
GYNAECOLOGY

Outcome of High-Risk Stage IA2 - IIA Cervical Cancer Treated with Radical Hysterectomy and Pelvic Lymphadenectomy

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ABSTRACT

Objective To evaluate the survival and complications of high-risk stage IA2 - IIA cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy.

Design Retrospective descriptive study.

Setting Division of Gynecologic oncology Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University.

Subject 156 patients with FIGO stage IA2 to IIA cervical cancer treated between January 1998 to January 2003, undergoing radical hysterectomy with pelvic lymphadenectomy and had at least one high risk pathological factors.

Intervention Pelvic lymphadenectomy was initially performed followed by radical hysterectomy. Patients with high risk pathological factors were treated with adjuvant radiation with or without concurrent chemotherapy.

Result With median follow up of 26 months, the projected 5-year progression-free survival and overall survival were 80.0% and 93.4% respectively. Treatment-related complication occurred in 15 patients (9.6%), all of these patients received adjuvant radiation. The incidences of lymph node metastasis and parametrial involvement were 18.8% and 11.2% respectively. Tumor recurrence occurred in 12 patients (7.7%) in which 8 of these had lymph node metastasis, the remaining had parametrial invasion.

Conclusion Stage IA2 - IIA cervical cancer patients with high-risk pathological factors had relatively high survival rate with low complication in this setting.

Key word: Stage IA2 - IIA cervical cancer, radical hysterectomy, pelvic lymphadenectomy, survival, complication

Cervical cancer is the most common gynecologic malignancy in developing countries. The standard treatment of early-stage cervical cancer includes either radical hysterectomy or radiation therapy which has been accepted as equally effective in terms of local control and survival. The 5-year disease-free survival for patients with stage IB-IIA cervical cancer treated with radical hysterectomy approaches 90%.⁽¹⁾ However, 10 to 25% of patients will ultimately relapse.^(2,3) Pathological risk factors predicting tumor recurrence include positive lymph nodes, positive parametrium, and positive surgical margins.⁽⁴⁾ The 5-year survival rate of these high-risk patients drops to 40-56% and decreases to less than 5% if recurrence occurs.⁽⁵⁾ Adjuvant radiation therapy has been reported to decrease the incidence of locoregional recurrence with little or no effect on overall survival.⁽⁶⁻⁹⁾ Neoadjuvant chemotherapy is also another alternative for patients with early-stage, cervical cancer with bulky tumor.^(10,11)

At present, concurrent chemoradiation appears to improve survival rates compared with radiation alone in patients found to have high-risk pathological factors after radical hysterectomy.⁽¹²⁾ Accordingly, the treatment guideline in our institute has been changed in the past 5 years, i.e. administering neoadjuvant chemotherapy in case of delayed operation or giving concurrent chemoradiation in high-risk patients after radical hysterectomy. The objective of this study is to evaluate the survival and complications of high-risk early stage cervical cancer patients undergoing radical hysterectomy in our hospital.

Materials and Methods

From January 1998 to January 2003, 561 patients with FIGO stage IA2 to IIA cervical cancer undergoing radical hysterectomy and pelvic lymphadenectomy at the Department of obstetrics and Gynecology, Chiang Mai University Hospital were

retrospectively analyzed. Among these patients, 156 (27.8%) had at least one of the high risk pathological factors that consisted of positive lymph nodes, positive parametrium or positive surgical margins. These 156 patients were evaluated for survival and complications.

The pathology specimens of these patients were evaluated and reported by either one of the two gynecologic pathologists (S.S or S.K.). Histological type, grading of differentiation, depth of cervical stromal invasion, lymph vascular space invasion (LVSI), parametrial infiltration, surgical margin status, and number of positive nodes were recorded.

The operation was carried out with initial pelvic lymphadenectomy followed by radical hysterectomy. In cases of bulky positive pelvic nodes, only pelvic and paraaortic lymph node dissection were performed, and radical hysterectomy was abandoned. It is the policy and agreement between the Gynecologic Oncology Division and Radiation Oncology Division in our hospital to retain the uterus in situ for appropriate radiation treatment. Neoadjuvant chemotherapy with cisplatin was given if the operative schedule was more than 4 weeks after diagnosis. Patients with high risk pathological factors were advised to receive concurrent cisplatin-based chemoradiotherapy. Radiation alone was given in patients who refused chemotherapy, had poor performance status or received treatment before 1999. The radiation usually started within 1 month after surgery.

Adjuvant 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) or four-field box beams; the daily fraction size was 1.8-2 Gy, five fractions per week. The additional 45-60 Gy were given in paraaortic area with the fractionation 1.8-2.0 Gy daily (five fractions per week) when the histology revealed metastasis to

para-aortic lymph node. Patients with positive vaginal margin received intravaginal brachytherapy using a high-dose-rate remote after-loading technique. Brachytherapy was usually given in 2-7 fractions with a total dose of 4-6 Gy/0.5-0.75 cm below the vaginal mucosa. Concurrent chemoradiation was given Cisplatin 75 mg/m² every 3 weeks for 4 cycles regimen in the patients with abandoned radical hysterectomy and patients with high-risk factors after such operation. These patients received intracavitary brachytherapy delivered 40-50 Gy to point A.

