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Surgical Outcomes of Patients with Neuroblastoma in a Tertiary Centre in Hong Kong: A 12-year Experience

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Abstract

Introduction: Neuroblastoma has a heterogeneous clinical course. The prognosis varies widely depending on the age of diagnosis, extent of disease and tumour biology. However, the specific clinical outcome of this disease in Hong Kong has not been well characterised thus far. Complete tumour excision has been demonstrated to confer survival benefit on patients with advanced disease even if there is metastasis. Since year 2004, we have adopted a revised, more aggressive surgical approach in managing these patients. Here, we aim to review our experience in the management of this disease. ***Methods:*** A retrospective review was performed for the past 12 years to include all patients who presented with neuroblastoma in our institution. Data such as the survival, age at diagnosis, *MYCN* amplification status, the extent of tumour excision, and stage of the disease were recorded and analysed. ***Results:*** 37 patients were included in this study. Overall survival of our patients was 67.6%. Patients with Stage 1, 2 and 4S have 100% survival whereas stage 4 patients only have 41.4% survival. Since our revised surgical approach in 2004, patients who had been operated had a better survival. Survival of stage 4 patients with operation after 2004 was 57.1% whereas the survival of patients at the same stage before 2004 was only 30%. Age at diagnosis, completeness of tumour excision and stage of disease are also correlated with overall prognosis. Further, patients with the presence of *MYCN* gene amplification have apparently poorer survival but it is not statistically significant due to the small sample size. ***Conclusion:*** The management of patients with neuroblastoma remains a challenge. Advanced stage of disease, incomplete tumour excision and increased age at diagnosis were all associated with poor survival. We demonstrated a better survival for those who underwent a more aggressive surgical approach, though this is a technically demanding and time consuming procedure. Thus, the management of advanced neuroblastoma should be centralised in a centre with combined surgical, oncological and paediatric intensive care expertise.

Key words Neuroblastoma; Surgical excision; Survival

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Introduction

Neuroblastoma is a childhood neoplasm which arises from neural crest cell. It is one of the most common solid tumours in childhood and accounts for more than 7% of malignancies in patients younger than 15-year-old in the United States.[1] It most commonly arises from the adrenal medulla, but can occur anywhere along the sympathetic chain from neck to pelvis.

Neuroblastoma has a diverse clinical behaviour. Spontaneous regression of the tumour occurs in a subgroup

of patients, especially those who are diagnosed before 1 year of age.[2] Nonetheless, many patients who have advanced disease will end up in mortality despite aggressive multimodal management. Several factors have been identified to correlate with a favourable clinical outcome. These include age younger than 1 year at presentation, and complete tumour excision.[3] On the other hand, poor prognostic factors include advanced stage, older age, *MYCN* amplification, tumour cell ploidy and chromosomal abnormalities.[4]

With improved understanding of the disease, tumour biology has been recognised as important factor which affects survival. Indeed, a Neuroblastoma Grouping System, which is based on the International Risk Grouping System, has been developed by the Children's Oncology Group to stratify each patient's risks.[5] Patients are categorised into low, intermediate and high-risk according to the stage, age at diagnosis, histopathology, *MYCN* amplification and DNA index. Risk-based treatment is then stratified according to the risk factors.

The overall survival rate of patients with the disease remains suboptimal, especially for those with advanced disease. For the high risk group, the long-term survival rate is less than 40% in most studies.[6,7] From the experience of other tertiary centres, complete excision of tumour would correlate with better survival.[8-11] Recognising this fact and also with better surgical experience, we started from 2004 to perform gross total excision if possible for all patients, even in those with advanced disease. Our protocol consists of 4-5 courses of chemotherapy pre-operatively to shrink the size of tumour and render it less vascular. We will then attempt complete or 'near complete' excision even when the tumor is encasing the major vessels e.g. aorta, inferior vena cava and branches. This is definitely a high risk procedure and demands meticulous and expert surgical techniques. Since there is such a wide variation in outcome in neuroblastoma patients, local survival data is of paramount importance for parental counseling and formulating treatment goals. In this article, we aimed to investigate the clinical outcome in relation to the surgical approach for this disease in our centre. The association between survival and other confounding clinical factors was also analysed.

