Travel Burden and Clinical Presentation of Retinoblastoma: Analysis of 1,024 patients from 43 African Countries and 518 Patients from 40 European Countries

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Synopsis

In Europe, travel distance to retinoblastoma center is not a barrier to early diagnosis. In Africa, most cases that present live close to treatment centers, yet present late, and those living far do not present for treatment.

Abstract

Background

The travel distance from home to a treatment center, which may impact the stage at diagnosis, has not been investigated for retinoblastoma, the most common childhood eye cancer. We aimed to investigate the travel burden and its impact on clinical presentation in a large sample of retinoblastoma patients from Africa and Europe.

Methods

A cross-sectional analysis including 518 treatment-naïve retinoblastoma patients residing in 40 European countries and 1,024 treatment-naïve retinoblastoma patients residing in 43 African countries.

Results

Capture rate was 42.2% of expected patients from Africa and 108.8% from Europe. African patients were older (95% CI (-12.4)-(-5.4), p<0.001), had fewer cases of familial retinoblastoma (95% CI 2.0-5.3, p<0.001), and presented with more advanced disease (95% CI 6.0-9.8, p<0.001); 43.4% and 15.4% of Africans had extraocular retinoblastoma and distant metastasis at time of diagnosis, respectively, compared to 2.9% and 1.0% of the Europeans. To reach a retinoblastoma center, European patients travelled 421.8 km compared to Africans who travelled 185.7 km (p<0.001). On regression analysis, lower-national income level, African residence and older age (p<0.001), but not travel distance (p=0.19), were risk factors for advanced disease.

Conclusions

Fewer than half the expected number of retinoblastoma patients presented to African referral centers in 2017, suggesting poor awareness or other barriers to access. Despite the relatively shorter distance travelled by African patients, they presented with later stage disease. Health education about retinoblastoma is needed for carers and health workers in Africa in order to increase capture rate and promote early referral

Introduction

Rare cancers, defined as having an incidence of less than six cases per 100,000 population per year,[1] pose a particular burden on patients and professionals alike because of the need for specialist care, frequent lack of standardized treatments, and lack of funding for research.[2,3] It is not uncommon to have only 1 or 2 specialized referral centers in a country for a given type of rare cancer, to which most cases are referred. Such a policy of centralized tertiary centers may result in reduced access and a high travel burden on patients, which can lead to poorer quality of life, advanced disease at diagnosis, late treatment, and worse prognosis.[4,5]

Retinoblastoma is a rare, potentially deadly, childhood cancer. Its incidence is believed to be constant across populations, ranging from 1:16,000-18,000 live births.[6] In most countries only few specialized retinoblastoma centers exist. In Europe, for example, there is a single center in France, two in the UK and three in Russia, all in Moscow. Travel burden associated with retinoblastoma, to the best of our knowledge, has not been explored. This information, which also reflects on the accessibility to tertiary centers and their catchment area, is important for healthcare planning.

Prognosis of patients with retinoblastoma has improved significantly over the past 50 years to reach over 90% 5-year survival in Europe.[7–9] These improvements are attributed to several factors, including the implementation of national strategies associated with retinoblastoma referral pathways, and the introduction of novel and improved treatment modalities, several of which were developed in European specialized referral centers.[10–13] Indeed, in the field of retinoblastoma, Europe serves as a potential model for under-resourced regions of the world. In Africa, where birth rate is higher, resulting in higher retinoblastoma prevalence, these improvements in survival have not been observed. Reports on retinoblastoma from Africa are scarce and anecdotal evidence suggests that survival rates are as low as 50%,[14,15] and in some regions of Sub-Saharan Africa are even less than 30%.[16]

We have recently reported the stage at presentation of more than 4,000 newly diagnosed retinoblastoma patients from over 150 countries analysed by national-income level.[17] The aim of the present study is to use the data from all countries in Africa and Europe to: (1) investigate and compare the travel burden experienced by patients, (2) compare the stage at time of diagnosis and (3) investigate risk factors for advanced disease at time of diagnosis. Such information is important to better understand the current gaps in retinoblastoma service provision and to inform policy makers at national and international levels.

