

RESEARCH COMMUNICATION

Recurrence Patterns after Radical Hysterectomy in Stage IB1-IIA Cervical

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Abstract

Objectives: The purpose of this study was to evaluate the patterns of recurrence and its associated factors in stage IB1-IIA cervical cancer cases after radical hysterectomy. **Methods:** We retrospectively reviewed the 655 medical records of patients with cervical cancer who underwent radical surgery at Chiang Mai University Hospital between January 2003 and December 2006. All patients had a type III radical hysterectomy and complete systematic bilateral pelvic lymphadenectomy. Post-operative adjuvant pelvic radiation therapy was given concurrently with weekly cisplatin 40 mg/m² for 6 cycles to patients with at least one major risk or two intermediate-risk factors. Sites of disease recurrence, time to relapse of disease, and postoperative overall survival were analyzed and all possible clinicopathological factors related to the risk of recurrence were determined. **Results:** The median time to recurrence was 11.5 months (range, 2-45 months). There was no significant differences in the mean time to recurrence between local and distant recurrence groups (14.6 ±3.9 months vs. 16.2±5.3 months; $p=0.632$). The 3-year survival rates of patients with local and distant recurrences were 67.6% (95% CI=45.6 to 89.6%) and 39.8% (95% CI=11.8 to 67.8%), respectively ($p=0.602$). Tumor size was the only clinicopathological prognostic factor associated with overall survival. **Conclusion:** Patients with stage IB1-IIA cervical cancer should have close surveillance during the first two years of radical surgery. Tumor size of greater than 2 cm at the time of primary surgery appears to be significantly related to the prognosis of patients with recurrence. With an understanding of the natural history of cervical cancer recurrence, an optimal method of follow-up and prospective clinical trial for markers of metastatic potential to detect recurrence need to be conducted in the future.

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Introduction

Cervical cancer is the second most common cancer and the leading cancer-related cause of death in relative young women worldwide (Jemal et al., 2008). According to the American Cancer Society's Global Cancer Facts and Figures 2007, an estimated 555,094 new cases of cervical cancer occurred worldwide, and 309,808 people died of the disease. More than 85% of the new cases and deaths (an estimated 473,430 and 272,238 cases, respectively) occurred in developing countries. It is one of women's major public health problems in Thailand with an age-standardized incidence rate (ASR) of 24.7 per 100,000 woman-year (Srivatanakul, 2007). Patients with FIGO stage IB1- IIA cervical cancer are appropriately treated by either radical surgery or radiation therapy, with equivalent results (Wilkinson and Malik, 1998). Radical hysterectomy and bilateral pelvic lymphadenectomy offer an 80-85% cure rate (Hoskins, 1976; Morley and Seski, 1976; Landoni et al., 1997), however, relapse occurs in

10-20% of these patients (Kenneth and Fu, 1996; Keys et al., 1998). Failure to obtain local-regional disease control usually results in death.

The purpose of this study was to evaluate the patterns of recurrence in patients with stage IB1-IIA cervical cancer after radical hysterectomy and the factors related to recurrence.

Materials and Methods

Between January 2003 and December 2006, 655 patients with newly diagnosed FIGO stage IB1-IIA cervical cancer underwent a radical hysterectomy and bilateral pelvic lymphadenectomy at Chiang Mai University Hospital, Thailand. Among them, 44 operations were abandoned due to positive pelvic lymph nodes for malignancy on frozen sections and excluded from this analysis. The remaining 611 patients had primary radical surgical treatment, that is, type III radical hysterectomy and complete systematic bilateral

