# THE ROLE OF ADJUVANT RADIOTHERAPY IN ENDOMETRIAL

## *CANCER : RESULTS IN PATIENTS WITH INTERMEDIATE RISK*

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## ABSTRACT

**Purpose:** To determine the results of adjuvant radiotherapy in patients classified as intermediate risk after surgical staging for endometrioid adenocarcinoma of endometrial cancer.

**Method:** Between 1998 and 2005, 85 patients with FIGO stage IA-IIA,B disease received adjuvant radiotherapy following surgical staging for endometrioid adenocarcinoma at Radiation Oncology Unit, Chiang Mai University. Eight patients received postoperative pelvis external radiotherapy (WP) and fifty patients received postoperative pelvis external radiotherapy and vaginal brachytherapy (WP+B) and twenty-seven patients received vaginal brachytherapy (B) alone. Fifty-three patients were classified as high intermediate risk disease and thirty-two patients have low intermediate risk disease. Median follow-up was 27 months(range 21-33 months). The end point were pattern of failure (locoregional recurrence, distant metastasis, or both), 2-year disease free survival (DFS) and 2-year overall survival (OS).

**Results:** Seven (8.2%) patients developed a relapse. The overall loco-regional failure rate and distant metastatic failure rates were 2.3% and 5.9%, respectively. The 2-year disease-free survival and 2-year overall survival for high intermediate risk were 61% and 53%, respectively. There was no difference in 2-year overall survival among patients classified as high intermediate risk versus low intermediate risk (53% vs. 58%, log-rank test, p=0.26) or in terms of radiation treatment received among external pelvic radiotherapy plus vaginal brachytherapy versus vaginal brachytherapy alone (60% vs. 60%, log-rank test, p=0.4).

**Conclusion:** Different type of adjuvant radiotherapy were not statistically significant to 2-year disease free survival and 2-year overall survival with high intermediate risk endometrial adenocarcinoma. High intermediate risk group had trend to decrease in 2-year disease free survival and 2-year overall survival than low intermediate risk group.

## INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the United States with an estimated 39,080 new cases and 7,400 deaths in 2007 (1). It was the third common gynecologic malignancy detected at devision of gynecologic oncology,Faculty of Medicine, Maharaj Nakorn Chiang Mai Hospital. In the 2006, there were 84 patients (11.5%) with endometrial cancer who treated in Maharaj Nakorn Chiang Mai Hospital (2). The majority of patients (80%) of endometrial cancers were diagnosed of early stage (International Federation of Gynaecology and Obstetrics [FIGO] stage I. The standard treatment for endometrial cancer is surgery including an exploratory laparotomy, total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO), peritoneal cytology, pelvic and para-aortic lymphadenectomy (3). If risk factors are present, that is, myometrial invasion to 50% or more of the myometrial width and/or grade 2 or 3 histology, adjuvant radiotherapy (RT) is indicated to reduce the risk of pelvic relapse. Adjuvant radiotherapy for patients with surgical stage I and II disease remains controversial. Three randomized trials have demonstrated a benefit for pelvic control with the addition of external radiotherapy without a clear benefit to survival (4-6). A phase III study by the Gynecologic Oncology Group (GOG 99) randomized patients with the surgical stage IB, IC, II (occult) disease to observation or pelvic external radiotherapy (4). The incidence of recurrence was higher for patients in the observation arm (12%) than in pelvic radiotherapy arm (4%),p=0.007, though no reported difference in survival was noted. With the subsequent publication of the Postoperative Radiotherapy in Endometrial Carcinoma (PORTEC) study randomized patients with the surgical stage I (grade I with deep(≥50%) myometrial invasion; grade 2 with any invasion; or grade 3 with superficial (<50%) invasion) to observation or pelvic radiotherapy (7). The 5-year actuarial locoregional recurrence rates was 4% in radiotherapy group and 14% in the observation group($p<0.001$). the actuarial 5-year overall survival rates were similar in the two groups. Vaginal brachytherapy was not permitted in both studies. A number of groups have reported low vaginal failure rates with vaginal vault brachytherapy alone with limited morbidity (8-11).

