RESEARCH ARTICLE

Salvage Treatment and Outcomes of Locally Advanced Cervical Cancer after Failed Concurrent Chemoradiation with or without Adjuvant Chemotherapy: Post Hoc Data Analysis from the ACTLACC Trial

Tussawan Asakij[1], Jakkapan Khunnarong[2]*, Siriwan Tangjitgamol[3], Kanisa Rongsriyam[4], Ekkasit Tharavichitkul[5], Chokaew Tovanabutra[6], Kannika Paengchit[7], Jirasak Sukhaboon[8], Lieutenant Col. Apiradee Kridakara[9], Thiti Atjimakul[10], Piyawan Pariyawateekul[11], Prapai Tanprasert[12]

Abstract

   Objectives: To evaluate the type of salvage treatment and outcomes of patients with locally advanced cervical cancer who failed treatment with concurrent chemoradiation with or without adjuvant chemotherapy. **Methods:** This was post hoc analyses of data from the randomized trial which included 259 patients who had FIGO stage IIB-IVA and had either pelvic radiation therapy concurrent with cisplatin followed by observation or paclitaxel plus carboplatin. Data of the patients who failed primary treatment were collected: type of salvage treatments, time to progress after salvage therapy, progression-free (PFS) and overall survivals (OS). **Results:** After primary treatment, 85 patients had either persistence (36.5%), progression (18.8%), or recurrences (44.7%). The sites of failure were loco/regional in 52.9%, systemic failure in 30.6%, and loco-regional and systemic in 16.5%. Chemotherapy was given in 51.8%, being the sole therapy in 34.1%. Majority were combination agents (31.8%), with paclitaxel/carboplatin as the most common regimen. Radiation to the metastatic sites along with chemotherapy was used in 14.1% whereas palliative radiation therapy or supportive care was used in approximately 10% of each. The median time from the start of salvage treatment to progression was 9.2 months (range 0.2-64.0 months) with median PFS of 11.2 months (95% CI, 7.2-15.3 months). Median overall survival 27.3 months (95% CI, 4.4-69.6 months). **Conclusions:** Chemotherapy, either alone or with radiation therapy, was the most common salvage treatment in LACC after failure from primary treatment. The time to progress and PFS were less than 1 year with OS of approximately 2 years.

   Keywords: Adjuvant chemotherapy- concurrent chemoradiation therapy- locally advanced cervical cancer-salvage

Introduction

   The International Federation of Gynecology and Obstetrics (FIGO) has classified cervical cancer into stage I to stage IV. The latest revision of FIGO staging in 2019 had incorporated imaging study into staging process and re-subgrouped early stage (stage IB and stage IIA) by the size of tumor and added a subgroup of stage IIIC for positive retroperitoneal lymph node (Pecorelli et al., 2009;

Bhatla et al., 2019).
   Stage is a major indicator for prognosis and the type of treatment for cervical cancer. Early stage (stage I-IIA) has high chance of cure with either surgery or radiation. This is in contrast with advanced stage (stage IVB) when the cure is unlikely and when chemotherapy or other palliative treatment is considered. The locally advanced cervical cancer (LACC; stage IIB-IVA) has modest prognosis with concurrent chemoradiation

[1]Radiation Oncology Section, Lampang Cancer Hospital, Thailand. [2]Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Thailand. [3]Women's Health Center, MedPark Hospital, Bangkok, Thailand. [4]Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Thailand. [5]Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Chiang Mai University, Thailand. [6]Radiation Oncology Section, Chonburi Cancer Hospital, Thailand. [7]Gynecologic Oncology section, Lampang Cancer Hospital, Thailand. [8]Radiation Oncology Section, Lopburi Cancer Hospital, Thailand. [9]Radiation Oncology Section, Bhumibol Adulyadej Hospital, Thailand. [10]Department of Obstetrics and Gynecology, Prince of Songkla University, Thailand. [11]Obstetrics and Gynecology Section, Bhumibol Adulyadej Hospital, Thailand. [12]Obstetrics and Gynecology Section, Rajburi Hospital, Thailand. *For Correspondence: jak020@hotmail.com

