GYNAECOLOGY

Survival Rate of Cervical Cancer Patients According to the 2018 FIGO Staging System: A tertiary hospital based study, Vajira Hospital, Bangkok

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ABSTRACT

Objectives: To validate survival rate of cervical cancer patients based on the revised 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system.

Materials and Methods: Medical records of cervical cancer patients from 2006-2015 were reviewed. The locally-advanced patients without radiological imaging or incomplete medical records were excluded. All included patients were assigned as FIGO 2018 staging criteria.

Results: Of the 226 patients with cervical cancer analyzed. Mean age was 51 ±12 years (17-90 years). Squamous cell carcinoma was the most common cell type in 159 patients (70.4%). According to FIGO 2018 staging criteria, 81 patients (35.8%) were upstaged. The 5-year progression-free survival (PFS) of stage IB1, IB2 and IB3 were 83.3%, 90.0% and 84.2%, respectively and the 5-year overall survivals (OS) were 71.4%, 92.2% and 62.5%, respectively. The PFS and OS were not different among 3 sub-stages. The 5-year PFS of stage IIIB, IIIC1 and IIIC2 were 68.6%, 89.3% and 62.5%, respectively and the 5-year OS were 71.4%, 92.2% and 62.5%, respectively. The PFS and OS of stage IIIB and IIIC2 were not significantly different (p = 0.163 and 0.166, respectively) while survival of stage IIIC1 was significantly higher than stage IIIB (p = 0.025 and 0.017, respectively) and IIIC1 (p = 0.001 and 0.001, respectively).

Conclusion: The revised 2018 FIGO staging system for cervical cancer was useful to distinguish survival rates of patients with locally-advanced disease and distant metastasis while the survival rate of sub-stages of early-stage disease was no different. Stage III disease, para-aortic metastasis was the most impact on the survival rate.

Keywords: FIGO 2018 staging, validation, cancer, cervix, survival rate.

อัตราการอยู่รอดของผู้ป่วยมะเร็งปากมดลูกตามการกำหนดระยะโรค *2018 FIGO staging system: การศึกษาในโรงพยาบาลตติยภูมิ, โรงพยาบาลวชิรพยาบาล กรุงเทพมหานคร*

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บทคัดย่อ

***วัตถุประสงค์**: เพื่อศึกษาอัตราการอยู่รอดของผู้ป่วยมะเร็งปากมดลูกตาม International Federation of Gynecology and Obstetrics 2018 staging system*

***วัสดุและวิธีการ**: รวบรวมข้อมูลของผู้ป่วยมะเร็งปากมดลูกทั้งหมดที่มารักษาที่โรงพยาบาลวชิรพยาบาลระหว่างปี 2006-2015 จากฐานข้อมูล ผู้ป่วยที่นำมาวิเคราะห์ต้องมีภาพรังสีก่อนผ่าตัดหรือผลพยาธิเกี่ยวกับต่อมน้ำเหลือง*

***ผลการศึกษา**: ผู้ป่วยมะเร็งปากมดลูก 226 ราย อายุเฉลี่ย 51±12 ปี เป็น Squamous cell carcinoma มากที่สุด 159 ราย หลังจากแบ่งระยะตาม FIGO 2018 staging พบมีระยะของโรคเพิ่มขึ้นจำนวน 81 ราย อัตราการรอดชีวิตโดยโรคสงบระยะ 5 ปี ของ IB1, IB2 and IB3 คือ ร้อยละ 83.3, 90.0 และ 84.2 อัตราการรอดชีวิตโดยรวม 5 ปี คือ ร้อยละ 71.4, 92.2 และ 62.5: ซึ่งไม่ต่างกัน อัตราการรอดชีวิตโดยโรคสงบระยะ 5 ปี ของ IIIB, IIIC1 และ IIIC2 คือ ร้อยละ 68.6, 89.3 และ 62.5 อัตราการรอดชีวิตโดยรวม 5 ปี คือ ร้อยละ 71.4, 92.2 และ 62.5 ตามลำดับ อัตราการรอดชีวิตโดยโรคสงบและอัตราการรอดชีวิตโดยรวม ของ IIIB และ IIIC2 ไม่ต่างกัน (p = 0.163, 0.166) แต่ IIIC1 มากกว่า IIIB (p = 0.025, 0.017) และ IIIC1 (p = 0.001, 0.001)*