Methods

The study methodology, data collection and quality assurance process have been described in detail previously.[17] Briefly, the data were collected through a 1-year cross-sectional analysis of treatment-naïve retinoblastoma patients who presented to retinoblastoma referral centers across the world from January 1, 2017, to December 31, 2017. Data on country of residence, sex and laterality of retinoblastoma were considered essential minimum criteria for inclusion. In the present analysis, patients that resided in African and European countries were included. The study was approved by the London School of Hygiene & Tropical Medicine institutional review board (reference no. 14574) in accordance with the tenets of the Declaration of Helsinki. Participating centers, according to local institutional and national guidelines, applied to and received ethics clearance in their countries.

Data collected from medical charts included patient country of residence, initial clinical sign leading to referral, distance travelled from home to retinoblastoma center, sex, family history of retinoblastoma, age at time of diagnosis at retinoblastoma center, tumor laterality, and stage according to the 8th edition of the American Joint Committee on Cancer (AJCC) clinical Tumor, Node, Metastasis, Hereditary (cTNMH) scheme,[18] and the International Retinoblastoma Staging System.[19] For travel distance calculation, a Google-based map was used and the orthodromic distance (i.e. “as the crow flies”) between home and the retinoblastoma center was measured. In case both were in the same city or site, the distance was considered to be zero, unless mentioned otherwise by the retinoblastoma center that submitted the data. Data on national-income level, crude birth rate, country surface area and population size were retrieved from the United Nations World Population Prospects.[20]

Statistical analysis

Analyses were performed using R software[21] and IBM SPSS statistics v25.0 (IBM corp, Chicago, IL). The predicted number of new retinoblastoma patients per country was calculated as follows: country population*crude birth rate/1,000/17,000.[22] The predicted number does not take into account deviations from the average percentage with familial retinoblastoma, in which the risk of the offspring is ~1/2 rather than 1/17,000. The predicted number per continent was the sum for all countries in that continent. Fisher’s exact test and Student’s *t*-test was used to compare categorical and continuous variables between groups. A one-way ANOVA was used to test differences in the age at the time of diagnosis between the continents and the Kruskal-Wallis test to test for differences in travel distance between the continents. Binomial logistic regression was used to model the effect of income level, continent, travel distance from home to retinoblastoma center, age at diagnosis, family history of retinoblastoma, and tumor laterality on the likelihood of children having advanced disease at presentation (cT4). A value of $p<0.05$ was considered significant and data throughout the manuscript are presented as mean (standard deviation (SD) with 95% confidence interval (CI)).

Results

The analytic sample included 1,542 newly diagnosed retinoblastoma patients. Of these, 518 (33.6%) resided in 40 European countries and 1,024 (66.4%) in 43 African countries. Using an average incidence figure of 1/17,000 live births,[6] the observed capture rates were 42.2% and 108.8% of expected patients from Africa and Europe, respectively.

Clinical data were available for both the African and European sub-cohorts for over 90% of patients, with the exception of travel distance, which was available for 81.5% and 84.6% of the patients, respectively. **Table 1** shows the clinical data of the study patients by continent.

Table 1. Clinical data of 518 European and 1,024 African retinoblastoma patients.			
Parameter	**European sample, n (%)**	**African sample, n (%)**	**Significance**
Travel distance from home to retinoblastoma center[1]			p<0.001
Mean distance in km (Std., 95% CI)	421.8 (814.6; 328.6-537.5)	185.7 (201.0; 168.0-205.2)	
Reported cases	396/468 (84.6)	736/903 (81.5)	
Age at diagnosis			p<0.001
Mean age in months (Std., 95% CI)	22.0 (27.6; 19.7-24.4)	30.9 (21.0; 28.7-32.8)	
Reported cases	514/518 (99.2)	1,015 (99.1)	
Sex			p=0.75
Male	280 (54.0)	544 (53.1)	
Female	238 (46.0)	480 (46.9)	
Reported cases	518/518 (100)	1,024/1,024 (100)	
Laterality			p=0.07
Unilateral	357 (68.9)	751 (73.3)	
Bilateral	161 (31.1)	273 (26.7)	
Reported cases	518/518 (100)	1,024/1,024 (100)	
Familial retinoblastoma			p<0.001
No	468 (91.6)	910 (97.2)	
Yes	43 (8.4)	26 (2.8)	
Reported cases	511/518 (98.6)	936/1,024 (91.4)	
Primary tumor (T)			p<0.001
cT1	76 (14.9)	32 (3.3)	≤cT2 vs >cT2
cT2	237 (46.6)	134 (13.9)	
cT3	192 (37.7)	465 (48.3)	
cT4	4 (0.8)	331 (34.4)	
Reported cases	509/518 (98.3)	962/1,024 (93.9)	
Regional lymph node (N)			p<0.001
NX	34 (6.6)	265 (26.8)	N0 vs N1
N0	482 (93.2)	636 (64.4)	
N1	1 (0.2)	86 (8.7)	
Reported cases	517/518 (99.8)	987/1,024 (96.4)	
Distant metastasis (M)			p<0.001
M0	513 (99.0)	830 (84.6)	M0 vs M1[2]
cM1	1 (0.2)	110 (11.2)	
pM1	4 (0.8)	41 (4.2)	
Reported cases	518/518 (100)	981/1,024 (95.8)	
Extraocular retinoblastoma			p<0.001
No	503 (97.1)	561 (56.6)	
Yes[3]	15 (2.9)	430 (43.4)	
Reported cases	518/518 (100)	991/1,024 (96.8)	

