CHILDHOOD CANCER SURVIVOR STUDY
ANALYSIS CONCEPT PROPOSAL

Project Title: Cognitive and behavioral outcomes in survivors of neuroblastoma

Working Group: Psychology

Investigators:

Daniel Zheng	daniel.zheng@yale.edu	Lead
Nina Kadan-Lottick	nina.kadan-lottick@yale.edu	Mentor
Kevin Krull	kevin.krull@stjude.org	Mentor
Lisa Diller	lisa_diller@dfci.harvard.edu	
Pim Brouwers	ebrouwer@mail.nih.gov	
Wendy Leisenring	wleisenr@fhcrc.org	
Rebecca Howell	rhowell@mdanderson.org	
Jin Shei Lai	js-lai@northwestern.edu	
Les Robison	les.robison@stjude.org	
Greg Armstrong	greg.armstrong@stjude.org	
Lyn Balsamo	lyn.balsamo@yale.edu	
Kevin Oeffinger	oeffingk@mskcc.org	

Background and Rationale

From 1975 to 2005, advances in treatment for neuroblastoma have resulted in an increase in 5-year overall survival from 46% to 71% [1]. Therefore, we now have the opportunity to better understand what late effects are experienced by long-term survivors. There are several reasons to believe that subgroups of neuroblastoma survivors are at elevated risk for neurobehavioral impairments. Many patients receive cytotoxic treatments at very young ages (median age of diagnosis is 17.3 months) when normal psychosocial development can be disrupted [2, 3]. There is also a known association between cognitive functioning and neurologic vulnerability at younger ages after both cranial radiation as well as chemotherapy alone [4-6]**.** Neuroblastoma chemotherapy regimens contain several agents that are directly neurotoxic or result in cardiovascular insufficiency, which in turn is hypothesized to cause similar impairment [7-9]. These concepts remain understudied in long-term survivors of neuroblastoma.

A number of neurotoxic agents are now routinely used in the treatment of high-risk neuroblastoma, notably cisplatin and vincristine, which have both been linked with peripheral neuropathy [8, 10, 11]. Peripheral neuropathy can in turn affect visual motor integration [12]. Studies in children with ALL suggest that impaired visual motor integration disrupt the development of higher level cognitive abilities and may be associated with poor math outcomes [13, 14]. In addition to peripheral neuropathy, cisplatin also results in hearing loss which impacts learning and socialization [15]. While the effects on hearing are well established, more research is needed to better determine how they manifest in neurobehavioral outcomes. A previous Childhood Cancer Survivor

Study (CCSS) analysis with a heterogeneous group of diagnoses found hearing loss to be a major predictor of neurobehavioral impairment in the domains of task efficiency, organization, memory, and emotional regulation [16]. Lastly, retinoic acid has recently become a mainstay of maintenance therapy for high-risk neuroblastoma. However, no studies are available to comment on the long-term effect this has on neurobehavioral outcomes, even though the drug is dose-limited by neurotoxicity [8, 17].

While the studies are not yet available, there are other reasons to believe that neuroblastoma survivors may be at elevated risk for neurobehavioral impairment. These include both the early age of biologic insult to a developing brain [4], as well as the experience of intensive cancer treatment disrupting normal psychosocial development [18, 19]. There is also compelling evidence suggesting that vascular toxicity from anthracyclines and chest and neck radiation may result in cognitive impairment [7]. These factors are important to consider in neuroblastoma patients, as doxorubicin is a commonly used induction agent for high-risk cases [8].

An important strength of the Childhood Cancer Survivor Study is the ability to take into account detailed treatment exposures, which have changed considerably over the last several decades. Standard of care for these patients has followed two major trends: 1) lower-risk patients have been treated with progressively de-escalating therapies vs. 2) higher-risk patients have received increasingly more intensive treatments including increased doses of multiagent chemotherapy for induction, myeloablative dosing with autologous stem cell transplantation for consolidation, and introduction of retinoid compounds [9, 8].

Cognitive and behavioral late effects have been understudied in neuroblastoma patients [20-23]. The Childhood Cancer Survivor Study is an optimal and informative sample to address this gap in research because there is uniform ascertainment of these measures with standardized instruments in patients who were diagnosed over the evolving paradigms of treatment.

Hypothesis

(1) Neuroblastoma survivors will demonstrate increased cognitive and behavioral impairment compared to their siblings.

