Surgical outcome analysis of paediatric thoracic and cervical neuroblastoma

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Abstract

OBJECTIVE: To identify factors determining the surgical outcome of primary cervical and thoracic neuroblastoma.

METHODS: Twenty-six children with primary thoracic neuroblastoma presented over the last 14 years were analysed for age, mode of presentation, tumour histopathology, biology and outcome.

RESULTS: Primary thoracic neuroblastoma was presented in 16 boys and 10 girls at a median age of 2 years (range 6 weeks–15 years). The International Neuroblastoma Staging System (INSS) classified these as Stage 1 (8), Stage 2 (5), Stage 3 (6) and Stage 4 (7). Computed tomography defined the tumour location at the thoracic inlet (11), cervical (2), cervico-thoracic (3), mid-thorax (9) and thoraco-abdominal (1). Twenty-two children underwent surgery that allowed an adequate exposure and resection. Surgical resection was achieved after initial biopsy and preoperative chemotherapy in 15 children, whereas primary resection was performed in 7 children. Four patients with Stage 4 disease underwent chemotherapy alone after initial biopsy; of which, two died despite chemotherapy. Favourable outcome after surgical resection and long-term survival was seen in 19 (86.4%) of the 22 children. Three had local recurrence (14 to 21 months postoperatively), all with unfavourable histology on initial biopsy. The prognostic factors that determined the outcome were age and INSS stage at presentation. In this series, all patients under 2 years of age are still alive, while mortality was seen in five older children.

CONCLUSION: Thoracic neuroblastoma in children under 2 years of age irrespective of stage and histology of the tumour results in long-term survival.

Keywords: Thoracic neuroblastoma • Children • Outcome • Dartevelle’s incision • Thoracoscopy

INTRODUCTION

Neuroblastoma is the most commonly occurring soft-tissue malignancy of childhood and the third most common paediatric malignancy after central nervous system tumours and leukaemia. Neuroblastoma has a reported incidence of 1 in 8000 to 1 in 10 000 [1] anywhere along the sympathetic chain commonly within the adrenal medulla. Thoracic neuroblastomas account for up to 15% of all neuroblastomas [2]. Although neuroblastomas in general have an overall survival rate of 55% [3], thoracic-located neuroblastomas are associated with a better outcome [4]. However, it is not clear from various studies in the literature as to what factors determine the favourable outcome in this group of neuroblastoma. The purpose of this study was to identify the prognostic factors determining morbidity and mortality of primary thoracic neuroblastoma. The study also describes and discusses the effectiveness of a known incision used for the resection of pancoast tumour for the cervico-thoracic neuroblastoma.

MATERIALS AND METHODS

Between January 1995 and January 2009, 26 children with primary thoracic neuroblastoma managed at the Birmingham Children's Hospital were analysed for age, mode of presentation, histopathology and biology of the tumour and outcome. Tumours were classified using the International Neuroblastoma Staging System (INSS) [5]. Statistical analysis was considered unnecessary by an expert. The need for the preoperative chemotherapy was discussed in the multidisciplinary meetings with the oncologists, surgeons and radiologists depending on the resectibility and spread of the tumour at presentation. Tumour biopsy and subsequent chemotherapy were considered only in extensive tumours. Surgery was carried out with either a standard lateral or a posterio-lateral thoracotomy in all cases except three cervico-thoracic neuroblastomas and two cervical neuroblastomas. The cervical neuroblastomas were approached through a transverse crease incision exposing the tumour and the important anatomical structures. The modified technique of exposure...
used for the cervico-thoracic neuroblastoma for their adequate resection is described.

