

Treatment Patterns and Surgical Outcomes of Stage IA1 Cervical Carcinoma

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ABSTRACT

OBJECTIVE The primary objective was to determine the 5-year overall survival rate and 5-year disease-free survival rate of patients with CACx IA1 treated at Chiang Mai University Hospital and the secondary objective was to describe treatment modalities as well as their associated complications.

METHODS Patients with stage IA1 cervical cancer diagnosed from January 2001 to June 2018 at Chiang Mai University Hospital were retrospectively reviewed. Inclusion criteria included previously untreated patients diagnosed with stage IA1 cervical cancer (2018 FIGO staging system). Exclusion criteria were patients with recurrent cervical cancer, other gynecologic malignancies, and those in a pregnant state. The analysis included treatment patterns, surgical types, and clinicopathologic variables, i.e., nodal metastasis, parametrial involvement, positive surgical margins, deep stromal invasion (DSI), lymph-vascular space invasion (LVSI), adjuvant treatment, 5-year disease-free survival, and 5-year overall survival. All pathologic slides were reviewed by gynecologic pathologists. The Kruskal-Wallis test, Fisher's exact test, the Kaplan-Meier method and log-rank test were used for statistical analysis.

RESULTS Of the 184 patients included in this study, simple hysterectomy was the most common treatment (57.3%), followed by modified radical hysterectomy (MRH) and radical hysterectomy (RH) (27.6% and 9.7% respectively). Conization and radiation were chosen in a few cases. At the median follow up time of 40.8 months, the 5-year disease free survival rate was 99.1% and the 5-year overall survival rate was 95.0%. Pelvic lymph node dissection was done in 62 cases (33.7%), but only one case (0.54%) had pelvic lymph node metastasis.

CONCLUSIONS The surgical and survival outcomes for women with stage IA1 cervical cancer are excellent. They can be effectively treated with less radical interventions such as simple hysterectomy and conization. Lymph node metastasis is rare at this stage (0.54%); therefore, lymphadenectomy may possibly be omitted.

KEYWORDS cervical cancer, IA1, treatment outcome

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INTRODUCTION

Cervical cancer ranks as the fourth most frequently detected cancer and the fourth primary

contributor to cancer-related fatalities among females globally (1). The majority of new cases and deaths stem from low and middle-income

countries, posing economic and social challenges for the Thai health system.

In recent years, there has been a notable increase in the adoption of cervical cancer screening programs incorporating PAP smear and/or high-risk human papillomavirus (HPV) testing. This trend has led to the earlier identification of preinvasive lesions, microinvasive, and early-stage cervical cancer. The implementation of this strategic approach has resulted in a significant reduction in the morbidity and mortality associated with cervical cancer.

In 2018, the updated staging criteria for carcinoma of the cervix uteri by the International Federation of Gynecology and Obstetrics classified stage IA1 cervical cancer as a microscopic carcinoma confined to the cervix uteri with stromal invasion of less than 3 mm in depth (2). Diagnosis necessitates microscopic examination of a conization encompassing the entire lesion. The treatment modalities for stage IA1 cervical cancer vary from conservative approaches (conization/trachelectomy), to hysterectomy (type 1–type 3), and radiation. The outcomes are excellent and comparable among the various modalities, with a five-year survival rate of 97.5% (3). The recurrence rate and death rate from the cancer are 0.8% and 0.2% respectively.

The choice of treatment is predominantly influenced by factors like fertility aspiration and patient compliance. Moreover, prognostic considerations, including lymph-vascular space invasion (LVSI), cell type, internal margin status, and pathology findings from post-conization endocervical curettage, significantly impact the treatment decision-making process (4).

The foremost determinant of survival is lymph node metastasis and is contingent on the depth of stromal invasion and LVSI. A study conducted by Benedet et al. (5) indicated that the rate of lymph node metastasis is 2.6% for LVSI-positive cases, decreasing to 0.3% for LVSI-negative cases.

