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ผลการรอดชีวิตของผู้ป่วยเนื้องอกนิวโรบลาสโตมาระยะที่ 4 ที่ได้รับการผ่าตัด ในโรงพยาบาลศรีนครินทร์

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Survival Outcome of Patients with Stage 4 Neuroblastoma after Tumor Resection in Srinagarind Hospital

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หลักการและวัตถุประสงค์: มากกว่าครึ่งหนึ่งของผู้ป่วยนิวโรบลาสโตมาอยู่ในระยะที่ 4 ด้วยระยะแพร่กระจายของตัวโรค ณ เวลาที่วินิจฉัย ซึ่งนำไปสู่อัตราการป่วยและอัตราการเสียชีวิตที่สูง คณะผู้แต่งมุ่งศึกษาผลการรอดชีวิตของผู้ป่วยนิวโรบลาสโตมาระยะที่ 4 ที่ได้รับการผ่าตัดเนื้องอกที่โรงพยาบาลศรีนครินทร์ นอกจากนี้ยังมีการศึกษาปัจจัยการพยากรณ์การรอดชีวิตของผู้ป่วยโรคนี้ด้วย

วิธีการศึกษา: การทบทวนเวชระเบียนย้อนหลังของผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นโรคนิวโรบลาสโตมาระยะที่ 4 ตั้งแต่ปีพ.ศ. 2549 ถึง 2558 ที่โรงพยาบาลศรีนครินทร์ มหาวิทยาลัยขอนแก่น ใช้การวิเคราะห์การรอดชีวิต (survival analysis) และการวิเคราะห์การถดถอยคอกซ์ (Cox-regression analysis) สำหรับปัจจัยพยากรณ์

ผลการศึกษา: ผู้ป่วย 61 รายประกอบด้วยเพศชาย 32 ราย (ร้อยละ 52) เพศหญิง 29 ราย (ร้อยละ 47) ได้รับการวิเคราะห์พบว่า มีอายุเฉลี่ยคือ 4 ปี ได้จัดกลุ่มผู้ป่วยที่ไม่ได้รับการผ่าตัดเอาเนื้องอกออกได้มี 21 ราย ในขณะที่ 38 รายได้รับการผ่าตัดซึ่งประกอบด้วยการผ่าตัดที่สามารถเอาก้อนเนื้องอกออกได้หมดและไม่สามารถเอาก้อนออกได้หมด (25 และ 13 ราย ตามลำดับ) ในข้อมูลการเสียชีวิตพบว่าโดยรวมแล้วหลังได้รับการวินิจฉัยผู้ป่วยเสียชีวิตมีจำนวนทั้งสิ้น 43 ราย (ร้อยละ 72) อัตราการเสียชีวิตเมื่อเปรียบเทียบกลุ่มที่ไม่ได้รับการผ่าตัดเอาเนื้องอกออก กลุ่มผ่าตัดที่สามารถเอาก้อนเนื้องอกออกได้หมดและไม่สามารถเอาก้อนออกได้หมดเท่ากับ ร้อยละ 2.7 ร้อยละ 2.36 และ ร้อยละ 1.6 ตามลำดับ ระยะเวลาการรอดชีวิตเฉลี่ยเมื่อเปรียบเทียบกลุ่มที่ไม่ได้รับการผ่าตัดเอาเนื้องอกออก กลุ่มผ่าตัดที่สามารถเอาก้อนเนื้องอกออกได้หมดและไม่สามารถเอาก้อนออกได้หมด คือ 11.43 เดือน 23.10 เดือน และ 35.87 เดือน ตามลำดับ เมื่อเปรียบเทียบอัตราการรอดชีวิตระหว่างกลุ่มที่ไม่ได้รับการ

Background and Objectives: More than half of patients with neuroblastoma were in stage 4 with metastatic disease at diagnosis, leading to high morbidity and mortality rates. We aimed to study the survival outcome of the patients who had stage 4 neuroblastoma at Srinagarind Hospital. Prognostic factors for survival were also determined.

Methods: A retrospective cohort review medical records of stage 4 neuroblastoma patients, from 2006 to 2015 at Srinagarind Hospital, Khon Kaen University. Using survival analysis for survival outcome and Cox-regression analysis for prognostic factors.

