RESEARCH ARTICLE

Prognostic Impact of Histology in Patients with Cervical Squamous Cell Carcinoma, Adenocarcinoma and Small Cell Neuroendocrine Carcinoma

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Abstract

Background: Clarifying the prognostic impact of histological type is an essential issue that may influence the treatment and follow-up planning of newly diagnosed cervical cancer cases. This study aimed to evaluate the prognostic impact of histological type on survival and mortality in patients with cervical squamous cell carcinoma (SCC), adenocarcinoma (ADC) and small cell neuroendocrine carcinoma (SNEC). Materials and Methods: All patients with cervical cancer diagnosed and treated at Chiang Mai University Hospital between January 1995 and October 2011 were eligible. We included all patients with SNEC and a random weighted sample of patients with SCC and ADC. We used competing-risks regression analysis to evaluate the association between histological type and cancer-specific survival and mortality. Results: Of all 2,108 patients, 1,632 (77.4%) had SCC, 346 (16.4%) had ADC and 130 (6.2%) had SNEC. Overall, five-year cancer-specific survival was 60.0%, 54.7%, and 48.4% in patients with SCC, ADC and SNEC, respectively. After adjusting for other clinical and pathological factors, patients with SNEC and ADC had higher risk of cancer-related death compared with SCC patients (hazard ratio [HR] 2.6; 95% CI, 1.9-3.5 and HR 1.3; 95% CI, 1.1-1.5, respectively). Patients with SNEC were younger and had higher risk of cancer-related death in both early and advanced stages compared with SCC patients (HR 4.9; 95% CI, 2.7-9.1 and HR 2.5; 95% CI, 1.7-3.5, respectively). Those with advanced-stage ADC had a greater risk of cancer-related death (HR 1.4; 95% CI, 1.2-1.7) compared with those with advanced-stage SCC, while no significant difference was observed in patients with early stage lesions. Conclusion: Histological type is an important prognostic factor among patients with cervical cancer in Thailand. Though patients with SNEC were younger and more often had a diagnosis of early stage compared with ADC and SCC, SNEC was associated with poorest survival. ADC was associated with poorer survival compared with SCC in advanced stages, while no difference was observed at early stages. Further tailored treatment-strategies and follow-up planning among patients with different histological types should be considered.

Keywords: Survival - mortality - cervical cancer - histology - prognostic impact - Thailand

Asian Pac J Cancer Prev, **14 (9)**, 5355-5360

Introduction

Cervical cancer is the third most common cancer among women worldwide, accounting for approximately 13% of all cancers in women, with 529,800 new cases and 275,100 deaths in 2008. More than 85% of the cases and about 88% of all deaths occurred in developing countries (Ferlay, 2010; Jemal et al., 2011). At the same time, the incidence of cervical cancer has decreased dramatically in developed countries with well-developed screening programs concomitant with substantial survival improvements over the last two decades (Smith et al., 2000; Liu et al., 2001; Mathew and George, 2009).

The most common type of cervical cancer is squamous cell carcinoma (SCC) which comprises approximately 75% of all cervical cancers (Kosary, 1994; Farley et al., 2003).The second most common type is adenocarcinoma (ADC) accounting for about 20% (Wang et al., 2004). The remaining cases consist of rare histological types including small cell neuroendocrine carcinoma (SNEC) (Kosary, 1994; Farley et al., 2003). Over time, the rates of invasive SCC have declined, while the incidence of

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ADC (Smith et al., 2000; Wang et al., 2004; Mathew and George, 2009) and SNEC (Vinh-Hung et al., 2007) have increased. A previous US study based on the Surveillance, Epidemiology, and End Results (SEER) data revealed a 42% reduction in age-adjusted incidence rates of SCC from 1973-1977 to 1993-1996, while the age-adjusted incidence rates of ADC increased by 29%. The proportion of ADC has increased by 95.2% relative to SCC (from 12.4-24.2%) and by 107.4% relative to all cervical cancers (from 10.8-22.4%) during the same periods (Smith et al., 2000). These trends may be attributed to screening programs that have successfully detected pre-invasive SCC (Mathew and George, 2009). The increase in ADC probably results from an increased prevalence of HPV infection in the general population (Vinh-Hung et al., 2007), an insufficient of cytology screening program to detect pre-invasive lesions ADC (Smith et al., 2000; Liu et al., 2001) or the increased ability to diagnose the disease (Bray et al., 2005).