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pelvic lymphadenectomy (common iliac, external iliac, circumflex iliac, internal iliac, obturator, and parametrial nodal chains). Post-operative adjuvant pelvic radiation therapy was given concurrently with weekly cisplatin 40 mg/m² for 6 cycles to patients with at least one of the following major risk factors: parametrial invasion, involved surgical margins, and positive lymph nodes or those with two intermediate-risk factors: lymphovascular space invasion (LVSI) > 10 spaces and deep cervical stromal invasion. Postoperative radiation therapy alone was given to elderly patients with creatinine clearance < 40 ml/min. After approval by the Research Ethics Committee, the medical records were retrospectively reviewed for clinicopathological data including age, stage of disease according to FIGO (1995) classification, tumor grade, histological type, depth of cervical invasion, tumor size, LVSI, pelvic lymph node (PLN) metastasis, sites of recurrence, and time to relapse of disease. All histopathologic slides were reviewed by two gynecologic pathologists (S.S., S.K.) of our institution without knowledge of the clinical outcome. On Haematoxylin and Eosin (H&E)-stained sections, the presence of LVSI was considered positive when tumor cells were noted within a vascular or lymphatic space obviously lined by flattened endothelial cells. Histological classification was based on WHO criteria. Overall survival was calculated from the date of diagnosis to the date of death or the last follow-up visit. Postoperative progression-free survival was calculated from the date of completion of treatment to the date of recurrence or the last follow-up visit. After completion of treatment, all patients were followed every 3 months in first year, every 4 months in second year and every 6 months thereafter. Recurrence was defined by clinical, radiological, or imaging evidence and was pathological proved by tissue biopsy or ultrasound-guided fine-needle aspiration as appropriate. Recurrences were classified as local if they were detected in the pelvis, or vagina and as distant if they were detected in extrapelvic locations. The minimum follow-up period was 2 years.

Statistical analysis

Association between the clinicopathological variables was analyzed using Chi-square or Fisher's exact test where appropriate. Survival was calculated using the Kaplan-Meier method. The comparison of survival difference was performed by log-rank test. Probability values of <0.05 were considered statistically significant. Statistical analyses were performed using the SPSS for Windows (version 15.0) software package.

Results

Of the 611 patients that were eligible in this study, 38 (6.2%) developed recurrence of disease. The median age at diagnosis was 42 years (range 30-66) and the median parity was 2.0 (range 1-6). Twenty-seven (71%) patients were premenopausal. The majority of patients (52.6%) were in stage IB1. The clinicopathological characteristics of the patients are described in Table 1. The details of patients who received adjuvant treatment after radical surgery due to various indications are shown in Table 2

Table 1. The Clinicopathological Characteristics of 38 Patients with Recurrent Cervical Cancer

Characteristics	No. of pts (%)
Age (years)	
≤ 40	13 (34.2)
> 40	25 (65.8)
FIGO (1995) stage	
IB1	20 (52.6)
IB2	9 (23.7)
IIA	9 (23.7)
Tumor grade	
I	8 (21.1)
II	15 (39.5)
III	13 (34.2)
Undifferentiated	2 (5.3)
Histologic type	
Squamous cell carcinoma	20 (52.6)
Non-squamous cell carcinoma	18 (47.4)
Tumor size (cm)	
≤ 2	6 (15.8)
> 2	32 (84.2)
LVSI	
Negative	4 (10.5)
Positive	34 (89.5)
Depth of cervical stromal invasion	
≤ 1/2	4 (10.5)
> 1/2	34 (89.5)

Table 2. Indications for Postoperative Adjuvant Therapy

Risk factors	N (%)
Pelvic lymph node metastasis	13 (34.2)
Parametrial involvement	7 (18.4)
Positive vaginal margins	5 (13.2)
Lymph vascular space invasion (LVSI)	34 (89.5)
Deep cervical stromal invasion	34 (89.5)

Table 3. Sites of Recurrence in Stage IB1-IIA Cervical Cancer after Radical Surgery

Sites of recurrence	N (%)
Local	21 (55.3)
Distant	15 (39.5)
Combined	2 (5.2)

and sites of disease recurrence are shown in Table 3. More than 80% of those who had disease recurrence presented with tumor size > 2 cm, LVSI, and deep cervical stromal invasion. Pelvic lymph node metastasis was found in 13 of 38 patients (34.2%) of the recurrent group and in 9 of 17 cases (52.9%) of the group that had distant recurrence after postoperative adjuvant therapy ($p=0.04$). Forty-two percent of patients with positive nodes had more than one site of pelvic node involvement. Lymph node metastasis was found in 12 (35.3%) patients who had LVSI compared to 1 (25.0%) of those without LVSI. In addition, LVSI was present in 18 (85.7%) patients who had local relapse and 16 (94.1%) cases in the group of distant recurrence. Among 38 patients with recurrence cervical cancer, adjuvant therapy given after radical surgery was as follows: 16 (42.1%) concurrent weekly cisplatin (40

