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Retinoblastoma: correlation of invasion of the optic nerve and choroid with prognosis and metastases

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SUMMARY The histological sections of 74 retinoblastoma patients were reviewed. The extent of optic nerve invasion was correlated with choroidal/scleral extension. Choroidal invasion carries 100% survival provided that the sclera, iris, and whole optic nerve are not also involved. Invasion of the optic nerve beyond the lamina cribrosa also carries 100% survival provided that the resection line is free and that invasion does not involve the sclera or iris. Plentiful rosettes were usually found in those tumours that had not extended beyond the choroid or as far as the resection line of the optic nerve and were therefore associated with a good prognosis. The absence of rosettes did not necessarily indicate a poor prognosis. The site of metastases was related to optic nerve and scleral/extrascleral extension. The various systems of staging retinoblastoma are compared, and a new system is proposed to cover the whole spectrum of the disease and to offer a reliable guide to prognosis and treatment.

Retinoblastoma is generally accepted as having an increasing mortality which correlates with the extent of invasion of the optic nerve, as judged by histological examination of the nerve after enucleation (Brown, 1966). It has been shown that the prognosis becomes significantly worse once the tumour has extended past the lamina cribrosa (Carbajal, 1958; McKenzie in Zimmerman, 1961; Brown, 1966). Invasion of the choroid by retinoblastoma is also considered to be a poor prognostic sign (Carbajal, 1958; McKenzie in Zimmerman, 1961; Brown, 1966; Herm and Heath, 1956; Miron *et al.*, 1966; Taktikos, 1966; Duke-Elder, 1967; Sevel *et al.*, 1974).

The first 3 of these authors showed that the mortality rate increased with increasing involvement of the choroid. Redler and Ellsworth (1973), however, found by examining serial sections of the eyes that choroidal invasion was both more common and less dangerous than previously believed.

The purpose of this study was to see whether our findings conformed with those of other authors with regard to optic nerve and choroidal extension and, if so, to see if a more accurate prognosis could be obtained by the correlation of one with the other. The findings in this direction have led us to formulate a new clinicopathological staging system which we consider to be a useful guide to prognosis and treatment.

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Clinical data

Between 1952 and 1975, 95 patients with retinoblastoma were referred to the Ocular Tumour Clinic at Groote Schuur Hospital, Cape Town; 26 (27%) of these patients had bilateral disease. Two patients who presented with advanced unilateral disease subsequently developed tumour in the opposite eye as a result of direct spread from one optic nerve to the other via the optic chiasma. They have been included in the unilateral group. None of the patients gave a family history of retinoblastoma, although 2 patients each had 1 parent with a healed unilateral retinal scar, and 1 patient with unilateral retinoblastoma has since had a child who developed retinoblastoma.

The histological sections of 74 patients were reviewed; 17 of these had bilateral disease, and in 11 cases both eyes were available for histological examination. These patients have all been followed up for a minimum of 3 years or until death. Twenty-one (22%) were excluded from the survey because there was insufficient histological material or inadequate follow-up. The slides were 5 μm thick and stained with haematoxylin and eosin. Further

sections were required for the evaluation of 15 eyes. Serial sections were not done.

Three of the 57 unilateral cases received no further treatment. Seven patients received deep *x*-ray therapy to the orbital contents and apex of the orbit, and 41 patients were treated with prophylactic cytotoxic drugs in addition to orbital irradiation (Sealy, 1977). Five patients were treated with chemotherapy and orbital and craniospinal irradiation because they were found to have a positive brain scan and/or malignant cells in the cerebrospinal fluid (CSF). One patient had an exenteration and chemotherapy for advanced local disease.

Four of the 17 bilateral cases had bilateral enucleations followed by orbital irradiation; 3 of these also received prophylactic chemotherapy. One patient had bilateral enucleations followed by orbitocranial irradiation and chemotherapy because of a positive brain scan and CSF cytology. After enucleation of the more severely affected eye in the remaining 12 patients the second eye was treated with external irradiation and chemotherapy. In addition a radioactive tantalum plaque was used in 5 patients. Four of these 12 patients subsequently experienced local treatment failure, requiring enucleation, and 2 further patients were similarly treated for vitreous haemorrhage and secondary glaucoma.

Staging

Because of the advanced stage of the tumour in the eyes of many of our patients we have not been able to use the scheme proposed by Reese and Ellsworth (1963) and therefore use the following system:

Stage I. Lesions amenable to local therapy.

