RESEARCH ARTICLE

Locoregional Spread and Survival of Stage IIA1 versus Stage IIA2 Cervical Cancer

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Abstract

This study was undertaken to compare surgical outcomes and survival rates of patients with the 2009 International Federation of Gynecology and Obstetrics (FIGO) stage IIA1 versus IIA2 cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy (RHPL). Patients with stage IIA cervical cancer undergoing primary RHPL between January 2003 and December 2012 at Chiang Mai University Hospital were retrospectively reviewed. The analysis included clinicopathologic variables, i.e. nodal metastasis, parametrial involvement, positive surgical margins, deep stromal invasion (DSI)), lymph-vascular space invasion (LVSI), adjuvant treatment, and 5-year survival. The chi square test, Kaplan-Meier method and log-rank test were used for statistical analysis. During the study period, 133 women with stage IIA cervical cancer, 101 (75.9 %) stage IIA1, and 32 (24.1 %) stage IIA2 underwent RHPL. The clinicopathologic variables of stage IIA1 compared with stage IIA2 were as follows: nodal metastasis (38.6% vs 40.6%, p=0.84), parametrial involvement (10.9% vs 15.6%, p=0.47), positive surgical margins (31.7% *vs* 31.3%, p=1.0), DSI (39.6% *vs* 53.1%, p=0.18), LVSI (52.5% *vs* 71.9%, p=0.05) and adjuvant radiation (72.3% *vs* 84.4%, p=0.33). With a median follow-up of 60 months, the 5-year disease-free survival (84.6% *vs* 88.7%, p=0.67) and the 5-year overall survival (83.4% vs 90.0%, P=0.49) did not significantly differ between stage IIA1 and stage IIA2 cervical cancer. In conclusion, patients with stage IIA1 and stage IIA2 cervical cancer have comparable rates of locoregional spread and survival. The need for receiving adjuvant radiation was very high in both substages. The revised 2009 FIGO system did not demonstrate significant survival differences in stage IIA cervical cancer treated with radical hysterectomy. Concurrent chemoradiation should be considered a more suitable treatment for patients with stage IIA cervical cancer.

Keywords: Cervical cancer - stage IIA - survival - radical hysterectomy

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Introduction

Cervical cancer is the most common gynecologic malignancy in developing countries (Jemal et al., 2011). In Thailand, cervical cancer ranks second after breast cancer and is still a major public health problem. The age standardized incidence rate of cervical cancer and deaths from this cancer in Thailand is 24.5 and 12.8 per 100,000 women per year, respectively (Ferlay et al., 2010).

The International Federation of Gynecology and Obstetrics (FIGO) recently revised the staging system for cervical cancer especially stage IIA which has been subclassified into stage IIA1 and stage IIA2 based on the tumor size (≤4 cm and >4cm, respectively) (Pecorelli et al., 2009). Several studies have shown that a tumor size of larger than 4cm significantly reduces the disease-free survival and overall survival comparing to a smaller tumor (Delgado et al., 1990; Perez et al., 1998; Quinn et al., 2006; Horn et al., 2007). Management of early-stage cervical cancer (stage IB-IIA) includes either radical hysterectomy with pelvic lymphadenectomy (RHPL), or radiation therapy, which have been considered equally effective in terms of local control and survival (Hopkins and Morley, 1991; Landoni et al., 1997). Radical hysterectomy is an optimal treatment in young women with the major benefits of preserving both sexual and hormonal functions. This treatment modality also provides additional information of surgico-pathological risk factors affecting survival outcome of the patients. After surgery, adjuvant radiation is recommended in patients with high- risk pathological factors, i.e. positive pelvic nodes, positive parametrium and positive surgical margin to reduce pelvic recurrence (Soisson et al., 1990). A previous large study noted that patients with stage IIA2 cervical cancer were at higher risk to receive postoperative adjuvant radiation than those with stage IIA1 (77.5% *vs* 60.5%, respectively) (Garg et al., 2011).

The objective of this study was to compare the rate of locoregional spread and survival of patients with stage IIA1 to those with stage IIA2 cervical cancer who were

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treated with primary radical surgery in our institution.

