การให้รังสีรักษาหลังการผ่าตัดช่วยลดการกลับเป็นซ้ำเฉพาะที่ในผู้ป่วยมะเร็งปากมดลูกระยะแรกที่ไม่มีการกระจายไปต่อมน้ำเหลืองซึ่งมีปัจจัยเสี่ยงต่อการกลับเป็นซ้ำเท่านั้น ความล้มเหลวของการรักษาที่พบในการให้รังสีหลังการผ่าตัดมีพบจากกรณีการกลับเป็นซ้ำนอกช่องเชิงกราน*