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INDIVIDUAL GROWTH MODELS OF CHANGE IN PEABODY PICTURE VOCABULARY SCORES OF CHILDREN TREATED FOR BRAIN TUMORS

by

Ying Shen

Under the Direction of Yu-Sheng Hsu

ABSTRACT

The individual growth model is a relatively new statistical technique. It is now widely used to examine the trajectories of individuals and groups in repeated measures data. This study examines the association of the receptive vocabulary over time and characteristics of children who were treated for brain tumors. The children undertook different types of treatment from one to any combinations of surgery, radiation and chemotherapy. The individual growth model is used to analyze the longitudinal data and to address the issues behind the data. Results of this study present several factors' influences to the rate of change of PPVT scores. The conclusions of this thesis indicate that the decline in the PPVT scores is associated with gender, age at diagnosis, socioeconomic status, type of treatment and Neurological Predictor Scale.

INDEX WORDS: Longitudinal data, Individual growth model, Fractional polynomial transformation

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by

Ying Shen

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Science

in the College of Arts and Sciences

Georgia State University

2007

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by

Ying Shen

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Committee: Dr. Tricia King
Dr. Xu Zhang

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Office of Graduate Studies
College of Art and Sciences
Georgia State University
December 2007

TABLE OF CONTENTS

List of Tables…….. viii

List of Figures……. x

List of Abbreviations…….. xi

Chapter One: Introduction…….. 1

1.1 Background ……. 1

1.2 Source of data ……... 2

1.3 Method of analysis …… 5

Chapter Two: Methodology……. 6

2.1 The Hierarchical Linear Model (HLM) ……. 6

2.2 Fractional Polynomial Transformation …… 8

2.3 Statistical analysis ……... 9

2.3.1 Individual Growth Models for Treatments and other Variables …….. 10

2.3.2 Individual Growth Models for Neurological Predictor Scale and other variables…….. 20

Chapter Three: Results and Discussion …… 30

3.1 Models for treatments and other variables …… 30

3.1.1 Model without interactions …… 30

3.1.2 Model with interactions ……. 30

3.1.3 Model with variable transformation …….. 31

3.2 Models for Neurological Predictor Scale and other variables …… 32

3.2.1 Model without interactions …… 32

3.2.2 Model with interactions ……. 33

3.1.3 Model with variable transformation …….. 33

Chapter Four: Conclusion and Future Research…… 35

References…… 36

Appendix A: SAS Code …… 38

Appendix B: Models for time beginning from diagnosis date ……... 57

List of Tables

Table 1.1: Descriptive Table of Treatments, Gender, Age at diagnosis and SES classes……..…… 3

Table 1.2: Descriptive Table of PPVTSS, NPS_total, and Time …….……. 4

Table 1.3: Time point count distribution …… 4

Table 2.1: Solution for fixed effects ……..…… 10

Table 2.2: Fixed effects for the model without interactions for the treatments and other variables …… … 11

Table 2.3: Random effects for the model without interactions for the treatments and other variables …… 11

Table 2.4: Fixed effects for the model with interactions for the treatments and other variables …… 13

Table 2.5: Random effects for the model with interactions for the treatments and other variables …… 14

Table 2.6: Results of fractional polynomial transformation for SES, age at diagnosis and time …… 15

Table 2.7: Results of testing the significance of variables…… 16

Table 2.8: Fixed effects for the model with variable transformation for the treatments and other variables ……. 17

Table 2.9: Random effects for the model with variable transformation for the treatments and other variables …… 17

Table 2.10: Fixed effects for the model without interactions for Neurological Predictor Scale and other variables …… 20

Table 2.11: Random effects for the model without interactions for Neurological Predictor Scale and other variables …… 21

Table 2.12: Fixed effects for the model with interactions for Neurological Predictor Scale and other variables …… 23

Table 2.13: Random effects for the model with interactions for Neurological Predictor Scale and other variables …… 23

Table 2.14: Results of testing the significance of Neurological Predictor Scale ……..... 26

Table 2.15: Fixed effects for the model with variable transformation for Neurological Predictor Scale and other variables …….. 27

Table 2.16: Random effects for the model with variable transformation for Neurological Predictor Scale and other variables …… 27

Table 3.1: Comparison of models for treatments and other variables…… 32

Table 3.2: Comparison of models for Neurological Predictor Scale and other variables…….. 34

List of Figures

Figure1.1: Individual PPVT score trajectories …… 5

Figure 2.1: Individual grow curves for some categories using model without interactions for treatments and other variables…… 12

Figure 2.2: Individual grow curves for some categories using model with interactions for treatments and other variables……. 14

Figure 2.3: Individual grow curves for some categories using model with variable transformation for treatments and other variables.. 18

Figure 2.4: Individual growth curves for treatment and other variables ..….. 19

Figure 2.5: Individual grow curves for some categories using model without interactions for Neurological Predictor Scale and other variables……. 22

Figure 2.6: Individual grow curves for some categories using model with interactions for Neurological Predictor Scale and other variables……. 24

Figure 2.7: Individual grow curves for some categories using model with variable transformation for Neurological Predictor Scale and other variables……. 28

Figure 2.8: Individual growth curves for Neurological Predictor Scale and other variables ……..……. 29

List of Abbreviations

SES	Socioeconomic Status
PPVTSS	Peabody Picture Vocabulary Test Standard Scores
NPS_CH	Chemotherapy
NPS_Rad	Radiation
NPS_total	Neurological Predictor Scale

Chapter One: Introduction

1.1 Background

Brain tumors are a life-threatening and chronic ailment for many children and comprise approximately 22% of childhood cancers and tumors originating in the central nervous system, and are the second only to leukemia in cause of death among childhood cancers [1, 2]. The standard treatments for brain tumors are surgery, radiation therapy, chemotherapy, and any combinations of the three treatments.

Surgery is the primary form of treatment for brain tumors that lie within the membranes covering the brain or in parts of the brain that can be removed without damaging critical neurological functions. Because a tumor is likely to recur if any tumor cells are left behind, the goal of surgery is to remove the entire tumor whenever possible. It is frequently used in combination with other intervention when necessary [3].

Radiation therapy and chemotherapy are generally used as secondary or adjuvant treatments for tumors that cannot be managed using only surgery. However, radiation and chemotherapy may be used without surgery if the tumor is inoperable. Radiation therapy uses high-energy x-rays or other types of ionizing radiation to stop cancer cells from dividing. Because the developing brain of a child is very sensitive to radiation therapy, it is deliberately limited [3]. Chemotherapy required for the more aggressive tumors uses chemicals (drugs) that have a toxic effect on tumor cells as they divide. Survival rates of children with certain types of brain tumors have been significantly improved by the treatment of radiation therapy and chemotherapy.

The children who have undergone treatment for brain tumors which have direct impact on crucial brain structures underlying behavior may be more likely to exhibit behavior problems than their peers. Although studies have found that survivors are at risk for a variety of physical, medical, cognitive, and/or psychosocial late effects, the particular risk factors having an impact on children's psychosocial and behavioral functioning are not fully understood. These late effects may be directly related to the type of treatment (surgery, chemotherapy, and/or radiation), characteristics of the disease (tumor size and type), and individual demographic factors, such as age and socioeconomic status [4].

1.2 Source of Data

The data for this study comes from a longitudinal study conducted by Robin Morris of Georgia State University over 15 years ago. Trica King in collaboration with Robin Morris and other researchers are evaluating the survivors of childhood brain tumors from the original longitudinal study when began at the time when they undertook diagnosis and treatments. Drs. Tricia King and Robin Morris (Department of Psychology) and along with Dr. Yu-Sheng Hsu (Mathematics and Statistics Department) are conducting studies to identify the predictors of longitudinal data such as the PPVT [5]. Peabody Picture Vocabulary Test (PPVT) is a measure of receptive vocabulary for Standard English and a screening test of verbal ability. In this study, we analyzed change in PPVT scores over time in these children.

Between 1985 and 1996, 98 patients participated in the longitudinal study and 93 out 98 patients' information were complete. The patients' data include PPVT scores,

date of birth of the participant, gender, socioeconomic status, treatments the patient undertook, Neurological Predictor Scale the patient had, date of the diagnosis, and date of taking PPVT test. The age of diagnosis of those 93 patients is ranged from 0.4 to 16.7 years old. The Neurological Predictor Scale is ranged from 2 to 11. The range of observation per patient is from 1 to 11.

Table 1.1: Descriptive Table of Treatments, Gender, and SES classes

Variables	Patients					Observations				
	with		without			with		without		
Surgery	79		14			391		42		
Chemo	25		68			138		295		
Radiation	62		31			283		150		
	Patients					Observations				
Male	50					235				
Female	43					198				
Age<=7 years old	58					306				
Age>7 years old	35					127				
	Patients					Observations				
SES classes	1	2	3	4	5	1	2	3	4	5
	8	19	23	30	13	40	117	105	122	49

The potentially predictive variables included in this study are gender, age at diagnosis, Socioeconomic Status Class (SES), surgery, chemotherapy, radiation, time since treatment and Neurological Predictor Scale (NPS_total). A family's socioeconomic status is based on family income, parental education level, and parental occupation. There are five levels for SES class in which class1 is the highest level and

class 5 is the lowest level. Neurological Predictor Scale (NPS_total) is a nonratio, ordinal scale. It is a sum of patients' rated scores across 4 domains which are tumor-related conditions, operative events, radiation treatment, and chemotherapy [6].

Table 1.2: Descriptive Table of PPVTSS, NPS_total, Age at diagnosis and Time

Variables	Mean	Standard Deviation	Range
PPVT Standardized Score	89.2909931	19.5685721	40 to 132
Neurological Predictor Scale	6.2494226	2.0610263	2 to 11
Age at diagnosis (years)	5.7768538	3.5683538	0.4 to 16.7
Time(years between treatment and measurement)	2.6656600	3.5572518	0 to 15.9

The data consisted of 433 records on 93 individuals. The frequency distribution of the number of time points is seen in Table 1.3. The data on 45 children who have more than two time points are displayed graphically in Fig. 1.1.

Table 1.3: Time point count distribution

Number of Time Points	Frequency	Percent	Cumulative Percent
1	38	40.86	40.86
2	10	10.75	51.61
3	8	8.61	60.22
More than 3	37	39.78	100.00

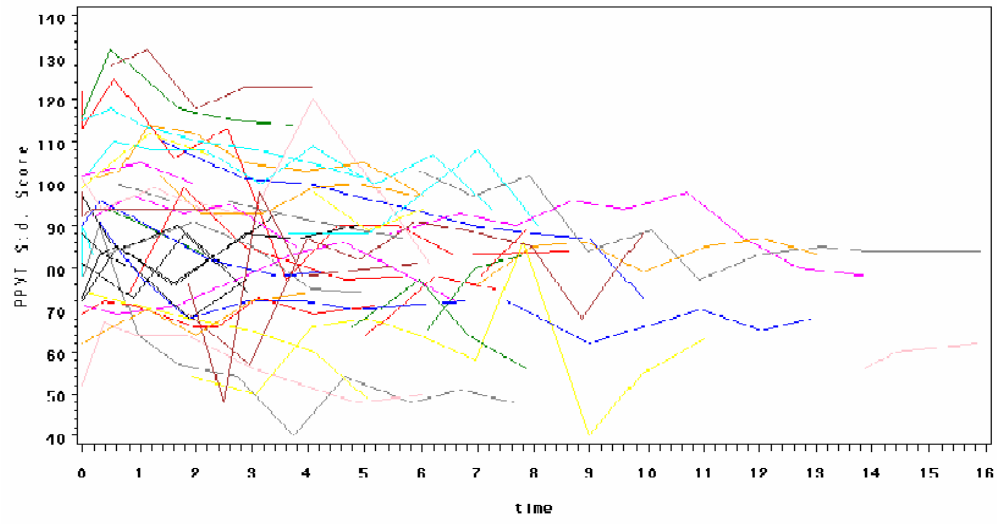


Figure 1.1 Individual PPVT score trajectories (raw data, n=45)

1.3 Method of Analysis

In order to analyze change over time in psychological studies, there are numerous traditional methods that can be applied. These include the mixed model analysis of variance (ANOVA) and the multivariate approach to repeated measures (MANOVA), the analysis of covariance (ANCOVA) or residualized change analysis, and the analysis of covariance with reliability correction (ANCOVARC).

In this study, we will use individual growth model to analyze the changes over time in PPVT data. Much study shows that it is both possible and desirable to model change at the individual level [7]. The individual growth model is a relative new statistical technique now widely used to examine the unique trajectories of individuals and groups in repeated measures data.

Chapter Two: Methodology

In this chapter, the individual growth models we get are presented. Since repeated measurements were taken on each child obtained over time, hierarchical linear models were used for the analysis of change. To explain the change over time of standard scores of PPVT, two sets of variables were considered. One set includes Years between date of treatment and date of exam (Time), Gender, Age at diagnosis, SES classes, Treatments (surgery, radiation and chemotherapy), and potential interactions of these variables. The other one consists of Years between date of treatment and date of exam (Time), Gender, Age at diagnosis, SES classes, Neurological Predictor Scale (NPS_total), and potential interactions of these variables. The patients are assumed to be random and other variables are fixed effects in the model. Fractional polynomial transformation was applied in this study for the continuous variables.

2.1 The Hierarchical Linear Model (HLM)

Longitudinal studies sometimes known as repeated measures are encountered in a wide variety of disciplines. Longitudinal data is the union of cross-sectional and time series data. The balanced design in longitudinal data analysis assumes a complete data set with an equal number of measurements over time for each subject, while the unbalanced design has incomplete data without equal time intervals or time points for each subject [8, 9]. Literature shows that hierarchical linear model (HLM) can be employed in longitudinal data analysis.

When HLM is applied to longitudinal data analysis, the level 1 units are the repeated measures for each subject and the level 2 units consist of subjects. The repeated measures are conceived as nested within each subject. The level 1 model includes time or/and quadratic time as the predictor(s). The within-subject model is:

$$Y_{ti} = \pi_{0i} + \pi_{1i} T_{ti} + e_{ti} \tag{1}$$

By convention, within person effects are indicated by the symbol π. Y_{ti} represents the outcome for individual i measured at time t. T_{ti} represents time from the base line assessment for person i. The slope π_{1i} is the linear growth rate for the ith person. The intercept, π_{0i}, represents the expected outcome of the person at baseline, also called initial status. The within-person residuals, e_{ti}, are assumed $N(0, \sigma^2)$.

At level 2, the goal is to investigate variations in the estimates of intercept and slopes in level 1 model. The between-subjects models are:

$$\begin{aligned} \pi_{0i} &= \beta_{00} + \beta_{01} x_{1i} + ... + \beta_{0p-1} x_{p-1i} + u_{0i} \\ \pi_{1i} &= \beta_{10} + \beta_{11} x_{1i} + ... + \beta_{1p-1} x_{p-1i} + u_{1i} \end{aligned} \tag{2}$$

Accordingly, $\beta_{00} and \beta_{10,}$ represent the expected baseline and slope, respectively. The coefficients for the predictors indicate how much these expected values increase or decrease. The random effects at level 2, u_{0i} and u_{1i} are assumed to be

$$\begin{bmatrix} u_{0i} \\ u_{1i} \end{bmatrix} - N\left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_{00}^2 & \sigma_{01}^2 \\ \sigma_{10}^2 & \sigma_{11}^2 \end{pmatrix}\right] \tag{3}$$

Substitute Equation (2) into (1), we can reduce the 2-level model.

2.2 Fractional Polynomial Transformation

Fractional polynomial transformation was developed by Royston and Altman [10]. In order to determine what the value of p, the exponent of x^p yields the best model for the covariate, Royston and Altman proposed replacing full maximum likelihood estimation of power by a search through a small but reasonable set of possible values. For a single continuous covariate, the transformation procedure is

$$f(x, \boldsymbol{\beta}) = \beta_0 + x\beta_1$$

Where $\boldsymbol{\beta}$ denotes the vector of model coefficients. One way to generalize this function is to specify it as

$$f(x, \boldsymbol{\beta}) = \beta_0 + \sum_{j=1}^{J} F_j(x)\beta_j$$

The functions $F_j(x)$ are a particular type of power function. The value of the first function is $F_1(x) = x^{p_1}$. The remaining functions are defined as

$$F_j(x) = \begin{cases} x^{p_j}, p_j \neq p_{j-1} \\ F_{j-1}(x)\ln(x), p_j = p_{j-1} \end{cases} \quad \text{for } j = 2,\ldots,J$$

The power can be any number, in most applied settings it is among those in the set P = {-2, -1, -0.5, 0, 0.5, 1, 2, 3}. The value $p_j = 0$ denotes the log of variable.

Implementation of the method requires, for J = 1, 8 models from $p_1 \in \mathrm{P}$ are fitted. The best model is the one with the largest log likelihood. For J = 2, 36 models form the distinct pairs of powers, $(p_1, p_2) \in \mathrm{P} \times \mathrm{P}$ are fitted. Again the best model is the one with the largest log likelihood.

