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Childhood Cancer Survivor Study
Analysis Concept Proposal

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Title: The long-term complications of treatment in neuroblastoma survivors

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1.0 Overall Background and Rationale:

Neuroblastoma is a cancer with heterogeneous clinical manifestations and behaviors. Whereas localized tumors can usually be cured by surgical resection alone,[1] metastatic tumors frequently progress despite intensive chemoradiotherapy.[1-2]While the overall survival rate of low-risk neuroblastoma is more than 90%, the overall survival rate for high-risk neuroblastoma patients remains less than 30% at 5 years.[1] However, with the use of high-dose chemotherapy regimens, cis-retinoic acid and immunotherapy, a subset of patients with high-risk disease achieve and maintain a complete remission.[2-4]

Low-risk neuroblastoma patients represent the majority of the neuroblastoma survivors.[1] However, only a limited number of studies have assessed the long term complications from treatment for these patients. These studies described small cohorts of patients treated 20 to 40 years ago. [5-11]In the previous decades, the low-risk patients were more heavily treated with combinations of radical surgery, radiation therapy (often orthovoltage radiation therapy) and chemotherapy.[1] The most common long-term complications reported for these patients are musculoskeletal and neurological problems. [5-11]

The data about the long-term complications from treatment of high-risk neuroblastoma survivors are also limited.[12-18]Given the intensive multimodality therapy and, often, the

young age at the time of the treatment, these patients are at risk for long term complications. A recent analysis of a cohort of 63 high-risk neuroblastoma survivors treated at Memorial Sloan Kettering Cancer Center (MSKCC) showed that 95% of the survivors developed at least one long-term complication and 29% more than three complications. Hearing loss was the most frequent complication (62%), followed by primary hypothyroidism (24%), ovarian failure (41% of female survivors), musculoskeletal problems (19%), pulmonary dysfunction (19%) and neurocognitive dysfunction (13%). 24% of these complications were mild, 44% moderate, 28% severe and 4% very severe. Subsequent malignant neoplasms were noted in 4 (6%) of these patients.[19]

2.0 Sections of the Proposal

This proposal will be presented in two different sections with specific aims and hypotheses. The analyses are as follow:

Analysis 1: The endocrine late effects and the second malignant neoplasms (SMN) in neuroblastoma survivors.
Analysis 2: The musculoskeletal, neurological and sensory problems in neuroblastoma survivors.

Given the broad scope of these aims and analyses, it may be preferable to report the end results of each of these in two separate papers. A final decision will be made once the analyses have been completed.

3.0 Analysis 1: The endocrine late effects and SMN in neuroblastoma survivors

3.1 Specific Background and Rationale

As mentioned in the previous section, a limited number of studies have shown that neuroblastoma survivors are at risk for endocrine problems following their treatment. These problems include primary hypothyroidism, ovarian failure, testicular dysfunction and poor growth.[12, 13, 18]

A risk of SMN has been found in neuroblastoma survivors.[20-29] The cumulative incidence of SMN at 20 years after neuroblastoma treatment is around 3% and the risk increases with time.[23] The most common SMN reported after neuroblastoma are myelodysplasia/leukemia, thyroid neoplasm, soft tissue sarcomas and osteosarcomas and renal cell carcinoma.[20-29]

3.2 Specific Aims

In this population of survivors of neuroblastoma:

3.2.1 Determine the prevalence of these categories of medical conditions: **endocrine and SMN**.

3.2.2 Compare the hazard ratio, reported as the relative risk (RR), of each medical condition **(outcome)** between neuroblastoma survivors and the sibling comparison group (**case-sibling comparisons**).

3.2.3 Compare the hazard ratio, reported as the relative risk (RR) of each outcome among the survivors as a function of treatment group (**case-case comparisons**):

a) **surgery only** vs
b) **surgery plus other therapies (either chemotherapy and/or radiation therapy)**

3.3 Hypotheses

3.3.1 Survivors of neuroblastoma will have an increased risk of endocrine complications and SMN compared to sibling controls.