Stage II. Lesions unsuitable for conservative local therapy but still ostensibly confined to the eye and orbit.

Stage III. Lesions which have spread beyond the orbit, that is, to local lymph nodes, adjacent bones, or to the central nervous system, but have not yet undergone blood-borne metastases.

Stage IV. Lesions which have undergone haematogenous metastases.

Stage I is a clinical staging and treatment is aimed at preserving vision. Enucleation is indicated in stage II, and its substages are based on the histological examination of the enucleated eye. For the purposes of this analysis, the following dual substage system has been adopted. Stage II: substages N0, N1, N2, N3; substages C0, C1, C2, C3*a* and *b*, C4*a*, *b*, and *c*. The first substage is based on nerve involvement and was the system used by McKenzie in Zimmerman (1961) (0, I, II, III). The second substage is based on involvement of the rest of the eye. The choroidal involvement is based on McKenzie in Zimmerman's (1961) classification, but it is extended to include involvement of the anterior uvea and sclera.

STAGE II

N0: *Nerve negative*—no tumour in the optic nerve.

N1: *Anterior lamina cribrosa*—tumour invasion of the optic nerve head up to or in the lamina cribrosa but not extending beyond it.

N2: *Posterior lamina cribrosa*—tumour invasion beyond the lamina cribrosa but not as far as the resection line.

N3: *Whole nerve*—tumour involvement of the nerve right up to the resection line, or when the optic nerve was not visualised but convincing radiological evidence of optic foramen erosion was present.

N?: Stage of nerve unknown. No nerve present in multiple sections examined.

C0: *Choroid negative*—no tumour involvement of the choroid.

C1: *Superficial choroid*—tumour involvement of the superficial layers of the choroid up to half its thickness.

C2: *Deep choroid*—tumour involvement of the whole thickness of the choroid without penetration of the sclera, ciliary body, or iris.

C3*a*: *Into sclera* ± *ciliary body*—tumour involvement of the full thickness of the choroid with penetration of the sclera. The ciliary body may or may not be involved, but the iris and anterior chamber are free of tumour.

C3*b*: *Into sclera, ciliary body, iris, and anterior chamber*—tumour involvement of the full thickness of the choroid with penetration of the sclera and tumour either in or replacing the ciliary body, iris, and anterior chamber.

C4*a*: *Through sclera* ± *ciliary body*—tumour extension right through the sclera. The ciliary body may or may not be involved but the iris and anterior chamber are free of tumour.

C4*b*: *Through sclera, ciliary body, iris, and anterior chamber*—tumour extension right through the sclera and tumour either in or replacing the ciliary body, iris, and anterior chamber.

C4*c*: *Eye disorganised* — total destruction by tumour. The nerve was recognisable in 5 out of 9 cases.

Results

Table 1 correlates survival with the extent of tumour spread down the nerve and with extension into the choroid, sclera, and anterior uveal tract. In bilateral cases, in which both eyes were available

Table 1 *Retinoblastoma—3 year survival correlated with tumour extension in 74 patients*

Alive / Dead	N 0	N1	N2	N3	N?
C0	5	10	3		
C1	2	5	1	2	1
C2	1	4	2	2 / 2	2
C3a			1	1 / 3	
C3b				1 / 3	
C4a			1	2	2 / 1
C4b		1	1	6	
C4c	1			4	2 / 2

for histological examination, for the purposes of correlating the stage of the disease with survival each substage was based on the greater degree of tumour involvement of the 2 eyes considered together. The results show that the 3-year survival is 100% for all cases up to stage N2, C2 (33 patients), i.e., provided the resection line of the nerve is free of tumour and provided also that tumour involvement of the choroid does not extend into the sclera, ciliary body or iris.

Beyond stage N2, C2 the overall survival is 34% (38 patients, N2, C1, and C2 patients excluded). Survival in stage N3 alone is 23% (26 patients), and in stages C3 and 4 alone it is 28% (32 patients).

Four patients had C4*a* lesions with ciliary body involvement. Three of them have survived for 4, 6, and 13 years respectively. Tumour involvement of the ciliary body and iris was seen in 13 patients and was always accompanied by extension into the anterior chamber. It was also accompanied by choroidal and scleral extension, except in 1 case where there was only superficial choroidal involvement. This patient has survived 23 years, but there are only 2 survivors among the other 12 patients.

