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The Survival after Surgery of Clinically Early-stage Cervical Cancer in Chonburi Hospital and Multivariable Analysis of Prognostic Factors Influencing Survival

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ABSTRACT

Objectives: To evaluate 5-year overall survival (OS), 5-year disease-free survival (DFS), recurrent rate and identified prognostic clinicopathological factors of patients with clinically early-stage cervical cancer treated with primary surgery in Chonburi Hospital.

Materials and Methods: The medical records of early-stage cervical cancer patients undergoing surgery treatment from January 2012 to September 2023 were reviewed. OS and DFS were obtained. Patients' age, stage, tumor size, histologic type, depth, degree of stromal invasion, lympho-vascular space invasion (LVSI), surgical margin, pelvic node status, and adjuvant treatment were assessed for correlation with DFS.

Results: Three hundred and twelve patients were included. The mean age was 46.8 ± 11.6 years, and the median follow-up was 67.0 months. Fifty-three patients (17.2%) developed recurrent disease. The 5-year OS was 100%, 93.9%, 88.5%, and 81.8% (p = 0.001) according to the International Federation of Gynecology and Obstetrics (FIGO) 2018 stage IA, IB1, IB2, and IB3, respectively. The 5-year DFS was 100%, 95.1%, 87.5%, and 74.5%, correspondingly (p = 0.001). The discordance between clinical and surgical upstaging was 13.8% according to FIGO 2018 criteria. In multivariate analysis, stage beyond IB3, tumor size over 4 cm, LVSI, and deep stromal invasion were significant prognostic variables. In contrast, adjuvant postoperative radiotherapy (PORT) in the intermediate and high-risk groups was the protective factor for DFS with a hazard ratio of 0.39 [0.20 – 0.76, p = 0.006].

Conclusion: The 5-year OS and DFS of clinically early-stage cervical cancer were 85.3% and 84.0%, respectively. PORT was the protective factor for recurrence.

Keywords: cervical cancer, survival, surgery, radical hysterectomy, recurrence.

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อัตราการรอดชีวิตหลังการผ่าตัดในผู้ป่วยมะเร็งปากมดลูกระยะเริ่มต้นในโรงพยาบาลชลบุรี และการวิเคราะห์แบบพหุปัจจัยถึงตัวแปรที่มีผลต่อการพยากรณ์โรค

สุวภรณ์ ถินสถิตย์, ทศพล เจียมตน

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาอัตราการรอดชีวิตโดยรวมที่ 5 ปี อัตราการปลอดโรคที่ 5 ปี อัตราการกลับเป็นซ้ำ และศึกษาปัจจัยทางคลินิกและพยาธิวิทยาที่มีผลต่อการพยากรณ์โรคในผู้ป่วยมะเร็งปากมดลูกระยะเริ่มแรกที่รับการรักษาแรกด้วยการผ่าตัดในโรงพยาบาลชลบุรี*

วัสดุและวิธีการ: *ทะเบียนผ่าตัดและเวชระเบียนของสตรีที่ถูกวินิจฉัยเป็นมะเร็งปากมดลูกระยะเริ่มต้นและได้รับการรักษาแรกด้วยการผ่าตัดระหว่าง มกราคม 2555 - กันยายน 2566 จะถูกนำมาทบทวนและคำนวณอัตราการรอดชีวิตโดยรวมและอัตราการปลอดโรคปัจจัยทางคลินิกและพยาธิวิทยา ได้แก่ อายุ ระยะ ขนาดมะเร็ง ชนิดซองเซลล์ ความลึก และระดับการลุกลามเข้าเนื้อเยื่อเกี่ยวพัน การลุกลามเข้าหลอดเลือดหรือหลอดน้ำเหลือง การพบมะเร็งที่ขอบชิ้นเนื้อ การกระจายที่ต่อมน้ำเหลืองอุ้งเชิงกราน และการได้รับรังสีรักษาเสริมหลังผ่าตัด จะถูกนำมาวิเคราะห์ความสัมพันธ์กับอัตราการปลอดโรค*

