CHAPTER III

RESEARCH DESIGN AND METHODOLOGY

Primary research question

1. Are there differences of survival rate between adenocarcinoma and squamous cell carcinoma in locally advanced cervical cancer patients?

Secondary research questions

1. Is there any different radiosensitivity of these two histological types?
2. Are there differences in patterns of tumor recurrence and distant metastasis between adenocarcinoma and squamous cell carcinoma in locally advanced cervical cancer patients?

Objectives

Primary objective

1. To compare 5-year overall survival rate between adenocarcinoma and squamous cell carcinoma in locally advanced cervical cancer patients.

Secondary objectives

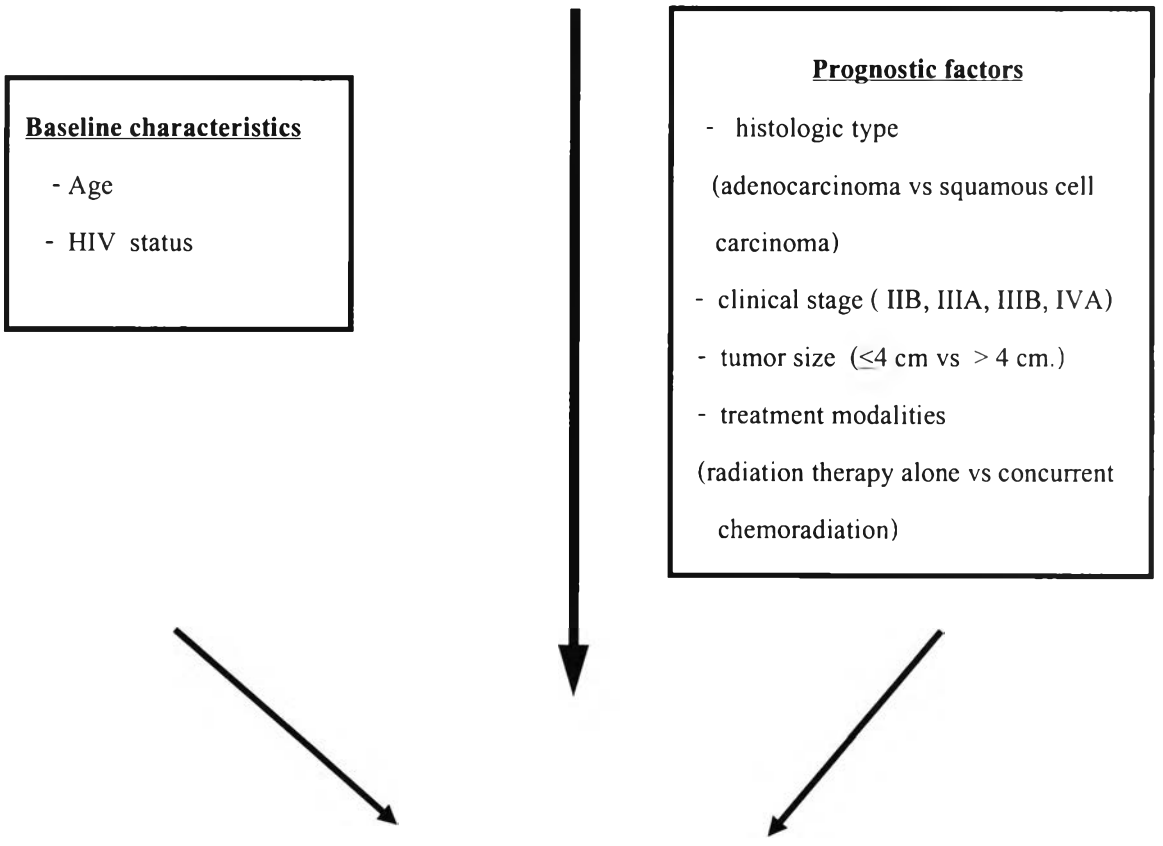
1. To compare response to radiation therapy between adenocarcinoma and squamous cell carcinoma
2. To compare patterns of local recurrence and distant metastasis between adenocarcinoma and squamous cell
   carcinoma in locally advanced cervical cancer patients.

Hypothesis

Adenocarcinoma of locally advanced cervical cancer have a worse survival than squamous cell carcinoma with 10-20% difference in 5-year overall survival rates, and have more distant metastatic rates than squamous cell carcinoma.