As per recent guidelines regarding the management of microinvasive cervical cancer (6, 7), in cases where the tumor lacks LVSI, conization with negative margins or extrafascial hysterectomy is advisable for women who have completed child-bearing. When LVSI is present, consideration should be given to pelvic lymphadenectomy, coupled with modified radical hysterectomy. For

patients expressing a desire for fertility preservation, cervical conization with close monitoring is deemed reasonable. These recommendations reflect variations in the aggressiveness of treatment, potentially impacting patient morbidity. Notably, some recent studies indicate a very low risk of parametrial invasion at this stage, suggesting that a less radical surgery may be a viable option. Lee et al. similarly proposed conization alone with vigilant follow-up, irrespective of margin status or LVSI (8).

Though several studies on this issue have been published, more studies are still needed to improve future meta-analysis and to further study various aspects, especially rare cell type, rare modalities of treatment, and prognostic factors. Moreover, each center should develop its own data for evaluation of the treatment outcomes. Accordingly, we conducted this study with the primary objectives of determining the 5-year overall survival rate and the 5-year disease-free survival rate of patients with stage IA1 cervical cancer treated at Chiang Mai University Hospital and secondarily to describe treatment modalities as well as their associated complications.

METHODS

A retrospective analysis was conducted on patients diagnosed with stage IA1 cervical cancer and treated at Chiang Mai University Hospital in Chiang Mai, Thailand, from January 2001 to June 2018. All cases were sourced from the clinical database of the Gynecologic Oncology Division, including comprehensive reviews of the clinical charts, operative reports, and pathology reports of each patient. Additionally, all histopathological reports underwent review by a specialist in gynecologic pathology.

Eligibility criteria included previously untreated patients diagnosed with stage IA1 cervical cancer, classified according to the 2018 FIGO staging system. For this study, stage IA1 cervical cancer, or microinvasive cancer, was defined as a microscopic tumor with stromal invasion not exceeding 3 mm in depth. The diagnosis should be established through examination of conization, hysterectomy, or trachelectomy specimens. Exclusion criteria encompassed patients with recurrent cervical cancer, other gynecologic malignancies, and those in a pregnant state.

Treatment strategies were categorized into three options: (1) conservative treatment by conization, (2) hysterectomy, and (3) radiation (vaginal brachytherapy). Within the hysterectomy strategy, irrespective of the surgical approach, groups were distinguished as follows: (a) simple hysterectomy group (extrafascial hysterectomy), (b) modified radical hysterectomy (MRH) group (class 2 Piver-Rutledge-Smith classification or type B Querleu-Morrow classification), and (c) radical hysterectomy (RH) group (class 3 Piver-Rutledge-Smith classification or type C Querleu-Morrow classification). The decision regarding pelvic lymph node dissection or sampling was based on the surgeon's discretion.

The procedure of MRH with pelvic node dissection (PND) was performed on patients exhibiting LVSI. RH and PND were conducted on patients with either the presence of LVSI or the identification of cancer cells in endocervical curettage specimens during the loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC). Systematic pelvic lymphadenectomy involved the removal of all fatty tissue along both sides of the common iliac, external iliac, internal iliac vessels, and the lymphatic tissue in the obturator fossa. Para-aortic lymphadenectomy was only undertaken when gross metastasis to the common iliac nodes or para-aortic nodes was suspected.

Pathological variables of the cervical tumor were considered as follows: (i) histological cell type, (ii) depth of stromal invasion, (iii) LVSI was considered as positive if tumor cells were found in the lymph-vascular spaces, (iv) parametrial involvement, (v) lymph node status, (vi) residual tumor, defined as remaining tumor cells detected on hysterectomy specimens following cervical conization or biopsy, and (vii) vaginal margin status.

Following the primary surgical intervention, all patients underwent regular follow-up assessments at our hospital. The frequency of these assessments was established as every three months for the first year, every four months in the second year, every six months up to the fifth year, followed by yearly check-ups. The follow-up protocol, at the minimum, comprised cervical cytology and colposcopy, with directed biopsy performed when indicated. The time from the treatment date to either the recurrence diagnosis or to the last follow-up date was defined as the disease-free survival

period. Overall survival was characterized as the time from the treatment date to the date of death. This study received approval from the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University.

