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A comparison of nutritional status in patients with neuroblastoma in Rwanda and United Kingdom: a cross-sectional observational study conducted by the OxPLORE collaboration

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Abstract

Background: Cancer is a major global health concern and a leading cause of death in paediatric populations worldwide. Malnutrition contributes to a poor prognosis and remains the most common comorbidity leading to death in children with cancer. This retrospective study was developed through Oxford Paediatrics Linking Oncology Research with Electives (OxPLORE)—a medical student-led collaboration of paediatric surgeons and oncologists from low- and middle-income (LMIC) and high-income (HIC) countries. The aim of this study was twofold; firstly, to investigate the nutritional status and outcomes of neuroblastoma paediatric patients in two OxPLORE centres. Secondly, to facilitate the development of research skills of medical students as part of the OxPLORE initiative.

Results: Nine neuroblastoma patients were identified (YY, $n = 4$, XX, $n = 5$) over the study period. Nutritional status was poorer in YY patients (median *z*-score − 1.57 cf. − 0.7, $t = 1.16$, $p = 0.28$), which correlated with poorer survival in the YY cohort (75%), as compared to the XX cohort (100%). YY patients were older at presentation than the XX cohort (57 cf. 13 months, $t = 1.959$ $p = 0.09$). Further, tumour presentation was at a later stage in the YY group (75% stage IV).

Conclusion: This collaboration has shown a correlation in disparities in nutritional status and outcome of neuroblastoma in paediatric populations in YY and XX. These findings can inform institutional quality improvement. Further, this pilot study has highlighted the potential for medical students to undertake international research collaborations.

Keywords: Neuroblastoma, Nutritional status, United Kingdom, Rwanda, Medical students, Research collaboration

Background

Cancer is increasingly recognised to be a major global health priority and a leading cause of death in paediatric populations worldwide [1]. Solid tumours account for 30% of all childhood cancers and neuroblastoma is amongst the most common solid tumour malignancy [2]. Neuroblastoma, arising from neural crest cells [3], accounts for 15% paediatric tumour-related deaths worldwide [4–6]. Factors including late presentation of disease and abandonment of treatment have been outlined as impeding good outcomes [7–9].

Malnutrition contributes to a poor prognosis and remains the most common comorbidity leading to death in children with cancer [10]. Worldwide, 85% of children live in lower- and middle income countries (LMICs),

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and consequently, the burden of paediatric cancer is disproportionately represented in these settings [11]. Approximately, 50% of children with cancer in developing countries are malnourished [12]. Whereas, in high income countries (HIC) malnutrition tends to be seen in patients with advanced neuroblastoma [11]. A recent systematic review of clinical outcomes in paediatric solid tumour patients noted that abnormal body mass index (BMI) was associated with worse overall survival with several solid tumours [13].

This study was developed through collaboration between a medical student from Y (YY), Rwanda and a visiting elective student from X Hospital (XX), United Kingdom (UK) who were linked via the medical student research collaboration, Oxford Paediatrics Linking Oncology Research with Electives (OxPLORE). Both students aimed to develop research skills and had interests in global health, paediatric surgery and oncology. Medical students were supervised and supported by their lecturers at their respective medical schools and within the larger OxPLORE network. OxPLORE promotes bidirectional partnership between HIC and LMIC-based medical students, introduces students to the principles of clinical research and conducts robust data collection to guide advancements. The goal of this OxPLORE study was to describe nutritional status and outcomes in paediatric neuroblastoma patients and make comparisons between YY and XX.

Methods

The concept [14], development and methodology [15] of OxPLORE is described elsewhere. Medical students led the data collection and manuscript writing. Students sought supervision from trainees and consultants within their respective medical schools and hospitals to aid with obtaining ethical approval and completion of this project. Regular remote messaging and meetings facilitated communication between collaborators. Anonymised data exchange occurred through security password-encoded databases.

The completeness of this report was verified using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist [16].