Methods

This is a retrospective review of all patients with neuroblastoma admitted to our centre from January 1996 to April 2008. A total of 41 patients with confirmed diagnosis of neuroblastoma were identified and their hospital records were retrieved. Four patients were lost from follow up and were excluded from the study. As a result 37 patients were included in this study. Fisher's Exact test, Chi Square test and Kaplan-SMeier survival curve were used for data analysis. Significance is set at 95% confidence interval ($p<0.05$).

We defined 'complete excision' as gross tumour removal with no macroscopic tumour residue after the operation. Our protocol consists of 4-5 courses of chemotherapy pre-operatively, before attempting complete excision. The chemotherapy for localised tumours was of low intensity (modified POG low intensity regimen) whereas the chemotherapy for the advanced stage disease was of high intensity (modified N6 or N7 protocol of MSKCC). After surgery, further therapy will be given according to the risk group of the patients.

For the surgical technique, we adopted an approach first described by Kiely.[12] Briefly, an upper transverse incision was made in the abdomen. The ascending colon and duodenum were mobilised and reflected medially for tumours located on the right side. For advanced disease, the tumour usually wraps around the inferior vena cava. The cava was exposed and the lower limit of the tumour was approached. The tumour was split from the anterior side starting from the distal margin to proximal, taking care not to injure the IVC below. Any tumour vessels encountered were ligated and divided. After splitting the tumour, the anatomical relationship of vital structures became clearer for further safe tumour resection. For left-sided tumours, the descending colon was mobilised and reflected. Here, the tumour is usually found wrapping around the aorta. The approach in these cases is similar to right-sided tumours (Figure 1).

Results

The demographic data of the 37 patients was presented in Table 1. The mean age at diagnosis was 28.3 months (range 0-84 months). The mean duration of follow up was 58.3 months (range 8-141 months). The commonest primary site is in the adrenal gland (18 out of 37 patients), followed by the retroperitoneum (13) and thorax (4). One patient presented with primary tumour in the neck and one in the pelvis respectively. There were two patients with stage 4S disease and they were only treated with low intensity chemotherapy.

Table 1 Demographic data for patients with neuroblastoma

Male: Female	27:10	
Mean age at diagnosis	28.3±22.7 months	
Primary site		
Adrenal	18	48.60%
Retroperitoneal	13	35.10%
Thorax	4	10.80%
Others	2	5.40%
Total	**37**	

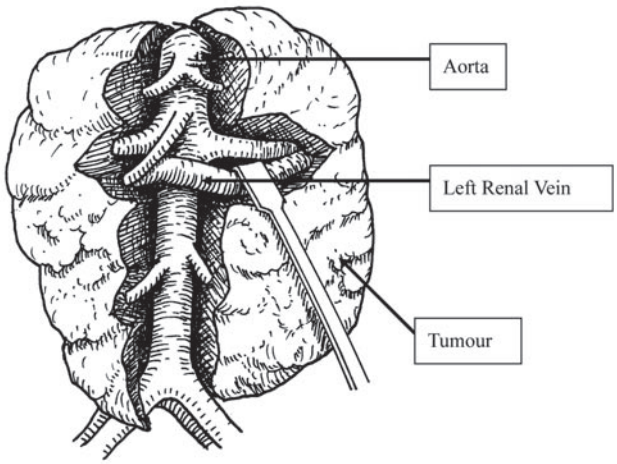

Figure 1 This is a schematic diagram showing a neuroblastoma wrapping around the major vessels.

Disease stage was assigned according to the International Neuroblastoma Staging System (INSS). The cohort of patients was mostly diagnosed at more advanced stages. 28 out of 37 patients (75.7%) were diagnosed with stage 3 or 4 disease. The distribution of stage and survival was illustrated in Table 2. Figure 2 illustrates CT scan findings of a typical patient under the protocol of aggressive surgery pre- and post-operatively. Figure 3 shows the anatomy of the major vasculature after total tumour removal.

The overall survival was 67.6%, with the survival curve plateauing off at around 60 months after diagnosis. There was no mortality in all patients with stage 1, 2 or 4S diseases; whereas the survival of patients with stage 4 disease was only 41.1%. There was significant correlation between the stage of disease and survival (p=0.03) (Figure 4).