The relevant question is whether either of the two best models is significantly better than the linear model. The partial likelihood ratio test is used to test it. For J = 1,

$$G(1,p_1) = -2\{L(1) - L(p_1)\}$$

Where L(1) denotes the log likelihood for the linear model and $L(p_1)$ denotes the log likelihood for the best J = 1 model. This partial likelihood test statistic is approximately distributed as χ^2 with 1 degree of freedom under the null hypothesis of linearity in x. For J = 2,

$$G(p_1,(p_1,p_2)) = -2\{L(p_1) - L(p_1,p_2)\}$$

Where $L(p_1,p_2)$ denotes the log likelihood for the best J = 2 model. This partial likelihood test statistic is approximately distributed as χ^2 with 2 degree of freedom under the null hypothesis that the second function is equal to zero.

2.3 Statistical Analysis

SAS PROC MIXED provides a very flexible environment in which to model many types of repeated measures data. It allows the growth parameters for each individual to be examined as random effects in the model. Individual-level covariates can be entered into the model as fixed effects to determine their impact on the dependent variable alone and in interaction with the growth parameters. The structure of the variance-covariance matrix of the repeated measurements can also be examined and entered into the model. In this study, proc mixed is used to build individual growth models on two set of predictors.

2.3.1 Individual Growth Models for Treatments and other variables

The variables interested are Years between date of treatment and date of exam (Time), Gender, Age group, SES classes, Treatments (surgery, radiation and chemotherapy). The patients are divided into two age groups according to the age of diagnosis at cutting point seven-year-old. Based on Surgery (0=No, 1=Yes), Chemotherapy (0=No, 1=Yes), Radiation (0=No, 1=Yes), Age group (0: age at diagnosis is less than 7 years old, 1: otherwise), Gender (1=Female, 0=Male), and SES class (1, 2, 3, 4, 5), 160 categories are defined.

Quadratic Time is considered as a potential predictor in the first two models in order to investigate the quadratic change in PPVT scores. In the first model, only single terms are analyzed. Table 2.1 shows the solution for fixed effects for the initial step of model building.

Table 2.1: Solution for Fixed Effects

Effect	Estimate	Standard Error	DF	Pr > |t|
Intercept	110.67	7.8946	45	<.0001
time	-3.3137	1.0105	32	0.0011
time_sq	0.2037	0.08930	25	0.0231
SES	-5.8808	1.3023	322	<.0001
agegr	8.1566	3.8134	322	0.0379
Surgery	-0.7040	5.1393	322	0.8917
NPS_Ch	-2.8210	3.6591	322	0.4448
NPS_Rad	-0.5594	4.2634	322	0.8962
Genderf	1.6664	3.1643	322	0.6010

Based on this initial model, backward variable selection is used to obtain the final model. All the variables in the final model are at 0.05 significant levels. Table 2.2

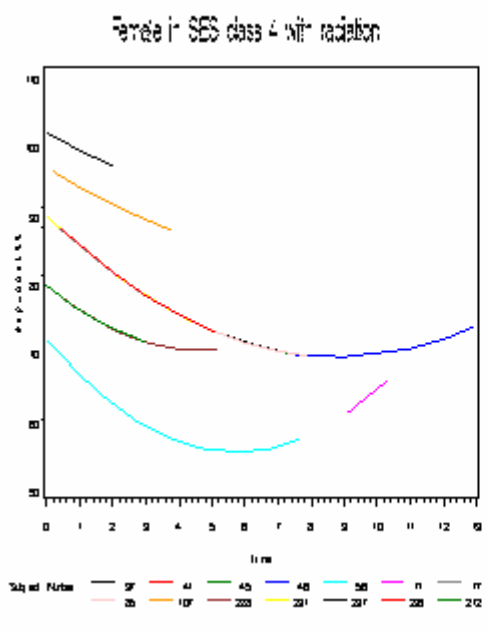
shows the solution for fixed effects of the final model. The variables, surgery, chemotherapy, radiation and gender are not included since they are not significant effects. Table 2.3 presents the random effects which is the variances of the intercept, linear slope and quadratic slope.

Table 2.2: Fixed effects for the model without interactions for treatments and other variables

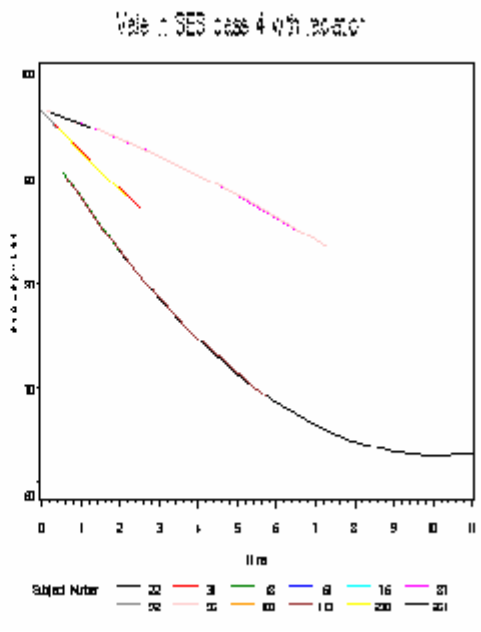
Effect	Estimate	Standard Error	DF	Pr > |t|
Intercept	108.67	4.2888	49	<.0001
time	-3.4005	0.9075	379	0.0002
time_sq	0.1995	0.07458	379	0.0078
SES	-5.6309	1.1189	49	<.0001
agegr	8.7254	3.6458	49	0.0206

Table 2.3: Random effects for the model without interactions for treatments and other variables

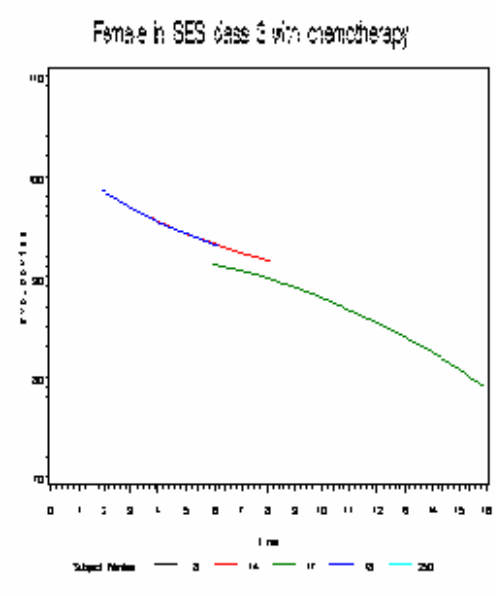
Cov Parm	Estimate	Standard Error	Z Value	Pr Z
UN(1,1)	126.26	38.5125	3.28	0.0005
UN(2,1)	4.0708	11.8356	0.34	0.7309
UN(2,2)	8.5480	6.6839	1.28	0.1005
UN(3,1)	-1.8365	0.9877	-1.86	0.0630
UN(3,2)	-0.5837	0.5927	-0.98	0.3247
UN(3,3)	0.05677	0.05445	1.04	0.1486



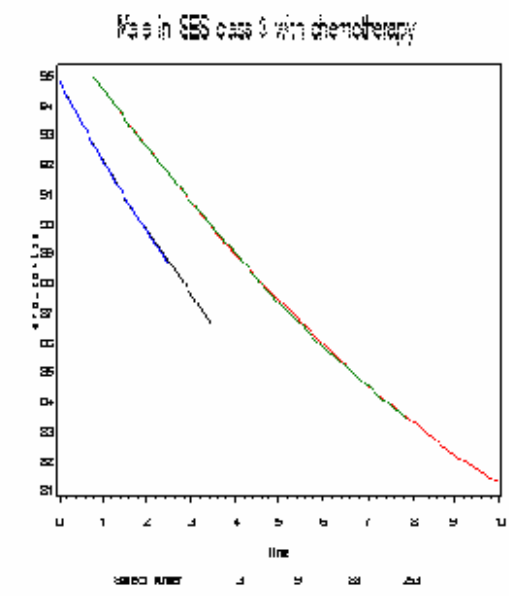
Female in SES class 4 with radiation



Male in SES Class 4 with radiation



Female in SES class 3 with chemotherapy



Male in SES class 3 with chemotherapy

Figure 2.1 Individual grow curves for some categories using model without interactions for treatments and other variables

The fitted lines of Figure 2.1 were obtained using this model for different categories which are female in SES class 4 with radiation, male in SES class 4 with radiation, female in SES class 3 with chemotherapy, and male in SES class 3 with chemotherapy.

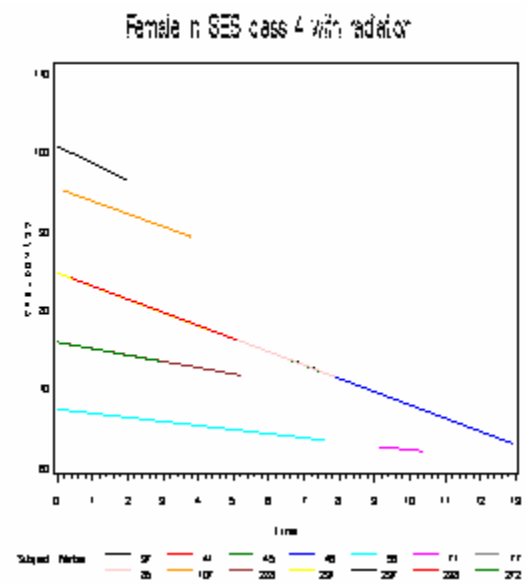
Interaction effects are an important consideration for any model and must be thoroughly explored to determine if there is a significant interaction that should be included in the model. Therefore, the interaction effects between variables are considered. Backward variable selection method was used to obtain the second model. The fixed effects of this model are showed in Table 2.4 and the variances of the intercepts and slopes are presented in Table 2.5. The fitted lines of Figure 2.2 were obtained using this model for different categories.

Table 2.4: Fixed effects for the model with interactions for treatments and other variables

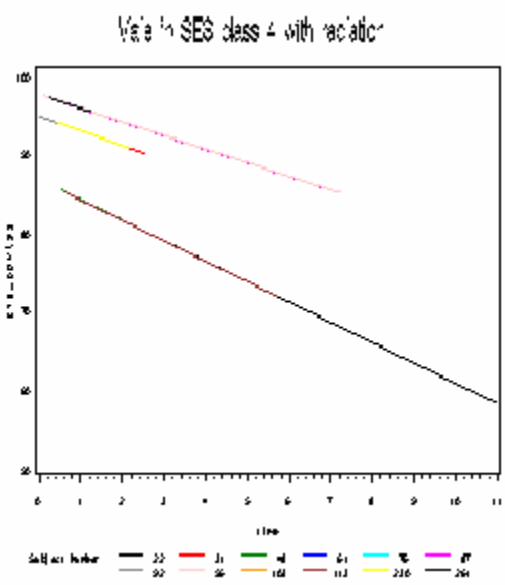
Effect	Estimate	Standard Error	DF	Pr > |t|
Intercept	114.46	5.9135	46	<.0001
SES	-5.5096	1.4460	46	0.0004
genderf	-2.4104	4.5038	46	0.5951
genderf*NPS_Ch	17.7229	7.3977	46	0.0207
time	-10.1627	2.2317	379	<.0001
time*NPS_Rad	8.6434	2.2625	379	0.0002
NPS_Ch	-13.2480	5.0315	46	0.0115
NPS_Rad	-0.8168	4.4896	46	0.8564

Table 2.5: Random effects for the model with interactions for treatments and other variables

Cov Parm	Estimate	Standard Error	Pr Z
UN(1,1)	168.49	46.6410	0.0002
UN(2,1)	-10.4186	5.5151	0.0589
UN(2,2)	1.3735	0.6981	0.0246



Female in SES class 4 with radiation



Male in SES class 4 with radiation

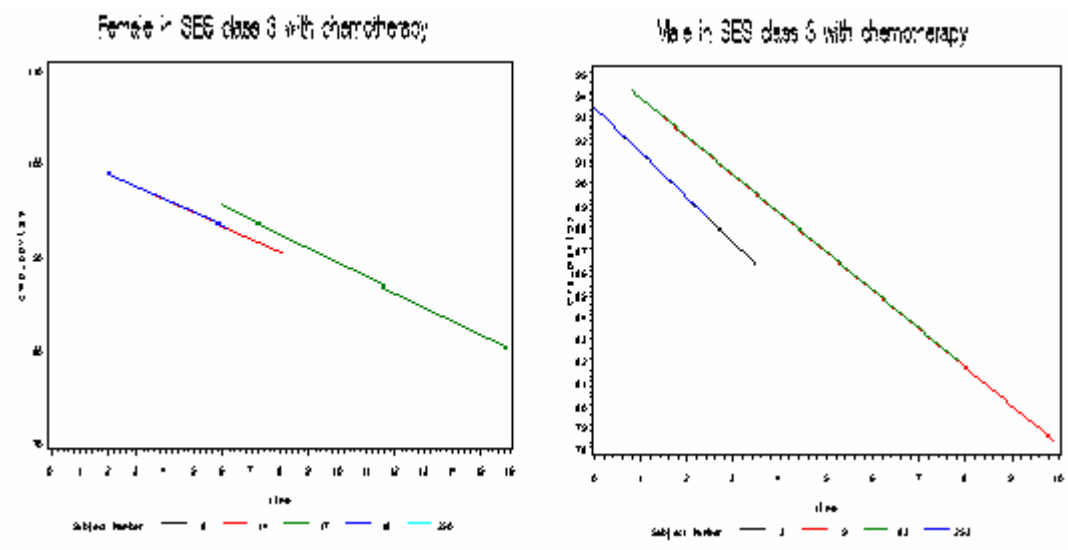


Figure 2.2 Individual grow curves for some categories using model with interactions for treatments and other variables

In the former two models, quadratic time was considered as a potential predictor. In the third model, fractional polynomial transformation was applied to continuous variables, SES, age at diagnosis, and time. For convenience, time was shifted two units before variable transformation. Table 2.6 shows the results of fractional polynomial transformation calculation.

Table 2.6: Results of fractional polynomial transformation for SES, Age at diagnosis, and Time

Variable	P1	P2
SES	-0.5	-1
Age at diagnosis	-0.5	0.5
Time	-2	-2

According to the results, the following transformations were applied before model building.

$$sestr1 = SES^{-0.5}$$
$$sestr2 = \frac{1}{SES}$$
$$timetr1 = (time + 2)^{-2}$$
$$timetr2 = timetr1 * \ln(time + 2)$$
$$agedxtr1 = (age_dx)^{-0.5}$$
$$agedxtr2 = \sqrt{age_dx}$$

After the variable transformation, every single variable was tested. Table 2.7 shows the results. Variable Surgery and Gender were not considered as potential predictors since their p-values were larger than 0.05.

Table 2.7: Results of testing the significance of variables

Effect	NumDF	DenDF	FValue	ProbF
sestr1	1	431	62.44301	2.31E-14
sestr2	1	431	55.3219	5.58E-13
agedxtr1	1	431	17.37366	3.71E-05
agedxtr2	1	431	39.77901	7.06E-10
genderf	1	431	1.405572	0.236446
timetr1	1	431	55.53379	5.07E-13
timetr2	1	431	60.94025	4.51E-14
NPS_Ch	1	431	18.50414	2.1E-05
NPS_Rad	1	431	23.96981	1.39E-06
Surgery	1	431	1.142278	0.28577

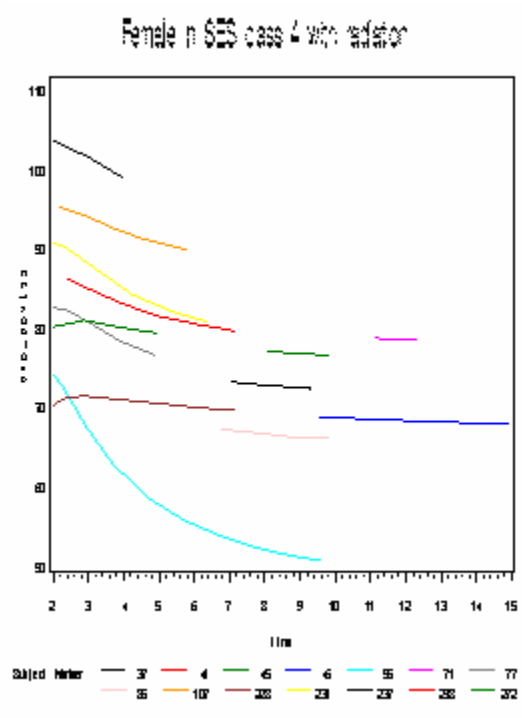
The fixed effects are showed in Table 2.8. Table 2.9 shows the random effects of the hierarchical model. The fitted lines of Figure 2.3 present individual growth curves for some categories.

