# RETINOBLASTOMA IN UZBEKISTAN

*MOURATOVA T.**

## ABSTRACT

Retinoblastoma incidence and mortality rates associated with age, sex, and ethnic background between 1978 and 1999 have been studied. Statistical analysis of normal and standardised incidence rates was performed on 972 patients. For 21 years, annual retinoblastoma incidence for both sexes has increased. There was no difference in cumulative retinoblastoma incidence between males and females. Among all ethnic groups living in Uzbekistan, the highest retinoblastoma incidence occurred among Tartars and Uzbeks who frequently marry their family members. There was no difference in mortality of males and females. Over a 5-year period from the moment of diagnosis, almost every third child with retinoblastoma died of metastases. Most of retinoblastoma cases were represented by patients with late diagnosis. Before 1978, there was no information in Uzbekistan about the number of patients with malignant eye tumours, including retinoblastoma.

## RÉSUMÉ

Nous avons étudié les taux d'incidence et de mortalité du rétinoblastome basés sur l'age, le sexe et l'origine ethnique entre 1978 et 1999. L'analyse statistique des taux d'incidence normaux et standardisés a été effectuée sur 972 patients. Depuis 21 ans, l'incidence annuelle du rétinoblastome a augmenté pour les deux sexes. Il n'y a eu pas de différence en incidence cumulative de rétinoblastome entre les hommes et les femmes. Parmi tous les groupes ethniques en Ouzbékistan, l'incidence de rétinoblastome la plus élevée a été trouvée parmi les Tatars et les Ouzbeks qui contractent fréquemment des mariages consanguins. On n'a trouvé aucune différence en mortalité entre les hommes et les femmes. Presque chaque troisième enfant attent de rétinoblastome mourrait a cause des métastases 5 ans après le premier diagnostic. La plupart des cas de rétinoblastome sont des patients chez qui le diagnostic a été posé tardivement. Avant 1978 il n'y avait aucune information sur le nombre de patients avec une tumeur oculare maligne incluant le rétinoblastome en Ouzbékistan.

KEY-WORDS:

Retinoblastoma. Incidence. Mortality. Ethnic groups. Uzbekistan.

MOTS-CLÉS

Rétinoblastome. Incidence. Mortalité. Groupes ethniques. Ouzbékistan.

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* *Department of Ophthalmology, Institute of Oncology and Radiology, Tashkent, Uzbekistan*

*received: 28.05.03*
*accepted: 12.07.03*

## INTRODUCTION

Retinoblastoma is a malignant tumour of the retina that is found mainly in children. Most cases are diagnosed before the age of 5 years. Retinoblastoma can be unifocal or multifocal, unilateral, bilateral or even trilateral (19), hereditary or non-hereditary, familial or sporadic.

Clinically, leukocoria and strabismus (7) are the two most frequent signs of typical retinoblastoma. The incidence of retinoblastoma reported in the literature ranges from 1:10000 (4) to 1:34000 (3). It is difficult to compare the incidence of retinoblastoma in different countries as some authors base their findings upon retinoblastoma incidence of live births (4, 16, 22) while others consider the age of patients such as >5 years (4, 22), from 0-14 (2), 0-17 (16), <5 or < 9 years (18), >10 years (8, 21), >15 years (15). Moll et al (9) base their study of retinoblastoma incidence upon both live births and age of patients calculated in a 5-year birth cohort. Except for that, time period of retinoblastoma incidence in the literature was from 1862 (9) to 1994 (2) (Table 1).

