RESEARCH COMMUNICATION

Survival and Prognostic Factors Comparing Stage IB 1 versus Stage IB 2 Cervical Cancer Treated with Primary Radical Hysterectomy

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Abstract

This study was undertaken to compare the survival rates of stage IB 1 versus stage IB 2 cervical cancer patients and to evaluate the prognostic factors after treatment primarily with radical hysterectomy and pelvic lymphadenectomy (RHPL). Patients with stage IB cervical cancer undergoing primary RHPL at Chiang Mai University Hospital between January 2002 and December 2009 were evaluated for survival and recurrence. Clinicopathological variables were analyzed to identify the prognostic factors affecting the survival of the patients. During the study period, RHPL was performed on 570 stage IB 1 and 110 stage IB 2 cervical cancer patients. With a median follow-up of 48 months, the 5-year disease-free survivals were 98.1% and 82.8% respectively ($p < 0.001$). Multivariate analysis identified four significant prognostic factors affecting survival including sub-staging, non-squamous cell carcinoma histology, lymph node metastasis and the presence of lymph-vascular space invasion. In conclusion, with a primary radical hysterectomy, stage IB 1 cervical cancer patients have a significantly better survival rate than those with stage IB 2. Significant prognostic factors for stage IB cervical cancer include tumor histology, nodal status, and the presence of lymph-vascular space invasion.

Keywords: Radical hysterectomy - cervical cancer - stage IB - survival - prognostic factor

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Introduction

Cervical cancer is the second most common after breast cancer among female cancers worldwide including Thailand (Ferlay et al.,2010). The age standardized incident rate of cervical cancer and deaths from this cancer in Thailand is 24.5 and 12.8 per 100,000 women per year, respectively. In 2008, there will be an estimated 9,999 newly diagnosed cervical cancers and 5,216 deaths from this disease in Thailand (Ferlay et al.,2010). Approximately one third of women with cervical cancer in the Chiang Mai University Hospital are in stage I in which surgical treatment is generally offered.

The International Federation of Gynecology and Obstetrics (FIGO) has subdivided stage IB cervical cancer based on the clinically visible tumor size of 4 cm into stage IB 1 (≤4 cm) and IB 2(>4 cm) (Pecorelli 2009). Treatment options for patients with stage IB cervical cancer include radical hysterectomy with pelvic lymphadenectomy (RHPL) and radiation therapy with or without chemotherapy.

The choice of treatment depends on various factors including patient performance, competence of the surgeon, available resources as well as patient and physician's preferences. The surgical approach is frequently offered to young women because of its potential to preserve ovarian function and vaginal pliability compared to radiation therapy. This modality also provides additional information of surgico-pathological risk factors affecting survival outcome of the patients.

This study was conducted to compare the survival of patients with stage IB 1 versus IB 2 cervical cancer treated primarily with RHPL and to evaluate the prognostic factors affecting survival of patients with stage IB disease in a single institution over a period of 8 years.

Materials and Methods

After receiving approval from the Research Ethics Committee, the medical records of women with cervical cancer stage IB undergoing primary radical hysterectomy at Chiang Mai University Hospital between January 2002 and December 2009, were reviewed. Abstracted data included patients' age, FIGO stage, cell types, detailed characteristics of surgical specimens, i.e. tumor histology and grade, lymph-vascular space invasion (LVSI),

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depth of stromal invasion, surgical margin involvement, parametrial extension, lymph node metastasis, and disease-free survival. All surgical specimens were examined by gynecologic pathologists at Chiang Mai University Hospital.

All radical hysterectomies were performed by the authors with in-training fellows as assistants. The tumor diameter was clinically measured at an outpatient department. All patients underwent a complete bilateral pelvic lymphadenectomy.

Adjuvant chemoradiation using weekly cisplatin was given if at least one of the following pathological findings including vaginal margin involvement, prametrial extension, and lymph node metastasis were noted on pathological examination of the surgical specimens.

Patients were followed every three to four months in the first two years after completion of treatment and every six months thereafter. A pelvic examination was performed every visit. Further investigations were carried out when indicated. Disease-free survival was defined as the time frame between the date of the operation and the date of diagnosis of a recurrence.

The statistical analyses were carried out using SPSS version 17 (SPSS, IL, USA). Disease-free survival was calculated using the Kaplan-Meier method and differences in survival were compared with the log-rank test. Multivariate analysis using a Cox-proportional hazards model was used to adjust for prognostic factors and to estimate hazard ratio (HR) with 95% confidence interval (CI). A P-value <0.05 was considered statistically significant.

Results

During the study period, of the 843 women with stage IA-IIA cervical cancer who underwent RHPL, 570 and 110 women were stage IB 1 and stage IB 2, respectively. The mean age of stage IB 1 and IB 2 patients were 45 years (range, 19-75) and 42 years (range, 24-61), respectively. Approximately 65 % of women had squamous cell carcinoma histology. One hundred and eight (15.9%) women had a grade 3 tumor. All patients underwent a complete bilateral pelvic lymphadenectomy with a mean number of 26 nodes removed. The mean number of positive nodes was two.

