# CHAPTER V

## DISCUSSION, CONCLUSION AND RECOMMENDATION

### 5.1 Discussion

The aim of this study is to clarify whether digital application of estrogen cream or placebo cream can prevent early vaginal occlusion in cervical cancer patients after complete radiotherapy. Radiotherapy or concurrent chemoradiotherapy is one of the most modern treatment modality for advanced cervical cancer. Vaginal brachytherapy is administered in combination with external radiotherapy . Instead of low dose rate brachytherapy (LDR) ,at present, high dose rate brachytherapy (HDR) is commonly used. It administers a higher dose of radiation (iridium 192) over a short period of time (usually less than 10 minutes) on an outpatient basis (*2-4*) as we have used for all patients in this study. Vaginal shortening / occlusion or stenosis is a recognized toxicity of brachytherapy. It occurs as a result of both radiation-induced menopause and direct damage to the vaginal mucosa, connective tissues and small blood vessels leading to denuding of the vaginal epithelium and subsequently leads to thinning of the vaginal mucosa and formation of adhesions and fibrosis lead to loss of elasticity (*7,12-13*). When the adhesion are not broken down , shortening, contractions and , for some women, complete obliteration of the vagina may develop ( *14* ) .

In this study, baseline characteristics of the patients in both groups were not different. Vaginal shortening (vaginal length after intervention less than baseline) occurred about 19 %. The incidence from other reports were varied in wide range from 1.2 % (*15*) to 88 % (*16-18*) because of inconsistent definitions and inconsistency of methods for assessing vaginal changes (*17*). Even though, the incidence of vaginal shortening in estrogen group was 12.5 % which less than 26.9 % in placebo group, but there was no statistically significant difference. Neither the age of the patient nor stage of disease contributed to the degree of vaginal stenosis (*4,16*) as we found in this study. However, Brunner et al. (*6*) observed that women with stage II and III cervical cancer experienced increased vaginal shortening than those with stage I disease.

The time of onset of vaginal stenosis has been differently reported. Hartman and Diddle (*17*) reported 2.8% of 221 patients experiencing total vaginal obliteration 1 month after completing brachytherapy. Flay and Matthews (*7*) found that 73 % of 16 patients had significant stenosis at 6 weeks, while Poma (*5*) reported maximum stenosis occurring at 3 months. In this study, owing to practice guideline in Siriraj Hospital (*2*), we had enrolled the patients at 4 weeks after complete radiation, for daily vaginal cream application with digital pressure-dilator at bed time . While the survey from 35 radiation centres in Australia, it recommended that the use of vaginal dilators be initiated either prior to brachytherapy or within 2 weeks of completion (*19,20*). And the frequency of use of vaginal dilators was varied, which included twice a day (*5*), second daily (*21*), two or three times a week (*12, 22-24*), and daily for 3 months then twice a week for 3 months (*13*).

The duration of use for dilators ranged from 6 weeks to indefinitely or as long as the woman wanted a functional vagina (*19,20*) , while the patients in this study used vaginal cream daily for 4 weeks, due to limitation of study time which we expected to see firstly the short term outcome. Although, Chadha et al. (*24*) recommended the routine use of vaginal dilators only for women who are not sexually active. For both groups , all patients had no sexual practice during this study.

Before intervention (at 4 weeks after completion of radiation), the vaginal lengths ranged from 60-90 mm. and 60-85 mm. in estrogen and placebo group respectively, which no statistically significant difference. As suggested by Bruner et al.(*6*) normal vaginal length was 8-9 cm., there was 50 % from 58 patients in this study ( 50 % in estrogen group and 57.7% in placebo group ) had vaginal length more or equal than 80 mm at baseline. And after daily application of 0.5 gram cream with digital pressure-dilator for 4 week period, the changes of vaginal lengths were not statistically significant difference between estrogen and placebo group, even though mean change in millimeter in estrogen group (Mean $\pm$ SD = 3.0 $\pm$ 5.7) was more than in placebo group (Mean $\pm$ SD = 1.7 $\pm$ 5.3). This might be because of too short period of intervention to show the different effect between estrogen and placebo cream. Or it was only the mechanical effect from digital pressure-dilator without any lubricant.

After radiotherapy, vaginal changes are not only direct from radiation effect, but also because of estrogen deprivation from radiation castration, especially in pre-menopausal patients. It caused thinning of vaginal epithelium, loss of rugae, then it became early shortening and agglutination. The use of vaginal cream for its proposed benefits in promoting re-epithelialisation and increased vascularity of the vaginal mucosa and hence reducing vaginal stenosis (*4,13,16,17,22,25,26*). In this study, we exclude menopausal patients and apply vaginal cream 0.5 gm. of conjugated estrogen in estrogen group and 0.5 gm. of non-estrogen in placebo group (composition as shown in appendix). Mean serum estradiol was about 17.6±9.7 , ranged between 10.0 to 49.0 pg/ml. in estrogen group which quite not different in placebo group and other study in menopause (*25*). Neither patient in placebo nor in estrogen group had serum estradiol higher than 50 pg/ml. which implied that there was no systemic absorption as recommended in Cochrane Review (*9*) and other studies in non-radiated vagina (*25-27*). And there was no linear relationship between change of vaginal length and change of serum estradiol. However, by vaginal cytology as used in some studies (*28,29*), there was an improvement of vaginal epithelium in estrogen group, which showed statistically significant decreasing percentage of parabasal cell more than placebo cream.

With individual instruction, how to apply the vaginal cream with digital pressure, the patients in both groups had quite a good compliance. Even though at first, they felt ashamed and it caused some minimal bleeding after vaginal cream application. But after using cream, and evaluation by vaginal symptoms score, most patients had satisfaction about 90 %, with no difference in both groups. Although, there was only one patient in placebo group had complaint about vaginal itching during the 4 th. week and stopped using cream, but she had no symptom at the follow-up date . No significant evidence showed that estrogen or placebo cream aggravated cervical tumor as reported in some studies (*12,18*). Only one patient in estrogen group had clinical persistent disease, which was followed up and treated according to practice guideline .

**5.2 Conclusion**

This study showed that after completion of radiotherapy for 2 months, the incidence of vaginal shortening was about 19 %, 12.5 % in estrogen group which less than 26.9 % in placebo group, but there was no statistically significant difference ($P$=0.193). When assessment of the change of vaginal lengths, after the application of digital pressure plus vaginal estrogen cream (Mean ± SD = 3.0 ± 5.7 mm.), it did not show any statistically significant difference ($P$=0.403)

compared with placebo cream (Mean $\pm$ SD = 1.7$\pm$ 5.3 mm). However, by estrogen cream with patients' satisfaction, it showed the improvement of the general health of the vagina, by decreasing the percentage of parabasal cell more significantly than placebo cream ($P$<0.001). And with 0.5 gm of conjugated estrogen vaginally, serum estradiols were still in menopausal level, without systemic absorption, and no any side effect. Additionally, patient's instruction was very important to succeed for prevention of early vaginal occlusion after radiotherapy in cervical cancer.

**5.3 Recommendation**

Vaginal dilator is commonly recommended for the cervical cancer patients receiving radiotherapy to maintain their vaginal functions, including sexual function . Lubricants, especially estrogen cream has shown to improve vaginal mucosa locally for avoiding of its systemic effects. Combination of mechanical vaginal dilator together with medical hormonal vaginal application, may be more effective intervention for early prevention of vaginal occlusion. However, the onset of intervention , the frequency , the duration , type and dose of estrogens are the variable factors that may reveal in different results. Further studies to optimize the benefit of mechanical and / or medical intervention in this aspect should be warranted.