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Clinical features and survival among children with retinoblastoma in Uganda

Keith M Waddell,1,2 Kenneth Kagame,1,2 Andrew Ndamira,2 Amos Twinamasiko,2 Susan V Picton,3 Ian G Simmons,3 W Tom Johnston,4 Robert Newton5,6

ABSTRACT
Aims To characterise the clinical features, treatment and outcome of children diagnosed with retinoblastoma in Uganda.
Methods The study comprised a 6-year nationwide enrolment with follow-up.
Results In total, 282 cases were enrolled, 26% (72) were bilateral; 6% were lost to follow-up. Almost all diagnoses in the first affected eye were International Classification of Retinoblastoma group E or worse. Histology was available for 92%; of those, 45%, had extraocular tumour at diagnosis. Enucleation of the first eye was done for 271; 94 received radiotherapy to the socket and in the last 2 years, 70 children received chemotherapy. At close of study, 139 children had died. Survival, as determined in a proportional hazards model adjusted for age, sex, laterality and treatment era (pre or post introduction of chemotherapy), varied by extent of the tumour (p<0.001); children with only intraocular involvement were 80% less likely to die (HR=0.21, 95% CI 0.12 to 0.35) compared with children with extraocular involvement.
Conclusions Diagnostic delay results in relatively high mortality among children with retinoblastoma in Uganda. There is an urgent need for more effective treatment modalities, particularly chemotherapy, and nationwide efforts to encourage earlier access to medical care.

INTRODUCTION
Retinoblastoma is reported to be commoner in tropical countries than in the developed world, but population-based studies are few.1–3 Retinoblastoma also has worse outcome with high mortality, but follow-up in most studies is limited.4 In Uganda, enucleation had been the only treatment available for most cases, a minority also receiving radiotherapy. Chemotherapy as part of initial treatment had not been introduced when this study began. To characterise cases diagnosed in Uganda, we did a 6-year nationwide study documenting current practice, histology and outcomes. A home visiting team obtained near complete follow-up. It became evident that mortality was unacceptably high and so, in the final 2 years of the study, with the aim of improving survival, we introduced a programme of neo-adjuvant and adjuvant chemotherapy in one referral centre in southwestern Uganda. Details of this programme and its impact is the subject of another report. Here, we describe disease characteristics at presentation and subsequent survival of children with retinoblastoma in Uganda.

MATERIALS AND METHODS
Starting in January 2006, ophthalmologists in Uganda were invited to enter cases into the study whilst retaining management; recruitment ended in December 2011. A standard form documented demography, clinical features, treatment and follow-up. Staging was according to the International Classification of Retinoblastoma (ICRB).5 Counsellors, using vernacular, gave information about the disease, its treatment and the study, and parents signed or thumb-printed they understood and consented. A brief lifestyle and health questionnaire was used. Data were entered and stored on a database using EPINFO software (CDC.gov). When possible, blood was taken during anaesthesia and tumour specimens collected and put into RNA later (Ambion, Inc; techserv@ambion.com) and then transferred to the Uganda Virus Research Institute and stored at −80°C. Some patients received radiotherapy at Mulago Hospital, Kampala, with the country’s sole machine (cobalt 60; dose 39 Gy in 13 fractions). A few with metastases were referred to the Uganda Cancer Institute for late chemotherapy. The team responsible for follow-up of children made extensive use of mobile phones and home visits to track progress.

The impact of various factors on survival was initially described using Kaplan–Meier plots and life-table methods. Further analyses using proportional hazards regression were conducted to examine the impact on survival of factors, such as laterality, extent, sex and age at diagnosis. Appropriate tests of the proportional hazards assumption were carried out.

The study was approved by the Ethics Committee of Mbarara University (Ruharo is affiliated) and by the Uganda National Council for Science and Technology. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

RESULTS
In 6 years, 282 cases were enrolled (144 (51%) boys and 138 (49%) girls). Seventy-two (26%) were bilateral and seven had family histories (five families) of retinoblastoma. The median age at diagnosis of unilateral cases was 33 months (IQR 23–48; range 4–130), and of bilateral 17.5 months (IQR 9.5–25; range 1–72). Follow-up beyond treatment was obtained for 263 of 282 children (94%), which was to the end of study (May 2013) or death for 257 (91%). Median follow-up for those alive was 35 months (IQR 25–53.5; range 3–86); for those who died, it was 7 months (IQR 5–14; range 1–58).