Results of previous studies on the prognostic impact of the histological type in patients with cervical cancer are inconclusive. Several studies have reported that histological type is an important prognostic factor (Nakanishi et al., 2000; Takeda et al., 2002; Vinh-Hung et al., 2007; Chen et al., 2008; Zivanovic et al., 2009; Lee et al., 2010; Park et al., 2010). A US study of patients from 1997 to 2003 in the SEER database found 5-year overall survivals of 32.5% for patients with SNEC, 74.3% for ADC and 64.6% for SCC (Chen et al., 2008). Some studies have reported 2.6-2.9 times higher mortality among patients with early stage ADC compared with early-stage SCC patients over 10-19 years of follow-up (Nakanishi et al., 2000; Takeda et al., 2002; Park et al., 2010; Mabuchi et al., 2012) while others have not found any significant difference in survival among patients with SCC and ADC (Shingleton et al., 1995; Lee et al., 2006; Fregnani et al., 2008; Kasamatsu et al., 2009; Narukon et al., 2010). Moreover, only few studies have included patients with SNEC.

Clarifying the prognostic impact of histological type is an essential issue that may influence the treatment and follow-up planning of newly diagnosed cervical cancer cases (Vinh-Hung et al., 2007). The aim of this study was to evaluate the prognostic impact of histological type on survival and mortality among patients with SCC, ADC and SNEC in Thailand.

Materials and Methods

Setting

This cohort study was conducted after approval by the ethics review board of Chiang Mai University Hospital, Thailand. Chiang Mai University Hospital has 1,400 beds and serves an average of 1,000,000 out patients and 50,000 in patients annually. The hospital has many expert fields including the Department of Pathology and Division of Gynecologic Oncology, Department of Obstetrics and Gynecology. The hospital also serves referred patients with complicated diseases from other hospitals in northern Thailand.

Inclusion criteria

All patients with cervical cancer who were diagnosed and treated at Chiang Mai University Hospital between January 1995 and October 2011 were eligible. We recruited all patients with histologically confirmed SNEC, whereas we randomly enrolled a weighted sample of patients with ADC and SCC. To imitate the distribution of ADC and SCC, the proportion of SCC patients were approximately five times greater than that of ADC. Available histopathologic slides and specimens were re-examined by a gynecologic pathologist, in cases where the pathological data was incomplete.

Data on covariates

Clinical and pathological data were abstracted from medical records, pathology reports and cancer registry reports. Dates of patient deaths were obtained from medical records and/or the registry of the Thai Ministry of Interior. Our study outcome was cancer-related death. We defined cancer-specific survival as the time from the date of treatment to the date of cancer-related death, last follow-up, or censoring, whichever came first. The variables included in the analyses were age at diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage, tumor size, lymph node metastasis, lymphovascular space invasion, parametrial involvement, depth of stromal invasion, histological type and treatment.

All patients were clinically staged according to FIGO staging criteria. We defined early stage as FIGO stages I-IIA and advanced stage as stages IIB-IVB. According to treatment guidelines, patients with early stage of diseases were usually treated with primary radical hysterectomy and pelvic lymphadenectomy. Neoadjuvant chemotherapy with cisplatin was given to patients whose operative schedule was longer than a month from the first visit. The pathological findings were used as indicators for further individualized adjuvant therapy which included radiation therapy, concurrent chemoradiation therapy and chemotherapy. Patients with advanced stage diseases were typically treated with radiation therapy with or without chemotherapy.