**Technique used for resection of cervico-thoracic neuroblastomas**

Cervico-thoracic neuroblastomas have been successfully excised by using an adaption of the Dartevelle incision [6] (Fig. 1). The patient is placed in a supine position with a roll under the shoulders to extend the neck. An L-shaped anterior incision is made and clavicle is divided lateral to the insertion of sternocleidomastoid muscle. The sternocleidomastoid muscle with its clavicular insertion are retracted medially and the lateral two-third of clavicle is retracted to expose the supraclavicular fossa. The scalenus anterior muscle is then divided to expose the deeper vessels and the tumour extending into the thoracic inlet. The tumour is dissected free from the internal jugular vein and brachiocephalic confluence followed by clearance from the arteries. The neuroblastoma is generally closely associated with carotid and subclavian arteries and may require sharp dissection in the adventitia of these vessels to achieve effective clearance. The phrenic and vagus nerves are identified and preserved. Once the tumour resection is complete, both ends of the clavicle are approximated by suturing the periosteum with long-lasting absorbable sutures. This gives good cosmetic results without long-term consequences to shoulder joint mobility and stability. It is similar to the Nazari modification [7] whereby the clavicle is sutured to the sternum. This incision and approach was used in the resection of three of our cervico-thoracic neuroblastoma cases.

**RESULTS**

Sixteen boys and 10 girls presented at a median age of 2 years (range 6 weeks–15 years), with primary thoracic neuroblastoma.

**Clinical presentation**

The systemic symptoms in 26 tumours were weight loss and failure to thrive; additionally 18 children were anaemic. Specifically, the majority of cases presented with respiratory symptoms such as shortness of breath, while five cases presented with stridor and one with bronchiolitis. There were other associated symptoms such as dysphagia in five tumours. Neurological symptoms such as Horner's Syndrome (four tumours), paraparesis (two tumours), dancing eye syndrome (one tumour) were associated. Clinically, palpable mass was present in one case, while one was detected incidentally on chest X ray.

Surgical clearance was attempted after an initial period of chemotherapy in 15 patients despite their anatomical extension and bulk (Fig. 2). Included in this group were two children with hourglass extension through intravertebral foramen causing spinal cord compression who responded well to chemotherapy. Chemotherapeutic cycles caused regression of the spinal canal extension allowing surgical resection without laminectomy. One additional child who was conservatively managed and monitored as multiple biopsies diagnosed the tumour as ganglionneuma. She presented at the age of 15 years with sciatica-like pain radiating to her right leg and a limp. An MRI scan showed tumour extension into her spinal canal. Resection including laminectomy resulted in only partial symptom resolution. Additionally, three patients (Stage 4, two patients; Stage 3, one patient) with unfavourable histology received further courses of postoperative chemotherapy. Seven patients underwent primary surgical resection; of which, two received subsequent chemotherapy. Four patients with Stage 4 disease underwent chemotheraphy alone after histological diagnosis. Of these four, disease progression rendered two of them inoperable but the other two patients <1 year of age has survived.

Three patients in this series with unfavourable histology had surgical resection and developed recurrence on follow-up. One patient with Stage 2 disease at thoracic inlet underwent primary surgical resection, but did not receive postoperative chemotherapy. In this patient, recurrence was identified on follow-up and he was managed with further surgery and postoperative intensive

![Figure 1: Modified Dartevelle’s incision for exposure of cervico-thoracic neuroblastoma in children. The darker dashed line is our modification which has been useful in most instances. The line on the clavicle lateral to sternomastoid muscle is the point of division of clavicle. The incision is lowered along the dotted line as described in Grunenwald’s modification with an osteomuscular flap (the medial part of manubrium is divided to lift the clavicle along with the intact sterno-clavicular joint and the sternocleidomastoid muscle) to expose the deeper and more extensive thoracic component.](image1)

