CHAPTER IV

RESULTS

4.1 Demographic and baseline data

Sixty four patients who met the eligibility criteria were enrolled in this double-blinded study. Thirty two patients were randomly assigned to the estrogen group (E) and the other thirty two patients to placebo group (P). Six patients in the placebo group were excluded from the analysis because of the following reasons: one patient had hormone therapy due to menopausal symptom (hot flush) , one patient had lost her vaginal cream on the way back home at the first visit date, and the other four patients lost to follow up at week 4 due to their 3-4 week postponed appointment with a radio-oncologist. And these six patients had no significant events .

All patients were treated with concurrent chemoradiotherapy with weekly cisplatin or carboplatin. The total radiation dose ranged from 7500 to 8500 cGy with four fractions of high dose rate.

Patients' demographic and baseline characteristics such as age, parity, cesarean section, body mass index (BMI), tumor staging, tumor size, vaginal length , percentage of parabasal cell > 25, serum estradiol, and sexual practice were presented in Table 2.

Table 2 Patients' demographic and baseline characteristics

	Estrogen (n=32)		Placebo (n=26)		*P Value*
	Mean(SD)	Min-Max	Mean(SD)	Min-Max	
Age (years)	44.1(6.5)	30-54	45.5(5.8)	34-54	0.206
Parity	2.7(1.5)	0-7	2.9(1.3)	0-5	0.516
Cesarean section	15.6 %		7.6 %		0.442
Body Mass Index(BMI)	22.7(3.5)	15.4-29.3	22.3(15.8)	15.8-32.8	0.609
Tumor size $\geq$ 4 cm.	46.9 %		34.6 %		0.346
Tumor stage					
Stage I	6.3 %		7.7 %		0.841
Stage II	50.0 %		42.3 %		
Stage III	43.7 %		50.0 %		
Vaginal length (mm.)	76.9(7.1)	60-90	76.0(7.4)	60-85	0.452
Parabasal cell >25 %	90.6 %		100 %		0.245
Serum estradiol (pg/ml)	17.7 (8.1)	5.9-32.0	20.1 (10.1)	10.0-39.0	0.320
Sexual practice	0		0		

Note: Percentage of parabasal cell from maturation index

4.2 Primary outcome analysis

The primary outcome of this study was the absolute difference in the vaginal length (mm) at baseline and after the use of vaginal cream for 4 weeks. The distribution of change in vaginal length after cream usage in both groups were shown in Figures 2, 3 and4. There was no statistically significant difference (P = 0.403) in mean change of vaginal length post digital application of vaginal cream between estrogen (Mean $\pm$ SD = 3.0 $\pm$ 5.7) and placebo group (Mean $\pm$ SD = 1.7 $\pm$ 5.3). The mean $\pm$ SD of the vaginal length at week 4 in the estrogen and placebo group were 79.9$\pm$6.4 millimeter (ranged from 67 to 94) and 77.6$\pm$6.9 millimeter (ranged from 63 to 90) respectively, Table 3. Eleven out of fifty eight patients (19 %) had vaginal shortening. There was no statistically significant difference (P= 0.193) in incidence of vaginal shortening in estrogen group (4 /32, 12.5 %) and placebo group (7 / 26, 26.9 %) as presented in Table 3. All patients had no sexual practice during the study.

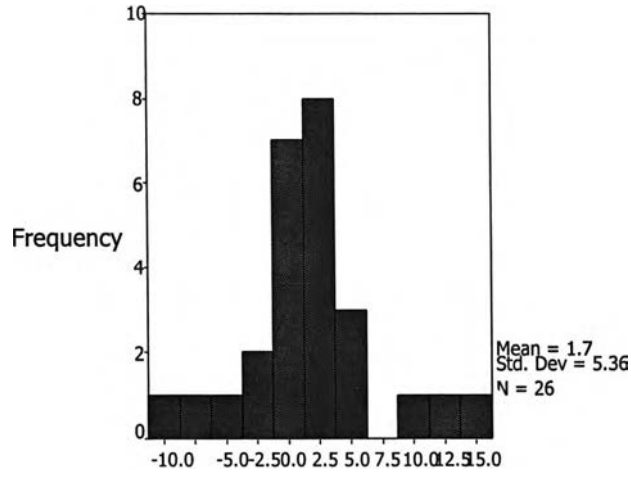

Figure 2 Histograms of change from baseline in vaginal length (mm), after 4 weeks of cream usage , ranged from -10 to 14 in placebo group.