3.3.2 The group of neuroblastoma survivors treated with **surgery only** will be at lower risk for late complications than the group of survivors treated with **surgery and other modalities of treatment (either chemotherapy and/or radiation therapy)**

3.4. Analysis Framework

3.4.1 Outcomes of interest (baseline questionnaire items)

3.4.1.1 **Endocrine outcomes**: self-reported diagnosis of:

- Hypothyroidism (E.2)
- Growth hormone deficiency (E.8)
- Growth hormone injections (E.9)
- Medication needed to initiate puberty (E.11)

3.4.1.2 **Second malignant neoplasms (SMN):** Externally validated SMN only

- New malignancy
- Recurrence
- Breast lump removal/biopsy

3.4.2 Subject Population (Table1)

- Cases: Neuroblastoma survivors
- Controls: All CCSS siblings
- Controls: Neuroblastoma survivors treated with surgery only (in the case-case comparison)

3.4.3 Exploratory Variables

- **Outcome Variables**: see above

- Exposure variables:
- Exposure to any chemotherapy
- Exposure to Cyclophosphamide and Cyclophosphamide cumulative dose
- Exposure to any radiation therapy
- Radiation therapy field(s): sites and doses

- Potential confounders and effect modifiers:
- Gender
- Ethnicity
- Age at diagnosis
- Year of diagnosis
- Current age
- Time interval between neuroblastoma diagnosis and current age

3.5 Analyses

The analyses will be conducted at the Statistical Center at Fred Hutchison Cancer Research Center.

3.5.1 Obtain the prevalence of each medical condition **(outcome) (Table2)**

3.5.2 Compare the hazard ratio, reported as the relative risk (RR), of each medical condition **(outcome)** between neuroblastoma survivors and the sibling comparison group **(case-sibling comparisons) (Table 2)**

3.5.3 Compare the hazard ratio, reported as the relative risk (RR), of each outcome among the survivors as a function of treatment group (**case-case comparisons**):

a) surgery only vs

b) surgery plus other therapies (either chemotherapy and/or radiation therapy) (Tables 3A-3B)

3.5.4 SPECIFIC ANALYSES: **(Tables 4 and 5)**

Determine the relative risk (RR) of developing **hypothyroidism** following the exposure **to cranial, neck, chest radiation therapy** and **total body irradiation (TBI).**

-Determine the relative risk (RR) of developing **ovarian failure** (medication needed to initiate puberty) following the exposure to **Cyclophosphamide** and evaluate if there is a **dose relationship.**

-Determine the relative risk (RR) of developing **ovarian failure** (medication needed to initiate puberty) following the exposure to **abdominal, pelvic**, **spinal radiation therapy and total body irradiation (TBI).**

-Determine the relative risk (RR) of developing **growth hormone deficiency** after exposure to **cranial radiation therapy** and **total body irradiation (TBI).**

- Determine the relative risk (RR) of developing a s**econd malignant neoplasms (SMN) following the exposure to chemotherapy and/or any radiation therapy.**

Analyses will be adjusted for age at diagnosis, gender and other variables as appropriate.

For the radiation therapy data, the first pass data or best available will be used for the main analysis.

4.0 Analysis 2: The musculoskeletal, neurological and sensory problems in neuroblastoma survivors.

4.1 Specific Background and Rationale:

Musculoskeletal effects described in neuroblastoma survivors include scoliosis, kyphosis, hypoplasia and fibrosis of bone and soft tissues, as well as slipped capital femoral epiphysis. [6-8] Most of the patients who develop scoliosis have been treated with moderate to high doses of orthovoltage radiation therapy (1500-5000cGy) and received asymmetric irradiation of the spine.[6-8]

Neurological deficits reported in this population include paresthesias, mild to severe paresis, paraplegia and neurogenic bladder. [6-Error! Bookmark not defined.] These complications are related to the disease itself (intraspinal tumors) and/or to surgery.

Hearing loss secondary to cisplatin and/or carboplatin exposure is well described [30-33].The hearing loss is more pronounced in the high frequency range but speech frequencies can also be affected. There is controversial data concerning the cisplatin dose relationship with the development of the ototoxicity[32, 33].

4.2 Specific Aims:

In this population of survivors of neuroblastoma:

4.2.1 Determine the prevalence of these categories of medical conditions: **musculoskeletal, neurological and sensory problems.**

4.2.2 Compare the hazard ratio, reported as the relative risk (RR), of each medical condition **(outcome)** between neuroblastoma survivors and the sibling comparison group (**case-sibling comparisons**)

4.2.3 Compare the hazard ratio, reported as the relative risk (RR), of each outcome among the survivors as a function of treatment group (**case-case comparisons**):

a) surgery only vs
b) **surgery plus other therapies (either chemotherapy and/or radiation therapy)**

4.3 Hypotheses

4.3.1 Survivors of neuroblastoma will have an increased risk of musculoskeletal and neurological complications and sensory impairments compared to sibling controls.

