

# Neuroblastoma: the challenge remains

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In 1910, James Homer Wright reviewed a series of previously reported cases of metastatic cancers in children and recognised their common neural origin. All affected children had adrenal tumours with bundles of cells, now known as Homer-Wright rosettes, which resembled foetal adrenal tissue. He coined the disease 'neuroblastoma'.<sup>(1)</sup> Similar to other kinds of malignant diseases at that time, all the children died.

Neuroblastoma is a group of embryonal small round cell tumours that arise from the sympathetic nervous system. In over 60% of cases, the disease has been metastatic at the time of diagnosis. Contemporary treatment of neuroblastoma is tailored according to the biological behaviour of the disease, which is best delineated by the patient's age, disease staging and molecular changes. Here, the heterogeneity of neuroblastoma is best exemplified by its contrasting clinical outcomes among the different groups of patients. Early-staged (Stages 1 and 2) patients are often cured with surgery alone, without the adjuvant use of chemotherapy or radiotherapy. The majority of children with metastatic diseases (Stage 4) would succumb even after intense treatment with chemotherapy, surgery and high-dose therapy followed by haematopoietic stem cell transplantation. Yet, infants with adrenal neuroblastoma and metastases limited to the skin, liver and bone marrow (Stage 4S) often experience remission even without treatment. Genetic and molecular changes in the tumour, such as chromosome 1p deletion, gain of chromosome 17q and especially amplification of MYCN oncogene, portend a poorer prognosis. The presence of MYCN amplification, for instance, is regarded by many as an indication for more aggressive treatment in children with non-Stage 4 diseases.<sup>(2)</sup>

Advances in the treatment of children over one year of age with metastatic or Stage 4 neuroblastoma have only resulted in a modest improvement in survival during the past 101 years. The application of high-dose chemotherapy followed by autologous haematopoietic stem cell rescue as a consolidation treatment after conventional chemotherapy results in better survival rates compared with maintenance chemotherapy. Higher event-free survival rates at 40%–50% are seen in recent studies and when cis-retinoic acid treatment is used after high-dose therapy.<sup>(3)</sup>

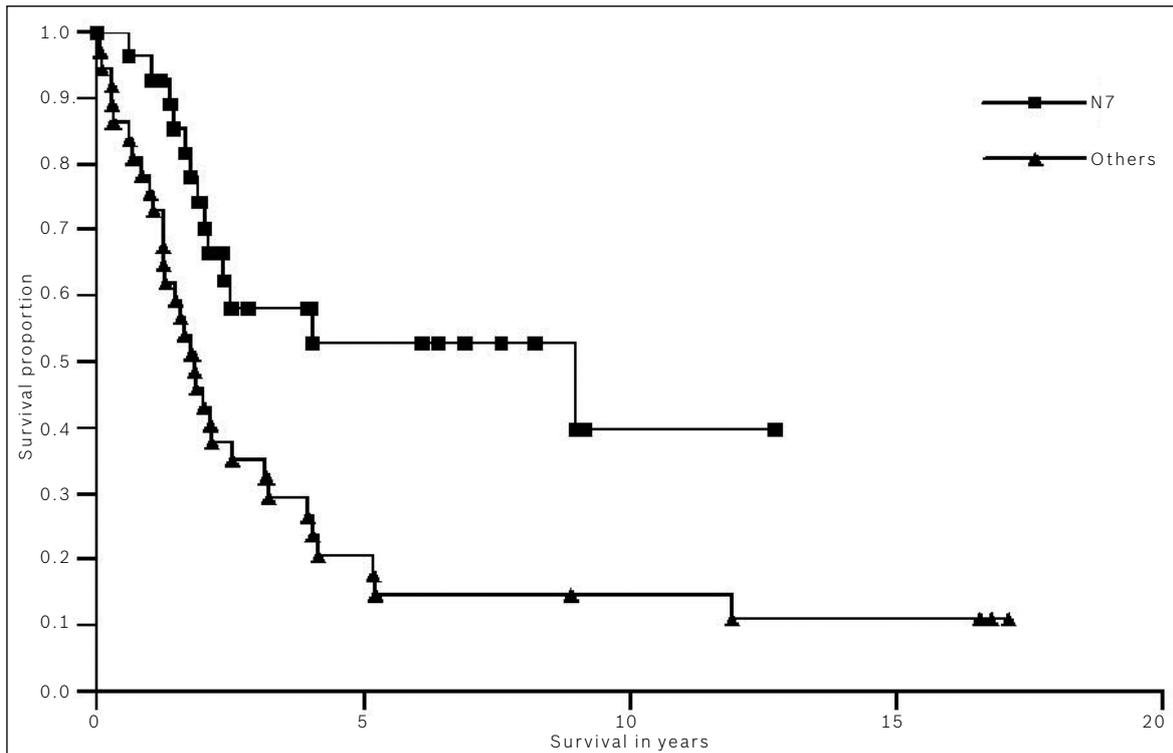
However, this modest improvement of survival in children with metastatic neuroblastoma has only been reported in Europe and North America. Among Asian countries, with the exception of Japan, metastatic neuroblastoma seems to be as lethal as it was a century ago. A PubMed search fails to