Three out of 9 patients in whom the eye was totally destroyed have survived 4, 12, and 16 years respectively.

Histological evaluation included recording the presence or absence of true Flexner-Wintersteiner rosettes in the tumour (Table 2). Among the bilateral cases, where both eyes were available for examination, 5 patients were excluded because there was a difference in rosette status between the 2 eyes and they therefore could not be evaluated in terms of survival. The other 6 bilateral cases were included because both eyes showed the same features, that is, bilateral presence or absence of rosettes.

Plentiful rosettes were seen in the eyes of 12 patients, occasional rosettes in the eyes of 6 patients, and no rosettes in the eyes of the remaining 51 patients. One of the 12 patients in whom plentiful rosettes were seen died. This patient had an N2, C4*b* tumour. The remaining 11 patients, with tumours ranging from N0, C0 to N2, C2, all survived 3 years or more. Among those patients in whom no rosettes were present all those with tumours up to N2, C2 survived and 9 (29%) of those with tumours beyond N2, C2 also survived. The difference in survival between those with and those without rosettes is statistically significant at the 5% level.

METASTASES

The cause of death was unknown in 6 of the 26 patients who died, and no metastases were recorded. Of the remaining 20 patients necropsies were performed on 13, and in 7 patients who did not have a necropsy there was clinical, histological, radiological, or cytological evidence of tumour spread.

Metastases have also been seen in 5 patients who are alive, their disease being controlled by irradiation and long-term chemotherapy. Metastases in these 25 patients (20 dead, 5 living) have been divided into the following groups: (1) Metastases of the central nervous system (CNS). Intracranial metastases, tumour involvement of the spinal cord or meninges. (2) Distant metastases—blood-borne metastases in the bones or viscera, tumour in the distal lymph nodes. (3) Local disease—recurrent disease in the orbit or adjacent bones, local lymph node involvement (preauricular, cervical, or submandibular).

There is some dispute whether skull lesions are the result of lymphatic spread (Meighan and Michaelson, 1938; Duke-Elder, 1967), direct dissemination (Merriam, 1950; Knapp in Merriam, 1950; Carbajal, 1959), or haematogenous spread (Merriam, 1950; Carbajal, 1959). In this series there

Table 2 *Relationship of rosettes to survival in 69 retinoblastoma patients*

	Number of patients			
	Total	*Survived 3 years*		*Dead*
		Up to	*Beyond*	*All beyond*
	69	*N2, C2*	*N2, C2*	*C2, N2*
Plentiful rosettes	12	11	—	1
Occasional rosettes	6	2	2	2
No rosettes	51	20	9	22

Table 3 *Relationship of metastases to whole nerve and scleral/extrascleral involvement*

Stage	Total number of patients	Metastases						
		CNS only	CNS plus local	CNS plus distant	CNS plus distant plus local	Distant only	Distant plus local	Local only
N3	16	4	4	1	5	1	1	—
C3 C4	21	3	4	1	7	—	3	3

was 1 case with local disease and a skull lesion but no other evidence of distant disease; it has been included in the local disease group. In another case there was involvement of the frontal and parietal bones, alveolus, and left tibia, but no evidence of local orbital recurrence or lymph glands; this has been placed in the distal group. Two other cases had involvement of the alveolus and masseter respectively, again without evidence of local orbital recurrence or lymph glands. They have also been placed in the distant or haematogenous group. The remaining 5 cases with skull metastases had evidence of both local and distant disease and have therefore been included in both groups.

Metastases were seen as follows: CNS only, 5; CNS and local, 4; CNS and distant, 1; CNS, distant and local, 7; distant only, 2; distant and local, 3; local only, 3; total, 25. Table 3 summarises the site of metastases in relation to whole nerve and scleral/extrascleral involvement.

The whole nerve was involved in 16 of these 25 patients. CNS metastases were found in 14 patients (87·5%), distant metastases in 8 (50%), and local disease in 10 patients (62·5%). Two patients who had CNS metastases and are alive have now survived 5½ years (previously reported by Stannard *et al.*, 1975) and 2 years respectively, having been treated by irradiation and long-term chemotherapy.

