RESEARCH ARTICLE

Ovarian Metastasis and other Ovarian Neoplasms in Women with Cervical Cancer Stage IA-IIA

Vijit Ngamcherttakul[2], Irene Ruengkhachorn[1,2]*

Abstract

Objectives: To determine the prevalence and predicting factors of ovarian metastasis, and evaluate the histology of other ovarian neoplasms in women with early-stage cervical cancer. Methods: The medical records of women with cervical cancer stage IA-IIA who underwent primary surgical treatment at Siriraj Hospital, Mahidol University from January 2007 to December 2011 were used for the study. Demographic, clinical and histopathologic data of the women who underwent salpingo-oophorectomy were reviewed. Results: Of 264 women, the mean age was 52.3 years. The types of hysterectomy procedures were composed of 210 radical hysterectomy, 9 modified radical hysterectomy, 40 simple hysterectomy, and 5 abandoned hysterectomy. The prevalence of ovarian metastasis was 0.76% (2/264). All of ovarian metastatic patients were older than 60 years old, postmenopause, and had macroscopical stage IB1 cervical cancer. Others ovarian tumors were found in 7 patients including 1 synchronous ovarian carcinoma, 1 serous cystadenoma, 1 fibroma, and 4 teratoma. Conclusions: In cases of early-stage cervical carcinoma of the population studied, ovarian preservation could be another option in <60-year-old patients, with non-neuroendocrine cell type, stage IA, and no extracervical or ovarian lesions.

Keywords: Cervical cancer - early-stage - ovarian metastasis - surgery - ovarian preservation

Asian Pacific J Cancer Prev, **13 (9)**, 4525-4529

Introduction

In Thailand, cervical cancer has high burden with an age standardized incidence rate (ASR) of 18.1 per 100,000 person-years (Attasara et al., 2010). In GLOBOCAN 2008, the incidence was 9,999 and 5,216 women were dead from this disease in Thailand (Ferley et al., 2010). The early-stage cervical cancer has been detected increasingly by the cytological screening program. The favorable oncologic outcomes of early-stage cervical cancer patients could be achieved from either primary surgery or concurrent chemoradiation therapy (CCRT). The main surgical interventions are class I-III hysterectomy and selective pelvic lymphadenectomy according to clinical staging of the diseases. Salpingo-oophorectomy is not required for surgical treatment procedures.

Nowadays, ovaries are still valuable organs beyond the menopausal period, by producing plenty of hormones. For benign gynecologic diseases, the risk of death from surgical menopausal associated diseases such as osteoporosis, hip fracture, coronary heart disease or stroke were higher than the risk from ovarian cancer. Patients' survival times were significantly reduced when an incidental oophorectomy was performed in patients who were <65 years old. Therefore, the accepted patients' age in which a prophylactic oophorectomy could be performed was ≥65 years old (Parker et al., 2005).

Ovarian preservation has been considered for improving the quality of life in young cervical cancer patients. However, this issue remains controversial because of awareness of ovarian metastasis. Literature reports the rate of ovarian metastasis in cervical cancer as 0.5-11% (Toki et al., 1991; Natsume et al., 1999; Shimada et al., 2006). A retrospective study in 597 patients with stage IB-IIB cervical cancer, presented the rate of ovarian metastasis was 0.5%. After classified by histopathology, the rate in squamous cell carcinoma (SCCA) and adenocarcinoma were 0.19% and 5.5%, respectively. The authors suggested bilateral salpingo-oophorectomy in adenocarcinoma of cervix (Toki et al., 1991). Natsume et al. studied 82 patients with non-squamous cell cervical carcinoma, and found that deep stromal invasion (DSI) was the only independent risk factor for ovarian metastasis (Natsume et al., 1999). Because the ovarian metastasis rate had a wide proportion with inconclusive predictors, clinicians have difficulty deciding whether to perform incidental bilateral salpingo-oophorectomy or keep the ovaries to maintain hormonal function.

