RESEARCH ARTICLE

Trends in Survival of Childhood Cancers in a University Hospital, Northeast Thailand, 1993-2012

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Abstract

Background: In Thailand, a national treatment protocol for childhood leukemia and lymphoma (LL) was implemented in 2006. Access to treatment has also improved with the National Health Security system. Since these innovations, survival of childhood LL has not been fully described. Materials and Methods: Trends and survival of children under 15 with childhood cancers diagnosed between 1993 and 2012 were investigated using the hospital-based data from the Khon Kaen Cancer Registry, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand. Childhood cancers were classified into 12 diagnostic groups, according to the ICCC based on the histology of the cancer. Survival rates were described by period, depending on the treatment protocol. For leukemias and lymphomas, survival was assessed for 3 periods (1993-99, 2000-5, 2006-12) while for solid tumors it was for 2 periods (before and after 2000). The impacts of sex, age, use of the national protocol, and catchment area on leukemia and lymphoma were evaluated. Overall survival was calculated using the Kaplan-Meier method while the Cox proportional hazard model was used for multivariate analysis. Trends were calculated using the R program. Results: A total of 2,343 childhood cancer cases were included. Survival for acute lymphoblastic leukemia (ALL) from 1993-9, 2000-5, and 2006-12 improved significantly (43.7%, 64.6%, and 69.9%). This was to a lesser extent true for acute non-lymphoblastic leukemia (ANLL) (28.1%, 42.0%, and 42.2%). Survival of non-Hodgkin lymphoma (NHL) also improved significantly (44%, 65.5%, and 86.8%) but not for Hodgkin disease (HD) (30.1%, 66.1%, and 70.6%). According to multivariate analysis, significant risk factors associated with poor survival in the ALL group were age under 1 and over 10 years, while not using the national protocol had hazard ratios (HR) of 1.6, 1.3, and 2.3 respectively. In NHL, only non-use of national protocols was a risk factor (HR 3.9). In ANLL and HD, none of the factors influenced survival. Survival of solid tumors (liver tumors, retinoblastomas) were significantly increased compared to after and before 2000 while survival for CNS tumors, neuroblastoma and bone tumors was not changed. Conclusions: The survival of childhood cancer in Thailand has markedly improved. Since implementation of national protocols, this is particularly the case for ALL and NHL. These results may be generalizable for the whole country.

Keywords: Childhood cancer - trend - survival - Thailand

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Introduction

Cancer in children is rare but has a good prognosis. Over the last three decades, childhood cancer mortality has declined dramatically in resource-rich countries (Ries et al., 1999; Gutta et al., 2005). The decrease is partially due to the effects of understanding tumor biology, as well as improvements in diagnostic and therapy including stem cell transplantation (Redner, 2011).

In general, the incidence of cancer in children changes little; however, the incidence trend increased because of better diagnosis. The incidence reported by the Thai Pediatric Oncology Group (Thai POG) for the whole country between 2003 and 2005 was 74.9 per million (Wiangnon et al., 2011) while for the homogenous population in Khon Kaen province between 1985 and 2009 was 83 per million (Wiangnon et al., 2014). In resource-rich countries, the overall survival (OS) surpassed 70% (Gutta et al., 2005; O'Learly et al., 2008), however, in Thailand the OS was lower. The ThaiPOG reported an OS of 55% between 2003 and 2005 for childhood cancer for the whole country (Wiangnon et al., 2011). In Khon Kaen, the OS of population-based childhood cancer between 1985 and 2009 was 52% (Wiangnon et al., 2014).

Despite the rarity of childhood cancer, as poverty-related causes of death decline, it is becoming an important cause of death in Thailand. Between 2007 and 2008, the respective cancer related mortality rates in Thai children

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6-12 and 13-18 was 2.16 and 2.13 per 100,000 (Sutra et al., 2009). Lacking of pediatric hemato-oncologist in general hospital, almost all childhood cancer cases were referred to and treated in tertiary centers and university hospitals (Wiangnon et al., 2010).