Table 2.8: Fixed effects for the model with variable transformation for treatments and other variables

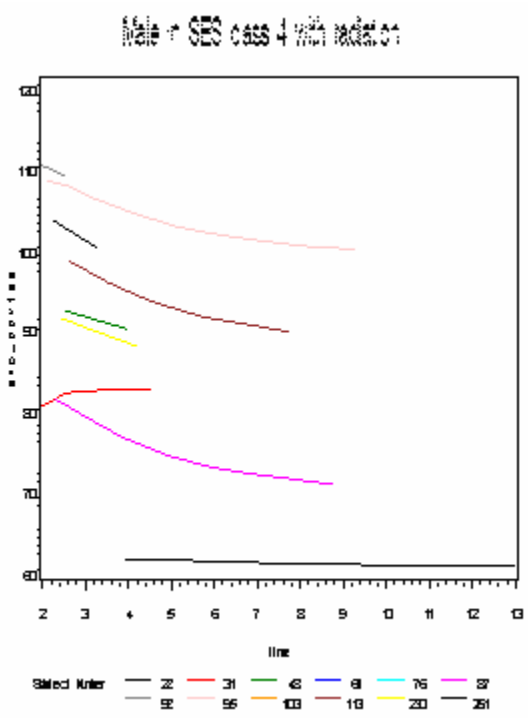
Effect	Estimate	Standard Error	DF	Pr > |t|
Intercept	83.9155	45.2855	88	0.0672
sestr1	-166.01	135.06	88	0.2223
sestr1*timetr1	-4025.36	1549.60	333	0.0098
sestr1*timetr2	7745.86	2576.42	333	0.0028
sestr2	144.94	94.9725	88	0.1306
timetr1*sestr2	2817.46	1067.15	333	0.0087
timetr2*sestr2	-5436.34	1775.24	333	0.0024
timetr1	1282.81	526.40	333	0.0153
timetr2	-2269.15	878.04	333	0.0102
agedxtr2	6.4448	2.0919	88	0.0028
timetr2*NPS_Rad	-161.59	80.1186	333	0.0445
NPS_Rad	25.3565	13.5932	88	0.0655

Table 2.9: Random effects for the model with variable transformation for treatments and other variables

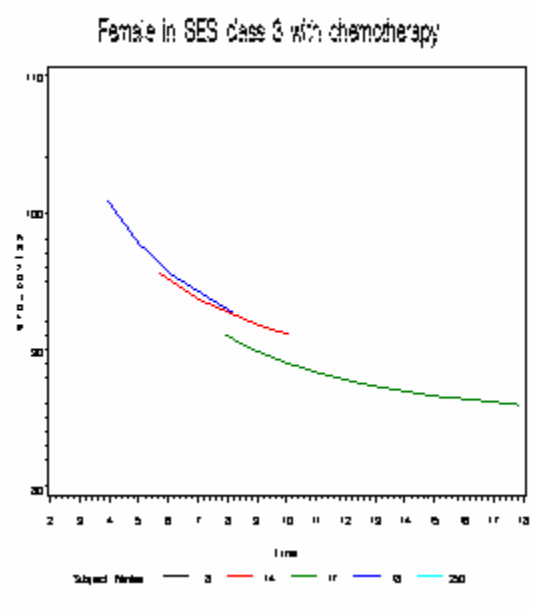
Cov Parm	Estimate	Standard Error	Pr Z
Intercept	167.41	36.8730	<.0001
timetr1	148.31	1444.61	0.4591
timetr2	4226.77	3544.09	0.1165



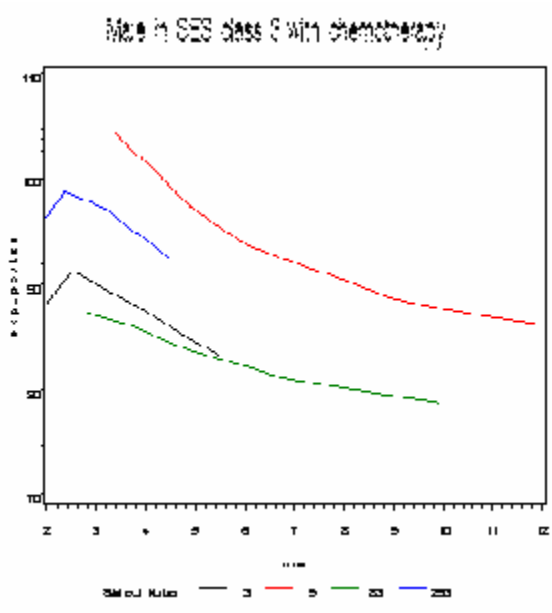
Female in SES class 4 with radiation



Male in SES class 4 with radiation



Female in SES class 3 with chemotherapy

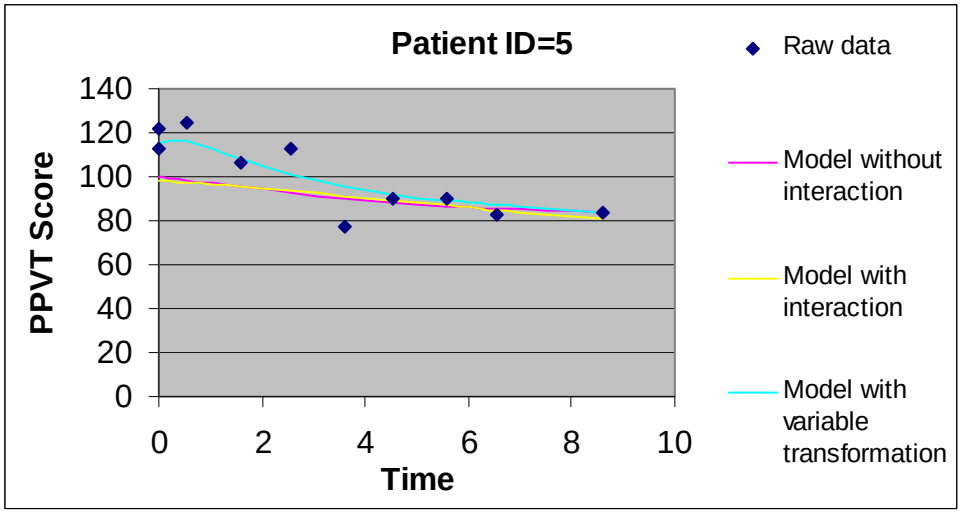


Male in SES class 3 with chemotherapy

Figure 2.3 Individual grow curves for some categories using model with variable transformation for treatments and other variables

The individual growth curves can be obtained based on these models for comparison.

Figure 2.4 are individual growth curves for two patients.



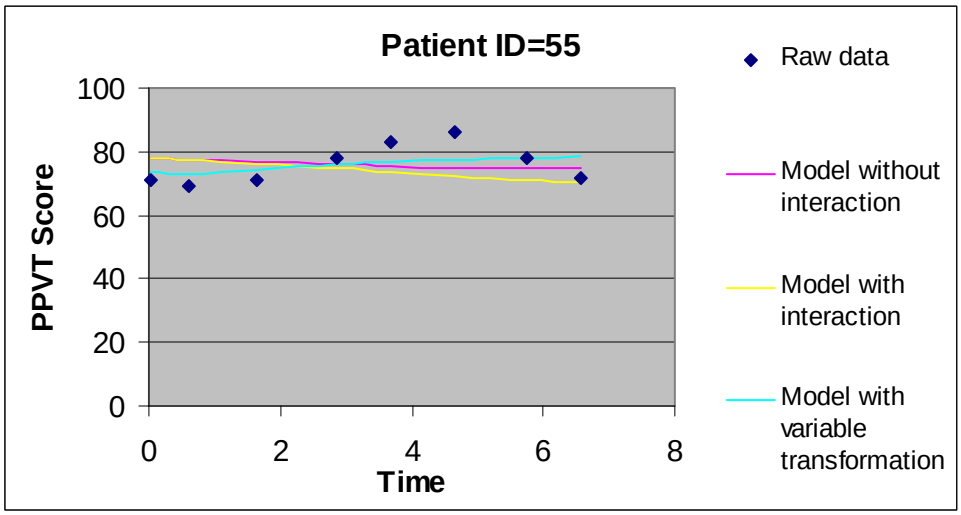


Figure 2.4: Individual growth curves for treatments and other variables

2.3.2 Individual Growth Models for Neurological Predictor Scale and other variables

The variables interested are Years between date of treatment and date of exam (Time), Gender, Age group, SES classes, and Neurological Predictor Scale (NPS_total). The patients are divided into two age groups according to the age of diagnosis at cutting point seven-year-old. Based on Age group (0: age at diagnosis is less than 7 years old, 1: otherwise), Gender (1=Female, 0=Male), and SES class (1, 2, 3, 4, 5), 20 categories are defined.

Quadratic Time is considered as a potential predictor in the first two models in order to investigate the quadratic change in PPVT scores.

In the first model, only single terms are considered. The solution for fixed effects is presented in Table 2.10. The variables, quadratic time and gender, are not included since they don't have significant effects on patients' PPVT scores. Table 2.11 shows the random effects which are the variances of the intercept and linear slope.

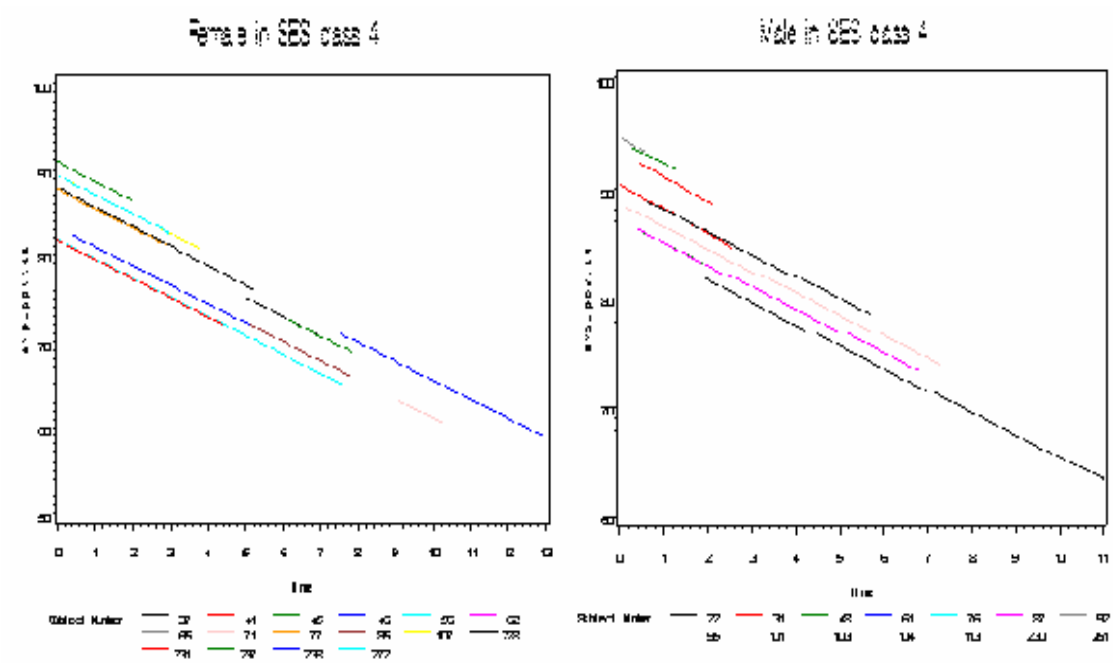
Table 2.10: Fixed effects for the model without interaction effects for Neurological Predictor Scale and other variables

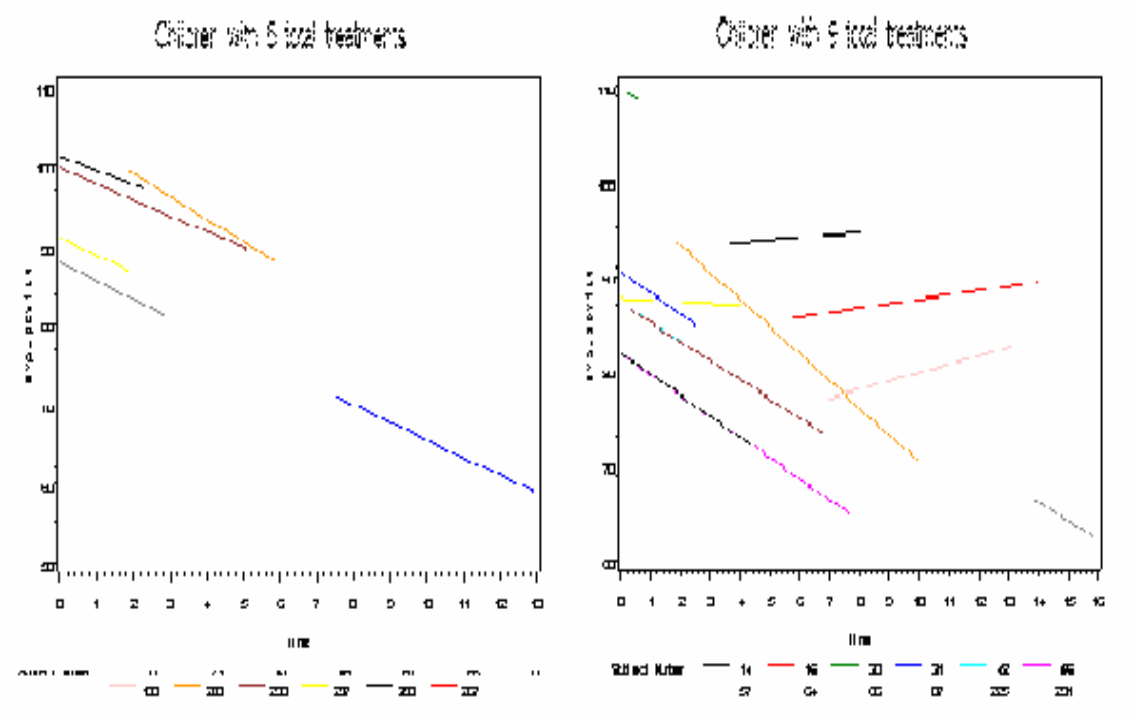
Effect	Estimate	Standard Error	DF	Pr > |t|
Intercept	118.66	4.4628	16	<.0001
SES	-6.0842	1.0476	16	<.0001
agegr	6.9888	2.6796	16	0.0190
time	-1.7021	0.6394	412	0.0081
NPS_total	-1.4556	0.4969	412	0.0036

Table 2.11: Random effects for the model without interaction effects for Neurological Predictor Scale and other variables

Cov Parm	Estimate	Standard Error	Pr Z
UN(1,1)	22.1920	15.8987	0.0814
UN(2,1)	-4.6762	5.1549	0.3643
UN(2,2)	3.9081	2.5472	0.0625

The fitted lines of Figure 2.5 were obtained using this model for different categories which are female in ses class 4, male in ses class 4, children with 5 NPS_total, and children with 9 NPS_total.





Children with 5 NPS_total Children with 9 NPS_total

Figure 2.5 Individual grow curves for some categories using model without interactions for Neurological Predictor Scale and other variables

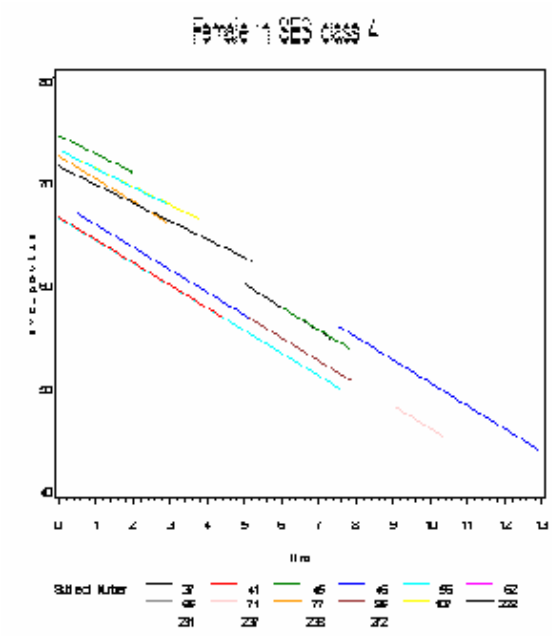
In the second model, the interactions between variables are considered to investigate the change in patients' PPVT. Table 2.12 shows the solution for fixed effects of this model and Table 2.13 shows the random effects. The fitted lines of Figure 2.6 were obtained using this model for different categories.