Patients were followed regularly after completion of treatment, with a minimal follow-up time of 6 months (6 - 66 months, median 26). During follow-up, treatment failure was defined either by pathological proof of recurrence or by image study showing regrowth of tumor or enlargement of lymph nodes.

The complications and treatment outcome were collected by reviewing the medical record. In cases of loss to follow-up, the patients and her family were contacted by phone or mail to obtain the data.

Statistical analysis of the data was carried out by the SPSS version 10.0 statistical software for window. Survival curves were constructed using the Kaplan-Meier method. The study was conducted under the ethical approval of the Research Ethics Committee of Chiang Mai University Hospital.

Results

The characteristics of all 156 patients are displayed in Table 1. The mean age was 45 years (range 28-71). Approximately 80% of the patients were stage IB1 cervical cancer. The mean tumor size was 2 cm in diameter with a maximum size 6 cm. Of 28 patients with unseen cervical lesion at the time of staging, 26 had stage IB1 and only 2 had stage Ia2. These patients were diagnosed by conization (22) and cervical punch biopsy (4). Squamous cell carcinoma was the most common cell type, accounting for 79.5% followed by adenocarcinoma accounting for 14%.

Pelvic lymphadenectomy followed by radical

hysterectomy which was performed in 135 patients, the remaining 21 patients underwent only pelvic and para-aortic lymph node dissection. The mean number of removed lymph nodes was 29 (range 3 - 56). Twenty-one patients received cisplatin chemotherapy prior to the scheduled operation.

Of the 154 patients who received adjuvant treatment after the operation, 112 (72.8%) received concurrent chemoradiation while 41 (26.3%) received radiation alone. In these 41 patients, brachytherapy was given in 11 patients (26.8%) with only positive vaginal margin. Combination chemotherapy consisting of cisplatin and etoposide for 6 courses was administered in 1 patient with small cell neuroendocrine who had 5 positive pelvic nodes. She is still alive without clinical recurrence for 55 months. Among 2 patients who did not receive adjuvant treatment, 1 patient had only microscopic metastasis to one side of parametrium and no recurrence was detected after 3 years of follow-up. The remaining one refused adjuvant treatment, she had bilateral parametrial microscopic metastasis and still alive well without evidence of tumor recurrence for 34 months.

Table 2 shows pathological risk factors of the 156 patients. Forty-seven patients had more than 1 risk factor. The incidence of lymph node metastasis and parametrial involvement in our 561 patients were 18.8% and 11.2% respectively.

Treatment-related complications occurred in 15 patients (9.6%) including, symptomatic lymphocyst (5), lymphedema (3), radiation hemorrhagic cystitis (3), and bowel obstruction (3) vesicovaginal fistula (1). All of these patients received adjuvant radiation treatment. In cases of bowel obstruction, 2 patients required surgery to lysis adhesion because of failed conservative treatment.

Twelve patients (7.7%) developed tumor recurrence, 9 had distant recurrence, 2 had locoregional recurrence and 1 had combined local and distant recurrences. Eight of these patients had lymph node metastasis, the remaining 4 had parametrial invasion. The projected 5-year disease-free survival and overall survival of these high risk patients were 80.0% and

93.4% respectively as shown in Fig. 1. and Fig. 2.

Table 1. Patient characteristics (N = 156)

Characteristics	Number (%)
FIGO Stage	
IA2	2(1.3)
IB1	124(79.5)
IB2	8(5.1)
IIA	22(14.1)
Pathology	
Squamous cell	124(79.5)
Adenocarcinoma	22(14.1)
Adenosquamous	7(4.5)
Small cell neuroendocrine	1(0.6)
Mixed	2(1.3)
Treatment	
Radical hysterectomy + PL	135(86.5)
PL & paraaortic node dissection	21(13.5)
Adjuvant treatment	
Radiation alone	41(26.3)
Concurrent chemoradation	112(71.8)
Chemotherapy alone	1(0.6)
No treatment	2(1.3)

FIGO = International Federation of Obstetrics and Gynecology

PL = Pelvic lymphadenectomy, CA = carcinoma

Table 2. Pathological risk factors (N = 156)

Pathological risk factor	Number (%)
Lymph node metastasis	105(67.3)
Parametrial invasion	62(39.7)
Unilateral	47
Bilateral	15
Positive vaginal margin	35(22.4)
For HSIL	24
For invasive CA	11
Positive parametrial margin	1(0.6)