Generally, adjuvant RT is recommended for patients with intermediate- and high-risk endometrial cancer following surgery to decrease locoregional recurrences. It is controversial issue about type of adjuvant RT. Three options of RT are commonly employed: vaginal brachytherapy (B), pelvic external beam radiotherapy (WP), or their combinations (WP+B).

Our treatment policy at Radiation Oncology Unit, Faculty of Medicine, Chiang Mai University has evolved over the last 8 years for this group of patients. Earlier in the course of this era, patients were treated with external radiotherapy and vaginal cuff brachytherapy. With subsequent publication of the PORTEC study (7) and GOG 99(4), we have changed in our treatment policy towards pelvic external radiotherapy for patients with intermediate risk endometrial cancer. The purpose of this study is to retrospectively review the results of adjuvant radiotherapy for surgically staged intermediate risk patients.

## RESEARCH QUESTION

What is the pattern of failure in surgical staged intermediate risk endometrial cancer patients with difference type of adjuvant radiotherapy?

## STUDY OBJECTIVES

1. To assess the pattern of failure of whloe pelvis with (WP+B) or without vaginal brachytherapy (WP) or vaginal brachytherapy (B) alone as adjuvant treatment for surgically staged endometrial cancer with intermediate risk patients.

2. To assess the 2-year disease free survival and 2-year overall survival in various type of adjuvant radiotherapy (WP, WP+B, B)

## TYPE OF STUDY

Retrospective study

## METHODS

The clinical records of patients treated with postoperative radiation for intermediate risk endometrial carcinoma fitting the criteria for GOG 99(4) at the Department of Radiation Oncology at Chiang Mai University between 1998 and 2005 were reviewed. All patients underwent surgery included TAH-BSO, peritoneal washing, as well as a pelvic+/-para-aortic lymphadenectomy. All patients had endometrioid adenocarcinoma. Eighty-five patients were eligible to the criteria. The Chiang Mai University Ethical Committee approved this retrospective record review.

Patients were stratified in to either high or low intermediate risk group based on risk factors defined by GOG 99(4). These risk factors for recurrence were defined as: tumor grade 2-3, lymphovascular space invasion and outer half myometrial invasion. Patient with high intermediate risk (HIR) disease were defined as: (1) patients less than 50 years old with all risk factors, (2) patients $\geq$ 50 years old with two risk factors and (3) patients $\geq$ 70 years old with one risk factor. Fifty-three patients were identified at high intermediate risk (HIR) and thirty-two patients were identified with low intermediate risk (LIR).

Postoperative radiotherapy was initiated at 4-6 weeks after surgery. For patients receiving high dose rate vaginal brachytherapy, a Nucletron high dose rate unit with Iridium-192 as the source was used. Various sizes of a

vaginal cylinder or two ovoids were used to fit to vaginal cavity. Patients receiving XRT were treated using either anterior-posterior opposed fields or a four field box technique with megavoltage beams. Eight patients received external radiotherapy, twenty seven patients received vaginal brachytherapy alone and fifty patients received both external radiotherapy and vaginal brachytherapy. The prescription for XRT was 46-50 Gy to the whole pelvis. Daily fractions of 2 Gy was used. If XRT and vaginal brachytherapy were combined, vaginal brachytherapy would add two fractions of 600 cGy at 0.5 cm from surface of applicators. The prescription of vaginal brachytherapy alone was 50 Gy to the upper one third of vagina with various fractionation schemes.

Patients were examined at 3-month intervals for the first two years after treatment, then at 6-month intervals for the next 3 years, then yearly afterward. Some patients were examined by gynecologic oncology staffs after follow up by radiation oncology staffs for the first two times after complete radiation therapy.

Time to recurrence was calculated from the date of surgery to the time of histological confirmation of recurrence. Time to distant metastasis was calculated from the date of surgery to the time of clinical or radiological confirmation. Disease free and overall survivals were calculated using Kaplan-Meier estimates and calculated from the date of diagnosis of recurrence. The log-rank test was used to compare the survival curves. Disease free survival was calculated from the date of completion of primary treatment to the date of recurrence. Overall survival was defined from the date of completion of primary treatment with failure defined as death irrespective of the cause and censoring at the date of last contact for patient still alive. Statistical analysis was performed using the SPSS software version 13.0.