All analyses were performed using Stata version 15 (StataCorp LLC, College Station, TX, USA). Continuous variables are expressed as mean $\pm$ SD or median (interquartile range) as appropriate and categorical variables are expressed as frequency (%). Comparisons among various groups were performed using the Kruskal-Wallis test and Fisher's exact test. The Kaplan-Meier method was used in the analysis of survival rate, and differences were tested for statistical significance using the log-rank test. A *p*-value of less than 0.05 was considered to be significant.

RESULTS

Of the initial 193 patients with stage IA1 cervical cancer, eight were excluded due to missing data in the medical records and operative notes. Only one patient opted for conization due to fertility desires, leaving 184 patients eligible for this study. The study's flow chart is depicted in [Figure 1](#), and [Table 1](#) and [2](#) present treatment patterns and clinicopathological variables. The mean age of the study group was 48.7 years (SD: 8.8).

Among the 184 patients, 158 (85.9%) were diagnosed with stage IA1 cervical cancer through LEEP, 8 (4.3%) through CKC, and 18 (9.8%) through other methods (post-hysterectomy specimen, cervical biopsy, endo-cervical curettage). Surgical interventions included simple hysterectomy for 106 (57.6%) patients, MRH for 51 (27.7%), RH for 18 (9.8%), and radiation for nine (4.9%) patients. Twelve (6.5%) patients were HIV-infected, and only 1.4% had negative results from prior cervical cytology screening by PAP smear. The most common histology result was squamous cell carcinoma (85.9%), followed by adenocarcinoma (12.0%).

Lymph-vascular space invasion was present in 12 (7.2%) cases. Pelvic lymph node dissection was performed on 62 (33.7%) patients, with the mean number of nodes removed in MRH being 20 (range 10-27) and the mean RH being 24 (range 15-26). Only one case (0.6%) showed pelvic lymph node metastasis, and no parametrium involvement was found. Only one case had lymph node invasion at the obturator region, which was in

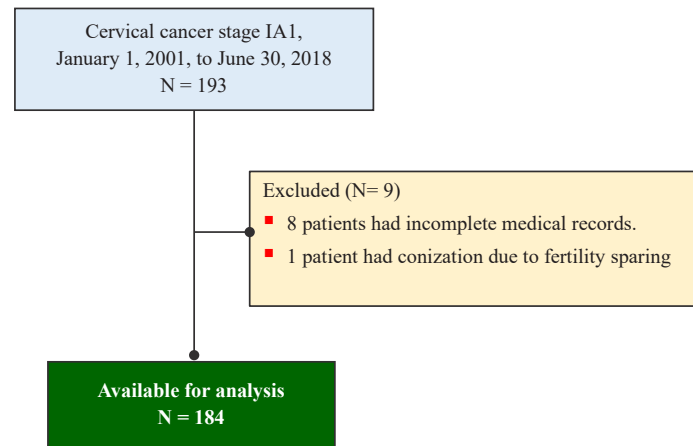


Figure 1. Flow chart of the study

Table 1. Baseline characteristics and outcomes of the patients in this study (n=184)