Srinagarind Hospital is a referral and university hospital at Khon Kaen University in northeastearn Thailand. Before the year 2000, the treatment protocols used were institutional. After 2000, the protocols were based on international standards. Compliance to therapy had been a major problem that resulted in poor outcomes. Until 2003, the National Security Office (NHSO) implemented universal health coverage nationwide to help patients gain access to health care service without any charge and since then adherence to intensive cancer treatments has risen dramatically (Tangcharoensathien et al., 2010). In 2006, the NHSO provided and supported a disease management program nationwide for the treatment of childhood leukemia and lymphoma, which resulted in improved survival of acute lymphoblastic leukemia to 73%. The survival of ANLL was not, however, satisfactorily improved at the national level (Seksarn et al, 2011). Recently, ThaiPOG has proposed protocols for all types of childhood cancer and these protocols have been implemented nationwide since 2015.

This study aims to assess the long-term, hospital-based, retrospective study of the survival and trends of survival of childhood cancer after the changes to the national diagnosis and treatment guidelines.

Materials and Methods

Data on all childhood cancers were retrieved from the hospital-based data set of the Khon Kaen Cancer Registry between 1993 and 2012. Cancer sites, morphology, and behavior were coded according to the International Classification of Diseases for Oncology-3rd edition (ICD-O-3) (WHO, 2000). Tumor types were grouped according to the International Childhood Cancer Classification (ICCC) (Kramarova et al, 1996). Both histologically-verified and non-verified patients were included. All patients were observed until the end of December 2013. Cases of foreign patients were excluded. Survival was described by the treatment protocol period. For leukemias and lymphoma, the survival was assessed based on 3 periods (1993-99, 2000-5, and 2006-12) while for solid tumors it was 2 periods (before and after 2000). The impacts of sex, age, use of national protocol, and catchment area on leukemia and lymphoma were evaluated. Overall survival was calculated using the Kaplan-Meier method while the Cox proportional hazard model was used for multivariate analyses. Trends were calculated using R program.

Results

There were 2,343 cases of childhood cancer including unspecified ones. The respective mean and median age was 6.4 (SD=4.5) and 6 (0-14) years. Boys were affected more than girls (boys=1,292, girls=1,051, ratio 1.2:1). The peak for incidence was between 0 and 4 years. The follow-up duration totaled 101,250 months. The death rate was 1.25 per 100 person-months (95%CI: 1.28-1.32). The 5-year overall survival was 89% (95%CI: 85.7-92.4) in boys and 87.2% (95%CI: 83.7-90.9) in girls for all cancers.

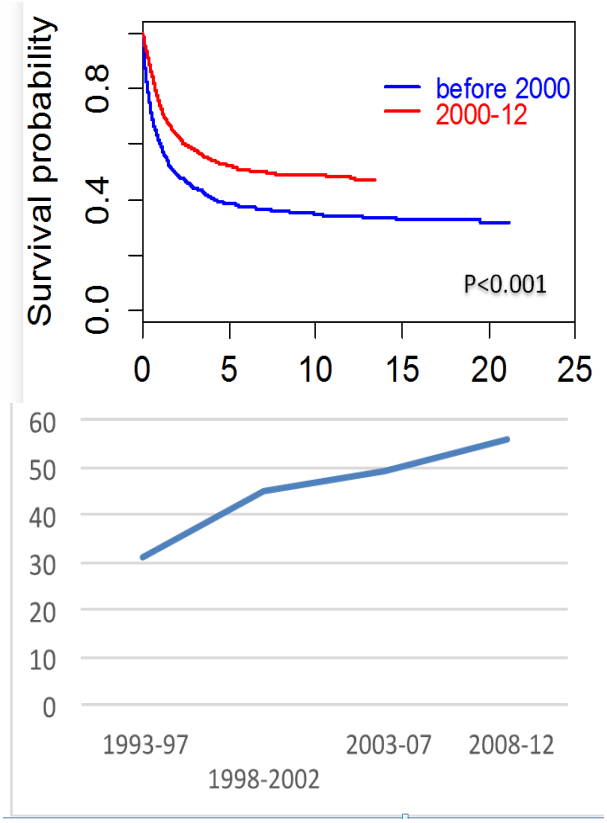

Figure 1. Survival and Trend of Childhood Cancers for Both Sexes between 1993 and 2012, Srinagarind Hospital, Khon Kaen, Thailand

Table 1. Survival of Childhood Leukemia and Lymphoma for Both Sexes between 1993 and 2012 at Srinagarind Hospital, Khon Kaen, Thailand

