RESEARCH COMMUNICATION

# Association Between Prognostic Factors and Disease-Free Survival of Cervical Cancer Stage IB1 Patients Undergoing Radical Hysterectomy

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## Abstract

**This study was designed to identify prognostic factors of patients with cervical cancer stage IB1 undergoing radical hysterectomy. The medical records and specimens of two hundred and five patients with cervical cancer stage IB1 undergoing radical hysterectomy at Songklanagarind Hospital from July 1995 to June 2005 were reviewed. Patients' age, tumor size, histologic type, tumor grade, depth of invasion, degree of stromal invasion, lymph-vascular space invasion (LVSI), surgical margin status, pelvic node status, and adjuvant treatment were assessed for correlation with disease-free survival (DFS). The mean age of these patients was 44.2 years and the median follow up was 56 months. Twenty five patients (12.2%) developed recurrent disease. The overall 5-year DFS was 86%. In univariate analysis, depth of invasion, degree of stromal invasion, LVSI, and pelvic node status were significant prognostic factors. In multivariate analysis, degree of stromal invasion remained the only independent prognostic factor. In conclusion, degree of stromal invasion was the main independent predictor of prognosis in surgical cases of cervical cancer stage IB1.**

**Key Words:** Cervical cancer - prognostic factor - radical hysterectomy - survival

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## Introduction

The cornerstone treatment of early stage (IB and IIA) cervical cancer can be either surgery via radical hysterectomy with pelvic node dissection or radiotherapy with or without concurrent chemotherapy. Similar clinical outcomes (overall or disease-free survival) for these two strategies have been reported (Landoni et al., 1997). In Thailand, Songklanagarind Hospital in particular, most early stage cervical cancer patients without severe medical illness choose primary treatment by surgery. Radiation is usually reserved for the surgically unfit patients. Adjuvant radiation after surgery is usually recommended for those who are at high risk of recurrence, i.e. having lymph node metastasis, parametrial involvement or positive surgical margin (Guttmann, 1970). Despite the effect of postoperative radiotherapy on decreasing the incidence of local recurrence being demonstrated, its role in increasing survival is controversial (Delgado et al., 1990; Kridelka et al., 1999; Sedlis et al., 1999; Ayha et al., 2004).

Many clinicopathologic studies had described a number of prognostic factors for cervical cancer, such as clinical stage, tumor histology, size of primary tumor, depth of invasion, tumor grade, parametrium involvement, lymph node involvement, and lymph-vascular space invasion (LVSI) (Eifel et al., 1995; Sevin et al., 1995; Aoki et al., 2000; Trattner et al., 2000; Kristensen et al., 1999; Ayhan et al., 2004). Nevertheless, no advantage method has been established for identified patients who were destined to develop recurrent disease.

Therefore, we conducted the present study to identify patient and tumor variables (ie., patients' age, tumor size, histologic type, tumor grade, depth of invasion, degree of stromal invasion, LVSI, surgical margin involvement, pelvic node involvement, and adjuvant treatment) related to recurrence in women with cervical cancer stage IB1 undergoing radical hysterectomy with pelvic lymphadenectomy.

## Materials and Methods

Following approval from the Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University, the medical records of patients who had been diagnosed preoperatively by punch biopsy or cone excision as cervical cancer, International Federation of Gynecology and Obstetrics (FIGO) stage IB1 and had undergone radical hysterectomy with pelvic lymphadenectomy at Songklanagarind Hospital between July 1st, 1995 and June 30th, 2005 were reviewed. Patients

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with clear cell or nueroendocrine type or second primary cancer, or who received preoperative chemotherapy or whose medical records were lost, or whose pathological material was not available for review, were excluded from this study.

In our hospital, all patients were clinically staged as recommended by FIGO and underwent radical hysterectomy (type III) and pelvic lymphadenectomy (FIGO Cancer Committee, 1986). Routinely, the criteria for adjuvant radiotherapy or concurrent chemoradiation included pelvic node involvement and/or surgical margin involvement. Tumor size was determined by the attending gynecologic oncologist during pelvic examination preceding surgery.