![Figure 2: CT scan showing an extensive apical neuroblastoma: the tumour crossed the midline and extended into the left thoracic cavity.](image2)
Surgical resection in children <2 years of age resulted in 100% survival were seen in 19 (86.4%) children of the 22; three favourable outcomes after surgical resection and long-term survival regardless of the stage of disease at presentation. However, he developed recurrence in spite of postoperative chemotherapy and died of progressive disease. The third patient, who was 2 months of age at presentation, had primary resection of left apical neuroblastoma and received postoperative chemotherapy for unfavourable histology. He was noticed to have recurrence on follow-up. He underwent surgery for the recurrence and remains disease free at follow-up of 12 years. The histology of his recurrence was maturing ganglioneuroblastoma. The median period of follow-up was 4.2 years (range 2.7–14 years). New onset Horner’s syndrome occurred in three patients after excision of neuroblastoma. Postoperative chyllothorax was seen in two patients, which resolved with conservative management with no subsequent recurrence on follow-up.

Five children of the 26 died. They presented with Horner’s syndrome (1), paraparesis (1) and systemic symptoms of malignancy (weight loss, lethargy, anorexia—3). The tumours found in these children were apical in three, mid-thoracic in one and cervico-thoracic in one. The INSS tumour stages in these children at presentation were Stage 4 (2), Stage 3 (2) and Stage 2 (1). Two of the Stage 4 patients underwent initial diagnostic biopsy only and did not respond to chemotherapeutic regimen, while the other two responding to chemotherapy underwent surgical resection. The local recurrence was also identified after primary resection of the Stage 2 tumour with unfavourable histology that was initially followed-up. He died of progressive disease in spite of second resection and intensive postoperative chemotherapy and stem-cell rescue.

Mortality in this series was 19.2% (5 of 26 cases); all of these five cases were diagnosed in children >2 years of age (range 2.5–6 years). Prognostic factors that determined the mortality were:

1. Age at presentation
2. INSS stage at presentation

Favourable outcomes after surgical resection and long-term survival were seen in 19 (86.4%) children of the 22; three patients with unfavourable histology had recurrent tumours. Surgical resection in children <2 years of age resulted in 100% long-term survival regardless of the stage of disease at presentation and histology.

**Cervical (n = 2)**

There were two cases of cervical neuroblastoma extending into the thoracic inlet. They had complete excision using a cervical approach (transverse skin incision above the clavicle). One of the patients underwent primary excision biopsy that identified an undifferentiated neuroblastoma at the age of 6 weeks and did not receive postoperative chemotherapy. The other patient (age 3) had favourable histology and subsequent to chemotherapy underwent complete resection. These patients are currently well and disease free at 6 and 12 years, respectively.

**Cervico-thoracic (n = 3)**

Macroscopically, gross resection was achieved using the modified Dartevelle’s approach after initial diagnostic biopsy and chemotherapy in all three patients (Fig. 3). Histologically, one of the patients had undifferentiated neuroblastoma and was Stage 4 at presentation, but responded to preoperative chemotherapy to allow resection of his residual tumour. He died 16 months postoperatively with metastatic disease in spite of intensive postoperative chemotherapy. The other two patients, after successful surgical resection, remain disease free and are considered cured after 5 and 8 years of follow-up.

**Thoracic inlet/apical (n = 11)**

There were 11 cases of apical neuroblastoma; of which, 10 were resected via thoracotomy and one had thoracoscopic biopsy only (Fig. 4). Eight patients from this group survived, seven had favourable and one had unfavourable histology. Two of the eight were >2 years of age at diagnosis and received preoperative chemotherapy after initial biopsy. Three patients under 1 year of age had primary resections. They are all disease free at >7 years of follow-up. Three patients in this group who died were >2 years at diagnosis. Two had macroscopic clearances but recurred with only one having adjuvant chemotherapy. Histologically, they had undifferentiated neuroblastoma and died of metastatic disease 2 years after initial presentation and subsequent diagnosis. One had a thoracoscopic biopsy but did not survive, having had progressive disease despite chemotherapy.

