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The effect of age distribution on the prognosis of retroperitoneal neuroblastoma

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Abstract

Retroperitoneal neuroblastoma is a rare subtype of neuroblastoma and the role of age in its clinical prognosis is still unknown.

To describe the age distribution and investigate the association between age and survival outcomes in patients diagnosed with retroperitoneal neuroblastoma.

We retrospectively analyzed patients registered for retroperitoneal neuroblastoma in the Surveillance, Epidemiology, and End Results (SEER) national database from 1973 to 2015. Age distribution was described and Cox proportional hazard regression was used to evaluate the measured effect of age on overall survival and disease-specific survival.

A total of 399 retroperitoneal neuroblastoma patients with a median follow-up of 53.0 (interquartile range 17.0–133.5) months were included. We found a unimodal distribution of age with a median age of diagnosis to be 1.0 (interquartile range 0.0–4.0) years. Univariate analysis suggested that transformed age was associated with an increased risk of total death and disease-specific death (OR = 4.2, 95% CI 3.0–5.9; OR = 4.7, 95% CI 3.2–6.8). Adjusted smoothed plots showed a nonlinear correlation between age and disease-specific death. The risk of disease-specific death did not increase sharply as the age increased until reaching the inflection point (age < 3 years, OR = 0.4, 95% CI 0.2–1.0; age ≥ 3 years, OR = 1.2, 95% CI 0.9–1.5). There was, however, a linear relationship between age and total deaths (OR = 1.0, 95% CI 0.7–1.2). Adjusted multivariate Cox regression analysis showed that ages ≥ 3 years were associated with a significant increased risks of disease-specific death and total death (OR = 2.5, 95% CI 1.7–3.8; OR = 2.3, 95% CI 1.6–3.3, respectively).

There was a unimodal age distribution of retroperitoneal neuroblastoma usually presented in infants or younger child. Older age was associated with a lower chance of overall survival and the risk of disease-specific death increased sharply after 3 years of age.

Abbreviations: AJCC = American Joint Committee on Cancer, CI = confidence intervals, HRs = hazard ratios, ICD = International Classification of Diseases, INRG = International Neuroblastoma Risk Group, INRGSS = International Neuroblastoma Risk Group Staging System, INSS = International Neuroblastoma Staging System classification, SEER = Surveillance, Epidemiology, and End Results.

Keywords: age distribution, disease-specific survival, overall survival, retroperitoneal neuroblastoma, retrospective study

1. Introduction

Neuroblastoma is relatively rare, yet it is the most common cancer in babies and the third most common cancer in childhood.[1] Data from the National Cancer Institute suggests neuroblastoma affects approximately 1 in every 7000 children.[2] The incidence rate is highest in the first year of life and gradually decreases with age, becoming extremely rare after 10 years of age.[3] The World Cancer Report reveals neuroblastoma remains one of the most fatal cancers in early childhood, contributing to 15% of cancer deaths in children.[4]

Neuroblastoma can arise from neuroblasts (pluripotent sympathetic cells) anywhere along the sympathetic nervous system chain from the neck to the pelvis. Retroperitoneal neuroblastoma represented the most common type of primary neuroblastoma, usually occurred in adrenal gland.[5] Due to its rare occurrence, current evidence regarding the prognoses of neuroblastoma is largely extrapolated from small retrospective studies or cohorts with limited follow-up. Though the International Neuroblastoma Risk Group (INRG) has developed a standard classification system,[6,7] scarce evidence exists concerning the effect of age distribution on the prognosis of retroperitoneal neuroblastoma. Recent studies suggested that age of onset can exert impact on the therapeutic strategy and prognosis of neuroblastoma, whose pattern may also be affected byprimary site of the tumor.[6,8,9] Therefore, the objective of our study is to investigate the effect of age distribution on the prognosis of all-cause mortality and cancer-specific survival of patients with retroperitoneal neuroblastoma.