Some case descriptions received from ophthalmologists in the nationwide study were incomplete,
but nearly all diagnoses in the first affected eye were group E or already extraocular, with none below group D, except for two with group C. All cases, except the two group C, were offered enucleation, which was done for 271 (96%), 31 bilaterally; others declined or died soon after. Histology was accessed for 249 of 271 operated cases (92%) and was retinoblastoma for 234. Diktyoma was suggested for 13 cases because of palisading of cells, but clinically these were advanced retinoblastoma, so were treated and analysed as such. No tumour was reported for two cases after chemotherapy but they were clinically definite. When tumour extent was reported as part of histology, 86 of 191 (45%) had optic nerve or orbital involvement. Radiotherapy was given to sockets of 94 children after enucleation (eight bilaterally) and to three intact globes. A further 18 received radiotherapy for recurrence, some following surgical debulking. Late chemotherapy for metastasis was given to 19 children at the Uganda Cancer Institute. Among bilateral cases, the stages at diagnosis of tumour in the second eye ranged from A to E or extraocular, so treatment varied; for 20 of these, treatment was either declined or the child died before it was started. In the final 2 years of the study, 70 children received chemotherapy during initial management.

At latest follow-up, 132 children were alive. There were 125 confirmed deaths and 14 presumed dead having uncontrolled tumour at last contact, giving 139 dead in total; 11 were lost to follow-up. Among children diagnosed before the introduction of chemotherapy, survival at 36 months was 43% (95% CI 37% to 53%). Table 1 shows survival of 166 children with known outcome treated before the introduction of chemotherapy, stratified by tumour extent and radiotherapy. In the absence of radiotherapy, none of the children with extraocular spread at diagnosis survived; with radiotherapy, 34% survived. Among those cases judged to be still intraocular at diagnosis, a quarter died irrespective of whether they received radiotherapy. Overall, survival, as determined in a proportional hazards model adjusted for age, sex, laterality and treatment era (pre or post introduction of chemotherapy), varied by extent of the tumour ($p<0.001$, figure 1). Children with intraocular involvement only, had an 80% lower risk of dying (HR=0.21, 95% CI 0.12 to 0.35) compared with children with extraocular involvement.

Table 1 Survival of 166 children with known outcome treated prior to the introduction of chemotherapy, by tumour extent and radiotherapy

<table>
<thead>
<tr>
<th>Extent</th>
<th>Intraocular (%)</th>
<th>Extraocular (%)</th>
<th>Undetermined (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>12 (75)</td>
<td>11 (34)</td>
<td>11 (58)</td>
<td>34 (51)</td>
</tr>
<tr>
<td>Died</td>
<td>4 (25)</td>
<td>21 (66)</td>
<td>8 (42)</td>
<td>33 (49)</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>32</td>
<td>19</td>
<td>67</td>
</tr>
<tr>
<td><strong>No radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>25 (74)</td>
<td>0 (0)</td>
<td>14 (52)</td>
<td>39 (39)</td>
</tr>
<tr>
<td>Died</td>
<td>9 (26)</td>
<td>38 (100)</td>
<td>13 (48)</td>
<td>60 (61)</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>38</td>
<td>27</td>
<td>99</td>
</tr>
<tr>
<td>Total cases</td>
<td>50</td>
<td>70</td>
<td>46</td>
<td>166</td>
</tr>
</tbody>
</table>

Extraocular: optic nerve or sclera involved or orbital tumour present at diagnosis; either eye if bilateral.
Intraocular: none of the above or optic disc visibly uninvolved; both eyes if bilateral.
Extent undetermined: not reported or histology not available.
Radiotherapy: to the socket after enucleation during initial treatment, excluding recurrence.

Macroscopic orbital tumour occurred in 72 children (27 at enucleation, 45 at recurrence); 71 died even if given radiotherapy and chemotherapy (67 confirmed dead and 5 presumed dead having uncontrolled tumour). The one survivor had an early recurrence and is currently alive 33 months after diagnosis, following chemotherapy and radiotherapy. When proptosis was recorded, 7 of 48 were alive at last follow-up (14–43 months after diagnosis). Thirteen had other surgery before the correct diagnosis; survival was none of four after evisceration, one of four after trabeculectomy, and four of five after cataract. No survivors are known of 19 having late chemotherapy for metastasis at the Uganda Cancer Institute.