4.3.2 The group of neuroblastoma survivors treated with **surgery only** will be at lower risk for late complications than the group of survivors treated with **surgery and other modalities of treatment (either chemotherapy and/or radiation therapy)**

4.4. Analysis Framework

4.4.1 Outcomes of interest (baseline questionnaire items)

4.4.1.1 **Bone and joint Health:** self-reported diagnosis of:

- Scoliosis surgery (I.2)
- Osteoporosis (E.10)

4.4.1.2 **Neurological problems:** self-reported diagnosis of:

- Paralysis (J.2)
- Seizures (J.5)
- Problems with balance (J.8)
- Tremor or movement problems (J. 9)
- Weakness in arms or Weakness in legs (J10, J.11)
- Decreased sense of touch, feeling in hands, fingers, arms or leg (J.12)
- Prolonged pain or abnormal sensation in arms, legs or back (J.13)

4.4.1.3 **Sensory Problems:** self-reported diagnosis of:

- Hearing loss and Deafness (C.1 and C.2)
- Blindness (C.8)
- Cataracts (C.9)

4.4.2 Subject Population (Table 1)

- Cases: Neuroblastoma survivors
- Controls: All CCSS siblings
- Controls: Neuroblastoma survivors treated with surgery only (in the case-case comparison)

4.4.3 Exploratory Variables

- Outcome Variables: see above

- Exposure variables:

- Exposure to any chemotherapy
- Exposure to Cisplatin and Cisplatin cumulative dose
- Exposure to any radiation therapy
- Radiation therapy field(s): sites and doses

-Potential confounders and effect modifiers:

-Gender
-Ethnicity
-Age at diagnosis
-Year of diagnosis
-Current age
-Time interval between neuroblastoma diagnosis and current age

4.5 Analyses

The analyses will be conducted at the Statistical Center at Fred Hutchison Cancer Research Center.

4.5.1 Obtain the prevalence of each medical condition **(outcome) (Table 6)**

4.5.2 Compare the hazard ratio, reported as the relative risk (RR), of each medical condition **(outcome)** between neuroblastoma survivors and the sibling comparison group **(case-sibling comparisons) (Table 6)**

4.5.3 Compare the hazard ratio, reported as the relative risk (RR) among the survivors as a function of treatment group (**case-case comparisons**): **(Tables 7A-7C)**

a) **surgery only** vs
b) **surgery plus other modalities of treatment (either chemotherapy and/or radiation therapy)**

4.5.4 SPECIFIC ANALYSES (Tables 8 A-8D)

-Determine the relative risk (RR) of developing a **severe scoliosis** (surgery needed) following the exposure to **laminectomy, laparotomy, thoracotomy, chest and spine radiation therapy and total body irradiation (TBI).**

- Determine the relative risk (RR) of developing any of the **neurological outcome** following the exposure to **vincristine, autologous bone marrow transplantation, cranial radiation and total body irradiation (TBI).**

-Determine the relative risk (RR) of developing any of the **neurological outcome** with an age at diagnosis of **under 1 year old** versus **older than one year old.**

- Determine the relative risk (RR) of developing **hearing loss and deafness** following the exposure to **Cisplatin** and evaluate if there is a **dose relationship.**

- Determine the relative risk (RR) of developing **hearing loss and deafness** following the exposure to **cranial radiation therapy**, and **total body irradiation (TBI).**

-Determine the relative risk (RR) of developing any of the **visual outcome** following the exposure to **cranial radiation and total body irradiation (TBI)**

Analyses will be adjusted for age at diagnosis, gender and other variables as appropriate.

For the radiation therapy data, the first pass data or best available will be used for the main analysis.

Table 1: Characteristics of neuroblastoma survivors and sibling cohorts

Characteristic	Survivors (n = 830)	Siblings (n=3846)
Gender		
Male	387(47%)	1846(48%)
Female	443(53%)	2000(52%)
Vital status at baseline questionnaire		
Alive	802(97%)	
Dead	28(3%)	
Age at diagnosis (years)		
< 1	456(55%)	
1 – 4	298(36%)	
5 – 9	57(7%)	
10 – 14	12(1%)	
15 – 20	6(0.7%)	
Age at interview (years)		
< 10	32(4%)	76(2%)
10 – 19	543(65%)	1006(26%)
20 – 29	234(28%)	1364(35%)
30 – 39	20(2%)	1093(28%)
40 – 49	1(.1%)	307(8%)
Year of diagnosis		
1970 – 1978	335(40%)	
1979 – 1984	368(44%)	
1985 – 1986	127(15%)	
Survival time (years)		
5 – 9	76(9%)	
10 – 14	299(36%)	
15 – 19	258(31%)	
20 – 24	168(20%)	
> 25	29(4%)	
Treatment group		
Surgery only (S)	199(24%)	
Surgery plus other therapies (either chemotherapy and/or radiation therapy)	632 (76%)	