ผลการศึกษา: *จากผู้ป่วยมะเร็งปากมดลูก 312 ราย อายุเฉลี่ย 46.8 ± 11.6 ปี ค่ามัธยฐานการตรวจติดตามคือ 67 เดือน พบมะเร็งกลับเป็นซ้ำ 53 ราย คิดเป็นร้อยละ 17.2 อัตราการรอดชีวิตโดยรวมที่ 5 ปี คือ ร้อยละ 100, 93.9, 88.5, 81.8 (p = 0.001) ของระยะ IA, IB1, IB2 และ IB3 ตาม International Federation of Gynecology and Obstetrics (FIGO) 2018 ตามลำดับ อัตราการรอดชีวิตโดยปลอดโรคที่ 5 ปี คือ 100%, 95.1%, 87.5% และ 74.5% (p = 0.001) ตามลำดับ โดยพบระยะมะเร็งหลังผ่าตัดเพิ่มขึ้นจากระยะทางคลินิค ร้อยละ 13.8 ตามเกณฑ์ของ FIGO 2018 จากการวิเคราะห์พหุตัวแปรพบว่าระยะของมะเร็งมากกว่า IB3, ขนาดมะเร็งมากกว่า 4 เซนติเมตร การลุกลามเข้าหลอดเลือดหรือหลอดน้ำเหลือง และการลุกลามเข้าเนื้อเยื่อเกี่ยวพันชั้นลึก มีผลลดอัตราการปลอดโรค ในทางกลับกันการได้รับรังสีรักษาเสริมหลังผ่าตัดในกลุ่มความเสี่ยงปานกลางและความเสี่ยงสูง เป็นปัจจัยเพิ่มอัตราการปลอดโรค (Hazard ratio of 0.39, 0.20 – 0.76, p = 0.006)*

สรุป: *อัตราการรอดชีวิตโดยรวมที่ 5 ปี และอัตราการปลอดโรคที่ 5 ปี ร้อยละ 85.3 และร้อยละ 84.0 ตามลำดับ การได้รับรังสีรักษาเสริมหลังผ่าตัดเป็นปัจจัยลดการกลับเป็นซ้ำ*

คำสำคัญ: *มะเร็งปากมดลูก, อัตราการรอดชีวิต, อัตราการปลอดโรค, การผ่าตัด, การกลับเป็นซ้ำของมะเร็ง*

Introduction

Cervical cancer ranks as the most prevalent malignancy among all gynecological cancers in Thailand, serving as the primary cause of mortality for up to 342,000 individuals out of 604,000 women diagnosed with cervical cancer in 2020[1]. According to the 2021 cancer registry, Chonburi province ranks third in terms of the number of newly diagnosed cancer patients, trailing behind Bangkok and Chiang Mai provinces[2]. Chonburi Hospital, a longstanding tertiary care facility, accommodates a substantial caseload of cervical cancer patients, approximately ranging from 100 to 200 cases annually. Patients diagnosed at an early stage typically undergo surgical intervention as the primary treatment modality[3]. In cases where there exists a risk of disease recurrence, patients are referred for adjunctive therapy, including radiation or concurrent chemoradiotherapy, at the neighboring Chonburi Cancer Hospital. The hospital actively engages in collaborative research endeavors focusing on locally advanced-stage patients and maintains continuous surveillance of patients' post-treatment.

Internationally, numerous studies have examined survival rates post-treatment across various stages of cervical cancer, comparing the efficacy of different treatment modalities[3-5]. A study conducted in 2008 in the United States evaluated stage IA1–IB patients who underwent radical surgery or radiation therapy, reporting 5-year survival rates ranging from 87% to 92%[4].

In Thailand, studies conducted in many regions display an average 5-year overall survival rate of early-stage cervical cancer range of 62.3 to more than 90.0%[6-10]. Notably, some studies identified clinicopathological factors influencing survival rates, such as histology subtype, tumor size, lymphovascular space invasion (LVSI), and deep stromal invasion, but remain controversial[6-10]. Some studies showed the variables associated with the parametrial invasion that could surgically upstage cervical cancer that underwent radical hysterectomy were deep stromal invasion and pelvic lymph node metastasis, but lack of survival outcomes[11, 12].