Materials and Methods

After the Research Ethics Committee approval, medical records of patients with stage IIA cervical cancer undergoing RHPL between January 2003 and December 2012 at Chiang Mai University Hospital were reviewed. All cases were identified from the clinical database of the Gynecologic Oncology Division. Clinical charts, operative reports and pathology reports were reviewed. Patients with stage IIA cervical cancer were classified as stage IIA1 group based on a tumor size of ≤4cm and as stage IIA2 group if the tumor size was >4cm. The clinical tumor size was determined by gynecologic oncologists. The operation was carried out with initial pelvic lymphadenectomy followed by radical hysterectomy. The systematic pelvic lymphadenectomy was carried out by removing all fatty tissue along both sides of the common iliac, external iliac, and internal iliac vessels, and also the lymphatic tissue in the obturator fossa. Para-aortic lymphadenectomy was performed only when gross metastasis to the common iliac nodes or para-aortic nodes was suspected. All slides were reviewed by gynecologic pathologists.

Patients with any high-risk pathological factors such as lymph node metastasis, parametrial invasion or positive surgical margins for cancer and patients who had two intermediate-risk pathological factors including deep stromal invasion (DSI) and lymph-vascular space invasion (LVSI) received adjuvant concurrent chemoradiation with platinum- based chemotherapeutic regimen. Radiation alone was administered in patients who refused chemotherapy or with a poor performance status. Vaginal brachytherapy was given in patients with positive surgical margin for high-grade squamous intraepithelial lesion (HSIL).

After completion of treatment, all patients were followed up at our hospital every 3 months in year 1, every 4 months in year 2, then every 6 months up to year 5 and yearly thereafter. The period between the date of surgery and the date of recurrence diagnosis or the date of the last follow up was defined as disease-free interval. Overall survival was calculated considering the period between the date of surgery and the date of death.

Proportion (%) was used to describe categorical data. Descriptive data were listed as mean (standard deviation) and discrete data were reported as number (percentage). Differences between the two groups in categorical variables such as clinical stage, histology, parametrial involvement, surgical margin status, DSI, LVSI, adjuvant treatment, and the recurrence rate were assessed using Chi square and Fisher's exact test. The overall survival and the disease-free survival were estimated using Kaplan-Meier methods and were tested for statistical significance using log-rank test. All statistical analyses were two-tailed, and p-value of less than 0.05 was considered statistical significance. All analyses were performed using SPSS statistical software, version 12 (SPSS Inc., Chicago, IL).

Results

During the study period, 133 patients with stage IIA cervical cancer, 101 (75.9%) stage IIA1, and 32 (24.1%) stage IIA2 were treated with RHPL. Clinicopathologic variables of the stage IIA1and stage IIA2 patients were shown in Table 1. Mean ages, pelvic lymphadenectomy, pelvic and para-aortic lymphadenectomy and total number of nodes removed were similar in both groups. There was no statistically significant difference between stage IIA1 and stage IIA2 with regard to nodal metastasis, parametrial involvement, positive surgical margin, DSI, LVSI, ovarian metastasis, and adjuvant treatment. Patients with stage IIA2 cervical cancer displayed statistically significant higher proportion of adenocarcinoma histology and

Table 1. Clinicopathologic Variables of Patients with Stage IIA1 versus Stage IIA2 Cervical Cancer

Variables	Stage IIA1 (N=101)	Stage IIA2 (N=32)	p value
Age, years			
Mean (SD)	46 (8.6)	43 (6.6)	0.098
Lymphadenectomy			0.19
Pelvic	101 (100.0%)	32 (100.0%)	
Pelvic and Para-aortic	13 (12.9%)	1 (3.1%)	
Total number of nodes removed			
Means (SD)	27 (11)	29 (12)	0.41
Operation time (minute) (SD)	218 (48)	217 (47)	0.88
Blood loss (ml.) (SD)	535(425)	560(539)	0.76
Cell type			< 0.01
Squamous cell carcinoma	79 (78.2 %)	7 (21.9 %)	
Adenocarcinoma	18 (17.8 %)	19 (59.4 %)	
Adenosquamous	3 (3.0 %)	5 (15.6 %)	
Neuroendocrine	1 (1.0%)	1 (3.1 %)	
Tumor grade			0.96
Well differentiated	31 (30.7 %)	9 (28.1 %)	
Moderately differentiated	52 (51.5 %)	17 (53.1 %)	
Poorly differentiated	18 (17.8 %)	6 (18.8 %)	
Lymph node status			0.84
Negative	62 (61.4 %)	19 (59.4 %)	
Positive	39 (38.6 %)	13 (40.6 %)	
Parametrial involvement	11 (10.9 %)	5 (15.6 %)	0.47
Lymph-vascular space invasion			0.05
Negative	48 (47.5 %)	9 (28.1 %)	
Positive	53 (52.5 %)	23 (71.9 %)	
Deep stromal invasion ≤ 3 mm	40 (39.6%)	17 (53.1%)	0.18
Vaginal margin status			1
Negative	69 (68.3 %)	22 (68.7 %)	
Positive for HSIL	20 (19.8 %)	7 (21.9 %)	
Positive for cancer	12 (11.9 %)	3 (9.4 %)	
Ovarian metastasis	1 (1.0 %)	1 (3.1%)	0.42
Postoperative treatment			0.33
None	28 (27.7 %)	5 (15.6 %)	
Radiation therapy	20 (19.8 %)	6 (18.8 %)	
Chemoradiation	53 (52.5 %)	21 (65.6 %)	
Recurrence			0.28
Pelvis	7 (6.9 %)	2 (6.3 %)	
Distant	8 (7.9 %)	-	