2. Materials and methods

2.1. Identification of the cohort study

The Surveillance, Epidemiology, and End Results (SEER) database is a national database of cancer research from the

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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National Cancer Institute, which contains epidemiology and survival data covering almost 26% of the United States population.[10] We obtained the required approval from the SEER program and approached the database form with SEER*stat software version 8.3.2.

All cases of neuroblastoma in the SEER database between years 1973 to 2015 were retrieved to assess the prognosis of retroperitoneal neuroblastoma. In order to restrict the primary occurrence site of the tumor to the retroperitoneum, we used the code C48.0-Retroperitoneum. Additionally, we set the ICD.O.3 histological behavior code to be 9500/3: Neuroblastoma, NOS. The following baseline data records were collected: Age at diagnosis, gender, year of diagnosis, race, AJCC stage, summary stage, histology grade, tumor size, surgical procedures, positivity of lymph node dissection, radiation sequence with surgery, chemotherapy, and metastasis to bone.

2.2. Statistical analysis

The primary outcome was disease-specific survival time and it was defined as the time from the diagnosis of primary neuroblastoma until disease-specific death. Overall survival time was considered as the secondary outcome. Dichotomous descriptive data was presented as observed counts and percentages. Continuous data was presented as a median interquartile range. As ages of the included patients were strongly skewed left, we transformed age to lg (1+age) for analysis. Univariate analysis was performed to assess factors affecting survival outcomes, including: age, gender, summary stage, surgical procedures, positivity of lymph node dissection, radiation sequence with surgery, chemotherapy, and metastasis to bone.

We further conducted a 2-piece linear regression model to assess the threshold effect of age on disease-specific survival time and overall survival time using a smoothing function. The threshold level, or inflection point, was determined with trial and error by selecting inflection points along a pre-defined interval and then identifying the inflection point that provided the maximum model likelihood. When identifying the inflection point, covariates were also adjusted, including: Gender, race, summary stage, surgical procedures, positivity of lymph node dissection, radiation sequence with surgery, chemotherapy, and metastasis to bone. After we obtained the inflection point, we divided the patients into 2 groups based on the age threshold level.

To further evaluate the independent effect of age distribution on survival outcomes, multivariate Cox proportional regression analysis was adopted to calculate hazard ratios (HRs) and 95% confidence intervals (CI). Covariates included in the models were gender, race, summary stage, surgical procedures, positivity of lymph node dissection, radiation sequence with surgery and chemotherapy. A 2-tailed P value $< .05$ was considered statistically significant. All data analyses were performed using R (http://www.R-project.org) and Empower(R) (www.empowerstats.com, X&Y Solutions, Inc. Boston, MA).

3. Results

A total of 399 retroperitoneal neuroblastoma patients (45.1% female and 54.9% male) diagnosed between 1973 and 2015 were recruited in our study. Baseline characteristics of this cohort were summarized in Table 1. The majority of the population was white (77.1%). The staging system included AJCC stage and summary stage of the SEER database. Only a relatively small portion of the tumors were localized (15.2%). Over half of the patients (53.7%) already had distant metastasis, and 31.1% of the tumors were regional. Most patients underwent surgery (67.2%). Among those only 8.5% had radical removal of the tumor, while others received debulking surgery. Data concerning surgical margin status (R0, R1, R2) were not available. Dissection of the lymph nodes revealed 61.1% positivity. During the perioperative period, 17.0% patients received radiotherapy and 75.7% patients received chemotherapy. Median follow-up of the entire cohort was 53.0 months (interquartile range of 17.0–133.5 months).

The median age of diagnosis was 1.0 year (interquartile range of 0.0–4.0 years). We observed a unimodal distribution of age, namely most retroperitoneal neuroblastoma occurring in infants. The age distribution was shown in Figure 1. The incidence of retroperitoneal neuroblastoma was infrequent in the >30 years

Table 1

Baseline characteristics of patients diagnosed with retroperitoneal neuroblastoma.