[1]50/518 (9.7%) European and 121/1,024 (11.8%) African retinoblastoma patients travelled across borders for diagnosis and primary treatment (not included in the analysis).
[2]M1 = cM1+pM1.
[3] based on the International Retinoblastoma Staging System.[19]
NA – not applicable.

Travel burden and retinoblastoma center catchment area

Overall, the mean travel distance from home to a retinoblastoma center was 233.3 km (468.78; 207.0-259.0). To reach an retinoblastoma center within the country of residence, patients from European countries travelled on average more than twice

the distance compared to patients from African countries: 421.8km (814.6; 328.6-537.5) and 185.7km (201.0; 168.0-205.2), respectively (p<0.001, **eTable 1** in the appendix). **Figure 1** shows the number of retinoblastoma centers by country and continent (see **eFigure 1** in the appendix for geographical location of the centers). No significant differences were found in the mean number of retinoblastoma centers per country in Africa and Europe: 1.8 (1.8; 1.2-2.4) and 1.4 (0.9; 1.1-1.7), respectively (p=0.22). Similarly, on analysis of the mean country population size and country surface area, differences between African and European countries were non-significant (p=0.32 and p=0.89, respectively). The catchment area of each retinoblastoma center in Africa and Europe is represented in **Figure 2** by the mean travel distance ± Std. While the distribution of retinoblastoma centers in Europe covers the entire continent, in many African countries, large parts remain underserviced.

Presentation to retinoblastoma center

Age at time of diagnosis

For the entire sample, the mean age at time of diagnosis at a retinoblastoma center was 27.9 months (95% CI 26.7-29.0): 22.0 months (27.6; 19.7-24.4) for European patients compared to 30.9 months (21.0; 28.7-32.8) for those from Africa (diff = (-8.9), 95% CI (-12.4)-(-5.4), p<0.001).

Bilateral and familial retinoblastoma

Overall, 28.1% of the patients presented with bilateral disease, and 4.5% had a family history of retinoblastoma. Of the African patients, 26.7% had bilateral disease at the time of diagnosis compared to 31.1% of the European patients (OR 0.8, 95% CI 0.6-1.0, p=0.07). A positive family history was reported for 2.8% vs 8.4% of the African and European patients, respectively (OR 3.2, 95% CI 2.0-5.3, p<0.001).

Referral to an retinoblastoma center for screening in case of positive family history of retinoblastoma was uncommon in Africa as compared to Europe: 3/26 (11.5%) of the familial cases in Africa vs 31/42 (73.8%) in Europe (OR 20, 95% CI 5.3-100.0, p<0.001). All three screened African patients were staged cT1 at time of diagnosis. Of the African familial cases, 57.7% had advanced intraocular (cT3) or extraocular retinoblastoma (cT4) at time of diagnosis. In comparison, of the European familial cases, 64.3%, 31.0%, and 4.8% were staged cT1, cT2 and cT3, respectively.