Results: 61 patients, 32 male (52%), 29 female (47%) were analyzed. Median age of patients was 4 years. 21 patients were categorized in unresectable group, while 38 were resectable which consisted of complete and incomplete resection (25 and 13 cases, respectively). In overall mortality data, 43 patients (72%) died after diagnosis. The mortality rates of unresectable complete resection and incomplete resection groups were 2.7%, 2.36%, and 1.6%, respectively. The median survival times of unresectable, complete resection, incomplete resection group was 11.43, 23.10, and 35.87 months, respectively. There were no statistically significant differences of survival experience between resectable and unresectable groups (p = 0.239), between complete resection and unresectable groups (p = 0.524), and between incomplete resection and unresectable group (p = 0.149).

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ผ่าตัดกับกลุ่มที่สามารถผ่าตัดได้พบว่าไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ (p = 0.239) นอกจากนี้พบว่าไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติของอัตราการรอดชีวิตระหว่างกลุ่มผ่าตัดที่สามารถเอาก้อนเนื้องอกออกได้หมดและไม่สามารถเอาก้อนออกได้หมด (p = 0.524) และกลุ่มผ่าตัดไม่ที่สามารถเอาก้อนเนื้องอกออกได้หมดกับกลุ่มที่ไม่ได้รับการผ่าตัดเอาเนื้องอกออก (p = 0.149)

สรุป: จากการศึกษาพบว่าไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติของอัตราการรอดชีวิตของผู้ป่วยนิวโรบลาสโตมาระยะที่ 4 ระหว่างกลุ่มที่ไม่ได้รับการผ่าตัดกับกลุ่มที่สามารถผ่าตัดได้ สำหรับปัจจัยการพยากรณ์โรค ได้แก่ ตำแหน่งของเนื้องอกที่กระดูกสันหลัง กลุ่มอายุมากกว่า 18 เดือน กลุ่มที่ผล VMA ในปัสสาวะเป็นบวก และกลุ่มที่มีการแพร่กระจายไปที่ตับ

คำสำคัญ: นิวโรบลาสโตมา; การผ่าตัดเนื้องอก; การรอดชีวิต

Conclusions: No significant differences of survival outcome between resectable and unresectable groups in stage 4 neuroblastoma. Prognostic factors are tumor location at spine, age group (>18 month), positive urine VMA and presentation of liver metastasis.

Keywords: neuroblastoma; tumor resection; survival

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Introduction

Neuroblastoma is one of the most common malignant extracranial solid tumors in children aged less than 1 year up to 15 years.[1–3] Neuroblastoma arises from the primitive neural crest cells which give rise to the sympathetic chains. The sympathetic chains, which are the fundamental part of sympathetic nervous system, locate in any parts of the body: head, chest, abdomen, spine. The most common site of neuroblastoma was in the abdomen, where 50-70% was located at the adrenal glands.[4–6]

The presentation of disease depends on a primary location, for example neck mass, abdominal mass, abdominal pain, chest discomfort whereas others present with symptoms of metastatic disease e.g. fever, anemia and bleeding from bone marrow suppression, bone pain or pathologic fracture.[1,4]

Unfortunately, more than half of the patients presented with metastatic disease (stage 4) at diagnosis, of whom were considered as high-risk group.[2,4] Outcome of high-risk neuroblastoma was poor with high mortality rate.[4,5,7,8] One study reported data of 27 patients with neuroblastoma of stage 3 (4%) and stage 4 (96%) who were treated during 1990-1995 in Khon Kaen University.[7] The median survival time was 9 months with 1-year, 2-year, and 3-year overall survival rates of 33.3% 18.5% and 14.8%, respectively.[7]

Multimodality of treatment were given to high risk group patients. The line of treatment included: induction phase (includes chemotherapy and surgical resection), consolidation phase (tandem cycles of myeloablative therapy and stem cell transplantation) and post-consolidation/ maintenance phase (radiation therapy to the site of the primary tumor and residual metastatic sites, immunotherapy, and retinoid therapy).9 The role of surgery for this particular group of patients had been a controversy regarding an advantage of primary tumor resection after chemotherapy.[9–12] In Thailand, data from Queen Sirikit National Institute of Child Health found that 70% of the patients had stage 4 neuroblastoma; 55% of them had tumor resection.[13]

This research aimed to study survival outcome of patients with stage 4 neuroblastoma who were treated in Srinagarind Hospital, Khon Kaen University. Prognostic factors of the patients were also studied.

Materials and Methods

This was a retrospective cohort study which was approved by the Khon Kaen University Ethics Committee for Human Research (HE601132). The study was conducted based on the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines.