ICCC group	Survival (%)		
Leukemias (N=940)	1993-9 (95%CI)	2000-5 (95%CI)	2006-12 (95%CI)
Acute lymphoblastic leukemia (N=708)	37.1 (31-44)	58.4 (52-65)	63.9 (57-70)
Acute non- lymphoblastic leukemia (N= 156)	13.3 (6.3-28)	29.1 (19.3-43.9)	26.8 (17-42.2)
Others (N= 76)			
Lymphomas (N= 209)			
Hodgkin disease (N=34)	71.4 (30.1-100)	88.2 (74.2-100)	88.9 (70.6-100)
Non-Hodgkin lymphoma (N=126)	25.0 (14.2-44)	48.9 (36.5-65.5)	72.0 (59.8-86.8)

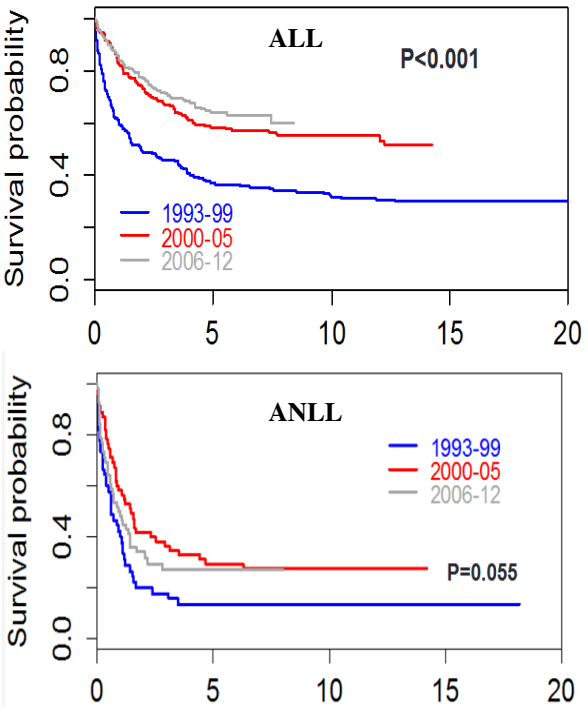

Figure 2. Survival of Children with Acute Lymphoblastic Leukemia (ALL) and Acute Non-Lymphobalstic Leukemia (ANLL) between 1993 and 2012, Srinagarind Hospital, Khon Kaen, Thailand

Table 2. Survival of Childhood Solid Tumors for Both Sexes between 1993 and 2012

ICCC group	5-year survival	
	1993-9 (95%CI)	2000-12 (95%CI)
CNS neoplasms (N= 318)	43.0 (34.0-54.3)	46.7 (40.5-53.8)
Neuroblastoma (N=124)	22.6 (11.7-43.3)	21.0 (14.0-31.6)
Retinoblastoma (N=119)	40.5 (27.4-59.9)	70.0 (60.6-80.9)
Renal tumors (N=60)	72.2 (54.2-96.2)	78.1 (62.1-89.8)
Hepatic tumors (N= 53)	14.3 (3.9-51.5)	52.9 (39.2-71.6)
Malignant bone tumors (N=140)	21.1 (8.8-50.3)	28.0 (22.4-40.8)
Soft tissue sarcomas (N= 107)	50.0 (32.2-77.5)	42.4 (32.8-54.4)
Germ cell tumors (N= 141)	51.4 (37.3-71.0)	65.9 (57.2-75.8)

Most of the pediatric cancers were histologically-confirmed (77%) but the proportion varied between 61% for cancer of the central nervous system (ICCC group III) and 100% for leukemia (ICCC group I). Survival of patients with leukemia/lymphoma and solid tumors are described in Tables 1 and 2. After 2000, survival of all cancers improved significantly and trend in survival was increasing gradually (Figures 1 and 2).

The survival of children with ALL improved significantly since using the national protocol in 2006, resulting in a survival rate of 36.6%, 58%, and 62.9% for the respective periods (Figure 2). Factors affecting survival, were age at diagnosis > 10 years and getting treatment before 2000 (Table 3). The survival of children with ANLL treated after 2000 was higher than those treated before; however, the difference is not statistically significant (Figure 2). According to the multivariate analysis on survival, there was no effect of sex, age at diagnosis, treatment era and residing in catchment area.

For lymphoma, survival of non-Hodgkin lymphoma (NHL) improved significantly over time (44%, 65.5%, and 86.8%) but not a significant change for Hodgkin disease (HD) (30.1%, 66.1%, and 70.6%) (Table 1, Figure 3).