This study was undertaken in the area of high incidence of cervical cancer. The purposes of this study were (i) to assess the rate and (ii) factors associated with ovarian metastasis, (iii) and to determine the histology of patients

*[1]Gynecologic Oncology Division, [2]Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok , Thailand *For correspondence: irene_siriraj@yahoo.com*

that have salpingo-oophorectomy due to other ovarian diseases in women with early-stage cervical carcinoma.

Materials and Methods

The sample size was determine by using the expected percentage of ovarian metastasis 9% (as presented in extensive research regarding ovarian metastasis in cervical cancer), the distance from prevalence to the estimate was 0.04, the confidence limit of 95%, and two-sided interval analyses. Following the stardard calculation, the study required a minimum of 220 samples. After approval by the Siriraj Institutional Review Board, the computerized database of stage IA-IIA cervical cancer patients who had primary treatment by surgery between January 1, 2007 and December 31, 2011 was retrieved. The medical records of patients who had planned for primary surgical treatment and received a minimum of salpingo-ophorectomy were reviewed.

The data were collected on the baseline characteristics, clinical presentations, operative findings, histopathologic reports, and surgical outcomes.

In our institute, clinical staging was determined by co-operation of gynecologic and radiation oncologists according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) recommendations (Pecorelli et al., 2009). The surgical procedures were operated either with opened or laparoscopic approaches. In the situation of inoperable or any obviously metastatic diseases, tissue biopsy was sent for pathologic diagnosis and the hysterectomy procedure was abandoned. The histopathology of specimens were evaluated by one of three gynecologic pathologists and reviewed by all in doubtful cases. The histopathology types and grading were defined as the Broder's classification. DSI was determined by the invasion of cancer into the deep third of cervical stroma. Lymph-vascular space invasion (LVSI) was reported when both present and absent. Operators and anesthesiologists estimated intra-operative blood loss by calculating from suction with fluid input and output, and from surgical swabs. For the postoperative complications, urinary retention is defined as inability to void after postoperative day 7. Wound infection was diagnosed by attending physicians.

The statistic analyses were performed using SPSS 14 software. Data were presented in mean and standard deviation (SD), median, range, number (n) and percentage (%), as appropriate. The data were planned for analyses: Student t-test or Mann-Whitney U test were used for continuous data and Chi-square or Fisher's exact tests were used for categorical data. All tests were two-sided, and statistical significance was considered when a P value was <0.05.

Results

During the study period, the primary treatment of 385 stage IA1-IIA cervical cancer patients were planned for hysterectomy with/without pelvic node dissection. 264 patients underwent salpingo-oophorectomy as well. Of which, unilateral salpingo-oophorectomy were considered in 16 patients with unilateral ovarian cyst, and five patients with previous contralateral salpingo-oophorectomy for benign diseases. All of these, 21 patients, had no pelvic recurrence during a median follow-up period of 24

Table 1 Demographic Data and Tumor Characteristics of 264 Early-stage Cervical Cancer Patients with Salpingo-oophorectomy

Variables		No. of patients (%)	Ovarian Metastasis	
			No	Yes
Age (years)	≤ 45	57 (21.6)	57	0
	> 45	207 (78.4)	205	2
Menopausal status				
	Pre	130 (49.2)	130	0
	Post	134 (50.8)	132	2
Parity	Nulliparous	33 (12.5)	32	1
	Multiparous	231 (87.5)	230	1
Presenting symptoms				
	Check up	148 (56.1)	148	0
	Bleeding	88 (33.3)	87	1
	Discharge	15 (5.7)	15	0
	Pelvic pain	6 (2.3)	6	0
	Pelvic mass	1 (0.4)	1	0
	Others	(2.3)	5	1
FIGO stages	IA1	50 (18.9)	50	0
	IA2	10 (3.8)	10	0
	IB1	198 (75.0)	196	2
	IB2	3 (1.1)	3	0
	IIA1	3 (1.1)	3	0
Histology	SCCA	168 (63.6)	167	1
	Adenocarcinoma	11 (4.2)	0	0
	Neuroendocrine	2 (0.8)	1	1
	Mixed*	3 (1.1)	3	0
	Undifferentiated	1 (0.4)	1	0
Tumor grade (n=155)				
	1	65 (41.9)	65	0
	2	79 (51.0)	78	1
	3	11 (7.1)	10	1
Tumor size (cm)	≤3	216 (81.8)	214	2
	>3	48 (18.2)	48	0

