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Association between breast cosmesis and two common radiotherapy regimens

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Association between breast cosmesis and two common radiotherapy regimens

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B.S.
Nanjing Agricultural University
2017

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Abstract

Association between breast cosmesis and two common radiotherapy regimens
By Yawen Wang

Background: As the adjuvant therapy to lumpectomy, radiation therapy is critical for patients to lower the local recurrence and mortality rate. However, this radiation therapy may worsen breast cosmesis in the long term. There remains a gap in the evidence as to whether the different types of radiation regimens have different effects on breast cancer thickening. This study focuses on 1) the association between time and skin thickness under two types of radiation therapies; and 2) other factors that may affect this association.

Methods: A total of 143 patients were recruited in the study, where 84 patients received conventional fractional radiation and 59 patients underwent hypo-fractional radiation. Five evaluation time points using ultrasound technique were included in this one-year longitudinal study. Descriptive analysis was performed on patients' characteristics and skin thickness ratio. Linear mixed models were fitted to 1) find the relationship between time and skin thickness for each type of radiation therapy and 2) determine significant factors affect this association.

Results: Axillary lymph node dissection (ALND) was the only clinical factor that was significantly ($p = 0.009$) different in two treatment groups. Skin thickness ratio increased during the first four evaluation and a drop at the last evaluation in both treatment groups. Smoking status, T stage, N stage, stages, chemotherapy status, ALND and age were significant covariates relating to the skin thickness ratio in the univariate analysis. After the multivariable analysis, the skin thickness ratio was not significantly associated to time ($p = 0.1639$) and no difference in the pattern between two treatment groups ($p = 0.9318$) was detected. ALND was the only variable that had a significant ($p = 0.0006$) association with skin thickness ratio.

Conclusion: We did not find a time-effect or a treatment-effect on the skin thickness ratio. ALND was the only significant factor affecting the skin thickness ratio. Since there was a relatively small sample size and unbalanced data between two treatment groups, further studies may focus on a matched data analysis or larger sample size.

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Table of Contents

1 Introduction

Among all the cancers in women, breast cancer is the most common[1]. In 2018, there were a total of 330,080 breast cancer cases including invasive breast cancer and non-invasive breast cancer[2]. According to the American Cancer Society, it is estimated that there will be 268,600 new cases of invasive breast cancer among American women, which makes up about 30% of newly diagnosed cancer in 2019[2-4]. African-American women under 45 have higher risk of breast cancer than white women[2]. Age is the biggest risk factor for breast cancer, and the risk of breast cancer becomes larger when women have a family member with breast cancer (mother, sister or daughter)[2]. The incidence rates of breast cancer are increasing by 0.4% each year[4], however, the mortality rate of breast cancer decreased in recent years, largely due to advanced treatment, increased awareness, and earlier detection[2]. In US, the number of survivors of breast cancer is about 3.5 million, which constitutes the largest part of cancer survivors and more than half of them are expected to be alive at least 5 years[1, 5].

Conserving surgery, also called lumpectomy, is a surgery that remove cancer from breast as well as retain the shape of breast and nipple area[6]. Radiation therapy is an adjuvant therapy to eliminate remaining cancer cells. This therapy is critical for breast cancer patients, since it lowers the local recurrence and mortality rate[7]. In addition, this type of therapy must be taken per a specific regimen (daily, two or three times per week)[7, 8]. Study has showed that the survival rates of lumpectomy with radiation therapy and mastectomy are the same[9]. Long-term quality of life is the major concern for breast cancer patients as they are expected to have extended survival times. However, one problem for women who choose lumpectomy is a cosmetic issue, in which the breast is smaller and firmer with scars and numbness due to the surgery[6]. Radiation therapy afterwards may even worsen this situation with some acute and chronic side effects: skin changes, cardiac toxicity, reproductive dysfunction and pneumonitis[5].

Conventional whole breast radiation, accelerated (hypo-fractionated) whole breast radiation, and partial breast radiation are three main radiation therapy regimens adjuvant to lumpectomy therapy. Conventional whole breast radiation is a standard therapeutic procedure delivered during a five-to-seven-week period[10]. A total of 50 Gray (dose of the therapy) will be given to a patient in a 5-week treatment, which results in 2 Gray in each of 25 treatments[11]. An alternative regimen that is increasingly becoming popular is an accelerated (hypo-fractionated) whole breast irradiation. This involves a reduced dose and reduced treatment time. The criteria are usually 42.5 Gary in 16 daily fractions or 40 Gary in 15 daily fractions. This regime is less costly and benefits patients with reduced medical resources[12].The accelerated partial-breast irradiation treatment is taken about 1 to 2 weeks with total 34 Gary[13]. Radiation area is targeted on the initial location of tumor in breast with 1 cm or 2 cm margin[13]. 3-D conformal radiation therapy and intraoperative radiation therapy (IORT) are two types of therapies[14]. Like accelerated (hypo-fractionated) whole breast irradiation, it has shorter treatment time. Moreover, it could minimize radiation exposure, reduce invasive procedures and increase success probability in saving healthy breast tissue[14].

Cosmetic breast changes is one remaining problem resulting from radiotherapy, which can have a significant effect on patients' quality of life in the future[15]. Some studies have shown that shorter RT time period with reduced dose will not be inferior to the traditional RT regimen for women with breast cancer[12, 16]. However, we still lack studies showing the difference in side effect: skin changes between different regimens. Studies based on conventional irradiation points out radiation-induced skin thickening[17].There remains disputation whether hypofractionation increase fibrosis or worsen cosmetic. Two studies indicate that conventional therapy and hypofractionation had the same effect on skin[18, 19]. However, one study shows that the skin was worsened by hypofractionation therapy[20, 21]. Moreover, some other factors

may be related to the severity of the toxicity: total dose, fraction, location, other therapies and personal characteristics including age, smoking status, BMI, disease staging[15].

