RESEARCH ARTICLE

Surgical Outcomes of Patients with Stage IA2 Cervical Cancer Treated with Radical Hysterectomy

Sukanda Mahawerawat[1], Kittipat Charoenkwan[1], Jatupol Srisomboon[1], Surapan Khunamornpong[2], Prapaporn Suprasert[1], Charuwan Tantipalakorn Sae-Teng[1]*

Abstract

Background: This study was undertaken to evaluate the surgical outcomes of patients with stage IA2 cervical cancer treated with radical hysterectomy. Data for 58 patients who underwent modified radical hysterectomy or radical hysterectomy with pelvic lymphadenectomy between January 2003 and December 2012 at Chiang Mai University Hospital were retrospectively reviewed. The analysis included clinico-pathological risk factors (nodal metastasis, parametrial involvement), adjuvant treatment, 5-year disease-free survival and 5-year overall survival. All pathologic slides were reviewed by a gynecologic pathologist. Follow-up methods included at least cervical cytology and colposcopy with directed biopsy if indicated. Univariate analysis was performed to identify factors associated with median survival. At the median follow up time of 73 months, the 5-year disease-free survival and the 5-year overall survival were 97.4% and 97.4%, respectively. Two (3.4%) patients had pelvic lymph node metastases. In a univariate analysis, there was no statistically significant association between survival and prognostic factors such as age, histological cell type, lymph-vascular space invasion, vaginal margin status and lymph node status. Surgical and survival outcomes of women with stage IA2 cervical cancer are excellent. No parametrial involvement was detected in our study. Patients with stage IA2 cervical cancer may be treated with simple or less radical hysterectomy with pelvic lymphadenectomy.

Keywords: Cervical cancer - stage IA2 - microinvasive cervical cancer

Asian Pac J Cancer Prev, **14 (9)**, 5375-5378

Introduction

Cervical cancer is the second most common cancer in women worldwide. The global yearly number of cervical cancer for 2008 was 530,232 and the annual deaths were 275,008. In Thailand the estimated annual numbers of new cases and deaths from cervical cancer were 9,999 and 5,216, respectively (Ferlay et al., 2010).

The International Federation of Gynecologists and Obstetricians (FIGO), in 1985, for the first time, quantified the histological definition of stage IA carcinoma of the cervix in that the maximum measurable invasion should not exceed 5 mm in depth and 7 mm in width.

Vascular space involvement, either venous or lymphatic, should not alter the staging. In 1994, FIGO revised the staging of stage I with subdivision to stage IA1 and IA2. Stage IA1 was defined as measured stromal invasion not greater than 3.0 mm in depth and horizontal extension of not greater than 7.0 mm. Stage IA2 was defined as measured stromal invasion of 3.0 mm and not greater than 5.0 mm with a horizontal extension of not greater than 7.0 mm. Vascular space involvement, either venous or lymphatic, should not alter the staging, but should be specifically recorded because it may affect treatment decisions. Microinvasive cancer can be diagnosed only microscopically. All visible macroscopic lesions even with limited invasion are classified as stage IB cancers (Creasman, 1999). The current FIGO staging system was recently updated in 2009, the definition of stage IA2 is still the same as FIGO 1994 (Pecorelli et al., 2009). The management of stage IA2 cervical cancer has been controversial. Modified radical hysterectomy (MRH) or radical hysterectomy (RH) with pelvic lymph node dissection (PND) has been the standard surgical treatment for patients with stage IA2 cervical cancer in many institutions. However, stage IA2 cervical cancer is often diagnosed in younger women. The conservative surgery for women wishing to preserve their fertility has been reported (Mejia-Gomez et al., 2012). The incidence of lymph node metastasis in stage IA2 cervical carcinoma ranged from 0-9.7% (Pluta et al., 2009; Rogers and Luesley, 2009). Lymph-vascular space invasion (LVSI) seems to be an important risk factor for lymph node metastases in stage IA2 cervical cancer (Rogers and Luesley, 2009).