Statistical analysis

We estimated 5-year cancer-specific survivals of SCC, ADC and SNEC overall and stratified by clinical and pathological risk factors, assuming non cancer related death to be a competing cause of death. To compare mortality according to histological type, we used competing-risk multivariable regression to determine crude and adjusted hazard ratios (HR) with 95% CI using SCC as reference. Subsequently, to describe survival according to histological type, we plotted adjusted cancer-specific survival curves overall and stratified by stage. In early stage patients, we adjusted for age, FIGO stage, tumor size, lymph node involvement, depth of stromal invasion and treatment. Overall analyses and analyses restricted to patients with advanced stage were adjusted for age, FIGO stage and treatment. We considered P values of less than 0.05 as statistically significant and all tests were two-tailed. STATA statistical software version 11 was used for all statistical analyses.

Results

Patient characteristics

A total of 8,745 women with cervical cancer were diagnosed and treated at Chiang Mai University Hospital between January 1995 and December 2011. We included a sample of 2,108 (23.1%) of these patients in this study. Of these, there were 1,632 (77.4%) patients with SCC, 346 (16.4%) with ADC and 130 (6.2%) with SNEC. Median age at diagnosis was 51 years [interquartile range (IQR) 26-87] for patients with SCC, 48 years (IQR 29-76) for patients with ADC, and 43 years (IQR 28-72) for those with SNEC ($p<0.001$). Median tumor size was 1.3 cm (IQR 0.1-5.5) for SCC, 2 cm (IQR 0.2-5) for ADC and 2 cm (IQR 0.2-5) for SNEC. Patients with SNEC were more often diagnosed with early stage cancer compared with patients with SCC and ADC (63.1% of patients with SNEC vs. 26.5% of patients with SCC and 28.9% of those with ADC). Nonetheless, tumor size ≥4 cm, lymph node metastasis, parametrial involvement, deeper stromal invasion and lymphovascular space invasion were more frequent among surgically-treated patients with SNEC, compared with patients with ADC and SCC (Table 1).

Cancer-specific survival

The overall five-year cancer-specific survival was 60.0% for patients with SCC, 54.7% for ADC, and 48.4% for patients with SNEC (Table 1). Five-year cancer-specific survival among patients with early stage was 88.1% for SCC, 90.3% for ADC, and 64.0% for SNEC. Five-year cancer-specific survival in advanced stage patients was 49.7%, 39.1%, and 18.0% for patients with SCC, ADC and SNEC, respectively.

More than 90% of the patients died of cancer-related causes regardless of histological type (Table 2). For patients with SCC and ADC, most deaths occurred in patients with advanced stage (92.8% and 96.4%, respectively) whereas for SNEC 47.5% of cancer-related deaths occurred in patients with early stage cancer. Regardless of stage, median cancer-specific survival was substantially lower for patients with SNEC and ADC compared with SCC. However, none of the patients with early stage reached median cancer-specific survival (Table 2).

Figure 1 shows cancer-specific survival curves according to histological type and stage. After adjusting for age at diagnosis, FIGO stage, and treatment, patients with ADC had 1.3 times (95%CI, 1.1-1.5) higher risk of cancer-related death while those with SNEC had 2.6 times (95%CI, 1.9-3.5) higher risk compared with patients with SCC (Table 3). Analyses stratified according to stage showed that mortality of patients with ADC was not significantly different from that of patients with SCC among patients with early stage (adjusted HR 0.8; 95%CI, 0.3-1.9) while ADC was associated with increased mortality among patients with advanced stage

Table 1. Clinical and Pathological Characteristics and Five-Year Cancer-Specific Survival of Patients with Cervical Squamous Cell Carcinoma, Adenocarcinoma and Small Cell Neuroendocrine Carcinoma

