CHAPTER IV

RESULTS

Patients' characteristics and treatment

Of all 423 patients with stage IIB-IVA, 141 had ACA and 282 patients had SCC were included in this study. Mean age of patients was 50.25 + 10.65 years. More than half of patients were in stage IIB. Clinical staging was equal percent of patients in each stage, while other factors including age, tumor size, HIV infection, and treatment modalities were comparable between both cell types (Table 1). Median total treatment time (TTT) for ACA and SCC were 52.0 days (range, 43-100 days) and 50.0 days (range, 42-102 days), respectively. Due to the long time for enrolled patients, variations of treatment modalities across the 13-year period were found. Thirty-eight patients (19 for ACA and 19 for SCC) were planned ahead to receive radical hysterectomy and pelvic/paraaortic lymph node dissection as adjuvant treatment after completion RT (35/268 patients) and CCRT (3/155 patients). Those patients did not receive any treatments later neither pathological results showed no disease nor residual disease.

Outcome of treatment

After completion of treatment, there were 367/ 385 (95.3%) of patients had clinical CR. Only small number of patients (18 patients, 4.7%) had persistent disease. Of those who had persistent disease, three patients (16.7%) and 15 patients (83.3%) were in stage IIB and IIIB, respectively. Of 38 patients who received adjuvant surgery, 22 (57.9%) had complete pathological response, 12 (31.6%) had residual disease in cervix and four (10.5%) had residual disease in para-aortic nodes. Notably, pathological reports revealed that ACA significantly had more residual disease after treatment than SCC ($p=0.049$), and also had statistically significant lower overall CR rate than SCC ($p = 0.004$) (Table 2).

Table 1 Baseline characteristics and prognostic variables of patients

Baseline characteristics	Number (%)	
	SCC (N=282)	ACA (N=141)
Age (mean ± SD)	50.83±10.78	49.10±10.30
Anti HIV positive	3 (1.1%)	4 (2.8%)
Stage		
IIB	170 (60.3%)	85 (60.3%)
IIIB	110 (39.0%)	55 (39.0%)
IVA	2 (0.7%)	1 (0.7%)
Size		
≤ 4 cm	152 (53.9%)	73 (51.8%)
> 4 cm	130 (46.1%)	68 (48.2%)
Treatment modalities		
Radiation therapy alone	180 (63.8%)	88 (62.4%)
Concurrent chemoradiation	102 (36.2%)	53 (37.6%)
- cisplatin	20 (7.1%)	13 (9.2%)
- carboplatin alone	65 (23.1%)	29 (20.6%)
- carboplatin+5-FU	17 (6.0%)	11 (7.8%)

Abbreviation: SCC, squamous cell carcinoma; ACA, adenocarcinoma

Table 2 Treatment outcomes

Treatment Outcomes	Number (%)		Relative risk	95%CI	p-value
	SCC (N=282)	ACA (N=141)			
- Time to complete response (385) (median ,range)	1 (0-4)	2 (0-5)	-	-	0.001
- Clinical response (385)					0.233
- Persistent of disease	10 (3.8%)	8 (6.6%)	1.72	0.70 , 4.26	
- Complete response	253 (96.2%)	114 (93.4%)			
- Pathological response (38)					0.049
- Partial pathological response	5 (26.3%)	11 (57.9%)	2.20	0.95 , 5.12	
- disease at cervix	4 (21.0%)	8 (42.1%)			
- disease at para-aortic node	1 (5.3%)	3 (15.8%)			
- Complete pathological response	14 (73.7%)	8 (42.1%)			
- Overall response (423)					0.004
- Partial response	15 (5.3%)	19 (13.5%)	2.53	1.33 , 4.83	
- Complete response	267 (94.7%)	122 (86.5%)			
-Overall recurrence					
- Local recurrence	11 (3.9%)	3 (2.1%)	0.55	0.16 , 1.94	0.346
- Distant recurrence	44 (15.6%)	21 (14.9%)	0.95	0.59 , 1.54	0.848
- Both	5 (1.8%)	5 (3.5%)	1.94	0.57 , 6.57	0.279