(CCRT). Although CCRT which is the current standard treatment could yield superior survival than radiation alone, approximately one third of the patients with LACC treated with CCRT still experienced persistent or recurrent diseases (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008). One treatment option aiming to improve survival in this LACC patients is adjuvant chemotherapy (ACT) after CCRT. However, data of survival benefit by the ACT from randomized trials were inconsistent (Lorvidhaya et al., 2003; Veerasan et al., 2007; Dueñas-González et al., 2011; Tang et al., 2012; Tangjitgamol et al., 2019).

Management of LACC after failure from CCRT depends on several factors e.g. location of diseases, size of lesions, disease-free interval, the patient's performance status, and the availability of professional care providers and instruments. Surgery has limited role in persistence or recurrence cancer, but it may be considered for isolated lesions in the central pelvis (Marnitz et al., 2006). Metastatic tumor resection might be considered if the disease is limited to only few foci and are expected to be totally resected and with preferably free margins before salvage chemotherapy (Tangjitgamol et al., 2004). Limited re-irradiation to focal lesion in the pelvis or at other sites to relive symptoms may be considered (Randall et al., 1993). In the other circumstances when there are evidence of distant or metastatic diseases which are not good candidates for surgery or radiation, palliative treatment with chemotherapy or supportive management by symptoms are more appropriate (Monk et al., 2005).

This study evaluated the type of salvage treatment and outcomes of LACC patients who had been treated with CCRT with or without adjuvant chemotherapy in a randomized trial (Tangjitgamol et al., 2019).

Materials and Methods

The study retrieved data from the dataset of one randomized trial in Thailand (ACTLACC trial; COA-CREC 002/2013, NCT02036164 and TCTR 20140106001) which compared CCRT alone or CCRT plus ACT in LACC. The study was approved by the Institutional Review Board for research involving human subject (COA 093/2020).

In brief, the inclusion criteria of the trial were: cervical cancer patients who aged 18 to 70 years, had FIGO stage IIB-IVA (by FIGO 2009), and had no para-aortic lymph node enlargement > 1 cm or were suspicious for cancer metastasis from screening CT scan, and had histopathology of squamous cell carcinoma, adenocarcinoma, or adeno-squamous carcinoma. All patients received weekly cisplatin 40 mg/m2 concurrent with pelvic radiation therapy. The 129 patients in the control arm had surveillance without any additional treatment whereas the 130 patients in the study arm received paclitaxel 175 mg/m^2 IV plus carboplatin AUC 5 every 4 weeks for 3 cycles. For this study, the patients who had available data of salvage treatment after primary treatment failure (persistence, progression, or recurrence) and outcomes after treatment were included.

Regarding the clinical assessment, complete physical examination performed at baseline included: vaginal and rectal examination, chest x-ray, whole abdominal computed tomography, and laboratory tests. During concurrent chemoradiation treatment, all patients had a weekly physical examination, CBC, Bun and Cr. The same approach was performed on day one of each ACT cycle with an addition of LFTs and electrolytes for the patients in the study arm who had ACT.

The status of tumor after treatment in all patients was assessed monthly for 4 months after CCRT (or during the 3-monthly cycles of ACT and 1 month after the least cycle). The assessment was then conducted every 3-4 months for 24 months and every 6 months according to the standard practice. The surveillance according to the trial continued unless there were persistent diseases, progression, or recurrence requiring salvage treatment. During the surveillance, complete physical examination was done in every visit whereas whole abdominal CT scan were planned every 6 months for 2 years and chest-x ray yearly, or whenever clinically indicated.