## RESULTS

Median age of patient at diagnosis was 58 years (range 32-86 years). Patient and tumor characteristics at the time at initial treatment are listed in Table 1.Median follow-up for all patients was 27 months(range 21-33 months). Overall, there were seven (8.2%) patients that developed a relapse. The overall loco-regional failure rate and distant metastatic failure rates were 2.3% and 5.9%, respectively. For patients treated with pelvic radiotherapy and vaginal brachytherapy, two patients developed an isolated upper vaginal recurrence and two developed extra-pelvic disease (bone and lung). Three patients that received pelvic radiotherapy alone developed extra-pelvic metastatic disease. The characteristics and sites of failure stratified by

adjuvant radiotherapy modality are shown in table 2. Among the patients that subsequently developed recurrent disease, five patients were initially classified as high intermediate risk group according to GOG 99(4). Two patients with low intermediate risk group that failed initial combined pelvic radiotherapy plus vaginal brachytherapy and pelvic radiotherapy alone had lung and abdominal metastasis.

The 2-year disease free and overall survivals for high intermediate risk were 61% and 53%, respectively. There were no difference in 2-year disease free and overall survival with respect to risk factors (p=0.25 and 0.26) (Fig 1a-1b). Among 50 patients that received external radiotherapy with brachytherapy, thirty patients were classified as having high intermediate risk disease, while 20 patients had low intermediate risk disease. Among 27 patients that received vaginal brachytherapy alone, 17 patients had HIR disease and 10 had LIR disease. The patients that received external radiotherapy alone, 3 patients has HIR disease and 5 had LIR disease. There was no difference in 2-year overall survival among patients with HIR and LIR disease that received vaginal brachytherapy alone (55% vs. 39%, log-rank test, p=0.87) (Fig 2a). High intermediate risk patients that received brachytherapy vs. brachytherapy and XRT had no difference in 2-year overall survival (60% vs. 60%, log-rank test, p=0.4) (Fig 3a-3b). The median time to recurrence for all patients was 6 months (range 5-12 months).

**Table 1** Characteristics of 85 patients with intermediate risk endometrial cancer

| characteristic | Number of patients (%) |
|---|---|
| **Age** | |
| <50 | 13 (15) |
| 50-69 | 59 (70) |
| ≥70 | 13 (15) |
| **Stage** | |
| IB | 17 (20) |
| IC | 47 (55) |
| IIA | 9 (11) |
| IIB | 12 (14) |
| **Grade** | |
| 1 | 32 (38) |
| 2 | 33 (39) |
| 3 | 20 (23) |
| **Lymphovascular space invasion** | |
| Yes | 36 (49) |
| No | 38 (51) |
| **Depth of myometrial invasion** | |
| <50% | 29 (35) |
| ≥50% | 55 (65) |
| **High intermediate risk (GOG99 criteria)** | |
| Yes | 53 (62) |
| No | 32 (38) |
| **Type of treatment** | |
| WP | 8 (10) |
| WP+ B | 50 (59) |
| Brachytherapy (B)alone | 27 (31) |
| **Type of surgery** | |
| Complete staging | 69 (81) |
| Incomplete staging | 16 (19) |

Some pathological characteristics were missing due to different treatment center.

Table 2. Characteristics of the seven patients with developed recurrence stratified by treatment modality

| RT | Age (years) | Stage | Grade | LVSI | Depth of invasion | Disease status | Time to recurrence (months) | Site of recurrence |
|---|---|---|---|---|---|---|---|---|
| WP/brachy | | | | | | | | |
| 1 | 64 | IC | 3 | No | ≥50% | DOI | 11 | Upper vagina |
| 2 | 68 | IC | 1 | Yes | ≥50% | AWD | 6 | Upper vagina |
| 3 | 39 | IIB | 2 | Yes | <50% | DOD | 11 | Lung |
| 4 | 63 | IIA | 2 | No | ≥50% | AWD | 12 | Bone |
| WP | | | | | | | | |
| 5 | 49 | IC | 3 | No | ≥50% | DOD | 6 | Abdomen |
| 6 | 56 | IC | 2 | No | ≥50% | DOD | 5 | Bone,abdomen,subcutaneous |
| 7 | 60 | IIB | 3 | Yes | ≥50% | DOD | 5 | Lung |