Despite the wealth of international research, there remains a dearth of comprehensive data regarding survival rates, disease-free rates, recurrence rates, and the clinicopathological factors influencing outcomes specific to Chonburi province or the Eastern region of Thailand. Such information is crucial for monitoring treatment effectiveness, identifying variations in care, improving the patient supervision process and guiding resource allocation policy in our region.

Materials and Methods

This study represented a single-center, retrospective descriptive study conducted at Chonburi Hospital, Thailand. Ethics approval was granted by the Institutional Review Board of the Chonburi Hospital Medical Education Center under a waiver of informed consent (ref. 2966RH3). The study included all clinically early-stage cervical cancer patients who had been diagnosed preoperatively by punch biopsy or excisional procedure and clinical examination and underwent hysterectomy between January 1, 2012, and September 30, 2023.

In our hospital, all patients were clinically staged as recommended by the International Federation of Gynecology and Obstetrics (FIGO); tumor size was determined solely by the attending gynecologic oncologist during a pelvic examination or colposcopy preceding surgery. However, a minority of our patients could have preoperative imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) because of the long waiting period in our nonprofit, civil hospital setting. The patient must be aimed for primary hysterectomy or radical hysterectomy with pelvic lymphadenectomy (RHND). Patients whose

hysterectomies were abandoned, received neoadjuvant chemotherapy or preoperative irradiation, or with second primary cancer were excluded. The type of hysterectomy depended on the surgeon's decision based on FIGO recommendation. All hysterectomy underwent here was done via laparotomy. Generally, the criteria for referral for postoperative concurrent chemoradiation included pelvic node metastasis, parametrial invasion and/or surgical margin involvement in the high-risk group (Peter criteria)[13], and adjuvant radiation in the intermediated-risk group according to Sedlis criteria[14]. The radiotherapy took place in Chonburi Cancer Hospital with the cooperation of radiologic oncologists.

After completion of treatment, all patients returned to surveillance by history taking and clinical examination every 3-4 months during the first and second year, then every 6 months until the fifth year, and annually thereafter. The vaginal stump cytology was performed at least once a year. Recurrence was defined either by pathological proof or imaging. Disease-free survival (DFS) was calculated as the duration from the day of surgical treatment to the first time of tumor recurrence or death. All deaths were registered by the hospital database and the Cancer Registry Unit of Chonburi Hospital. All patients' statuses were rechecked using the hospital's National Health Security Office (NHSO) unit and the Department of Provincial Administration, Minister of Interior, using the death certificate database. OS was defined as the duration from the surgery until death, regardless of the causes of mortality. Cause of death was extracted by reviewing medical records if expired in the hospital or as defined in the death certificate by physician and authority staff if died outside the hospital. In the case of patients who lost to follow-up, DFS and OS data were censored at the time of patients known to be still alive since the last visit. All alive patients were confirmed directly by calling; survival data were right censored on September 30, 2023.

All pertinent clinical data were obtained and retrospectively reviewed from the medical records include birthdate, comorbidity, body weight, height, type of hysterectomy and associated procedures. Pathological factors include cell type, tumor size, depth, degree of stromal invasion, LVSI, number of pelvic lymph nodes exhibiting metastasis, surgical margin, parametrial and lower uterine segment invasion. Patients diagnosed before 2021 were re-stage according to FIGO's revised criteria 2018 (2021 update). Exclusion was also applied to individuals with incomplete medical record information.

The authors aimed to evaluate the 5-year OS and DFS of all early-staged cervical cancer cases meeting eligible criteria during the study period as the primary objective. Sample size calculation was based on the formula for two sample comparisons of the survival proportion using 1-tail alpha equal 0.05 and power 90%. OS of squamous cell carcinoma (SCC) and adenocarcinoma (AC) of the cervix from the prior study was used for calculation[15]. At least 113 participants per group were needed.

Statistical analysis was undertaken using STATA 14 (StataCorp, College Station, TX). Continuous data were presented as mean (standard deviations) or median (interquartile range, IQR), contingent on the normality of each distribution, while categorical data were delineated using counts and percentages. The Kaplan-Meier method

determined overall survival and disease-free survival at 5 years. Potential clinicopathological factors associated with DFS were compared using the log-rank test. The Cox proportional hazard regression model assessed the risk of recurrent disease or DFS. Univariate and multivariable analysis using significance for all statistical tests was set at a p value < 0.05.