(2) This impairment will be associated with increased intensity of therapy, including use of cisplatin, transplant, and retinoic acid.

Proposed Specific Aims

Our specific aims are to:

(1) Characterize overall patterns and severity of cognitive and behavioral difficulties in long-term survivors of neuroblastoma, as measured by standardized instruments and use of special education services.

(2) Compare the severity in cognitive and behavioral problems between siblings and survivor treatment groups based on treatment intensity.
   - Group 1: No chemotherapy
   - Group 2: Chemotherapy without cisplatin, without transplant
   - Group 3: Chemotherapy with cisplatin, without transplant
   - Group 4: Chemotherapy with cisplatin, with transplant

   Please note that these groups may be modified once cross-tab frequencies of treatment exposures from the CCSS cohort are available. We will specifically consider whether there are sufficient numbers of survivors who received transplant, as well as whether or not to include or replace this group with those who have received retinoic acid.

(3) Identify patient and treatment-related predictors of cognitive and behavioral problems in long-term survivors of neuroblastoma.

Methods

Study population
Neuroblastoma survivors in the Childhood Cancer Survivor Study diagnosed from 1970 to 1999 (includes both the original and expansion cohort) who participated in the Baseline <18 survey, along with sibling controls who also participated in the Baseline <18 survey.

Outcome Variables
The primary outcome will be the Behavior Problem Index (BPI), a 32-item questionnaire originally developed for the National Health Survey to describe cognitive, behavioral and emotional functioning [24]. For each item, parents were asked about their child's behavior on a Likert scale ranging from 1 ("Not True") to 3 ("Often True"). This tool examines the five domains of depression/anxiety, headstrong behavior, attention deficit, peer conflict/social withdrawal, and antisocial behavior, and has been previously validated in a CCSS sample [25]. We will also examine social networks via questions included with the BPI.

- For the original cohort, the BPI corresponds to questions J.19a-w, J.20a-e, and J.21a-d on the Baseline <18 survey.
- For the expansion cohort, the BPI corresponds to questions K.4a-w, K.5a-e, and K.6a-d on the Baseline <18 – expanded survey.
    - Similar to the CCSS paper validating this instrument [25], significant elevation in a domain will be defined as a score 1.3 standard deviations (approximating 10% of the sibling population) or more above the sibling group's mean score in that domain.
- Social networks (i.e. number of close friends and frequency of interactions) will be compared between survivors and siblings. These questions correspond to Baseline items J.16 and J.17 for the original cohort and items K1 and K2 for the expansion cohort.

As secondary outcomes, we will analyze the following:

- Education (special education resources and highest level [less than high school vs. high school diploma vs. some college])
    - For the original cohort, special education (yes vs. no; reason for special education) corresponds to question O.3 on the Baseline <18 survey. For the expansion cohort, this corresponds to question R.3 on the Baseline <18 – expanded survey.
    - For the original cohort only, highest level of education corresponds to question A.3 on the Follow-up 4 survey in 2007. Highest level of education in the expansion cohort cannot yet be obtained, as the survivors were 12-17 years of age at parent report.
- Employment (current employment status [working full-time vs. working part-time vs. caring for home or family vs. unemployed and looking for work vs. unable to work due to illness or disability vs. retired vs. student vs. other])
    - For the original cohort only, employment corresponds to question A.4 on the Follow-up 4 survey in 2007
- Peripheral neuropathy
    - For both the original and expansion cohort, the presence of neuropathy has been analyzed across a number of CCSS surveys and coded by a trained nosologist.
    - For both cohorts, this secondary outcome has also been graded according to the Common Terminology Criteria for Adverse Events (CTCAE) grading schema. We are specifically interested in survivors who exhibit neuropathy that is Grade 2 or higher. According to CTCAE, Grade 2 for peripheral motor and sensory neuropathy is defined as “Moderate symptoms; limiting instrumental ADL” [26].
- Hearing loss
    - For both the original and expansion cohort, the presence of hearing loss has been analyzed across a number of CCSS surveys and coded by a trained nosologist.
    - For both cohorts, this secondary outcome has also been graded according to the CTCAE grading schema. We are specifically interested in survivors who exhibit hearing loss that is Grade 3 or higher. According to CTCAE, Grade 3 for hearing loss is defined as “hearing loss with hearing aid or intervention indicated; limiting self care ADL” [26].