Table 1. Retinoblastoma incidence in the literature by period of observation

| Country | Period | Age | Incidence | Reference |
|---|---|---|---|---|
| The Netherlands | 1862-1995 | >15 yrs | 1:17,000 | Moll et al, 1997 (9) |
| Germany | 1961-1980 | >10 yrs | 0,54:100,000 | Lommatzsch et al, 1985 (8) |
| Singapore | 1968-1995 | < 9 yrs<br>< 5 yrs | 2,4:1m<br>11,1:1m | Saw et al, 2000 (18) |
| Great Britain | 1969-1980 | 0-17 yrs | 1:23,000 | Sanders et al, 1988 (16) |
| USA | 1974-1976 | >15 yrs | 3.58:1m | Pendegrass et al, 1980 (15) |
| USA | 1974-1985 | >10 yrs | 5.8:1m | Tamboli et al, 1990 (21) |
| Malawi | 1975 | >5 yrs | 1:10,000 | BenEzra et al, 1976 (4) |
| Singapore | 1976-1995 | >5 yrs | 1:15,789 | Tan et al, 1997 (22) |
| Namibia | 1983-1988 | >15 yrs | 5,8:1m | Wessels et al, 1997 (24) |
| Mexico | 1990-1994 | 0-14 yrs | 3,2:1m | Amozorrutia-Allegria et al, 2002 (2) |

Many authors found no difference in retinoblastoma incidence among males and females (8, 9, 14, 15), yet BenEzra et al (4) found overrepresentation of girls among unilateral retinoblastoma (61.1%) and of boys among bilateral cases (58.9%).

There is discussion in the literature regarding retinoblastoma incidence in different ethnic groups. Devessa (5) argues that there were 10,8 cases per million white children, compared to 9.8 cases per million black children. Pendegrass et al (15) found no difference in retinoblastoma incidence for whites and blacks, "other non-whites had rates greater than four times those of whites". Among all observed patients, more than 50% of whites and 25% of blacks have had retinoblastoma before 2 years of age. Survival rate of blacks is significantly lower than that of whites (12). Mortality rate of retinoblastoma varies from 8,3% (13) to 45% (25). Children diagnosed in their first year had a slightly higher survival than those diagnosed later on (17).

## PATIENTS AND METHODS

Before 1978, there was no information about the number of patients with malignant tumours in Uzbekistan. Since 1978, the Institute of Oncology and Radiology of the Academy of Sciences of Uzbekistan (IOR) has been collecting the data about patients with each localisation of the malignant tumours including malignant ocular tumours of adults and children (11). We gathered information concerning only new cases of malignant eye tumours from 1978 to 1999, including retinoblastoma. Over 21 years, the retinoblastoma register has been updated and now contains 972 cases (487 males and 485 females), of whom 87.7% (853 patients) were treated in the Department of Ophthalmology at the IOR. For statistical analysis by age and sex, the number of retinoblastoma patients was divided in 0-4, 5-9, and 10-14 age subgroups. To calculate normal and standardised rates, similar number of children population (per

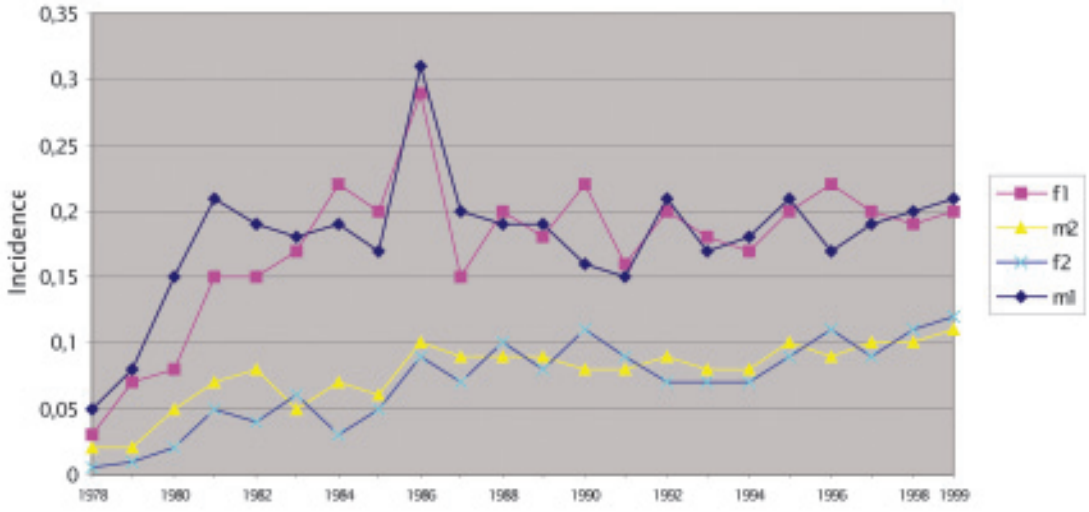


*Fig 1.* Annual retinoblastoma incidence: normal (m1 and f1) and standardised (m2 and f2) rates for males and females per 100,000 children in 1978-1999