Results

During the study period, three hundred and thirty-nine patients were diagnosed with early-stage cervical cancer and scheduled for simple hysterectomy or radical hysterectomy. Seventeen hysterectomies were abandoned due to gross intraoperative parametrial invasions, gross lymph node metastasis, or positive extra-cervical metastatic evidence on the frozen section. A total of 312 cases were eligible for analysis. The median follow-up time was 67.0 months (IQR 23.1, 111.5 months). The average age was 46.8 ± 11.6 years, with a mean body mass index (BMI) of 24.5 ± 4.8 kg/m^2. The majority of cases (97.4%) were of Thai ethnicity, totaling 304 cases. Fifteen patients (4.8%) were immunocompromised, and 46 (14.7%) were associated with cardiovascular disease or metabolic syndrome. Preoperative imaging (computerized tomography (CT) or magnetic resonance imaging (MRI)) was performed in 58 cases (18.59%) and within normal limits. According to the FIGO's revised criteria 2018 (2021 update), the number of cases was classified as following stages: IA1 = 32 (10.3%), IA2 = 4 (1.3%), IB1 = 82 (26.3%), IB2 = 96 (30.8%), IB3 = 55 (17.6%), and stage higher than IB3 = 43 (13.8%). The majority of cases were squamous cell carcinoma 181 (58.0%), followed by adenocarcinoma 114 (36.5%), and other cell types 17 (5.4%). The type of surgery included radical hysterectomy in 88.5% of cases, modified radical hysterectomy in 7.1%, and simple hysterectomy in 4.5%. Pelvic lymph nodes were removed in 94.9%, with a median of 20 nodes removed per patient. Pathology results showed lesions larger than 4 cm in 74 (23.7%), 122 (35.9%) had deep invasion into the stroma, and 129 (46.7%) had lymphovascular space invasion, which met the criteria for moderate risk of recurrence according to Sedlis criteria of 97 cases (31%). The cancer had spread to pelvic lymph nodes in 28 (10.1%) cases, to the parametrium in 22 (8.0%) cases, and the presence of cancer cells at the surgical margin in 25 (8.0%). According to Peter's criteria, they were classified as high risk of recurrence in 48 (15.4%) cases. Therefore, 145 patients needed adjuvant radiotherapy after surgery, but only 119 received adjuvant treatment. postoperative radiotherapy (PORT) was exclusively in 42 (15.2%) cases and concurrent with platinum in 73 (26.4%) cases. Those who did not receive adjuvant treatment, including those who had pelvic irradiation < 25.0 Gy (incomplete treatment), refused treatment, and those who had poor performance status totaled 29 (9.3%) cases. Discordance between clinical and surgical staging was 43 (13.8%). Overall death was 59 (18.9%), with 46 deaths within 5 years. Due to the overall survival rate of more than half, the expected median survival time estimated using Kaplan-Meier was 119.5 months (95%CI 113.6-125.5). The recurrence rate was 17.0%, with 50 cases recurring within 5 years since hysterectomy. The rate of loss to follow-up more than 2 years was 9.3%. The data was demonstrated in Table 1.

Table 1. Demographic data and clinicopathological characteristics.