Objectives

This OxPLORE study aimed to describe and compare nutritional status at presentation and outcomes in paediatric neuroblastoma patients at YY and XX. The secondary aim of this study was to facilitate the research partnership and learning of medical students involved in the OxPLORE collaboration.

Study design and setting

This cross-sectional observational study included two collaborating centres:

(1) YY, Kigali, Rwanda.
(2) XX, England, UK.

A retrospective medical record review was performed of all children under 16 years old (YY) and under 16 years old (XX) presenting with neuroblastoma between January 2016 and June 2018.

XX uses an electronic patient registration system, allowing identification of children diagnosed with neuroblastoma. In YY, patients were identified via inpatient ward registries and clinician notes. There were no patient exclusion criteria other than age.

Variables and outcomes

This study reports early outcomes, which are defined as those occurring in the 29-month study period. The primary outcome was nutritional status at presentation, defined by WHO weight and height z-scores. Secondary outcomes included: survival to the point of discharge or death, whichever came first; stage of tumour at presentation; treatment modality (surgery and/or adjuvant medical); and post-operative morbidity. Post-operative morbidity was categorised as per the Clavien–Dindo scale classification: stage 1 (deviation from normal post-operative course without need for intervention), stage 2 (requiring pharmacological treatment), stage 3 (requiring surgical, radiological or endoscopic intervention), and stage 4 (life threatening events needing intensive care and/or involving organ failure) [17].

Data collection, management and analysis

Data were extracted retrospectively from patient files. Contact was not made with the patient and/or caregivers. Anonymised data was inputted into a password protected database. The tool was agreed a priori by participating researchers, allowing reliable and institutionally relevant comparison, before commencing data collection. Data were analysed centrally using GraphPad Prism version 8 (KF). Data are presented as median (range) unless otherwise stated and p values of < 0.05 considered statistically significant. t test was used to compare continuous variables. We acknowledge missing data, but no statistical methods employed to account for them.

Ethics

Consent was not gained from patients or caregivers as the study was retrospective and did not involve any

patient contact, only a review of the patient files. There was no perceived riskor incentives. Confidentiality was ensured and all data anonymised. Institutional endorsement was sought at both participating centre's review boards where the research protocol was reviewed and approved by the research and ethics committee board of YY (Ref: EC/YY/680/2018) and XX (Ref: 4741).

Results

YY, located in the capital city of Rwanda, Kigali, is a large national referral centre for paediatric tumours that serves a larger population of ~ 5,000,000 children. XX is a regional referral centre for paediatric tumours that serves a smaller population of ~ 655,000 children (Table 1).

Patient presentation

There were nine neuroblastoma patients who were identified and treated (YY, $n = 4$, XX, $n = 5$) over the study period (Table 2). The median age at presentation varied between the two centres—the YY patients were older than the XX patients (57 cf. 13 months, $t = 1.959$ $p = 0.09$). The XX cohort had a male predominance: $N = 4/5$ cf. $N = 2/4$ in YY.

Nutritional status at presentation varied between the two centres (Fig. 1). The Rwandan cohort presented with lower weights than the XX cohort (median z-score − 1.57 cf. − 0.7, $t = 1.16$, $p = 0.28$). Further, height was lower in YY than in the XX group (median z-score − 2.2 cf. 1.45, $t = 2.64$, $p = 0.057$).

Patients presented with different stage disease between YY and XX (Fig. 2). The disease stage was more advanced in YY than in XX (75% cf. 40% stage III/IV in YY and XX, respectively).

Management and outcomes

Survival over the study period was 3/4 patients in YY and 5/5 patients in XX. The cause of death in the YY patient was advanced tumour stage (IV), and death occurred within two weeks of admission. The median length of stay was longer in YY (19, 11–30 days), as compared to XX (5, 3–8 days).