All patients aged between 1 and 15 years old who had a diagnosis of stage 4 neuroblastoma and treated in Srinagarind Hospital, Khon Kaen University from January 1st, 2006 to December 31st, 2015 were included. The patients who had incomplete data recorded were excluded. Stage of disease was assigned according to the International Neuroblastoma Staging System (INSS).[14] Data collected included patient's age at the time of diagnosis, first presentation, primary tumor site, metastatic sites, bone marrow status at diagnosis, induction chemotherapy, surgical resection of primary tumor, intraoperative and post-operative

complications, survival outcome, and status of disease after treatment.

Treatment for patients with stage 4 neuroblastoma was approached according to Thai-POG protocol15 which include chemotherapy, tumor resection, local radiotherapy, and retinoid therapy. An unresectable tumor was defined from the first imaging study or intra-operative findings. Complete resection was defined as total tumor resection without any gross residual diseases whereas an incomplete resection defined as subtotal, near total, or partial resection as described in the operative records.

Data were summarized as using percentage for categorical data and using means and standard deviation for continuous data. In addition, non-parametric Wilcoxon rank-sum test and Fisher's exact test were used for continuous and categorical variables, respectively. For the survival analysis, Kaplan–Meier analyses were used to estimate overall survival (OS) comparing between resectable and unresectable groups. Cox-regression analyses were performed to determine the prognostic factor that associated to survival outcomes. A p-value less than 0.05 were considered significant. The statistical analyses were conducted using STATA software (StataCorp, Texus, USA).

Results

Sixty-three patients, who had diagnosis of stage 4 neuroblastoma, were identified during the study period. Two patients were excluded due to incomplete medical record. The median age of patients at diagnosis was 3.7 years (min-max; 1-14.7 years); 52.5% (n = 31) were male and 47.5% (n =28) were female. Majority of patients presenting with a primary abdominal tumor, being non-adrenal (n=24, 40.7%) followed by adrenal tumors (n=22, 37.3%). The other sites of tumor were thoracic (n=6, 10.2%), head and neck (n=4, 6.8%), and spinal (n=2, 3.4%). One patient had unrevealed primary site of tumor in which the diagnosis of neuroblastoma was made from bone marrow tissue sampling.

For the clinical presentations, more than half of patients presented with two symptoms or more. Mass lesion was the most common symptom (of abdomen, neck and scalp), followed by fever, bone pain and anemia. Other infrequent symptoms included abdominal pain, proptosis, raccoon eye and paraplegia. The data showed that approximately three-quarters of patients had more than single site of metastasis. The location most frequently metastasis was bone, followed by bone marrow, lymph node, lung and liver and brain, respectively. Basic characteristic features of the patients and tumors are shown in Table1.

Table 1 Demographic data

Demographic data	Number (59)
Sex (%)	
Male	31 (52.54)
Female	28 (47.48)
Age (years)	
Mean (SD)	4.06 (2.45)
Median (min-max)	3.67 (1 – 14.67)
Primary tumor site (%)	
Thoracic	6 (10.17)
Abdomen (intra- and retroperitoneum)	24 (40.68)
Head and neck	4 (6.78)
Adrenal gland	22 (37.29)
Spine	2 (3.39)
Unknown	1 (1.69)
Clinical presentation	
Mass	
Abdominal mass	22
Neck mass	5
Scalp mass	1
Abdominal pain	8
Bone pain	15
Fever	29
Anemia	12
Proptosis	7
Raccoon eyes	3
Paraplegia	1
Metastatic site	
Lung	12
Liver	4
Bone	43
Brain	4
Lymph node	20
Bone marrow	37

After induction chemotherapy, surgical resection of the primary tumor was performed in 38 patients (64.41%) whereas other 21 patients (35.59%) still had unresectable tumors. Among the resectable group, complete resection was achieved in 25 patients (65.79%) and incomplete resection in 13 patients (34.21%). Surgical complications occurred in 10 patients, including massive intra-operative blood loss (1.64%), adjacent organ and/or great vessels injury (13.12%), normal organ removal with the tumor (6.56%). Post-operation, one case died due to severe pulmonary edema.

After the median follow-up time of 24.03 months, the mortality rate of the unresectable, complete resection and incomplete resection groups were 2.7%, 2.36% and 1.6%, respectively. The corresponding median survival time were 11.43, 23.1 and 35.87 months. The 5-year overall survival of all patients in the study was 23.43% (95% CI: 12.93% -35.72%) (Figure1).

Survival outcomes between the unresectable, complete resection and incomplete resection groups were compared (Figure2). There were no significant differences of survival of the resectable group compared to unresectable group (p = 0.239), complete resection compared to unresectable groups (p = 0.524), and incomplete resection and unresectable groups (p = 0.149). The recurrence of disease occurred in 17 patients among the complete resection group.