The mean age at diagnosis for survivors and non-survivors were 22.8±20.3 months and 39.75±24.0 months

Table 2 Survival rates at different stages of disease

Stage	No. of patients	No. of deaths	Survival rate
1	2	0	100.0%
2	5	0	100.0%
3	11	2	81.8%
4	17	10	41.1%
4S	2	0	100.0%
Total	**37**	**12**	**67.6%**

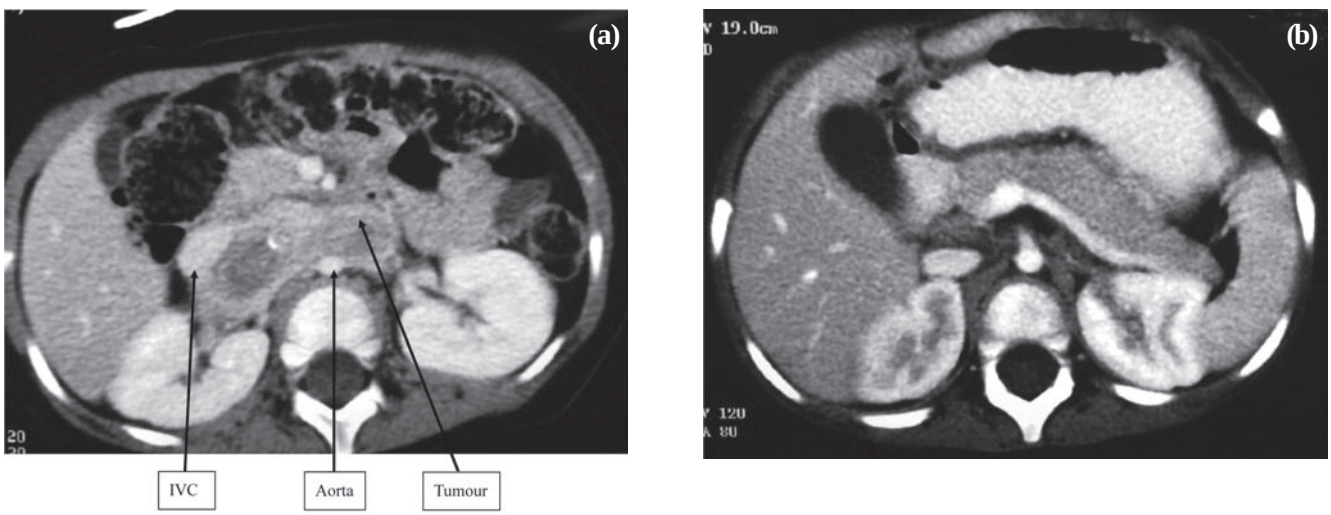

Figure 2 (a) This is a CT scan picture showing tumour mass encasing aorta and in close proximity of inferior vena cava (IVC) and other important vessels. (b) This is a CT scan picture showing status after operation. There is no more tumour mass around the major vessels.

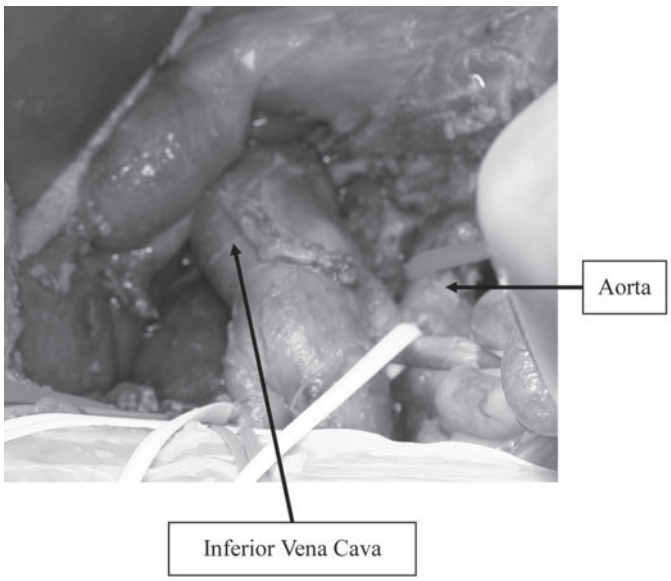

Figure 3 This picture shows abdominal vasculature after tumour dissection.

respectively, which is significantly different ($p<0.05$). As reported in the literature, younger age at diagnosis, especially for those less than one year of age, would confer better prognosis. If one year of age was used as the cut-off, the survival was much better for patients who were less than 1 year of age at the time of diagnosis (Table 3). The mortality rate of patients who were diagnosed with the disease later than one-year-old was 40% while it was only 16.6% for those who were diagnosed younger than one-year-old. Though there was no significant difference in the survival in the 2 groups ($p=0.15$), this may be due to the overall small number of patients included in the calculation.