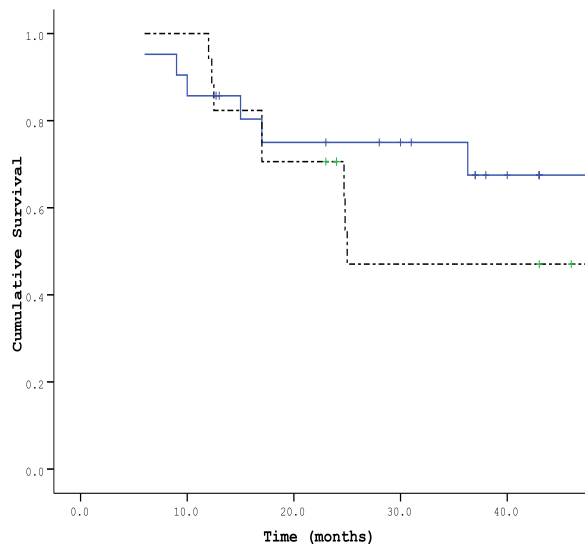


Figure 1. Comparison of Kaplan-Meier Survival Curves in Patients with Local Relapse (Upper Bar) and Distant Recurrence (Lower Bar), $p=0.602$

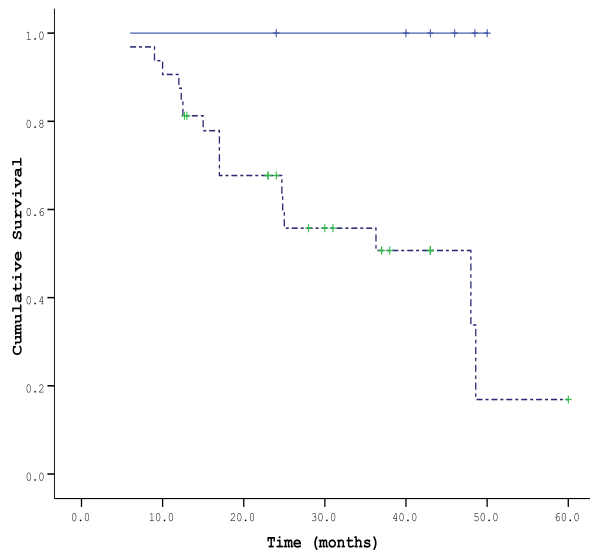


Figure 2. Comparison of Kaplan-Meier Survival Curves in Patients with Tumor Size Smaller than 2cm (Upper Bar) and Tumor Size 2cm or Larger (Lower Bar), $p=0.03$

mg/m²) and radiotherapy, 2 (5.3%) radiotherapy alone, 16 (42.1%) no adjuvant treatment, and 4 (10.5%) cisplatin (75 mg/m², d1)/etoposide (100 mg/m², d1-3) every 3 weeks for 6 cycles due to small cell neuroendocrine carcinoma of cervix. Of the 16 patients who had no indication for postoperative adjuvant therapy, 13 (81.2%) developed local relapses and 3 (18.8%) had distant recurrence. The median time to recurrence was 11.5 months (range, 2-45 months). There was no significant difference in the mean time to recurrence after completion of treatment between the local and distant recurrence groups (local, 14.6 ± 3.9 months; distant, 16.2 ± 5.3 months; $p=0.632$). The distant sites of recurrence were supraclavicular lymph node, lungs, brain, paraaortic lymph node, bone, liver, and small bowel. At a median follow-up of 26.5 months, 3-year survival rates of the patients with local and distant recurrences were

67.6% (95%CI=45.6 to 89.6%) and 39.8% (95%CI=11.8 to 67.8%), respectively ($p=0.602$) (Figure 1). Tumor size was the only clinicopathological prognostic factor associated with overall survival. Patients with a tumor size less than 2 cm showed good postoperative survival. The 5-year survival rates were 100% for those with tumor size smaller than 2 cm, and 16.9% for those with tumor size of 2 cm or larger ($p=0.03$) (Figure 2).