***สรุป**: FIGO2018 staging มีประโยชน์ในการบอกความแตกต่างของการอยู่รอดระหว่างระยะลุกลามเฉพาะที่และระยะแพร่กระจายในผู้ป่วยมะเร็งปากมดลูก ในขณะที่ระยะย่อยไม่สามารถบอกความแตกต่างได้ การลุกลามไปที่ต่อมน้ำเหลือง para-aortic มีผลต่ออัตราการอยู่รอดมากที่สุด*

***คำสำคัญ**: FIGO 2018 staging, มะเร็ง, ปากมดลูก, อัตราการอยู่รอด*

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Introduction

Cervical cancer is the fourth most common cancer in women worldwide. There was 569,847 new cases and 311,365 deaths in 2018. The majority of new cases and deaths occur in developing countries[1]. The International Federation of Gynecology and Obstetrics (FIGO) purposed the staging system for cervical cancer depending on pelvic examination and simple imaging studies[2] because the prevalence of cervical cancer is mainly in low-resourced areas including Thailand.

In 2018, the FIGO staging system was revised[3,4]. The new staging system allows the use of any imaging modality and/or pathological findings for determining the stage. However, some clinicians in low-resourced conditions can assess the patient clinically as before[4]. Table 1 shows the changes in FIGO staging system of cervical cancer between FIGO 2009[2] and 2018 staging system[3,4]. In stage IA, lateral extension has no longer been included. Stage IB is divided by tumor size into 3 sub-stages. Status of retroperitoneal lymph node is more concern in the new staging system. Metastatic lymph node on imaging or pathological studies is assigned stage IIIC (IIIC1 for only pelvic lymph node and IIIC2 for positive para-aortic lymph node) (Table 1).

Table 1. Changes in the FIGO staging system of cervical cancer.

Stage	2009 staging system	2018 staging system
IA1	Stromal invasion < 3 mm in depth and extension of ≤ 7 mm	Stromal invasion < 3 mm in depth
IA2	Stromal invasion > 3 mm and < 5 mm in depth and extension of ≤ 7 mm	Stromal invasion ≥ 3 mm and < 5 mm in depth
IB1	Tumor size ≤ 4 cm in greatest dimension	- Tumor size ≥ 5 mm depth of stromal invasion, and < 2 cm in greatest dimension - Positive margin of conization
IB2	Tumor size > 4 cm in greatest dimension	Tumor size ≥ 2 cm and < 4 cm in greatest dimension
IB3	N/A	Tumor size ≥ 4 cm in greatest dimension
IIA1	Tumor involve upper 2/3 of vagina and size ≤ 4 cm in greatest dimension	Tumor involve upper 2/3 of vagina and size < 4 cm in greatest dimension
IIA2	Tumor involve upper 2/3 of vagina and size > 4 cm in greatest dimension	Tumor involve upper 2/3 of vagina and size ≥ 4 cm in greatest dimension
IIIC1	N/A	Pelvic lymph node metastasis only*
IIIC2	N/A	Para-aortic lymph node metastasis*

* Either radiographic (r) or pathologic (p) studies confirmed metastasis
N/A, not available; FIGO, the International Federation of Gynecology and Obstetrics

The new staging system was validated by a retrospective study using The Surveillance, Epidemiology, and End Results (SEER) Program in the United States between 1988 and 2014[6]. The cause-specific survival is significantly difference among stage IB but survival in stage IIIC1 varies which it depends on the tumor size.

In Thailand, cervical cancer is the second most common cancer in women with 8,622 new cases and 5,015 deaths in 2018[5]. The 2009 FIGO

staging system had been applied for a past decade. Advance imaging modalities and minimally invasive surgery (MIS) are more available in some urban areas. The objective of this study was to determine the 5-year overall survivals (OS) and progression-free survival (PFS) according to the recent FIGO staging system.