This study focuses on the effects of two different therapies: conventional fractionation and hypo-fractionated radiation on breast cancer patients. We only take cosmetic deformity (skin changes) into consideration as main side effect of radiation. The goal of the study is to detect associations of skin changes and important clinical factors (age, BMI etc.) to examine whether such associations varied by different type RT fractionation regimens. Skin thickness measurement data were collected by ultrasound. The principal aims of the study were to:

1) find whether there is a significant skin thickness ratio change over the course of time with different RT fractionation regimens;

2) analyze clinical factors including age, body mass index, race, breast side, smoking status, menopause status, cancer status, estrogen receptor, progesterone receptor, HER2, chemo status, herceptin, hormone status, sentinel lymph node (SLN), axillary lymph node dissection (ALND) affect the pattern of these changes.

The results of proposed study may benefit patients and help clinicians to choose the better treatment in order to minimize the skin changes and improve patient quality of life. In section 2, research design, data collection and statistical analysis method are described. Section 3 presents the results of model fitting and section 4 includes the final conclusions and further study discussions.

2 Method

2.1 Research Design & Data Collection

2.1.1 Sample

The study was open to early-diagnostic breast cancer women in 4 clinical locations: (1) Emory Healthcare Clifton Campus, (2) Grady Health System, (3) Emory University Hospital Midtown,

and (4) Emory St, Joseph's Hospital. 143 female patients with diverse characteristics were recruited under an IRB approved protocol, with 84 in conventional fractional radiation group and 59 in hypo-fractional radiation group. Recruited women participated in a 1-year longitudinal study with 5 scans. A baseline evaluation was conducted at one week prior to radiation treatment. Two evaluations for acute toxicity were conducted during radiotherapy, approximately 5 weeks and 6 weeks post radiotherapy, respectively. For late toxicity, two remaining evaluations were carried out at 6 months and 12 months following radiotherapy.

Clinical data including age, body mass index, race, breast side, smoking status, menopause status, cancer status, estrogen receptor, progesterone receptor, HER2, chemo status, herceptin, hormone status, sentinel lymph node (SLN), axillary lymph node dissection (ALND) were also collected. Race consisted of two subgroups: Caucasian and African American. Breast side was coded as left and right. Smoking status, chemo status, hormone status, herceptin, SLN, ALND were all dichotomized into either yes or no. Menopause status was categorized as pre menopause status and post menopause status. Three types were defined in cancer status: T stage, N stage, and stages. T stage[22] had three categories: no evidence of a primary tumor (it cannot be found); tumor can be found in submucosa (T1); and tumor can be detected in muscularis propria (T2). N stage[22] was classified as whether the cancer had not spread to nearby lymph nodes and had spread to nearby lymph nodes. Stage[22] included stage 0: the cancer was localized to the breast tissue and had not spread to nearby tissues; stage I: a small cancer or tumor that had not grown deeply into nearby tissues; stage II: larger cancers or tumors that had grown more deeply into nearby tissue; and Stage III: more severe condition than stage II. Estrogen receptor, progesterone receptor and HER2 indicated whether the participant had a positive test or not.

2.1.2 Radiation Treatment

About 4-8 weeks after lumpectomy, patients in the two groups received different types of radiotherapy treatment. For the conventional fractionation radiation treatment group, patients all underwent the same prescribed identical doses. A total dose of 50.0 Gray at 2.0 Gray per fraction was given to the whole breast. Lumpectomy cavity and incision scar were received a 10.0 Gy boost at 2.0 Gy per fraction with electrons[23].The treatment was delivered daily during a 6-week period excluding weekends. Exclusion of supraclavicular radiation patients were performed. For the hypo-fractionated radiation treatment group, a dose of 2.66 Gary per day during a 3-week period was given to the whole breast or chest wall with tangents (modulated with either wedges or field-n-field technique). Lumpectomy cavity and incision scar were treated with boost treatment on the same day, which was 15 fractions with 0.54 Gy per day. Homogeneity was assured by modulated beams. All treatment plans followed standard International Commission on Radiation Units & Measurements (ICRU-50) guidelines.

2.1.3 Patient Ultrasound Imaging

Every patient received 5 ultrasound scans during the study. Ten scan locations were provided to choose from for each scan: upper, medial, lower, lateral and tumor bed locations of the treated and untreated breasts. All evaluations are performed by ultrasound technique on patients' both sides breast tissue. Ultrasound data of the untreated contralateral breasts are considered as the control for irradiated breast. It took about 5-10 minutes to take images, which were stored on a computer for subsequent processing and analysis. This non-invasive, novel ultrasonic imaging technique was developed by Dr. Liu[24]. This technique along with standard B-mode ultrasonography could further display the sub-resolution tissue features [24-26]. The quantitative ultrasound technique utilizes the raw radio frequency data of skin layers (epidermis and dermis) to figure out the skin thickness. Computation of the skin thickness estimation was used by the following equation [24]:

$$D = \frac{vM}{2f_s}$$

$where$ v is the speed of sound $(1540\,{}^{m}/_{s})$

M is the sample points

f_s is the sampling frequency

Radiotherapy frequency echo time anterior (epidermis) and posterior skin layer (hypodermis) was used. At every 0.05s time intervals with wave propagation direction, sampling points were collected for data acquisition.

2.2 Statistical Analysis Method

The SAS statistical package V9.3 (SAS Institute, Inc., Cary, North Carolina) [27] was used for all data management and analyses.

2.2.1 Descriptive Statistics

For descriptive statistics by group, two sample t tests were performed for continuous variables including BMI and age (Table 1) and Chi square tests were performed for the categorical variables (Table 1). All missing data were excluded. The outcome variable skin thickness ratio was considered as a continuous variable, which was calculated by skin thickness irritated divided by skin thickness normal. The mean and standard error of the outcome variable among the two groups at different measurement time points with p-value were also calculated, respectively (Table 2).

