

Review of 1375 enucleations in the TongRen Eye Centre, Beijing

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Abstract

Purpose To review clinical causes for ocular enucleations and the histopathological features of the enucleated globes in a large third-referral centre in China.

Methods The retrospective study included 1375 globes enucleated in the Beijing TongRen Hospital between January 2003 and November 2006. The medical records were reviewed, and the clinical indications for enucleation and histopathological findings were evaluated.

Results The enucleated eyes accounted for 0.97% of all operated patients registered in the hospital and for 29.5% of all surgical specimens received in the pathological department. The age distribution showed two peaks at an age group of 0–10 years (main enucleation cause: retinoblastoma) and at an age group of 30–40 years (main cause: trauma). In the whole study group, trauma was the most common clinical diagnosis (62.5%) leading to enucleation, followed by tumours (28.5%), surgically treated or untreated ocular diseases (5.7%), and infectious or inflammatory diseases (1.7%). With respect to the histopathological findings, phthisis bulbi (36.4%) was the most frequent finding followed by ocular malignant tumours (28.5%), and acute severe ocular injury (19.9%). Uveal metastases were the second most common intraocular malignant tumour in adults, in the majority of globes secondary to a primary lung cancer.

Conclusions The rate of 1% of enucleations per patient operated and the relatively high rate of ocular traumata as primary cause for enucleation suggest to improve further safety conditions and primary surgical care. The relatively high rate of ocular tumours as cause for enucleations suggests to promote the wide-spread clinical introduction of chemoradioactive tumour therapy.

Eye (2008) 22, 1404–1409; doi:10.1038/sj.eye.6702919; published online 29 June 2007

Keywords: ocular enucleation; ocular trauma; ocular tumour; phthisis bulbi; retinoblastoma

Introduction

Enucleation of a globe is the end-stage therapeutic step in the treatment of ocular diseases. Although the procedure is relatively rarely performed, an analysis of the demographic data of patients undergoing globe enucleation and of the causes for enucleation can give hints for the spectrum of severe ocular conditions, for differences between countries in the causes for enucleation of globes, and for tendencies when causes for enucleations are compared between different periods. For Western countries, the spectrum of diseases leading to globe enucleations have previously been reported, analysed, and compared.^{1–5} Since there is almost no information available for China, it was the purpose of the present study to investigate the causes for globe enucleations and its associated demographic and clinical factors in one of the leading referral ophthalmic centres in the country.

Materials and methods

The TongRen Eye Centre has been one of the largest and best-known eye centres in China, serving patients from all regions and provinces in China. All eyes enucleated in the TongRen Eye Centre have routinely been histologically examined in the hospital's department of ocular pathology. In the study period from January 2003 to November 2006, the pathology department received 1375 enucleated eyes. For 1354 (98.5%) eyes, the clinical and histopathological charts provided complete data of age, sex, presenting symptoms, duration of symptoms, clinical diagnosis including cause for enucleation, and findings of the

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Received: 22 January 2007
 Accepted in revised form: 1 June 2007
 Published online: 29 June 2007

histopathological examinations including dimensions of the eyes. For 21 (1.5%) globes, the data were partially incomplete. For all eyes included in the study, histologic paraffin sections stained with hematoxylin–eosin were available.

The main clinical diagnoses as cause for enucleation were divided into seven groups: anterior staphyloma; tumour or suspected tumour, acute ocular injury, absolute glaucoma, painful blind eye, phthisis bulbi, and so on. The cases with two indications were categorized into both groups. The primary causes were categorized as trauma, tumour, infection or inflammation, and surgically treated or untreated ocular diseases (which include retinal detachment, primary glaucoma, cataract, or corneal dystrophy), and others. In the tumour group, misdiagnosis was defined as histologically finding a clinically unsuspected tumour.

Statistical analysis was performed using a commercially available statistical software package (SPSS for Windows, version 11.5, SPSS, Chicago, IL, USA). The data are given as mean \pm standard deviation. χ^2 tests were used to compare proportions. All *P*-values were two-sided and were considered statistically significant when the values were less than 0.05.