Table 2.12: Fixed effects for the model with interaction effects for Neurological Predictor Scale and other variables

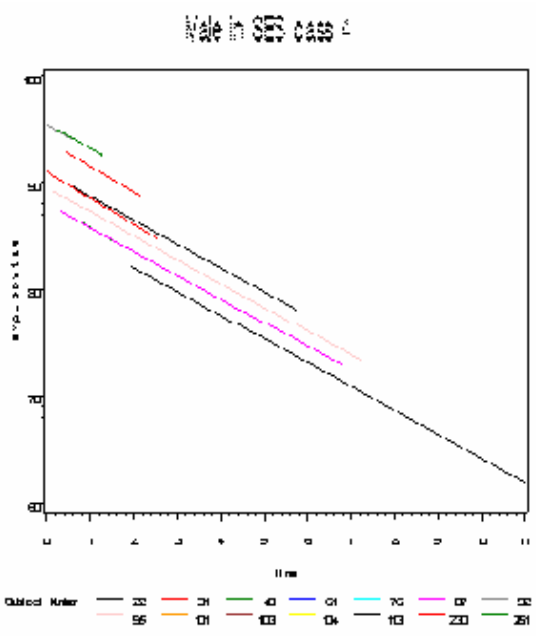
Effect	Estimate	Standard Error	DF	Pr > |t|
Intercept	113.08	4.8967	14	<.0001
SES	-4.1534	1.2509	14	0.0051
SES*genderf	-4.4570	2.0187	14	0.0444
agegr	5.4483	2.5270	14	0.0490
genderf	15.2616	6.6654	14	0.0381
time	-1.7203	0.6244	412	0.0061
NPS_total	-1.4828	0.4973	412	0.0030

Table 2.13: Random effects for the model with interaction effects for Neurological Predictor Scale and other variables

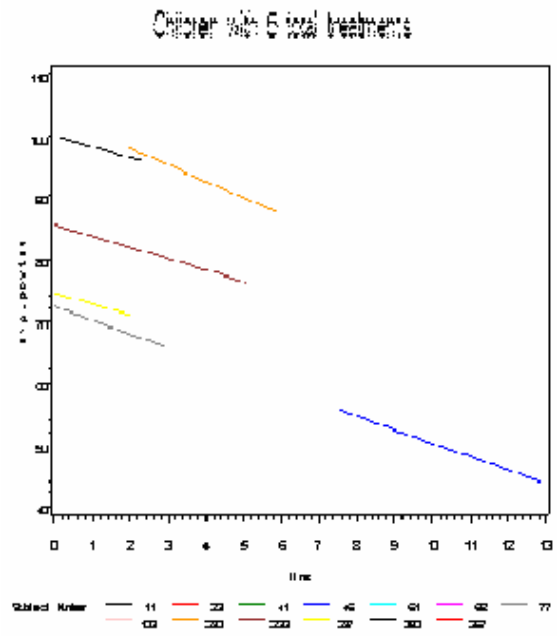
Cov Parm	Estimate	Standard Error	Pr Z
UN(1,1)	29.8876	21.1802	0.0791
UN(2,1)	-8.3105	6.4492	0.1975
UN(2,2)	3.8318	2.5418	0.0658



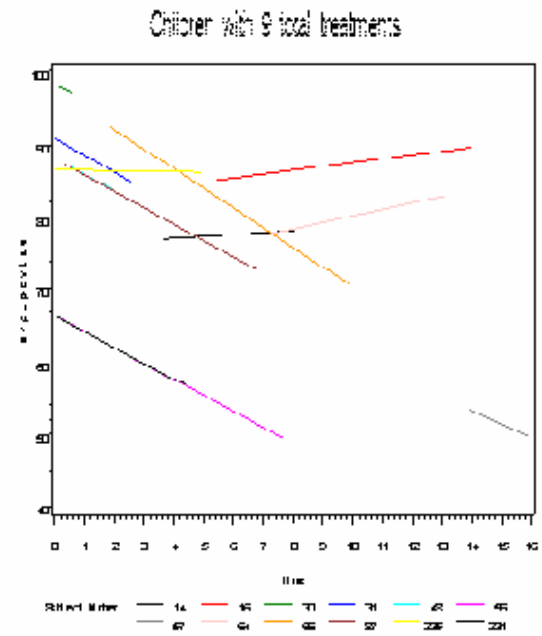
Female in SES class 4



Male in SES class 4



Children with 5 NPS_total



Children with 9 NPS_total

Figure 2.6 Individual grow curves for some categories using model with interactions for Neurological Predictor Scale and other variables

In the third model, quadratic time is not considered as a potential predictor. The fractional polynomial transformation is applied to determine the powers for continuous variables like SES, age at diagnosis, time and Neurological Predictor Scale (NPS_total). The following transformations were applied for these variables.

$$sestr1 = \frac{1}{\sqrt{SES}}$$

$$sestr2 = \frac{1}{SES}$$

$$timetr1 = \frac{1}{(time+2)^2}$$

$$timetr2 = timetr1 * \ln(time+2)$$

$$agedxtr1 = \frac{1}{\sqrt{age_dx}}$$

$$agedxtr2 = \sqrt{age_dx}$$

$$totaltr1 = \frac{1}{NPS_total^2}$$

$$totaltr2 = \frac{1}{NPS_total}$$

The results of test for significance of the variables are showed in Table 2.14. Variable Surgery and Gender are not considered as potential predictors since their p-values are larger than 0.05.

Table 2.14: Results of testing the significance of Neurological Predictor Scale

Effect	NumDF	DenDF	FValue	ProbF
sestr1	1	431	62.44301	2.31E-14
sestr2	1	431	55.3219	5.58E-13
agedxtr1	1	431	17.37366	3.71E-05
agedxtr2	1	431	39.77901	7.06E-10
genderf	1	431	1.405572	0.236446
timetr1	1	431	55.53379	5.07E-13
timetr2	1	431	60.94025	4.51E-14
NPS_Ch	1	431	18.50414	2.1E-05
NPS_Rad	1	431	23.96981	1.39E-06
Surgery	1	431	1.142278	0.28577
totaltr1	1	431	4.268787	0.039416
totaltr2	1	431	16.51335	5.74E-05

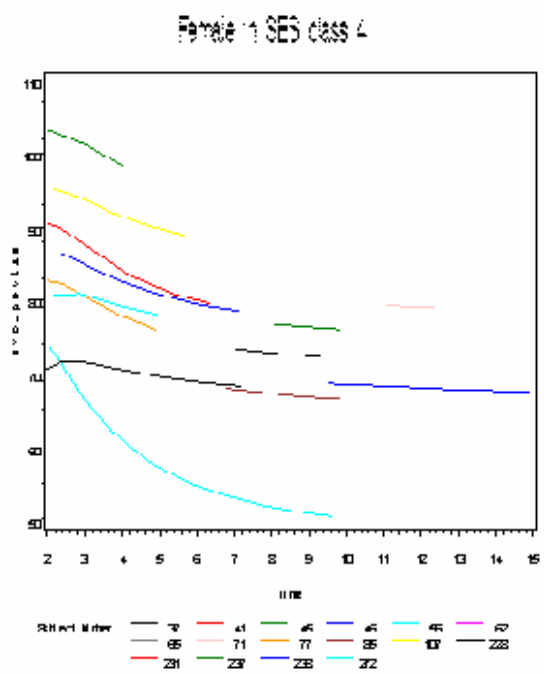
The potential predictors, sestr1, sestr2, agedxtr1, agedxtr2, timetr1, timetr2, nps_ch, nps_rad, totaltr1, totaltr2 and their interactions are analyzed to build the model using PROC MIXED. Table 2.15 shows the fixed effects and Table 2.16 shows the random effects. The fitted lines in Figure 2.7 were obtained using this model.

Table 2.15: Fixed effects for the model with variable transformation for Neurological Predictor Scale and other variables

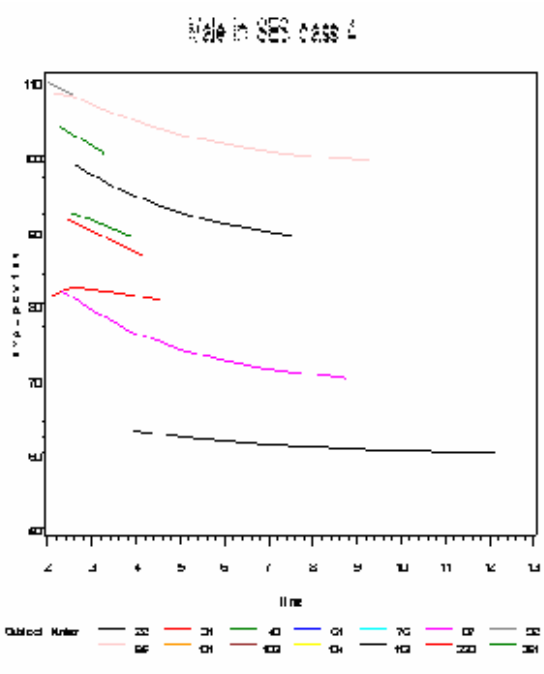
Effect	Estimate	Standard Error	DF	Pr > |t|
Intercept	75.3855	47.5474	84	0.1166
sestr1	-121.20	130.09	84	0.3542
sestr1*timetr1	-4139.79	1542.20	334	0.0076
sestr1*timetr2	7973.02	2543.21	334	0.0019
sestr2	72.1730	93.5447	84	0.4426
sestr2*agedxtr2	18.5059	8.4949	84	0.0322
timetr1*sestr2	2923.85	1061.65	334	0.0062
timetr2*sestr2	-5695.32	1753.11	334	0.0013
agedxtr1	32.6504	14.8082	84	0.0302
agedxtr1*totaltr1	-1044.50	435.01	84	0.0186
agedxtr2	-0.2725	6.0928	84	0.9644
timetr1	1308.22	524.23	334	0.0131
timetr2	-2456.94	864.85	334	0.0048
totaltr1	153.06	261.13	84	0.5593
totaltr2	164.61	83.9317	84	0.0532

Table 2.16: Random effects for the model with variable transformation for Neurological Predictor Scale and other variables

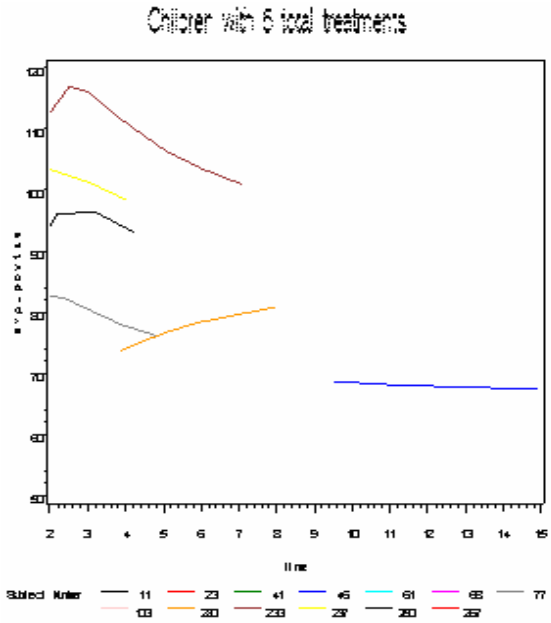
Cov Parm	Estimate	Standard Error	Pr Z
Intercept	154.92	33.0145	<.0001
timetr1	378.44	1300.80	0.3856
timetr2	2715.01	3056.25	0.1872



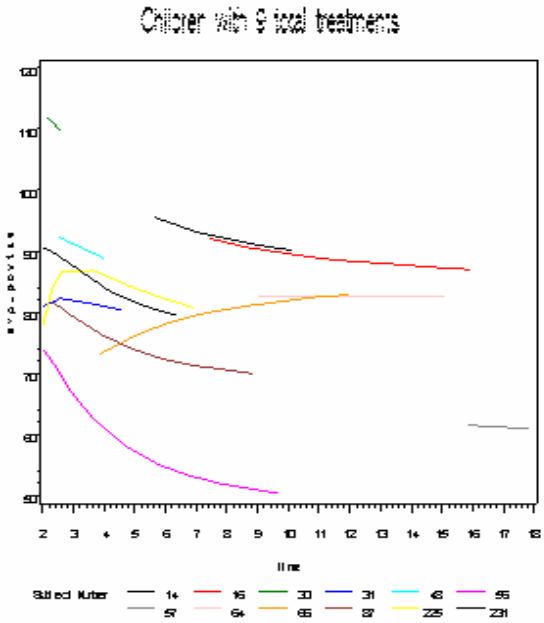
Female in SES class 4



Male in SES class 4



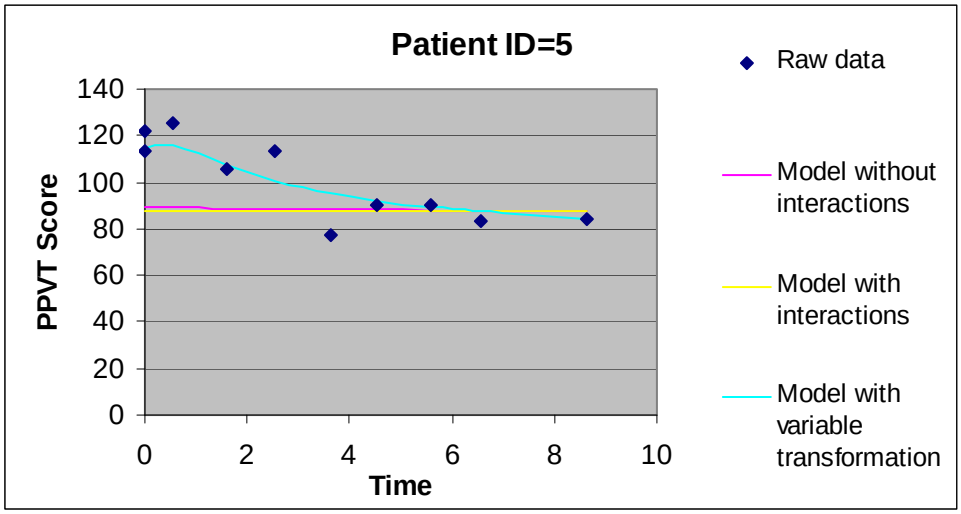
Children with 5 NPS_total



Children with 9 NPS_total

Figure 2.7 Individual grow curves for some categories using model with variable transformation for Neurological Predictor Scale and other variables

The individual growth curves can be obtained based on these models. Figure 2.8 are individual growth curves for two patients.



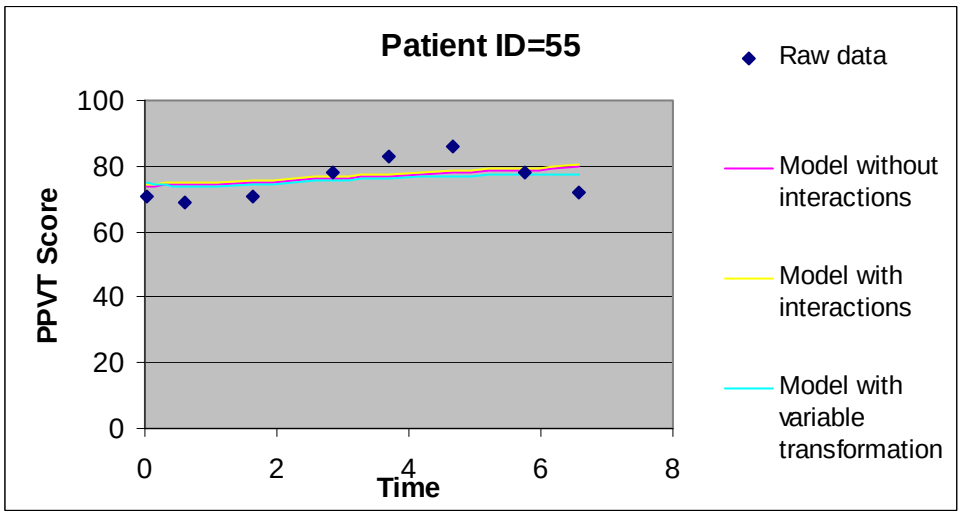


Figure 2.8: Individual growth curves for Neurological Predictor Scale and other variables

Chapter Three: Results and Discussion

In this chapter, the six individual growth models presented in previous chapter are discussed respectively and compared with each other.

3.1 Models for treatments and other variables

3.1.1 Model without interactions

Table 2.1 and Table 2.2 present the results of fitting this model. There is a significant mean PPVT difference due to ses class and age group. The average PPVT score at origin time is 103.1 for ses class1 and age less than 7 years old and is 111.8 for ses class 1 and age not less than 7 years old. For the same age group, the score decreases 5.6 as ses class increases one level. The coefficients of time and quadratic time indicate that the mean value decreases at 3.4 per year but the rate is slightly slow down (0.2 per quadratic year).

The estimated variance of intercepts and slopes is 126.26 (p=0.0005), 8.54 (p=0.1006) and 0.06 (p=0.1486) respectively. The significant intercept variance means that individuals vary in the level of PPVT score; the non-significant slope variances indicate that they don't vary very much in rate and direction of change in PPVT score.

3.1.2 Model with interactions

The results of fitting this model are presented in Table 2.4 and Table 2.5. There is a significant interaction between gender and chemotherapy for mean PPVT difference. With other factors being equal, female with chemotherapy patients have

higher average PPVT score than that of male by 17.7. The main effects of radiation (p=0.8564) and gender (p=0.5961) are non-significant. The average PPVT score decreases while ses class increases one level with other factors unchanged. The PPVT will decrease significantly if chemotherapy is given. There is a significant difference in the rate of PPVT change across time where patients with radiation have a little bit higher score than the baseline mean PPVT. However, the rate of increase across time in PPVT score (10.2 per year) is driving it going down. The surgery and age at diagnosis are no longer significant effects in this model.