2.2.2 Linear Mixed Model

2.2.2.1 Univariate Analysis

First, the linear mixed model (1) was performed to test whether there was any significant change over time and to detect whether there was any significant difference between the two treatment groups. The unstructured covariance structure was used in the model. The conventional fractional radiation group was considered as the reference group. The significance

level was set at 0.05. Random terms were fit to allow for patient-specific intercept. Time in the random statement measured the variance in the effects of time on skin changes across patients.

$$Ratio_{ij} = \beta_0 + \theta_{0i} + (\beta_1 + \theta_{1i})Time_{ij} + \beta_2 Group_i + \varepsilon_{ij} \quad (1)$$

Where:

- $Ratio_{ij}$ is the value of skin thickness ratio for the j^{th} patients of n_i observations in the i^{th} treatment groups;
- β_0, β_1, β_2 are the fixed-effect coefficients for intercept, time-effect and group-effect;
- θ_{0i}, θ_{1i} are the random-effect coefficient for intercept and time-effect;
- ε_{ij} is the error for observation j in group i.

Second, the linear mixed models (2) were performed to test whether there was any significant change over time, to detect whether there was any significant difference between the two treatment groups and to find whether other significant clinical factors affect the association. We still adopted the unstructured covariance structure. The factors were first each put into the model to test the significance (age, body mass index, race, breast side, smoking status, menopause status, cancer status, estrogen receptor, progesterone receptor, HER2, chemo status, herceptin, hormone status, SLN, ALND). Random intercept and random time-effect were also considered in this model. The conventional fractional radiation group was considered as the reference group. The significance level was set at 0.05.

$$Ratio_{ij} = \beta_0 + \theta_{0i} + (\beta_1 + \theta_{1i})Time_{ij} + \beta_2 Group_i + \beta_3 Factors_m + \varepsilon_{ij} \quad (2)$$

Where:

- $Ratio_{ij}$ is the value of skin thickness ratio for the j^{th} patients of n_i observations in the i^{th} treatment groups;
- β_0, β_1, β_2, β_3 are the fixed-effect coefficients for intercept, time-effect, group-effect and factor-effect;
- θ_{0i}, θ_{1i} are the random-effect coefficient for intercept and time-effect;

- ε_{ij} is the error for observation j in group i.

2.2.2.2 Multivariable Analysis

Third, after finding all the significant factors, we included them all into the linear mixed model (3) with unstructured covariance structure to determine the best model to predict skin thickness ratio. Again, we chose random intercept and random time effects here. Since the sample size was quite small in this study, putting too many explanatory variables into the model made the linear mixed model unstable. Hence, we set significance level at 0.1.

$$Ratio_{ij} = \beta_0 + \theta_{0i} + (\beta_1 + \theta_{1i})Time_{ij} + \beta_2 Group_i + \beta_3 Age + \beta_4\, Smoking\ Staus_{z1} + \beta_5\, T\ stage_{z2} + \beta_6\, N\ stage_{z3} + \beta_7\, Stage_{z4} + \beta_8 Chemo\ Statues_{z5} + \beta_9 ALND_{z6} + \varepsilon_{ij} \quad (3)$$

Where:

- $Ratio_{ij}$ is the value of skin thickness ratio for the j^{th} patients of n_i observations in the i^{th} treatment groups;
- β_0, β_1, β_2, β_3, β_4, β_5, β_6, β_7, β_8, β_9 are the fixed-effect coefficients for intercept, time-effect, group-effect, age-effect, smoking-effect, T stage-effect, N stage-effect, stage-effect, chemotherapy-effect;
- θ_{0i}, θ_{1i} are the random-effect coefficient for intercept and time-effect;
- ε_{ij} is the error for observation j in group i.

3 Results

3.1 Patient Characteristics

Descriptive statistics are listed in Table 1. The dataset was not balanced between the two treatment groups with 84 in the conventional treatment group and 59 in the hypofractionated treatment group.

There was little difference in mean age (around 55) between the two groups. The conventional treatment group patients had lower BMI with a mean of 29.59 compared to the hypofractionated treatment group with a mean of 31.66. Both continuous characteristics were not significantly different between the two treatment groups. Examination of the patients' demographic data demonstrated that the groups were well matched on race, breast side, smoking status, menopause status, cancer status, estrogen receptor, progesterone receptor, HER2, chemo status, herceptin, hormone status and SLN. However, ALND was the only variable that was significantly different between the two groups ($p = 0.009$). 40.58% of patients in the conventional treatment group did not receive lymph node removal surgery while only 18.52% patients in the hypofractionated treatment group underwent surgery. However, among patients who did not have this surgery, a higher percentage in hypofractionated treatment group in comparison to that of conventional treatment group was detected (81.48% and 59.42% respectively).

Skin thickness ratio (Table 2) for both treatment groups increased from baseline through the fourth evaluation with there being a statistically significant difference between the conventional and the hypofractional treatment groups at evaluation third time point ($p = 0.037$). However, for both of the treatment groups, the mean skin thickness ratio started to decrease and trend towards baseline by the fourth evaluation. Skin thickness ratio of conventional treatment group was 1.30 (se= 0.037) at baseline, reached to its peak (1.66 with se=0.051) at the forth evaluation and declined to 1.46 (se = 0.042) at the last evaluation. While in the hypofractionated treatment group, although the baseline was almost the same as the former group, the peak skin thickness ratio value was only 1.51 (se = 0.067) and just finally dropped to 1.50 (se = 0.065). However, the mean increase in skin thickness ratio was larger in the conventional treatment group than that in the hypofractionated treatment group.