Variable	Value*
Age (yr)	1.0 (0.0–4.0)
Year of diagnosis	2003 (1993–2009)
Follow-up time (mo)	53.0 (17.0–133.5)
Sex	
Female	180 (45.1%)
Male	219 (54.9%)
Race	
White	306 (77.1%)
African American	63 (15.9%)
Other	28 (7.1%)
Summary stage	
Localized	59 (14.8%)
Regional	120 (30.1%)
Distant	208 (52.1%)
Unknown	12 (3.0%)
Histology grade	
Grade I	8 (2.0%)
Grade II	6 (1.5%)
Grade III	133 (33.3%)
Grade IV	39 (9.77%)
Unknown	213 (53.4%)
Surgical procedures	
No surgery	131 (32.8%)
Debulking surgery	234 (58.6%)
Radical surgery	34 (8.5%)
Lymph Node biopsy	
Positive	150 (37.6%)
Negative	236 (59.2%)
Unknown	13 (3.3%)
Radiotherapy	
No	331 (83.0%)
Yes	68 (17.0%)
Chemotherapy	
No	97 (24.3%)
Yes	302 (75.7%)
Treatment	
No surgery	128 (32.1%)
Surgery only	204 (51.1%)
Adjuvant radiotherapy	59 (14.8%)
Neoadjuvant radiotherapy	2 (0.5%)
Radiotherapy before and after surgery	2 (0.5%)
Intraoperative with perioperative radiotherapy	4 (1.0%)

* Value expressed as median (interquartile range) or N (%).

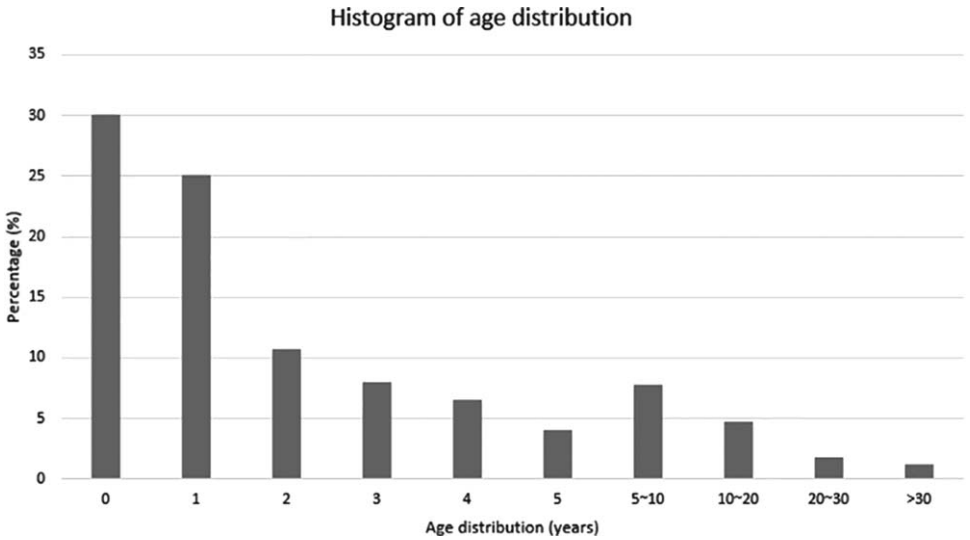

Figure 1. Age distribution.

age group. Univariate analysis suggested transformed age was associated with an increased risk of total death and disease-specific death (OR = 4.2, 95% CI 3.0–5.9; OR = 4.7, 95% CI 3.2–6.8). Adjusted smoothed plots showed a nonlinear correlation between age and disease-specific death. The risk of disease-specific death did not increase sharply with age until reaching the inflection point (age < 3 years, OR = 0.4, 95% CI 0.2–1.0; age≥3 years, OR = 1.2, 95% CI 0.9–1.5, Fig. 2, Table 2). Additionally, there was a linear relationship between age and total deaths (OR = 1.0, 95% CI 0.7–1.2).