*squamous cell carcinoma with adenocarcinoma, FIGO, the International Federation of Gynecology and Obstetrics; SCCA, squamous cell carcinoma.

Table 2 Characteristic of the Two Patients with Ovarian Metastasis

Age (yrs)	FIGO stages	Histology	Tumor (cm)	Laterality	Ovary (cm)	Hyst	U	PLN	PRM	LVSI
61	IB1	SCCA	3	Uni	6	Abandon	n/a	n/a	n/a	n/a
68	IB1	NE	2	Bilat	micro	RH	+	neg	+	+

*Bilat, bilateral; Hyst, hysterectomy; LVSI, lymph-vascular space invasion; micro, microscopic lesion; NE, neuroendocrine carcinoma; neg, negative; n/a, not available; PLN, pelvic lymph node metastasis; PRM, parametrium metastasis; SCCA, squamous cell carcinoma; U, uterine metastasis; Uni, unilateral; +, positive

months. The clinical and histologic features of patients were collected and presented in Table 1. All patients had mean age and body mass index (BMI) of 52.3 years (range 30-78, median 51) and 24.5 kg/m^2 (range 14.8-40.6), respectively. The data of contraceptive methods were available from 171 women, showed that hormonal contraception was used by 33 women (19.3%) and 52 women (19.7%) received tubal sterilization. From the 192 available records of smoking history, only 4 women (2.1%) smoked. The underlying diseases in history were collected from 209 records showed 100 women (47.8%) had previous medical problems such as diabetes mellitus or hypertension. The diagnostic procedures were achieved from cervical biopsies of 137 patients, fractional curettage of nine patients, and diagnostic conization of 118 patients. From 207 records of tumor characterictics, 98 patients (47.3%) had microscopic lesions, 62 patients (30%) had exophytic lesions, and 46 patients (22.7%) had infiltrative/ulcerative lesions. Thirty patients (11.4%) were operated in laparoscopic approach. According to clinical staging, the hysterectomy procedures were radical hysterectomy (RH) for 210 patients (79.5%), modified radical hysterectomy (MRH) for 9 patients (3.4%), and simple hysterectomy for 40 patients (15.2%). All of RH and MRH patients were received pelvic lymphadenectomy. Five patients (1.9%) were considered for abandoned hysterectomy and received radiation therapy. Mean operative time was 259.3±86.7 minutes. Intra-operative complications were found in 45 patients (17%), due to the following; >500 mL of blood loss (38/45, 82.9%), bladder or ureteric injuries (5/45, 11.1%), pelvic nerve injuries (2/45, 4.4%). Postoperative complications occurred in 55 patients: 1 wound infection, and 54 urinary retentions.

Two patients had ovarian metastasis and the data were summarized in table 2. Thus, the rate of ovarian metastasis in our population was 0.76% (2/264). One patient had microscopic ovarian metastasis, whereas the other had macroscopic ovarian lesions. Table 3 displayed the histopathologic data from surgical specimens correlated with ovarian metastasis of 264 early-stage cervical cancer patients. DSI and LVSI were reported in 139 and 181 records, respectively.