	mean	SD
Age (years)	46.8	± 11.6
BMI (kg/m^2)	24.5	± 4.8
	n	**Percent**
Race		
Thai	304	97.4%
Other Southeast Asians	8	2.6%
Underlying disease		
Immunocompromised	15	4.8%
Cardiovascular or metabolic syndrome	46	14.7%
Stage (revised FIGO 2018)		
IA1	32	10.3%
IA2	4	1.3%
IB1	82	26.3%
IB2	96	30.8%
IB3	55	17.6%
Above IB3	43	13.8%
Cell type		
Squamous cell carcinoma	181	58.0%
Adenocarcinoma	114	36.5%
Neuroendocrine carcinoma	14	4.5%
Others	3	0.9%
Procedure		
Radical hysterectomy	276	88.5%
Modified radical hysterectomy	22	7.1%
Simple hysterectomy	14	4.5%
Pelvic lymphadenectomy	296	94.9%
Para-aortic lymphadenectomy	4	1.3%
Median number of pelvic lymph nodes retrieved (IQR)	20	(15-26)
Postoperative adjuvant treatment modality		
No indication for adjuvant treatment	166	53.2%
Adjuvant radiotherapy	42	15.2%
Concurrent chemoradiotherapy	73	26.4%
Adjuvant chemotherapy (without radiotherapy)	4	1.3%
Incomplete or denial of adjuvant treatment	24	7.7%
Omission based on the radiotherapist's opinion and the patient's performance status	5	1.6%
Adverse prognostic factor (not including the micro-invasive stage) (n = 276)		
Presence of LVSI	129	46.7%
Large tumor size (> 4 cm)	74	23.7%
Deep stromal invasion	112	35.9%
Parametrial invasion	22	8.0%
Lymph node metastasis	28	10.1%
Categorized into intermediate risk group (Sedlis criteria)	97	31.0%
Categorized into high-risk group (Peter criteria)	48	15.4%
Discordance between clinical and surgical staging	43	13.8%
Median follow-up time (months, IQR)	67.0	(23.1, 111.5)
Expected median survival time (months, 95%CI)	119.5	(113.6-125.5)
Rate of lost surveillance > 2 year	29	9.3%
Overall recurrence	53	17.0%

SD: standard deviation, BMI: body mass index, SEA: Southeast Asians, FIGO: Federation of Gynecology and Obstetrics, IQR: interquartile range, LVSI: lymphovascular space invasion, CI: confidence interval

Overall survival and disease-free survival

During the study period, the overall survival rate for all stages of cervical cancer was found to be 85.3%. The 5-year OS for patients with early-stage cervical cancer treated with surgery at Chonburi Hospital were as follows: IA1 100%, IA2 100%, IB1 93.9%, IB2 88.5%, IB3 81.8%, and higher than IB3 53.5%. The average 5-year overall survival rate was 86.2 %. When considering specific causes of death from cervical cancer, 5-yr cancer-specific survival were as follows: IA1 100%, IA2 100%, IB1 96.3%, IB2 91.7%, IB3 81.8%, and higher stage IB3 55.8%. The 5-year cancer-specific survival rate from all stages of our study was 87.2%.

Among the 312 patients, 53 (17%) experienced a recurrence of cervical cancer. Half of these recurred in the first two years (media 17.4 months (IQR 9.5-12.1)). Recurrence was confirmed by biopsy or fine needle aspiration or imaging. Five-year disease-free survival rates were 100% for stages IA1 and IA2. However, stages IB1, IB2, IB3, and those higher than IB3 had recurrence rates of 4.9%, 12.5%, 25.5%, and 48.8%, respectively. The proportion of survival was plotted in Fig. 1. and 2.

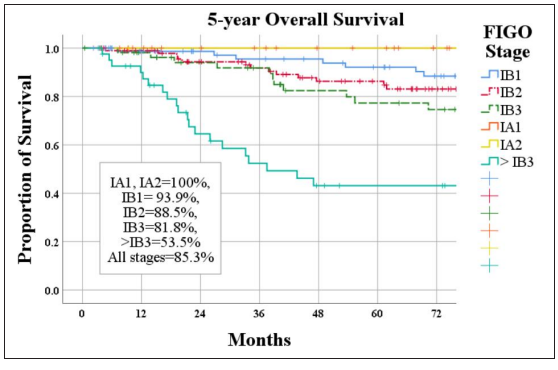

Fig. 1. 5-year overall survival in Kaplan-Meier curve, according to International Federation of Gynecology and Obstetrics 2018 stage.

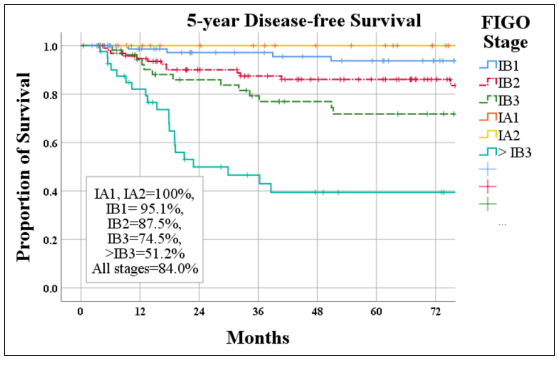

Fig. 2. 5-year disease-free survival in Kaplan-Meier curve, according to 5-year overall survival in Kaplan-Meier curve, according to International Federation of Gynecology and Obstetrics 2018 stage 2018 stage.