During the follow-up, out of a total of 145 deaths, 124 were attributed to neuroblastoma. Univariate predictive analysis suggested age, summary stage, surgery, nonradical surgery, positivity of lymph node dissection, radiotherapy, chemotherapy, and metastasis to bone were predictors of total death and disease-specific death. After observing the age inflection point, we further divided the cohort into 2 groups – age<3 years and age≥3 years. To further assess the independent effect of older aged child on survival, we performed multivariate Cox proportional regression analysis including 3 models. Kaplan–Meier survival curve of disease-specific death is shown in Figure 3. Crude analysis showed age≥3 years was associated with significantly increased rate of disease-specific death (OR = 3.3, 95% CI 2.3–4.7). Adjusted multivariate models also suggested similar results

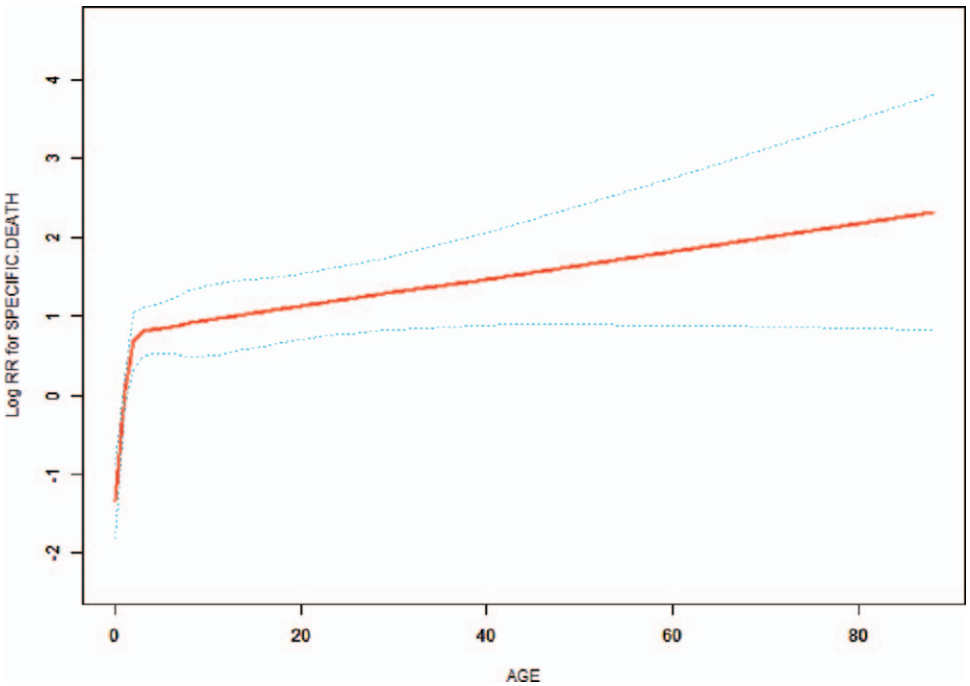

Figure 2. Correlation between age and disease-specific death.

Table 2

Threshold effect analysis of age on survival outcomes using piece-wise linear regression.

Outcome:	Disease-specific death*	Total death*
Model I		
Linear β	1.0 (0.7, 1.2) 0.748	1.0 (0.7, 1.2) 0.737
Model II		
Turning point (K)	3	3
< K β1	0.4 (0.2, 1.0) 0.045	0.4 (0.2, 1.0) 0.053
> K β2	1.2 (0.9, 1.5) 0.235	1.2 (0.9, 1.5) 0.243
Difference between β1 and β2	2.9 (1.0, 8.5) 0.048	2.8 (1.0, 7.9) 0.057

* Outcomes were expressed as HR (95% CI) *P*-value; β, regression coefficient.

(Model I: OR = 2.5, 95% CI 1.7–3.6; Model II: OR = 2.5, 95% CI 1.7–3.8, Table 3). As for long-term all-cause mortality, the crude model indicated age≥3 years was correlated with a significantly increased risk of all-cause mortality (OR = 2.8, 95% CI 2.0–3.9), which was also confirmed by adjusted multivariate models (shown in Table 3).