100,000) in the same age and sex subgroups was used.
Retinoblastoma incidence in different ethnic groups was compared to the number of ethnic children population in Uzbekistan. Children population data was taken from the Statistics Committee of the Republic of Uzbekistan. All exponents were statistically tested and considered statistically significant if intersecting 95% confidence interval.

## RESULTS

Annual male retinoblastoma incidence between 1978 and 1999 increased from 0.050 in 1978 to 0.210 in 1999 (normal rate) and from 0.020 in 1978 to 0.110 in 1999 (standardised rate) (Fig 1).

Annual female retinoblastoma incidence increased from 0.030 in 1978 to 0.195 in 1999 (normal rate) and from 0.015 in 1978 to 0.120 in 1999 (standardised rate) meaning that annual retinoblastoma incidence rates have grown between 1978 and 1999 by 4.2 times (CI 95%, normal rate) and by 5.5 times (CI 95%, standardised rate) for males. Female normal rate in the same period has grown by 6.5 times (CI 95%) and standardised rate by 8.0 times (CI 95%).

Statistically significant difference of annual male incidence in some years is balanced by annual female incidence in other years and cumulative incidence rate for both sexes is therefore the same.
If dividing patients with retinoblastoma by sex and age subgroups of 0-4, 5-9 and 10-14 years, the highest cumulative rate per 100,000 children falls on age group of 0-4 years and is 6.1 and 5.9 for males and females respectively (Table 2), the peak of incidence, however, falling on the 2$^{nd}$ year of life - 5.7 males and 4.8 females per 100,000 children between 1978 and 1987 (10).
Among 123 ethnic groups living in Uzbekistan, Tartars and Uzbeks have the highest retinoblastoma rates per 100,000 children population (Table 3).
Despite the number of retinoblastoma among Tartars was significantly less than in Russian ethnic group, retinoblastoma incidence was the highest. In dividing conditionally all types of malignant eye tumours by 4 groups (Fig 2), it is evident that retinoblastoma comes in first place (69,4%), orbital tumours in second (22,2%), eyelid skin tumours in third (12%) and conjunctival tumours (6,4%) in the last place for both sexes.

Table 2. Cumulative retinoblastoma incidence rates (males and females) by age subgroups per 100,000 children in 1978-1999.

| Age groups | Number of patients/cumulative rate | Male | Female | Both |
|---|---|---|---|---|
| 0-4 | Number of patients | 459 | 453 | 912 |
| | Cumulative rate | 6,1 | 5,9 | 5,8 |
| 5-9 | Number of patients | 19 | 23 | 42 |
| | Cumulative rate | 2,1 | 2,5 | 2,4 |
| 10-14 | Number of patients | 9 | 9 | 18 |
| | Cumulative rate | 0,6 | 0,4 | 0,5 |
| Total | Number of patients | 487 | 485 | 972 |
| | Cumulative rate | 5,9 | 5,7 | 5,4 |

Table 3. Cumulative retinoblastoma incidence rates by age and ethnic subgroups in 1978-1999 per 100,000 children population

| Ethnic group | Number of patients in age subgroups | | | Incidence rate in age subgroups | | |
|---|---|---|---|---|---|---|
| | 0-4 | 5-9 | 10-14 | 0-4 | 5-9 | 10-14 |
| Uzbeks | 597 | 21 | 7 | 7,7 | 2,8 | 1,1 |
| Tartars | 92 | 10 | 4 | 15,9 | 8,4 | 1,7 |
| Russians | 138 | 4 | 3 | 6,5 | 1,9 | 0,9 |
| Kazakhs | 54 | 3 | 2 | 5,3 | 1,7 | 0,2 |
| Karakalpaks | 19 | 2 | 1 | 6,2 | 0,3 | 0,2 |
| Others | 19 | 2 | 1 | 4,4 | 1,8 | 0,8 |
| Total | 912 | 42 | 18 | 5,9 | 2,4 | 0,5 |