Disease status: DOD, died of disease ; AWD, alive with disease; DOI, died of intercurrent disease; LVSI, lympovascular space invasion

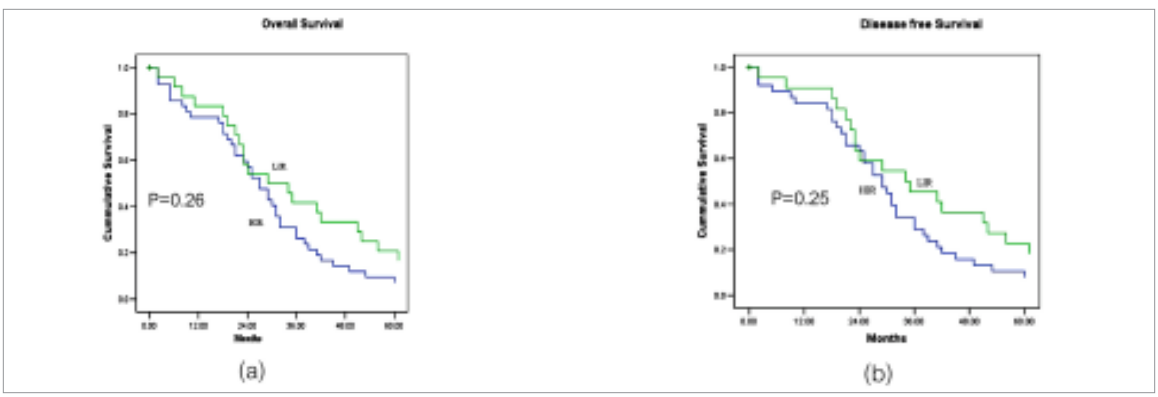


Fig1. Overall survival (a) and Disease free survival (b) of all patients stratified by LIR(n=32) and HIR(n=53)

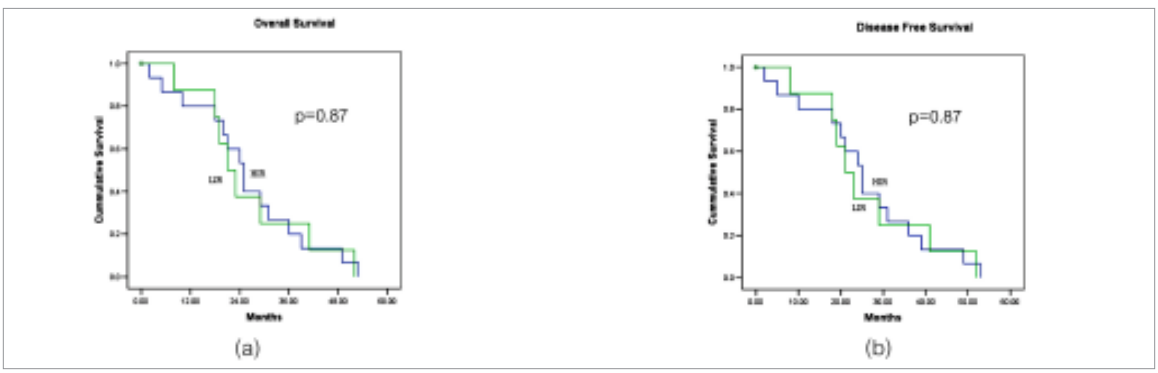


Fig 2. Overall survival (a) and Disease free survival (b) among patients that received brachytherapy alone, stratified by HIR(n=53) and LIR(n=32)


Fig 3. Overall survival (a) and disease free survival (b) for patients classified as high intermediate risk (HIR) stratified by radiation modality (brachytherapy alone,n=17, and brachytherapy plus external radiotherapy, n=30)

Only one patient had grade 3 rectal toxicity after vaginal brachytherapy alone, no severe gastrointestinal toxicity was found to be related to external beam pelvic radiotherapy.