Tumor staging

Overall, the most common cTNM stages were cT3 (44.7%), N0 (74.3%), and M0 (89.6%). Significantly more patients from African countries as compared to European countries had at time of diagnosis advanced retinoblastoma (i.e. >cT2; OR 7.7, 95% CI 6.0-9.8, p<0.001), extraocular retinoblastoma (OR 25.7, 95% CI 15.1-43.6,

p<0.001), lymph node involvement (OR 65.2, 95% CI 9.0-469.7, p<0.001), and metastasis (OR 18.7, 95% CI 7.6-45.8, p<0.001). Overall, 43.4% and 15.4% of the African patients had at time of diagnosis extraocular retinoblastoma and distant metastasis, respectively, compared to 2.9% and 1.0% of the European patients, respectively.

Risk factors for advanced disease at time of diagnosis

Lower-national-income level, African continent, older age at presentation, familial retinoblastoma, and bilateral retinoblastoma (p≤0.010), but not distance from home to retinoblastoma center (p=0.19), were found to be significant factors for the prediction of cT4 category (i.e. extraocular disease). On logistic regression, national-income level, continent, and age at presentation were found to be independent, significant predictors for cT4 category (**Table 2**). On further analysis by continent, no predictors were found for the European subgroup, whereas for the African, older age and lower-income level (p<0.001) were found to be significant predictors of cT4 category (**eTable 2** in the appendix).

Table 2. Predictors of advanced retinoblastoma disease at presentation (cT4): univariate and multivariate analysis.

Variable	Category	B	S.E.	Corrected p-value	OR	95% CI for OR	
						Lower	Upper
Univariate analysis							
Income level	Low vs lower-middle	1.04	0.14	<0.001	2.82	2.13	3.74
	Low vs upper-middle	1.25	0.15	<0.001	3.50	2.60	4.70
	Low vs high	1.89	0.34	<0.001	6.64	3.44	12.82
	Lower-middle vs upper-middle	1.47	0.31	<0.001	4.33	2.38	7.90
	Lower-middle vs high	2.32	0.50	<0.001	10.19	3.80	27.35
	Upper-middle vs high	3.18	1.04	<0.001	23.96	3.11	184.62
Continent	Africa vs Europe	0.84	0.10	<0.001	2.32	1.90	2.82
Familial retinoblastoma	Yes vs no	1.51	0.52	0.001	4.54	1.64	12.57
Bilaterality	Yes vs no	0.38	0.15	0.010	1.46	1.10	1.94
Distance from home to Rb center[1]				0.19			
Age at diagnosis[1]				<0.001			
Multivariate analysis (binomial logistic regression)							
Income level	Lower-middle	0.90	0.15	<0.001	2.45	1.83	3.30
	Upper-middle	1.48	0.34	<0.001	4.38	2.26	8.47
	High	3.08	1.18	0.001	21.74	2.14	220.82
Continent	Europe	2.34	0.62	<0.001	10.37	3.07	35.01
Age at diagnosis[2]	≥24 months	-1.33	0.16	<0.001	0.27	0.19	0.37
Constant		1.07	0.16	<0.001	0.34		

[1]t-test for numerical variables.
[2]median age = 24.2 months (categorical variable).
OR – odds ratio, CI – confidence interval.

Discussion

Our findings confirm a large disparity in the presentation patterns of retinoblastoma between patients from African and European countries. Patients from Africa were significantly older, nearly half of them had extraocular spread at time of diagnosis, and nearly one fifth had distant metastasis. Of the European patients, less than 3% had extraocular tumor spread and only 1% had metastatic spread at time of diagnosis. Patients from lower-income level countries, those from the African continent, and older patients at time of diagnosis were at increased risk to have advanced retinoblastoma. Interestingly, distance patients travelled in order to reach a retinoblastoma referral center did not play a role in this risk. These results are in contrast to previous analyses of other forms of cancer, including breast, colon, lung, and skin melanoma,[23–26] as well as rare cancers such as Merkel cell carcinoma,[27] in which high travel burden correlated with advanced-disease stage. Noteworthy, all of the above referenced studies were single-center rather than multicenter multinational studies, as the present one.

Analysis of the travel burden, however, in conjunction with data on the number of retinoblastoma centers in African and European countries, and demographic data, including country population and surface area, suggest a more complex picture. Patients from African countries travelled less than half the distance compared to European patients in order to reach a specialized retinoblastoma treatment center. Assuming that nearly all retinoblastoma centers in the participating African countries were contacted and recruited, our findings suggest that these centers serve mainly patients that reside in close vicinity.