Characteristics	Treatment groups				Overall	p-value
	SH n=106 (57.6%)	MRH n=51 (27.7%)	RH n=18 (9.8%)	RT n=9 (4.9%)		
Age, mean $\pm$ SD (years)	47.7 $\pm$ 8.1	50.4 $\pm$ 8.7	47.6 $\pm$ 7.6	54.7 $\pm$ 15.4	48.7 $\pm$ 8.8	0.140 ^a
Histology						<0.001 ^b
SCCA	102 (96.2)	38 (74.5)	10 (55.6)	158 (85.9)		
Adenocarcinoma	3 (2.8)	12 (23.5)	7 (38.9)	22 (12)		
Adenosquamous	1 (0.9)	1 (2)	1 (5.6)	3 (1.6)		
Mixed type	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)		
LVSI						<0.001 ^b
Negative	105 (99.1)	44 (86.2)	14 (77.7)	172 (93.4)		
Positive	1 (0.9)	7 (13.8)	4 (22.3)	12 (6.6)		
Lymph node dissection						<0.001 ^b
No	102 (96.2)	11 (21.6)	0 (0.0)	122 (66.3)		
Yes	4 (3.8)	40 (78.4)	18 (100)	62 (33.7)		
5-year disease-free survival rate (%)	98.6 (90.3-99.8)	100.0	100.0	99.1 (94.0-99.9)		0.88 ^c
5-year overall survival rate (%)	94.2 (83.1-98.1)	97.1 (81.4-99.6)	100.0	95.0 (88.2-98.0)		0.26 ^c
Follow-up time median (inter-quartile range), months	42.2 (20.2-77.2)	41.8 (15.4-81.4)	37.5 (23.6-61)	40.8 (20-74.8)		0.50 ^d

^a, ANOVA test; ^b, Fisher's exact test; ^c, Log rank test; ^d, Kruskal-Wallis test

MRH, modified radical hysterectomy; RH, radical hysterectomy; RT, radiation therapy; SH, simple hysterectomy

the MRH group. This patient received an adjuvant treatment of concurrent chemoradiation after surgery. Also, only one patient had a vaginal margin involvement of cancer, which was in the simple hysterectomy group, and she received laser vaporization after treatment. The number of residual tumors found during surgery after cervical conization or biopsy was not significantly different between the groups. There was one patient who requested fertility preservation management; she was a 30-year-old woman with an abnormal

cytologic screening result. The histologic result from LEEP indicated squamous cell carcinoma of the cervix stage IA1 with positive margin for pre-invasive lesion. She refused hysterectomy, and re-LEEP was done as an alternative procedure with satisfactory results. She is currently doing well and has one child. The median follow-up time for all patients was 40.8 months (20.0-74.8).

Complications of surgical treatment, detailed in Table 3, included 4 (2.4%) cases with massive intra-operative blood loss ($\geq 1,000$ mL), 2 (1.2%)

Table 2. Clinico-pathological variables of surgical treatment patients (n=175)

Characteristics	Treatment groups				p-value
	SH	MRH	RH	Overall	
Number of lymph nodes removed	0 (0.0-0.0)	20 (10.0-27.0)	24 (15.0-26.0)	0 (0.0-18.0)	<0.001 ^a
Positive lymph nodes*					0.39 ^b
No	106 (100.0)	50 (98.0)	18 (100.0)	174 (99.4)	
Yes	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.6)	
Vaginal margin*					1.00 ^b
Not involved	101 (95.3)	49 (96.1)	18 (100.0)	168 (96)	
Vg HSIL	4 (3.8)	2 (3.9)	0 (0.0)	6 (3.4)	
Vg SCCA	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.6)	
Residual tumor*					0.430 ^b
No	86 (81.1)	37 (72.5)	15 (83.3)	138 (78.9)	
Yes	20 (18.9)	14 (27.5)	3 (16.7)	37 (21.1)	

*Data are expressed as number (%); ^aKruskal Wallis test; ^b Fisher's exact test

MRH, modified radical hysterectomy; RH, radical hysterectomy; SH, simple hysterectomy

Table 3. Complication of surgical treatment patients (n=175)