Table 2: Medical Outcomes (endocrine and SMN) reported in NB survivors and relative risk of each outcome compared to siblings (case-sibling comparison group)

Medical Condition	Total reported Outcomes			
	N (%)	Yes	Rate	RR (95%CI)
Endocrine impairments				
Hypothyroidism	28(3.4)			
Growth hormone deficiency	28(3.4)			
Growth hormone injections	20(2.4)			
Medication needed to initiate puberty	22(2.6)			
Second cancer				
New malignancy	19(2.3)			
Recurrence	10(1.2)			
Breast lump removal/biopsy	15(1.8)			

Table 3A: Endocrine related outcomes by treatment group among cases

Outcome	Variable	Nb	RR	95% CI	p-value
Hypothyroidism					
	S				
	S + O				
Growth hormone deficiency					
	S				
	S + O				
Growth hormone injections					
	S				
	S + O				
Medication needed to initiate puberty					
	S				
	S + O				

S: surgery
S + O: surgery and other modalities of treatment (either chemotherapy and/or radiation therapy)

Table 3B: SMN by treatment group among cases

Outcome	Variable	Nb	RR	95% CI	p-value
New malignancy					
	S				
	S + O				
Recurrence					
	S				
	S + O				
Breast lump removal/biopsy					
	S				
	S + O				

S: surgery
S + O: surgery and other modalities of treatment (chemotherapy and/or radiation therapy

Table 4: Specific risk factors for the occurrence of a particular endocrine outcome (comparison between patients with and without the risk factor)

	Nb	RR	95% CI	p-value
Hypothyroidism				
Cranial radiation therapy				
Yes				
No				
Neck radiation therapy				
Yes				
No				
Chest radiation therapy				
Yes				
No				
Total body irradiation				
Yes				
No				
Medication needed to initiate puberty (ovarian failure)				
Cyclophosphamide				
Yes				
No				
Cyclophosphamide dose				
≤5 g				
5-10 g				
>5 g				
Abdominal radiation therapy				
Yes				
No				
Pelvic radiation therapy				
Yes				
No				
Spine radiation therapy				
Yes				
No				
Growth hormone deficiency				
Cranial radiation therapy				
Yes				
No				
Total body irradiation				
Yes				
No				

Table 5: Specific risk factors for the occurrence of second malignant neoplasms (SMN) (comparison between patients with and without the risk factor)

	Nb	RR	95% CI	p-value
Exposure to any chemotherapy				
Yes				
No				
Exposure to any radiation therapy				
Yes				
No				

Table 6: Medical outcomes (musculoskeletal, neurological and sensory) reported in NB survivors and relative risk of each outcome compared to siblings (case-sibling comparison group)

Medical Condition	Total reported Outcomes			
	N (%)	Yes	Rate	RR (95% CI)
Musculoskeletal impairments				
Scoliosis surgery	41(4.9)			
Osteoporosis	13(1.6)			
Neurological impairments				
Paralysis	47(5.7)			
Seizures	49(5.9)			
Problems with balance	64(7.7)			
Tremor or movement problems	38(4.6)			
Weakness in arms or legs	130(15.7)			
Decreased sense of touch, feeling in hands, fingers, arms or legs	72(8.7)			
Prolonged pain or abnormal sensations in arms, legs or back	86(10.4)			
Sensory				
Hearing loss/deafness	39(4.7)			
Blindness	30(3.6)			
Cataract	22(2.6)			

Table 7A: Musculoskeletal related outcomes by treatment group among cases

Outcome	Variable	Nb	RR	95% CI	p-value
Scoliosis surgery					
	S				
	S + O				
Osteoporosis					
	S				
	S + O				

S: surgery
S + O: surgery and other modalities of treatment (either chemotherapy and/or radiation therapy)

Table 7B: Neurological outcomes by treatment group among cases

Outcome	Variable	Nb	RR	95% CI	p-value
Paralysis					
	S				
	S + O				
Seizures	S				
	S + O				
Problems with balance					
	S				
	S + O				
Tremor or movement problems					
	S				
	S + O				
Weakness in arms or legs	S				
	S + O				
Decreased sense of touch, feeling in hands, fingers, arms, legs					
	S				
	S + O				
Prolonged pain or abnormal sensation Arms, legs or back					
	S				
	S + O				