Table 3 Survival of patients according to age

Age	Non-survivors	Survivors	Total
<1	2	10	12
>1	10	15	25

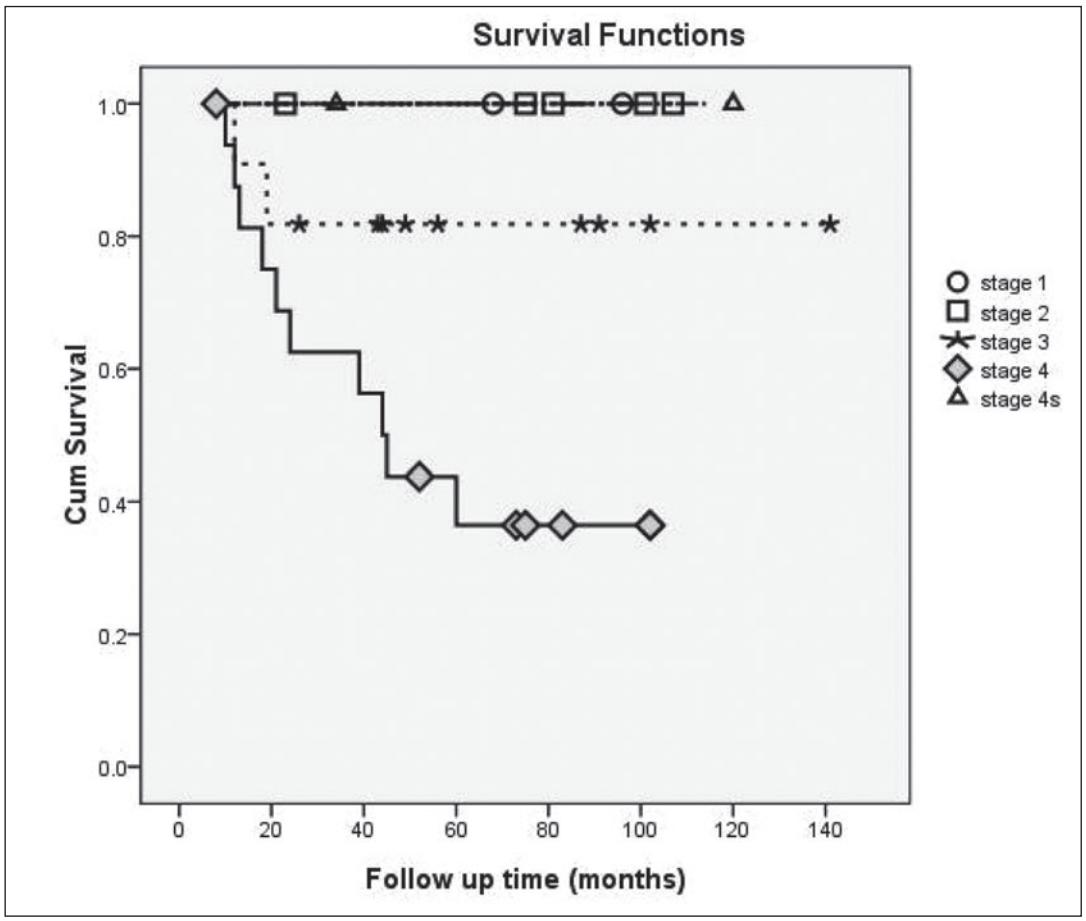

Figure 4 Survival curve of neuroblastoma with different stages (1996-2008).