Variables	Treatment groups				p-value
	SH	MRH	RH	Overall	
Intra-operative blood loss > 1,000 mL*					0.140
No	100 (99.0)	48 (94.1)	18 (100.0)	166 (97.6)	
Yes	1 (1.0)	3 (5.9)	0 (0.0)	4 (2.4)	
Acute febrile*					0.040
No	96 (95.0)	43 (84.3)	18 (100.0)	157 (92.4)	
Yes	5 (5.0)	8 (15.7)	0 (0.0)	13 (7.6)	
Urinary tract injury*					-
No	101 (100.0)	51 (100)	18 (100.0)	170.0 (100)	
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Bowel injury*					0.160
No	101 (100.0)	49 (96.1)	18 (100.0)	168 (98.8)	
Yes	0 (0.0)	2 (3.9)	0 (0.0)	2 (1.2)	
Lymphedema*					0.040
No	100 (99.0)	48 (96.0)	16 (88.9)	164 (97.0)	
Yes	1 (1.0)	2 (4.0)	2 (11.1)	5 (3.0)	
Bladder dysfunction*					0.050
No	100 (99.0)	46 (92.0)	17 (94.4)	163 (96.4)	
Yes	1 (1.0)	4 (8.0)	1 (5.6)	6 (3.6)	

*Data are expressed as number (%). The p-values are based on Fisher's exact test.

MRH, modified radical hysterectomy; RH, radical hysterectomy; SH, simple hysterectomy

with bowel injury, and 13 (7.6%) with febrile morbidity. No urinary tract injuries were reported.

Late complications included significant lymphedema in 5 (3.0%) patients and bladder dysfunction in 6 (3.6%) patients, with recovery duration ranging from 6 weeks to 6 months.

Figures 2 and 3 present Kaplan-Meier survival probability plots for disease-free survival and overall survival. The 5-year disease-free survival rate was 99.1%, with no statistically significant difference between the groups ($p = 0.88$). There was only one case of recurrent cervical cancer in this

series, occurring at the vaginal stump 9 months after simple hysterectomy. The patient was then given vaginal brachytherapy and is currently doing well. The 5-year overall survival rate was 95.0%, also without significant differences between the groups ($p = 0.26$).

DISCUSSION

Insights gained from this study include the following: (1) treatment outcomes were excellent in our series, resulting in a 5-year disease-free survival rate of 99% and 5-year overall survival

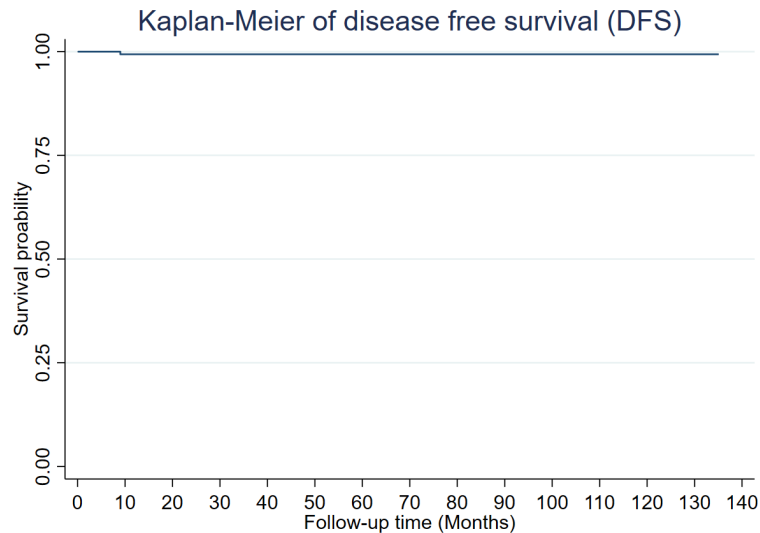


Figure 2. Kaplan-Meier disease-free survival (DFS)