S: surgery

S + O: surgery and other modalities of treatment (either chemotherapy and/or radiation therapy

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Table 7C: Sensory problems by treatment group among cases

Outcome	Variable	Nb	RR	95% CI	p-value
Hearing loss/ Deafness	S				
	S + O				
Blindness					
	S				
	S + O				
Cataract					
	S				
	S + O				

S: surgery
S + O: surgery and other modalities of treatment (either chemotherapy and/or radiation therapy

Table 8A: Specific risk factors for the occurrence of a severe scoliosis (surgery needed) (comparison between patients with and without the risk factor)

	Nb	RR	95% CI	p-value
Laminectomy				
Yes				
No				
Laparotomy				
Yes				
No				
Thoracotomy				
Yes				
No				
Spine RT				
Yes				
No				
Chest RT				
Yes				
No				
TBI				
Yes				
No				

Table 8B: Specific risk factors for the occurrence of any neurological outcome (comparison between patients with and without the risk factor)

	Nb	RR	95% CI	p-value
Age at diagnosis				
<1 year old				
>1 year old				
Exposure to Vincristine				
Yes				
No				
Autologous Bone Marrow Transplantation				
Yes				
No				
Cranial RT				
Yes				
No				
Total Body Irradiation				
Yes				
No				

Table 8C: Specific risk factors for the occurrence of hearing loss and deafness (comparison between patients with and without the risk factor)

	Nb	RR	95% CI	p-value
Cisplatin				
Yes				
No				
Cisplatin dose				
>300 mg/m^2				
300-600 mg/m^2				
>600 mg/m^2				
Cranial radiation therapy				
Yes				
No				
Total body irradiation				
Yes				
No				

Table 8D: Specific risk factors for the occurrence of any visual outcome (comparison between patients with and without the risk factor)

	Nb	RR	95% CI	p-value
Cranial RT				
Yes				
No				
TBI				
Yes				
No				

References

[1] Brodeur GM, Maris JM. Neuroblastoma..In Pizzo PA, Poplack DG (eds), Principles and Practice of Pediatric Oncology, 4th Edition, Philadelphia, PA: Lippincott, Williams & Wilkins, 2002, pp. 895-937.

[2] Kushner BH, LaQuaglia MP, Bonilla MA et al.Highly effective induction therapy for stage 4 neuroblastoma in children over 1 year of age. J Clin Oncol 1994; 12: 2607-2613.

[3] Cheung NKV, Kushner BH, Cheung IY et al. Anti-G_{D2} antibody treatment of minimal residual stage 4 neuroblastoma diagnosed at more than 1 year of age. J Clin Oncol 1998;16:3053-3060.

[4] Matthay KK, Villablanca JG, Seeger RC et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. N Engl J Med 1999; 341:1165-1173.

[5] Mayfield JK, Riseborough EJ, Jaffe N et al. Spinal deformity in children treated for neuroblastoma: the effect of radiation and other forms of treatment. J Bone Joint Surg 1981;63:183-193.

[6] Pastore G, Antonelli R, Fine W et al. Late effects of treatment of cancer in infancy. Med Pediatr Oncol 1982;10:369-375.

[7] Kajanti M. Neuroblastoma in 88 children: clinical features, prognostic factors, results and late effects of therapy. Ann Clin Res 1983;15(Suppl 39):1-68.

[8] Pastore G, Zurlo MG, Acquaviva A et al. Health status of young children with cancer following discontinuation of therapy. Med Pediatr Oncol 1987;15:1-6.

[9] Azizkhan RG, Shaw A, Chandler JG. Surgical complications of neuroblastoma resection. Surgery 1985;97:514-517.

[10] Nitschke R, Smith EI, Shochat S et al. Localized neuroblastoma treated by surgery: a Pediatric Oncology Group Study. J Clin Oncol 1988;6:1271-1279.

[11] Cruccetti A, Kiely EM, Spitz L et al. Pelvic neuroblastoma: low mortality and high morbidity. J Pediatr Surg 2000;35:724-728

[12] Willi SM, Cooke K, Goldwein J et al. Growth in children after bone marrow transplantation for advanced neuroblastoma compared with growth after transplantation for leukemia or aplastic anemia. J Pediatr 1992;120:726-732.

[13] Olshan JS, Willi SM, Gruccio D et al. Growth hormone function and treatment following bone marrow transplant for neuroblastoma. Bone Marrow Transplant 1993;12:381-385.