Results

General demographic information

In the study period, 1375 enucleated ocular globes of 1373 patients were sent to the ocular pathology department. The patients who underwent enucleation accounted for 4.5% (1373/30 392) of all patients who had been admitted to the Eye Centre and had undergone ocular surgery ('indoor patients'), and they accounted for 0.97% (1373/141 245) of all patients operated during the study in the TongRen Eye Centre ('indoor' patients and 'outdoor' patients). The globes formed about one-third (1375/4654 or 29.5%) of all surgical specimens received at the hospital's department of ocular pathology during the study period. The age of the patients (age of 21 patients unknown) ranged from 1 month to 93 years (mean \pm SD: 28.7 \pm 19.2 years; median: 30 years). The age distribution of these patients in each decade of life was shown in Figure 1. There were significantly ($P < 0.0001$, binomial test) more male patients ($n = 989$ (72%)) than female patients ($n = 384$ (28%)) in the total study population. Differentiating the whole study population into subgroups, the preponderance of males *vs* females was significant in the trauma group (698 males *vs* 161 females; $P < 0.0001$) and in the tumour group (266 males *vs* 166 females; $P < 0.01$). In the subgroup with ocular infection or inflammation, in the subgroup with ocular surgeries

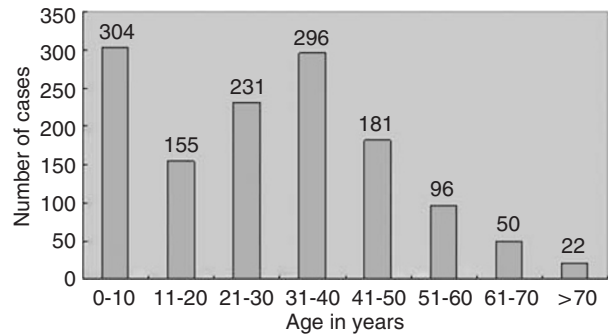


Figure 1 Age distribution of the enucleation in each decade of life.

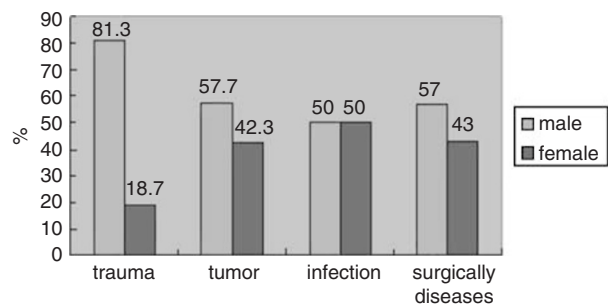


Figure 2 Sex distribution of each aetiology.

and in the subgroup including all remaining patients, the males and females were equally distributed (Figure 2).

Indications and aetiologies distribution

The clinical indications for enucleation were as follows: 500 (36.4%) phthisis bulbi; 392 (28.5%) ocular tumour; 273 (19.9%) acute injury; 170 (12.4%) staphyloma; 139 (10.1%) absolute glaucoma; 36 (2.6%) painful blind eye; and 34 (2.5%) others (Table 1). Phthisis bulbi and tumour were the two main indications for enucleations. In the phthisis bulbi group and in the staphyloma group, the main reasons for enucleations were cosmetology and alleviation of symptoms. In the acute injury group, the main reasons for enucleations were severe destruction of globe without chance for surgical rehabilitation and preservation of the globe independently of visual outcome, and the concern of sympathetic ophthalmia.

Aetiologically, the primary causes for enucleation were as follows: 859 (62.5%) trauma; 392 (28.5%) tumour; 79 (5.7%) surgically treated or untreated ocular diseases; 24 (1.7%) infection or inflammation; and 21 (1.5%) others (Figure 3). In trauma group, the main types of injury included traffic accidents, burst injury (mainly firecracker and bottles), and sharp object perforating injury. In tumour group, there were 206 cases of retinoblastoma and 144 cases of melanoma.