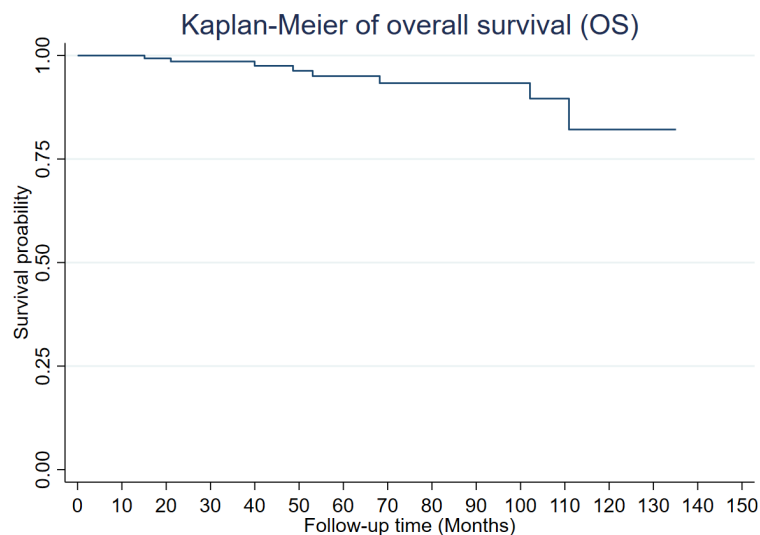


Figure 3. Kaplan-Meier overall survival (OS)

rate of 95%, regardless of treatment modalities. However, the more extensive surgery was associated with a higher rate of minor complications; (2) simple hysterectomy is the most common modality for stage IA1, accounting for 57.6% of cases, followed by modified radical hysterectomy (27.7%), (3) the histological cell type adenocarcinoma tended to have a higher incidence of more extensive surgery (MRH, RH), though the choice of treatment was mainly based on surgeons' preference. 4) Lymph node metastasis was identified in only 1 out of 184 (0.54%). Because of the low prevalence of non-squamous cell types in this series, the favorable outcomes of this study are mainly reflective of stage IA1 of squamous cell type. Note that the rates of lymph node metas-

tasis and LVSI were very low and were equally distributed among the treatment subgroups. The low prevalence or small sample size might explain the lack of significant associations between the presence of lymph node metastasis, LVSI and survival outcomes. Note that the rates of modified radical and radical hysterectomy were relatively high in this study. This is attributed to the high rate of positive margins for preinvasive lesions identified in the histologic results of conization specimens.

The outcomes for stage IA1 cervical cancer patients in this study are highly favorable, with a 5-year disease-free survival rate of 99.1% and an overall survival rate of 95.0%. A study conducted by Wright et al. examined 1,409 stage IA1 cervical

cancer patients using SEER data in the USA (9). In their study, 40% of the patients underwent conization, while the remaining 60% underwent hysterectomy. The 5-year overall survival rates did not differ significantly between the two groups (98% and 99%, respectively). Their findings suggest the efficacy of conization, particularly for young women. However, it is important to note that the mean age of patients in our study was higher than that of the aforementioned research. Notably, only one patient in our study opted for conization for fertility preservation, and she has experienced no recurrence of the disease and continues to fare well.

Squamous cell carcinoma is the most common type of cervical cancer, and historically it has been perceived to have a more favorable prognosis than adenocarcinoma or adenosquamous cell carcinoma. Consequently, physicians tended to administer more aggressive treatments for microinvasive cervical cancer with adenocarcinoma cell types. As demonstrated in this study, patients in these groups often opted for more radical surgeries, such as MRH and RH. However, the treatment outcomes did not exhibit significant differences between these different cell types of cancer. Spoozak et al. reported that the adenocarcinoma cell type constituted 24.8% of microinvasive cervical cancer cases and was more prevalent in white and younger patients. Notably, conization was found to be a safe and effective treatment for this specific cell type (10). Furthermore, according to a study by Bean et al., the metastasis rate of the adenocarcinoma cell type to lymph nodes was 0.97%, compared to 0.72% observed in the squamous carcinoma cell type for stage IA cervical cancer (11). The authors suggested conservative treatments for patients with adenocarcinoma cell types in this stage.