The response defined by the RECIST 1.1 criteria was concluded at approximately 4 months after CCRT or 1 month after the last ACT, or earlier when an event of disease progression occurred. Primary treatment failure included persistence, progression, or recurrence. Persistence was defined as presence of existing tumor at the end of 4 months after CCRT (1 month after the last ACT) whereas progression referred to an increase in size of existing lesion or an appearance of new lesions at any time during treatment or within the first 4 months after CCRT. Any evidence of disease after complete response were defined as recurrence and classified as loco-regional and/or systemic.

Clinical outcomes including response rate after treatment, progression-free (PFS) and overall survivals (OS) of all patients in the trial were presented in our primary report (Tangjitgamol et al., 2019). This study collected the following data for post-hoc analysis: age at diagnosis, FIGO stage, performance status of the patients at the time of event, treatment-free interval after primary treatment, type of salvage treatments, time to progress after salvage therapy which referred to the duration from the initiation of salvage treatment to disease progression. PFS and OS of this group of patients were obtained from salvage therapy to progression or from primary treatment to death, respectively.

Data of all patients who had treatment initiated according to their randomized groups were analyzed using SPSS statistical software, version 22.0 (IBM Corp., Armonk, NY, USA). Data from subgroup analysis were compared by Chi-square test. Survival data were analyzed by the Kaplan-Meier method and compared between groups with a log-rank test. P-values < 0.05 were considered statistically significant.

Results

From 259 patients who were enrolled into the study and after a median follow-up of 40.9 months (range 3.2 – 69.8 months), primary failure was encountered in 85 patients (32.8%). The failures were persistence in 31

Table 1. Type of Salvage Treatment by the Type of Primary Treatment (N=85)

Salvage treatment	All (N=85)	Primary treatment	
		CCRT (n=39)	CCRT/ACT (n=46)
Chemotherapy	29 (34.1)	15 (17.6)	14 (16.5)
Combination drugb	27 (31.8)	15 (17.6)	12 (14.1)
Carboplatin or gemcitabine	2 (2.4)	-	2 (2.4)
Radiation therapy	8 (9.4)	3 (3.5)	5 (5.9)
Extra-pelvic lymph nodea	3 (3.6)	2 (2.4)	1 (1.2)
Pelvis (cervix)	2 (2.4)	-	2 (2.4)
Bone	3 (3.6)	1 (1.2)	2 (2.4)
Combined treatment	18 (21.3)	11 (13)	7 (8.3)
Chemotherapy + radiation to para-aortic node (n=11) or bone (n=1)	12 (14.1)	8 (9.4)	4 (4.7)
Spine or cecum resection + chemotherapy	2 (2.4)	1 (1.2)	1 (1.2)
Spine surgery (n=2) or vulva surgery (n=1) + radiation	3 (3.6)	2 (2.4)	1 (1.2)
Spine surgery then radiation and chemotherapy	1 (1.2)	-	1 (1.2)
Surgery (radical hysterectomy)	2 (2.4)	1 (1.2)	1 (1.2)
Supportive care	9 (10.6)	4 (4.7)	5 (5.9)
Unknown	19 (22.4)	5 (5.9)	14 (16.5)

aExtra-pelvic lymph nodes included para-aortic (n=3), supraclavicular (n=1) or para-aortic/supraclavicular (n=1); bCombination drug included paclitaxel/carboplatin (n=14), cisplatin/ 5-Fluorouracil (n=11), and cisplatin/ paclitaxel (n=2)

(36.5%), progression in 16 (18.8%), and recurrences in 38 (44.7%). No significant differences of primary failure rates between 129 patients who had only CCRT or 130 patients who had CCRT and ACT were found (detail of events in each group were presented elsewhere). The most common site of primary treatment failure was loco-regional (45 patients; 52.9%) followed systemic failure (26 patients; 30.6%), and loco-regional and systemic (14 patients; 16.5%).