The estimated variance of intercept and slope is 168.49 (p=0.0002) and 1.3735 (p=0.0246) respectively. The significant intercept variance means that individuals vary in the level of PPVT score; the significant slope variance indicates that they vary in rate and direction of change in PPVT score.

3.1.3 Model with variable transformation

Compared with the other two models, this model is complicated. Table 2.8 and Table 2.9 present the results of fixed effects and random effects. The rate of increase across time in PPVT score is non-linear. Table 3.1 presents some fit statistics of these three models.

Table 3.1: Comparison of models for treatments and other variables

Statistic	Model without interactions	Model with interactions	Model with variable transformation
-2 Res Log Likelihood	3539.9	3512.0	3157.9
AIC(the smaller the better)	3553.9	3520.0	3165.9
AICC(the smaller the better)	3554.2	3520.1	3166.0
BIC(the smaller the better)	3567.6	3527.8	3176.1

3.2 Models for Neurological Predictor Scale and other variables

3.2.1 Model without interactions

Table 2.10 and Table 2.11 present the results of fitting this model. There is a significant mean PPVT difference due to ses class, age group and Neurological Predictor Scale. The average PPVT score at origin time is 112.5 for ses class1, age less than 7 years old and no treatments and is 119.5 for ses class 1, age not less than 7 years old and no treatment. For the same age group with no treatment, the mean score decreases 6.1 as ses class increases one level. The higher level of total Neurological Predictor Scale has lower mean PPVT. The rate of increase in PPVT is driving the mean value decreasing at 1.7 point per year.

The estimated variance of intercept and slope is 22.1920 (p=0.0814) and 3.9081 (p=0.0625) respectively. The non-significant intercept variance means that individuals vary not much in the level of PPVT score; the significant slope variance indicates that they vary in rate and direction of change in PPVT score.

3.2.2 Model with interactions

Table 2.12 and Table 2.13 show the results of fitting this model. There is a significant interaction between gender and ses class for mean PPVT difference. With other factors being equal, female in ses class 1 patients have lower average PPVT score than that of male by 4.5. There is significance due to the main effects of the total number of treatment (p=0.003) where the average PPVT for subjects without treatment is 113.1 and is 111.6 for patients taking only 1 treatment with other factors being equal. The average PPVT score decreases while ses class increases one level with other factors unchanged. The mean PPVT will increase significantly if age at diagnosis increases. The rate of increase across time in PPVT score (1.7 point per year) is driving it going down.

The estimated variance of intercept and slope is 29.89 (p=0.08) and 3.8 (p=0.07) respectively. The non-significant intercept variance means that individuals vary not much in the level of PPVT score; the non-significant slope variance indicates that they vary not significantly in rate and direction of change in PPVT score.

3.2.3 Model with variable transformation

Table 2.15 and Table 2.16 present the results of fixed effects and random effects for this model. The rate of increase across time in mean PPVT score is non-linear. The variables ses class, age at diagnosis and Neurological Predictor Scale have complicated significant effects of change in PPVT. However, gender is no longer a significant effect in this model. Table 3.2 presents some fit statistics of these three models.

Table 3.2: Comparison of models for Neurological Predictor Scale and other variables

Statistic	Model without interactions	Model with interactions	Model with variable transformation
-2 Res Log Likelihood	3537.2	3523.6	3114.3
AIC(the smaller the better)	3545.2	3531.6	3122.3
AICC(the smaller the better)	3545.3	3531.7	3122.4
BIC(the smaller the better)	3553.0	3539.4	3132.5

Chapter Four: Conclusion and Future Research

It has been shown in the literature on the developmental late-effects of radiation therapy that the increased survival rate is associated with the risk of suboptimal behavior, emotional, and cogitative outcomes [4, 11].

In this study, the analyses using individual growth models show a linear decline in average PPVT score over time. The quadratic rate, however, is not clear for this data set. Different treatment shows different effect on the change in PPVT. In this study, surgery shows the least effect, the chemotherapy tends to let the average PPVT score go down, and radiation therapy tends to accelerate the change rate. The average score decreases as Neurological Predictor Scale increases. The age at diagnosis also affects the score. The patients at diagnostic age older than 7 years old tend to have higher score than that of people at age less than 7 years old.

The individual growth model in modeling longitudinal change has been applied to many research fields. This study highlights the usefulness of this method in modeling change in children's learning and memory variables.

Since only 45 patients (about 40% of the sample) have more than 2 measurements, a larger sample size is needed for more sophisticated statistical analyses and greater statistical power. For example, the quadratic rate of change may be addressed and more accurate trajectories of the scores can be studied.

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[12] SAS Institute, Inc., SAS/STAT User's Guide, The SAS System Version 9.

[13] SAS Institute, Inc., SAS/Insight User's Guide, The SAS System Version 8.