3.2 Linear Mixed Models

3.2.1 Univariate Analysis

Table 3 presents the results of our analysis of the skin thickness ratio using Model (1). From the mixed-effects model, a marginally significant time effect ($p = 0.055$) but not a group effect ($p = 0.256$) were found. Figure 1 additionally shows the mean skin thickness ratio changes over time between the two groups. Model (2) with two forced variable time and group parameters were then fitted separately for each clinical factor. Among all the factors, only smoking status, T stage, N stage, stages, chemo status, ALND and age were significant variables (Table 4). Skin thickness ratio was significantly different ($p = 0.009$) in the chemotherapy group (0.1612 units higher) as compared to the non-chemotherapy group. A statistically significant 0.2097 unit increase in skin thickness ratio was detected in smoking patients compared to non-smoking patients ($p = 0.005$). Skin thickness ratio were significantly different in the various types of cancer stages, where p-values are 0.005 in T stages, <0.001 in N stages and <0.001 in stages. Skin thickness ratio was significantly 0.4277 units higher in patients receiving lymph node removal surgery than that of patients who didn't receive surgery ($p < 0.001$). With 1 unit increase in age there was 0.0065 units increase in skin thickness ratio ($p = 0.0026$). Figure 2-8 further display mean skin thickness ratio changes over time among two group by each significant clinical characteristic.

3.2.2 Multivariable Analysis

Outcomes of model (3) are shown in Table 5. We found that skin thickness ratio was not significantly related to time ($p = 0.1639$) and there was no difference in the pattern detected between the two treatment groups. ALND was the only clinical factor that had a significant ($p = 0.0006$) association with skin thickness ratio. Patients who had lymph node removal surgery had 0.3160 units increase in skin thickness ratio than patients who didn't receive surgery.

4 Conclusion and Discussion

The purpose of the study is to detect associations of skin changes and important clinical factors to examine whether such associations varied by different type RT fractionation regimens. In this study we did not find any association between skin thickness ratio change and the course of time. In addition, the change pattern was not affected by the different treatment group. However, whether the patient had surgical removal of lymph nodes was significantly related to the skin thickness ratio change.

At present it remains difficult for doctors to predict whether patients will suffer from side effects and severe toxicity resulting from whole breast radiotherapy[28]. From previous studies, side effects and toxicity severity including skin erythema, desquamation, and/or cutaneous thickening and hardening within the breast were related to patient characteristics (smoking status, race and BMI), chemotherapy and hormone therapy[29]. In our study, we did not find any group effect or factor effect on skin thickness ratio. Undoubtedly, the relatively small sample size in this study with smaller number of patients in these subgroups limited conclusions regarding these factors. Future analysis will test interaction between different treatment groups and clinical factors on breast thickening.

A previous study has shown that axillary lymph node dissection was related to the epidermal thickening after whole-breast radiation therapy [28]. Furthermore, this lasted up to 1 year[30]. Our study validated the association between axillary lymph node dissection and skin thickening. Again, due to the small sample size, we failed to include interaction terms into the linear mixed models. The surgery-effect in two treatment groups might be tested if we included the interaction terms.

We chose a linear mixed model as our main analysis approach rather than repeated-measures analysis of variance (ANOVA). Linear mixed model had some advantages over the latter, as it had more flexibility and was efficient[31]. The greatest advantage of the linear mixed model was that it could include fixed effect and random effect at the same time, exporting sample

average parameters and observation specific parameters. Additionally, the time variable was treated as continuous data in our study, which could only be analyzed by linear mixed model. Repeated measures ANOVA would not be able to handle repeated measurements with a continuous factor. Moreover, the sample sizes in the two groups were not balanced, which linear mixed model allows for this variability. One important aspect in applying linear mixed model was to decide the variance covariance structure. Five types of structure could be considered: variance components, autoregressive (1), compound symmetry, unstructured and toeplitz. We finally chose unstructured structure since it allowed every variance to be different and fitted the most parameters.

As previously mentioned, unbalanced data in two treatment groups was one of the limitations in this study. One study found that unbalanced data in two comparison groups might lead to bias in treatment efficacy[32]. Longitudinal studies were easily confronted with unbalanced data in groups due to dropout, missing data and treatment switching, which were sensitive to this type of bias. Therefore, we might induce some bias because of the unbalanced study design. Another limitation was that we had a relatively small size, resulting in problems such as bias in prediction, loose significance level in choosing significant variables, and failure of adding interaction term in the model. Unstableness of the model was a problem when we forced too many interaction terms under this relatively sample size circumstance.

In conclusion, conventional whole breast radiation and hypo-fractionated whole breast radiation had a similar effect on skin thickness ratio in 143 patients. Axillary lymph node dissection had a significant impact on skin thickness ratio. Patients may select any regimen and less axillary surgery may be warranted in clinical scenarios. Further studies should focus on using matched data to refit the model and conducting a study with larger sample size to better estimate the association.

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6 Tables and Figures

Table 1 Descriptive Statistics for patients' characteristics

Characteristics		**N**	**Proportion / Mean (SD)**		**p-value**
			Conventional (n=84)	Hypo-fractional (n=59)	
Breast	Left	79	52.38	59.32	0.4112
	Right	64	47.62	40.68	
Race	Caucasian	83	61.90	53.45	0.315
	African	59	38.10	46.55	
Smoking	No	111	82.14	72.41	0.168
	Yes	31	17.86	27.59	

Menopause Status	Pre	48	34.52	32.76	0.772
	Post	95	65.48	67.24	
Stage	0	28	19.05	20.34	0.546
	I	42	26.19	33.90	
	II	61	44.05	40.68	
	III	12	10.71	5.08	
T-Stage	0	28	19.05	20.34	0.767
	1	64	42.86	47.46	
	2	51	38.10	32.20	
N-Stage	0	90	58.54	72.41	0.091
	1	50	41.46	27.59	
Estrogen Receptors	Negative	37	26.19	25.42	0.918
	Positive	106	73.81	74.58	
Progesterone Receptor	Negative	50	36.90	32.20	0.562
	Positive	93	63.10	67.80	
HER2	Negative	83	71.01	73.91	0.734
	Positive	32	28.99	26.09	
Chemo Status	NO	63	42.89	45.76	0.730
	YES	80	57.14	54.24	
Herceptin	0	126	86.90	89.83	0.595
	1	17	13.10	10.17	
Hormone Status	No	46	32.14	32.20	0.994
	Yes	97	67.86	67.80	
SLN	No	38	32.47	22.41	0.199
	Yes	97	67.53	77.59	
ALND	No	85	59.42	81.48	0.009
	Yes	38	40.58	18.52	
Age		143	55.14 (10.26)	55.76 (11.29)	0.734
BMI		143	29.59 (9.84)	31.66 (9.57)	0.160