Materials and Methods

After the ethics committee approval, medical records of all patients with cervical cancers from January 2006 to December 2015 were reviewed. The early-stage patients with pre-operative imaging (computerized tomography (CT) or magnetic resonance imaging (MRI)) or pathological study of pelvic and para-aortic lymph nodes were eligible. For the locally-advanced or distant disease, pre-treatment CT or MRI should be recorded. We excluded the patients with incomplete medical record. Patient characteristics, clinicopathologic data, treatment, disease outcomes and follow-up period were collected by review of medical records. All cases were defined the stage based on FIGO 2018 staging system[3,4].

All patients were treated based on 2009 FIGO staging system. For early-stage disease, extrafascial hysterectomy is a treatment for stage IA1 disease and radical hysterectomy with pelvic lymphadenectomy (RHPL) is a treatment for stage IA2, IB1 and IIA1 disease. Adjuvant concurrent chemoradiation (CCRT) or radiation after surgery are considered in high-risk patients including positive lymph node, positive surgical margin, positive parametrium, positive lymphovascular space invasion (LVSI), deep stromal invasion and large tumor size. For locally-advanced disease, CCRT is a treatment of choice. Palliative chemotherapy or best supportive care is introduced to stage IVB disease. After treatment completion, patients were followed-up every 3 months for the first 2 years, 6 months for 3-5 years, then annually. Palliative chemotherapy or pelvic radiation is a treatment option for recurrent disease.

All data were analyzed using SPSS statistical software, version 22.0. Descriptive statistics were used to analyze demographic data and were summarized as numbers with percentage or median with range. OS and PFS of the patients according to the prior and new stages were analyzed by the Kaplan-Meier method. The log-rank test was used to examine the statistical difference.

Table 2. Characteristics of 226 cervical cancer patients.

	N (%)
Mean age ± SD (years)	51.5 ± 12
Marital status	
- Single	70 (31.0)
- Married	119 (52.7)
- Divorced	17 (7.5)
- Widow	20 (8.8)
Histopathology	
- Squamous cell carcinoma	159 (70.4)
- Adenocarcinoma	56 (24.8)
- Adenosquamous carcinoma	1 (0.4)
- Neuroendocrine tumor	9 (4.0)
- Mixed cell types	1 (0.4)

SD: standard deviation

Results

From January 2006 and December 2015, 405 cervical cancer patients were identified. Seventeen women with incomplete medical records and 162 women without CT or MRI were excluded. The characteristics of 226 patients are summarized in Table 2. The mean age was 51.5 ± 12 years (range of 17-90 years). The most common cell type was squamous cell carcinoma (70.4%).

Based on the 2018 FIGO staging system, 81 patients (35.8%) were upstaged (Table 3). Twenty-eight early-stage patients were diagnosed as a higher stage because the cut-off tumor size had been changed. Of 46 women formerly staged as IB1 disease, 20 (43.5%) and 1 (2.2%) were upstaged to sub-stages IB2 and IB3, respectively. Of 7 patients formerly staged as IB2 disease, 4 (57.1%) were upstaged to sub-stages IB3. Of 44 patients staged as IIIC disease, 24 patients (54.5%) were assigned by CT or MRI and 20 patients (45.5%) were assigned by pathological finding. Thirteen patients (29.5%) were previously stage IB1 by 2009 staging system and 31 patients (71.5%) were previously locally-advanced disease (stage IB2, IIB, IIIA and IIIB).

Table 3. Numbers of patients staged by 2009 and 2018 staging criteria.

FIGO 2009	N (%)														
	IB1	IB2	IB3	IIA1	IIA2	IIB	IIIA	IIIB	IIIC1r	IIIC1p	IIIC2r	IIIC2p	IVA	IVB	Total
IA1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1
IA2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1
IB1	10	20	1	-	-	2	-	-	1	11	-	1	-	-	46
IB2	-	-	4	-	-	-	-	-	-	3	-	-	-	-	7
IIA1	-	-	-	5	1	-	-	-	1	-	-	-	-	-	7
IIA2	-	-	-	-	1	-	-	-	-	-	-	-	-	-	1
IIB	-	-	-	-	-	36	-	-	5	2	3	1	-	2	49
IIIA	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1
IIIB	-	-	-	-	-	-	-	35	5	-	9	1	2	3	55
IVA	-	-	-	-	-	-	-	-	-	-	-	-	24	-	24
IVB	-	-	-	-	-	-	-	-	-	-	-	-	-	34	34
Total	12	20	5	5	2	38	0	35	12	16	12	4	26	39	226