Appendix A: SAS Code

```
Libname A 'C:\Documents and Settings\yinshen\My Documents\Thesis\DX';
/* Merge BTPPVT_NPS_TREATMENT and yusheng_tmt_PPVT_test.xls to
generate the total study cohort */

proc import datafile='C:\Documents and Settings\yinshen\My
Documents\Thesis\DX\yusheng_tmt_PPVT_test.xls' out=test dbms=excel
replace;run;

proc sort data=a.btppvt_nps_treatment out=treatment; by idnum;run;
proc sort data=test(rename=(id_number=idnum)) out=test; by idnum;run;

data character;
        set test;
            if idnum;
        age_dx=yrdif(DOB, Date_of_Dx_, 'ACT/ACT');run;

data a.total;
        merge treatment character;
        by idnum;
            if idnum;
        if NPS_Rad=2 or NPS_Rad=3 then NPS_Rad=1;
            time=yrdif(Date_of_Dx_, dateppvt,'ACT/ACT');
run;
data a.cohort;
set a.total(keep=idnum dob dateppvt ppvtss ses gender Date_of_Dx_
surgery nps_rad nps_ch nps_total age_dx time);
genderf=0; if gender='F' then genderf=1;
sur='w/o';if surgery=1 then sur='W';
ch='w/o';if nps_ch=1 then ch='W';
rad='w/o';if nps_rad=1 then rad='W';
time2=time+2;
time_sq=time**2;
if ses=. then delete;
if ppvtss=. then delete;
if age_dx<0 then delete; *id=226;
p1=-2;p2=-1;p3=-0.5;p4=0;p5=0.5;p6=1;p7=2;p8=3;
run;

proc export data=a.cohort
     outfile='C:\Documents and Settings\yinshen\My
Documents\Thesis\DX\BZ1024.xls'
     dbms=excel
     replace;
run;

/****Profile Plots****/
goption reset=all;
symbol interpol=join  repeat=300  ;
proc gplot data=a.cohort;
     plot ppvtss* time=idnum;
     run;quit;
```

```
/****Fractional Polynomial Transformation****/
*ods trace on/listing label;
ods trace off;

%macro fractional(res, var);
data out1factor out2factor;
        if 1=1 then delete;
            run;
%do n=1 %to 8;
data sample&n;
       set a.cohort;
       if p&n=0 then u1=log(&var);else u1=&var**p&n;
       run;

ods output  Mixed.FitStatistics=out&n;
proc mixed data=sample&n;
       class genderf NPS_Rad NPS_Ch surgery;
         model &res=u1;
         run;

data out&n;
            merge out&n(obs=1)  a.cohort(obs=1);
            f1=p&n;D=Value;
            keep f1 D;
            run;
data out1factor;
        set out1factor out&n;
            run;
%do m=1 %to 8;
data sample&n&m;
       set a.cohort;
       if p&n=0 then u1=log(&var);else u1=&var**p&n;
       if p&m=p&n then u2=log(&var)*u1;else if p&m=0 then
u2=log(&var);else u2=&var**p&m;
         run;

ods output  Mixed.FitStatistics=out&n&m;
proc mixed data=sample&n&m ;
     class genderf NPS_Rad NPS_Ch surgery;
        model &res=u1 u2;
       run;
data out&n&m;
            merge out&n&m(obs=1)  a.cohort(obs=1);
            f1=p&n;f2=p&m;D=Value;
            keep f1 f2 D;
            run;
data out2factor;
        set out2factor out&n&m;
            run;
%end;
%end;

proc iml;
        use out1factor;
            read all var{f1 D} into model1;
```

```
            close out1factor;
            L1=model1[1,2]; P1=model1[1,1];
            nrow1=nrow(model1);
            do i=2 to nrow1;
                if model1[i,1]=1 then L=model1[i,2];
                  if model1[i,2]<L1 then do;
               L1=model1[i,2];P1=model1[i,1];
                  end;
            end;
            use out2factor;
            read all var{f1 f2  D} into model2;
            close out2factor;
            L2=model2[1,3]; P21=model2[1,1];P22=model2[1,2];
            nrow2=nrow(model2);
            do i=2 to nrow2;
                if model2[i,3]<L2 then do;
               L2=model2[i,3];P21=model2[i,1];P22=model2[i,2];
                  end;
            end;

            if L-L1>3.84 then do; /*chi-sq(.95,1)=3.84; chi-
sq(.95,2)=5.99; chi-sq(.95,3)=7.81;*/
               if L1-L2>5.99 then print 'the best is model2 with
power' P21  'and' P22;
               else print 'the best is model1 with power' P1;
            end;
            else do;
           if L-L2>7.81 then print 'the best is model2 with power' P21
'and' P22;
               else print 'the best is linear model' ;
            end;
            quit;
%mend fractional;
%fractional (ppvtss, time);
*%fractional (ppvtss, time2);
%fractional (ppvtss, ses);
%fractional (ppvtss, age_dx);
%fractional (ppvtss, nps_total);
data three;
        set a.cohort;
            sestr1=ses**(-0.5);sestr2=ses**(-1);
      /* timetr1=time2**(-0.5);timetr2=time2**(-1); */
            agedxtr1=age_dx**(-0.5);agedxtr2=age_dx**(0.5);
            totaltr1=NPS_Total**(-2);totaltr2=NPS_Total**(-1);
            run;

*Variable:  SES Age_dx genderf time time_sq NPS_Ch NPS_Rad Surgery;
*GROUP patients by Nps-Rad Nps_Ch Surgery Genderf Ses agegr, typically
sub=160;
data one;
   set a.cohort;
   if ses=. then delete;
   if ppvtss=. then delete;
   if age_dx gt 7 then agegr=1; else agegr=0;
   if Nps_Rad=0 then sub=1;else sub=2;
```

```
   if Nps_Ch=1 then sub=sub+2;
   if Surgery=1 then sub=sub+4;
   if genderf=1 then sub=sub+8;
   do i=1 to 5;
        if ses=i then sub=sub+16*(i-1);
   end;
   if agegr=1 then sub=sub+80;
run;
proc sort data=one out=two;by sub;run;

*model without interactions;

proc mixed data=two covtest;
   class idnum sub sur gender ch rad;
   model ppvtss=time time_sq ses agegr gender sur rad ch/s;
run;
proc mixed data=two covtest;
   class idnum sub sur gender ch rad;
   model ppvtss=time ses agegr ch/s;
run;

proc mixed data=two covtest;
   class idnum sub sur gender ch rad;
   model ppvtss=time ses agegr ch/s;
   random intercept time/s  sub=sub  type=un;
run;
*ods trace on;
ods trace off;
ods output  Mixed.SolutionR=mixs;
ods output  Mixed.SolutionF=fixs;
proc mixed data=two covtest;
   class idnum sub sur gender ch rad;
   model ppvtss=time ses ch/s;
   random intercept time/s  sub=sub  type=un;
run;

proc transpose data=mixs out=mix;
     by sub;
       var estimate;
       id effect;
       run;

data fixs;
set fixs;
if estimate=0 then delete;
run;
proc transpose data=fixs out=fix;
     var estimate;
       id effect;
       run;

data fix;
     set fix(drop=_name_ rename=(intercept=fint time=ft ses=fses
ch=fch));
     do i=1 to 433;
```

```
     output;
     end;
     drop i;
     run;
data test1;
     merge two fix;
       run;

data test2;
     merge test1 mix(drop=_name_ rename=(intercept=rint time=rt ));
     by sub;
       run;

data test3;
     set test2;
       exp_ppvtss=(fint+rint)+(ft+rt)*time+fses*ses+fch*nps_ch;
       run;

data m11;
     set test3(rename=(exp_ppvtss=exp_ppvtss1));run;

data ses1 ses2 ses3 ses4 ses5;
     set test3;
       if ses=1 then output ses1;
       else if ses=2 then output ses2;
       else if ses=3 then output ses3;
       else if ses=4 then output ses4;
       else output ses5;
       run;

data ses4radf ses4radm;
     set ses4;
       if Nps_Rad=1 & genderf=1 then output ses4radf;
       if Nps_Rad=1 & genderf=0 then output ses4radm;
       run;
data ses3chf ses3chm;
     set ses3;
       if Nps_ch=1 & genderf=1 then output ses3chf;
       if Nps_ch=1 & genderf=0 then output ses3chm;
       run;

goption reset=all ;
symbol interpol=join  repeat=300  ;
axis1 label = (a=90 );

proc gplot data=ses4radf;
     title 'Female in SES class 4 with radiation';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=ses4radm;
     title 'Male in SES class 4 with radiation';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=ses3chf;
     title 'Female in SES class 3 with chemotherapy';
```

```
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=ses3chm;
     title 'Male in SES class 3 with chemotherapy';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;


proc gplot data=ses4;
     plot (exp_ppvtss ppvtss)*time=idnum/vaxis = axis1;
     run;quit;

*model with interactions;
%macro mix_inter(res, var1, var2, var3, var4, var5, var6, var7, var8);
      proc mixed data=two;
            class idnum sub sur ch rad gender;
            %let reg=;
            %let item=;
            %do i=1 %to 7;
                %let it=&&var&i;
                %do j=&i+1 %to 8;
                    %let item=&item &&var&i*&&var&j;
                %end;
                %let reg=&reg &it &item;
                %let item=;
                %if &i=7 %then %let reg=&reg &var8;
             %end;
             model &res=&reg ;
             run;
%mend mix_inter;
%mix_inter(ppvtss, ses, agegr, gender, time, time_sq, Ch, Rad, sur );

proc mixed data=two covtest;
class idnum sub sur ch rad gender;
model ppvtss=SES  SES*Gender SES*time  SES*time_sq  SES*sur agegr
agegr*time_sq   agegr*ch
             agegr*rad  agegr*sur  Gender  time*Gender time_sq*Gender
ch*Gender rad*Gender
             sur*Gender  time  time*time_sq   time*rad   time_sq
time_sq*rad  ch  ch*rad
             sur*ch   rad     sur*rad   sur   ;
run;
proc mixed data=two covtest;
class idnum sub sur ch rad gender;
model ppvtss=SES  SES*Gender agegr
             agegr*rad  agegr*sur  Gender  time*Gender ch*Gender
rad*Gender
             time  time*rad   time_sq  time_sq*rad  ch
             sur*ch   rad sur   ;
run;

proc mixed data=two covtest;
class idnum sub sur ch rad gender;
model ppvtss=SES  SES*Gender agegr
```

```
             agegr*rad  agegr*sur  Gender  time*Gender ch*Gender
rad*Gender
             time  time*rad   time_sq  time_sq*rad  ch
             sur*ch   rad sur   /s;
random intercept time time_sq/s type=un sub=idnum;
run;

ods output  Mixed.SolutionR=mixs;
ods output  Mixed.SolutionF=fixs;
proc mixed data=two covtest;
class idnum sub sur ch rad gender;
model ppvtss=SES Gender  time*Gender ch*Gender rad*Gender
             time  time*rad   time_sq  time_sq*rad rad ch /s;
random intercept time time_sq/s type=un sub=idnum;
run;

proc transpose data=mixs out=mix;
     by idnum;
       var estimate;
       id effect;
       run;

data fixs;
set fixs;
if estimate=0 then delete;
if effect='time*Gender' and gender='F' then effect='timef';
if effect='time*Gender' and gender='M' then effect='timem';
if effect='ch*Gender' and gender='F' then effect='chf';
if effect='ch*Gender' and gender='M' then effect='chm';
if effect='rad*Gender' and gender='F' then effect='radf';
if effect='rad*Gender' and gender='M' then effect='radm';
run;
proc transpose data=fixs out=fix;
     var estimate;
       id effect;
       run;
data fix;
     set fix(drop=_name_ rename=(intercept=fint ses=fses gender=fgen
timef=ftimef
           timem=ftimem chf=fchf chm=fchm radf=fradf radm=fradm
time_rad=ftimerad
             time_sq=ftimesq time_sq_rad=ftimesqrad));

     do i=1 to 433;
     output;
     end;
     drop i;
     run;
data test1;
     merge two fix;
       run;
proc sort data=test1;
by idnum;
run;
data test2;
```

```
     merge test1 mix(drop=_name_ rename=(intercept=rint time=rt
time_sq=rtsq));
     by idnum;
       run;

data test3;
     set test2;
       if gender='F' then

exp_ppvtss=(fint+rint)+fses*ses+fgen+(ftimef+rt)*time+fchf*nps_ch+frad
f*nps_rad

+ftimerad*time*nps_rad+(ftimesq+rtsq)*time_sq+ftimesqrad*time_sq*nps_r
ad;
       else

exp_ppvtss=(fint+rint)+fses*ses+(ftimem+rt)*time+fchm*nps_ch+fradm*nps
_rad

+ftimerad*time*nps_rad+(ftimesq+rtsq)*time_sq+ftimesqrad*time_sq*nps_r
ad;
       run;
data m12;
     set test3(rename=(exp_ppvtss=exp_ppvtss2));run;

data ses1 ses2 ses3 ses4 ses5;
     set test3;
       if ses=1 then output ses1;
       else if ses=2 then output ses2;
       else if ses=3 then output ses3;
       else if ses=4 then output ses4;
       else output ses5;
       run;

data ses4radf ses4radm;
     set ses4;
       if Nps_Rad=1 & genderf=1 then output ses4radf;
       if Nps_Rad=1 & genderf=0 then output ses4radm;
       run;
data ses3chf ses3chm;
     set ses3;
       if Nps_ch=1 & genderf=1 then output ses3chf;
       if Nps_ch=1 & genderf=0 then output ses3chm;
       run;

goption reset=all ;
symbol interpol=join  repeat=300  ;
axis1 label = (a=90 );

proc gplot data=ses4radf;
     title 'Female in SES class 4 with radiation';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=ses4radm;
     title 'Male in SES class 4 with radiation';
```

```
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=ses3chf;
     title 'Female in SES class 3 with chemotherapy';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=ses3chm;
     title 'Male in SES class 3 with chemotherapy';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;

proc gplot data=female;
     plot (exp_ppvtss ppvtss)*time=idnum/ vaxis = axis1;
     run;quit;

*model with variable transformation;

proc mixed data=three covtest;
class idnum ch rad sur gender;
model ppvtss=sestr1 sestr1*sestr2 sestr1*time sestr1*gender
sestr1*agedxtr1 sestr1*agedxtr2 sestr1*sur sestr1*ch sestr1*rad
             sestr2 sestr2*time sestr2*gender sestr2*agedxtr1
sestr2*agedxtr2 sestr2*sur sestr2*ch sestr2*rad
                   time time*gender time*agedxtr1 time*agedxtr2
time*sur time*ch time*rad
                   gender gender*agedxtr1 gender*agedxtr2 gender*sur
gender*ch gender*rad
                   agedxtr1 agedxtr1*agedxtr2 agedxtr1*sur agedxtr1*ch
agedxtr1*rad
                   agedxtr2 agedxtr2*sur agedxtr2*ch agedxtr2*rad
                   sur sur*ch sur*rad ch ch*rad rad;
run;
proc mixed data=three covtest;
class idnum ch rad sur gender;
model ppvtss=sestr1 sestr1*sestr2 sestr1*time sestr1*gender
sestr1*agedxtr2 sestr1*rad
             sestr2 sestr2*time sestr2*agedxtr2  sestr2*rad
                   time time*gender  time*rad
                   gender gender*ch gender*rad
                   agedxtr1 agedxtr1*ch
                   agedxtr2 agedxtr2*rad
                   sur ch rad/s;
random intercept time/s sub=idnum type=un;
run;

ods output  Mixed.SolutionR=mixs;
ods output  Mixed.SolutionF=fixs;
proc mixed data=three covtest;
class idnum ch rad sur gender;
model ppvtss=sestr1

                   time time*gender  time*rad
                   gender gender*ch gender*rad
                   agedxtr2 agedxtr2*rad
                   ch rad/s;
```

```
random intercept time/s sub=idnum type=un;
run;
proc transpose data=mixs out=mix;
     by idnum;
       var estimate;
       id effect;
       run;

data fixs;
set fixs;
if estimate=0 then delete;
if effect='time*Gender' and gender='F' then effect='timef';
if effect='time*Gender' and gender='M' then effect='timem';
if effect='ch*Gender' and gender='F' then effect='chf';
if effect='ch*Gender' and gender='M' then effect='chm';
if effect='rad*Gender' and gender='F' then effect='radf';
if effect='rad*Gender' and gender='M' then effect='radm';
run;
proc transpose data=fixs out=fix;
     var estimate;
       id effect;
       run;
data fix;
     set fix(drop=_name_ rename=(intercept=fint sestr1=fses1
time=ftime timef=ftimef
           time_rad=ftimerad gender=fgen chf=fchf chm=fchm radf=fradf
radm=fradm
             agedxtr2=fage2 agedxtr2_rad=fage2rad));
     do i=1 to 433;
     output;
     end;
     drop i;
     run;
data test1;
     merge three fix;
       run;

data test2;
     merge test1 mix(drop=_name_ rename=(intercept=rint time=rt ));
     by idnum;
       run;

data test3;
     set test2;
       if gender='F' then

exp_ppvtss=(fint+rint)+fses1*sestr1+(ftime+rt+ftimef)*time+ftimerad*ti
me*nps_rad+fgen
+fchf*nps_ch+fradf*nps_rad+fage2*agedxtr2+fage2rad*agedxtr2*nps_rad;
     else

exp_ppvtss=(fint+rint)+fses1*sestr1+(ftime+rt)*time+ftimerad*time*nps_
rad
+fchm*nps_ch+fradm*nps_rad+fage2*agedxtr2+fage2rad*agedxtr2*nps_rad;
       run;
```

```
data m13;
     set test3(rename=(exp_ppvtss=exp_ppvtss3));run;

data ses1 ses2 ses3 ses4 ses5;
     set test3;
       if ses=1 then output ses1;
       else if ses=2 then output ses2;
       else if ses=3 then output ses3;
       else if ses=4 then output ses4;
       else output ses5;
       run;

data ses4radf ses4radm;
     set ses4;
       if Nps_Rad=1 & genderf=1 then output ses4radf;
       if Nps_Rad=1 & genderf=0 then output ses4radm;
       run;
data ses3chf ses3chm;
     set ses3;
       if Nps_ch=1 & genderf=1 then output ses3chf;
       if Nps_ch=1 & genderf=0 then output ses3chm;
       run;

goption reset=all ;
symbol interpol=join  repeat=300  ;
axis1 label = (a=90 );

proc gplot data=ses4radf;
     title 'Female in SES class 4 with radiation';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=ses4radm;
     title 'Male in SES class 4 with radiation';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=ses3chf;
     title 'Female in SES class 3 with chemotherapy';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=ses3chm;
     title 'Male in SES class 3 with chemotherapy';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;


proc gplot data=female;
     plot (exp_ppvtss ppvtss)*time=idnum/ vaxis = axis1;
     run;quit;

proc sort data=m11;
     by idnum time;
proc sort data=m12;
     by idnum time;
       run;
data nps;
```

```
     merge m11(keep=idnum ppvtss time Exp_ppvtss1) m12(keep=idnum
Exp_ppvtss2)
           m13(keep=idnum Exp_ppvtss3);
     by idnum;
       run;
proc export data=nps
     outfile='C:\Documents and Settings\yinshen\My
Documents\Thesis\DX\NPS.xls'
     dbms=excel
     replace;
run;

                                        /********/
/*Variable:  SES Age_dx genderf time time_sq NPS_total;*/
*GROUP;
data one;
   set a.cohort;
   if age_dx gt 7 then agegr=1; else agegr=0;
   if genderf=0 then sub=1;else sub=2;
   if agegr=1 then sub=sub+2;
   do i=1 to 5;
        if ses=i then sub=sub+4*(i-1);
   end;

run;
proc sort data=one out=two;by sub;run;

*model without interactions;

proc mixed data=two covtest;
       class idnum sub gender;
         model ppvtss=SES Agegr time  time_sq gender NPS_total;
         run;
proc mixed data=two covtest;
       class idnum sub gender;
         model ppvtss=SES Agegr time NPS_total/s;
         run;

proc mixed data=two covtest;
       class idnum sub gender;
         model ppvtss=SES Agegr time NPS_total/s;
         random intercept time  /s  sub=sub  type=un;
         run;
ods output  Mixed.SolutionR=mixs;
ods output  Mixed.SolutionF=fixs;
proc mixed data=two covtest;
       class idnum sub gender;
         model ppvtss=SES Agegr NPS_total/s;
         random intercept /s  sub=sub  type=un;
         run;

proc transpose data=mixs out=mix;
     by sub;
       var estimate;
       id effect;
```

```
        run;

proc transpose data=fixs out=fix;
     var estimate;
       id effect;
       run;
data fix;
     set fix(drop=_name_ rename=(intercept=fint ses=fses agegr=fage
nps_total=ftotal));
     do i=1 to 433;
     output;
     end;
     drop i;
     run;
data test1;
     merge two fix;
       run;

data test2;
     merge test1 mix(drop=_name_ rename=(intercept=rint ));
     by sub;
       run;

data test3;
     set test2;
       exp_ppvtss=(fint+rint)+fses*ses+fage*agegr+ftotal*nps_total;
       run;
data m21;
     set test3 (rename=(exp_ppvtss=exp_ppvtss1));run;

data ses1 ses2 ses3 ses4 ses5;
     set test3;
       if ses=1 then output ses1;
       else if ses=2 then output ses2;
       else if ses=3 then output ses3;
       else if ses=4 then output ses4;
       else output ses5;
       run;

data ses4f ses4m;
     set ses4;
       if genderf=1 then output ses4f;
       else output ses4m;
       run;
data total5 total9;
     set test3;
       if Nps_total=5 then output total5;
       if Nps_total=9 then output total9;
       run;

goption reset=all ;
symbol interpol=join  repeat=300  ;
axis1 label = (a=90 );

proc gplot data=ses4f;
```

```
     title 'Female in SES class 4';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=ses4m;
     title 'Male in SES class 4';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=total5;
     title 'Children with 5 total treatments';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=total9;
     title 'Children with 9 total treatments';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;

*model with interactions;

proc mixed data=two covtest;
       class idnum sub gender;
         model ppvtss=SES ses*agegr ses*time ses*time_sq ses*gender
ses*nps_total
                    Agegr agegr*time agegr*time_sq agegr*gender
agegr*nps_total
                    time  time*time_sq time*gender time*nps_total
                    time_sq time_sq*gender time_sq*nps_total
                    gender gender*nps_total NPS_total;
         run;
proc mixed data=two covtest;
       class idnum sub gender;
         model ppvtss=SES ses*time_sq ses*gender
                    Agegr agegr*nps_total time_sq gender  NPS_total;
         run;

proc mixed data=two covtest;
       class idnum sub gender;
         model ppvtss=SES ses*time_sq ses*gender
                    Agegr agegr*nps_total time_sq gender  NPS_total/s
;
            random intercept time_sq/s sub=sub type=un;
            run;

proc mixed data=two covtest;
       class idnum sub gender;
         model ppvtss=SES ses*gender
                    Agegr time_sq gender  NPS_total/s ;
            random intercept time_sq/s sub=sub type=un;
            run;
ods output  Mixed.SolutionR=mixs;
ods output  Mixed.SolutionF=fixs;
proc mixed data=two covtest;
       class idnum sub gender;
         model ppvtss=SES ses*gender
                    Agegr gender  NPS_total/s ;
            random intercept/s sub=sub type=un;
```

```
            run;

proc transpose data=mixs out=mix;
     by sub;
       var estimate;
       id effect;
       run;
data fixs;
set fixs;
if estimate=0 then delete;
run;
proc transpose data=fixs out=fix;
     var estimate;
       id effect;
       run;
data fix;
     set fix(drop=_name_ rename=(intercept=fint ses=fses
ses_gender=fsesgen agegr=fage
gender=fgen nps_total=ftotal));
     do i=1 to 433;
     output;
     end;
     drop i;
     run;
data test1;
     merge two fix;
       run;

data test2;
     merge test1 mix(drop=_name_ rename=(intercept=rint ));
     by sub;
       run;

data test3;
     set test2;
       exp_ppvtss=(fint+rint)+fses*ses+fsesgen*ses*genderf+fage*agegr
+fgen*genderf+ftotal*nps_total;
       run;
data m22;
     set test3 (rename=(exp_ppvtss=exp_ppvtss2));run;

data ses1 ses2 ses3 ses4 ses5;
     set test3;
       if ses=1 then output ses1;
       else if ses=2 then output ses2;
       else if ses=3 then output ses3;
       else if ses=4 then output ses4;
       else output ses5;
       run;

data ses4f ses4m;
     set ses4;
       if genderf=1 then output ses4f;
       else output ses4m;
       run;
```

```
data total5 total9;
     set test3;
       if Nps_total=5 then output total5;
       if Nps_total=9 then output total9;
       run;

goption reset=all ;
symbol interpol=join  repeat=300  ;
axis1 label = (a=90 );

proc gplot data=ses4f;
     title 'Female in SES class 4';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=ses4m;
     title 'Male in SES class 4';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=total5;
     title 'Children with 5 total treatments';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=total9;
     title 'Children with 9 total treatments';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;

*model with variable transformation;

proc mixed data=three covtest;
class idnum gender;
model ppvtss=sestr1 sestr1*sestr2 sestr1*time sestr1*gender
sestr1*agedxtr1 sestr1*agedxtr2 sestr1*totaltr1 sestr1*totaltr2
             sestr2 sestr2*time sestr2*gender sestr2*agedxtr1
sestr2*agedxtr2 sestr2*totaltr1 sestr2*totaltr2
                   time time*gender time*agedxtr1 time*agedxtr2
time*totaltr1 time*totaltr2
                   gender gender*agedxtr1 gender*agedxtr2
gender*totaltr1 gender*totaltr2
                   agedxtr1 agedxtr1*agedxtr2 agedxtr1*totaltr1
agedxtr1*totaltr2
                   agedxtr2 agedxtr2*totaltr1 agedxtr2*totaltr2
                   totaltr1 totaltr1*totaltr2 totaltr2;
run;
proc mixed data=three covtest;
class idnum gender;
model ppvtss=sestr1 sestr1*sestr2 sestr1*time sestr1*gender
sestr1*agedxtr2
             sestr2 sestr2*time sestr2*gender sestr2*agedxtr2
sestr2*totaltr2
                   time
                   gender gender*totaltr2
                   agedxtr1  agedxtr1*totaltr1
                   agedxtr2 agedxtr2*totaltr1
                   totaltr1 totaltr2;
```

```
random intercept time /s sub=idnum type=un;
run;

proc mixed data=three covtest;
class idnum gender;
model ppvtss=sestr1 sestr1*gender time  gender agedxtr1
agedxtr1*totaltr1 totaltr1 totaltr2/s;
random intercept time /s sub=idnum type=un;
run;
ods output  Mixed.SolutionR=mixs;
ods output  Mixed.SolutionF=fixs;
proc mixed data=three covtest;
class idnum gender;
model ppvtss=sestr1 sestr1*gender gender agedxtr1  agedxtr1*totaltr1
totaltr1 totaltr2/s;
random intercept/s sub=idnum type=un;
run;

proc transpose data=mixs out=mix;
     by idnum;
       var estimate;
       id effect;
       run;
data fixs;
set fixs;
if estimate=0 then delete;
run;
proc transpose data=fixs out=fix;
     var estimate;
       id effect;
       run;
data fix;
     set fix(drop=_name_ rename=(intercept=fint sestr1=fses1
sestr1_gender=fses1gen
gender=fgen  agedxtr1=fage1 agedxtr1_totaltr1=fage1total1
totaltr1=ftotal1
totaltr2=ftotal2));
     do i=1 to 433;
     output;
     end;
     drop i;
     run;
data test1;
     merge three fix;
       run;

data test2;
     merge test1 mix(drop=_name_ rename=(intercept=rint ));
     by idnum;
       run;

data test3;
     set test2;
       exp_ppvtss=(fint+rint)+fses1*sestr1+fses1gen*sestr1*genderf
```

```
+fgen*genderf+fage1*agedxtr1+fage1total1*agedxtr1*totaltr1+ftotal1*tot
altr1+ftotal2*totaltr2
;
       run;
data m23;
     set test3(rename=(exp_ppvtss=exp_ppvtss3));run;


data ses1 ses2 ses3 ses4 ses5;
     set test3;
       if ses=1 then output ses1;
       else if ses=2 then output ses2;
       else if ses=3 then output ses3;
       else if ses=4 then output ses4;
       else output ses5;
       run;
data ses4f ses4m;
     set ses4;
       if genderf=1 then output ses4f;
       else output ses4m;
       run;
data total5 total9;
     set test3;
       if Nps_total=5 then output total5;
       if Nps_total=9 then output total9;
       run;

goption reset=all ;
symbol interpol=join  repeat=300  ;
axis1 label = (a=90 );

proc gplot data=ses4f;
     title 'Female in SES class 4';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=ses4m;
     title 'Male in SES class 4';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=total5;
     title 'Children with 5 total treatments';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;
proc gplot data=total9;
     title 'Children with 9 total treatments';
     plot exp_ppvtss *time=idnum/ vaxis = axis1;
     run;quit;

proc sort data=m21;
     by idnum time;
proc sort data=m22;
     by idnum time;
       run;
data npstotal;
```

```
     merge m21(keep=idnum ppvtss time Exp_ppvtss1) m22(keep=idnum
Exp_ppvtss2)
           m23(keep=idnum Exp_ppvtss3);
     by idnum;
       run;
proc export data=npstotal
     outfile='C:\Documents and Settings\yinshen\My
Documents\Thesis\DX\NPStotal.xls'
     dbms=excel
     replace;
run;
```