Table 2 Skin Thickness Ratio at Different Time Points[1] among Two Groups

	Mean (Standard Error)				
Group	Baseline	RT	Post RT1	Post RT2	Post RT3
Conventional	1.30(0.037)	1.53(0.050)	1.63(0.053)	1.66(0.051)	1.46(0.042)
Hypofractional	1.31(0.050)	1.40(0.053)	1.45(0.066)	1.51(0.067)	1.50(0.065)
P-value	0.865	0.069	0.037	0.074	0.557

[1] Time Point. Baseline: the evaluation will be performed one week prior to radiation treatment. Two acute toxicity evaluations will be performed one time during RT (5 weeks) and at 6 weeks post RT. For late toxicity, 2 additional evaluations will be done at 6-, and 12-months.

Table 3 Linear Mixed Models Estimating Time-Effect and Group-Effect on Skin Thickness Ratio

Characteristics		Estimate	P-value
Time		0.0002	0.055
Group	Conventional	-	-
	Hypofractional	-0.0722	0.256

Table 4 Clinical Parameter Estimates from Univariate Mixed Models

Characteristics	**Levels**	**Estimate**	**P-value**
Breast	Left	-	-
	Right	-0.0060	0.923
Race	Caucasian	-	-
	African American	0.1044	0.100
Smoking	No	-	-
	Yes	0.2097	0.005
Menopause Status	Pre	-	-
	Post	0.0280	0.674
	0	-	-

Stage	I	0.1044	<0.001
	II	0.3443	
	III	0.2253	
T-Stage	0	-	-
	1	0.2148	0.005
	2	0.2765	
N-Stage	0	-	-
	1	0.3230	<0.001
Estrogen Receptors	Negative	-	-
	Positive	0.0621	0.385
Progesterone Receptor	Negative	-	-
	Positive	0.0005	0.994
HER2	Negative	-	-
	Positive	-0.0243	0.767
Chemo Status	NO	-	-
	YES	0.1612	0.009
Herceptin	0	-	-
	1	-0.0720	0.456
Hormone Status	No	-	-
	Yes	0.0992	0.137
SLN	No	-	-
	Yes	0.0806	0.264
ALND	No	-	-
	Yes	0.4277	<0.001
Age		0.0006	0.026
BMI		0.0057	0.142

Table 5 Parameters Estimates from Multivariate Mixed Model

Characteristics	Levels	Estimate	P-value
Time	-	0.0002	0.1639
Group	Conventional	-	-
	Hypofractional	-0.0067	0.9318
Smoking	No	-	-
	Yes	0.1289	0.137
Stage	0	-	-
	I	0.0891	0.148
	II	0.0989	
	III	-0.1633	
T-Stage	0	-	-
	1	-0.0187	0.862
	2	0	
N-Stage	0	-	-
	1	0.184	0.101
Chemo Status	NO	-	-
	YES	0.0746	0.377
ALND	No	-	-
	Yes	0.3160	0.0006
Age	-	0.0044	0.229