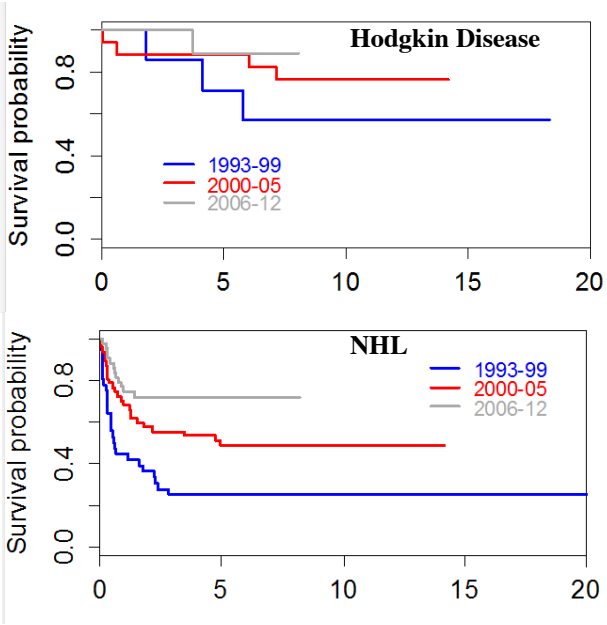

Figure 3. Survival of Children with Hodgkin Disease and Non-Hodgkin Lymphoma (NHL) between 1993 and 2012, Srinagarind Hospital, Khon Kaen, Thailand

Table 3. Factors Affecting Survival of Patients with Acute Lymphoblastic Leukemia

Variable		Univariate analyses		Multivariate analyses	
		HR (95%-CI)	P-value	HR (95%-CI)	P-value
Sex	Male	1		1	0.19
	Female	0.88 (0.71-1.09)	0.248	0.86 (0.69-1.08)	
Age group	1	1		1	
	<1	1.62 (1.00-2.62)	0.0474*	1.55 (0.96-2.50)	0.076
	>10	1.36 (1.04-1.78)	0.0241*	1.62 (1.23-2.12)	<0.001*
Period	≥ 2006	1		1	
	<1999	2.38 (1.82-3.11)	<0.001*	2.59 (1.97-3.40)	<0.001*
	2000-05	1.19 (0.90-1.59)	0.22	1.26 (0.95-1.67)	0.111
Catchment area	Inside region	1		1	
	Other	1.15 (0.93-1.43)	0.189	1.23 (0.99-1.53)	0.058

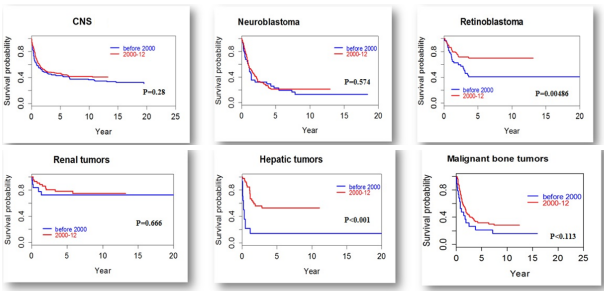

Figure 4. Survival of Children with solid tumors before and after 2000, Srinagarind Hospital, Khon Kaen, Thailand

According to the multivariate analysis on survival, there was no effect of sex, age at diagnosis, treatment era and residing in catchment area to the survival in HD while in NHL, only the non-use of national protocols was a risk (HR 3.9; 95%CI, 2.02-7.90).

In solid tumors, the survival of solid tumors (liver tumors, retinoblastoma) were significantly increased compared to those after and before 2000 while survival for CNS tumors, neuroblastoma and bone tumors were unchanged (Table 2). The respective survival improvement of liver tumor and retinoblastoma was 14.3% *vs*. 52.9%, and 40.5% *vs*. 70%. In renal tumors, the survival remained high and did not change (72.2% *vs*. 74.7%). In brain tumors, survival was not significantly different before and after 2000 (40.9 *vs*. 46%). Likewise, in neuroblastoma the survival before and after 2000 was comparable (19.4% *vs*. 19.6%). In bone tumors, survival improved but not significantly (15.8% *vs*. 30.2%) (Figure 4).