Overall, four patients underwent surgical resection of neuroblastoma ($n = 1$ at YY and $n = 3$ at XX). Amongst those, all at YY and 2/3 at XX received pre-operative chemotherapy with Children's Oncology Group Study (COG) based regimen. Patients who were not operated, either had a good response to chemotherapy alone ($n = 1$ at YY and $n = 2$ at XX) or were deemed inoperable, given stage of tumour presentation ($n = 2$ at YY). Post-operative morbidity was greater at YY than XX. At YY the only operated patient had stage II morbidity, requiring pharmacological intervention. Whereas in XX, 2/3 of operated patients had stage I morbidity, requiring no intervention; the other patient had stage II morbidity.

Table 1 Summary of participating centres, available resources and oncology service

	YY[a]	XX[b]
Country population[c]	11,610,000	64,716,000
Under 5 mortality rate[c]	34.3Per 1000 live births	4.3Per 1000 live birth
Human development index[d]	0.524158/189 countries	0.92214/189 countries
Population under 18 years	5.4 million	655,000
Referral centre for paediatric cancer	YesNational	YesRegional
New paediatric cancer patients (year)	50–100	107
Paediatric cancer treatment since	2012	> 20 years
Paediatric cancer inpatient beds	12	9
Number of paediatric cancer surgeons	1	1
Number of paediatric oncologists	1	4
Number of paediatric anaesthetists	1	6
Paediatric intensive care	Yes	Yes
Paediatric dieticians	Yes	Yes
Nurse/patient ratio	1: 8	1: 1–3
Treatment protocol	SIOP	SIOP
Radiotherapy	Yes	Yes
Free health care provision	No	Yes

[a] YY, Centre Hospitalier Universitaire Kigali, Kigali, Rwanda

[b] XX, X Hospital, Oxford, UK

[c] UNICEF 2018

[d] United Nations Development Program 2017

Table 2 Patients diagnosed with neuroblastoma presenting at two collaborating centres over the 29-month study period

	Rwanda	UK	
Patients	$n = 4$	$n = 5$	–
Male (%)	2 (50%)	4 (80%)	–
Age at diagnosis[a] (months)	57 (6–73)	13 (2–40)	$p = 0.09$**
Weight in kg [a]	14 (8–21)	9.8 (5–14)	
Z score	− 1.57 (− 3.86–0.85)	− 0.7 (1.2 to − 0.91)	$p = 0.28$**
Height in cm[a]	93.75 (59–117)	86.65 (73.3–100)	
Z score	− 2.2 (− 2.4–0.72)	1.45 (1.4–1.5)	$p = 0.057$**
Stage			
I–II	1	3	–
III–IV	3	2	–
Pre-operative chemotherapy	2	3	–
Surgery	1	3	–
Post-operative morbidity (Clavien-Dindo)			
I–II	1	2	–
III–IV	0	1	–
Mortality (%)	1 (25%)	0	–

[a] Median (range)

**Unpaired *t* test

Partnership development

This collaboration has educational value for young researchers as is evidenced through the presentation of results by medical students from YY (EM) and XX (SG), and surgical trainee (KF) at three international conferences in 2019. We have benefited from an experience in overcoming the challenges of international research collaboration, such as variable local protocols for ethical approval, time differences for communication, and data collection. The collaboration currently has limited funding and LMIC students successfully applied to competitive research awards for funding enabling attendance at conferences, which served as an additional experience in research skill development. Furthermore, this collaboration was an opportunity to develop communication skills in peer-peer and junior-senior relationships.

Discussion

We observed poorer nutritional status of neuroblastoma patients in the YY cohort, in addition to lower survival rates. Data from the UNICEF-WHO-World Bank collaborative estimate stunting in children under 5 as 37% in Rwanda [18]. Malnutrition can contribute to poorer survival rates through several mechanisms. Firstly, through weakened immunity and susceptibility to increased infection rates. This has been widely reported amongst malnourished paediatric cancer patients. Further, alterations to body composition in lean tissue and fat mass, affect the distribution and metabolism of chemotherapy agents [19]. Our findings are consistent with other studies of children with stage IV neuroblastoma [20]. Further, there is evidence that malnourished children with more advanced disease have poorer prognosis in developing recurrent disease or death at 1 year post-treatment initiation [21].