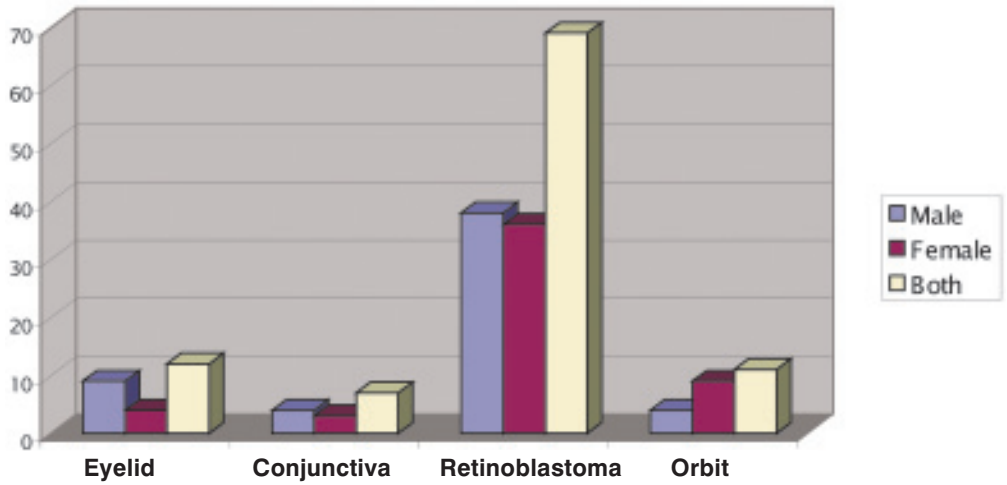


*Fig 2.* Retinoblastoma among other malignant eye tumours (%)

From the moment of diagnosis, 12.5% of children survived for less than 1 year, 5.8% for 1 year, 4.2% for 3 years, 1.7% for 4 years, and 0.8% for 5 to 9 years. At the same time, the longer period after the diagnosis and the earlier the treatment has begun, the more chances to survive. There were 73.8% of children with intraocular retinoblastoma, 15.2% with extraocular retinoblastoma growth (Fig 3) and 12.0% with metastases. Most children with intraocular retinoblastoma showed some signs of secondary glaucoma or the tumour filling the whole eye.