Thirty-five out of 37 patients were operated on. One patient was operated in another centre. As a result, the completeness of tumor excision could not be ascertained. When we compared the survival of patients who had complete tumor excision with those who did not, there was significant improved survival ($p<0.001$), with the survival rate approaching 91% in patients with complete tumor excision (Figure 5). When we divided all the patients into those who had operation before or after 2004, there were 14 patients who had operation after 2004 and 23 patients before 2004. The completeness of surgical resection in patients with stage 3 and 4 patients was illustrated in Table 4. All stage 1 and 2 patients had complete resection from both periods. All 5 stage 3 patients had complete resection with the new approach whereas only half of the patients had complete resection before 2004. As for stage 4 disease, more patients had complete resection with the new approach. Since early stage neuroblastoma patients are known to have good prognosis, we then looked at the data of patients with stage 4 diseases only. The survival rate is again higher in stage 4 patients with the new approach at 57.1% and only 30% in stage 4 patients with operation before 2004, though this is not statistically significant on log rank test of the Kaplan-Meier survival curve. The survival curves which compare the new and old approach for stage 3 and 4 patients were shown on Figures 6 and 7

Table 4 Completeness of tumour resection in stage 3 and 4 patients with the new and old approach

		Before 2004	After 2004	Total
Stage 3	complete	3	5	8
	incomplete	3	0	3
	Total	**6**	**5**	**11**
Stage 4	complete	3	4	7
	incomplete	6	3	9
	unknown	1	0	1
	Total	**10**	**7**	**17**

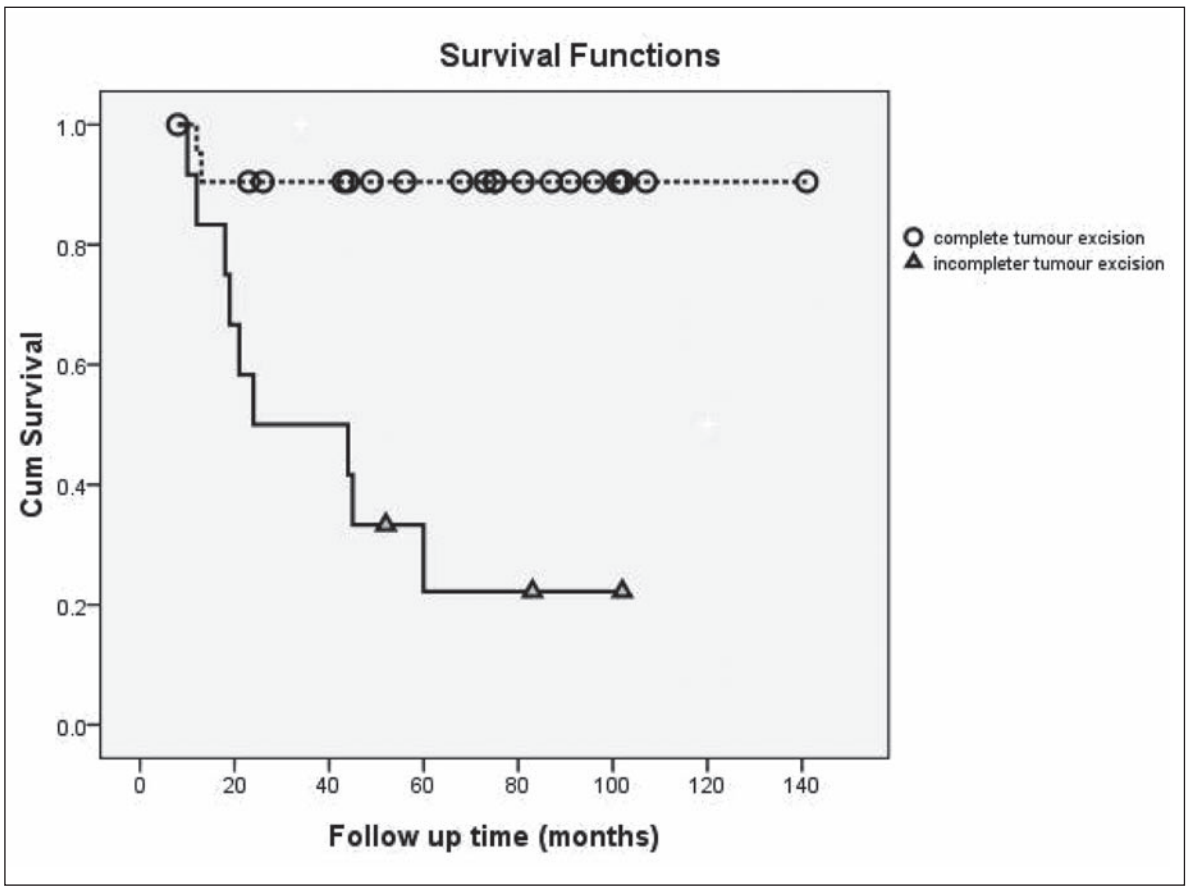

Figure 5 Survival curve of patients with complete and incomplete tumour excision.