[14] Kaste SC, Hopking KP, Bowman LC et al. Dental abnormalities in children treated for neuroblastoma. Med Pediatr Oncol 1998;30:22-27.

[15]Barr RD, Chalmers D, De Pauw S et al. Health-related quality of life in survivors of Wilms' tumor and advanced neuroblastoma: a cross-sectional study. J Clin Oncol 2000;18:3280-3287.

[16]Koyle MA, Hatch DA, Furness PD III et al. Long-term urological complications in survivors younger than 15 months of advanced stage abdominal neuroblastoma. J Urol 2001;166:1455-1458.

[17] Hölttä P, Alaluusua S, Saarinen-Pihkala UM et al. Long-term adverse effects on dentition in children with poor-risk neuroblastoma treated with high-dose chemotherapy and autologous stem cell transplantation with or without total body irradiation. Bone Marrow Transplant 2002;29:121-127.

[18]Van Santen HM, de Kraker J, van Eck BLF et al. High incidence of thyroid dysfunction despite prophylaxis with potassium iodide during ^{131}I-metaiodobenzylguanidine treatment in children with neuroblastoma. Cancer 2002;94:2081-2089.

[19] Laverdière C, Gurney J, Sklar C. The long-term complications of treatment and quality of life of survivors of neuroblastoma. In: Cheung NKV and Cohn S (eds): Neuroblastoma. New York, NY: Springer-Verlag (in press).

[20] Meadows AT, Baum E, Fossati-Bellani F et al. Second malignant neoplasms in children: an update from the Late Effects Study Group. J Clin Oncol 1985;3:532-538.

[21] de Vathaire F, François P, Hill C et al. Role of radiotherapy and chemotherapy in the risk of second malignant neoplasms after cancer in childhood. Br J Cancer 1989;59:792-796.

[22] Kushner BH, Cheung NKV, Kramer K et al. Neuroblastoma and treatment-related myelodysplasia/leukemia: the Memorial Sloan-Kettering experience and a literature review. J Clin Oncol 1998;16:3880-3889.

[23]Neglia JP, Friedman DL, Yasui Y et al. Second malignant neoplasms in five-year survivors of childhood cancer: Childhood Cancer Survivor Study. J Nat Cancer Inst 2001;93:618-629.

[24]Le Deley MC, Leblanc T, Shamsaldin A et al. Risk of secondary leukemia after a solid tumor in childhood according to the dose of epipodophyllotoxins and anthracyclines : a case-control study by the Société Française d'Oncologie Pédiatrique. J Clin Oncol 2003;21:1074-1081.

[25]Tucker MA, Morris Jones PH, Boice JD Jr. et al. Therapeutic radiation at a young age is linked to secondary thyroid cancer. Cancer Res 1991;51:2885-2888.

[26]Weiss B, Vora A, Huberty J et al. Secondary myelodysplastic syndrome and leukemia following ^{131}I-metaiodobenzylguanidine therapy for relapsed neuroblastoma. J Pediatr Hematol/Oncol 2003;25:543-547.

[27] Rubino C, de Vathaire F, Dottorini ME et al. Second primary malignancies in thyroid cancer patients. Br J Cancer 2003;89:1638-1644.

[28] Acharya S, Sarafoglou K, LaQuaglia M et al. Thyroid neoplasms after therapeutic radiation for malignancies during childhood or adolescence. Cancer 2003;97:2397-2403

[29] Bassal M, Kadan-Lottick NS, Neglia J et al. Risk of rare adult-type carcinomas as a subsequent malignant neoplasm in survivors of childhood cancer: The Childhood Cancer Survivor Study. ASCO 2004 Annual Meeting Proceedings.

[30]Schell MJ, McHaney VA, Green AA et al Hearing loss in children and young adults receiving cisplatin with or without prior cranial irradiation. J Clin Oncol 1989 7:754-760

[31]Parsons SK, Neault MW, Lehmann LE et al Severe ototoxicity following carboplatin-containing conditioning regimen for autologous marrow transplantation for neuroblastoma. Bone Marrow Transplant 1998 22:669-674

[32]Skinner R, Pearson ADJ, Amineddine HA et al Ototoxicity of cisplatinum in children and adolescents. Br J Cancer 1990 61:927-931

[33]Simon T, Hero B, Dupuis W et al) The incidence of hearing impairment after successful treatment of neuroblastoma [german]. Klin Padiatr 2002 214:149-152