Besides the ovarian metastasis, the ovarian neoplasms were found in 7 patients including 1 synchronous ovarian carcinoma, 1 serous cystadenoma, 1 fibroma, and 4 teratoma. Additionally, 7 patients had ovarian removal due to endometriotic cysts. The synchronous primary ovarian serous carcinoma was diagnosed in a 43 year-old patient with squamous cell carcinoma of cervix stage IB1 and the right ovary was not obviously enlarged. She received adjuvant radiation and chemotherapy with complete response in the period of 15 months.

Table 3 Correlation between Histopathologic Data from Surgical Specimens and Adnexal Metastasis of 264 Early-stage Cervical Cancer Patients

Variables	Ovarian Metastasis	
	No	Yes
DSI (n=139)		
No (%)	93 (100)	0
Yes (%)	45 (97.8)	1 (2.2)
LVSI present (n=181)		
No (%)	119 (100)	0
Yes (%)	61 (98.4)	1 (1.6)
PLN involvement (n=226)		
No (%)	207 (99.5)	1 (0.5)
Yes (%)	18 (100)	0
PRM involvement (n=219)		
No (%)	208 (100)	0
Yes (%)	10 (90.9)	1 (9.1)
Uterine involvement (n=259)		
No (%)	256 (100)	0
Yes (%)	2 (66.7)	1 (33.3)
Vaginal involvement (n=219)		
No (%)	212 (100)	0
Yes (%)	6 (85.7)	1 (14.3)

*DSI, deep stromal invasion; LVSI, lymph-vascular space invasion; PLN, pelvic lymph node; PRM, parametrium

Discussion

Nowadays, the cervical cancer prevention strategies and early sexual life style result in increased detection rate of early-stage of cervical cancer and decreased patients' age from the past. The incidence of stage IA2-IB2 cervical cancer in women aged 15-49 year-old was high as 60.6% (Benedet et al., 2003). One of the advantages in treatment of early-stage cervical cancer by surgery is to preserve the ovary. Thus, doctors and patients have to make decisions

Table 4 Review Literatures of Ovarian Metastasis in Early-stage Cervical Cancer

Authors	No.	Stages	OVmet (%)	SCCA (%)	Adeno (%)	Umet (%)	PLNmet (%)	OVmet Predictors
Brown et al. 1990	25 nonsq	I	1 (4), m	n/a	1/25 (4)	n/a	n/a	Postmenopause, Adnexal pathology, PLNmet
Sutton et al. 1992	990	IB	6 (0.6)	4/750 (0.5)	2/121 (1.7)	n/a	n/a	Extracervical lesion
Landoni et al. 2007	1,695	IA2-IIA	16 (0.9)	7/1,284 (0.5)	9/380 (2.4)	n/a	2.9 vs 0.4%, p<0.001	Age ≥ 45, Adenocarcinoma, DSI, Higher stage,
Nakanishi et al.[a]2001	1,304	IA-IIB[e]	29 (2.2), 20 m, 14 uni	14/1,064 (1.3)	15/240 (6.3)	P[b]	P[c]	Umet, PLNmet, PRMmet, Stage
Shimada et al.[d]2006	3,471	IB-IIB[f]	52 (1.5)	29/2,925 (0.8)	29/546 (5.3)	n/a	Did not correlate	Adenocarcinoma

*Adeno, adenocarcinoma; DSI, deep stromal invasion; LVSI, lymph-vascular space invasion; m, microscopic lesion; nonsq, non squamous histology; n/a, not available; OVmet. Ovarian metastasis; ; P, p-value; PLNmet, pelvic lymph node metastasis; PRMmet, Parametial metastasis; SCCA, squamous cell carcinoma; Umet, uterine metastasis; uni, unilateral involvement, [a]In stage IA-IIA cervical cancer, the ovarian metastatic rate was 12/1,066 (1.1%). Based on histology, the rate were 7/204 (3.4%) of adenocarcinoma and 5/862 (0.6%) of SCCA type, of which 1 patient was in stage IA. P[b], p value were 0.011 and 0.008 for predicting the likelihood of ovarian metastasis between SCCA and adenocarcinoma. P[c], p value were non-significant and 0.025 for prediction of ovarian metastasis between SCCA and adenocarcinoma. [d]The ovarian metastatic rate in stage IA-IB cervical cancer was 23/2,600 (0.9%). According to histology, the rate were 16/414 (3.9%) of adenocarcinoma and 7/2,186 (0.3%) of SCCA histology. [e](147 IA, 792 IB, 127 IIA), [f](2,600 IA-IB).