Taking into account the low capture rate in Africa, underlying causes for the findings of this study are multifactorial; they include poor awareness by carers and health workers, lack of knowledge about clinical presentation by health workers, travel distance and cost to reach a specialized retinoblastoma treatment center, and probably the absence of specialized retinoblastoma treatment centers in some parts of Africa.

It is well-documented that poor awareness of retinoblastoma both by the public and health workers can lead to delays in diagnosis.[28–31] Delayed retinoblastoma diagnosis, in turn, leads to poor outcome.[32–34] Poor awareness and health education is likely to be the main factor for those cases that reside in proximity to a treatment center; yet, presented late. Initiatives are addressing this need by creating twinning programs that link centers from higher- and lower-resource countries, as well as interventions such as public awareness campaigns, and health worker education.[29,31,35–39] There is a pressing need, to promote this action at national and global level. In a rare curable cancer such as Rb, with a finite number of patients worldwide, such action is feasible.

Barriers to health care in Africa have been reported in relation to several medical fields, including oncology,[40,41] ophthalmology,[42–46] and pediatrics.[42,44,47] Most barriers, whether financial, structural (i.e. accessibility), lack of transport, poor roads, were also found relevant in the context of retinoblastoma in Africa.[48–50] Possible solutions should be inclusive and account for all factors; most are not in the

scope of the present study. Number and distribution, however, of retinoblastoma centers in a country is a matter that warrants further discussion. The need for and number of retinoblastoma centers derive first and foremost from the number of new retinoblastoma cases in a country. There should be enough centers with an appropriate distribution to serve all patients within a country. On the other hand, there should not be too many, as expert centers need to remain “vivid”, an ability that relates directly to the number of cases managed, as was shown in other rare malignancies.[51] In this sense, European and African countries face different challenges. In Europe, with a low birth rate and therefore low prevalence of retinoblastoma, the need for a treatment center in countries with 1-2 new cases per year is questionable. In Africa, with a high birth rate and increasing population, the situation is more complex. New retinoblastoma centers will be needed where there is a large population (10 million population and 20-30 new retinoblastoma cases/year) with no available center. The number and distribution of retinoblastoma treatment centers need to be tailored to the country’s requirements.

Familial retinoblastoma was significantly more common in European than in African countries. A possible explanation is the high survival rate of hereditary cases in Europe due to early diagnosis and efficient treatments. This possibly could explain the high capture rate of retinoblastoma in Europe too, higher than the predicted annual number. Further studies are warranted to better understand the trends in retinoblastoma incidence in Europe. Three quarters of the European familial cases were screened for retinoblastoma (i.e. examined before clinical signs were evident) and most were diagnosed with early disease stage. In Africa, screening rate was as low as 11.5% of the familial cases, lower than previously reported in “developing countries” outside Africa.[52] Screening may result in less invasive treatments being needed, resulting in higher chances for eye salvage and better vision.[53,54] Retinoblastoma patients from both continents should receive future counselling regarding the need for screening of their offspring, especially the ~30% that presented with bilateral disease whose children have a nearly 50% chance of developing retinoblastoma. Interestingly, rates of bilateral cases were similar between Africa and Europe. Most of them are known to result from sporadic germline mutations. The proportion of cases with familial retinoblastoma who presented with bilateral disease was also similar. Given the risk factor analysis, which showed that lower-income level and African continent were independently associated with advanced disease, it is possible that other, unrecorded variables are responsible for disease progression before diagnosis is made in Africa, as well as for tendency to present with bilateral retinoblastoma. Further studies should explore these possibilities.

Our study has limitations. First, the orthodromic distance was used as a surrogate for the travel burden, whereas other related factors that may play a role were not taken into account, especially travel costs, time costs, loss of parental income, availability and mode of transportation, road conditions, availability of transport, and the actual distance travelled from home to a specialized referral retinoblastoma center. Second, our study was cross-sectional by design and some of the data were collected

in a retrospective manner (centers that were recruited after January, 2017), with the inherent limitations of such a design. Nevertheless, we were able to collect data from an unprecedented number of retinoblastoma centers and countries and to perform a quality and assurance process to make sure that the data are accurate. Third, our sample was a convenience sample, and although repeated attempts were made to reach every retinoblastoma treatment center in Africa and Europe, it is possible that some were missed. Notably, centers in Namibia (n=1), Sierra Leone (n=1) and Somalia (n=1) that were contacted did not join in the study, hence no information on these centers was available. In addition, only 1 out of 2 centers in Kenya, and 1 out of 2 in Algeria, joined in the study, and similarly, no information was available on those centers that did not join in.