Figure 1 Mean Skin Thickness Ratio Over Time Among Two Groups

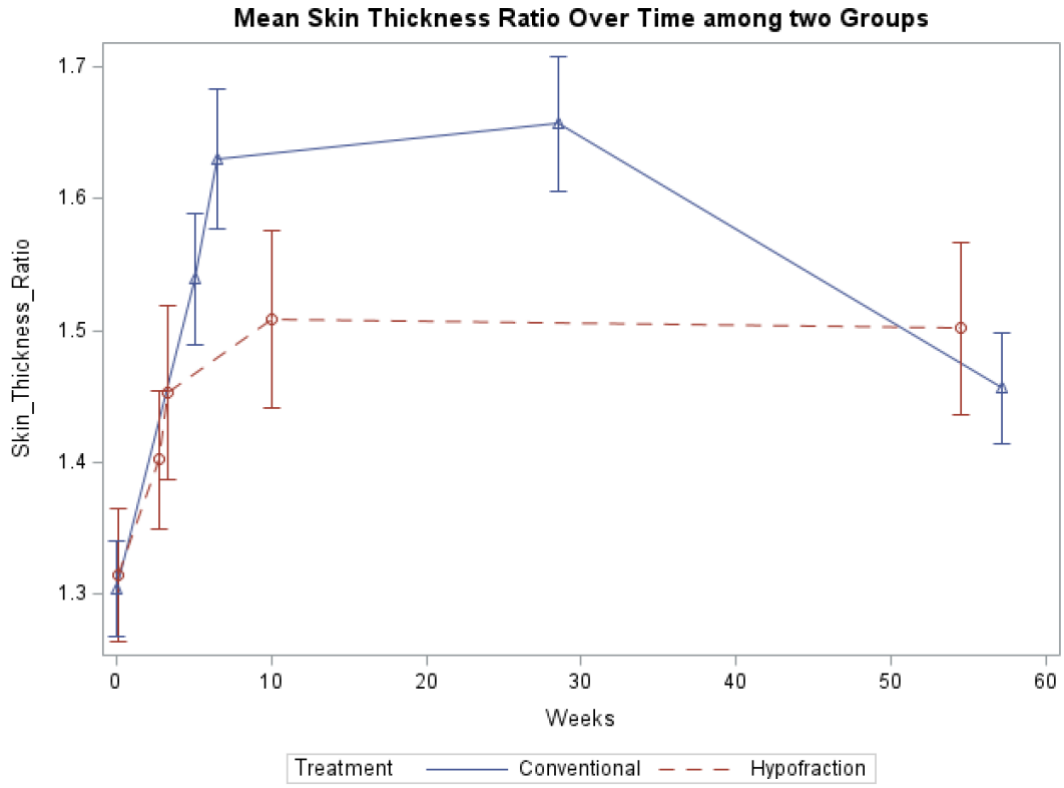

Figure 2 Mean Skin Thickness Ratio Over Time Among Two Groups by Smoking Status

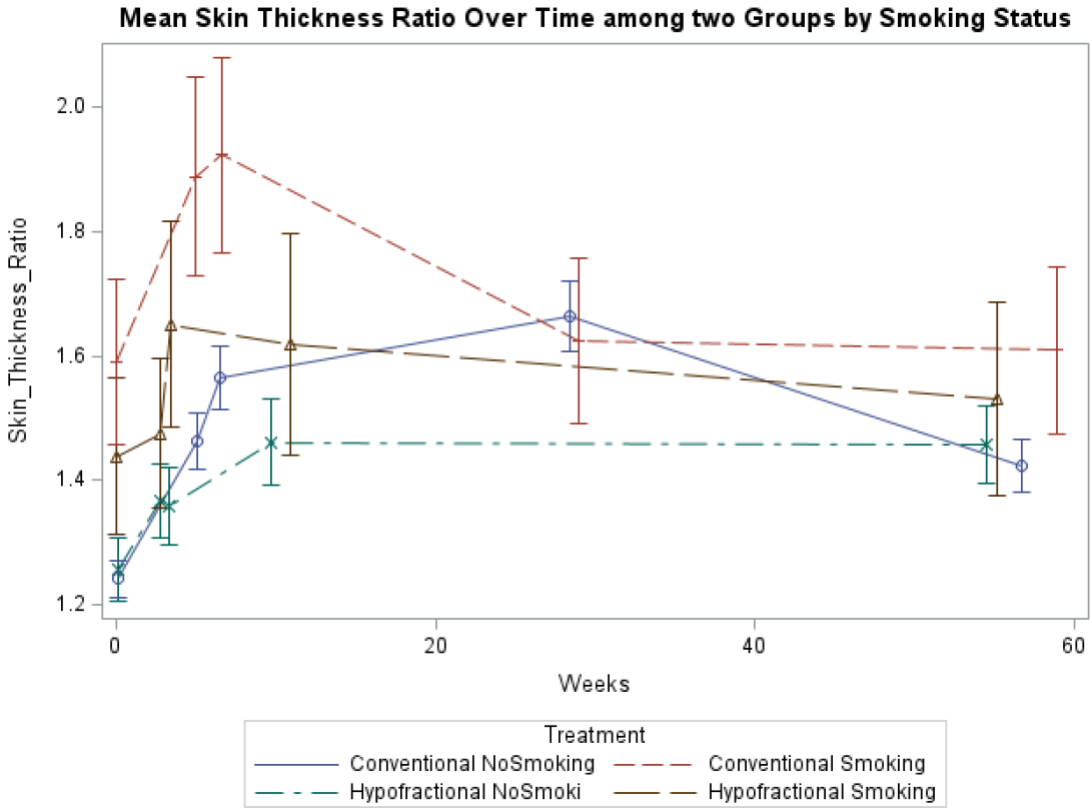

Figure 3 Mean Skin Thickness Ratio Over Time Among Two Groups by T Staging

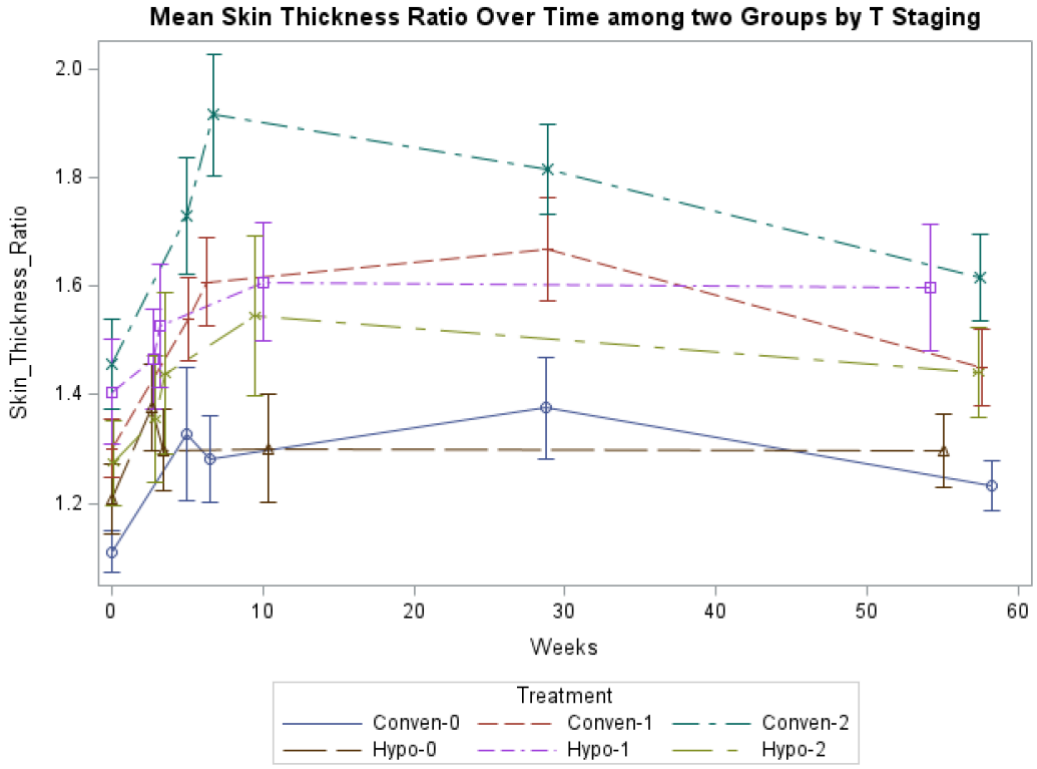