The most common mode of salvage treatment after primary treatment failure was chemotherapy (51.8%), being the sole therapy in approximately one third (34.1%). Majority of which were combination agents (31.8%), with paclitaxel/carboplatin as the most common regimen. Radiation to the affected metastatic sites along with chemotherapy was used in 14.1% whereas palliative radiation therapy or supportive care was used in approximately 10%. Of note, 2 patients (2.4%) had pelvic re-irradiation. Table 1 demonstrates the type of salvage treatment according to primary treatment. In summary, no difference in the management options between the patients who had CCRT or CCRT plus ACT was found.

Among 66 patients who had data regarding the type of salvage therapy and results of treatment, the median time to progress from the start of salvage treatment to progression was 9.2 months (range 0.2-64.0 months) with median PFS of 11.2 months (95% confidence interval [CI] 7.2-15.3 months). The time to progress and PFS after salvage therapy were studied according to their characteristic features, their diseases, type of primary and salvage treatments (Table 2). Age over 40 years, good performance status (ECOG 0-1), treatment-free interval longer than 6 months, systemic sites of failure, and having surgery or combined salvage treatment had longer PFS than the others. Significantly, favorable prognostic features for PFS by univariable analysis were

stage II and treatment-free interval > 6 months. On the other hand, good performance status and longer treatment-free interval were significant good prognostic factors by multivariable analysis.

From 85 patients who failed primary treatment, 54 (63.5%) of them died at the time of data analysis whereas 31 were still alive with disease and having second-or further-line chemotherapy or palliative treatment. Median overall survival 27.3 months (95% CI 4.4-69.6 months). Table 3 shows OS according to their characteristic features, their diseases, type of primary and salvage treatments. Features which had favorable prognosis on OS were the same as those for PFS, with stage II disease, good performance status, and treatment-free interval longer than 6 months be independent favorable prognostic features for OS.

We also explored OS of 24 patients who had radiotherapy as a salvage treatment. The median OS of the 13 patients who had para-aortic node radiation and of the 2 patients who had cervical re-irradiation were 38.8 months (95% CI 31.8-56.3 months) and 34.4 months (95% CI 28.5-36.7 months) respectively. The median OS was shorter among 8 patients who had radiation to bone lesions, 24.7 months (95% CI 7.5-41.9 months).

Discussion

With an effort to search for a scheme to improve outcome of patients with LACC, we had conducted a randomized trial (ACTLACC trial) to evaluate the role of adjuvant chemotherapy after CCRT (Tangjitgamol et al., 2019). No improvement of response rate and survival with ACT after CCRT compared to only CCRT could were found approximately one third of LACC patients in the trial had failure after primary treatment of either CCRT or CCRT plus ACT. This rate was in accordance with

Table 2. Time to Progress and Progression-Free Survival According to Characteristic Features of the Patients and Type of Salvage Therapy (N=66)