The strength of ten prognostic variables investigated for this study included patients' age, tumor size, histologic type, tumor grade, depth of invasion, degree of stromal invasion, lymph-vascular space invasion (LVSI), surgical margin involvement, pelvic node involvement, and adjuvant treatment. All pertinent clinical data were obtained and retrospectively reviewed from the medical records (patients' age, tumor size, adjuvant therapy, recurrence and death). All deaths are registered by the Medical Statistical Unit and Cancer Registry Unit of Songklanagarind Hospital and the Department of Provincial Administration, Minister of Interior, using certificates issued by a physician stating the cause of death. All living patients were confirmed directly by calling, mailing and/or checking the census records from the Hatyai City Municipality. Two hundred and five cases of cervical cancer stage IB1 fulfilled the criteria and were enrolled in this historical cohort study.

*Histopathologic evaluation*

All pathologic materials (hysterectomy specimens, slides of cervical biopsies and/or conization) were reviewed for each case. The tumors were classified according to the World Health Organization (Tavassoli FA and Devilee P, 2003), and graded as well, moderately or poorly differentiated. The presence or absence of direct extension into the parametria or vaginal cuff, the presence or absence of metastasis to pelvic lymph nodes, depth of invasion, degree of stromal invasion and LVSI were recorded. The depth of invasion was measured in millimeters from the basement membrane of the surface epithelium. If a cone biopsy was performed preoperatively and the deep surgical margin was positive for tumor, depth

**Table 1. Clinicopathologic Characteristics of Cervical Cancer Patients Stage IB1 Who were Treated with Radical Hysterectomy**

| Variable | Number (%) |
|---|---|
| Age (years) | |
| ≤ 40 | 81 (39.5) |
| > 40 | 124 (60.5) |
| Tumor size (cm) | |
| ≤ 2 | 141 (68.8) |
| > 2 | 64 (31.2) |
| Depth of invasion (mm) | |
| ≤ 10 | 153 (74.6) |
| 11-15 | 43 (21.0) |
| > 15 | 9 (4.4) |
| Degree of stromal invasion | |
| Inner 1/3 | 87 (43.3) |
| Middle 1/3 | 67 (33.3) |
| Outer 1/3 | 47 (23.4) |
| Histologic type | |
| Squamous | 130 (63.4) |
| Adenocarcinoma | 70 (34.2) |
| Adenosquamous | 5 (2.4) |
| Grade | |
| 1 | 62 (30.2) |
| 2 | 93 (45.4) |
| 3 | 50 (24.4) |
| Lymph-vascular space invasion | |
| No | 72 (35.1) |
| Yes | 133 (64.9) |
| Surgical margin involvement | |
| No | 188 (91.7) |
| Yes | 17 (8.3) |
| Pelvic node involvement | |
| No | 193 (94.2) |
| Yes | 12 (5.8) |
| Adjuvant therapy | |
| No | 185 (90.2) |
| Yes | 20 (9.8) |