Figure 4 Mean Skin Thickness Ratio Over Time Among Two Groups by N Staging

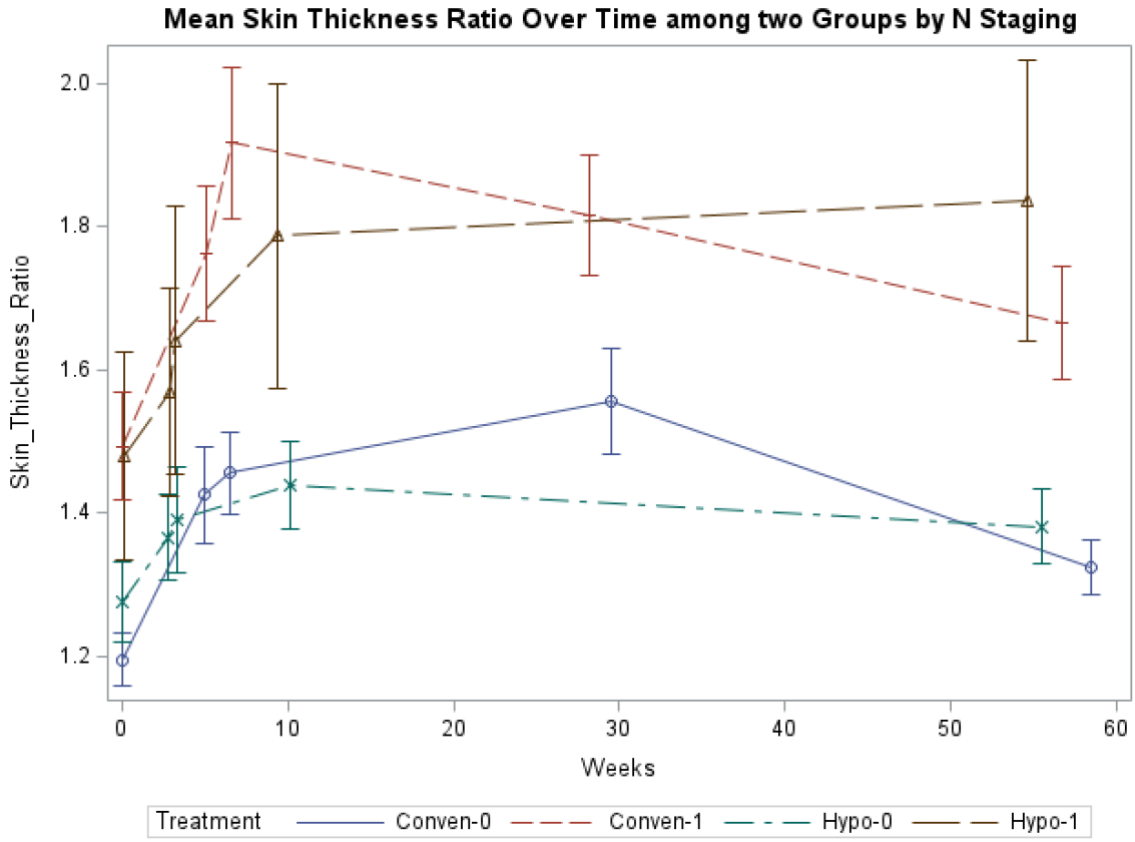

Figure 5 Mean Skin Thickness Ratio Over Time Among Two Groups by Stage

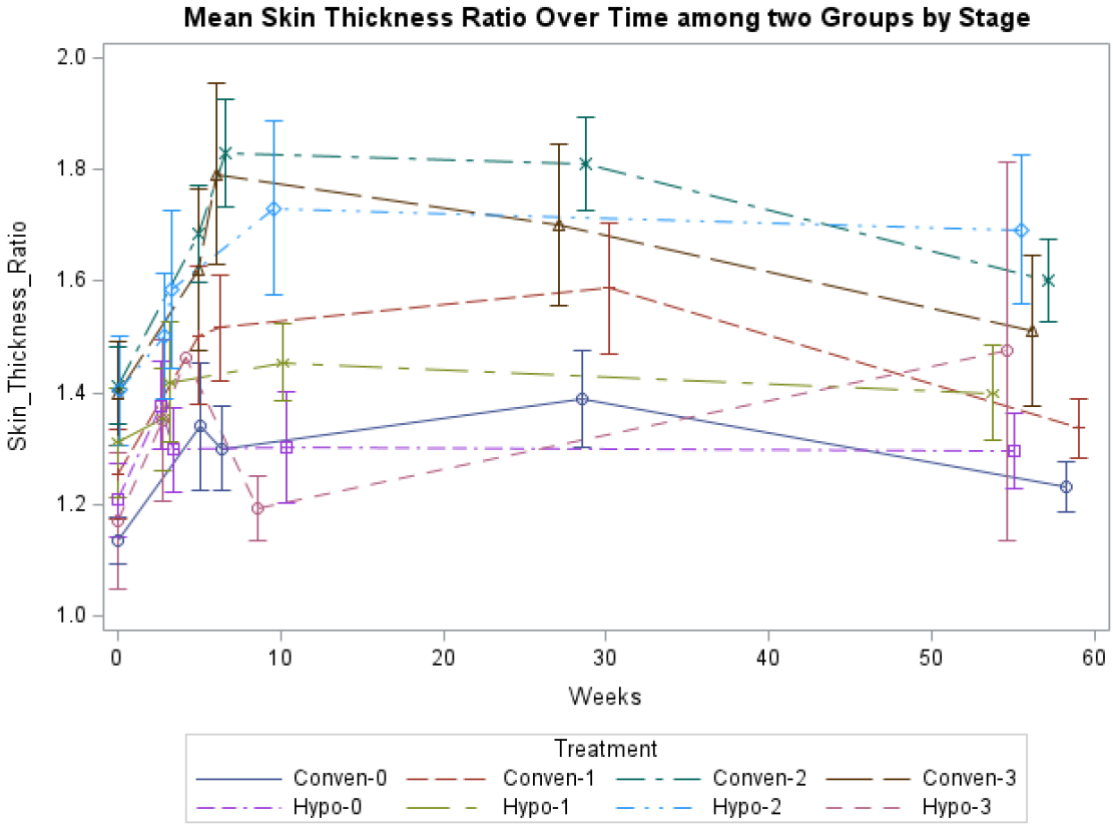

Figure 6 Mean Skin Thickness Ratio Over Time Among Two Groups by Chemotherapy Status