Characteristic features	Time to progress (month; range)	PFS, median (month; 95% CI)	Unadjusted HR (%; 95% CI)	Adjusted HR (%; 95% CI)
Age			0.69 (0.32-0-1.48)	1.17 (0.49-2.78)
≤ 40 years (n=12)	4.1 (0.4-64)	3.30 (0.00-7.47)		
> 40 years (n=54)	10.9 (0.2-62.5)	12.30 (8.86-15.74)		
Stage			1.81 (1.02-3.23)	1.65 (0.82-3.13)
II (n=37)	9.8 (0.2-64)	12.37 (1.98-22.76)		
III-IV (n=29)	6.9 (0.3-62.5)	10.47 (2.94-17.99)		
Performance status			1.59 (0.88-2.86)	1.92 (1.02-3.62)
0-1 (n=63)	9.8 (0.2-64)	11.23 (7.31-15.16)		
2-4 (n=3)	1.4 (0.4-17.9)	1.37 (7.21-15.25)		
Treatment-free interval			0 (0-0.16)	0 (0-0.14)
≤ 6 months (n=25)	2.9 (0.2-5.5)	2.93 (1.68-4.19)		
> 6 months (n=41)	16.5 (6.1-64)	18.62 (3.50-34.16)		
Type of failures			0.73 (0.72-1.60)	0.19 (0.87-2.07)
Local (n=45)	17.1 (0.3-64.0)	10.5 (6.9-14.1)		
Systemic (n=26)	16.5 (0.2-59.5)	15.4 (6.8-23.9)		
Local and Systemic (n=14)	10.0 (0.4-40.2)	7.6 (1.6-13.6)		
Primary treatment			1.61 (0.90-2.87)	1.47 (0.75-2.87)
CCRT (n=34)	12.3 (0.3-59.5)	12.37 (6.96-17.78)		
CCRT+ACT (n=32)	6.8 (0.2-64)	8.03 (2.16-13.91)		
Salvage therapy			1.25 (0.92-1.71)	1.02 (0.77-1.35)
Radiation therapy (n=8)	12.1 (2.1-27.6)	12.90 (8.69-17.11)		
Surgery (n=2)	46.9 (29.8-64)	29.80 (18.4-72.6)		
Chemotherapy (n=29)	8.5 (0.3-62.5)	9.83 (2.41-17.25)		
Combined treatment (n=18)	15.1 (2.3-59.5)	23.07 (4.07-42.07)		
Supportive care (n=9)	1.4 (0.2-4.5)	2.93 (0-2.82)		

Note: Performance status referred to performance status of the patients at the time of event; Time to progress referred to duration from the start of salvage therapy to progression of disease; Treatment-free interval referred to duration from the last date of primary treatment to the date of even

the systematic review including trials involving CCRT in LACC with individual data analysis by the Cochrane (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008).

Unlike early-stage cervical cancer in which salvage treatment depends mainly on the type of primary treatment (surgery or pelvic radiation), the LACC which failed primary CCRT (persisted, locally/ systemically progressed, or recurred) had only few options of salvage therapy. The management depended on many factors, with sites of failure appeared to be the most important factor determining the type of salvage treatment. Other factors which may impact the option of treatment were performance status, attitude and financial or reimbursement system of the patients.

Generally, chemotherapy has been the most common salvage treatment in many gynecologic cancers including cancer of cervix when local treatment was not possible or not useful. As demonstrated in this study that more than half of the patients who had failure after primary treatment received chemotherapy, either alone or combined with other treatments. Combination chemotherapy was more commonly used than single agent. This practice was probably based on data from previous studies showing

superior activity of doublet regimens (cisplatin with ifosfamide, paclitaxel, or topotecan) than cisplatin alone in terms of higher response rate, longer PFS, and with or without OS (Omura et al., 1997; Moore et al., 2004; Long et al., 2005). Among the cisplatin-based doublet regimen, no differences in response rate, PFS, OS, or quality of life were observed from its combination with either paclitaxel, vinorelbine, gemcitabine, or topotecan were observed (Monk et al., 2009). With an additional data from the Japanese trial (Kitagawa et al., 2015) showing comparable efficacy of cisplatin or carboplatin combined with paclitaxel, paclitaxel/ carboplatin had probably gained popularity as a salvage chemotherapy due to a more familiar and easier in clinical use than cisplatin/ paclitaxel as evidenced in our study. Although adding bevacizumab to doublet chemotherapy was found to significantly improve OS (18) 18Tewari KS, Sill MW, Long HJ 3rd, et al., (2014), a high cost of the agent did not allow a widely use in clinical practice especially in low/middle income areas including Thailand. Survivals of cervical cancer patients who had salvage chemotherapy reported from previous studies were usually short, with 5 months PFS and less than 12 months OS (Omura et al., 1997; Moore et al., 2004; Long et al., 2005). This

Table 3. Living Status and Overall Survival of Locally Advanced Cervical Patients who had Failure after Primary Treatment According to Characteristic Features of the Patients and Type of Salvage Therapy