Appendix B: Models for time beginning from diagnosis date

Individual Growth Models for Treatments and other variables

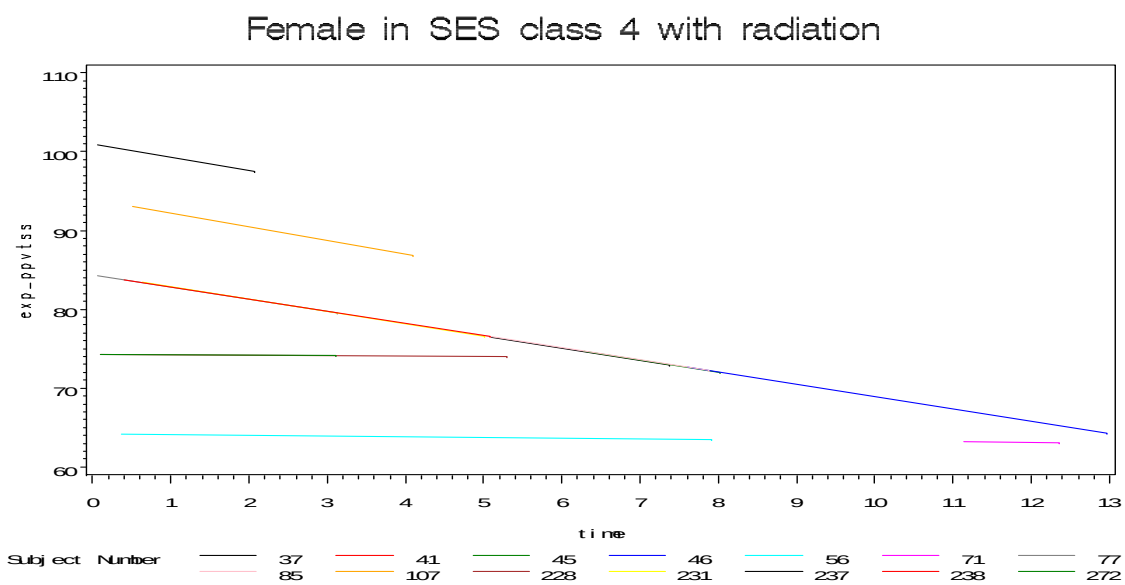
Model without interaction

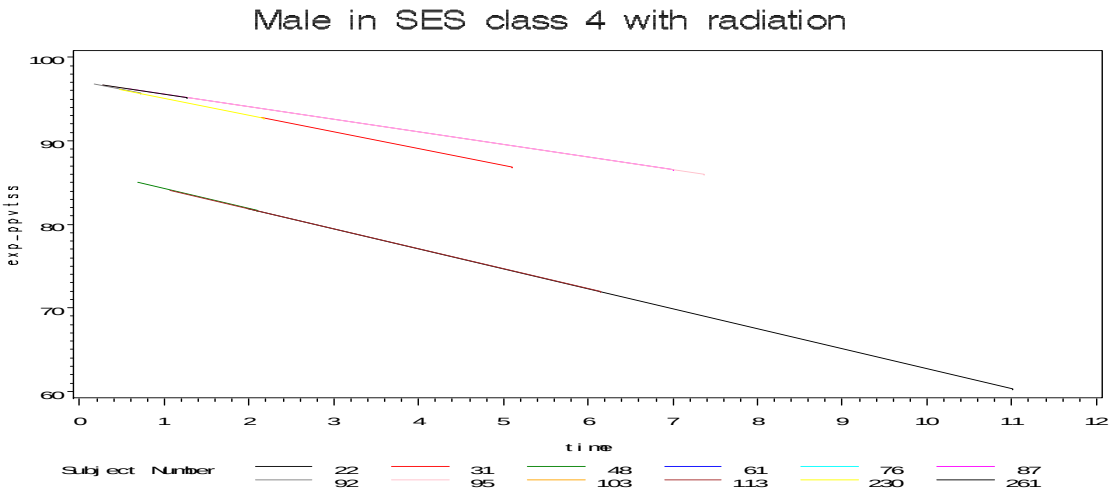
Type 3 Tests of Fixed Effects

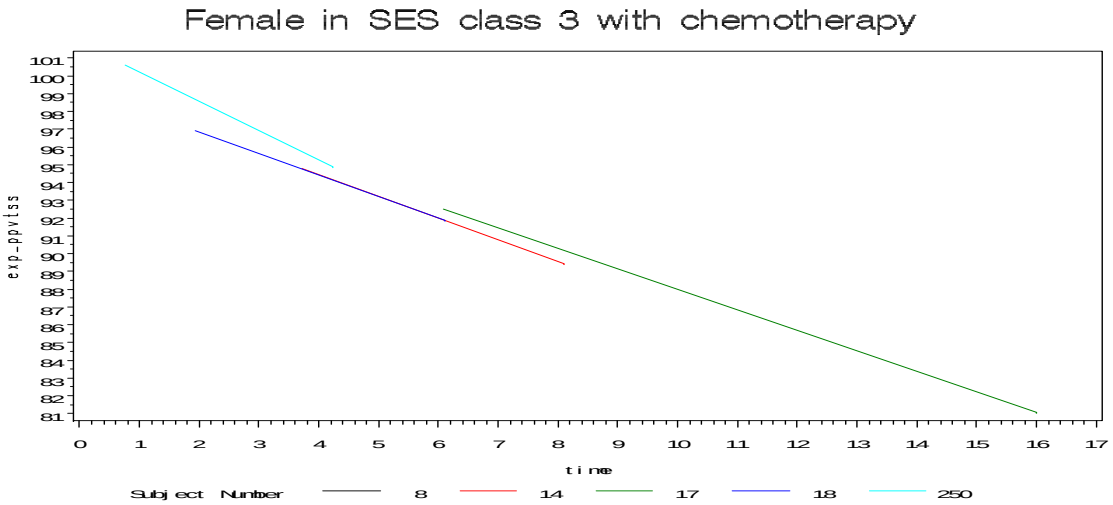
Effect	Num DF	Den DF	F Value	Pr > F
time	1	47	7.54	0.0085
SES	1	333	20.96	<.0001
ch	1	333	4.78	0.0295

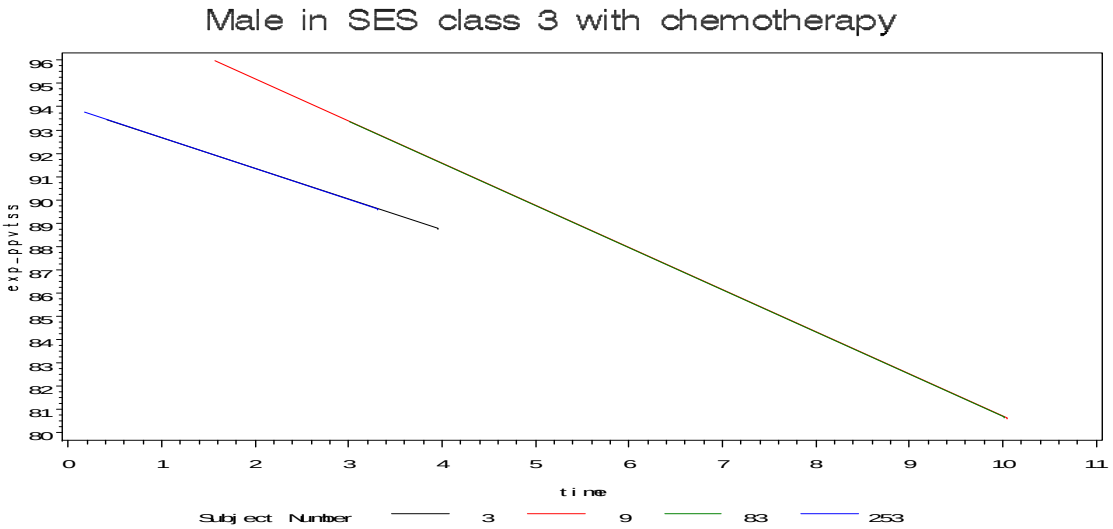
Fixed effects

Effect	ch	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		116.14	5.2092	49	22.29	<.0001
time		-0.9632	0.3507	47	-2.75	0.0085
SES		-6.4373	1.4059	333	-4.58	<.0001
ch	W	-8.0645	3.6886	333	-2.19	0.0295
ch	w/o	0	.	.	.	.




Male in SES class 4 with radiation
exp_ppvlss
time
Subject Number
22
31
48
61
76
87
92
95
103
113
230
261


Female in SES class 3 with chemotherapy
exp_ppvlss
time
Subject Number
8
14
17
18
250


Male in SES class 3 with chemotherapy
exp_ppvlss
time
Subject Number
3
9
83
253

Model with interactions

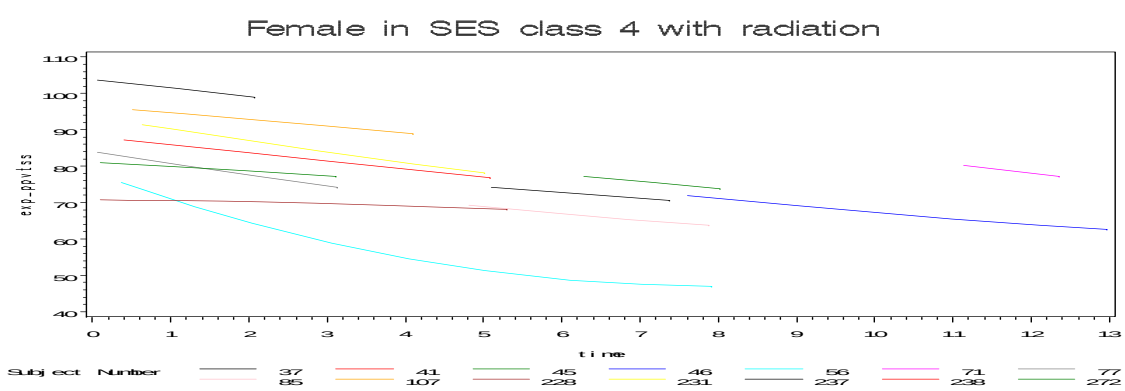
Type 3 Tests of Fixed Effects

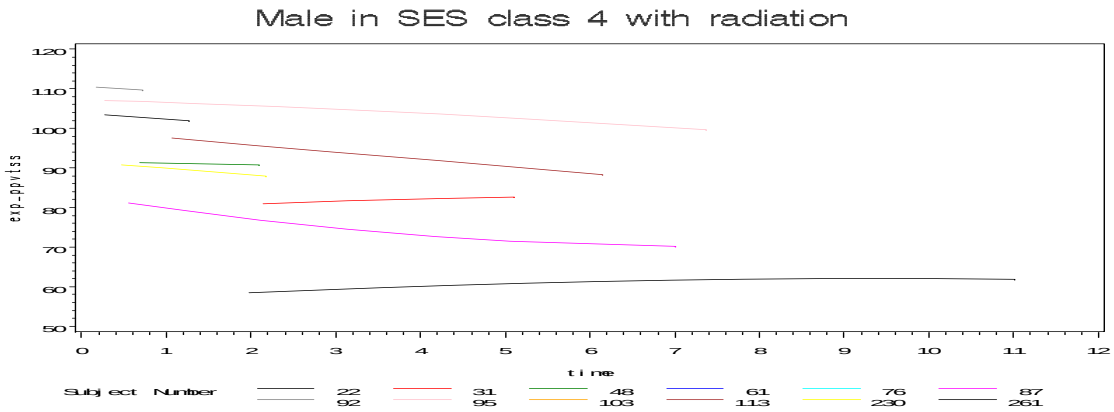
Effect	Num DF	Den DF	F Value	Pr > F
SES	1	187	12.86	0.0004
Gender	1	187	10.47	0.0014
time*Gender	1	187	8.73	0.0035
ch*Gender	1	187	16.04	<.0001
rad*Gender	1	187	4.79	0.0298
time	1	80	2.66	0.1069
time*rad	1	187	13.55	0.0003
time_sq	1	68	10.41	0.0019
time_sq*rad	1	187	10.45	0.0015
rad	1	187	1.52	0.2188
ch	1	187	0.22	0.6412

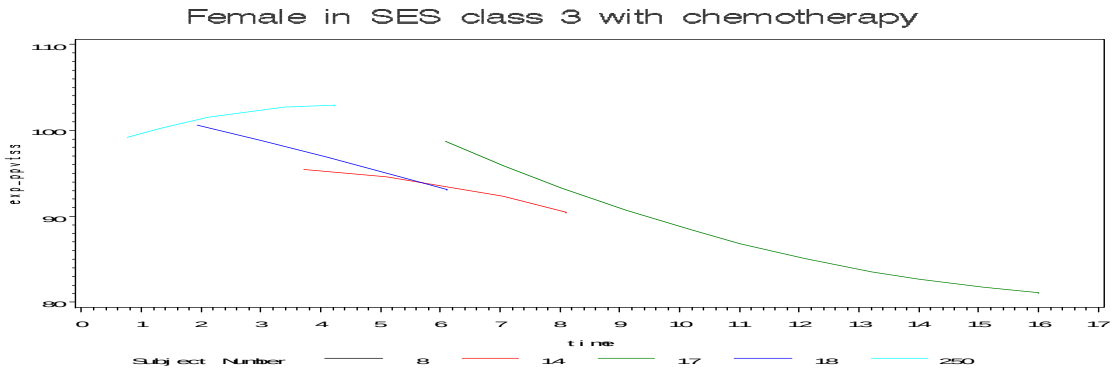
Fixed effects

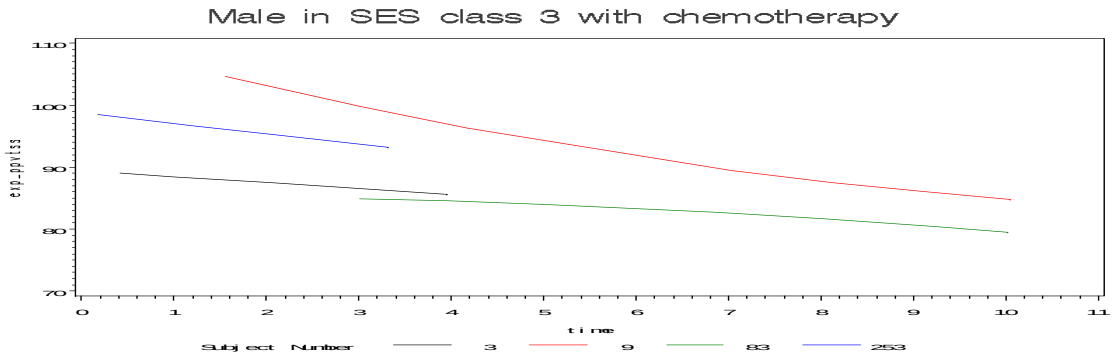
Solution for Fixed Effects

Effect	ch	rad	Gender	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept				98.7117	6.5155	86	15.15	<.0001
SES				-4.8269	1.3462	187	-3.59	0.0004
Gender			F	9.2571	6.0445	187	1.53	0.1273
Gender			M	0	.	.	.	.
time*Gender			F	2.7503	1.0447	187	2.63	0.0092
time*Gender			M	4.0336	1.0991	187	3.67	0.0003
ch*Gender	W		F	12.4467	5.1174	187	2.43	0.0159
ch*Gender	W		M	-15.7442	4.8515	187	-3.25	0.0014
ch*Gender	w/o		F	0	.	.	.	.
ch*Gender	w/o		M	0	.	.	.	.
rad*Gender		W	F	-1.9936	5.9981	187	-0.33	0.7400
rad*Gender		W	M	13.6874	5.8810	187	2.33	0.0210
rad*Gender		w/o	F	0	.	.	.	.
rad*Gender		w/o	M	0	.	.	.	.
time				0	.	.	.	.
time*rad		W		-4.7262	1.2837	187	-3.68	0.0003
time*rad		w/o		0	.	.	.	.
time_sq				-0.3452	0.09464	68	-3.65	0.0005
time_sq*rad		W		0.3467	0.1072	187	3.23	0.0015
time_sq*rad		w/o		0	.	.	.	.
rad		W		0	.	.	.	.
rad		w/o		0	.	.	.	.
ch	W			0	.	.	.	.
ch	w/o			0	.	.	.	.