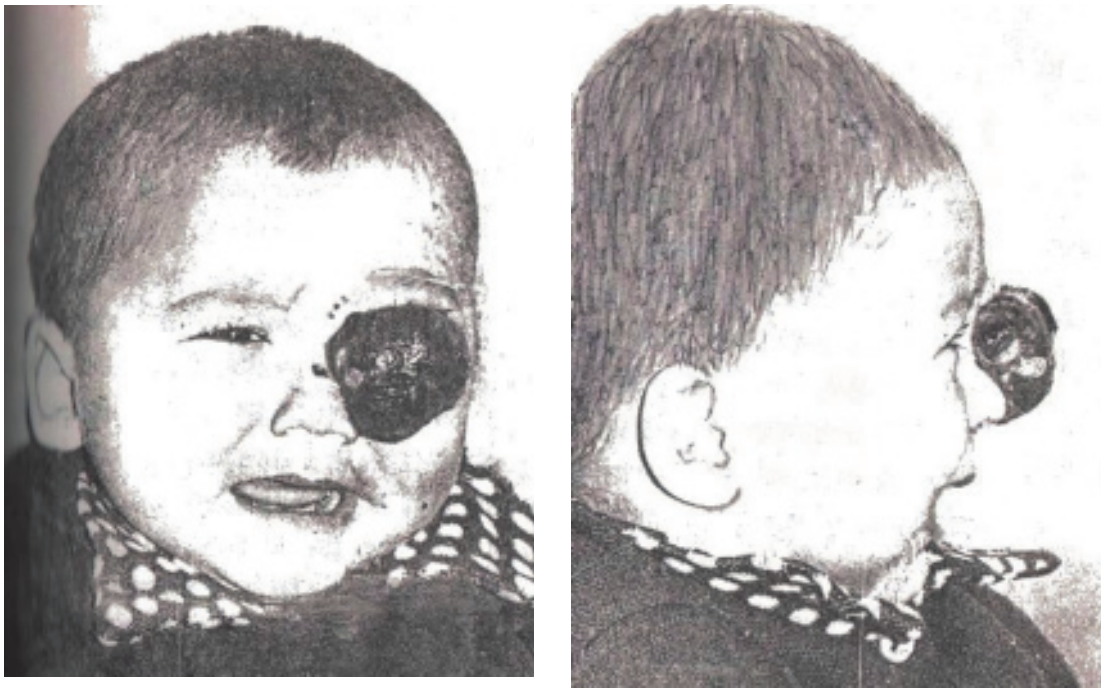

*Fig 3.* Patient K. aged 1.5. Diagnosis: retinoblastoma of left eye, extrabulbar growth, $T_3N_0M_0$

## DISCUSSION

In 1978-1999, annual normal and standardised incidence rates both for males and females have increased progressively. The same result was found by Moll et al (9) who studied the period between 1862-1944, i.e. 82 years. Stiller et al (20) found that non-hereditary retinoblastoma had a higher incidence among less affluent populations, suggesting an association with poor living conditions and maybe an infectious aetiology. Teleuova (23) believes that retinoblastoma was more often found in children living on the Alatau plain where water contains high levels of chemical compounds, as well as in big industrially polluted cities. The incidence of unilateral retinoblastoma in human populations increased dramatically with ambient erythemal dose of ultraviolet sunlight B-radiation. This is to support the hypothesis that sunlight plays an important role in the development of retinoblastoma (6). We found that the highest incidence of retinoblastoma was in Tartars and Uzbeks. These peoples have much in common, including religion and culture, and frequently practice consanguineous marriages that may affect retinoblastoma incidence.

Among three age groups, the highest incidence rate is in the 0-4 subgroup, with the peak of incidence falling on the 2$^{nd}$ year. Our 21-year research has demonstrated that statistically significant difference of annual incidence rates among males and females could have occurred in various years, but there is no sex difference in cumulative retinoblastoma incidence.

In Uzbekistan, every third child with retinoblastoma does not survive his 5$^{th}$ year of life because of the late diagnosis. After 25 years of diagnosis, 50% of bilateral retinoblastoma patients die and after 35 years 59% of patients die (1)

In the literature, there are many hypotheses of retinoblastoma development, ranging from impact of ultraviolet sunlight radiation (6), poor living conditions and probably infectious aetiology (20) to water pollution with chemical elements and industrial waste products (23). We found a whole set of reasons that could play a

role in the occurrence of retinoblastoma, namely: poor health of parents, particularly mothers, retinoblastoma in family history, chemical pollution of water and soil and specifically consanguineous marriages.
Consequently, annual retinoblastoma incidence for both sexes in Uzbekistan has increased for the last two decades, with male and female incidence varying in different years. Higher incidence in Tartar and Uzbek ethnic group emphasises the importance of taking ethnic dimension into account when making diagnosis and carrying out research.
Retinoblastoma incidence and mortality is the result of late diagnosis coupled with unsuccessful treatment and low common culture in some families. Most children with retinoblastoma in Uzbekistan have had late diagnosis which greatly influenced retinoblastoma incidence.

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*Request for reprints and correspondence:*
*Prof. Dr. Tamara MOURATOVA*
*Dendermondesteenweg 9/11*
*9230 Wetteren*
*Belgium*
*E-mail: tatumur@lycos.com*