Potential clinicopathological prognostic factors

The research data were analyzed to identify factors affecting 5-year DFS using the log-rank test and then Cox proportional hazard models. Significant factors reducing DFS were determined to be as follows: higher stages of cervical cancer had the greatest effect on lowering survival rates compared to stage IB1 (HR 15.46%, 95% CI 5.29-45.23), tumor

size larger than 4 centimeters (HR 7.79, 95% CI 2.69-22.54), deep stromal invasion (HR 10.84, 95% CI 3.34-35.20), presence of LVSI (HR 6.42, 95% CI 3.01-13.67), depth of invasion more than 10 millimeters, parametrial involvement, lower uterus segment invasion, unfree surgical margin, positive pelvic lymph node metastasis and those receiving adjuvant PORT. Notably, age and comorbidities did not significantly affect the survival rate. These findings are summarized in Tables 2 and 3.

Table 2. Univariate analysis of 5-year disease-free survival according to potential clinicopathological factors using log-rank test.

Clinicopathological factor	n	5-year disease-free survival	p value*
Age (years)			0.118
≤ 45	147	81.0%	
> 45	165	86.7%	
Underlying disease			0.219
No	251	84.9%	0.
Immunocompromised	15	66.7%	
Cardiovascular or metabolic syndrome	46	84.8%	
Histology			0.043
Squamous	181	89.0%	
Adenocarcinoma	114	78.1%	
Neuroendocrine	14	64.3%	
Tumor size (cm)			< 0.001
≤ 2	124	96.8%	
> 2	188	75.5%	
Depth of invasion (mm)			< 0.001
≤ 10	199	91.5%	
> 10	113	70.8%	
Degree of stromal invasion			< 0.001
Superficial 1/3	130	97.7%	
Middle 1/3	70	84.3%	
Deep 1/3	112	67.9%	
Lymphovascular space invasion			< 0.001
Absence	183	95.6%	
Presence	129	67.4%	
Lower uterine segment invasion			0.001
Absence	276	86.8%	
Presence	40	65.0%	
Surgical margin involvement			< 0.001
No	287	87.1%	
Yes	25	48.0%	
Parametrial invasion			< 0.001
No	290	86.6%	
Yes	22	50.0%	
Pelvic node metastasis (lymphadenectomy, n = 295)			< 0.001
Absence	267	86.9%	
Presence	28	46.4%	
Adjuvant postoperative radiotherapy or chemoradiotherapy (stage IB and above, n = 279)			0.025
No	164	86.6%	
Yes	115	75.7%	

* log-rank testl

Table 3. Univariate analysis of 5-year disease-free survival according to prognostic clinicopathological factors using Cox proportional hazard models in surgical stage IB1 and above.

Clinicopathological factor	Hazard ratio*	95% confidence interval	p value*
Stage (revised FIGO 2018)			0.004
IB1	1		
IB2	2.56	0.83-7.94	
IB3	5.14	1.68-15.78	
> IB3	15.46	5.29-45.23	
Histological cell type			0.034
Squamous	1		
Adenocarcinoma	1.89	1.05-3.40	
Neuroendocrine	2.79	1.05-7.43	
Tumor size (cm)			0.004
≤ 2	1		
> 2 to ≤ 4	4.73	1.64-13.69	
> 4	7.79	2.69-22.54	
Depth of invasion (mm)			< 0.001
≤ 10	1		
> 10	3.06	1.70-5.50	
Degree of stromal invasion			0.017
Superficial 1/3	1		
Middle 1/3	4.70	1.31-16.86	
Deep 1/3	10.84	3.34-35.20	
Lymphovascular space invasion			< 0.001
Absence	1		
Presence	6.42	3.01-13.67	
Lower uterine segment invasion			0.005
Absence	1		
Presence	2.42	1.31-4.50	
Surgical margin involvement			< 0.001
No	1		
Yes	5.57	2.94-10.56	
Parametrial invasion			< 0.001
No	1		
Yes	4.25	2.18-8.32	
Pelvic node metastasis			< 0.001
Absence	1		
Presence	5.80	3.15-10.68	
Adjuvant postoperative radiotherapy or chemoradiotherapy			0.031
No	1		
Yes	1.85	1.06-3.24	

* Cox proportional hazards regression analysis

In multivariate analysis, only surgically stage > IB3, tumor size larger than 4 centimeters, and deep stromal invasion remained statistically significant, contributing to a decreased 5-year DFS rate. However, adjuvant treatment, either radiotherapy or concurrent chemotherapy, increased the DFS rate after surgery. This data is demonstrated in Table 4.