**Table 2. Univariate Analysis and 5-Year Disease-Free Survival According to Potential Prognostic Variables**

| Variable | 5-year disease-free survival | 95% confidence interval | P value * |
|---|---|---|---|
| Age (years) | | | |
| ≤ 40 | 85.7 | 73.8-92.4 | 0.895 |
| > 40 | 86.2 | 77.1-19.9 | |
| Tumor size (cm) | | | |
| ≤ 2 | 86.4 | 77.8-91.8 | 0.270 |
| > 2 | 85.3 | 72.5-92.4 | |
| Depth of invasion (mm) | | | |
| ≤ 10 | 88.9 | 81.6-93.4 | 0.007 |
| 11-15 | 72.3 | 47.5-86.8 | |
| > 15 | 75.0 | 31.5-93.1 | |
| Degree of stromal invasion | | | |
| Inner 1/3 | 91.4 | 79.9-96.5 | 0.0005 |
| Middle 1/3 | 89.2 | 77.1-95.1 | |
| Outer 1/3 | 70.8 | 53.1-82.9 | |
| Histologic type | | | |
| Squamous | 85.0 | 76.4-90.6 | 0.933 |
| Adenocarcinoma | 87.2 | 72.7-94.3 | |
| Grade | | | |
| 1 | 90.4 | 75.9-96.4 | 0.525 |
| 2 | 84.3 | 73.0-91.2 | |
| 3 | 83.3 | 67.6-91.8 | |
| Lymph-vascular space invasion | | | |
| No | 91.4 | 83.6-95.5 | 0.007 |
| Yes | 76.8 | 63.0-86.0 | |
| Surgical margin involvement | | | |
| No | 86.3 | 79.3-91.0 | 0.294 |
| Yes | 82.5 | 46.1-95.3 | |
| Pelvic node involvement | | | |
| No | 86.3 | 79.3-91.1 | 0.035 |
| Yes | 81.5 | 43.5-95.1 | |
| Adjuvant therapy | | | |
| No | 85.2 | 77.9-90.2 | 0.765 |
| Yes | 93.3 | 61.3-99.0 | |

*Log rank test

**Table 3. Univariate Cox Proportional Hazard Models of Disease-Free Survival According to Potential Prognostic Variables**

| Variable | Hazard ratio | 95% confidence interval | P value * |
|---|---|---|---|
| Depth of invasion (mm) | | | |
| ≤ 10 | 1 | | 0.021 |
| 11-15 | 3.57 | 1.51-8.42 | |
| > 15 | 2.45 | 0.56-10.74 | |
| Degree of stromal invasion | | | |
| Inner 1/3 | 1 | | 0.002 |
| Middle 1/3 | 1.68 | 0.53-5.3 | |
| Outer 1/3 | 5.36 | 1.91-15.05 | |
| Lymph-vascular space invasion | | | |
| No | 1 | | 0.001 |
| Yes | 2.88 | 1.29-6.41 | |
| Pelvic node involvement | | | |
| No | 1 | | 0.076 |
| Yes | 3.00 | 1.03-8.73 | |

*Likelihood ratio test

**Table 4. Multivariate Cox proportional Hazard Models of Disease-Free Survival According to Potential Prognostic Variables**

| Variable | Hazard ratio | 95% Confidence Interval | P value* |
|---|---|---|---|
| Degree of stromal invasion | | | |
| Inner 1/3 | 1 | | 0.050 |
| Middle 1/3 | 1.43 | 0.43-4.77 | |
| Outer 1/3 | 3.77 | 1.14-12.46 | |
| Lymph-vascular space invasion | | | |
| No | 1 | | 0.328 |
| Yes | 1.60 | 062-4.10 | |
| Pelvic node involvement | | | |
| No | 1 | | 0.538 |
| Yes | 1.45 | 0.46-4.57 | |

*Likelihood ratio test

of invasion was defined as the sum of the depth of invasion found on radical hysterectomy specimen and the depth of invasion found on the cone biopsy. For degree of stromal invasion, deep stromal invasion was defined as a tumor invading the outer one third of the cervical stroma. LVSI was regarded as positive when neoplastic cells were seen within vascular or lymphatic spaces lined by flattened endothelial cells.

*Statistical analysis*

Disease-free survival (DFS) was calculated from the date of surgery until the date of recurrence, death or last follow-up, whichever occur earlier, and confined to those patients who showed complete clinical remission. Patients not having developed recurrence at the time of last follow up were considered as having censored DFS times. DFS was analyzed using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis was performed using Cox proportional-hazards regression. All tests were 2-sided; a P value of less than 0.05 was considered statistically significant. Statistical analysis of the data was carried out using STATA version 7 (Stata Corporation, Texas USA).