Characteristic features	Status, n (%)		OS (month; 95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
	Alive	Dead			
Age				0.61 (0.29-1.25)	0.62 (0.26-1.46)
≤ 40 years (n=14)	5 (35.7)	9 (64.3)	17.1 (4.4-69.6)		
> 40 years (n=71)	26 (36.6)	45 (63.4)	29.0 (4.8-67.9)		
Stage				2.06 (1.19-3.56)	2.16 (1.16-4.02)
II (n=45)	23 (51.1)	22 (48.9)	31.5 (4.4-69.6)		
III-IV (n=40)	8 (20.0)	32 (80.0)	25.3 (4.8-63.7)		
Performance status				1.43 (0.90-2.27)	2.18 (1.15-4.12)
0-1 (n=80)	31 (38.8)	49 (61.2)	27.3 (4.4-69.6)		
2-4 (n=5)	-	5 (100)	27.3 (6.9-44.7)		
Treatment-free interval				0.12 (0.06-0.24)	0.12 (0.06-0.24)
≤ 6 months (n=25)	2 (8.0)	23 (92.0)	14.1 (4.4-36.4)		
> 6 months (n=41)	21 (51.2)	20 (48.8)	38.7 (9.5-69.6)		
Type of failures				1.05 (0.73-1.52)	1.01 (0.64-1.59)
Local (n=45)	15 (33.3)	30 (64.7)	27.7 (20.6-34.9)		
Systemic (n=26)	13 (50)	13 (50)	35.9 (32.6-50.4)		
Local and Systemic (n=14)	3 (21.4)	11 (78.6)	16.8 (14.2.0-40.2)		
Primary treatment				1.24 (0.72-2.13)	1.18 (0.61-2.26)
CCRT (n=39)	16 (41.0)	23 (59.0)	27.9 (4.8-64.4)		
CCRT+ACT (n=46)	15 (32.6)	31 (77.4)	24.6 (4.4-69.6)		
Salvage therapy				1.036 (0.87-1.23)	1.17 (0.84-1.63)
Radiation therapy (n=8)	2 (25.0)	6 (75)	31.7 (4.4-59.6)		
Surgery (n=2)	2 (100)	-	61.2 (52.7-69.6)		
Chemotherapy (n=29)	9 (31.0)	20 (69.0)	25.2 (6.3-64)		
Combine treatment (n=18)	10 (55.6)	8 (44.4)	37.0 (9.5-64.4)		
Supportive care (n=9)	-	9 (100)	7.9 (4.8-16.2)		

Note: Performance status referred to performance status of the patients at the time of event; Treatment-free interval referred to duration from the last date of primary treatment to the date of event

study found nearly 10 months PFS and 25 months OS of the patients who received salvage chemotherapy. Possible reasons for the differences among studies were characteristic features of the patients, types of primary treatments. Other studies evaluated the efficacy of specific chemotherapy on patients who had various stages of cervical cancer who might have failed one or more prior treatments whereas this study focused on LACC patients who had failed only primary treatment.

Aside from chemotherapy, radiation therapy has certain roles in selected patients. In this study, focal irradiation alone or combination with other treatments to specific metastatic sites was used in nearly 30%. Aside from a palliative aim to relieve symptoms, PFS or OS might be extended if the lesions were eradicated. As evidenced in our study that the patients who had tumor directed radiation to para-aortic nodal region or cervix had prolonged OS of approximately 3 years. The good results from radiation therapy in our study was partly due to limited diseases (focal lesions without metastatic diseases). Previous study also reported higher OS rate among the patients with isolated para-aortic nodal metastasis after pelvic RT than those with other sites of lesions (Hong et al., 2004). Other favorable features

aside from small volume diseases and favorable sites of lesions which could be used as selective criteria especially for pelvic irradiation were absence of regional or distant metastases, vaginal wall at sub-urethral location rather than vaginal cuff, squamous rather than adenocarcinoma, and a use of certain radiation techniques (Randall et al., 1993; Brabham and Cardenes, 2009). Few studies reported high local control rate of over 60% with the use of interstitial re-irradiation (Randall et al., 1993; Brabham and Cardenes, 2009) or 50-100% with stereotactic ablative radiotherapy in the recurrent pelvic malignancy (Murray et al., 2017).