Table 4. Multivariate analysis of 5-year disease-free survival according to prognostic clinicopathological factors using Cox proportional hazard models.

Variable	Hazard ratio*	95% confidence interval	p value*
Stage > IB3	9.53	2.96-16.07	< 0.001
Tumor size > 4 cm	4.73	2.57-8.71	< 0.001
Deep 1/3 stromal invasion	4.73	1.09-20.62	0.038
Lymphovascular space invasion presence	3.91	1.61-10.25	0.004
Adjuvant postoperative radiotherapy or chemoradiotherapy	0.39	0.20-0.76	0.006

* Cox proportional hazards regression analysis

Discussion

Our study, in a single institute with over 300 patients over 12 years, showed that patients with clinically diagnosed early-stage cervical cancer who were primarily treated with radical hysterectomy and pelvic lymphadenectomy had good survival outcomes with a 5-year OS and DFS of 85.3% and 84.0%. Our OS was similar and consistent with global results of early-stage cervical cancer stratified into stage IA1–IB3 according to the revised FIGO 2018 staging criteria. These studies have reported 5-year OS ranging from 95.8%, 95.0%, 91.6%, 83.3%, and 76.1% in stages IA1 to IB3, respectively[3, 16]. In Thailand, the largest series of patients with stages IA-IIA (FIGO 2009) from Chiang Mai (Suprasert et al 2010)[10] impressively revealed an excellent 10-year disease-free survival of 90% with a 4-fold sample size greater than ours. Despite the relatively higher pelvic node metastasis, parametrial invasion, and vaginal margin involvement than our cohort, the 10-year DFS was better. A total of 66.5% of patients in this study underwent RHND without adjuvant treatment, whereas 12.1% received neoadjuvant chemotherapy. It might reflect the well-experienced clinical-surgical characteristics of the leading institute and the properly selected case. However, the difference in FIGO staging criteria and survival time frame might not ensure comparability. Another study from Songkhla (Chandeying et al 2017)[9] also revealed the 5-year DFS rate of stage IA2-IB1 (FIGO 2009) of AC at 89.3% (95%CI 83.2–93.2), SCC 88.7% (95%CI 84.8 - 91.7) which was similar to our DFS of stage IA2-IB2 (FIGO 2018). Almost all prior studies in Thailand usually used FIGO 2009 criteria, except one recent study from Bangkok (Bangsomboon et al 2022)[8] displayed the 5-year progression-free survival (PFS) of stage IB1, IB2, and IB3 were 83.3%, 90.0%, and 84.2%, respectively. The 5-year OS were 71.4%, 92.2%, and 62.5%, consecutively. The PFS and OS were not different among the 3 sub-stages of IB, which was inconsistent with ours. This disparity may result from the difference in sample size and baseline characteristics, especially the rate of surgically upstaging (35.8%, n = 81) compared to 13.8% (n = 43) of our cohort. Discordance in clinical and surgical staging of cervical cancer can affect survival rates, patients who are pathologically upstaged have a higher risk of recurrence and death[17]. This is because tumor size is a major factor in determining the best treatment planning and survival outcomes. The preferred treatment for tumors smaller than 4 cm is surgery, while primary chemoradiation is recommended for larger tumors. Finally, our results support the novel FIGO 2018 staging criteria in terms of survival and can be used to stratify both OS and DFS.