Predictor variables

We will collect from the Baseline survey date of birth, sex, and race/ethnicity. We will also obtain self-reported height and weight to calculate body mass index (BMI). BMI will be calculated by dividing weight in kilograms by height in meters squared and then classified according to the standards of the National Heart, Lung, and Blood Institute and the World Health Organization: 1) <18.5 kg/m2 as underweight, 2) 18.5–24.9 kg/m2 as normal weight, 3) 25–29.9 kg/m2 as overweight, and 4) >30 kg/m2 as obese [27, 28]. Cancer treatment information from medical record abstraction for each patient will be obtained, including date of diagnosis, chemotherapy (yes/no and cumulative dose),

radiation therapy (yes/no, dose, and site), surgery (yes/no), retinoic acid (yes/no). For chemotherapy, we will specifically examine whether patients received vincristine, cisplatin, and/or anthracyclines. For radiation sites, we will specifically examine cranial radiation (prescription dose, average dose to the brain, and dose to the 4 brain segments: posterior fossa, temporal lobe, frontal cortex, parietal or occipital lobe), chest/neck (average dose), or total body irradiation.

Data Analysis Plan

We will calculate descriptive statistics for demographic and treatment variables for cancer survivors in both the original cohort and the expanded cohort, as well as for their siblings. These statistics will be compared between the survivors stratified by treatment intensity (4 groups outlined in specific aim 2) and the siblings with generalized linear models with generalized estimating equations to account for potential within-family correlation [27], using identity or log-binomial link functions, for continuous and binary outcomes, respectively. .

For each domain of the BPI, we will compare survivors vs. siblings both with 1) mean scores and standard deviations, as well as 2) percentages of individuals with scores in a low functioning or impaired range (defined as falling within the worst 10% range of siblings' scores). We will use multivariable log-binomial regression with adjustment for current age, sex, and race. For comparing mean scores on each domain of the BPI between survivors and siblings, we will use generalized estimating equations to account for potential within-family correlation [29]. Log-binomial models will be used to assess the association of patient and treatment factors on cognitive and behavioral outcomes. Prevalence ratios for impairment in subgroups of survivors compared with the referent group will be reported with corresponding 95% confidence intervals, based on standard large sample inference method for generalized linear models. We will also examine interactions of younger age at diagnosis (<1 vs. ≥1 year) and treatment exposures (i.e. vincristine, platinum-containing agents, retinoic acid, radiation) and gender and treatment exposures. Separately, we will examine the association of the development of specific late effects (i.e. hearing loss, motor peripheral neuropathy) with cognitive and behavioral outcomes to understand if these late effects mediate impairment. SAS version 9.4 (SAS Institute, Cary, NC) will be used to conduct all analyses. Within the original cohort, we will use univariate binomial regression to examine the relative risk of poor adult education and employment outcomes using each BPI domain as a predictor.

Appendix. Skeleton Tables and Figures

Table 1. Participant Characteristics

Characteristic	Siblings		Overall Survivors		Survivors diagnosed from 1970-79		Survivors diagnosed from 1980-89		Survivors diagnosed from 1990-99	
	# (%)	p	# (%)	p	# (%)	p	# (%)	p	# (%)	p
Sex Female Male										
Race/ethnicity White Black Hispanic Other										
Age at diagnosis, years <1 1-1.99 2-4.99 5 and older										
Age at evaluation 12-14 15-17										
Highest Education Less than high school High school diploma Some college										
Overall treatment Surgery only Chemotherapy Radiation Chemotherapy and radiation No surgery, chemotherapy, or radiation Unknown										

Table 2. Comparison of parent-reported cognitive and behavioral outcomes between neuroblastoma survivors and their siblings

Group		**Anxiety/Depression**			**Headstrong**			**Attention Deficit**			**Peer Conflict/ Social Withdrawal**			**Antisocial**		
	No.	Mean (SD)	p	% impaired*	Mean (SD)	p	% impaired	Mean (SD)	p	% impaired	Mean (SD)	p	% impaired	Mean (SD)	p	% impaired
Siblings																
Neuroblastoma survivors, overall																
Treatment intensity No chemotherapy Chemotherapy without cisplatin Chemotherapy with cisplatin																

*Impaired is defined as 1.3 standard deviations above the mean for the sibling group's mean score for all domains.

