# CHAPTER V

## DISCUSSSION

The interest about ACA of cervical cancer has now been increasing. During the last two decades, the incidence of ACA was up to 20%. [6, 17-20] However, most of data of ACA were originated from United States or western countries which screening program is successful. There was no report the changing of this incidence from developing countries which screening programs were still unavailable for any women. Although ACA is seemed to be influenced to cervical cancer patients from a rising of number, but the prognostic and proper treatments for these patients are still considerably conflict issue. In 2010, Gein et al. reviewed the articles concerning ACA of cervical cancer and planned to concentrate in locally advanced stages.[6] However, most of reviewed studies had the greater number of patients in early stage (I-IIA). Thus, the goal for learning about locally advance stages has not achieved.

This study is the modern study in this decade which compared ACA to SCC in our own study and focused in locally advanced stages. However, one of the limitations of our study was pathological review which could not be done for all patients. We observed the radiosensitivity between both cell types in early outcomes by using surrogates as clinical response to RT/CCRT and time to clinical CR. For clinical response, ACA had more persistent of disease than SCC with nearly two-fold (6.6% vs 3.8%). As a result of these figures were too small, there were no meaningful for statistical tests. When additional surgery were taken place, ACA showed more residual tumor than SCC with marginally significant ($p=0.049$). Moreover, three out of four patients (75.0%) who had evidence of disease at para-aortic lymph nodes had pathology as ACA. The high incidence of disease at lymph node of ACA were consistent with studies in early stage which treated by primary surgery.[8,21] Nevertheless, the persistent response from clinical evaluation or partial response from pathological findings had no influence on 5-year OS which may be small number of these patients. In addition, one reason was possibly part of effect for these equal survivals due to adjuvant surgery after completion of RT was done in approximately 13.5% of ACA patients. If this procedure did not obtain, the difference of survival outcomes may be occurred. Time to clinical CR was also used to surrogate for radiosensitivity of two cell types. ACA used longer time to achieve CR by clinical than SCC when all prognostic factors were comparable. Although the early outcomes were not important for survival outcomes, these might be reflecting the tumor sensitivity to RT.[22] Huang et al. reported the poor response of ACA to RT and affected on patient's survival.[23] However, 24% of their ACA patients did not receive ICBT, because tumor was still bigger than 4 cm at the timing of ICBT. Additionally, there

were several investigations concerning the biologic markers of ACA and SCC such as MIB-1 and PC10 labeling indices[24], cyclooxygenase-2[25]and vascular endothelial growth factor (VEGF) of cancer cell.[26]All those studies confirmed a worse radiosensitivity of ACA in cervical cancer. However, our previous study about serum VEGF in locally advanced stages of cervical cancer did not show the different serum level between ACA and SCC.[27]

The patterns of treatment failure in our study were similar between both cell types. Distant recurrence was the most common site of treatment failure and had more frequency than pelvic recurrences around four times (Table 2). Few previous studies compared ACA and SCC in their own studies.[7, 9-11] Moreover there was small number of ACA patients particularly in advanced stages and did not report the patterns of treatment failure. Even though ACA was seemed to be more radioresistant than SCC, the much more significant factor than tumor histology was still being the advanced stages which had greater chance to have hematogenous spread. Some evidences about the patterns of treatment failure of ACA emerged from study of Eifel et al..[15] They found that the most common area of treatment failure was distant recurrence and had higher rate than SCC in stage IB.

In univariable analysis, there was no difference in all survival outcomes when compared ACA to SCC in the same stage (IIB vs IIIB/IVA), the same tumor size (≤ 4cm vs >4 cm), and the same treatment modalities (RT vs CCRT). Although all HRs of ACA were more than one for all matching factors, there was no enough evidence to confirm by statistical testing. The current results were consistent and inconsistent from previous literatures. We reviewed all these studies which explored both ACA and SCC in their own studies in table 5. Five-year OS in the present study was better than old studies which enrolled patients during the period of 1963-1985 [7, 9, 11], but were rather similar with the recent study from Taiwan.[10] The difference of study period, about 30 years, may be produced several variation such as criteria of enrolled patients or treatment modalities. However, the same finding from most studies illustrated that advanced stages affected on decreasing difference in 5-year OS between ACA and SCC.[7, 10, 11] Only one study found that ACA had a worse survival than SCC in all stages, but their patients in stage III had too low survival rate when compared to other studies.[9] In multivariable analysis, we included tumor histology to analyze with all known prognostic factors together. Only one factor which had strongest association with survival outcomes was clinical stage. Although ACA showed HR of 1.25, but there was still insufficient evidence of its influence on survival outcomes in locally advanced stages. Other factors including tumor size and treatment modalities were also meaningless for survival. CCRT had some area of benefit with 0.87 of HR (95% CI = 073-1.20), there was no difference with statistically significant.

At present we know that standard treatment for locally advanced cervical cancer is CCRT as well as cisplatin is the most favorable drug which used at concurrent time. In fact, this knowledge is generated from SCC patients. As a consequence, using the same treatment as SCC may be not appropriate for ACA patients. Some authors mentioned that taxane had good efficacy in advanced or recurrence of ACA.[28, 29] Huang et al. tried to study the role of paclitaxel in concurrent setting compared to cisplatin and RT alone in ACA patients.[23] Unfortunately, there was small number of patients in paclitaxel arm (13 patients). Therefore their results cannot provide the valuable answer. As a result, no evidence supports that whether or not taxane will be more appropriate with ACA than cisplatin when used as concurrence with RT. This cell type still needs to learn more for finding the suitable treatments in each stage. In addition to clinical stage and tumor histology, largely unknown factors of cervical cancer should be explored to search the valid predictor for tailor treatment to each patient.

**Table 5:** Studies which compared between adenocarcinoma and squamous cell carcinoma in cervical cancer

| Author [ref] | Year of enrolled patients | Stage | Number SCC : ACA | 5-year overall survival (%) SCC | ACA | p-value |
|---|---|---|---|---|---|---|
| Kilgore [7] | 1963-1985 | I | 128 : 130 | 83.9% | 73.8% | NS |
| | | II | 25 : 23 | 68.0% | 43.0% | NS |
| | | III/IV | 8 : 9 | 18.0% | 15.0% | NS |
| Kleine [11] | 1964-1985 | I | 119 : 64 | 88.0% | 76.0% | 0.003 |
| | | II | 101 : 55 | 60.0% | 41.0% | 0.009 |
| | | III | 44 : 22 | 33.0% | 27.0% | 0.1 |
| | | IV | 4 : 3 | - | - | - |
| Hopkins [9] | 1970-1985 | I | 370 : 124 | 90.0% | 60.0% | <0.001 |
| | | II | 186 : 40 | 62.0% | 47.0% | 0.01 |
| | | III | 114 : 25 | 36.0% | 8.0% | 0.002 |
| | | IV | 57 : 13 | NA | NA | NA |
| Chen [10] | 1977-1994 | I | 2,159 : 203 | 81.3% | 75.9% | 0.041 |
| | | II | 758 : 74 | 75.2% | 62.9% | 0.014 |
| | | III | 401 : 22 | 42.7% | 29.2% | 0.903 |
| | | IV | 58 : 3 | 26.1% | 0.0% | 0.541 |
| This study | 1995-2008 | IIB | 170 : 85 | 70.8% | 71.9% | 0.568 |
| | | IIIB/IVA | 112 : 56 | 47.4% | 41.1% | 0.139 |

Abbreviation: SCC, squamous cell carcinoma; ACA, adenocarcinoma; NS, not significant; NA, not available