4. Discussion

To the best of our knowledge, this is the first population-based national study of primary retroperitoneal neuroblastoma that assessed the association between age and the prognosis of the disease. Our study included a total of 339 patients diagnosed with primary retroperitoneal neuroblastoma over 42 years in a nationwide database, representing a helpful experience and review of this rare tumor type and contributing to further understanding of this subtype of neuroblastoma. According to our results, retroperitoneal neuroblastoma presented with a unimodal distribution with the tumor most frequently diagnosed in the first 3 years. Age was found to be an independent factor associated with both long-term all-cause mortality and disease-specific death. The correlation between total death and age was found to be linear, the risk of death increased 3-fold as the age increased 9 years. While the relationship of age with disease-specific death was nonlinear, the risk increased smoothly when the age grew from 0 to 3 years, and then increased more sharply as the age grew after 3 years. In addition, a significant difference in survival existed in patients aged >3 years and ≤3 years.

Over the past 3 decades, retroperitoneal neuroblastoma records in the SEER database indicated a steady increase in numbers of patients diagnosed. Initially 41 patients were diagnosed between 1972 and 1984, then 51 patients were diagnosed from 1984 to 1994, followed by a sharp increase to 103 patients from 1994 to 2004. In the last decade, the number of registered patients increased to 204. Based on the sharp increase

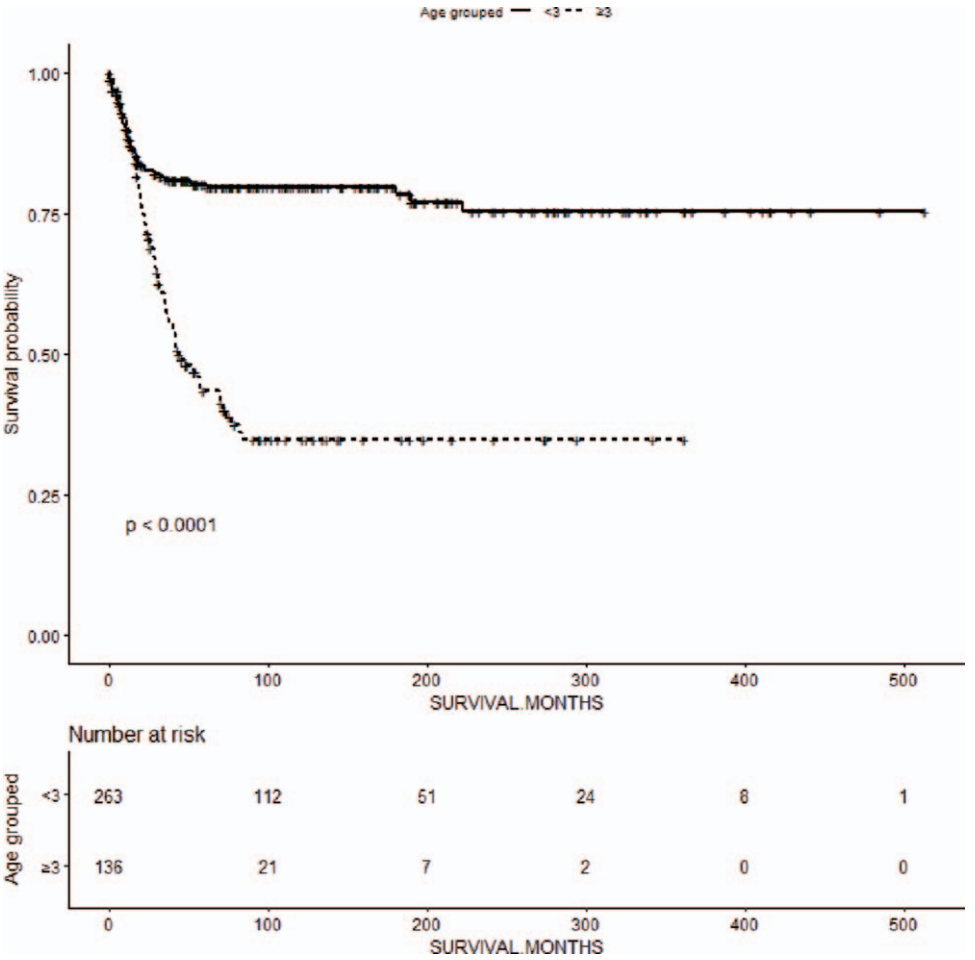

Figure 3. Kaplan–Meier survival curve of disease-specific death.