FIGO: the International Federation of Gynecology and Obstetrics

During 68 months of median follow-up time, there were 67 progression (29.6%) and 58 deaths (25.7%). Five-year PFS and OS of the 2009 and 2018 FIGO staging system are displayed in Table 4. For stage IB, the 5-year PFS and OS were not different between stage IB1 vs. IB2, IB2 vs. IB3 and IB1 vs. IB3 (Fig. 1A and 1B). The significant difference in PFS and OS was demonstrated in stage III (Fig. 1C and 1D). The 5-year PFS of stage IIIB, IIIC1 and IIIC2 were 68.6%, 89.3% and 62.5%, respectively and the 5-year OS were 71.4%, 92.2% and 62.5%, respectively, (Fig. 1C and 1D). The PFS and OS of stage IIIB and IIIC2 was not significantly different (p = 0.163 and 0.166, respectively).

Table 4. Five-year survival rate of 226 patients staged by 2009 and 2018 staging criteria.

	FIGO 2009 criteria			FIGO 2018 criteria		
	N (%)	5-yr PFS (%)	5-yr OS (%)	N (%)	5-yr PFS (%)	5-yr OS (%)
Stage I						
- IA1	1 (0.4)	100.0	100.0	-	-	-
- IA2	1 (0.4)	100.0	100.0	-	-	-
- IB1	46 (20.4)	84.8	91.3	12 (5.3)	83.3	91.7
- IB2	7 (3.1)	100.0	100.0	20 (8.8)	90.0	95.0
- IB3	-			5 (2.2)	100.0	100.0
Stage II						
- IIA1	7 (3.1)	85.7	100.0	5 (2.2)	80.0	100.0
- IIA2	1 (0.4)	0.0	0.0	2 (0.9)	50.0	50.0
- IIB	49 (21.7)	83.7	87.8	38 (16.8)	84.2	89.5
Stage III						
- IIIA	1 (0.4)	100.0	100.0	-	-	-
- IIIB	55 (24.3)	63.6	65.5	35 (15.5)	68.6	71.4
- IIIC1r	-	-	-	12 (5.3)	91.7	91.7
- IIIC1p	-	-	-	16 (7.1)	87.5	93.8
- IIIC2r	-	-	-	12 (5.3)	66.7	66.7
- IIIC2p	-	-	-	4 (1.8)	50.0	50.0
Stage IV						
- IVA	24 (10.6)	20.8	25	26 (11.5)	19.2	23.1
- IVB	34 (15.0)	2.9	2.9	39 (17.3)	5.1	5.1

FIGO: the International Federation of Gynecology and Obstetrics, PFS: progression-free survival, OS: overall survivals
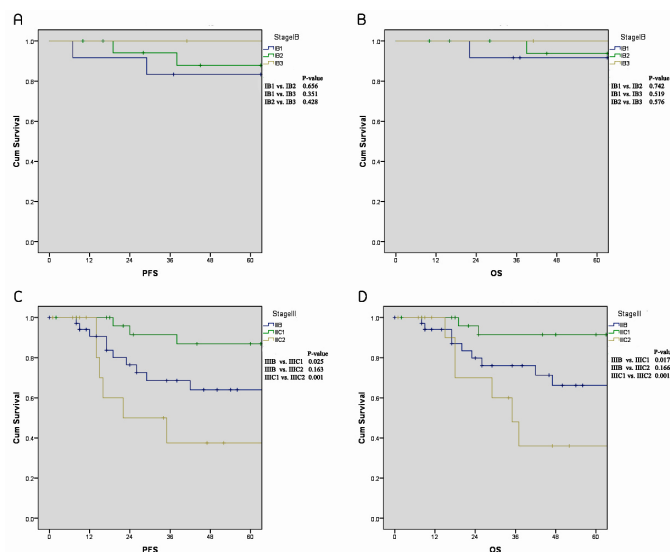
Fig. 1. (A) 5-year progression-free survival of stage IB1, IB2 and IB, (B) 5-year overall survival of stage IB1, IB2 and IB3, (C) 5-year progression-free survival of stage IIIB, IIIC1 and IIIC2, (D) 5-year overall survival of stage IIIB, IIIC1 and IIIC2.