Although our study focussed on nutritional status at presentation, it can be extrapolated that this would have a negative impact on the subsequent outcome and prognosis, unless poor nutritional status is reversed prior to commencing treatment. It is known that a multifactorial aetiology contributes to poorer nutritional status following treatment [22]. Tumour-related factors include metabolism alterations and inflammatory components [23]. Chemotherapy has well documented associations with nausea and vomiting, and subsequent weight loss [11]. These impacts of treatment will be greater on children who are presenting malnourished.

Given the evidence of greater mortality and morbidity associated with malnourishment in paediatric cancer patients, it is essential to develop an effective nutritional intervention to minimise weight loss and promote quality of life. The SIOP PODC Nutrition Working Group have published a framework for nutritional care based on the infrastructure of the institution in LMICs. They advocate for a thorough nutritional assessment consisting of anthropometry, biochemical assessment, clinical nutritional examination and dietary evaluation. They further propose nutritional support and recommend oral and

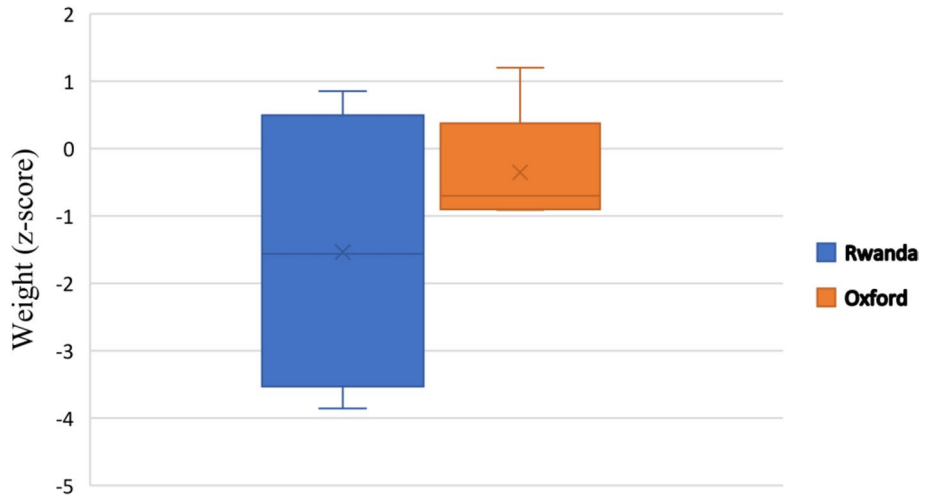

Fig. 1 Box and Whisker plots of weight at presentation

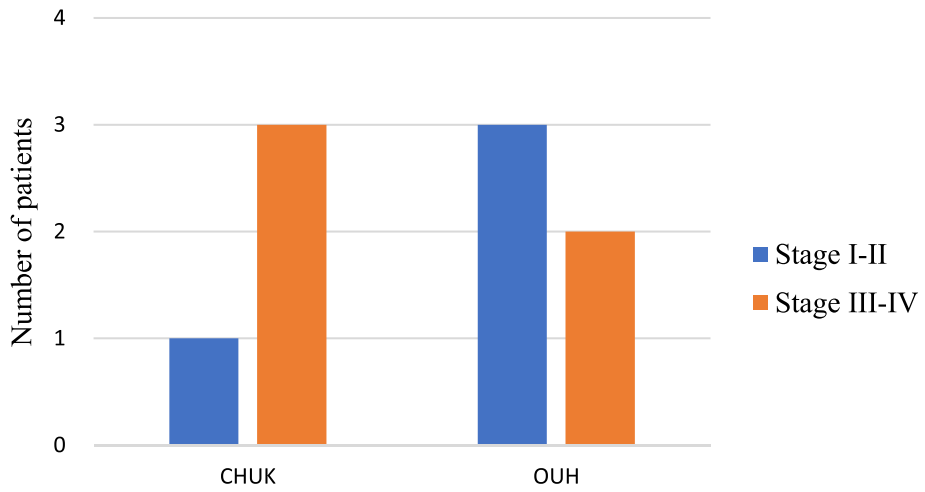

Fig. 2 Tumour stage at presentation in YY and XX

enteral feeding methods [24, 25]. Barriers to nutritional care in LMICs, such as access to nutritional products, trained personnel and the reliance on families to purchase nutritional supplements, are acknowledged. However, there are certainly changes to treatment regimens that can be implemented to optimise nutritional status. Some centres have introduced anti-emetic guidelines to support induction chemotherapy in neuroblastoma treatment regimes, with promising reductions in febrile neutropenia [26].

Finally, there are several methods that can be employed to determine nutritional status: weight and height *z*-scores, as measured in this report; triceps skinfold thickness and mid upper-arm circumference. The WHO *z*-score benefits from being comparable across ages and sexes. There is some evidence that arm anthropometry is a more sensitive measure to malnutrition than conventional weight- and height-based parameters [27]. This data was unavailable at our centres and thus, not included in this analysis.

This study investigated stage of presentation as a secondary outcome. A more advanced stage of tumour at diagnosis was noted in the YY cohort, in which 75% of neuroblastoma tumours were stage III/IV, as compared to 40% of neuroblastoma tumours in XX. The YY cohort of patients were also older than the XX cohort. Later