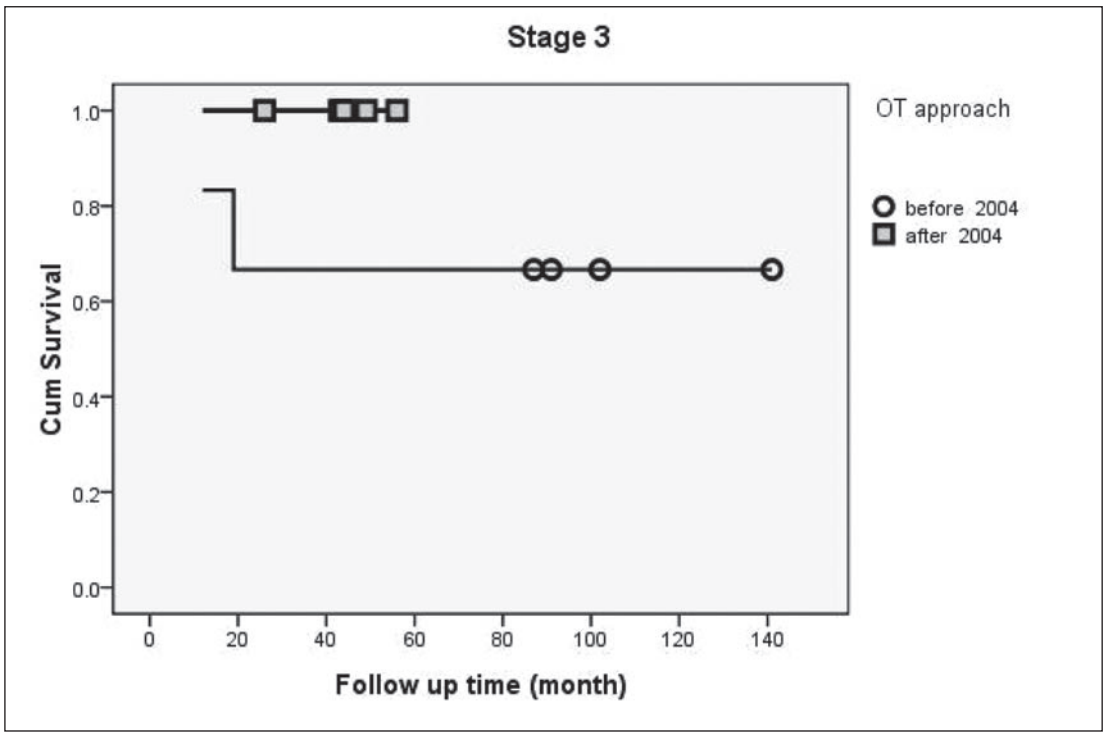

Figure 6 Comparison of stage 3 patients with new and old approach. It shows 100% survival of stage 3 patients with the new approach after 2004. The overall survival rate for the old approach was 66.7%.