Table 3. Association of patient and treatment factors with parent-reported cognitive and behavioral impairment among neuroblastoma survivors: univariate analysis

Patient or Treatment Factor	**Anxiety/Depression**			**Headstrong**			**Attention Deficit**			**Peer Conflict/ Social Withdrawal**			**Antisocial**		
	%	PR (95% CI)	p	%	PR (95% CI)	p	%	PR (95% CI)	p	%	PR (95% CI)	p	%	PR (95% CI)	p
Sex Male Female															
Ethnicity White Other															
Age at diagnosis <1 1-1.99 2-4.99 5 and older															
Decade of diagnosis 1970-79 1980-89 1990-99															
Chemotherapy Yes No															
Cisplatin Yes No															
Vincristine Yes No															
Retinoic Acid Yes No															
Anthracycline Yes															

No															
Cranial radiation (including scatter) Yes No															
TBI Yes No															
Chest/neck radiation Yes No															
Any vascular toxic treatment (anthracycline and/or chest/neck radiation) Yes No															
BMI (kg/m^2) < 18.5 18.5 – 24.9 25 – 29.9 > 30															
Hearing loss None, Grade 1 or Grade 2 Grade 3 or higher															
Peripheral motor neuropathy None or Grade 1 Grade 2 or higher															

Table 4. Association of patient and treatment factors with parent-reported cognitive and behavioral impairment among neuroblastoma survivors: multivariate analysis

Patient or Treatment Factor	**Anxiety/Depression**			**Headstrong**			**Attention Deficit**			**Peer Conflict/ Social Withdrawal**			**Antisocial**		
	%	PR (95% CI)	p	%	PR (95% CI)	p	%	PR (95% CI)	p	%	PR (95% CI)	p	%	PR (95% CI)	p

**Please note that this table will be constructed with backwards-stepwise regression. We will take into consideration that both cisplatin and hearing loss cannot be analyzed in the same model given the causal pathway (likewise with vincristine and neuropathy).*

Table 5. Relative risk of use of special education services, educational attainment and employment in neuroblastoma survivors diagnosed from 1970 – 1986, based on impairment* in cognitive and behavioral functioning

Cognitive and Behavioral Functioning as measured by the BPI	**Use of special education services**			**Educational attainment of some college or higher**			**Employment in the last 12 months**		
	No (%)	**RR**	**p**	**No (%)**	**RR**	**p**	**No (%)**	**RR**	**p**
Anxiety/Depression									
Impaired									
No impairment									
Headstrong									
Impaired									
No impairment									
Attention Deficit									
Impaired									
No impairment									
Peer Conflict/Social Withdrawal									
Impaired									
No impairment									
Antisocial									
Impaired									
No impairment									

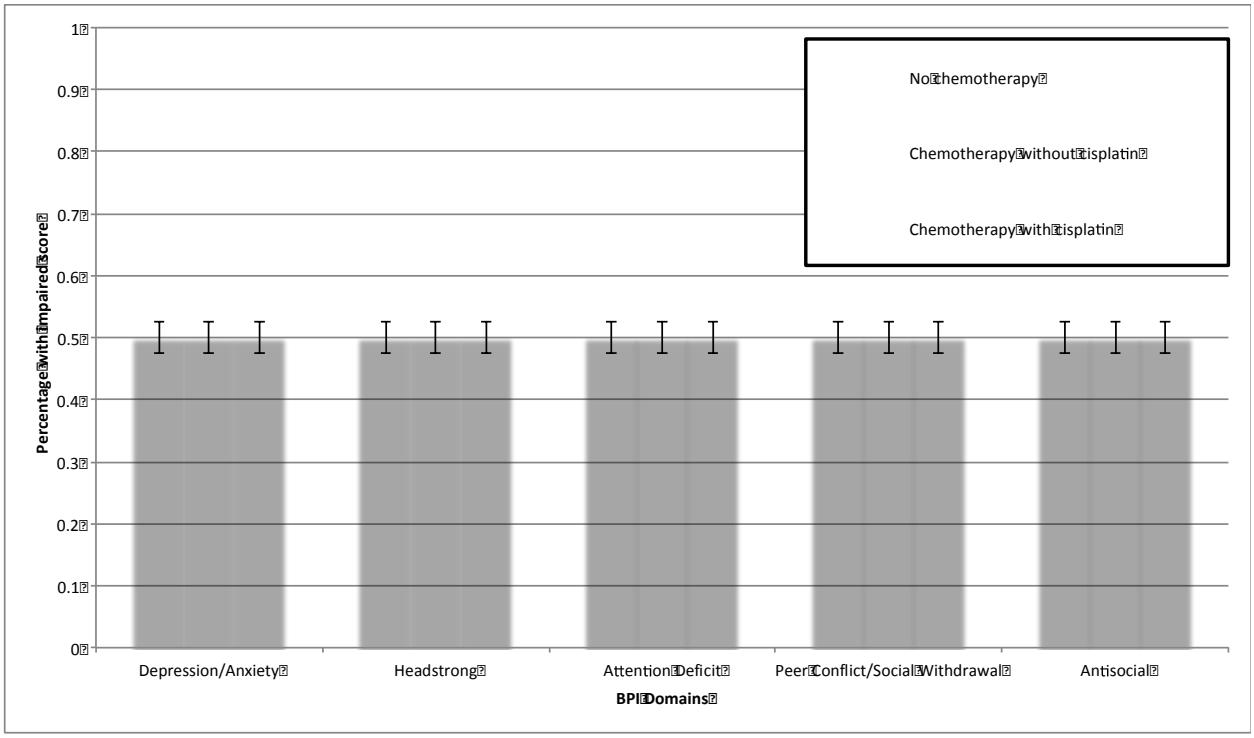
*Impaired is defined as 1.3 standard deviations above the mean for the sibling group's mean score for all domains.