**Mid-thoracic (n = 9)**

Seven of the nine mid-thoracic neuroblastomas were resected via thoracotomy, and one with incidental finding on chest x-ray was resected with thoracoscopic surgery. Four had primary resection without chemotherapy while four other had preoperative chemotherapy after biopsy. All these eight patients had favourable histology and are disease free at follow-up of 10 years. One patient who died was 6 years of age, had Stage 4 neuroblastoma with unfavourable histology on biopsy and did not respond to chemotherapy. One 15-year-old girl, conserved after initial biopsy in other children’s hospital, presented with pain and weakness in the right leg. In spite of initial biopsy showing mature ganglioneuroma and previous monitoring scans showing well-circumscribed tumour, the tumour must have

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Figure 3: CT scan showing a large cervico-thoracic tumour.
gradually grown to develop an intra-spinal extension and symptoms. This large tumour with its dumbbell extension was resected jointly with a neurosurgeon. She made good recovery and has no recurrence after 4 years of follow-up but still complains of weakness in her leg.

**Thoraco-abdominal (n = 1)**

The thoraco-abdominal neuroblastoma was resected via thoracotomy. This patient was Stage 3 at presentation, with bilateral thoracic disease extending through the crura of the diaphragm into the upper abdomen. She received preoperative chemotherapy with good response. The abdominal component was resected using a trans-diaphragmatic approach. The postoperative chylothorax was treated conservatively. She had unfavourable histology, but, after chemotherapy, is recurrence free 7 years postoperatively.

**DISCUSSION**

Our study contains a large group of primary thoracic neuroblastomas in children operated by one surgeon with long-term follow-up. The study demonstrates that the prognosis of thoracic neuroblastoma depends on the age of the patient and the stage of disease at presentation. Effective surgical resection resulted in a good outcome in the majority of cases that responded to chemotherapy irrespective of histology and the stage of the disease. Initial chemotherapeutic response to advanced and unfavourable histological disease is an important indicator to the overall surgical outcome.

This study not unexpectedly has confirmed the site-specific better prognosis in thoracic neuroblastoma. Long-term survival in 86.4% of cases was seen after surgical resection, irrespective of histology or the stage of neuroblastoma at presentation. The findings of our study are similar to other studies where 5-year survival of 77% is reported [8]. The bigger series containing all types of paediatric neuroblastoma did not analyse various sites within thoracic cage, stage and histological differentiation with regards to outcome [8–10]. One study suggested that mediastinal tumours were more localized compared with others and therefore carried a better outcome [4]. Our study suggests that not only the localized variety but also the Stage 4 tumours carry a better outcome, provided they responded to chemotherapeutic cycles after biopsy and surgical resection was complete.

Important independent variables determining better prognosis were infants <1 year of age and those with Stage 1, 2 and 4 disease compared with age >1 year, with Stage 3 and 4 disease in all types of neuroblastoma. Our study confirms the findings from reported studies that the surgical outcome is inversely related to the age at presentation [11]. In many studies, no attempt was made to demonstrate a correlation between improved survival with respect to the age at presentation and tumour staging in children with thoracic neuroblastomas [4, 8]. Only one study had identified a correlation of long-term survival with age at presentation, although other studies have implicated a better outcome in young infants [9]. Five of their seven cases of thoracic neuroblastoma <2 years of age were reported to have a long-term survival [9]. In our study, all children <2 years of age at presentation demonstrated a long-term survival irrespective of their stage of disease and histological differentiation. Children diagnosed after 2 years of age in our series have been associated with higher mortality and recurrences.

The Shimada classification, which is age related, shows that histological classification of the tumour into favourable (stroma rich) and unfavourable (stroma poor) in combination with N-myc amplification and allelic loss on the short arm on chromosome 1 (Chr1p) and gain of the long arm of chromosome 17 (Chr 17q) are important prognostic factors for survival [12]. N-myc amplification, which occurs in 30% of all varieties of neuroblastoma, has an important role in the modulation of the malignant phenotype and has been shown to be an important independent prognostic factor, irrespective of age and stage of the disease [13]. N-myc expression alone has no prognostic value, but N-myc amplification within tumour is associated with a poor outcome. Some of the chemotherapy treatment regimes may be altered depending on the N-myc amplification in neuroblastoma to improve the outcome. Although in our cohort none of the thoracic neuroblastoma demonstrated N-myc amplification, it is possible that N-myc amplification may be a determining factor in the thoracic neuroblastoma outcome.