Discussion

Over the past three decades, childhood cancer mortality has declined dramatically, particularly in resource-rich countries where overall survival has surpassed 70% (Ries et al., 1999; Gutta et al., 2005; O'Learly et al., 2008). The decrease is partially due to the effects of understanding tumor biology, improvements in diagnostics and therapies, including stem cell transplantation (Redner, 2011) and supportive care.

Overall survival (OS) in Thailand used to be lower than in developed countries. The Thai Pediatric Oncology Group (ThaiPOG) reported OS of childhood cancer for the nation between 2003 and 2005 was 55% (Wiangnon et al., 2011). In Khon Kaen - the center of the populous and impoverished northeastern region - OS for population-based childhood cancer between 1985 and 2009 was 52% (Wiangnon et al., 2014).

In Thailand in 2006, the national treatment protocol for childhood leukemia and lymphoma was therefore declared. All patients were to have equal access to a full range of treatments. Treatment compliance has been higher as patients and their families have greater 'trust' that the treatment is appropriate and not just all they can afford.

At Srinagarind Hospital - our university, referral center located in Khon Kaen-before 2000, the treatment protocols used were institutionally set. After 2000, the protocols were changed to reflect international standards. Compliance to therapy had been a major problem, resulting in poor outcomes. Until 2003, the National Security Office (NHSO) implemented universal health coverage nationwide to ensure patient access to healthcare services free-of-charge. Since then adherence to intensive cancer treatment has risen significantly (Tangcharoensathien et al., 2010). In 2006, the NHSO provided and supported a disease management program nationwide for the treatment of childhood leukemia and lymphoma (LL), which resulted in an improvement in survival to 73% of acute lymphoblastic leukemia (ALL). By comparison, the survival of acute non-lymphoblastic leukemia (ANLL) was not improved (Seksarn et al, 2011). Recently, the ThaiPOG proposed protocols for all kinds of childhood cancer and these protocols were implemented nationwide in 2015.

In the current study, the survival of ALL improved significantly over time. In contrast, this was not true of ANLL. Seksarn et al. (2011) demonstrated that any significant improvement in survival of ALL had been in low risk patients, not high risk ones as per criteria in LL disease management (Seksarn et al., 2011). In LL disease management policy, the treatment protocol for leukemia used a risk-adapted approach; however, the significant risk factors associated with poor survival in ALL were age group (<1 year and >10 years) and non-use of the national protocol (HR; 1.6, 1.3, 2.3). The survival of ANLL did not improve notwithstanding use of the LL disease management policy. The treatment protocol might have been more aggressive, resulting in relatively high treatment-related mortality (Seksarn, 2011).

For lymphoma, survival of non-Hodgkin lymphoma (NHL) improved significantly over time but did not significantly change for Hodgkin disease (HD). In the LL disease management policy, the treatment protocol for NHL was risk-adapted. In NHL, the non-use of national protocols was the only significant risk (HR 3.9). In HD, the treatment protocol remained similar, thus, survival remained high.

In solid tumors (e.g., liver tumors and retinoblastoma), survival was significantly increased compared to before and after 2000 while survival for CNS tumors, neuroblastoma and bone tumors were unchanged. In brain tumors, survival did not differ between before and after 2000. In our institution, not until recently, the rate of brain surgeries was low compared to the present (being 2016). Recently, the treatment of brain tumor has become more aggressive. The survival of neuroblastoma remained low. Basically, patients present at an advanced stage and chemotherapy alone has a dismal outcome. In addition to other treatment modalities, autologous stem cell transplantation (ASCT) could enhance survival in high-risk patients with neuroblastoma (Rani E et al., 2006). Better outcomes are expected since recently starting ASCT.

Vis-a-vis bone tumors, survival improved but not significantly as most patients presented at an advanced stage. Before 2015, we used a non-methotrexate-based protocol for osteosarcoma. The ThaiPOG protocol incorporated high-dose methotrexate for high-risk patients: the outcome has yet to be determined.

In renal tumors, survival has been relatively high and comparable to international reports, so the treatment protocols were not significantly changed. Survival of liver tumors has markedly improved even though the treatment protocol was not significantly changed. One reason is compliance to therapy since implementation of universal health coverage in Thailand in 2003 (Tangcharoensathien et al., 2010).

In conclusions, After implementing the national protocol for childhood cancer, the survival of ALL and NHL has improved markedly; however, survival for some diseases has not changed. These results may represent the outcomes for the whole country.