Although surgery has limited role in LACC, total pelvic exenteration could be considered for persistent diseases as well as central recurrences in previous irradiated field. Nearly 40% or 30% 5-year survival rates from pelvic exenteration as a primary treatment or salvage treatment in recurrent setting were reported (Marnitz et al., 2006). However, tailored surgery i.e. radical hysterectomy which could yield 3-year or 5-year OS of over 50% in few studies (Chiantera et al., 2014; Mabuchi et al., 2017; Li et al., 2018) may be applied in selected cases. Radical hysterectomy was performed in only 2 cases (2.4%) in this study. With limited persistent disease at cervix and

successful surgical procedure, over 2 years disease-free period was achieved with approximately 5 years survival duration. These figures were higher than those obtained by other salvage treatments. However, this must be interpreted with caution because of limited number of patients with only limited local failure.

The prognosis for LACC cervical cancer patients who failed from primary treatment with RT or CCRT was poor with median survival of 17 months or 5-year OS of only 10% (Hong et al., 2004; Liu et al., 2013). and less than 12 months in studies of salvage chemotherapy for advanced or recurrent cervical cancer of any stages (Omura et al., 1997; Moore et al., 2004; Long et al., 2005). Our study found 11 months median PFS after salvage treatment and 27 months median OS after the primary diagnosis. Possible reasons for the differences in outcomes from each study were mainly the stage of diseases and types of salvage treatments. Other studies evaluated the efficacy of specific treatment (especially chemotherapy) on patients who had various stages of cervical cancer who might have failed one or more prior treatments whereas this study focused on LACC patients who had failed only primary treatment. Other prognostic factors which had been recognized were, for example, performance status, treatment-free interval, and location of failure (Hong et al., 2004; Moore et al., 2010). In this study, we also found the patients who had better performance status, lower stage (stage IIB), and treatment-free interval > 6 months had significant longer PFS and OS than the others. These factors may be taken into consideration for a salvage treatment.

The goal of salvage therapy for LACC patients who had failed CCRT is generally palliation because of their modest to poor survival after the events. Hence, the clinical benefit gained from any palliative treatment should be balanced with their toxicities and impact on quality of life (Moore et al., 2004; Long et al., 2005; Monk et al., 2005). Aside from medical information, personal reasons i.e. beliefs or myths about salvage treatment might also contribute to treatment after primary treatment failure as evidenced in this study that nearly one fourth of the patients did not seek for further medical care at all.

In summary, chemotherapy was the most common salvage therapy for cervical cancer which failed from primary treatment with CCRT. Limited surgical resection of lesion or radiation therapy was mainly used as an adjunct. Radiation therapy alone to localized lesion was uncommonly used and less likely with definitive surgery of hysterectomy. The most important prognostic factors for PFS and OS found in this study were stage and treatment-free interval added with performance status for OS.

Author Contribution Statement

Conceptualization, T.S., L.V; Data curation, T.S., T.E., T.C., R.K., aA.T., P.K., S.J., P.S., K.A., H.J., C.K., W.S., bA.T., P.P., K.K., T.P., J.W., S.D., C.T., L.V; Formal analysis: T.S., I.W; Funding acquisition: T.S; Investigation, T.S., L.V; Project administration, T.S., T.E., T.C., A.T., P.K., S.J., P.S., K.A., H.J., K.K., S.B., L.P., S.J., L.V; Supervision, T.S., L.V; Validation: T.S., R.K; Writing - original draft, T.S; Writing - review & editing:

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Conflicts of Interest

The authors declared no conflicts of interest.

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