Discussion

Radical hysterectomy including pelvic lymphadenectomy and primary radiotherapy using a combination of external-beam teletherapy and brachytherapy are accepted treatments for stages IB (IB1-IB2) and IIA carcinoma of the cervix that show comparable results in terms of overall or disease-free survival (Landoni et al., 1997). For radiotherapy, it is given with concurrent cisplatin-based chemotherapy, based on 5 large randomized controlled trials that showed significant improvement in overall survival with the addition of chemotherapy. The preference of one over the other depends on the institution, the general condition of the patient, the oncologists involved, and tumor characteristics. Generally, surgery has often been preferred in young women because of the desire to preserve ovarian function (Webb, 1975). In this study, we analyze patterns of recurrent cervical cancer after radical surgery. Patients with cervical cancer may develop pelvic recurrence, distant metastases, or a combination of both. Other literature reports, a 10%-20% recurrence rate following primary surgery or radiotherapy in women with stage IB-IIA cervical tumors with no evidence of lymph node involvement, while up to 70% of patients with nodal metastases and/or more locally advanced tumors will relapse (Delgado et al., 1990; Stehman et al., 1991; Burghardt et al., 1992; Zaino et al., 1992). The frequency of recurrence in our series was 6.2%. Among 38 patients with recurrence, 16 (42%) cases were in the group that had radical hysterectomy and pelvic lymphadenectomy alone and another 16 (42%) were in the group receiving cisplatin-based concurrent chemoradiation (CCRT) after surgery. Local relapse was detected in 13 out of 16 (81%) and 5 out of 16 (31%) patients receiving surgery alone and CCRT after surgery, respectively. A possible explanation for these differences might be the fact that patients with pathological high-risk factors (positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium) had better pelvic control by CCRT after surgery. Most of the patients (69%) who had recurrence after CCRT had distant failure and correlated with prior pelvic lymph node metastasis ($p=0.04$), whereas, the patients who had no pathological high-risk factors still have a chance of recurrence and often have local relapse. Our data demonstrated that 19 (90%) patients with local relapse and 13 (76%) patients with distant recurrence had tumor size greater than 2 cm. In addition, a tumor size of greater than 2 cm was strongly correlated with poor survival in patients with recurrent cervical cancer. The majority of these recurrences occur within the first 2 years after completion of therapy. In

a retrospective review of over 500 patients treated at the University of Kentucky, 31% of patients developed tumor recurrence, 58% of these recurred within 1 year and 76% within 2 years (Van Nagell et al., 1979). In our series, initial recurrence occurred after a median of 11.5 months. However, there was no statistically significant difference in the mean time to recurrence between the local and distant recurrence groups. The frequency of isolated distant metastasis was 39.5% (15/38) in the recurrent group. These results suggest that distant recurrence may occur with no relation to local recurrence. Patients with recurrent disease who had pelvic lymph node metastasis at the time of primary radical surgery were likely to have distant recurrence compared with those who had negative nodes (69%, and 32% respectively, $p=0.04$). These results may suggest that even the use of adjuvant chemoradiation after radical surgery in cases with pelvic lymph node involvement, the potential of micrometastases outside the pelvis still remain. Look and Rocereto (1990) reported that the median time to pelvic relapse was 9.5 months for radical surgery patients and 10 months for irradiated patients. Also, the risk of distant metastases was 5.4% following radical surgery and 20% after radiation ($p=0.04$). In our series of 611 patients, the risks of distant recurrence and local relapse after radical surgery were 2.5% and 3.4%, respectively. Also the risk of having both sites of metastases was 0.3%.

In summary, all patients with stage IB1-IIA cervical cancer should have close surveillance during the first 2 years after radical surgery. Tumor size of greater than 2 cm at the time of primary surgery appears to be significantly related to prognosis of patients with recurrence. Patients with pelvic lymph node involvement also have a potential for distant recurrences. A deeper understanding of the natural history of cervical cancer recurrence will allow the optimal method of follow-up and prospective clinical trial for markers of metastatic potential to detect recurrence in the future.

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