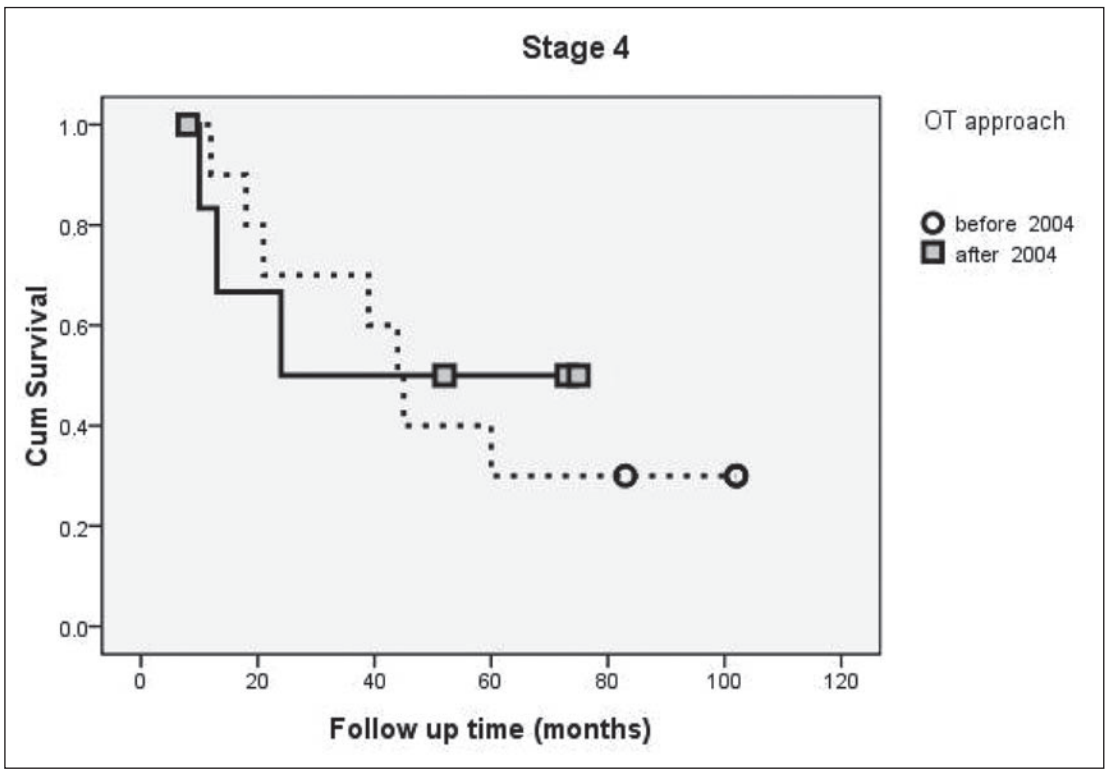

Figure 7 Comparison of stage 4 patients with new and old approach. The overall survival of new approach is slightly better than the old approach though it is not statistically significant.

respectively. With the new approach, stage 3 patients had 100% survival till now. In addition, the local relapse rate of those who underwent gross total resection was extremely low whereas patients with gross residual disease often relapsed locally with or without systemic relapse. Using the new approach, we encountered 2 intra-operative complications from 2004 to 2008. They were injury to aorta and renal vein respectively since neuroblastomas are known to encasing major vessels. Both of them were repaired with no long term complications so far.

For *MYCN* amplification status, it was examined in 12 of our patients. 2 out of 4 patients (50%) with positive *MYCN* amplification died whereas only 2 out of 8 patients (25%) with negative *MYCN* amplification died (Table 5). Statistical analysis could not be performed as the number of patients was too small. However, *MYCN* amplification is a known prognostic factor which is associated with poor survival especially for non-stage 4 patients.[13,14]

Discussion

According to the data of the Hong Kong Cancer Registry, the trend of sympathetic nervous system tumour was static from year 2001 to 2005. Thus, around 7-9 new cases were diagnosed every year in Hong Kong in this period.[15] Neuroblastoma is one of the most common solid tumours in childhood. Variable clinical course is observed from spontaneous tumour regression (as in infant with stage 4S disease), tumour maturation to a benign histologic form (as in infant with stage 4S disease or incidentally diagnosed localised tumour), to another extreme of uncontrollable metastasis.

Risk classification and treatment stratification are very important in deciding the most appropriate treatment for individual patients with neuroblastoma. Much effort has been given to find predictive factors to clarify clinical outcomes and hence to guide the treatment. The stage of the disease, the age at diagnosis, and *MYCN* oncogene amplification, and Shimada histological grading have all been documented as prognostic factors and are currently used in The International Neuroblastoma Classification System.[16] Treatment stratification will be based on these prognostic factors ranging from low intensity chemotherapy to intensive multi-modality approaches. Aggressive surgery is an important part of management in most of these patients.