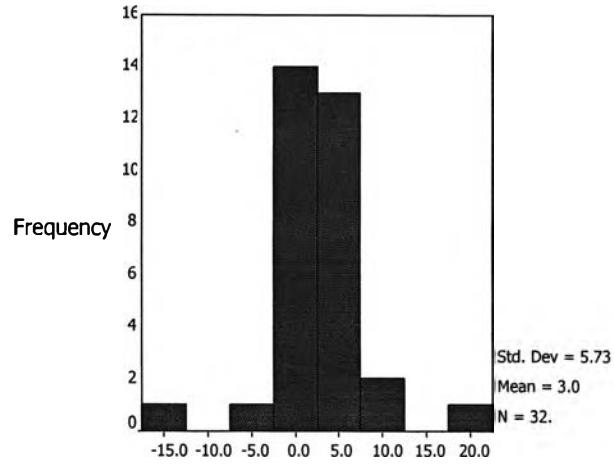

Figure 3 Histograms of change from baseline in vaginal length (mm), after 4 weeks of cream usage , ranged from -15 to 22 in estrogen group .

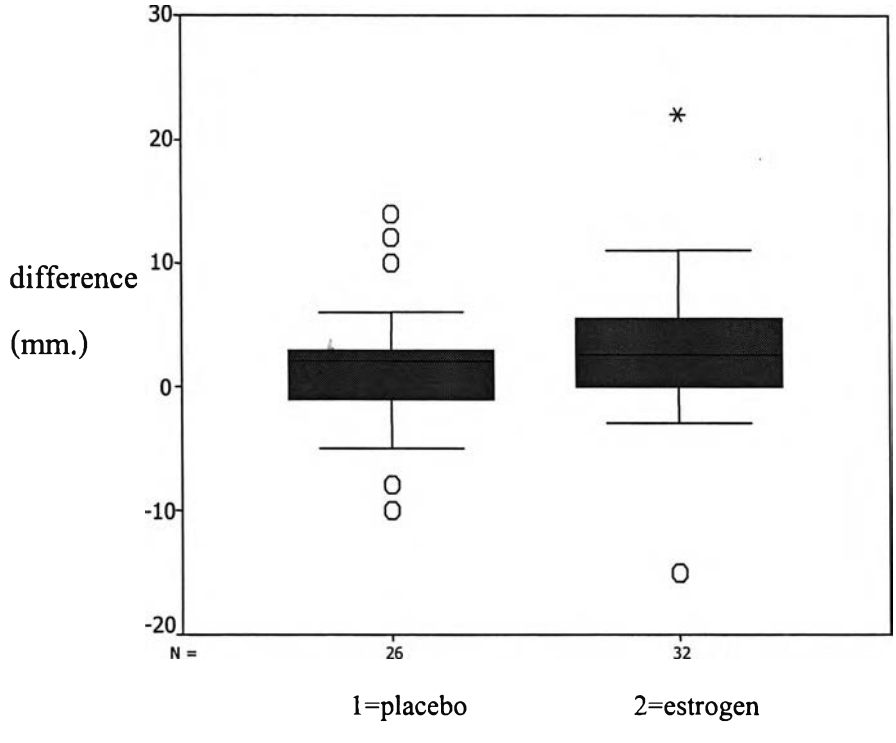

Figure 4 Box plots comparing absolute difference in change from baseline of vaginal length (mm) between estrogen and placebo group.

4.3 Secondary outcome analysis

4.3.1 Maturation index : Exfoliative cytology was applied for maturation index (MI) parabasal cell > 25 % was classified as poor vaginal epithelium . After 4 weeks of using vaginal cream, there was an improvement in vaginal epithelium from baseline with statistically significant difference in proportion of parabasal cell > 25% between estrogen and placebo group (31.3% vs. 96.1% , Table 3).

4.3.2 Serum estradiol : At baseline, there was no statistically significant difference in serum estradiol (pg/ml),($p = 0.322$) between estrogen and placebo group respectively (mean±SD : 17.7±8.1 vs. 20.1±10.1), Table 3. After using cream, serum levels of estradiol were less than 50 pg/ml. in both groups, ranging from 10.0 to 38.0 pg/ml and from 10.0 to 49.0 pg/ml in placebo and estrogen group respectively . And there was no statistically significant difference between the two groups (p =0.800).

Table 3 Comparison of vaginal length, incidence of vaginal shortening, maturation index (in percentage of parabasal cell) and serum estradiol between estrogen and placebo group, at baseline and 4 weeks after treatment.