diagnosis in the YY group could come from delays in seeking healthcare, and prior consultations with traditional healers [28]. Other studies corroborate that later stage at presentation and advanced age both contribute to poorer prognosis [29]. A previous OxPLORE study has also reported treatment delays as contributing to poorer outcomes in the treatment of paediatric Wilms' tumours in YY, as compared to XX [16].

Contrary to other studies in LMICs, inadequate resources for treatment are not a contributor to poor prognosis of neuroblastoma patients managed at YY. It is a well-resourced, dedicated oncology hospital which provides optimised delivery of chemotherapy to patients [30]. Further, we demonstrated treatment modality as being comparable between YY and XX. Through the adoption of national guidelines for treatment of major childhood cancers [31], Rwanda is successfully managing several tumours. Further, there are examples of effective chemotherapy delivery at district level hospitals by non-oncologists, through close collaboration and coordination with national referral centres [32]. This study has identified that treatment modalities are not contributing to discrepancies in outcomes of neuroblastoma tumour. Rwanda has made progress in the diagnosis and treatment of neuroblastoma through collaboration between paediatricians, oncologists, paediatric surgeons, radiologists and pathologists. Although this study demonstrated lower survival rates in the YY cohort (75%) as compared to the XX cohort (100%), our study reports small numbers of patients with limited follow up. Survival was markedly higher than intermediate-risk and the high-risk groups in South Africa, with survival rates of 66.7% and 27.6% respectively [33]. We acknowledge that we cannot comment further on survival in view of our short follow up period.

Post-operative morbidity requiring intervention was greater at YY than XX (1/1 compared to 1/3). This could correlate with more advanced tumours at presentation and more complex surgical resections; however, analysis of surgical techniques and peri-operative care is beyond the scope of this study.

This study was effective in developing research skills of participating medical students. This initiative was successful in YY, and we suggest this would apply to other LMICs, where doctors have increased working demands and limited time to conduct research themselves. The research collaboration was enabled by engaging medical students and giving them responsibilities, under the guidance of senior clinicians. Students in LMICs face challenges to performing research and the low dissemination of research from medical students and post-graduates from YY has been described [34]. The student-doctor partnerships developed, both within centres and globally, enabled bidirectional transfer of key research skills of data collection, analysis and academic writing, whilst being driven from the grass roots.