Table 1 Mean age, gender distribution, and number of cases in different clinical indication groups

Clinical diagnosis	No. of cases (%)	Mean age (years)	No. of cases	
			Male	Female
Tumour	392 (28.5)	44.4 (2–76)	226**	166**
Retinoblastoma	206 (15.0)	2.1 (1 month–10 years)	114	92
Melanoma	144 (7.9)	42.9 (4–78)	87*	57*
Anterior staphyloma	170 (12.4)	27.9 (1–77)	128***	42***
Acute injury	273 (19.9)	32.3 (6–65)	238***	35***
Absolute glaucoma	139 (10.1)	39.0 (1–93)	101**	38**
Painful blind eye	36 (2.6)	50.0 (3–85)	20	16
Phthisis bulbi or atrophya	500 (36.4)	31.9 (4–88)	379***	121***
Others	34 (2.5)	—	—	—

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.0001$.

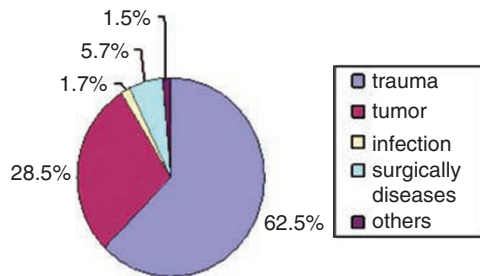


Figure 3 Aetiology distribution of enucleations.

Retinoblastoma was the commonest tumour in children (206/211) and melanoma was the commonest tumour in adult (144/181).

In surgically treated or untreated ocular diseases group, five enucleations were caused by the complications with cataract surgery (one case for corneal ulcer perforation, one case for atrophya, and two cases for absolute secondary glaucoma).

Histopathological findings

In the ocular trauma group consisting of 859 globes, the location of the ocular wounds was corneo-scleral (40.4%), corneal (38.0%) and scleral (23.3%). Six eyes showed complex wounds. Excluding globes that were enucleated shortly after an acute injury, abnormal histopathological findings were retinal detachment (70.5%), anterior synechiae and secondary angle closure (46.9%), marked glaucomatous cupping of the optic nerve head (40.1%), choroidal and vitreous haemorrhage (32.6%), pupillary membranes (14.3%), anterior chamber membranes (13.5%), marked inflammatory intraocular reactions (10.9%) including endophthalmitis (1.2%), intraocular ossification (10.9%), rubeosis iridis (5.3%), and cyclitic membranes (3.6%). Fourteen eyes (1.5%) showed findings typical for sympathetic ophthalmia such a granulomatous reaction to the melanin of the retinal

pigment epithelium and the melanocytes of the choroid. For these patients, the interval between ocular injury and enucleation ranged from 1 month to 50 years (mean 9.1 years, and median 2 years).

In the ocular tumour group, 206 globes showed a retinoblastoma. The tumour was unilateral in 194 eyes, and in 12 eyes, a bilateral retinoblastoma was detected. The interval between the onset of symptoms and the enucleation ranged from 1 day to 3 years (mean: 3.2 ± 4.9 months). There were 172 undifferentiated retinoblastomas, 18 differentiated retinoblastomas, and 13 eyes with a regressed retinoblastoma (without any previous therapy). Three undifferentiated tumour cases and one differentiated tumour partially showed regions with regressions. In varying percentages, the tumours involved the optic nerve head (78/206; 37.9%), the lamina cribrosa (44/206, 21.4%), the posterior surface of the lamina cribrosa (41/206, 19.9%), the end of the optic nerve at its cutting edge (5/206, 19.9%), and the retinal pigment epithelium (96/206, 46.6%), the choroid (33/206, 16.0%), the iris, and ciliary body (13/206, 6.3%), the anterior chamber angle (9/206, 4.4%), the sclera (4/206, 1.9%), and the scleral emissary veins (4/206; 1.9%).