## DISCUSSION

Adjuvant treatment for early stage endometrial cancer remains controversial. Three randomized studies in these patients have demonstrated decrease rates of pelvic relapse after radiotherapy without a clear benefit of survival. In the PORTEC study, patient with stage IB grade 2,3 or stage IC grade 1,2 endometrial cancer were randomized to observation or pelvic radiotherapy after TAH-BSO(7). However, lymphadenectomy was not routinely performed in this study. The 5-year loco-regional recurrence rate was 4% in the radiotherapy group and 14% in the observation group, $p<0.001$. The majority of loco-regional recurrent in POETEC study were the vagina (73%).

In the reported GOG 99 study (4), patients with intermediate risk endometrial adenocarcinoma (stage IB,IC,and IIA,B) were randomized to observation or pelvic radiotherapy after complete surgical staging which included lymphadenectomy. The two-year cumulative incidence of isolated local (pelvic or vaginal) recurrence was 8.9% with no adjuvant therapy vs. 1.6% with adjuvant pelvic radiotherapy (4). The incidence of isolated vaginal recurrence in GOG 99 was 72% of total loco-regional recurrence. There was no difference in overall survival observed in either study. Vaginal brachytherapy was not offered in either study.

Vaginal brachytherapy alone has been compared with pelvic radiotherapy plus vaginal

cuff brachytherapy in a phase III study that included 540 patients with stage I endometrial cancer. Lymphadenectomy was not performed. Aalders et al. found a 6.9% pelvic failure rate with vaginal brachytherapy alone compared with 1.9% ($p<0.001$) in the addition of pelvic external radiotherapy. There was no difference in 5-year overall survival(12).

Though all of these studies have demonstrated benefit to addition of adjuvant radiotherapy, no overall survival benefit has been demonstrated. The explanation is that patients with isolated local failure can be salvaged with radiotherapy. In a retrospective study by Lin et al., patient with isolated vaginal recurrence treated with external radiotherapy and/or vaginal brachytherapy had a 5-year disease-free survival of 68% (13). Endometrial cancer tends to affect an older population with comorbid illnesses, thus making a survival benefit was difficult to detect. In the PORTEC study, the incidence of overall complications with radiotherapy was 26% versus 4% in the observation arm ($p< 0.0001$)(14). The 5-year actuarial rates of severe (grade 3 or 4) complications were 3% in the radiotherapy arm versus 0% in the control arm. The GOG 99 study reported a statistically significant increasing of frequency and severity of hematological, gastrointestinal, genitourinary, and cutaneous complications with adjuvant radiotherapy($p<0.001$)(4). There were two deaths from bowel complications thought to be related to radiotherapy. Thus, limitation of adjuvant radiotherapy in older population is the morbidity associated with whole pelvic radiotherapy.

Several authors have reported their results with brachytherapy alone in this patient population. In a large retrospective study by Horowitz et al. of 164 surgically staged patients with stage IB, IC, or II endometrial cancer, high dose rate vaginal brachytherapy was found to provide excellent rate of loco-regional control. Their overall failure rate was 8.4% with only three (1.8%) pelvic or vaginal failure(15). From the retrospective review, Jolly et al. found the incidence of pelvic and vaginal failure were 4% after vaginal cuff brachytherapy compared with 2% in GOG 99 (8,4). Late grade 2 toxicity was significantly reduced by the use of vaginal brachytherapy. Solhjem et al. found no pelvic or vaginal recurrence after a median follow-up of 23 months in 100 patients with endometrial cancer who received only vaginal brachytherapy (16). The summary of local recurrence and distant metastasis after vaginal brachytherapy alone is shown in table 3.