Of 680 RHPL specimens, 88 (12.9%) had parametrial involvement, 112 (16.5%) had pelvic node metastasis, 29 (4.3%) had vaginal margin involvement, 358 (52.6%) had lymph-vascular space invasion (LVSI). Deep stromal invasion (outer third) was observed in 318 (46.8%) women. Approximately one-third of women (34%) received adjuvant treatment.

Women with stage IB2 had a significantly higher incidence of parametrial involvement (21.8% vs.11.2%, P=0.002), presence of LVSI (71.8% vs. 48.9%, P<0.001), and deep stromal invasion (72.7% vs. 41.8%, P<0.001) than those in stage IB 1. Twenty-five (22.7%) women with stage IB2 cervical cancer were found to have pelvic node metastasis compared to 15.3% of those with stage IB1 disease (P=0.053). Sixty-one (55.5%) patients with stage IB 2 cervical cancer received adjuvant treatment compared to 170 (29.8%) in those with stage IB 1 disease (P<0.001).

Table 1. Analysis of Disease-free Survival Stratified by Pathologic Factors

Variable	5-years DFS	P value*	Hazard ratio (95% CI)	P value†
Stage		<0.001		0.015
IB 1	98.1%		Ref. Level	
IB 2	82.8%		2.23 (1.17-4.25)	
Nodal status		<0.001		0.003
Negative	92.9%		Ref. Level	
Positive	81.3%		2.63 (1.40-4.96)	
Lymph-vasc invasion		<0.001		0.014
Negative	95.4%		Ref. Level	
Positive	86.7%		2.56 (1.21-5.45)	
Histology		0.001		<0.001
SCC	93.5%		Ref. Level	
Others	86.3%		3.38 (1.81-6.34)	
Depth of invasion		0.005		0.597
Inner third	94.3%		Ref. Level	
Outer third	86.7%		1.20 (0.61-2.38)	
Parametrial involvement		0.015		0.517
Negative	97.5%		Ref. Level	
Positive	86.6%		0.77 (0.35-1.69)	
Tumor grade		0.541		0.251
Grade 1	93.7%		Ref. Level	
Other	89.4%		1.50 (0.75-3.00)	
Vaginal margin		0.780		0.578
Negative	90.8%		Ref. Level	
Positive	92.5%		1.51 (0.35-6.42)	

DFS, disease-free survival; CI, confidence interval; *Obtained from log-rank test; †Obtained from Cox-Proportional hazards model

At the median follow-up time of 48 months (range, 1-105 months), 51 (7.5%) women were found to have recurrent disease. Women with stage IB 2 cervical cancer had a higher incidence of recurrence compared to those in stage IB 1 (16.4% and 5.8%, respectively). The 5-years disease-free survival were 98.1% and 82.8% for stage IB 1 and stage IB 2, respectively (P<0.001). Figure 1 shows the comparison of survival outcomes of women with stage IB 1 and IB 2 cervical cancer.

The log-rank test was used to determine the impact of various clinico-pathological factors on disease-free survival. Stage, nodal metastasis, presence of LVSI,

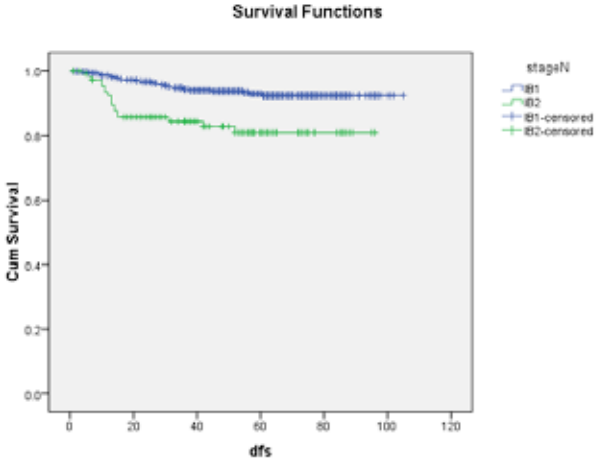

Figure 1. Survival of Patients with Stage IB 1 and Stage IB 2 Cervical Cancers

histology, parametrial involvement, and depth of stromal invasion were found to have an impact on recurrence in this initial analysis. From multivariate analysis, risk factors which independently impacted disease-free survival were tumor size, nodal status, presence of LVSI and histologic subtypes (Table 1).

Discussion

In this study, we found that after RHPL in women with stage IB cervical cancer, certain independent prognostic factors have provided provocative information predictive of the disease-free survival including sub-stage of stage IB cervical cancer, nodal status, presence of LVSI, and histologic subtypes.

Patients with stage IB 2 had higher recurrence and poorer survival than those with stage IB 1 cancers regardless of treatment modality (Delgado et al., 1989; Perez et al., 1992; Finan et al., 1996; Landoni et al., 1997). This subdivision by tumor dimension reflects the wide range of recurrence and survival rates of these patients with early-stage disease. The overall 5-year survival rates range from 80-95 % for patients with stage IB 1 cervical cancer to 60-80 % for patients with stage IB 2 disease (Eifel et al., 1994; Finan et al., 1996; Landoni et al., 1997; Brewster et al., 2001).