## Results

Two hundred and five patients with stage IB1 cervical cancer underwent radical hysterectomy with pelvic lymphadenectomy between July 1995 and June 2005. The mean age of these patients was 44.2 years (SD=9.4). Histopathologic diagnosis included 130 (63.4%) squamous cell carcinoma, 70 (34.2%) adenocarcinoma, and 5 (2.4%) adenosquamous carcinoma. The median follow up time was 56 months (range 1-140.5 months). Twenty five patients (12.2%) developed recurrent disease in the following sites: pelvis, 15 (7.3%) patients; distant sites, 10 (4.9%) patients; and pelvis plus distant sites, 5 (2.4%) patients. Fourteen patients (6.9%) died from disease. The demographic and pathologic data of the patients are summarized in Table 1.

The overall 5-year disease-free survival (DFS) was 86% (95% confidence interval [CI] = 79.3-90.7). Five-year DFS according to potential prognostic variables is shown in Table 2. In univariate Kaplan-Meier analysis, significant differences in DFS were observed across four factors: depth of invasion, degree of stromal invasion, lymph-vascular space invasion (LVSI) and pelvic node involvement. No evidence of a relationship with patients' age, tumor size, histologic type, grade, positive surgical margin or adjuvant therapy was found.

Using Cox proportional-hazards regression analysis the same four variables were separately significantly associated with DFS (Table 3). However, both LVSI and pelvic node involvement lost their significance when adjusted for either depth of invasion or degree of stromal invasion. The latter 2 variables were highly interrelated ($P < 0.0001$) and could not be included together in the same model. Degree of stromal invasion was slightly more strongly associated with DFS and remained marginally significant even after adjusting for LVSI and node involvement (Table 4). The 5-year DFS (and 95% CI) for the patient with tumors of inner 1/3, middle 1/3 and outer 1/3 stromal invasion was 91.4% (79.9-96.5%), 89.2% (77.1-95.1%) and 70.8% (53.1-82.9%) ($P = 0.0005$) (Figure 1).

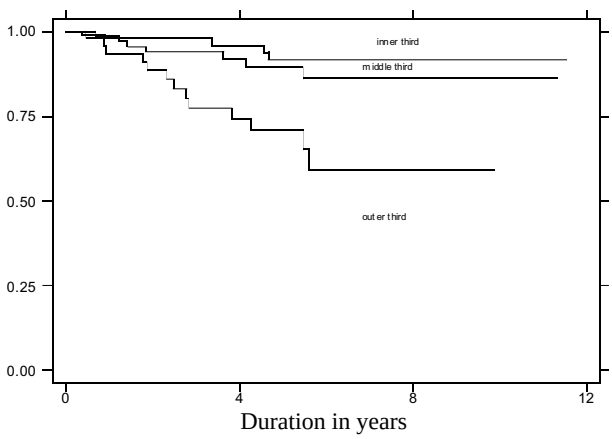


**Figure 1. Disease-Free Survival for Cervical Patients Who Have Degree of Stromal Invasion; Inner 1/3, Middle 1/3 and Outer 1/3**

## Discussion

The clinical outcomes of patients with cervical cancer FIGO stage IB1 after radical surgery have been reported to be 74%-87.6% for 5-year disease-free survival (DFS) and 83% - 91.0% for 5-year overall survival (Ayhan, et al., 2004; Trimbos, et al., 2004). In this study, 5-year DFS was 86%, which is comparable to those in the previous study. The recurrence rate in this study was 12.2%. These results are consistent with those of previous studies and suggest that the recurrence rate was 9.4%-16% (Ayhan et al., 2004; Trimbos et al., 2004). In our study, squamous cell carcinoma (63.4%) and adenocarcinoma (34.2%) was the common malignant cell type. The result was similar to previous studies ( Sevin et al., 1995; Aoki et al., 2000; Ayhan et al., 2004; Trimbos et al., 2004).