Our study's clinicopathological factors significantly associated with recurrence and DFS were FIGO 2018 stage > IB3, large tumor size, deep stromal invasion, and presence of LVSI. These variables were well-documented and consistented with global findings. Actually, our "stage > IB3" variable can resemble the presence of any Peter criteria that are generally used to categorize patients into high-risk groups for recurrence[13]. The other three significant factors, tumor size, deep stromal

invasion (DSI), and presence of LVSI, were also in the Sedlis criteria used to divide patients into intermediate-risk groups for recurrence[14]. Hence, this study reassures the clinical application of these two criteria. Postoperative radiotherapy, whether with or without concurrent chemotherapy (CCRT), usually reduced the recurrent rate in early-stage cervical cancer with large tumor size, LVSI, and DSI from 88% (pelvic radiation) versus 79% (no adjuvant treatment) or from 80% (CCRT) versus 63% (PORT) [13, 14]. Our study supports the adjuvant PORT helps improve disease-free survival with a hazard ratio of 0.39 (95%CI 0.20-0.76, p = 0.006). However, a recent study demonstrated that histology-specific nomograms can more accurately and linearly predict the risk of recurrence for both SCC and AC tumors, offering a more contemporary and tailored tool to determine adjuvant treatment[18]. Furthermore, a novel study found that among patients meeting one or two Sedlis criteria, there were no statistically significant differences in OS between those receiving PORT and those without adjuvant treatment, likely due to the increasingly accurate selection of cervical cancer patients eligible for surgery[19].

A strength of our study lied in the long follow-up duration on patients with early-stage cervical cancer surgically treated and monitored at Chonburi Hospital with a median surveillance time of 67.0 months (IQR 23.1-111.5). Second, the lost contact rate for over 2 years was low (9.3%) as we are the only hospital capable of radical hysterectomy in the city, and our cancer manager team and outpatient nurses were willing to reach out to patients when there was a disconnection. Third, our patients diagnosed before 2021 were re-stage according to FIGO's revised criteria 2018 (2021 update); therefore, our stage is current to the international agreement. Fourth, excluding patients with incomplete records may introduce selection bias; however, our hospital transitioned from hard-copy to electronic-based documentation in 2012, ensuring the validity and reliability of the available information. Fifth, the rate of pelvic lymphadenectomy concurrent with radical hysterectomy in our institute was high: 99.3% (296 from 298 type II and type III hysterectomies). Median number of pelvic lymph nodes retrieved (IQR) was 20 (15-26). Therefore, we can ensure the absence of microscopic nodal metastasis.

A limitation of the study was that a minority of our patients could have preoperative imaging such as CT or MRI because of the long waiting period in our nonprofit, civil hospital setting. Many studies recommend utilizing CT/MRI scans to determine the stage before treatment accurately[16, 20] Preoperative imaging can crucially help determine if a patient truly needs a radical hysterectomy or not. In our previous resource-constrained setting, it might have been difficult to assess the spread of the disease, which could have led to an incorrect treatment plan. This lack results in discordance between clinical and surgical staging. Second, due to Chonburi Hospital's inability to perform radiation therapy, we had to rely on treatment information from Chonburi Cancer Hospital as well. Third, we hardly performed paraaortic lymphadenectomy as suggested in part of the surgical staging procedures[5]. Fourth, we observed a proportion of non-adherence to PORT or denial of adjuvant radiotherapy. This issue should be explored and reviewed as we generally know that the adjuvant PORT improves OS and DFS, especially in either intermediate-risk or high-risk groups. Non-adherence to PORT is crucial in our regional context, the root cause should be investigated as it represents a missed opportunity to enhance patient outcomes. In 2021, the National Health Security Office (NHSO) announced the implementation of the Cancer Anywhere (CA) policy[21]. This program enabled access to radiotherapy in private hospitals in Chonburi and may offer potential strategies to mitigate prior constraints and improve survival outcomes in the future. Lastly, despite the survival outcome, the quality of life and the complications or sequelae from treatment also affect cancer survival patients[10, 22]. We look forward to exploring and conducting further studies on these issues in the future.

Conclusion

Patients with clinically early-stage cervical cancer who underwent surgery at Chonburi Hospital exhibited an overall 5-year survival rate of 85.3% and 5-year DFS of 84.0%. The FIGO 2018 stage beyond IB3, tumor size over 4 cm, LVSI, and deep stromal invasion were significant hazard clinicopathological factors for recurrence. In contrast, adjuvant PORT was the protective factor for recurrence.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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