In our study, higher INSS staging (Stage 4) at presentation was identified to be a poor prognostic factor with two of the five patients died were INSS 4 at presentation. The third patient who died was originally INSS 2 with unfavourable histology and recurrence was reclassified as INSS 4. The excellent outcome and survival have been demonstrated by a number of studies with combined chemotherapy and complete but not radical
surgery in paediatric neuroblastomas [14]. Our cohort has shown an excellent result using this strategy in children undergoing surgical resection after a period of chemotherapy. The failure of response to chemotherapy in some of our cases was associated with mortality. Furthermore, unfavourable histology in our cohort was also associated with an increased risk of recurrence and mortality. There was a notable inconsistency in the regime of chemotherapy after tumour resection revealing an unfavourable histology. Only one patient in our series, who had recurrence after surgery, received postoperative chemotherapy for unfavourable histology. He underwent successful resection of recurrent tumour and is alive on long-term follow-up. This subgroup in thoracic neuroblastoma with unfavourable histology on initial biopsy needs randomized control multi-centre trial to see whether postoperative chemotherapy can improve their outcome especially in Stages 1, 2 and 3. Currently, there is no guidance on continuing chemotherapy or giving chemotherapy after primary excision in unfavourable histology sub-group.

Our findings suggest that apical or thoracic inlet neuroblastoma had poor prognosis compared with any other sites in the thoracic cavity. Four of the five children who died had tumour located at the apex of the thoracic cage (the thoracic inlet [3] and cervicothoracic [1]). There are no studies in the literature comparing the outcome between different sites within the thoracic cage. Resection of thoracic inlet tumours is technically demanding, especially those extending into the neck. The application of Dartevelle’s incision that was initially described for Pancoast tumours in adults gave an excellent exposure and required resection of medial third of clavicle [7]. The concern with using this approach, especially in children, is that excision of the medial half of the clavicle reduces shoulder girdle stability [15]. The modification that we have adopted is a variant of the Nazari modification [7] whereby the clavicle is transected to allow an adequate exposure and then once the resection of the tumour is complete, both ends are approximated and the periosseous tissues closed using absorbable sutures. The bony healing of the clavicle was very good and all of our patients achieved a full range of movement around the shoulder joint. Further exposure into the thoracic cavity can be achieved by disarticulating the first and second ribs at the costo-chondral junction in case the tumour is extensive and has a larger intra-thoracic component. Although some paediatric surgeons have preferred Grunenwald’s modification of the osteomuscular flap whereby the medial part of manubrium is divided to lift the clavicle along with the intact sternoclavicular joint and the sternocleidomastoid muscle to expose the deeper structures [15, 16], it has to be emphasized that no single approach in these situation is perfect and therefore the surgeon should be familiar with other modifications and exposure in this area [7, 17]. We recommend our technique as it is useful in most situations in achieving good exposure and complete resection of neuroblastoma with minimal postoperative morbidity. Although three of our patients were operated by using this modified approach successfully, one of the children with unfavourable histology died due to subsequent recurrence and progressive disease.

In conclusion, this study demonstrates that effective surgical resection results in long-term survival in thoracic neuroblastoma especially in children <2 years of age. The value of chemotherapy in unfavourable histology thoracic neuroblastoma not only prior to surgery but also following resection needs further evaluation and standardization. Mature thoracic ganglioneuroma should also be resected as one of our cases became symptomatic. Small tumours can be successfully resected with thoracoscopic surgery.

Conflict of interest: none declared.

REFERENCES