Characteristic			Squamous cell carcinoma (n=1,632)		Adenocarcinoma (n=346)		Small cell neuroendocrine (n=130)	
			No. (%)	5-year cancer specific survival (95% CI)	No. (%)	5-year cancer specific survival (95% CI)	No.(%)	5-year cancer specific survival (95% CI)
Overall			1,632	60.0 (57.5-62.4)	346	54.7 (48.9-60.0)	130	48.4 (38.3-57.7)
Age at diagnosis (years)	<45		461 (28.3)	71.6 (67.1-75.5)	118 (34.1)	65.3 (55.5-73.5)	73 (56.2)	50.6 (37.3-62.4)
	45-60		758 (46.4)	60.1 (56.3-63.6)	178 (51.4)	52.5(44.4-59.9)	46 (35.4)	56.4 (37.7-71.5)
	>60		413 (25.3)	46.6 (41.5-51.6)	50 (14.5)	37.7 (24.0-51.3)	11 (8.4)	0
FIGO stage								
Early stage	I		349 (21.4)	89.8 (85.9-92.7)	92 (26.6)	91.8 (83.5-96.0)	71 (54.6)	65.1 (51.7-75.6)
	IIA		84 (5.1)	81.0 (70.5-88.2)	8 (2.3)	75.0 (31.5-93.1)	11 (8.5)	45.0 (6.1-79.6)
Advanced stage	IIB		448 (27.5)	66.9 (62.2-71.2)	100 (28.9)	64.3 (53.5-73.3)	26 (20.0)	25.4 (9.7-44.8)
	III		558 (34.2)	46.2 (41.9-50.5)	95 (27.5)	21.6 (13.3-31.3)	16 (12.3)	0
	IV		193 (11.8)	16.8 (11.5-23.0)	51 (14.7)	17.8 (7.8-31.1)	6 (4.6)	0
Treatment	Surgery alone		198 (12.1)	96.6 (92.8-98.5)	61 (17.6)	96.2 (85.7-99.0)	6 (4.6)	55.6 (7.3-87.6)
	Surgery+RT		43 (2.6)	81.5 (65.7-91.1)	7 (2.0)	100	7 (5.4)	75.0 (27.3-97.5)
	Surgery+CT		16 (0.9)	87.5 (58.6-96.7)	4 (1.2)	100	38 (29.2)	73.6 (56.3-85.9)
	Surgery+CCRT		68 (4.2)	80.4 (67.8-88.9)	14 (4.1)	76.6 (43.3-91.9)	21 (16.2)	30.2 (9.8-53.9)
	RT		788 (48.3)	47.2 (48.1-55.2)	128 (36.9)	40.9 (36.7-54.7)	26 (20.0)	34.0 (12.9-56.6)
	CT		50 (3.1)	12.7 (7.6-29.0)	16 (4.7)	12.5 (2.1-32.8)	2 (1.5)	0
	CCRT		469 (28.7)	52.5 (51.5-60.9)	116 (33.5)	35.9 (30.2-49.6)	30 (23.1)	24.7 (9.6-43.6)
Tumor size (cm)			(n=325*)		(n=85*)		(n=70*)	
		<4	298 (91.7)	90.9 (87.2-94.0)	74 (87.1)	95.4 (86.8-98.6)	55 (78.6)	65.8 (52.9-79.1)
		≥4	27 (8.3)	91.2 (68.7-97.8)	11 (12.9)	88.9 (43.3-98.4)	15 (21.4)	45.0 (14.8-71.7)
Lymph node involvement		VE-	266 (81.9)	93.8 (89.9-96.2)	75 (88.2)	96.8 (88.8-99.2)	56 (80.0)	73.5 (58.7-83.8)
		VE+	59 (18.1)	79.3 (65.5-88.0)	10 (11.8)	78.8 (38.1-94.3)	14 (20.0)	20.4 (32.8-47.8)
Parametrial involvement		VE-	277 (85.2)	93.1 (89.4-95.8)	81 (95.3)	95.7 (87.6-98.6)	58 (82.9)	66.7 (51.6-77.9)
		VE+	48 (14.8)	78.1 (61.7-88.2)	4 (4.7)	66.7 (5.4-94.5)	12 (17.1)	47.6 (15.3-74.6)
Depth of stromal invasion								
	Inner to middle 1/3		210 (64.6)	97.4 (93.8-98.9)	57 (67.1)	97.9 (86.4-99.7)	37 (52.9)	77.9 (58.4-89.1)
	Outer 1/3		115 (35.4)	79.1 (69.9-86.1)	28 (32.9)	87.3 (65.5-95.7)	33 (47.1)	44.3 (29.2-65.0)
Lymphovacular space invasion		VE-	178 (54.8)	96.2 (91.9-98.3)	51 (60.0)	100	22 (31.4)	69.3 (43.6-85.0)
		VE+	147 (45.2)	84.5 (77.4-89.9)	34 (40.0)	86.9 (68.3-94.8)	48 (68.6)	58.6 (44.9-74.8)