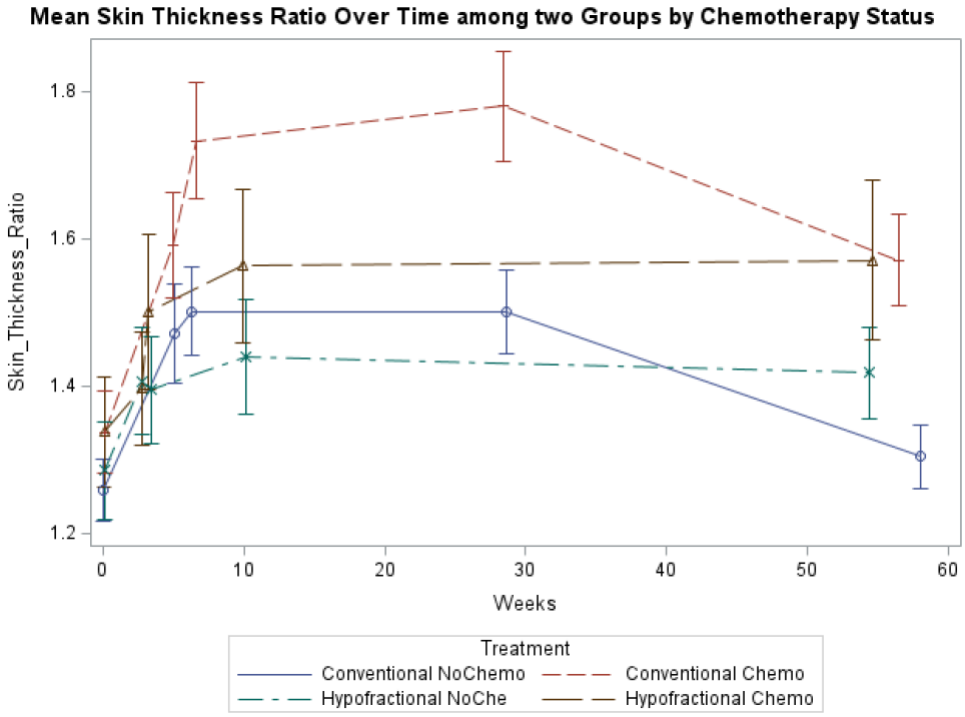

Figure 7 Mean Skin Thickness Ratio Over Time Among Two Groups by ALND

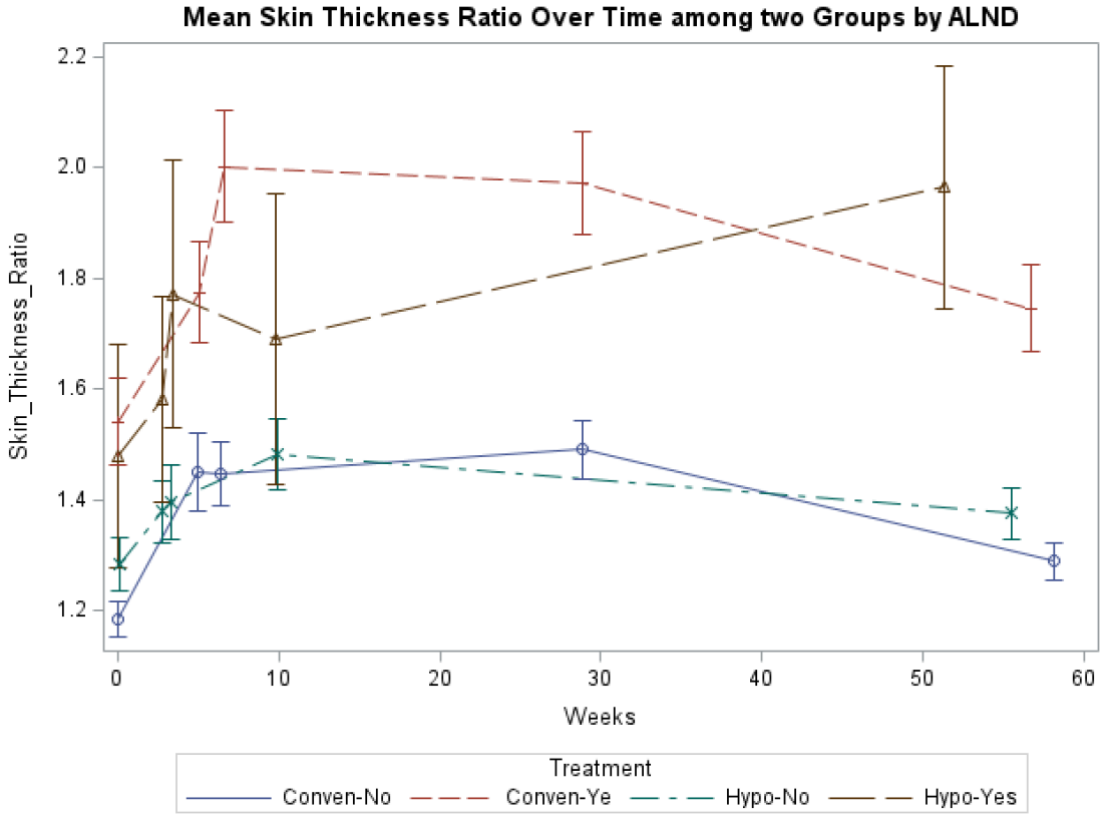

Figure 8 Mean Skin Thickness Ratio Over Time Among Two Groups by Age