We performed the bivariate analysis to evaluate prognostic factors which impacted survival outcome of the patients (Table2). The primary tumor locating at spine had a significant worst outcome (crude HR = 28.1, 95%CI: 4.14-190.83, p = 0.001). No significant

Table 2 Bivariate analysis: Cox regression analysis

Factors	Crude HR (95%CI)	p-value
Sex		0.509
Male	1	
Female	1.22 (0.67 – 2.23)	
Age		0.188
≤ 18 months	1	
> 18 months	2.04 (0.63 – 6.59)	
Urine VMA	0.97 (0.94-1.00)	0.052
Primary tumor site		
Abdomen	2.14 (0.72 – 6.30)	0.170
Head	1.52 (0.34 – 6.82)	0.585
Adrenal	1.37 (0.45 – 4.15)	0.574
Spine	28.10 (4.14 – 190.83)	0.001
Metastatic site		
Lung	0.96 (0.46-2.01)	0.915
Liver	2 (0.69-5.79)	0.239
Lymph node	1.17 (0.62-2.21)	0.634
Brain	0.98 (0.35-2.75)	0.972
Bone	0.61 (0.32-1.18)	0.154
Bone marrow	0.69 (0.37-1.27)	0.236
Number of metastasis		0.358
1 site	1	
2 sites	0.65 (0.32 – 1.33)	
≥ 3 sites	0.56 (0.25 – 1.27)	

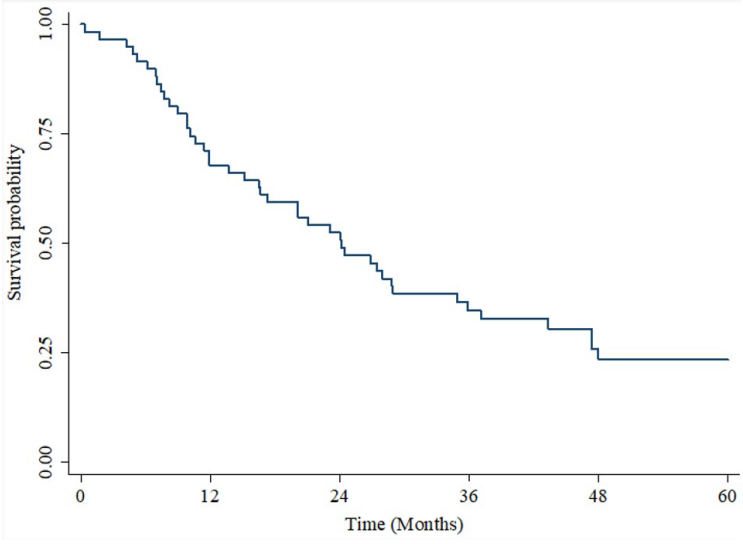

Figure1 Overall survival (OS) outcome of stage 4 neuroblastoma

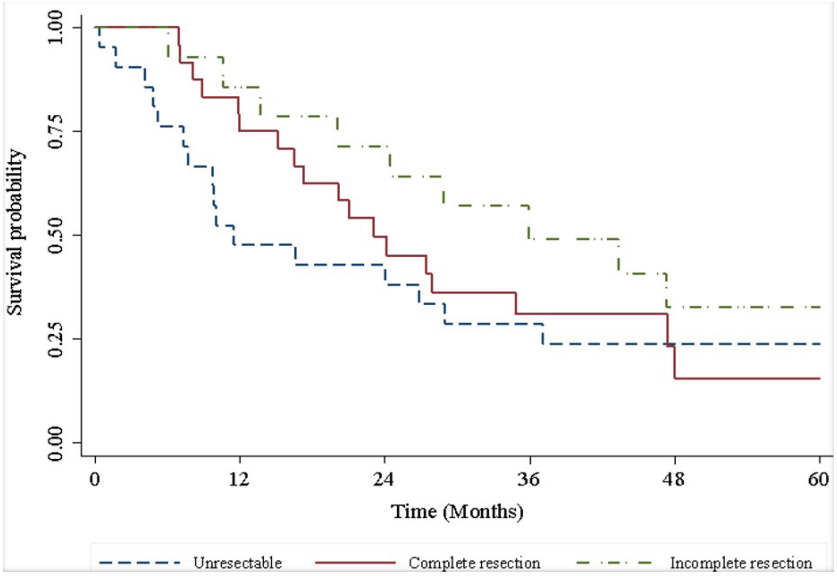

Figure 2 The overall 5-year survival outcome between unresectable, incomplete resection, and complete resection group.

differences of survivals by the factors of age, sex, primary tumor site, number of metastasis and site of metastasis. All factors from bivariate analysis were performed the multivariate analysis, and the results showed that age group (>18 month) (adjusted HR [95%CI]: 10.05 [1.34 – 75.58, p =0.025), positive urine VMA (adjusted HR [95%CI]: 0.96 [0.92 – 0.99], p =0.020) and presence of liver metastasis (adjusted HR [95%CI]: 3.57 [1.17 – 10.86], p =0.025) were significant independent prognostic factors for survival (Table 3).