Table 6. Comparison of social networks between neuroblastoma survivors and their siblings

Sex	**Characteristic**	**Siblings**		**Neuroblastoma Survivors**									
				Overall		No chemotherapy		Chemotherapy, no cisplatin, no transplant		Chemotherapy with cisplatin, no transplant		Chemotherapy with cisplatin and transplant	
Males		No(%)	p	No(%)	p	No(%)	p	No(%)	p	No(%)	p	No(%)	p
	Number of close friends 0 1 2 or 3 4 or more												
	Weekly interactions with close friends Less than 1 1 or 2 3 or more												
Females		No(%)	p	No(%)	p	No(%)	p	No(%)	p	No(%)	p	No(%)	p
	Number of close friends 0 1 2 or 3 4 or more												
	Weekly interactions with close friends Less than 1 1 or 2 3 or more												
Overall		No(%)	p	No(%)	p	No(%)	p	No(%)	p	No(%)	p	No(%)	p

	Number of close friends 0 1 2 or 3 4 or more						
	Weekly interactions with close friends Less than 1 1 or 2 3 or more						

Figure 1. Percentages and 95% confidence intervals of impairment in behavioral and cognitive domains in participants stratified by treatment intensity and compared with siblings overall. Impaired function is defined as 1.3 standard deviations above the mean for the sibling group's mean score.