The surgical outcomes are excellent with a 5-year overall survival rate of 95-100% in stage IA cervical cancer (Webb et al., 2001; Quinn et al., 2006). Although

*[1]Department of Obstetrics and Gynecology, [2]Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand *For correspondence: ctantipa@mail.med.cmu.ac.th*

the radical hysterectomy has a long tradition, surgical treatment for early-stage cervical cancer has been developing substantially over the last 10-15 years, especially toward a better understanding of anatomy and tailored radicality according to prognostic parameters (Pluta et al., 2009; Ditto et al., 2011).

The primary purpose of this study was to evaluate surgical outcomes and to determine the significant prognostic factors affecting survival of the patients with stage IA2 cervical cancer who had been treated at the Gynecologic Oncology Division, Chiang Mai University Hospital, Thailand.

Materials and Methods

A retrospective analysis of patients with stage IA2 cervical cancer treated between January 2003 and December 2012 at Chiang Mai University Hospital, Chiang Mai, Thailand was performed. All cases were identified from the clinical database of the Gynecologic Oncology Division. Clinical charts, operative reports and pathology reports were reviewed for all patients. Stages were assigned according to the 2009 FIGO staging system (Pecorelli et al., 2009).

All previously untreated patients with stage IA2 cervical cancer were eligible. Exclusion criteria included patients with recurrent cervical cancer, other gynecological malignancies and pregnancy. The MRH with PND was performed in patients with the absence of LVSI and RH and PND were done in the patients with the presence of LVSI or the presence of cancer cells in endocervical curettage specimens from the loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC). The systematic pelvic lymphadenectomy in the study 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 a gynecologic pathologist. In addition to the pathological variables of the cervical tumor, time to recurrence, disease-free survival and overall survival were obtained.

Pathological variables of the cervical tumor were considered as follows: *i*) Histological cell type; *ii*) Depth of stromal invasion; *iii*) LVSI, considered as positive if tumor cells were found in the lymphovascular spaces; *iv*) parametrial involvement; *v*) lymph node status; and *vi*) vaginal margin status.

After primary surgical treatment, all women were followed up at our hospital every three months for one year, every four months in the second year, and every six months up to five years and yearly thereafter. Follow-up methods included at least cervical cytology and colposcopy with directed biopsy if indicated. The period between the date of surgery and the date of recurrence diagnosis or the date of last follow up was defined as disease-free survival. Overall survival was defined as the period between the date of surgery and the date of death. This study was approved by the Research Ethics Committee at Faculty of Medicine, Chiang Mai University.

The overall survival and the disease-free survival were analyzed using the Kaplan- Meier methods and the difference was tested for statistical significance using the log-rank test. Mean was used to describe continuous data. Proportion (%) was used to describe categorical data. Descriptive data were listed as mean (standard deviation) and discrete data were reported as number (percentage). The p value of <0.05 was considered statistically significant. All analyses were performed using SPSS statistical software, version 12 (SPSS Inc., Chicago, IL).

Results

Fifty-eight patients were identified in this study. Clinico-pathological variables of the patients are shown in Table 1. The mean age of the study group was 48.5 years (SD 9.0). Of 58 patients, 53 (91.4%) were diagnosed with stage IA2 cervical cancer from the LEEP and five (8.6%) were diagnosed from the CKC. Surgery consisted of MRH in 12 (20.6%) patients and RH in 46 (79.4%) patients. Forty three patients (74.1%) underwent bilateral salpingo-oophorectomy, and three (5.2%) underwent unilateral salpingo- oophorectomy because of benign ovarian tumor. PND was done in all patients. In addition, four patients had both pelvic and para-aortic lymphadenectomy. The mean number of nodes removed was 23 (range 4-49). Two (3.4%) patients had pelvic lymph node metastases. All of the 58 patients, no parametrial involvement was found. Forty-nine patients (84.5%) had no residual disease in the hysterectomy specimens. Nine patients (15.5%) had residual HSIL, and none had residual cancer.