*Data on pathological-risk factors were only obtained from surgically-treated patients; Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; RT, radiation therapy; CCRT, concurrent chemoradiation therapy; CT, chemotherapy

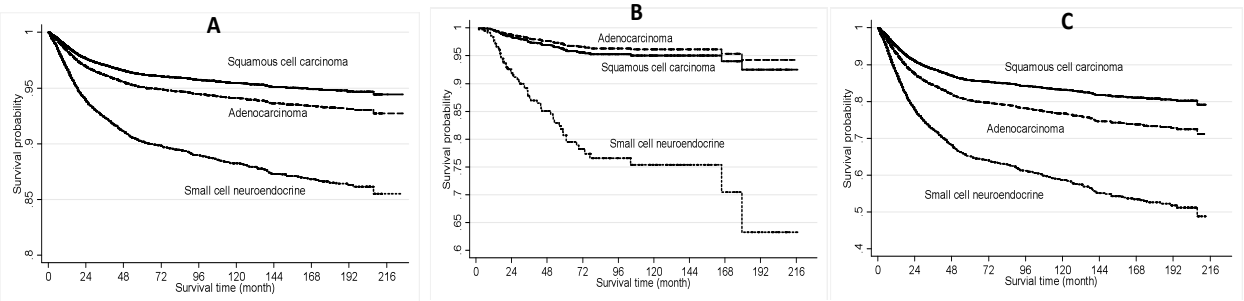

Figure 1. Adjusted Cancer-Specific Survival by Histological Type. A) Overall; **B)** Early Stage; and **C)** Advanced Stage

Table 2. Causes of Death and Median Cancer-Specific Survival in Patients with Cervical Cancer by Histological Type

Causes of death/ Median cancer-specific survival	Squamous cell carcinoma n (%)	Adeno carcinoma n (%)	Small cell Neuroendocrine n (%)	p value
Overall death	778 (100)	167 (100)	63 (100)	
Death from other causes	56 (7.2)	6 (3.6)	4 (6.4)	0.235*
Cancer-related death	722 (92.8)	161 (96.4)	59 (93.7)	
Early stage	62 (8.6)	11 (6.9)	28 (47.5)	<0.001*
Advanced stage	660 (91.4)	150 (93.1)	31 (52.5)	
Median cancer-specific survival (month)				
Overall	151.8	88.4	52.8	0.109†
Early stage	NR	NR	NR	<0.001†
Advanced stage	54.7	39.4	19.8	<0.001†

*Fisher exact test; †Wald test (global test); NR, median survival not reached

Table 3. Cancer-related Death in Patients with Cervical Cancer by Histological type and Stage at Diagnosis