identify any clinical treatment and outcome studies in the last ten years among the ten member countries of the Association of Southeast Asian Nations, which together are populated by over 590 million.

In this Oncology issue, Tan et al report a series of 43 children diagnosed with neuroblastoma over a period of 21 years in Singapore.<sup>(4)</sup> The patients are divided into three prognostic groups. 13 patients have Stage 1, 2 or 4S disease, and all are surviving without neuroblastoma. 11 patients are classified as intermediate risk due to Stage 3 disease. Eight patients survive the neuroblastoma after treatment with surgery and chemotherapy. Of the 19 children with Stage 4 neuroblastoma, 11 have died, seven have survived the disease, and one is receiving treatment for relapse. While patients with early-staged disease are enjoying excellent outcomes, those with Stage 4 disease have survival rates that are inferior to those of other developed countries. Due to the small patient sample over a relatively long period of recruitment, as well as the significant number of patients who dropped out from treatment, their findings do not permit a conclusion as to what the best treatment is for children with metastatic neuroblastoma.

The authors call for collaboration among the existing paediatric oncology centres in Singapore in order to advance the treatment of neuroblastoma. Collaborations at national and international levels, in which randomised controlled studies can be conducted on a large number of patients, have been making major progress in paediatric oncology. Does it make sense to ask all the paediatric oncologists in Singapore to work on the same treatment protocol when the annual incidence of neuroblastoma in the country is so low?

The Hong Kong Special Administrative Region (HKSAR) has a population that is roughly twice that of Singapore. Yet, children with cancers are treated in five different oncology units. Since 1993, these five treating institutions have decided to adopt unified protocols for most of the paediatric cancers. Each institution has the obligation to follow the treatment protocols closely and to report serious complications and patient outcomes on a timely basis. Each protocol is reviewed on an annual basis and is subject to modifications in view of worldwide developments and ongoing local treatment experience. A significant improvement in the outcomes of children with acute lymphoblastic leukaemia has been reported.<sup>(5)</sup> In children with metastatic neuroblastoma, the collaborative protocol has produced a five-year event-free survival rate of 53% as compared with 15% before the collaboration commenced (Fig. 1). In addition, a unified basis for treatment of childhood



**Fig. 1** Kaplan-Meier curves for event-free survival for children with Stage 4 neuroblastoma treated with the unified protocol (N7) since 1999 compared with children treated in an earlier cohort with various regimens (Others), showing a significantly better outcome under the unified protocol (Courtesy of Professor Godfrey Chan on behalf of the Hong Kong Paediatric Haematology and Oncology Study Group).

cancer has enabled the HKSAR to participate in international co-operative group studies and researches.

Hence, collaboration among the paediatric oncology centres in Singapore is a sensible step forward.

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