For many children included in the study, the precise mode of death is uncertain. Orbital fungation was common without radiotherapy but only one case was known after radiotherapy, so it was palliative. The common sites of metastasis were skull, or spine with paraplegia. There was one known case of hepatic metastasis and one with local lymph node involvement. One bilateral heritable case died with primary sarcoma of the femur. Five children died in remission after short febrile illnesses, apparently unrelated infections. However, the mode of death is known for the 20 who received chemotherapy as part of initial treatment. Fifteen had extraocular extension (seven with macroscopic orbital tumour) and most died with apparent intracranial extension, following headache, convulsions or unconsciousness.

DISCUSSION

Diagnostic delay results in relatively high mortality among children with retinoblastoma in Uganda. Nearly half of tumours were already extraocular at the time of diagnosis; among the 94% of 282 cases in whom outcome data were available, 56% had died after 36 months of follow-up. Indeed, prior to chemotherapy, even among cases with intraocular disease, mortality was 25% with radiotherapy and 26% without it. This emphasises the need for additional treatment modalities (such as...
chemotherapy) and for nationwide education campaigns with the aim of down-staging tumours at diagnosis. Furthermore, retinoblastoma masquerading as other conditions is relatively common and a high index of suspicion should be maintained for every child presenting with other ocular features.

Recruitment of 282 children with retinoblastoma in 6 years confirms the relatively high frequency of this malignancy in Uganda compared with Western populations, although only an unknown fraction of the totality of cases occurring was enrolled. However, it remains unclear if the true incidence of disease is higher, since the proportion of children among the population is higher in a country such as Uganda, than for example in the UK. Data from the population-based cancer registry, in Kampala, indicate that incidence of retinoblastoma may be three to four times higher than Western countries, but the figure is based on relatively few cases and uncertainty remains.\(^6\,7\) The proportion of all cases that were bilateral was 26% and their ages at diagnosis younger than unilateral cases, often being congenital; this percentage may underestimate the true figure given the high probability of the first tumour being fatal. Only five families were identified with more than one child affected, perhaps indicating that most were new mutations. It is uncertain if this heritable portion differs from the West before it was made by inspection, but opacities may obscure visualisation. Histology was accessed for most (92%) leaving few clinical contrasts with other African series and allows firm conclusions about outcome. Also in striking contrast to Western countries it confirmed high mortality.\(^9\,10\) This was expected with extracocular extension, but high mortality when only intraocular (as far as could be assessed from limited histology) was one reason for introduction of chemotherapy.

The literature has little guidance for clinicians in Africa on management or prognosis of retinoblastoma, though each ophthalmologist can expect to see several cases every year. Preoperative assessment was often limited and enucleation considered the only option, the length and state of the optic nerve not being noted. Adjuvant treatments may not be considered and histology not assessed. Examination of the fellow eye for curable tumours using indirect ophthalmoscopy with indenta-
tion may be omitted. Follow-up till at least age 7 years, watching for reactivated disease and for siblings, is sporadic.\(^11\) This needs to be changed but even with the best will, the prolonged management required is difficult with the limited resources in Africa, and adverse socioeconomic factors are known indicators of poor outcome.\(^12\) Management could be better coordinated if one or a few hospitals were designated national referral centres for all cases.

Radiotherapy is best avoided because of facial disfigurement, socket contracture and risk of later malignancy in the irradiated field.\(^13\) However, radiotherapy seems unavoidable with optic nerve invasion, though it is unknown if it could be omitted if this does not reach the resection margin. At present, Uganda has only one radiotherapy machine (cobalt 60) serving the entire population, so access is congested and introduction of conformal radiotherapy for all cancers is urgent. Many cases with extracocular extension did not receive radiotherapy and inevitably died. The study sponsored many children to access radio-
therapy, but even then, on its own it saved only 34%. With uninvolved optic nerve, radiotherapy is unnecessary because mortality was 25% with and 26% without this treatment; if used, all then suffer its disadvantages. With orbital tumour, it prevents fungation but rarely (one case out of 72) saves life. Introduction of chemotherapy may change the indications for use of radiotherapy.

In summary, the main obstacle to reducing mortality from retinoblastoma in Uganda is delayed presentation. Once a safe and effective treatment programme is in place, using a range of modalities, there is an urgent need in Uganda and other countries in sub-Saharan Africa, to address diagnostic delay, with national education campaigns encouraging people to come forward with affected children earlier. However, there is little point in initiating such schemes in the absence of effective treatment.

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Contributors  All authors contributed at all stages of this study, from conception to
the preparation of the manuscript.

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Committee of Mbarara Hospital.

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