Cancer-related death	Squamouse cell carcinoma		Adenocarcinoma		Small cell neuroendocrine	
	HR (95% CI)	p value†	HR (95% CI)	p value††	HR (95% CI)	p value†††
Overall						
Crude HR	-[a]	0.109	1.1 (0.9-1.4)	0.127	1.2 (0.9-1.6)	0.104
Adjusted HR*	-[a]	<0.001	1.3 (1.1-1.5)	0.002	2.6 (1.9-3.5)	<0.001
Early stage						
Crude HR	-[a]	<0.001	0.8 (0.4-1.4)	0.397	3.3 (2.1-5.2)	<0.001
Adjusted HR**	-[a]	<0.001	0.8 (0.3-1.9)	0.576	4.9 (2.7-9.1)	<0.001
Advanced stage						
Crude HR	-[a]	<0.001	1.3 (1.1-1.5)	0.005	1.8 (1.3-2.6)	0.001
Adjusted HR*	-[a]	<0.001	1.4 (1.2-1.7)	0.001	2.5 (1.7-3.5)	<0.001

*Adjusted for age, FIGO stage, and treatment; **Adjusted for age, FIGO stage, tumor size, lymph node involvement, depth of stromal invasion, and treatment; †Wald test (global test); ††Adenocarcinoma versus squamous cell carcinoma, p values from Wald test; †††Small cell neuroendocrine carcinoma versus squamous cell carcinoma, p values from Wald test.; NR, median survival not reached; [a]Reference

(adjusted HR 1.4; 95%CI, 1.2-1.7). Patients with early stage SNEC had 4.9 times (95%CI, 2.7-9.1) higher risk of cancer-related death, after adjusting for age at diagnosis, FIGO stage, tumor size, lymph node metastasis, depth of stromal invasion, and treatment, whereas those with advanced stage had 2.5 times (95%CI, 1.7-3.5) higher risk of cancer-related death compared with patients with SCC at comparable stages.

Discussion

This study revealed that histological type was an important prognostic factor in patients with cervical cancer. Regardless of stage, SNEC was associated with poorer survival compared with ADC and SCC while patients with ADC had a poorer survival than SCC, particularly among patients with advanced stage.

Few studies have examined the prognostic impact of cervical cancer histology among patients with SNEC, ADC and SCC and their findings remain inconclusive. In line with our findings, a population-based cohort study based on data from SEER during 1973-2002 revealed that patients with SNEC had the poorest survival followed by patients with ADC and SCC. Compared with non microinvasive SCC over 29 years of follow-up, the risk of cancer-related death was 1.9 times (95%CI, 1.6-2.4) higher among patients with SNEC, 1.5 times (95%CI, 1.2-1.9) higher among patients with mucinous ADC and 1.1 times (95%CI, 0.9-1.2) higher among patients with ADC excluding mucinous (Vinh-Hung et al., 2007). Another study based on SEER data found that patients with SNEC had significantly poorer survival than those with ADC and SCC after adjusting for stage (HR, 0.48; 95%CI, 0.37-0.61 for ADC and HR, 0.55; 95%CI, 0.43-0.69 for SCC). The marked difference in survival was particularly observed in early stage and node-negative patients (Chen et al., 2008). In our study, overall 5-year cancer-specific survival of SNEC patients did not reach 50%, though patients with SNEC were younger than those with SCC and ADC. Moreover, we found a higher proportion of pathological-risk factors including lymph node metastasis, parametrial involvement, tumor size ≥4 cm, deeper stromal invasion and lymphovascular space invasion in patients with SNEC compared with SCC and ADC.

Our findings further revealed a significantly higher risk of cancer-related death among patients with ADC overall and among patients with advanced stage compared with SCC, while no difference was found among patients with early stage cancer. On comparison with these findings, a recent US study of 24,562 patients from the SEER database reported that patients with ADC had higher risk of cancer-related death in both early (adjusted HR 1.4; 95%CI, 1.2-1.6) and advanced stage (adjusted HR 1.2; 95%CI, 1.1-1.3) compared with patients with SCC (Galic et al., 2012). In another study, patients with ADC had a poorer survival than those of SCC within the group of surgically-treated early-stage patients with either high pathological risk (i.e., involvement of parametrium, surgical margin, or pelvic lymph node) or intermediate risk (i.e., deep stromal invasion, lymphovascular space invasion, or tumor size >4 cm). This survival difference was observed regardless of the type of post-operative adjuvant therapy, with 5-year cancer-specific survival of 49.5% vs. 80.4%, respectively (p<0.001) in the high-risk group and 80.6% vs. 89.4%, respectively (p=0.030)