Table 3

| Author | Number of patients | Stage | % Isolated Loco-regional recurrence | % Distant metastasis |
|---|---|---|---|---|
| This study | 85 | IB-IIB | 2.3 | 5.9 |
| Lilie (24);2007 | 78 | IA-II | 2 | 7 |
| Chadha (11);1999 | 38 | IBG3-IC | 0 | 8 |
| Fanning(25);2001 | 66 | I-II | 0 | 3 |
| Jolly(8);2005 | 50 | IB-II | 4 | 0 |
| Horowitz(15);2002 | 164 | IB-II | 1.8 | 6 |
| Ng(9);2000 | 77 | IBG3-IC | 10 | 4 |
| Rittenberg(26);2003 | 53 | I | 1.8 | 5.5 |
| Solhjem(16);2005 | 100 | I | 0 | 3 |

This study included patients with lymhadenectomy 81%. Because our center is referral hospital, some patients was operated from other hospital. The results show a low risk of loco-regional recurrence following surgical staging and vaginal brachytherapy.

Prophylactic adjuvant radiotherapy does reduce local recurrence but selective salvage therapy may be just as effective and vaginal brachytherapy may be adequate prophylaxis for local recurrent disease. This issue is being explored prospectively in the current Dutch PORTEC 2 trial which is a multicentre randomized phase III trial comparing the external beam radiotherapy and vaginal brachytherapy. PORTEC 2 trial may be able to answer whether postoperative vaginal brachy-therapy alone is adequate to prevent vaginal relapse with a reduction of treatment-related morbidity and a better quality of life. The trial seems to include patients with one high-risk features(stage IC grade 1 or 2 and age ≥60 years, stage IB grade 3 and age ≥60 years, stage IIA any age grade 1 or 2, stage IIA any age grade 3 with less than half myometrial invasion)

This study was examining the failure patterns with vaginal brachytherapy alone, pelvic radiotherapy alone and combined pelvic radiotherapy plus vaginal brachytherapy in high intermediate risk by GOG 99 criteria. It was difference to GOG 99 criteria, we use depth of myometrial invasion <50% or ≥50%, GOG 99 used outer third myometrial invasion. There was a higher proportion of patients in our analysis that were classified as HIR

compared to GOG 99 (62% vs. 34%,respectively). In GOG 99, the HIR group of patients accounted for two-thirds of the recurrence and two-thirds of cancer related death. Two of the seven patients in our analysis that developed a subsequent recurrence initially were classified as high intermediate risk disease. Though there was no statistically significant difference in disease-free survival between the LIR and HIR subgroups (p=0.25), there was a trend towards decreased DFS with the HIR patients. The limited patient numbers likely precluded any statistical difference from being detect. Though the numbers were low, there was no difference in DFS among patient at HIR that received pelvic and vaginal cuff brachytherapy compared with brachytherapy alone. Pelvic radiotherapy alone can not be analyzed and shown in survival curve due to small number of patients (only three patients). Our results confirm that vaginal brachytherapy alone is adequate local therapy in HIR group and did not result in higher rates of pelvic failure. Adjuvant radiotherapy modality were not effect to DFS and overall survival.

Five patients developed distant metastasic disease (5.8%). In GOG 99, the use of radiotherapy did not appear to have an impact on rate of distant metastases in the no adjuvant treatment versus radiotherapy groups (6.4% vs. 5.3%)(4). Because of the limited number of patients, we did not identify any independent predictors of relapse in our group of patients. Six in seven patients who recurrence and distant metastasis had ≥50% depth of myometrial invasion, five patients were older than 50 years and only one patient had grade 1 endometrioid adenocarcinoma. Five in seven patients were classified as distant recurrence and median time to recurrence was 6 months (range 5-12 months). Risk factors for distant relapse have been described by a number of groups. In a study by Mariani et al., deep myometrial invasion (≥66%) was identified as the most significantly predictive factor of disease related survival, relapse free survival, and distant failure (<0.001)(17). Other risk factors for distant recurrence have been described including lymphovascular invasion, histological grade, cervical stromal invasion, positive lymph nodes, and positive cytology (18-23).

## CONCLUSION

In summary, we conclude that among patients with high intermediate risk endometrial adenocarcinoma, different adjuvant radiotherapy modalities were not statistically significant to improve disease free survival and overall survival. High intermediate risk group had trend to

decrease in DFS and overall survival than low intermediate risk group. For patients with high risk of distant failure, future clinical trials should also examine the role of adjuvant systemic chemotherapy in this group.

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