Women with stage IB 2 cervical cancer in the present study had a higher rate of parametrial involvement, LVSI, deep stromal invasion and nodal metastasis. Thus, a higher rate of receiving adjuvant treatment among stage IB 2 patients compared with that in the stage IB 1 group is certainly expected. However, patients with stage IB 2 still had a significantly lower 5-year disease-free survival rate after RHPL than did patients with stage IB 1 (82.8 % versus 98.1%), despite the more frequent use of adjuvant treatment in the former group. From multivariate analyses, women with stage IB 2 cervical cancer were approximately two times more likely to develop recurrent disease compared to stage IB 1 patients. These findings reaffirm the necessity of developing an appropriate treatment modality specifically for IB 2 cervical cancer patients.

The nodal status is a well recognized predicting factor for survival in patients with stage IB cervical cancer (Finan et al., 1996; Takeda et al., 2002; Lee et al., 2011). Patients without lymph node metastasis have better 5-year survival than those with lymph node metastasis, i.e. 85-95 % vs. 40-60 % (Finan et al., 1996; Moore and Stehman, 1996; Landoni et al., 1997; Takeda et al., 2002; Ho et al., 2004). Similarly, in our study, nodal status did have an impact on disease-free survival. From multivariate analysis, women with lymph node metastasis were 2.6 times more likely to develop recurrent disease than those with negative nodes.

LVSI was noted in 47.4% of radical hysterectomy specimens in the present study. Although the incidence of LVSI was significantly higher among stage IB 2 specimens than those with stage IB 1 (51.1% vs. 28.2%, respectively), LVSI remained an independent risk factor for predicting survival when adjusted by other clinico-pathological factors including tumor size. Patients with LVSI existing in hysterectomy specimens carried a significantly higher risk of having recurrent disease (adjusted HR=2.56, CI=1.21-5.45). Nonetheless, the relationship between LVSI and survival outcomes among women with stage IB cervical cancer in the literature is still controversial. Some previous studies concluded that LVSI was a significant factor for predicting survival (Zaino et al., 1992; Takeda et al., 2002; Ho et al., 2004; Rutledge et al., 2004) while others did not observe this correlation (Barber et al., 1978; van Nagell et al., 1978; Abdulhayoglu et al., 1980; Chung et al., 1980; Lee et al., 2011). This might be partly due to the differences in the details of specimen preparation technique, i.e. number of pathological section evaluated and inter-observer variability in determining LVSI between individual pathologists(Wright et al.,2001).

The prognostic value of histology subtypes in women with early stage cervical cancer is still inconclusive (Harrison et al., 1993; Finan et al., 1996; Grisaru et al., 2001; Takeda et al., 2002; Ho et al., 2004; Rutledge et al., 2004; Lee et al., 2006; Biewenga et al., 2011). This would be due to a wide variation between an individual study, mainly in the number of sample size, treatment modality and stage of disease. In a small series or those including women with stage IA disease, the difficulty in demonstrating a significant difference in survival outcomes between groups with various histologic subtypes is expected. When considering particular studies derived from a large cohort or population-based, patients with non-squamous cervical cancer carried poorer survival outcomes than that in patients with squamous cell carcinoma histology (Lau et al., 2009; Macdonald et al., 2009; Suprasert et al., 2010; Lee et al., 2011). For example, previous studies using the Surveillance, Epidemiology, and End Results (SEER) database which analyzed data of 4559 women with cervical cancer who had undergone radical hysterectomy observed that adenocarcinoma histology represented an aggressive histology phenotype and was associated with poorer survival (Macdonald et al., 2009). Recently, in a study by Lee et al. (Lee et al., 2011) which was conducted to determine the survival outcomes stratified by histologic subtype (pure adnocarcinoma vs. squamous cell carcinoma) in 755 women with stage IB-IIA cervical cancer after radical hysterectomy, adenocarcinoma histology posed a worse survival outcome than squamous cell carcinoma. In our study, women with non-squamous cell carcinoma histology were 3.4 times more likely to develop recurrent disease. These results, therefore re-emphasize the adverse prognosis of non-squamous cell carcinoma of the cervix and indicate the need to develop appropriate treatment modality in order to improve survival outcomes in patients with these high-risk factors.

The strength of this study included a considerably adequate sample size for the main outcomes with uniform surgical techniques for all patients in a single institution. Additionally, all pathologic specimens were examined by experienced gynecologic pathologists in our institute. However, due to the retrospective design of the study, other information for determining treatment outcomes, i.e. details of adjuvant treatment and surgical complications were unavailable.

In conclusion, with primary radical hysterectomy,

stage IB 1 cervical cancer patients have significantly better disease-free survival than those with stage IB 2. Other significant prognostic factors for predicting disease-free survival among patients with stage IB cervical cancer are tumor histology, nodal status, and the presence of lymph-vascular space invasion.

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