for ovarian preservation cases. Several reports evaluated the predictors of ovarian metastasis from cervical cancer; however, it has been difficult to diagnose. Furthermore, because of awareness of microscopic ovarian metastasis with poorer survival outcomes, it is difficult for surgeon to make a decision whether to remove the ovaries. Several researchers tried to explore factors associated with ovarian metastasis in cervical cancer.

Even though Thailand is the area of rather high ASR of cervical cancer, ovarian metastasis in cervical cancer in this study was 0.76%, comparable to previous studies (0.6-4.0%) (Brown et al., 1990; Sutton et al., 1992; Nakanishi et al., 2001; Shimada et al., 2006; Landoni et al., 2007). A study in the States in stage I cervical adenocarcinoma, found the rate of ovarian metastasis was 4% (Sutton et al., 1992). Italian data in stage IA2-IIA cervical cancer reported the rate was 0.9% (Landoni et al., 2007). However, data in Japan and Korea stated the rates were in range of 1.5-2.2% but they included the stage IIB patients also (Nakanishi et al., 2001; Shimada et al., 2006; Kim et al., 2008). The same most common human papillomavirus (HPV) oncologic types with equal virulence may be explained the similar rate of our study with previous reports. The ovarian metastasis could be by hematogenous, lymphatic, transtubal spreading, or directed invasion. Therefore, the higher stages of disease and adjacent organs involvement (pelvic lymph nodes, parametrium, uterus, and tubes) lead to the increasing rate. The rate of ovarian metastasis is slightly different between developing and developed countries and has no direct-change with the high or low incidence area of cervical cancer. Individual country physicians should be concerned about this variation.

This study showed that ovarian metastasis rate of SCCA was similar to that of adenocarcinoma cell types (1/167, 0.6% vs 1/95, 1.0%, respectively). In Gynecologic Oncology Group (GOG) report of 990 stage IB cervical cancer patients undergoing surgical treatment, ovarian metastasis rate was not statistically different between SCCA and adenocarcinoma histology (0.5 and 1.7%, respectively, p 0.19) (Sutton et al., 1992). However, the retrospective study in 1,695 patients with stage IA2-IIA cervical cancer by Landoni et al., the rate were statistic difference with histologic type (0.5% of SCCA and 2.4% of adenocarcinoma, p 0.0014) (Landoni et al., 2007). Previous studies showed significantly higher ovarian metastasis rate in which also included the cases of locally advanced stage cervical cancer (IIB, III) also (Tabata et al., 1987; Nakanishi et al., 2001; Shimada et al., 2006). Therefore, the data of histologic type for prediction of ovarian metastasis in early-stage cervical carcinoma were inconclusive.

Neuroendocrine cervical carcinoma is the most aggressive cell type, high potential of metastasis, and poor prognosis (Lee et al., 2008; Cohen et al., 2010; Wang et al., 2012). In cases of early-stage, the rates of LVSI, DSI, pelvic lymph node metastasis and parametrial invasion were high as 60%, 46%, 37% and 13%, respectively (Lee et al., 2008). Although, they have no data of ovarian metastasis in this cell type, certainly, the tendency of metastatic characteristic and the rate of ovarian metastasis were higher. In our study, the rate of ovarian metastasis in neuroendocrine cervical carcinoma was 1/2 (50%). Although there is a small sample size of neuroendocrine cervical carcinoma in our study, it may be hard to conclude. Due to nature of neuroendocrine carcinoma and the results of our study, we could suggest from our small sample size this way.