A malignant melanoma of the choroid was detected in 141 globes, a ciliary body melanoma in two eyes, and an iris melanoma in one eye. In the group of choroidal malignant melanomas, there were 90 (63.8%) globes with a spindle-cell-type tumour, 37 (26.2%) globes with a mixed-cell-type tumour, and 14 (9.9%) globes with an epitheloid-cell-type tumour. A local tumour invasion into the inner scleral layers was detected in 101 eyes (101/141; 72.3%), into the scleral emissary veins in 10 eyes (10/141; 7.1%), into the scleral canal in 34 eyes (34/141, 24.1%), into the orbit through the sclera in 6 eyes (6/141; 4.3%), into the orbit through scleral emissary veins in 1 eye (1/141; 0.7%), into the iris in 2 eyes (2/141; 1.4%), into the ciliary body in 16 eyes (16/141; 11.3%), into the optic nerve head in 6 eyes (6/141; 4.3%), into the retina in 3 eyes (3/141; 2.1%), and into the anterior chamber angle

Table 2 Histopathological diagnosis of the removed eyes with indications of ocular tumors excluding retinoblastoma and melanoma

<i>Histopathological diagnosis</i>	<i>No. of cases</i>
Metastatic carcinoma of choroid, ciliary body, and iris	8
Acute purulent or chronic inflammation	5
Melanocytoma of iris, ciliary body, and choroid	4
Conjunctival squamous cell carcinoma	4
Neurilemmoma of choroid and ciliary body	3
Subchoroidal or subretinal haemorrhage or exudation	3
Nonpigmented epithelio-adenocarcinoma of ciliary body	1
Cavernous haemangioma of choroids	1
Malignant lymphoma of choroids	1
Medulloepithelioma of ciliary body (teratoid)	1
Glioneuroma of ciliary body	1
Conjunctival malignant melanoma	1
Tuberculosis	1
Total	34

and trabecular meshwork in 1 eye (1/141; 0.7%). Other intraocular tumours besides malignant melanomas and retinoblastoma leading to enucleation of the globes included metastatic carcinomas in the choroid, ciliary body, and iris with lung cancer ($n=6$), clear cell carcinoma of the kidney ($n=1$), and adenocarcinoma ($n=1$) as the primary tumours (Table 2).

Misdiagnosis for enucleation

In the group of globes enucleated with the clinical diagnosis of an intraocular malignant tumour, one globe histologically revealed Coats' disease (clinically suspected retinoblastoma). Reversely, one globe with the clinical diagnosis of a terminal stage of Coats' disease histologically revealed a masked retinoblastoma. Six eyes were removed because of clinical diagnosis of a malignant uveal melanoma, while histology revealed a neurilemmoma of choroid and ciliary body ($n=2$), a leiomyoma of choroid and ciliary body ($n=1$), a haemangioma of the choroid ($n=1$), a melanocytoma of the choroid ($n=1$), and a localized suprachroidal haemorrhage ($n=1$). For eight eyes with a clinically suspected intraocular malignant tumour, histopathological examination showed a localized subretinal or suprachroidal haemorrhage ($n=2$), a granulomatous choroidal inflammation ($n=4$), an acute purulent inflammation ($n=1$), and a marked subretinal

exudation ($n=1$). Conversely, four eyes with a histologically detected malignant uveal melanoma had been clinically misdiagnosed as retinal detachments and had undergone pars plana vitrectomy with silicone oil endotamponade and eventual silicone oil removal in the referring eye hospital.

Discussion

Ocular enucleation is a therapeutic approach to the end stage of many ocular diseases leading to a painful blind eye. In addition, it has been the treatment of choice if an intraocular malignant tumour was suspected and no other globe-preserving therapy was available. The rate of ocular enucleation and the clinical causes leading to the recommendation for ocular enucleation reflect, therefore, the spectrum of severe ocular disorders and the availability of eye-salvaging treatment modalities such as sophisticated vitreoretinal surgery for ocular trauma and complicated retinal detachments and chemoradioactive therapy of ocular tumours. For China, as the data on the clinical causes for enucleations, on the rate of ocular enucleations and on the histopathological findings have not been known yet, it was therefore the purpose of the present study to assess these parameters in a third-referral ophthalmic centre.