	Estrogen(n=32)		Placebo(n=26		*P* Value
	Mean(SD)	Min-Max	Mean(SD)	Min-Max	
Vaginal length (mm.): Baseline	76.9(7.1)	60-90	76.0(7.4)	60-85	0.452
Week 4	79.9(6.4)	67-94	77.6(6.9)	63-90	0.500
Week 4- Baseline	0.3 (1.9)	(95% CI -3.7, 4.3)			
Incidence of vaginal shortening	12.5 %		26.9 %		0.193
Parabasal cell > 25%: Baseline	90.6 %		100 %		0.245
Week 4	31.3 %		96.1 %		**<0.001**
Serum estradiol(pg/ml): Baseline	17.7(8.1)	5.9 -32.0	20.1(10.1)	10.0- 39.0	0.322
Week 4	17.6(9.7)	10.0-49.0	17.1(8.1)	10.0- 38.0	0.800
Week 4- Baseline	-3.3(3.2)	(95% CI -9.7, 3.1)			

4.3.3 Patients' compliance : There were four patients with poor drug compliance. 2 out of 32 (6.3 %) and 2 out of 26 (7.7 %) in estrogen and placebo group respectively. One patient in placebo group complained about itching during the 4th week, and stopped using cream afterwards. Forgetting to use the cream at bed time was another reason for poor compliance.

4.3.4 Patients' satisfaction : According to total symptoms score defined in Table 1, 88.5 % and 93.8 % of the patients were satisfied (total score < 6) in placebo and estrogen group respectively, ($P = 0.648$).

4.3.5 Tumor response: All patients were evaluated at 4 week period as clinical response to concurrent chemotherapy , except only one patient in estrogen group who had clinically persistent disease. This patient was followed up by her radio-oncologist.

4.3.6 Correlation between change in vaginal length and change serum estradiol : There was no linear relationship (r = - 0.194) between change from baseline at week 4 in vaginal length (mm.) and in serum estradiol (pg/ml) as shown in Figure 5.

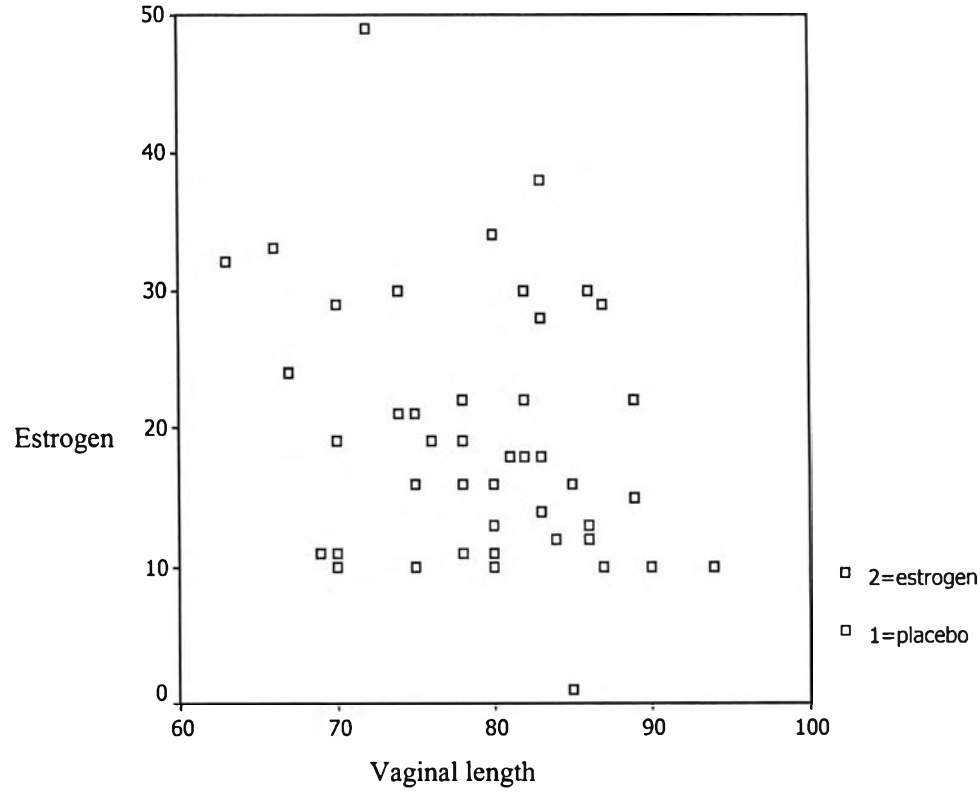

Figure 5 Correlation between change in vaginal length (mm) and in serum estradiol (pg/ml).