*Outcomes were presented as number (percentage), except for age, total number of nodes removed, operation time and blood loss presented as mean (standard deviation).

Table 2. Treatment-Related Complications

Complications	Stage IIA1 (N =101)	Stage IIA2 (N =32)	P-value
Excessive blood loss	14 (13.9 %)	5 (15.6 %)	0.8
Urinary tract injury	1 (1.0 %)	1 (3.1%)	0.42
Bowel obstruction	1 (1.0 %)	-	1
Pelvic abscess	1 (1.0 %)	-	1
Severe lymphedema	3 (3.0 %)	-	1
Persistent lymphocyst	2 (2.0 %)	1 (3.1%)	0.56
Persistent bladder dysfunction	2 (2.0 %)	-	1
Radiation osteonecrosis	1 (1.0 %)	-	1

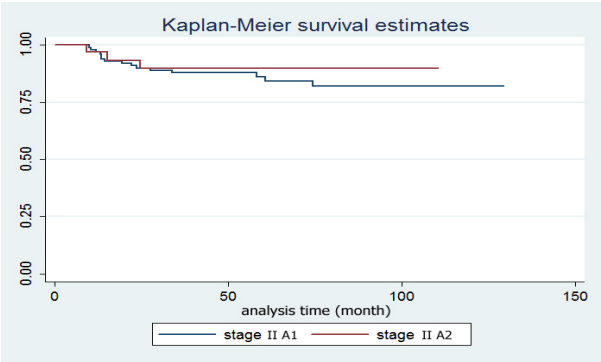

Figure 1. 5-year Disease - Free Survival of Patients with Stage IIA1 versus Stage IIA2 Cervical Cancer

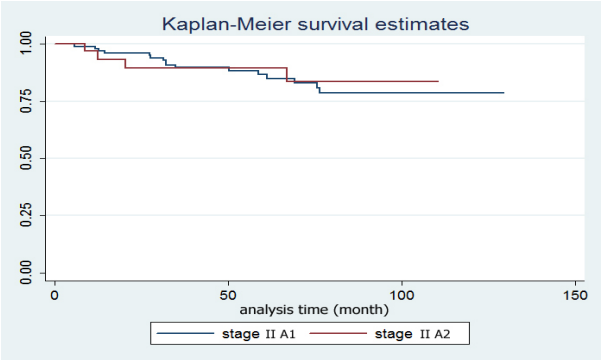

Figure 2. 5-year Overall Survival of Patients with Stage IIA1 versus Stage IIA2 Cervical Cancer

positive LVSI than those with stage IIA1 (59.4% *vs* 17.8 %, p<0.01, and 71.9% *vs* 52.5%, p=0.05, respectively). The need for postoperative adjuvant radiation with or without chemotherapy was 72.3% for stage IIA1 and 84.4% for stage IIA2. Fifteen (14.8%) patients with stage IIA1 developed recurrence of which eight had distant recurrence in lung, liver, brain, bone, and supraclavicular lymph node. For stage IIA2, two (6.3%) patients had pelvic recurrence and no patient had distant recurrence. Treatment-related complications are summarized in Table 2. Massive intraoperative blood loss (≥1,000 ml) occurred in 14 (13.9%) patients with stage IIA1 and 5 (15.6%) patients with stage IIA2. Three (3.0%) patients in stage IIA1 disease developed severe lymphedema; all of them received adjuvant radiation after the operation. Prolonged bladder dysfunction (≥6 weeks) was noted in two (2.0%) patients with stage IIA1disease. With a median follow-up of 60 months (range, 8-129 months), there was no statistically significant difference in the survival outcomes between stage IIA1 and stage IIA2 cervical cancer. The 5-year disease-free survivals were 84.6% and 88.7% for stage IIA1 and stage IIA2, respectively (p=0.67) (Figure 1). The 5-year overall survivals were 83.4% and 90.0% for stage IIA1 and stage IIA2, respectively (p=0.49) (Figure 2).