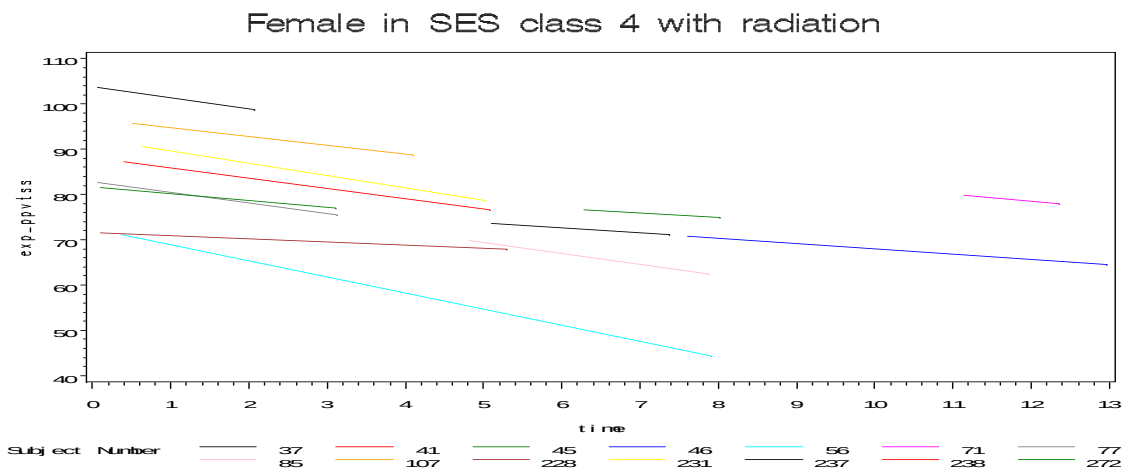
Model with variable transformations

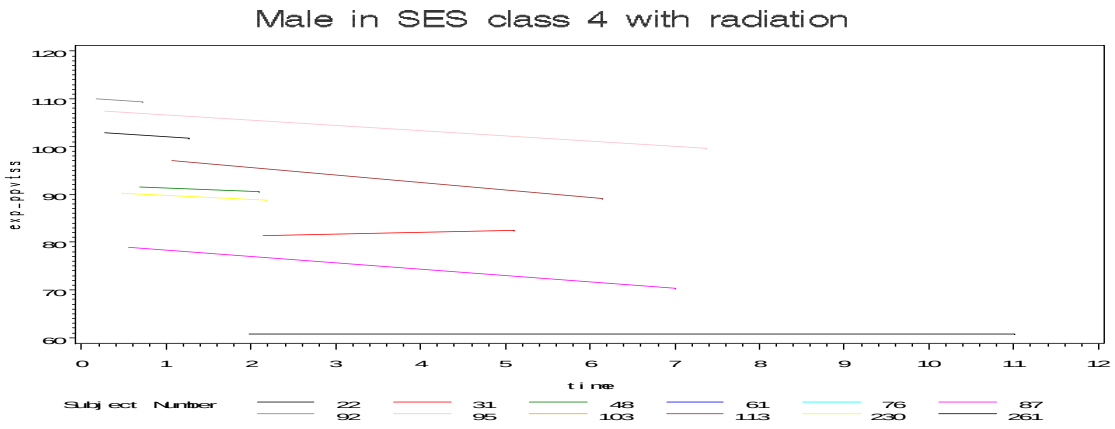
Fixed effects

Solution for Fixed Effects

Effect	ch	rad	Gender	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept				26.8187	12.7830	84	2.10	0.0389
sestr1				40.8228	10.9631	257	3.72	0.0002
time				1.8901	0.6046	80	3.13	0.0025
time*Gender			F	-1.4398	0.5808	257	-2.48	

0.0138							
time*Gender		M	0	.	.	.	.
time*rad	W		-2.4002	0.6207	257	-3.87	
0.0001							
time*rad	w/o		0	.	.	.	.
Gender		F	14.3624	6.0318	257	2.38	
0.0180							
Gender		M	0	.	.	.	.
ch*Gender	W	F	10.6573	6.1023	257	1.75	
0.0819							
ch*Gender	W	M	-9.6937	5.2042	257	-1.86	
0.0637							
ch*Gender	w/o	F	0	.	.	.	.
ch*Gender	w/o	M	0	.	.	.	.
rad*Gender	W	F	19.4082	12.9118	257	1.50	
0.1340							
rad*Gender	W	M	37.6917	13.6612	257	2.76	
0.0062							
rad*Gender	w/o	F	0	.	.	.	.
rad*Gender	w/o	M	0	.	.	.	.
agedxtr2			12.9758	4.0527	257	3.20	
0.0015							
agedxtr2*rad	W		-10.8517	4.8267	257	-2.25	
0.0254							
agedxtr2*rad	w/o		0	.	.	.	.
ch	W		0	.	.	.	.
ch	w/o		0	.	.	.	.
rad	W		0	.	.	.	.
rad	w/o		0	.	.	.	.




Male in SES class 4 with radiation
exp_ppvlss
time
Subject Number
22
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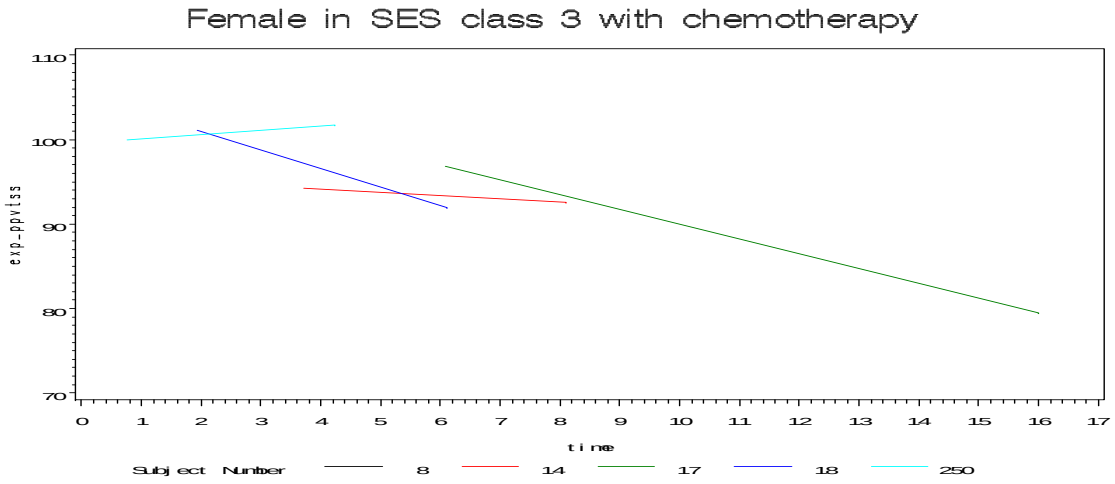

Female in SES class 3 with chemotherapy
exp_ppvlss
time
Subject Number
8
14
17
18
250

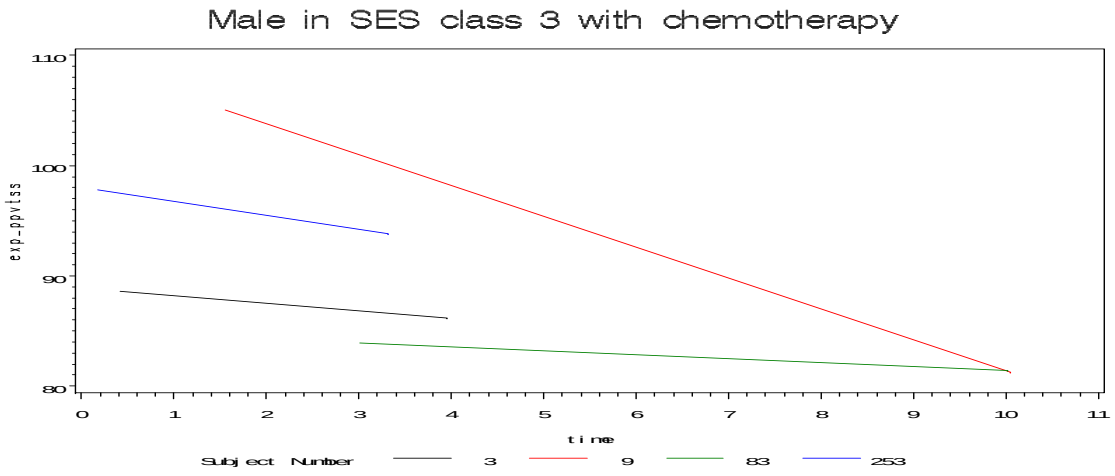
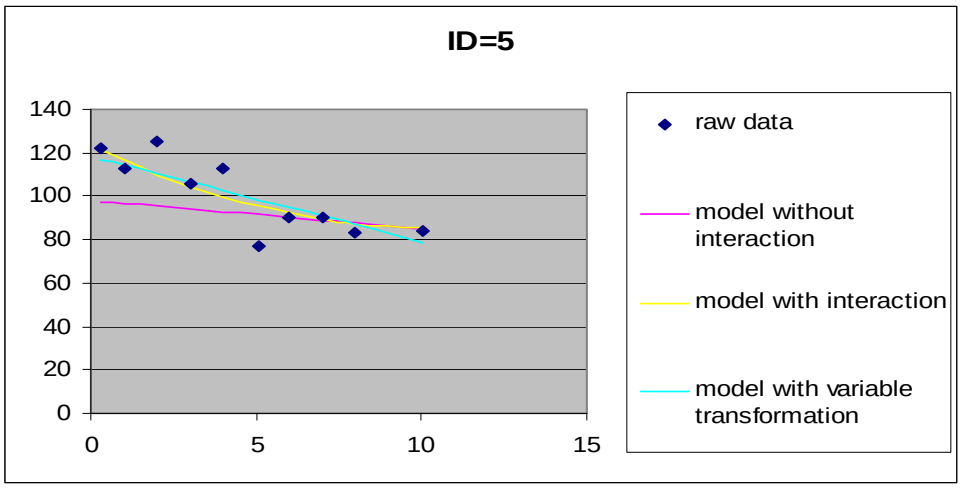
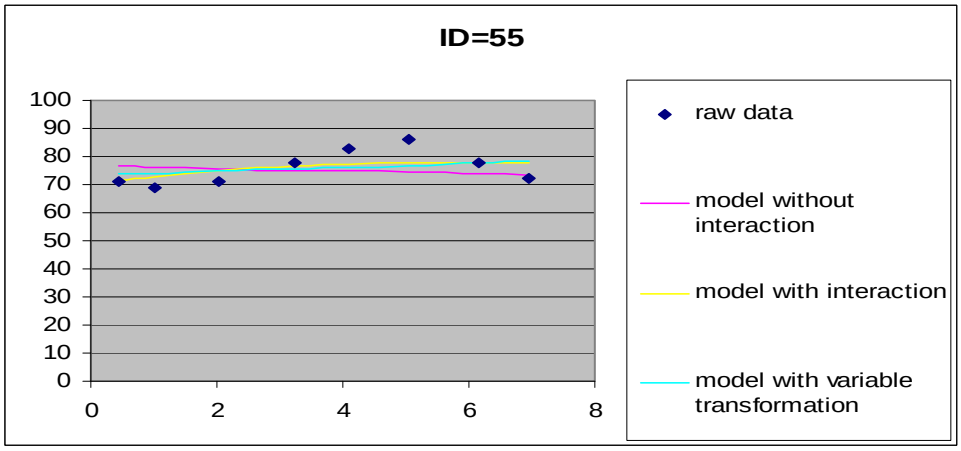

Male in SES class 3 with chemotherapy
exp_ppvlss
time
Subject Number
3
9
83
253

Table : Comparison of models

Statistic	Model without interactions	Model with interactions	Model with variable transformation
-2 Res Log Likelihood	3565.1	3206.0	3199.1
AIC(the smaller the better)	3573.1	3220.0	3207.1
AICC(the smaller the better)	3573.2	3220.3	3207.2
BIC(the smaller the better)	3580.9	3237.7	3217.2





Individual Growth Models for NPS_total and other variables

Model without interaction

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SES	1	413	26.05	<.0001
agegr	1	413	6.84	0.0092
NPS_total	1	413	24.84	<.0001

Fixed effects

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	119.03	4.8096	16	24.75	<.0001
SES	-5.9384	1.1635	413	-5.10	<.0001
agegr	7.7851	2.9770	413	2.62	0.0092
NPS_total	-2.1518	0.4318	413	-4.98	<.0001

Model with interactions

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SES	1	413	42.18	<.0001
SES*Gender	1	413	7.94	0.0051
agegr	1	413	9.44	0.0023
Gender	1	413	7.77	0.0056
NPS_total	1	413	27.62	<.0001

Fixed effects

Solution for Fixed Effects

Effect	Gender	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		112.15	4.6685	14	24.02	<.0001
SES		-3.6049	1.2299	413	-2.93	0.0036
SES*Gender	F	-5.5395	1.9663	413	-2.82	0.0051
SES*Gender	M	0	.	.	.	.
agegr		7.4935	2.4384	413	3.07	0.0023
Gender	F	18.0098	6.4601	413	2.79	0.0056
Gender	M	0	.	.	.	.
NPS_total		-2.2464	0.4275	413	-5.26	<.0001

Model with variable transformations

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
sestr1	1	340	21.63	<.0001
sestr1*Gender	1	340	5.50	0.0196

Gender	1	340	4.40	0.0366
agedxtr1	1	340	0.96	0.3286
agedxtr1*totaltr1	1	340	10.70	0.0012
totaltr1	1	340	0.28	0.6002
totaltr2	1	340	8.78	0.0033

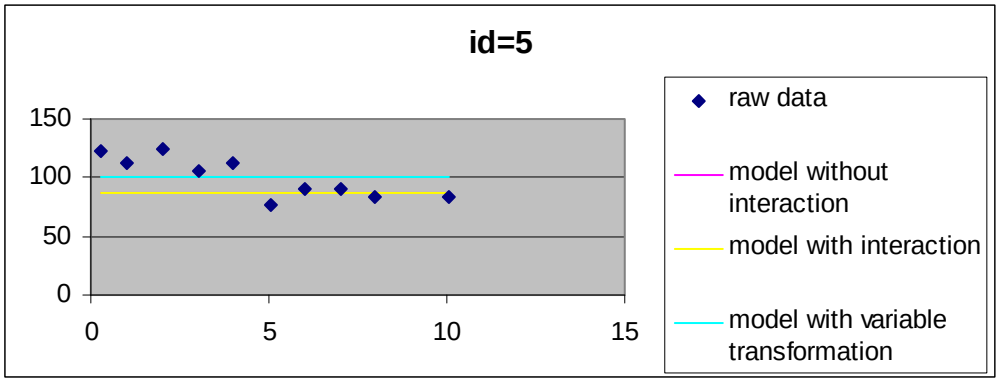
Fixed effects

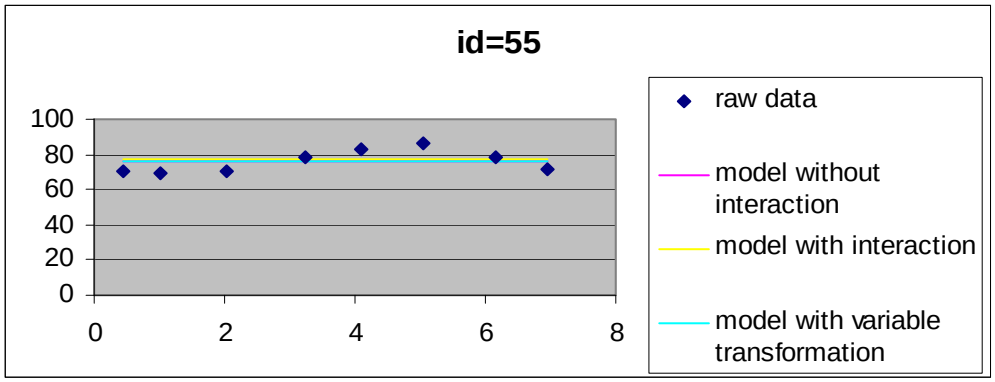
Solution for Fixed Effects

Effect	Gender	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		41.2304	12.4293	85	3.32	0.0013
sestr1		24.5774	12.7157	340	1.93	0.0541
sestr1*Gender	F	51.9852	22.1714	340	2.34	0.0196
sestr1*Gender	M	0	.	.	.	.
Gender	F	-28.6059	13.6342	340	-2.10	0.0366
Gender	M	0	.	.	.	.
agedxtr1		10.9135	11.1550	340	0.98	0.3286
agedxtr1*totaltr1		-1172.64	358.41	340	-3.27	0.0012
totaltr1		118.71	226.30	340	0.52	0.6002
totaltr2		235.17	79.3502	340	2.96	0.0033

Table : Comparison of models

Statistic	Model without interactions	Model with interactions	Model with variable transformation
-2 Res Log Likelihood	3677.6	3664.0	3254.6
AIC(the smaller the better)	3681.6	3668.0	3258.6
AICC(the smaller the better)	3681.6	3668.1	3258.6
BIC(the smaller the better)	3683.4	3669.9	3263.7




id=55
100
80
60
40
20
0
0
2
4
6
8
raw data
model without interaction
model with interaction
model with variable transformation