General demographic information

With no population-based data available for China, the findings of the present investigation showed that in the referral centre, ocular enucleations and enucleated globes accounted for 4.5% of all patients admitted to the eye centre and operated on; for about 1% of patients operated on; and for 29.5% of all surgical specimens received at the pathological department of the hospital during the study period. These figure may be higher than those reported by Vemuganti *et al*⁶ from India, where 0.17% of all new patients underwent ocular enucleation and where enucleated globes accounted for 8% of all surgical specimens. Particularly, the relatively high figure of 1% as the ratio of ocular enucleations to all ocular surgeries performed may suggest that the patients who had to undergo ocular enucleation arrived in a relatively bad ocular situation at the well-equipped third-referral hospital. In an attempt to reduce the rate of ocular enucleation, one may infer that intensified prevention of ocular traumata by improving the safety conditions of working, better primary surgery treatment of ocular traumata, and widespread introduction of chemoradiotherapy of ocular tumours, particularly of malignant choroidal melanomas and retinoblastomas, are warranted.

With respect to age, the study population showed two peaks: a first peak at the age group of 0–10 years with retinoblastoma as the main reason for enucleation; and a second peak at an age of 30–40 years with ocular trauma as the most common reason for enucleation. Patients with retinoblastoma constituted 67.8% (206/304) of the age group of 0–10 years. Patients undergoing enucleation due to ocular trauma had an age mostly ranging between 20 and 50 years with a peak at 31–40 years. One of the reasons for the age peak of 30–40 years in the ocular trauma group may be that at that age period, patients were in the most active period of their life and chances of injury either in work or at home, therefore, were higher. Similar figures as at the Beijing TongRen Eye Centre were reported by Obuchowska and coworkers, who found that in patients younger than 30 years, 84% of all enucleations were performed owing to ocular trauma.⁵

Correspondingly, in the study by Vemuganti *et al*, patients who were enucleated due to ocular trauma were younger than the remaining patients.⁶ In contrast to the double-hump distribution of ocular enucleations by age in the present study, Haile from Ethiopia and Sigurdsson *et al*^{4,7} from Iceland found an increasing rate of ocular enucleations with age. The difference between the studies may be caused by variations in the causes of enucleations in the different regions in addition to differences in the socioeconomic background.

Indications and aetiologies distribution

Comparing the aetiologies of conditions leading to ocular enucleation, ocular trauma was the leading cause, followed by malignant intraocular tumour, surgical complications, and intraocular infection or inflammation. With respect to clinical indications, phthisis bulbi (36.4%) was the most frequent clinical diagnosis followed by malignant intraocular tumour (28.5%), acute severe injury (19.9%), and anterior staphyloma (12.4%). In the United Kingdom, for the period from 1994 to 2003, Saeed *et al* reported a sequence of causes for ocular enucleations starting with ocular trauma, followed by phthisis bulbi and endophthalmitis.⁸ Although in the present study, the sequence of clinical indications for ocular enucleation was similar to the findings of de Gottrau and Naumann from Germany,^{1,2} with trauma (37.4%), malignant intraocular tumours (19.6%), systemic diseases (17.1%), surgical complications (14.1%), and intraocular infection and inflammation (7%) in the list, the proportion of ocular trauma (62.5%) and malignant intraocular tumours (28.5%) were higher in the present study. In the latter study, the reasons for ocular enucleations owing to ocular traumata might have slightly shifted from surgical difficulties in salvaging the eye and pain alleviation to eventually cosmetic reasons to remove the deformed eye.

Histopathological findings

Excluding globes with tumours and acute ocular injury, a retinal detachment (70.5%) and an intraocular haemorrhage (32.6%) were most commonly associated with phthisis bulbi. It may suggest to promote a more widespread use of sophisticated vitreo-retinal surgical techniques in China. Anterior synechiae and secondary angle closure of the anterior chamber angle (46.9%) were dominant histopathological changes in almost all globes with anterior staphylomata. Similar figures were reported by Vemuganti *et al*⁶ and de Gottrau *et al*.² Interestingly, a rubeosis iridis (5.3%) was less commonly detected in the present study compared with the study by de Gottrau.² While de Gottrau considered most of the secondary angle closures to be a consequence of the iris neovascularization, the present investigation suggested that the closure of the anterior chamber angle was more frequently caused by ocular trauma and inadequate surgical therapy of it. It resulted in a non-reformation of the anterior chamber with the traumatic wound still leaking, secondary peripheral athalamia and circular anterior synechiae, eventually leading to secondary angle-closure glaucoma and formation of anterior staphylomata at the original location of the ocular laceration. It may warrant an improvement in the primary surgical repair of ocular lacerations in China.