Sutton et al. published data of ten patients who had ovarian metastasis, which range of age was 24-62 years old (Sutton et al., 1992). Another study reported in 1,695 patients with early-stage cervical cancer, of which 15 patients had ovarian involvement. 13 from 15 ovarian metastasis patients were older than 45 years old. After using multivariate analysis, patients' age >45 years old was an independent risk factor for ovarian metastasis (Landoni et al., 2007). Of our studied patients, two patients who had ovarian metastasis were older than 60 years old. These evidences suggested that the cut point of patients' age considered for incidental salpingo-oophorectomy during surgical treatment for cervical cancer patients should be younger than 65 years old as in benign diseases. Based on our population, ovarian preservation might be considered for <60 year-old patients.

Our study was unable to detect a predictor of ovarian metastasis due to small sample size. Otherwise, one patient with microscopic ovarian metastasis in this study had multiple poor prognostic factors including: DSI, LVSI, and adjacent organ involvements (parametrium, uterus and vagina). Therefore, the authors convinced of meticulous examination of adjacent organs, intra-operatively specimen opening, and frozen section in suspicious case before making decision whether to perform ovarian preservation.

Five other series reported ovarian metastasis in early-stage cervical carcinoma as displayed in Table 4 (Brown et al., 1990; Sutton et al., 1992; Nakanishi et al., 2001; Shimada et al., 2006; Landoni et al., 2007). Only one patient in stage IA cervical cancer had ovarian metastasis. The predictive factors of ovarian metastasis were incomplete agreement. Otherwise, these reports suggested that the ovarian metastasis had a correlation with the tendency of extracervical spreading such as clinical and tumor features. The clinical characteristics such as old age, and postmenopause had a tendency to have silent endocervical lesion with distant metastasis occurred before symptoms. The tumor characteristics consisting of higher stage, DSI, uterine or pelvic lymph node involvement, parametrial metastasis were indirect signs of distant organ metastasis including the ovary. Based on the literature review, some predictors such as older than 45 years, DSI, uterine metastasis, pelvic lymph nodes or parametrium involvement were claimed to be associated with ovarian metastasis, whereas, no complete consistent of publications.

The suitable investigations to anticipated ovarian metastasis in early-stage cervical cancer are imaging studies. We might have indirect signs of this metastasis such as DSI, parametial or uterine involvements. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) have clinical benefit to determine the adjacent organ involvement in cervical cancer. In a systematic review,

the sensitivity of CT and MRI were 74% and 55% for detection of parametrial invasion, and 60% and 43% for detection of lymph node involvement (Bipat et al., 2003). Both imaging techniques had comparable specificities for parametrial invasion and lymph node involvement. For bladder invasion and rectum invasion the sensitivities for MRI were 75% and 71%, respectively, which higher than CT. The specificity of MRI to determine bladder invasion was significantly higher than that of CT (91% vs 73%). A prospective study revealed that Positron Emission Tomography/Computed Tomography (PET/CT) has more sensitivity in detection of lymph node metastasis than MRI (57.6% vs 30.3%) but no statistic difference in specificity (92.6% vs 92.6%) and accuracy (85.1% vs 72.7%) (Choi et al., 2006). In spite of excluding from the FIGO clinical staging investigations, CT or MRI, have clinical benefit in pre-operative assessment of early-stage cervical cancer. The more physicians known about the disease extension, the better decision could be made during the operation.

The limitation of this study is the retrospective study in nature, which some data were not recorded such as familial history of malignancy, underlying medical diseases that may affect to the risk of ovarian neoplasms or bad surgical outcomes, and pathological data of DSI or LVSI. Blood loss was estimated by swab count that is semi-subjective. Wound infection rate might be underestimated because some patients did not have postoperative surgical wound examination at our hospital. We have no data of long term follow-up outcomes and limited case numbers. Further study should be prospective and designed for accurate assessment of blood loss or wound infection events, adjunctive imaging or HPV typing studies, and the outcomes of diseases in long duration of follow-up.