Among 58 patients, 12 (20.7%) patients had massive intra-operative blood loss (≥ 1,000 ml), 2 (3.4%) had accidental tear of the vagina, and 2 (3.4%) had febrile morbidity. Regarding late complications, significant lymphedema occurred in 2 (3.4%) patients, bladder dysfunction was found in 5 (8.6%) patients with the duration between 6 weeks to 6 months. One (1.7%) patient developed lymphocyst at 6 weeks after surgery

Table 1. Clinico-Pathological Variables of Patients with Stage IA2 Cervical Cancer

Clinico-pathological variables			Outcomes*
Age, years	Mean (SD)		48.5 (9.0)
Operation	Modified radical hysterectomy		12 (20.6)
	Radical hysterectomy		46 (79.4)
Lymphadenectomy			
	Pelvic lymphadenectomy		54 (93.1)
	Pelvic and paraaortic lymphadenectomy		4 (6.9)
Total number of node remove		Mean (SD)	23 (8.9)
Salpingo-oophorectomy		None	12 (20.7)
		Unilateral	3 (5.2)
		Bilateral	43 (74.1)
Cell type	Squamous cell carcinoma		47 (81.0)
	Adenocarcinoma		11 (19.0)
LVSI**	Negative		52 (89.7)
	Positive		6 (10.3)
Lymph node status		Negative	56 (96.6)
		Positive	2 (3.4)
Vaginal margin positive for HSIL		Negative	55 (94.8)
		Positive	3 (5.2)

*Outcomes were presented as number (percentage), except for age and total number of nodes removed presented as mean (standard deviation) **LVSI: lymph-vascular space invasion

Table 2. Prognostic Significance of Clinico - Pathological Variables

Variables		Median survival (range, months)	p value
Age (y)	<60	73.1 (27-120)	
	≥60	84.5 (24-105)	0.06
Cell type	SCCA	73.8 (27-120)	
	Adenocarcinoma	72 (24-114)	0.59
LVSI	Negative	73 (24-120)	
	Positive	80 (27-100)	1.00
Lymph node status	Negative	73.1 (24-120)	
	Positive	75.7 (54-98)	1.00
Vaginal margin status	Negative	73.8 (24-120)	
	Positive for HSIL	53.5 (27-100)	1.00

*SCCA: squamous cell carcinoma, HSIL: high-grade squamous intraepithelial lesion, LVSI: lymph-vascular space invasion

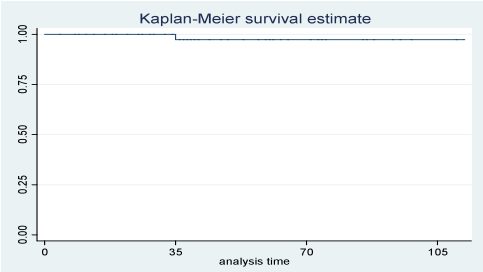

Figure 1. The Probability of 5-year Overall Survival (months) of Women with Stage IA2 Cervical Cancer

and spontaneously resolved at 3 months. Partial bowel obstruction occurred in 1 (1.7%) patient at 1 month post radical hysterectomy.

Table 2 shows the results of a univariate analysis of the association between the median survival and clinico-pathological variables including age, histological cell type, lymph-vascular space invasion, lymph node status and vaginal margin status. No statistically significant association was detected.

Postoperative concurrent chemoradiation with cisplatin was administered in two (3.4%) cases due to pelvic lymph node metastases. Postoperative vaginal brachytherapy was given in three (5.2%) cases because of positive vaginal margin for HSIL.

With a median follow-up of 73 months, the 5-year disease-free survival was 97.4% and the 5-year overall survival was 97.4% (Figure 1).