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References

Ajiki W, Tsukuma H, Oshima A (2004). Survival rates of childhood cancer patients in Osaka, Japan. *Jpn J Clin Oncol*, **34**, 50-4.

Gatta G, Capocaccia R, Stiller C, Kaatsch P, Berrino F, Terenziani M, and the UROCARE working group (2005). Childhood cancer survival trends in Europe: A EUROCARE Working group study. *J Clin Oncol*, **23**, 3742-51.

Cancer registration: Principles and Method. IARC Scientific Publications No.95, Lyon: International Agency for Research on Cancer. 159-76.

Kamsa-ard S, Wiangnon S, Suwanrungruang K, et al (2004). Khon Kaen cancer registry: survival of childhood malignancies recorded between 1993-1997. *Thai J Pediatr*, **43**, 25-31.

Kramarova E, Stiller CA, Ferlay J, Parkin DM, et al (1996). The international classification of childhood cancer. *Int J Cancer*, **68**, 759-65.

National Statistic Office. Statistical data bank and information dissemination division (2003). The 2000 population and housing census. Office of prime minister.

O'Learly M, Krailo M, Anderson JR, Reaman GH (2008). Progress in childhood cancer: 50 years of research collaboration, a report from the Children's Oncology Group. *Semin Oncol*, **35**, 484-93.

Pakakasama S, Veerakul G, Sosotthikul D, et al (2010). Late effects in survivors of childhood acute lymphoblastic leukemia: a study from Thai Pediatric Oncology Group. *Int J Hematol*, **91**, 850-4.

Parkin DM, Kramarova E, Draper GJ, et al (1998). International incidence of childhood cancer. Vol II. *IARC scientific publication*, **144**.

Rani E. G, Shuli L, Cheryl M, et al (2006). High-Risk Neuroblastoma Treated With Tandem Autologous Peripheral-Blood Stem Cell–Supported Transplantation: Long-Term Survival Update. *J Clin Oncol,* **24**, 2891-6.

Redner A (2011). Leukemias. In: Manual of pediatric hematology and oncology. Lanzkowsky P. 5th ed. Elsevier, Amsterdam, 518-66.

Ries LAG, Smith MA, Gurney JG, et al (eds) (1999). Cancer incidence and survival among children and adolescents: United States SEER program 1975-1995, National cancer institute, SEER program. NIH Pub, 99-4649. Bethesda, MD.

Seksarn P (2011). Outcome of childhood leukemia, ThaiPOG study. St. Jude-VIVA forum in pediatric oncology, Singapore.

Sutra S, Chirawatkul A, Bundhamcharoen K, Ekachampaka P, Wattanamano N (2009). Cause of death Analysis by age group. In: Child and adolescent health situation 2009. Working group for child and adolescent health situation in Thailand. The Royal College of Pediatricians of Thailand. Beyond Enterprise, 17-88.

Tangcharoensathien V, Swasdiworn W, Jongudomsuk P, et al (2010). Universal coverage scheme in Thailand: equity outcomes and future agendas to meet challenges. Background paper, 43; World health report, World Health Organization.

Thai Pediatric Oncology Group (2014). National protocol for treatment of childhood cancer 2014. Bangkok, M Print Corporation.

Wiangnon S, Kamsa-ard S, Jetsrisuparb A, et al (2003). Childhood cancer in Thailand 1995-1997. *Asian Pac J Cancer Prev*, **4**, 237-43.

Wiangnon S, Kamsa-ard S, Jetsrisuparb A, et al (2004). Childhood malignancies at Khon Kaen, Thailand: population-based cancer registry. *Thai J Pediatr*, **43**, 38-43.

Wiangnon S, Veerakul G, Nuchprayoon I, et al (2011). Childhood cancer incidence and survival 2003-5, Thailand: study from the Thai Pediatric Oncology Group. *Asian Pac J Cancer Prev*, **12**, 2215-20.

Wiangnon S, Jetsrisuparb A, Komvilaisak P, Sutra S (2012). Childhood neoplasms: analysis of Thai children 2010. *J Med Assoc Thai*, **95**, 123-33.

Wiangnon S, Jetsrisuparb A, Komvilaisak P, Suwanrungruang K (2014). Childhood cancer incidence and survival 1985-2009, Khon kaen, Thailand. *Asian Pac J Cancer Prev*, **15**, 7989-93.

World Health Organization (2000). In: International Classification of Diseases for Oncology. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, eds. 3rd ed. Geneva.