Conceptual Framework

All patient's medical record with locally advanced cervical cancer (stage IIB-IVA) and got treatment completely



Domain

Locally advanced cervical cancer patients

Keywords

Adenocarcinoma, Locally advanced cervical cancer, Treatment outcomes

Operational Definitions

Locally advanced stage

: Stage IIB, IIIA, IIIB, IVA based on staging system of the International Federation of Gynecology and Obstetrics (FIGO)[3]. All cervical cancer patients were mainly staged by pelvic examination to obtain clinical staging by radiation oncologist and gynecologic oncologist.

Squamous cell carcinoma

: Composed of generally recognizable polygonal squamous cells that may have individual cell keratinization and intercellular bridges. Cellular and nuclear pleomorphism is more obvious.[16]

Adenocarcinoma

: Marked glandular irregularity with effacement of the normal glandular architecture, the tumor extending beyond the deepest normal crypt. Cribi-form, papillary or solid patterns may be present.[16]

Adenosquamous carcinoma

: Composed of the mixture of malignant glandular and squamous epithelial elements.[16] In this study, we include adenosquamous carcinoma in adenocarcinoma group.

Radiation therapy

: External radiation therapy (XRT) consisted of 5,000-6,000 cGy delivered through standard technique with Cobalt-60 at 180-200 cGy per fraction and five fraction per week, combined with intracavitary therapy (ICRT) consisted of 600-700 cGy per fraction of Irridium-92, 4-5 fraction once a week.

Concurrent chemoradiation

: Radiation therapy combined with platinum-based regimen

Tumor size

: Based on pelvic examination by Radiation Oncologist and Gyneoncologist

Response of disease

: Clinical complete response (CR): there is no residual disease that can be identified on pelvic examination

: Persistent of disease: there is still disease that can be identified on pelvic examination at 3 months after completion of radiation therapy

: Time to clinical complete response (CR): calculated from the last date of treatment to the date when tumor cannot be detected by pelvic examination.

: Pathological complete response (CR): patients who did not had any disease from pathological reports when they received radical hysterectomy and pelvic/paraaortic lymph node dissection as adjuvant treatment after completion RT/CCRT.

: Residual disease: patients who still had disease from pathological reports when they received radical hysterectomy and pelvic/paraaortic lymph node dissection as adjuvant treatment after completion RT/CCRT.

: Overall complete response (CR): defined as the combination of numbers of clinical CR rate and pathological CR rate.

: Partial response (PR): was the combination of persistent disease (from RT/CCRT) and residual disease (from RT/CCRT and adjuvant surgery).

Local recurrence

: Presence of signs or symptoms of tumor recurrence at cervix, vagina or pelvic region with confirmed by pathology if possible.

Distant metastases

: Presence of any organs with tumor presence except in area of local recurrence with confirmed by pathology if possible.

Overall survival

: Calculated from the date of start treatment to the date of death from any causes.

Censored

: Used when patients were lost to follow-up, or still alive. This study will be censored at 31 December 2010.

Research Design

Retrospective cohort study.

Research Methodology

Population and sample

Target population is patients with locally advanced cervical cancer at Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University

Study population and sample are patients with locally advanced cervical cancer and got treatment completely at within 31 December 2008.

Sample size calculation

Based on primary objective is 5-year overall survival of patients with locally advanced cervical cancer. The recently study from Netherlands, the 5-year survival rates of ACA of cervical cancer patients with stage II and III were 37% and less than 9%, respectively.[13] For SCC cell type, there were better prognosis than ACA about 20% difference in 5-year overall survival rates.[6]
We used the PASS 2008 software to calculate the sample size for survival analysis and reliability. Steps of calculation are as follow:

1. Choosing survival analysis and reliability and use Log rank Tests of Freedman
2. Selected power = 0.80 or Beta = 0.20 and Alpha = 0.05
3. The sample proportion, we use ratio of SCC: ACA = 2:1 due to limited number of ACA. Therefore, proportion in group 1 or SCC is 0.67 and we estimate proportion lost during follow-up is 0.2.
4. Proportion surviving in group 1 or SCC in stage II from reviewed studies is 0.57 ,and proportion surviving in group 2 or ACA in stage II is 0.37

Log Rank Survival Power Analysis – Simple

Numeric Results with Proportion Lost to Follow Up = 0.2000

Hazard One-Sided

Power	N	N1	N2	S1	S2	Ratio	Alpha	Beta
0.8025	188	63	125	0.3700	0.5700	0.5654	0.0500	0.1975

Event Report when Proportion Lost to Follow Up = 0.2000

Power	E	E1	E2	S1	S2	Ratio	Hazard Alpha	One-Sided Beta
0.8025	75	25	50	0.3700	0.5700	0.5654	0.0500	0.1975

5. For stage III, with the same of others values, proportion surviving in group 1 and group 2 are 0.29 and 0.09, respectively