Table 3

Multivariate Cox proportional hazard regression analysis of the effect of age on survival outcomes.

Exposure	Crude	Model I	Model II
Disease-specific death			
Age			
<3 yr	1.0	1.0	1.0
≥3 yr	3.3 (2.3, 4.7) <0.001	2.5 (1.7, 3.6) <0.001	2.5 (1.7, 3.8) <0.001
Total death			
Age			
<3 yr	1.0	1.0	1.0
≥3 yr	2.8 (2.0, 3.9) <0.001	2.2 (1.5, 3.1) <0.001	2.3 (1.6, 3.3) <0.001

Model I: adjust for gender, age, summary stages; Model II: adjust for gender, race, summary stage, surgical procedures, positivity of lymph node dissection, radiation sequence with surgery and chemotherapy; values expressed as HR (95% CI) *P*-value.

in the number of cases in the SEER data, a greater clinical awareness of retroperitoneal neuroblastoma was reflected in proportion to the increase in the incidence of the disease. Notwithstanding, due to the very rare occurrence of retroperitoneal neuroblastoma in general, biological and clinical characteristics were still not fully understood.

More recently, several studies have investigated the age distribution of overall neuroblastoma and the relationship between age and prognosis.[11–13] The most common age of diagnosis was reported to be from 18 to 22 months old, and the majority of cases presented before 5 years old.[14] Our study found that retroperitoneal neuroblastoma has a similar age distribution compared with overall neuroblastoma. Based on data from the International Neuroblastoma Risk Group Staging System (INRGSS), it was commonly observed that diseases in infants younger than 18 months may spontaneously regress or be treated successfully with surgery.[14] By comparison, older children may have worse prognoses due to more aggressive and resilient tumors. However, the International Neuroblastoma Staging System classification (INSS) proposed that the age cutoff point for prognosis was 12 months compared with the INRGSS classification, which put the age at 18 months.[6,7] Yet, none of the classification systems addressed specific correlation between age and prognosis of retroperitoneal neuroblastoma. Endowed with the rich resource of the national database, our study suggestsed similar linear correlation between age and survival of retroperitoneal neuroblastoma – namely that older age was associated with worse clinical survival. In contrast with other studies, we found the inflection point was at 3 years of age – the risk of disease-specific death increased slowly for ages under 3 years and then increased more sharply for ages over 3 years. This relationship of age with survival outcomes in retroperitoneal neuroblastoma was similar to that in olfactory neuroblastoma, with different infection point in age.[15] Recent studies revealed potential association between age at diagnosis, genetic properties of the tumor cells and prognosis of neuroblastoma,[16] which may explain the results of our study. Besides, different cutting point of age may suggest retroperitoneal neuroblastoma is a unique subtype of neuroblastoma that required more exploration.

The major limitation of our study was unavoidable selection bias and intrinsic information bias, due to the fact that this was a retrospective review of the national database. Since data from the newly developed International Neuroblastoma Risk Group Staging System (INRGSS) were not available, a relatively rough summary stage of the SEER database was used instead, which may have introduced misclassification bias. Data from another widely used classification system – the International Neuroblastoma Staging System (INSS) – was also not available. Despite these limitations, our study also had considerable strengths. First, this was a detailed review of the national database that included long-term follow-up data on the prognosis of rare diseases. Second, we adopted 2 different multivariate Cox proportional regression models to assess the real effect of age >3 years on survival. After adjusting for different groups of potentially confounding factors, the effect measures of different models were still within 10%, thus proving the robustness of our results.[17]

5. Conclusion

This retrospective review of the largest series of retroperitoneal neuroblastoma cohort from the SEER database indicated that retroperitoneal neuroblastoma usually presented in the infants with a unimodal age distribution. Age was proved to be a significant prognostic factor in predicting overall survival and disease-specific survival. Older age was associated with worse overall survival, and the risk of disease-specific death was significantly higher and increased sharply after 3 years of age.