Some investigators found better survival for those patients who received complete excision.[10,11] Our experience is also in line with these findings. We did demonstrate better survival on patients with aggressive approach especially on stage 3 patients. Though the survival benefit is not statistically significant, we think the short follow up time and the small number of patients can account for this. And, this is the limitation in our study in comparing the 2 groups with different follow up time. We still look forward for the long term outcome of this new approach. However, we have also experienced intra-operative complications as previously reported by Kiely.[16] This high-lights the technical demand of this operation. Despite this, we have not thus far encountered immediate post-operative mortality from this aggressive surgical approach. Taken all points together, we would suggest that management of patients with advanced stage neuroblastoma should be concentrated in a centre with excellent surgical, oncological and intensive care support.

In this article, we demonstrated that survival rate of neuroblastoma patients in Hong Kong was similar to those reported in other developed countries. The improvement in survival is contributed by multiple factors including improvement in supportive care, enhanced surgical technique and multimodal therapeutic approaches including chemotherapy, immunotherapy and megatherapy with autologous haemopoietic stem cells transplantation. However, even with these multimodal approaches, the outcome of patients with stage 4 disease remained suboptimal. Exploration of more novel therapeutic approaches is required to further improve the outcomes of patients with advanced stage metastatic neuroblastoma.

Table 5 *MYCN* amplification status in survivors and non-survivors

***MYCN* amplification**	**Non-survivors**	**Survivors**	**Total**
Positive	2	2	4
Negative	2	6	8
Unknown	8	17	25
Total	**12**	**25**	**37**

References

1. National cancer institute. Surveillance, Epidemiology and End Results Database. http://seer.cancer.gov (accessed April, 2009).
2. Brodeur GM. Neuroblastoma: Biological insights into a clinical enigma. Nat Rev Cancer 2003;3:203-16.
3. Escobar MA, Grosfeld JL, Powell RL, et at. Long-term outcomes

in patients with stage IV neuroblastoma. J Pediatr Surg 2006; 41:377-81.
4. Weinstein JL, Katzenstein HM, Cohn SL. Advances in the diagnosis and treatment of neuroblastoma. Oncologist 2003;8: 278-92.
5. Castleberry RP, Pitchard J, Scavarda NJ, et al. The International Neuroblastoma Risk Group (INRG): a preliminary report. Eur J Cancer 1997;33:2113-6.
6. De Bernardi B, Nicholas B, Boni L, et al. Disseminated neuroblastoma in children older thena one year at diagnosis: comparable results with three consecutive high-dose protocols adopted by the Italian Co-Operative Group for Neuroblastoma. J Clin Oncol 2003;21:1592-601.
7. Matthay KK, Villablanca JG, Seeger RC, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologus bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer group. N Engl J Med 1999; 341:1165-73.
8. Von Schweinitz D, Hero B, Berthold F. The impact of surgical radicality on outcome in childhood neuroblastoma. Eur J Pediatr Surg 2002;12:402-9.
9. Powis M, Ineson JD, Holmes SJ. The effect of complete excision on stage II neuroblastoma: a report of the European Neuroblastoma Study Group. J Pediatr Surg 1996;31:516-9.
10. Adkins ES, Sawin R, Gerbing RB, London WB, Matthay KK, Haase GM. Efficaacy of complete resection for high-risk neuroblastoma: A Children's Cancer Group study. J Pediatr Surg 2004;39:931-6.
11. La Quaglia MP, Kushner BH, SuW, et al. The impact of gross total resection on local control and survival in high-risk neuroblastoma. J Pediatr Surg 2004;39:412-7.
12. Kiely E. A technique for excision of abdominal and pelvic neuroblastomas. Ann R Coll Surg Engl 2007;89:342-8.
13. Brodeur GM, Seeger RC, Schwab M, Varmus HE, Bishop JM. Amplification of N-myc in untreated human neuroblastomas correlates with advanced disease stage. Science 1984;224: 1121-4.
14. Seeger RC, Brodeur GM, Sather H, et al. Association of multiple copies of the N-myc oncogene with rapid progression of neuroblastomas. N Eng J Med 1985;313:1111-6.
15. Hong Kong Cancer Registry. Cancer in children and Adolescents (0-19years). http://www3.ha.org.hk/cancereg/e_stat.asp (accessed April 2009).
16. Cohn SL, Pearson AD, London WB, et al. The International Neuroblastoma Risk Group (INRG) classification system: an INR Task Force report. J Clin Oncol 2009;27:289-97.