In a surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix performed by the Gynecologic Oncology Group (GOG), Delgado et al. reported clinical tumor size, lymph-vascular space invasion (LVSI) and depth of invasion as independent prognostic factors in stage IB cervical cancer (Delgado et al., 1990). In this study, we analyzed the prognostic importance of clinicopathologic factors in 205 surgical cases of cervical cancer stage IB1. In univariate analysis, we were able to show depth of invasion, degree of stromal invasion (DSI), LVSI, or pelvic node involvement were statistically associated with 5-year DFS. After multivariate analysis only degree of stromal invasion remained as a independent prognostic factors.

Concerning tumor size, our results did not show that tumor size > 2 cm was a significant prognostic factor. The present findings seem to be consistent with many authors which reported tumor size > 4 cm critical effect on disease free and overall survival (Delgado et al., 1990; Kristensen et al., 1999; Ayhan et al., 2004; Trimbos et al., 2004). However, a study of Sevin showed a significant difference in 5-year DFS was found between tumor measuring 1 cm or smaller, 1.1-2 cm, and larger than 2 cm at greatest dimension (Sevin et al., 1995). A possible explanation for these contrasting findings is that the variety of methods used for clinical or pathological measurement.

Samlal et al. also found depth of invasion as a fraction of the tumor penetration of cervical stroma was as indepentdent risk factor for recurrence (Samlal et al., 1997). However, a study of Sevin found that depth of invasion of 5 mm or smaller, 6-10 mm, and larger than 10 mm was associated with a proportionally poorer survival of 92%, 74%, and 60%, respectively (Sevin et al., 1995). In our study, degree of stromal invasion was identified as the only significant independent prognostic factor for recurrence. The result is consistent with a GOG report, it was found that the risk of recurrence in patients with tumors invading the outer third of the cervix was very high and not influenced by the absolute depth of invasion in millimeters (Delgado et al., 1990).

Despite LVSI being significantly correlated with lymph node metastasis (van Nagell et al., 1978), the relationship between LVSI and survival of cervical cancer is inconsistent (Smiley et al., 1991; Zaino et al., 1992; Sevin et al., 1995; Grisaru et al., 2003; Ayhan et al., 2004). Several studies have revealed that LVSI to be a poor prognostic factor (Sevin et al., 1995; Grisaru et al., 2003; Ayhan et al., 2004), whereas in other studies, LVSI had no influence on survival (van Nagell, et al., 1978; Smiley et al., 1991). In the current study, we were unable to show LVSI to be an independent prognostic factor. Our finding is consistent with Creasman et al. who recently reported on a review of 25 multivariate analyzed studies of surgical pathologic independent risk factors in Stage IB–IIB carcinoma of the cervix and found that in only 3 of them (12%) was LVSI an independent risk factor while 88% and 61% of those evaluated, noted lymph node metastasis and tumor size/depth of invasion to be significant risk factors for survival (Creasman and Kohler, 2004).

Adenocarcinoma (Eifel et al., 1995; Samlal et al., 1997), grade (van Nagell et al., 1978; Kristensen et al., 1999; Grisaru et al., 2003), pelvic node involvement (Sevin et al. 1995; Aoki et al., 2000; Grisaru et al., 2003), and surgical margin (Sevin et al., 1995) of cervix are believed to have a less favorable prognosis. However, the findings in the current study do not support the previous research. This finding might be explained by the fact that we enrolled only early stage cases--at this stage prognostic indicators may not yet assumed prognostic significance. Clearly, the relatively small number of these variables seen in this study limits the power of detect any small effects. Age was also not found to be significant predictors of recurrence, as has been reported by others (Sevin et al., 1995, Trattner et al., 2000).

In conclusion, this study shows that in patients with cervical cancer stage IB1 undergoing radical surgery, degree of stromal invasion is the main independent prognostic indicator for subsequent recurrence. An adjuvant treatment after radical surgery such as radiotherapy with or without concurrent chemotherapy may be necessary for high risk patients.

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