Author contributions

All authors contributed to this research. Xiaoyan Liu contributed to manuscript writing and data analysis; Jichun Zhao contributed to manuscript writing, drafting conception and design and draft revision; Yukui Ma contributed to manuscript writing and drafting conception and design; and Lin Zhang and Jing Huang contributed to data collection, data analysis, and manuscript writing.

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References

[1] Maris JM, Hogarty MD, Bagatell R, et al. Neuroblastoma. Lancet 2007;369:2106–20.
[2] "Neuroblastoma Treatment". National Cancer Institute. August 25, 2016. Archived from the original on November 10, 2016. Retrieved November 10, 2016. https://www.cancer.gov/types/neuroblastoma/hp/neuroblastoma-treatment-pdq.

[3] Spix C, Pastore G, Sankila R, et al. Neuroblastoma incidence and survival in European children (1978-1997): report from the Automated Childhood Cancer Information System project. Eur J Cancer 2006;42:2081–91.
[4] World Cancer Report 2014. World Health Organization. 2014. Chapter 5.16. ISBN 978-9283204299. Archived from the original on September 19, 2016. https://www.who.int/cancer/publications/WRC_2014/en/.
[5] Friedman GK, Castleberry RP. Changing trends of research and treatment in infant neuroblastoma. Pediatr Blood Cancer 2007;49(Suppl 7):1060–5.
[6] Monclair T, Brodeur GM, Ambros PF, et al. The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report. J Clin Oncol 2009;27:298–303.
[7] Cohn SL, Pearson ADJ, London WB, et al. The International Neuroblastoma Risk Group (INRG) classification system: An INRG Task Force Report. J Clin Oncol 2009;27:289–97.
[8] Sung KW, Yoo KH, Koo HH, et al. Neuroblastoma originating from extra-abdominal sites: association with favorable clinical and biological features. J Korean Med Sci 2009;24:461–7.
[9] Jereb B, Bretsky SS, Vogel R, et al. Age and prognosis in neuroblastoma. review of 112 patients younger than 2 years. Am J Pediatr Hematol Oncol 1984;6:233–43.
[10] Surveillance, Epidemiology and End Results Program. About the SEER Program. [cited June 25, 2016]. Available at: http://seer.cancer. gov/about. Accessed January 25, 2019.
[11] Cheung NK, Zhang J, Lu C, et al. Association of age at diagnosis and genetic mutations in patients with neuroblastoma. JAMA 2012; 307:1062–71.
[12] Luo YB, Cui XC, Yang L, et al. Advances in the surgical treatment of neuroblastoma. Chin Med J (Engl) 2018;131:2332–7.
[13] Rosswog C, Schmidt R, Oberthuer A, et al. Molecular classification substitutes for the prognostic variables stage, age, and MYCN status in neuroblastoma risk assessment. Neoplasia 2017;19:982–90.
[14] Newman EA, Abdessalam S, Aldrink JH, et al. Update on neuroblastoma. J Pediatr Surg 2019;54:383–9.
[15] Yin Z, Wang Y, Wu Y, et al. Age distribution and age-related outcomes of olfactory neuroblastoma: a population-based analysis. Cancer Manag Res 2018;10:1359–64.
[16] Rosswog C, Schmidt R, Oberthuer A, et al. molecular classification substitutes for the prognostic variables stage, age, and MYCN status in neuroblastoma risk assessment. Neoplasia 2017;19:982–90.
[17] Slattery ML, Murtaugh MA, Quesenberry C, et al. Changing population characteristics, effect-measure modification, and cancer risk factor identification. Epidemiol Perspect Innov 2007;4:10.