This is the first study to compare neuroblastoma in Rwanda and another country. We acknowledge there are several limitations. Firstly, there are a limited number of outcomes due to limited information in the records. Our study and methodology are of simple design to evidence our novel concept of an international medical student-led partnership. There is also a limited number of patients at both centres, particularly at YY, which serves a large population as a national referral hospital. Therefore, we do not attempt to report the prevalence of neuroblastoma and these results cannot be generalised. Further, we are unable to comment fully on prognostic factors, given that medium to long term outcome data is not available and we could not draw conclusions regarding social determinants associated with morbidity and mortality. The focus of this study has been the differences in presentation between the two cohorts. Long-term studies and follow-up, for example institutional or national cancer registries, are needed to establish the determinants associated with the nutrition status, presentation at the late stage, efficacy of treatment and survival outcomes of neuroblastoma.

Conclusion

The OxPLORE collaboration has demonstrated the utility of medical student and junior doctor research partnerships between HICs and LMICs. This study has shown disparity in presentation of neuroblastoma, namely poorer nutritional status and advanced tumour stage in Rwanda when compared with the UK. We advocate for consideration in policy making to tackle these disparities and further studies investigating longer-term prognosis and outcome.

What is already known on this topic:

- Neuroblastoma is a common childhood cancer that arises from the development of primitive sympathetic ganglion.
- There is a paucity of neuroblastoma data in low-income settings.
- Neuroblastoma accounts for 15% of paediatric tumour related deaths worldwide.
- Poor nutritional status is responsible of treatment delays in cancer patients with advanced tumour stage.
- HICs-LMIC research partnerships have potential to advance clinical research.

What this study adds:

- Student-led research collaboration are effective to address the LMIC research gap.
- This study has shown disparity in presentation of neuroblastoma, namely poorer nutritional status and advanced tumour stage in Rwanda when compared with the UK.
- The comparison between centres helps both centres to track their quality improvement.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Abbreviations
OxPLORE: Oxford Paediatrics Linking Oncology Research with Electives; LMICS: Lower- and middle-income countries; HICs: High-income countries; UK: United Kingdom; YY: Y hospital; XX: X hospital; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; BMI: Body mass index; COG: Children's Oncology Group; EC: Ethics committee; UNICEF: United Nations International Children's Emergency Fund; WHO: World Health Organization; SIOP: International Society of Paediatric Oncology; PODC: Paediatric Oncology in the Developing Countries.

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Authors' contributions
All authors contributed equally to the writing of this correspondence. EM conceptualized and designed the study, carried out the literature search, oversaw the research proposal, oversaw the data analysis, reviewed the initial draft of the manuscript, and reviewed and revised the final manuscript. SG conceptualized and designed the study, carried out the literature search, oversaw the research proposal, oversaw the data analysis, reviewed the initial draft of the manuscript, and reviewed and revised the final manuscript. HH conceptualized and designed the study, carried out the literature search, oversaw the research proposal, oversaw the data analysis, reviewed the initial draft of the manuscript, and reviewed and revised the final manuscript. KF conceptualized and designed the study, carried out the literature search, oversaw the research proposal, oversaw the data analysis, reviewed the initial draft of the manuscript, and reviewed and revised the final manuscript. KL conceptualized and designed the study, carried out the literature search, oversaw the research proposal, oversaw the data analysis, reviewed the initial draft of the manuscript, and reviewed and revised the final manuscript. AK conceptualized and designed the study, carried out the literature search, oversaw the research proposal, oversaw the data analysis, reviewed the initial draft of the manuscript, and reviewed and revised the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
As this was a retrospective study, gaining consent from patients was not applicable and no patient was involved. The ethical approval was gained from research review boards of the participating centres under references EC/CHUK/680/2018 (Rwanda) and 4741 in (UK).

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