Log Rank Survival Power Analysis - Simple

Numeric Results with Proportion Lost to Follow Up = 0.2000

Power	N	N1	N2	S1	S2	Ratio	Hazard Alpha	One-Sided Beta
0.8029	87	29	58	0.0900	0.2900	0.5141	0.0500	0.1971

Event Report when Proportion Lost to Follow Up = 0.2000

Power	E	E1	E2	S1	S2	Hazard Ratio	One-Sided Alpha	Beta
0.8029	55	19	36	0.0900	0.2900	0.5141	0.0500	0.1971

From the calculations, sample sizes of stage II SCC and ACA are 125 and 63, respectively. While in stage III, sample size of SCC is 58, and ACA is 29. The total sample sizes of this study are 275 patients with locally advanced stage cervical cancer.

Inclusion criteria: are of all these followings

1. Patients with locally advanced cervical cancer
2. Tumor histology is adenocarcinoma or squamous cell carcinoma
3. Treated with radiation therapy alone or concurrent chemoradiation therapy completely

Exclusion criteria: is at least one of the followings

1. Presence of uncontrolled underlying disease
2. Presence or had history of cancer in other organs except in cervix

Maneuver

All medical records of locally advanced cervical cancer patients which have been finished treatment within December 2008 will be reviewed to find ACA and SCC. We matched ACA 1 case for SCC 2 cases. The first factor which we intended to match was clinical stage (stageIIB/IIIA/IIIB/IVA). The rest factors including tumor size ($\leq$ 4 cm vs > 4 cm), treatment modalities (RT vs CCRT) and treatment year were tried to match after that. When matching method was in processing, patient's treatment outcomes had not known yet for protection selection bias. Baseline characteristics and treatment outcomes were recorded in case record form.

Outcome Measurement

1. Censored will be used when patients were lost to follow-up or still alive at 31 December 2010.
2. The primary outcome measure is 5-year overall survival.
3. The secondary outcome measures are response to radiation therapy and pattern of treatment failure.
4. Base on physical examination, follow-up for all patients was about first 1-3 months after completing of treatment and then every 3-6 months until death.

Data Collection

1. Baseline characteristics of patients and kind of treatments would be reviewed from medical records and will be recorded in case record forms (CRF) and summarized as follows : (Appendix A)

2. Treatment outcomes

: Survival time is calculated from the date of start treatment to the date of death from any causes and counted in month

: Responses to radiation therapy are measured as complete response and persistent of disease.

: Duration of clinical complete response is calculated from the last date of treatment to the date of tumor cannot be detected by pelvic examination and counted in month

: Time and site of disease recurrence when had reported

Data Analysis

1. Descriptive statistics for baseline data

1.1 Continuous data, such as age, will be presented as mean and SD or median as appropriate and compare by unpaired t-test.

1.2 Categorical data, such as stage, tumor sizes, kinds of treatment will be presented as frequency (percentage).

2 Treatment outcomes

: Time to complete response to radiation therapy will be presented with mean and SD or median as appropriate and compare by unpaired t-test.

: Response to radiation therapy, tumor recurrence and distant metastases will be presented with frequency (percentage) and compared by using chi-square test or Fisher's exact test as appropriate. Results will be presented as crude hazard ratio(HR), 95% confidence interval (CI) and p-value.

2.1 Univariable analysis

: Survival times were calculated by using Kaplan-Meier methods and compare between both groups by using log-rank test. Additionally, we will also show the median survival for both groups.

2.2. Multivariable analysis

: Five-year overall survival rate of both groups were compared using Cox proportional hazards regression.

Ethical Considerations

1. This research needs to be performed in human subject. Therefore, the research proposal must be approved by the Ethics Committee before starting the study.
2. There are a lot of personal data, so all data will be kept in a personal computer belongs to the investigator. The entrance to the data will need a specific code. Results of the study will be presented in general, not as individual data.
3. This is retrospective study. Therefore, there is no intervention to take risk or any harm to patients.

Expected Benefit and Application

To know the treatment outcomes of ACA in locally advanced cervical cancer in terms of survival and response to radiation therapy. If there are worse survivals than SCC from their higher distant metastasis rates, the adjuvant chemotherapy after completed radiation therapy should be studied. However, pelvic recurrence may be remained the important problem too. Adjuvant surgery or study about the new regimens of chemotherapy when given concurrent with radiotherapy will need to take place.

Obstacle

There may be problems of loss to follow-up and incomplete data. Therefore, we calculated the sample sized to support this situation for 20%.

Limitations

In this study, there are only locally advanced stage of cervical cancer, so the results cannot apply to use with early stage cervical cancer.