During the follow-up period, 1 patient presented with a skull mass 3 years after the operation. Fine needle aspiration showed metastatic poorly differentiated carcinoma. She was 60 years old at initial diagnosis of stage IA2 squamous cell cervical carcinoma and treated with MRH with BPND, No high or intermediate-risk pathological factor was identified. She had underlying chronic obstructive pulmonary disease and died of this disease.

Discussion

In our analysis, the surgical outcomes of stage IA2 cervical cancer is excellent, the 5- year disease-free survival was 97.4% and the 5-year overall survival was 97.4%. Most patients underwent RH with PND. It has been suggested that stage IA2 cervical cancer with LVSI should be treated with the RH with PND (Kolstad, 1989;Benedet and Anderson, 1996). In our institute, we perform the MRH with PND in patients with absent LVSI and perform the RH and PND in the patient with present LVSI or positive cancer in endocervical curettage specimens from LEEP or CKC.

Many authors believed that the presence of tumor cells in such vessels is an adverse prognostic factor and that these patients should be treated aggressively. In our study, six (10.3%) patients had positive LVSI and there was no statistically significant difference in the median survival when compared with those without LVSI. Given the small sample size, it is likely that this study did not have adequate power to detect the association of LVSI and treatment outcome, which has been demonstrated in other larger studies(Kolstad, 1989; Burghardt et al., 1991).

Nodal spread has been universally accepted as the single most important prognostic factor for early invasive 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). The variation in number of nodes removed depended on several factors, including anatomy of the patient, status of local inflammation, extent of surgery, processing of the specimen, and its examination by pathologists (Sakuragi, 2007). In the present study, the mean number of nodes removed was 23 which was well within the usual range. The incidence of lymph node metastasis in stage IA2 cervical carcinoma was reported to range from 0-9.7% (Pluta et al., 2009; Rogers and Luesley, 2009). Such incidence in our study was 3.4% which was comparable with that from the previous studies.

In the previous studies (Mabuchi et al., 2012; Spoozak et al., 2012), for stage IA2 cervical cancer, survival was similar for squamous cell carcinoma and adenocarcinoma (hazard ratio, 0.51; 95% confidence interval, 0.18-1.47). In our study, the patients with adenocarcinoma histology displayed a similar outcome to those with squamous cell carcinoma histology.

Early-stage cervical carcinoma rarely metastasizes to ovary. The incidence reported in published series ranged 0-0.9% (Tabata et al., 1987; Toki et al., 1991; Landoni et al., 2007). Therefore, ovarian preservation at the time of radical hysterectomy in young patient undergoing surgery for early-stage cervical cancer seems to be relatively safe. There was no evidence of ovarian metastasis in the present study in patients who had the ovaries removed.

The risk of parametrial spread in women with microinvasive cervical cancer appears to be low (Covens et al., 2002). In our study, most of the patients underwent RH and no parametrial invasion was detected. We suggest the role of simple extrafascial hysterectomy in stage IA2 cervical cancer because radical or modified radical hysterectomy has high rate of urologic morbidity. A prospective randomized trial comparing class I versus class III radical hysterectomy showed no significant differences in overall 5-year survival between the two

groups (Landoni et al., 2012). We open new interesting way to upcoming protocols for the less extent surgery of these tumors.

The strength of the present study was the inclusion of the patients who were treated at a single institution with long-term follow-up. Thus, variation in operative techniques 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. Secondly, this study contained a relatively small sample size owing to the rarity of patients in the stage IA2 cervical cancer in our institute.

In conclusion, surgical and survival outcomes of women with stage IA2 cervical cancer are excellent. No parametrial involvement is detected in our study. Patients with stage IA2 cervical cancer may be treated with simple or less radical hysterectomy with pelvic lymphadenectomy.

References

Benedet JL, Anderson GH (1996). Stage IA carcinoma of the cervix revisited. *Obstet Gynecol*, **87**, 1052-9.

Burghardt E, Girardi F, Lahousen M, et al (1991). Microinvasive carcinoma of the uterine cervix (International Federation of Gynecology and Obstetrics Stage IA). *Cancer*, **67**, 1037-45.