Discussion

The 2018 FIGO staging system for cervical cancers allows any imaging modality and pathological assessment for tumor size, extension of tumor and metastatic retroperitoneal lymph nodes. The availability of advance imaging study has increased for last decade. Our study reported that 35.8% of all cases were upstaged by the revised criteria. Of 53 patients previously staged IB1 or IB2 disease, 25 patients (47.1%) were upstaged due to the change of the cut-off tumor size. For stage IB1 based on 2009 criteria, 20 patients (43.5%), 1 (2.2%), 12 (26.1%) and 1 (2.2%) were upstaged to sub-stages IB2, IB3, IIIC1 and IIIC2, respectively. For stage IB2, 4 patients (57.1%) and 3 (42.8%) were upstaged to sub-stages IB3 and IIIC1, respectively. The result of a retrospective study was similar to our study[7]. A total of 372 (87.5%) patients with stage IB1 or IB2 disease were assigned to a new staging system. Of 294 women formerly staged as IB1disease, 127 (43.2%), 29 (9.9%), 70 (23.8%), and 15 (5.1%) were upstaged to sub-stages IB2, IB3, IIIC1, and IIIC2, respectively. Of 131 patients formerly staged as IB2 disease, 66 (50.4%), 44 (33.6%), and 21 (16.0%) were upstaged to sub-stages IB3, IIIC1, and IIIC2, respectively[7].

On the literature review, the prevalence of stage IIIC1 was 25.9% and stage IIIC2 was 5.1%(8). In our cohort, the prevalence of stage IIIC1 was 12.4% and stage IIIC2 was 7.1%. The prevalence in our study was lower because 162 women without imaging were excluded. Our study revealed that 24 patients (54.5%) were assigned by CT or MRI and 20 patients (45.5%) were assigned by pathological finding. The sensitivity and specificity of imaging modalities to detect pelvic lymph node (PLN) and para-aortic lymph node (PALN) metastasis, had been reported in a retrospective study[9]. Yang et al found that that the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of imaging modalities in detection of pelvic lymph node metastases were 88.9%, 22.2%, 69.6% and 50%, respectively, and 62.5%, 92%, 71.4% and 88.5%, respectively in para-aortic lymph node metastases[8].

The other retrospective data in Belgium studied 204 patients with locally-advanced cervical cancer with normal or not overtly PALN metastasis on imaging underwent surgical PALN staging[10]. Of 204 cases with negative imaging, PALN metastases were present in 8% at surgical staging[10].

In terms of survival outcome, two retrospective studies in United States validated the revised 2018 FIGO staging system[6,8]. For stage IB, 5-year survival rates were 94.6-97.0% for stage IB1 disease, 86.2-92.1% for stage IB2 disease, and 78.1-83.1% for stage 1B3 disease[6,8]. For stage III, 5-year survival rates were 46.0% for stage IIIA[6], 42.6% for stage IIIB[6], 61.9-62.1% for stage IIIC1 disease[6, 8], and 39.4% for stage IIIC2 disease[8], respectively. In subgroup analysis of stage IIIC, 5-year survival rate depended on tumor size and tumor extension (T-stage)[6,8]. Our results revealed that the difference among sub-stages of stage III disease was significantly while the difference among sub-stages of early-stage disease did not present.

Our institute is one of the tertiary hospitals in Bangkok. The survival outcomes of our patients may represent the survival rate of cervical cancer in urban area. The limitation of this study was the retrospective design. Additionally, the advance imaging modalities were not available in the past. Many cases were excluded because of incomplete medical records or unknown imaging studies. Presently, the CT or MRI are affordable in many hospitals, a prospective study may conduct. In order to achieve a larger population, co-operation of multicenter is necessary.

Conclusion

In conclusion, 35.8% of all cases were upstaged based on the revised 2018 FIGO staging system for cervical cancer. The advance imaging studies and staging surgery are important for allocating the stage. The new staging criteria were useful to distinguish survival rates of patients with locally-advanced disease and distant metastasis while the survival rate of sub-stages of early-stage disease was no different. Of stage III disease, para-aortic metastasis was the most impact

on the survival rate.

Acknowledgement

Potential conflicts of interest

The authors declare no conflict of interest.

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