Table 3 Multivariate analysis: Cox regression analysis

Factors	Crude HR (95%CI)	p-value	Adjusted HR (95%CI)	p-value
Age (months)		0.188		0.025
≤ 18	1		1	
> 18	2.04 (0.63 – 6.59)		10.05 (1.34 – 75.58)	
Urine VMA	0.97 (0.94 – 1.00)	0.052	0.96 (0.92 – 0.99)	0.020
Metastatic site				
Liver	2.00 (0.69 – 5.79)	0.239	3.57 (1.17-10.86)	0.025

Discussion

Neuroblastoma is one of the most common malignant neoplasms in children which mostly presents with stage 4 at the first time of diagnosis.[4,7,8] Treatment for this advanced stage is still a challenge and requires a multidisciplinary approach. The 5-year overall survival outcome in patients with stage 4 neuroblastoma was 23-55%.[6,8,11,12] Our study found that the 5-year overall survival rate of stage 4 neuroblastoma patients was 23.43% which appears to be in the lower range than from the previous report.[7]

The role of primary tumor resection, which is typically performed at or near the end of induction chemotherapy, for advanced staged neuroblastoma had been a controversy. Adkins et al.[11] found that the resectability for high-risk neuroblastoma was improved after pre-operative chemotherapy, and they showed that there was no statistically significant different in the complication rates between complete and incomplete tumor resection. In 2015, Englum et al.[10] studied the outcome of tumor resection in high-risk neuroblastoma children, they suggested that the patient who had been received more than 90% of tumor removal associated with higher overall survival rate compare to those who received less than 90% of tumor removal. In addition, Mullassery et al.[9] showed that the gross total tumor resection had significantly increased in 5-year disease-free survival compared to the subtotal tumor resection patients. However, Simon et al.[16] found that the extent of tumor resection of first operation had no impact on the event-free survival and overall survival rate in the

stage 4 neuroblastoma with age older or equal 18 months at diagnosis. Additionally, Yeung et al.[12] categorized the tumor resection of high-risk neuroblastoma into three groups, including complete gross tumor resection, gross total resection (more than 95% of tumor) and subtotal tumor resection. Among three groups, there were no statistically significant difference of 5-year event-free and overall survival rate. Likewise, our studies found that there was no impact of tumor resection to survival outcome of stage 4 neuroblastoma. For the complications associated with surgical removal, Adkins et al.[11] found that complete tumor resection was not increase complications while Lei du et al.[17] the gross total resection group appeared to have more severe surgical complications, consistent with this study.

Neuroblastoma with intraspinal extension has high burden of long-term health problems as the bivariate analysis showed that the primary tumor at spine had a significant worse survival than that of other locations (crude HR = 28.1, 95%CI: 4.14-190.83, p = 0.001). Plantaz et al.18 found that in most cases of patient with intraspinal extension needed emergent surgery to relieve neurologic deficits. The timing of specific therapy initiation had a great effect on determining the neurological outcome. Early diagnosis may prevent permanent disability in children with malignant cord compression.19 According to the International Neuroblastoma Risk Group (INRG) classification system,20,21 over 18 months of age is one of the factors involved in the classification of stage 4 neuroblastoma into a high-risk group, consistent with the multivariate analysis found that age group (>18 month) (adjusted HR (95%CI): 10.05 (1.34 – 75.58), p =0.025).

Being a retrospective study was one of the limitations of our study. The other limitations included lacking of other post-operative complications and the amplification of MYCN data which is the one of the important factors for risk classification.20–22 Further prospective randomized studies might be required.

Conclusion

The 5-year overall survival rate of stage4 neuroblastoma patients appeared likely to be improved from our previous report, however, our study found no significant differences of survival outcome between resectable and unresectable group in stage 4 neuroblastoma. Tumor location at spine, age group (>18 month), positive urine VMA, and presentation of liver metastasis might be used for the poor prognostic prediction.

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