Pelvic lymphadenectomy can lead to persistent morbidity for patients, including complications like lymphocyst, lymphedema, pelvic nerve injury, and potential increases in operation time and blood loss. Current cervical cancer treatment guidelines emphasize the assessment of LVSI as a crucial component of treatment planning (6, 7). If LVSI is identified, pelvic lymphadenectomy is recommended in conjunction with modified radical hysterectomy. A study by Benedet indicated that the rate of lymph node metastasis was 2.6% for

LVSI-positive cases and 0.3% for LVSI-negative cases (5). However, studies by Spoozak, Haller, and Yahata et al. found no lymph node metastasis in stage IA1 cervical cancer, leading them to suggest the omission of lymphadenectomy in this cancer stage, regardless of LVSI status (10, 12, 13). Our study aligns with these findings. LVSI was detected in only 12 cases, and pelvic lymphadenectomy was performed in 62 cases (33.7%). Notably, only one case exhibited obturator lymph node metastasis, with no discernible association with LVSI status, and the patient remains in remission.

Both radical hysterectomy (RH) and modified radical hysterectomy (MRH) are considered as aggressive treatments for stage IA1 cervical cancer. However, our study revealed no statistically significant differences in overall survival rate and disease-free survival rate between radical surgery (RH and MRH) and simple hysterectomy. Given the very early stage of the disease, only one case exhibited tumor invasion into the vagina, and there were no cases of parametrial invasion. The residual tumors after conization were similar across all groups (70%-80%) and were not identified as a prognostic factor.

Baalbergen et al. and Yahata et al. conducted extensive studies on adenocarcinoma of the cervix stage IA over extended periods (80 months and 70.5 months, respectively) (13, 14). Baalbergen's study reported recurrence rates of 1.7% with conservative surgery and 2% with radical hysterectomy plus pelvic lymphadenectomy, which aligns with the findings from Yahata's study. Both studies concluded that conservative surgery, encompassing simple hysterectomy and conization, proved to be effective for stage IA1 cervical cancer.

Limited research exists on the efficacy of radiation therapy in microinvasive cervical cancer. In our study, utilization of that method was used primarily in cases with multiple comorbidities, accounting for 88.9% of such cases (8 of 9 cases). The radiation technique employed varied based on the preference of the oncologic radiologist and involved either pelvic external beam radiation or intracavitary radiation. Encouragingly, the outcomes in this patient subgroup were satisfactory, with no reported case of recurrence.

The strength of the present study is the inclusion of a large number of patients who were treated at a single institution, ensuring minimal variability in

operative techniques. Additionally, the thorough examination of all pathological specimens by expert gynecologic pathologists enhances the reliability of the findings. The weaknesses of this study are as follows: (1) the retrospective nature, leading to less reliability in some data, (2) heterogeneous modalities of treatment without specific criteria or indications for each modality but with decision making on treatment options based on surgeons' preference, (3) too small a sample size for subgroup analysis, for examples, the small number of cases with adenocarcinoma cell types, lymph node involvement, LVSI. Therefore, prognostic factors for survival rate could not be evaluated with high reliability.

CONCLUSIONS

In conclusion, our results support that stage IA1 cervical cancer has favorable survival outcomes and that simple hysterectomy is the treatment of choice. More extensive surgery does not seem to increase 5-year overall and 5-year disease-free survival rates but may be associated with a higher rate of complications. Nevertheless, the results should be interpreted with caution since the sample size of the patients receiving treatments other than simple hysterectomy was relatively low, possibly causing the result of non-significance of added value of more aggressive treatment. Radiation and conization may also be considered in some selected cases. Cell type and LVSI status did not affect the outcomes.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author contributions

U.A.: conceptualization, proposal development, study design, data collection, manuscript writ-

ing; S.S.: conceptualization, study design, data collection/validation, manuscript editing; C.T.: conceptualization, study design, supervision, data collection/analysis, manuscript editing; K.T.: conceptualization, data collection, manuscript editing; P.S.: conceptualization, data collection, manuscript editing; J.S.: conceptualization, data collection, manuscript editing.

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by Research Ethics Committee, Faculty of Medicine, Chiang Mai University (Research ID: OBG-2561-05847)

Informed consent statement

Not applicable

Data availability statement

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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