in the intermediate-risk group, while no significant difference was found in the low-risk group [95.9% vs. 99.1%, respectively (P=0.100)] (Mabuchi et al., 2012). In agreement with these finding, other studies have reported poorer survival only among early-stage patients with ADC who have lymph node metastasis compared with those with SCC (Nakanishi et al., 2000; Takeda et al., 2002; Rudtanasudjatum et al., 2011) while another study demonstrated a poorer survival of early-stage patients with ADC even though the clinical and pathological factors between the two groups were comparable (Park et al., 2010). In line with our findings, Fregnani et al. (2008) found no significant difference in survival between early-stage patients with ADC and SCC with 5-year disease-free survival of 87.9% and 85.7% (p=0.488), respectively. In this study, the authors also found lower histological grade, lower rate of lymphovascular space invasion, deeper stromal invasion and lymph node metastasis in patients with ADC compared with those with SCC (Fregnani et al., 2008). These findings could suggest the influence of other high-risk pathological factors rather than histology at early stage of disease.

One of the reasons for differences in survival according to histological type may be explained by their origin. As SCC arises from squamous epithelium at the squamocolumnar junction at the boundary between the squamous-lined exocervix and the columnar-lined endocervix, the abnormal cells of SCC or its precancerous lesions are likely to be more effectively detected by Pap smears in screening programs (Mathew and George, 2009). Since ADC arises from the endocervical mucus-producing columnar epithelial cells within the endocervix, which is anatomically less visible, ADC may be occult and not become clinically evident until at a more advanced stage (Schorge et al., 2008). In our study, the proportion of patients with advanced stage ADC was 2.5 times higher than early stage ADC, similar to the proportion of patients with advanced and early stage SCC. However, patients with advanced stage ADC had significantly higher risk of cancer-related death than those with SCC in multivariable analysis. Our finding may indicate a strong impact of ADC compared with SCC in advanced stage of disease. Unlike SCC and ADC, SNEC has a distinct natural history and its precancerous lesion is unknown (Wright et al., 2002). The detection of cells from SNEC is difficult since the diagnostic accuracy may be as low as 22.2% (Park et al., 2011). As a result, patients with SNEC are reportedly more likely to be diagnosed with an advanced stage than those with SCC and ADC (Chen et al., 2008). In contrast, our study revealed that patients with SNEC were more likely diagnosed at early stages compared with patients with SCC and ADC. Nonetheless, we found a higher proportion of cancer-related death among patients with early-stage SNEC compared with SCC and ADC.

The strength of our study includes the uniform treatment guidelines and pathological reviews from a single institute that minimize the diversion of treatment techniques and misclassification of histological diagnoses. Study limitations include the retrospective design. Moreover, we only had data on pathological risk factors from those patients who received primary surgery. Therefore, some pathological risk factor data was missing in patients with early stage who were not treated by surgery (about 22%). Consequently, the estimates for patients with early-stage model are less precise due to the small number of patients.

In conclusion, we found that the survival of patients with cervical cancer varied according to histological type, even after adjusting for other clinical and pathological differences. Patients with SNEC were younger with more diagnoses at early stage than those with ADC and SCC. Yet, SNEC was associated with the poorest survival. Among patients with advanced stage, ADC was associated with poorer survival compared with SCC, while no significant difference was found among patients with early-stage disease. Our finding may be useful for further tailored treatment-strategies and follow-up planning among patients in each histological type.

Acknowledgements

This paper was supported by the National Research University Project under Thailand's Office of the Higher Education Commission and The Graduate School, Chiang Mai University, Thailand. The authors declare that there is no conflict of interest.

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