References

1. Horner M, Ries L, Krapcho M, Neyman N, Aminou R, Howlader N et al. SEER Cancer Statistics Review, 1975-2006, National Cancer Institute. Bethesda, MD. 2009.
2. Goodman MT, Gurney J, Smith M, Olshan A. Sympathetic nervous system tumors. Cancer incidence and survival among children and adolescents: United States SEER Program. 1975;1995:65-72.
3. Pizzo PA, Poplack DG, Adamson PC, Blaney SM, Helman LJ. Principles and practice of pediatric oncology. Lippincott Williams & Wilkins Philadelphia, PA:; 2006.
4. Taylor HG, Alden J. Age-related differences in outcomes following childhood brain insults: an introduction and overview. Journal of the International Neuropsychological Society. 1997;3(06):555-67.
5. Buizer AI, De Sonneville LM, Van Den Heuvel-eibrink MM, Njiokiktjien C, Veerman AJ. Visuomotor control in survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only. Journal of the International Neuropsychological Society. 2005;11(05):554-65.
6. Buizer AI, de Sonneville LM, van den Heuvel–Eibrink MM, Veerman AJ. Chemotherapy and attentional dysfunction in survivors of childhood acute lymphoblastic leukemia: effect of treatment intensity. Pediatric blood & cancer. 2005;45(3):281-90.
7. Krull KR, Sabin ND, Reddick WE, Zhu L, Armstrong GT, Green DM et al. Neurocognitive function and CNS integrity in adult survivors of childhood hodgkin lymphoma. Journal of clinical Oncology. 2012;30(29):3618-24.
8. Maris JM. Recent advances in neuroblastoma. New England Journal of Medicine. 2010;362(23):2202-11.
9. Weinstein JL, Katzenstein HM, Cohn SL. Advances in the diagnosis and treatment of neuroblastoma. The Oncologist. 2003;8(3):278-92.
10. ROSENTHAL S, KAUFMAN S. Vincristine neurotoxicity. Annals of Internal Medicine. 1974;80(6):733-7.
11. Thompson SW, t LARRY ED, t MARIO KORNFELD M. Cisplatin N europath y. Cancer. 1984;54:1269-75.
12. Copeland DR, Dowell RE, Fletcher JM, Bordeaux JD, Sullivan MP, Jaffe N et al. Neuropsychological effects of childhood cancer treatment. Journal of Child Neurology. 1988;3(1):53-62.
13. Hockenberry M, Krull K, Moore K, Gregurich MA, Casey ME, Kaemingk K. Longitudinal evaluation of fine motor skills in children with leukemia. Journal of pediatric hematology/oncology. 2007;29(8):535-9.
14. Kaemingk KL, Carey ME, Moore IM, Herzer M, Hutter JJ. Math weaknesses in survivors of acute lymphoblastic leukemia compared to healthy children. Child Neuropsychology. 2004;10(1):14-23.
15. Gurney JG, Tersak JM, Ness KK, Landier W, Matthay KK, Schmidt ML. Hearing loss, quality of life, and academic problems in long-term neuroblastoma survivors: a report from the Children's Oncology Group. Pediatrics. 2007;120(5):e1229-e36.
16. Kadan-Lottick NS, Zeltzer LK, Liu Q, Yasui Y, Ellenberg L, Gioia G et al. Neurocognitive functioning in adult survivors of childhood non-central nervous system cancers. Journal of the National Cancer Institute. 2010;102(12):881-93.
17. Adamson PC, Widemann BC, Reaman GH, Seibel NL, Murphy RF, Gillespie AF et al. A Phase I Trial and Pharmacokinetic Study of 9-cis-Retinoic Acid (ALRT1057) in Pediatric Patients with Refractory Cancer A Joint Pediatric Oncology Branch, National Cancer Institute, and Children's Cancer Group Study. Clinical cancer research. 2001;7(10):3034-9.
18. Wallander JL, Varni JW. Effects of pediatric chronic physical disorders on child and family adjustment. Journal of Child Psychology and Psychiatry. 1998;39(1):29-46.

19. Patenaude AF, Kupst MJ. Psychosocial functioning in pediatric cancer. Journal of pediatric psychology. 2005;30(1):9-27.
20. Laverdière C, Cheung NKV, Kushner BH, Kramer K, Modak S, LaQuaglia MP et al. Long‐term complications in survivors of advanced stage neuroblastoma. Pediatric blood & cancer. 2005;45(3):324-32.
21. Carpentieri S, Diller L. Neuropsychological resiliency after treatment for advanced stage neuroblastoma. Bone marrow transplantation. 2005;35(11):1117-22.
22. Cohen L, Gordon J, Popovsky E, Gunawardene S, Duffey-Lind E, Lehmann L et al. Late effects in children treated with intensive multimodal therapy for high-risk neuroblastoma: High incidence of endocrine and growth problems. Bone marrow transplantation. 2014;49(4):502-8.
23. Laverdière C, Liu Q, Yasui Y, Nathan PC, Gurney JG, Stovall M et al. Long-term outcomes in survivors of neuroblastoma: a report from the Childhood Cancer Survivor Study. Journal of the National Cancer Institute. 2009;101(16):1131-40.
24. Zill N. Behavior problems index based on parent report. Child Trends; 1990.
25. Schultz KAP, Ness KK, Whitton J, Recklitis C, Zebrack B, Robison LL et al. Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. Journal of Clinical Oncology. 2007;25(24):3649-56.
26. Health UDo, Services H. Common terminology criteria for adverse events (CTCAE) version 4.0. National Institutes of Health, National Cancer Institute. 2009;4(03).
27. Panel NOEIE. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. 1998.
28. Organization WH. Physical status: The use of and interpretation of anthropometry, Report of a WHO Expert Committee. 1995.
29. Zeger SL, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. Biometrics. 1986:121-30.