Abbreviation: SCC, squamous cell carcinoma; ACA, adenocarcinoma

From a median follow-up of 10.2 years (range, 2.1-16.0 years), disease recurrences were found in 89/367 of patients who once had clinical CR after RT/CCRT. These recurrence occurred as pelvic recurrence in 14 (3.8%), distant recurrence in 65 (17.7%), and both pelvic and distant recurrence in 10 (2.7%). Among 22 patients who had undergone adjuvant surgery and had pathological CR, only one patient (4.5%) later developed pulmonary metastasis. Two patients (16.7%) and three patients (25.0%) out of 12 patients who had residual tumor at cervix later developed pelvic recurrence and distant recurrence, respectively. Seven patients (58.3%) were still alive without document of disease recurrence during follow-up time at 13.3 years. On the other hand, distant recurrences appeared in three (75%) of the four patients who had had residual disease in para-aortic nodes. Only one of them (25.0%) was still alive without disease during the 10.6 year of follow-up.

The most common sites of distant recurrence for all patients were paraaortic node (8.5%). Other sites of distant recurrence were lung (7.3%), supraclavicular lymph node (5.0%), liver (3.8%), bone (3.3%), inguinal node (0.5%) and axillary node (0.5%). Distant failure sites were similar for ACA and SCC. When we explored between ACA and SCC, no significant difference for pattern of failures can be found (Table 2). At the censored time; 197 patients (46.6%) were dead, 207 patients (48.9%) were still alive without any evidence of disease, three (0.7%) were alive with cervical cancer and 16 patients (3.8%) were lost to follow-up, but they showed no evidence of disease at their last visit. Of those who were dead; 105 (24.8%) were dead of cervical cancer, 13 (3.1%) were dead from second primary cancers, 9 (2.1%) were dead from unrelated causes, while 70 deaths (16.5 %) were unknown causes. The 5-year PFS rates of ACA compared to SCC were 58.5% and 59.7%, respectively (p=0.270). The corresponding 5-year OS rates were 59.9% and 61.7% (p=0.191).

Since there were only three patients with stage IVA, 1 of ACA and 2 of SCC, we included those in stage IIIB for survival analysis. In univariable analysis, there were no survival differences between ACA and SCC in each matching factor including stage, tumor size and types of treatment (Table 3). Although ACA had a trend of higher hazard ratios (HRs) than SCC, but there was no sufficient evidence to conclude these differences. Furthermore, we used Cox proportional hazards model to adjust all prognostic factors and included tumor histology in this analysis. Tumor stage was the only independent prognostic factor that affected on survival outcomes (Table 4). On the contrary, ACA which was interested in this study did not reach significant difference in survival outcomes when compared to SCC.

Table 3 Survival time: Univariable analysis

	5-year overall survival		Median overall survival		Hazard ratio	95% confidence interval	p-value
	SCC	ACA	SCC	ACA			
Stage							
IIB	70.8	71.9	NR	NR	1.13	0.74 , 1.72	0.568
IIIB /IVA	47.4	41.1	47.7	36.9	1.35	0.91 , 2.01	0.139
Size							
≤ 4 cm	68.5	64.6	155.5	90.9	1.13	0.75 , 1.68	0.562
> 4 cm	58.1	54.8	160.2	83.6	1.31	0.86 , 1.99	0.204
Treatment modalities							
Radiation therapy alone	60.8	61.2	155.5	85.9	1.26	0.89 , 1.79	0.194
Concurrent chemoradiation	63.2	56.4	NR	103.8	1.12	0.67 , 1.87	0.677

Abbreviation: SCC, squamous cell carcinoma; ACA, adenocarcinoma; NR, not reach

Table 4 Multivariable analysis for all factors

	Hazard ratio (adjusted)	95% confidence interval	p-value
Tumor histology			0.127
Squamous cell carcinoma	1		
Adenocarcinoma	1.25	0.94 , 1.67	
Stage			<0.001
IIB	1		
IIIB/IVA	2.33	1.74 , 3.11	
Size			0.797
≤ 4 cm	1		
> 4 cm	1.04	0.77 , 1.41	
Kinds of treatment			0.389
Radiation therapy alone	1		
Concurrent chemoradiation	0.87	0.73 , 1.20	