Discussion

The present study demonstrated comparable disease-free survival and overall survival between stage IIA1 and IIA2 cervical cancer treated with radical hysterectomy. This finding is in line with the previous studies (Garg et al., 2011; Lai et al., 2013).

Lymph node metastasis has important prognostic value for early-stage cervical cancer. Systematic pelvic lymphadenectomy is an important part of surgical treatment for early-stage cervical cancer. The mean or median number of pelvic nodes removed varied from 13-65 in previous reports (Sakuragi, 2007; Hosaka et al., 2011). In the EORTC-GCG study, removal of more than 11 pelvic nodes was suggested as one of the quality indications for pelvic lymphadenectomy (Verleye et al., 2009). In the present study, the mean number of nodes removed was 27 in stage IIA1cervical cancer and 29 in stage IIA2 which were well within the usual range. The incidence of lymph node metastasis in stage IIA cervical carcinoma was reported to range from 21.4% to 46% (Garg et al., 2011; Lai et al., 2013). Such incidence in our study was 38.6% for stage IIA1 and 40.6% for stage IIA2 which were comparable with those from the previous studies.

The previous studies found that LVSI was a factor associated with decreased survival (Takeda et al., 2002; Ho et al., 2004). In this study, women with stage IIA2 cervical cancer had a higher rate of positive LVSI than those with stage IIA1 (71.9% *vs* 52.5, p=0.05). Also, some studies have suggested that adenocarcinoma histology is associated with poorer outcome compared to squamous histology (Lai et al., 1999; Takeda et al., 2002; Macdonald et al., 2009; Mabuchi et al., 2012). In the current study, the higher incidence of adenocarcinoma histology in stage IIA2 cervical cancer was also demonstrated. However, the higher rates of these risk factors in the patients with stage IIA2 cancer did not translate into significantly worse survival outcome.

The incidence of ovarian metastases in early-stage cervical carcinoma in previous studies ranged from 0.5 to 19% (Sutton et al., 1992; Shimada et al., 2006; Landoni et al., 2007; Ngamcherttakul and Ruengkhachorn, 2012). Adenocarcinoma histology and age more than 45 years were statistically associated with the presence of ovarian metastases. In our study, we found the ovarian metastases in two patients, one (1.0%) in stage IIA1 (squamous cell carcinoma with age 56 years) and one (3.1%) in stage IIA2 (mucinous adenocarcinoma with age 52 years).

The reported incidence of parametrial invasion in early-stage cervical cancer was 5-30% (Trattner et al., 2001;Covens et al., 2002; Steed et al., 2006; Frumovitz et al., 2009). In our study, the rates of parametrial invasion were comparable between the groups (10.9 % in stage IIA1 *vs* 15.6 % in stage IIA2, p=0.47).

The SWOG 8797 study demonstrated the superior outcome of postoperative adjuvant CCRT compared to radiation therapy alone for stage IA2- IIA cervical cancer patients with high risk pathologic factors following radical hysterectomy (Peters et al., 2000). In our study, the need for postoperative adjuvant radiation alone or CCRT was very high in both study groups (72.3% in stage IIA1 and 84.4% in stage IIA2). Concerns regarding treatment-related toxicity have led some to question the suitability of giving combined treatment using both radical surgery and concurrent chemoradiation in patient stage IIA cervical cancer especially for those with stage IIA2. Given the high rate of postoperative radiation in this group of patients

with stage IIA cervical cancer, primary surgery can be reasonably omitted and chemoradiation should play an active role as a primary treatment. However, the role of neoadjuvant chemotherapy followed by radical surgery and tailored postoperative radiation would need further exploration.

The strength of the present study was the inclusion of the patients who were treated at a single institution. Thus, variation in operative techniques and treatment protocol was minimal. Moreover, all pathologic specimens were examined by expert gynecologic pathologists. However, certain limitations exist. As the design of this study was retrospective, some important data such as the parity of the patients and the patients' body mass index were not available.

In conclusion, the revised FIGO 2009 staging system for stage IIA cervical cancer did not represent different locoregional spread and survival outcomes between the two substages in our study population. Due to the high rate of adjuvant radiation, concurrent chemoradiation should be considered in patients with stage IIA2 cervical cancer.

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