In summary, our findings show that in European countries, travel distance from home to retinoblastoma center is not a barrier to early disease diagnosis. European patients travel on average more than 400 km and >60% present at stage cT2 or earlier. In Africa, the picture is more complex – patients travel on average less than 200 km, yet >80% present at stage cT3 or worse, suggesting that factors other than geographic distance to retinoblastoma center play a role in late disease diagnosis. Poor awareness and education by both care givers and health workers, other barriers to access, and possibly, number and distribution of specialist retinoblastoma treatment centers in those African countries in which the population is underserved, are key factors that warrant intervention on national and international levels. . Familial retinoblastoma is more common in Europe than in Africa, most probably due to death related to late disease presentation, and screening of patients at risk of developing retinoblastoma is more common in Europe. Comprehensive counselling of families and patients with germline disease (i.e. bilateral retinoblastoma and/or positive family history) may be found useful in order to detect the disease at early stage to increase survival rates in this highly curable malignancy.

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Figure Legends

Figure 1. Number of retinoblastoma centers in (A) Africa and (B) Europe. *Centers in Namibia (n=1), Sierra Leone (n=1) and Somalia (n=1) that were contacted did not join the study, hence no information was available from these centers. Of the two known Kenyan centers and two known Algerian centers that were contacted, only one from each country has joined in the study.

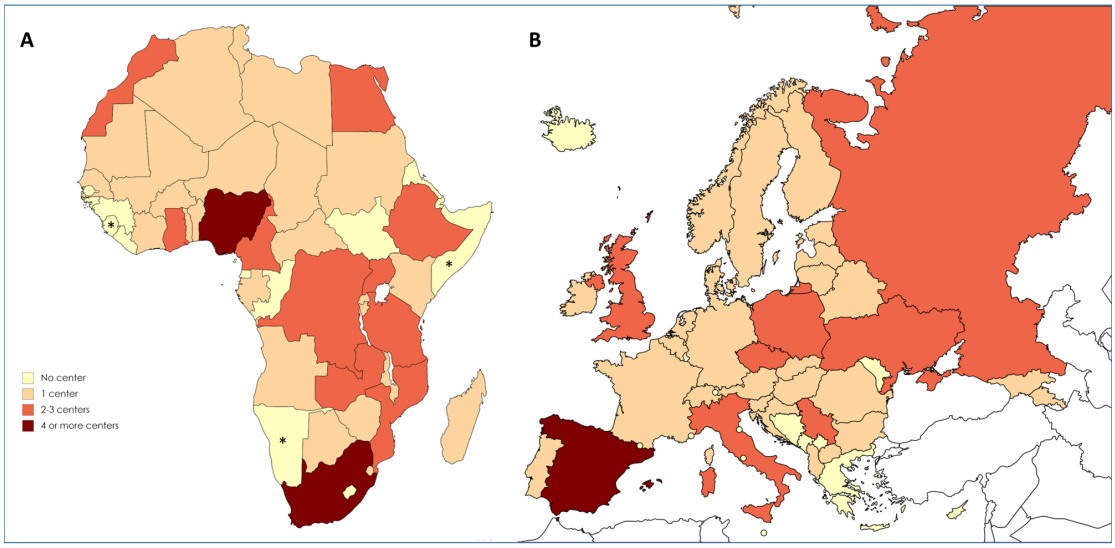

Figure 2. Retinoblastoma center catchment area in Africa and Europe. The red circles represent the mean patient travel distance and green circles, the travel distance Std. Patients in European countries travelled in average significantly longer distances (421.8 km±814.6) compared to patients from African countries (185.7 km±201.0) in order to reach an Retinoblastoma center ($p<0.001$). Superimposing the red and green circles on the map, Retinoblastoma centers in European countries cover the whole continent, whereas in Africa, large parts in many African countries remain uncovered.