Based on this study, in surgical treatment of early-stage cervical carcinoma, ovaries could be preserved in <60-year-old patients aged with non-neuroendocrine cell type, stage IA, and without any extracervical diseases or gross lesions of ovary. The clinicians should be provided for the data of ovarian metastasis and other neoplasms and also aware that incidental bilateral salpingo-oophorectomy probably makes some patients upset with surgical menopause. Nevertheless, doctor-patient relationship and with this current knowledge provided is still one of the most important issues in clinical practice.

Acknowledgements

This research was supported by Siriraj Research Development Fund. Conflict of interest, none of the authors have a conflict of interest.

References

Attasara P, Srivatanakul P, Sriplung H (2010). In: Cancer in Thailand volume.V 2001-2003. *Bangkok: Bangkok Med Publication*, **7**.

Benedet JL, Odicino F, Maisonneuve P, et al (2003). Carcinoma of the cervix uteri. *Int J Gynaecol Obstet*, **83**, 41-78.

Bipat S, Glas AS, van der Velden J, et al (2003). Computed tomography and magnetic resonance imaging in staging of uterine cervical carcinoma: a systematic review. *Gynecol Oncol*, **91**, 59-66.

Brown JV, Fu YS, Berek JS (1990). Ovarian metastases are rare in stage I adenocarcinoma of the cervix. *Obstet Gynecol*, **76**, 623-6.

Choi HJ, Roh JW, Seo SS, et al (2006). Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: a prospective study. *Cancer*, **106**, 914-22.

Cohen JG, Kapp DS, Shin JY, et al (2010). Small cell carcinoma of the cervix: treatment, survival outcomes of 188 patients. *Am J Obstet Gynecol*, **203**, 347.e1-6.

Ferlay J, Shin HR, Bray F, et al (2010). GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No.10.Lyon, France: International Agency for Research on Cancer. Available from: http://globocan.iarc.fr [Accessed 2012].

Kim MJ, Chung HH, Kim JW, et al (2008). Uterine corpus involvement as well as histologic type is an independent predictor of ovarian metastasis in uterine cervical cancer. *J Gynecol Oncol*, **19**, 181-4.

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.

Lee JM, Lee KB, Nam JH, et al (2008). Prognostic factors in FIGO stage IB-IIA small cell neuroendocrine carcinoma of the uterine cervix treated surgically: results of a multi-center retrospective Korean study. *Ann Oncol*, **19**, 321–6.

Nakanishi T, Wakai K, Ishikawa H, et al (2001). A comparison of ovarian metastasis between squamous cell carcinoma and adenocarcinoma of the uterine cervix. *Gynecol Oncol*, **82**, 504-9.

Natsume N, Aoki Y, Kase H, et al (1999). Ovarian metastasis in stage IB and II cervical adenocarcinoma. *Gynecol Oncol*, **74**, 255-8.

Parker WH, Broder MS, Liu Z, et al (2005). Ovarian conservation at the time of hysterectomy for benign disease. *Obstet Gynecol*, **106**, 219-26.

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

Shimada M, Kigawa J, Nishimura R, et al (2006). Ovarian metastasis in carcinoma of the uterine cervix. *Gynecol Oncol*, **101**, 234-7.

Sutton GP, Bundy BN, Delgado G, et al (1992). Ovarian metastases in stage IB carcinoma of the cervix: a Gynecologic Oncology Group study. *Am J Obstet Gynecol*, **166**, 50-3.

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.

Wang KL, Chang TC, Jung HM, et al (2012). Primary treatment and prognostic factors of small cell neuroendocrine carcinoma of the uterine cervix: A Taiwanese Gynecologic Oncology Group study. *Eur J Cancer*, **48**, 1484-94.