Covens A, Rosen B, Murphy J, et al (2002). How important is removal of the parametrium at surgery for carcinoma of the cervix? *Gynecol Oncol*, **84**, 145-9.

Creasman WT (1999). Stage IA cancer of the cervix: finally some resolution of definition and treatment? *Gynecol Oncol*, **74**, 163-4.

Ditto A, Martinelli F, Mattana F, et al (2011). Class III nerve-sparing radical hysterectomy versus standard class III radical hysterectomy: an observational study. *Ann Surg Oncol*, **18**, 3469-78.

Ferlay J, Shin HR, Bray F, et al (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, **127**, 2893-917.

Hosaka M, Watari H, Mitamura T, et al (2011). Survival and prognosticators of node-positive cervical cancer patients treated with radical hysterectomy and systematic lymphadenectomy. *Int J Clin Oncol*, **16**, 33-8.

Kolstad P (1989). Follow-up study of 232 patients with stage Ia1 and 411 patients with stage Ia2 squamous cell carcinoma of the cervix (microinvasive carcinoma). *Gynecol Oncol*, **33**, 265-72.

Landoni F, Maneo A, Zapardiel I, et al (2012). Class I versus class III radical hysterectomy in stage IB1-IIA cervical cancer. A prospective randomized study. *Eur J Surg Oncol*, **38**, 203-9.

Landoni F, Zanagnolo V, Lovato-Diaz L, et al(2007). Ovarian metastases in early-stage cervical cancer (IA2-IIA): a multicenter retrospective study of 1965 patients (a Cooperative Task Force study). *Int J Gynecol Cancer*, **17**, 623-8.

Mabuchi S, Okazawa M, Kinose Y, et al (2012). Comparison of the prognoses of FIGO stage I to stage II adenosquamous carcinoma and adenocarcinoma of the uterine cervix treated with radical hysterectomy. *Int J Gynecol Cancer*, **22**, 1389-97.

Mejia-Gomez J, Feigenberg T, rbel-Alon S, et al(2012). Radical trachelectomy: a fertility- sparing option for early invasive cervical cancer. *Isr Med Assoc J*, **14**, 324-8.

Pecorelli S, Zigliani L, Odicino F (2009). Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet*, **105**, 107-8.

Pluta M, Rob L, Charvat M, et al (2009). Less radical surgery than radical hysterectomy in early stage cervical cancer: a pilot study. *Gynecol Oncol*, **113**, 181-4.

Quinn MA, Benedet JL, Odicino F, et al (2006). Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet*, **95**, 43-103.

Rogers LJ, Luesley DM (2009). Stage IA2 cervical carcinoma: how much treatment is enough? *Int J Gynecol Cancer*, **19**, 1620-4.

Sakuragi N (2007). Up-to-date management of lymph node metastasis and the role of tailored lymphadenectomy in cervical cancer. *Int J Clin Oncol*, **12**, 165-75.

Spoozak L, Lewin SN, Burke WM, et al (2012). Microinvasive adenocarcinoma of the cervix. *Am J Obstet Gynecol*, **206**, 80-6.

Tabata M, Ichinoe K, Sakuragi N, et al (1987). Incidence of ovarian metastasis in patients with cancer of the uterine cervix. *Gynecol Oncol*, **28**, 255-61.

Toki N, Tsukamoto N, Kaku T, et al (1991). Microscopic ovarian metastasis of the uterine cervical cancer. *Gynecol Oncol*, **41**, 46-51.

Verleye L, Vergote I, Reed N, et al (2009). Quality assurance for radical hysterectomy for cervical cancer: the view of the European Organization for Research and Treatment of Cancer-Gynecological Cancer Group (EORTC-GCG). *Ann Oncol*, **20**, 1631-8.

Webb JC, Key CR, Qualls CR, et al (2001). Population-based study of microinvasive adenocarcinoma of the uterine cervix. *Obstet Gynecol*, **97**, 701-6.