Endophthalmitis and sympathetic ophthalmia

The frequency of endophthalmitis (1.2%) and sympathetic ophthalmia (1.5%) in the present study was similar to those reported from India.⁷ With the further intensification and spreading of antibiotic treatment, particularly in the prophylaxis of infectious endophthalmitis after ocular trauma and ocular surgery, one may expect a decrease in the rate of infectious endophthalmitis for the coming years in China. The rate of sympathetic ophthalmia was relatively high in the present study compared with reports from Western countries. The reasons for the discrepancies between the studies may be (1) that many patients in the present investigations had suffered severe ocular traumata, usually were not very well looked after at the primary care centre, and coming of all over China, had a long way to travel to reach the TongRen Eye Centre in Beijing; (2) that a prophylactic enucleation after acute trauma to prevent the development of ophthalmic ophthalmia has not commonly been performed in China; and (3) that some injured eyeballs showed early signs of sympathetic ophthalmia in the histopathologic examination without clinically detected signs of sympathetic ophthalmia in the remaining eyes.

Tumours

Intraocular malignant tumours and suspected tumours constituted a large part of the present study. Retinoblastoma and malignant uveal melanoma were the most common malignant tumours in children and adults, respectively. The ratio of retinoblastoma to malignant melanoma was 1.43:1. As reported by Vemuganti,⁶ the ratio was 9:1 in India, in contrast to France and Poland with ratios of 1:2 and 1:13, respectively.^{1,3} The geographical differences in the ratio may reflect a low incidence of malignant melanomas and a relatively high incidence of retinoblastoma in population groups originating closer to the equator. Clinically, leukokoria (76.5%) was the most common presenting sign in the patients with retinoblastoma in the present study. The late presentation may be one reason, which led to the relatively large number of ocular enucleations owing to retinoblastoma. In addition, chemotherapy of retinoblastoma has not yet been universally introduced into clinical practice, which may be another reason for the relatively high number of retinoblastoma-related ocular enucleations. Clinical implications of the figures on retinoblastoma may be to further intensify the clinical introduction of chemotherapy of retinoblastoma combined with better screening methods to detect retinoblastomas earlier in a stage which does not necessarily lead to enucleation.

Metastases to the choroid, ciliary body, and iris was the second common malignant tumours in adults, with lung cancer as being the most common primary tumour. It is in contrast to studies from Western countries, in which mamma carcinomas have usually been the primary tumours leading to choroidal metastases. Similar results as in the present investigations were reported from another study from China.⁹ The reason for the discrepancies between the Chinese studies and the Western studies may be the high incidence of lung cancer in China. Even in females, lung cancer is also more common than breast cancer in China. Out of the eight patients with metastatic uveal carcinomas, four patients (50%) were unaware of any primary malignant tumour. For the remaining four patients, ocular enucleation was performed to alleviate pain caused by secondary glaucoma or corneal perforation.

Misdiagnoses

A misdiagnosis of retinoblastoma with a rate of 0.48% was similar to previous studies.^{6,10} A misdiagnosis of malignant uveal melanoma with a rate of 4%, however, and the percentage of unsuspected malignant uveal melanoma (2.8%) was higher than in reports from Western countries.^{11,12} It may suggest that clinical

ophthalmologists may be more aware of the masquerade syndrome some malignant uveal melanomas can induce.

In summary, most ocular enucleations in the Beijing referral eye centre were owing to ocular trauma followed by intraocular malignant tumours. The high rate of about 1% of enucleations per patient operated on suggests that the early primary eye care may be further improved. The relatively high rate of ocular tumours as cause for enucleations suggests to promote the clinical introduction of radiation therapy of ocular tumours. The relatively high rate of ocular traumata as cause for enucleation suggests to improve further safety conditions and primary surgical care.

Acknowledgements

I thank Dr Lu Qingjun for revising the manuscript in detail.

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