HSIL = High grade squamous intraepithelial lesion

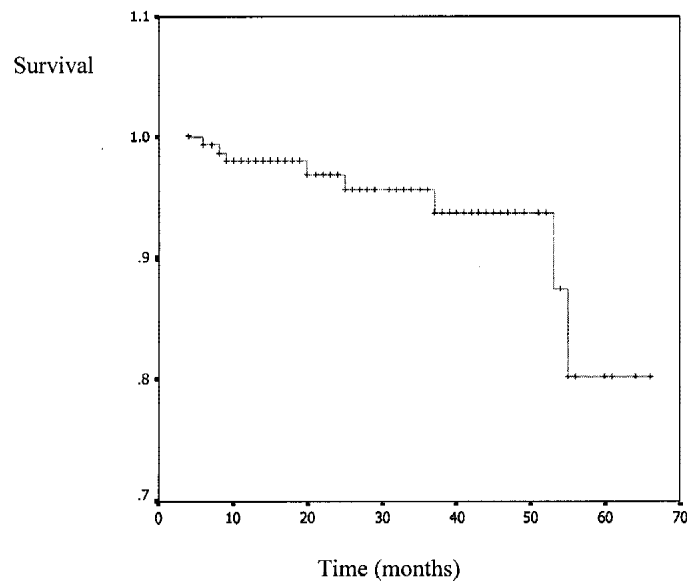


Fig. 1. Disease free survival.

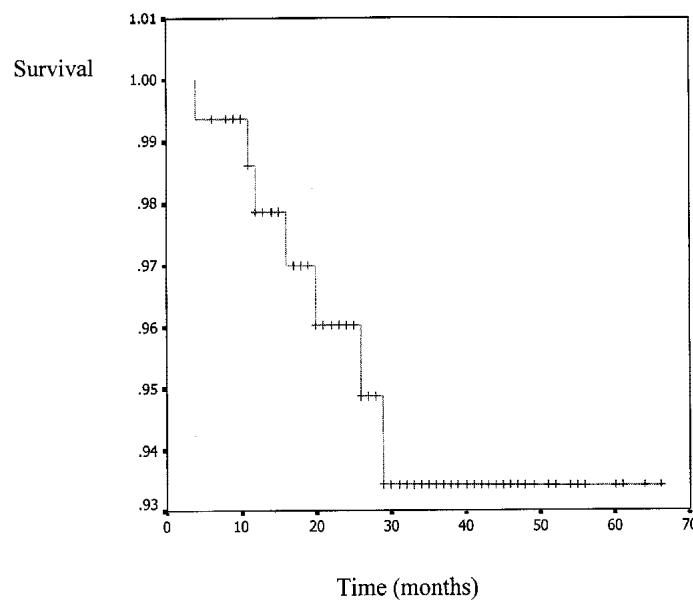


Fig. 2. Overall survival.

Discussion

The projected 5-year disease free survival (80%) and overall survival of early stage cervical cancer patients undergoing radical hysterectomy and found to have high risk pathological factors in this study are relatively higher than those of the previous studies that demonstrated a 5-year survival of 50-75%.⁽¹³⁻¹⁶⁾ These findings may result from short study period and

the positive effect of concurrent chemoradiation given to 71% of the patients after surgery. The study by Peters et al showed that the addition of cisplatin-based chemotherapy to radiation significantly improved the progression-free survival and overall survival in early-stage high-risk cervical cancer patients who underwent radical hysterectomy. The survival was 10% higher in the concurrent-chemoradiation group (81%)

compared with radiation alone group (71%).⁽¹⁰⁾ Furthermore, the higher survival rate and lower risk of recurrence in our study may result from the removal of all bulky positive nodes. Resection of grossly metastatic nodes has been shown to significantly improve patient survival when compared to those who did not receive lymph node removal.^(17,18)

The complication rate of 9.6% in patients treated with combined surgery and radiation in this study is slightly lower than reported by Kim et al which showed 16%.⁽¹⁶⁾ Eight patients in our study with higher risk for pelvic node metastasis, i.e. stage IB2 or IIA cervical cancer, underwent pelvic node dissection via extraperitoneal approach before entering the peritoneal cavity for radical hysterectomy. Metastasis lymph node were detected in 9 of extraperitoneal approach patients, radical hysterectomy was abandoned to avoid peritoneal injury and to preserve the uterus for proper radiation therapy. Extraperitoneal lymphadenectomy has been showed to decrease radiation-related bowel complication when compared with the intraperitoneal approach.^(19,20)

The incidence of lymph node (18.8%) and parametrial invasion (11.2%) in this study were comparable to those in other studies which showed such incidences of 15-20% and 11.4% respectively.^(21,22) Tanaka et al found that the numbers of positive pelvic nodes significantly affected patients survival. The 5- year survival of 62% for patients with one positive node decrease to 36% and 20% for those with two positive nodes and three or four positive nodes respectively. No patient survived to 5 years if positive nodes were more than five.⁽²³⁾ Lymph node metastasis is the strongest risk factor predicting tumor recurrence.⁽²⁴⁾ Among 12 patients with recurrence in our study, 8 had node metastasis, the remaining 4 patients had parametrial invasion. No recurrence occurred in patients with only positive vaginal margin in our study.

In conclusion, cervical cancer stage IA2 - IIA patients with high-risk pathological factors identified after the operation had relatively high survival rate with low complication.

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