The sclera and extraocular tissues were involved in 21 of the 25 patients. CNS metastases were found in 15 (71%), distant metastases in 11 (52%), and local disease in 17 patients (81%). Two C2 patients developed metastases. One of these (C2, N3) died of distant metastases, and the second (C2, N1) developed a metastasis in the masseter muscle 5 years after initial therapy. This has been controlled for 11 months with local deep *x*-ray therapy and chemotherapy. Yet another patient (N2, C4*a*) developed a mass in the ipsilateral temporal fossa and cervical gland—both proved histologically to be recurrent retinoblastoma—4 years after initial treatment. He has survived for 2 years after irradiation and prolonged chemotherapy. The latter 2 cases emphasise the importance of continued observation of these patients.

Twelve of the 13 patients with distant metastases died. The iris was involved or replaced in 8 of them (62%). In the remaining 12 patients who did not have distant metastases the iris was involved or replaced in 7 patients (58%).

Discussion

The frequency of bilateral disease was similar to that encountered by other authors, but the overall mortality of 39% was higher than that encountered by recent authors (Table 4). This could be attributable to the delay in presentation (Herm and Heath, 1956; Carbajal, 1958; Taktikos, 1966) (Table 5) and the late stage of presentation among our patients, many of whom are less sophisticated than those in other centres.

Table 4 *Incidence of bilateral disease and mortality of all retinoblastoma patients: review of literature*

	Total number of patients	Bilateral disease (%)	Mortality of total number of patients (%)
Callender in Zimmerman (1961)	45	25	
Duke-Elder (1940) reviewing other authors		20 to 30	
Adam			43
Leber			43
Merriam (1950)	759	27·6	
Herm and Heath (1956)	79	25	23·7
Carbajal (1958)	72	30·5	30
Reese (1963)		80	15 to 20
Howard and Ellsworth (1965)	235	59	
Jensen (1965)	69	30	23
Brown (1966)	462	57·6	31·4
Taktikos (1966)	287	39	16·7
Stafford *et al.* (1969)	618		29·9
Cassady *et al.* (1969)	230	35	20·9
Bedford *et al.* (1971)	139	80	8·3
Höpping *et al.* (1975)	228	75	6·1
Aherne and Roberts (1975)	50	46	16
Devesa (1975)	61	18	10
Present series	95	27	39

The overall average age at enucleation was 35·9 months (95 patients). The oldest patient in the series was 16 years. The average age among 3-year survivors was 31·6 months, and those who died presented at an average age of 43·7 months (Table 6). Leelawongs and Regan (1968) noted a similar difference of 24 and 32 months respectively.

Among patients with bilateral disease the average age was 17·3 months, whereas patients with unilateral disease presented at an average age of 42·8 months (Table 6). This supports the findings of a previous survey (Sevel *et al.*, 1973) and has been noted by several authors, including Dollfus and Auvert in Stallard (1955)—22 and 40 months, Mork (1961)—10 and 24 months, Jensen (1965)—15 and 29 months, Leelawongs and Regan (1968)—15 and 24 months, Knudson (1971)—15 and 32 months, Aherne and Roberts (1975)—8½ and 31 months, Lennox *et al.* (1975)—8 and 24 months, Matsunaga (1976), and Bonaiti-Pellie *et al.* (1976). The latter 2 authors also found that familial cases, whether bilateral or unilateral, presented at an earlier age than sporadic cases.

The mortality for unilateral cases was higher than for those with bilateral disease (but only at the 10% level of significance).

	Number of patients		
	Survived 3 years +	*Dead*	*Mortality*
Unilateral	38	30	44%
Bilateral	18	6	25%
Total	56	36	39%

One patient with unilateral disease and 2 patients with bilateral disease were lost to follow-up between 1 and 6 months after treatment.

The series of the Armed Forces Institute of Pathology (Reese, 1963) and Herm and Heath (1956) both found no difference in survival statistics between unilateral and bilateral cases, while Carbajal (1958) and Jensen (1965) found a higher mortality among those with bilateral disease. It should be noted from Table 4 that in some series (Bedford *et al.*, 1971; Höpping *et al.*, 1975; and Aherne and Roberts, 1975) a high percentage of bilateral cases was associated with a low mortality.

The average length of symptoms (6·9 months) is higher than that found by other authors (Table 5), and this figure should probably be higher still, as the duration of symptoms was unrecorded in 18 (19%) patients. The average duration of symptoms among 3-year survivors was 5·4 months, and among those who died it was 7·9 months. The duration of symptoms among those with bilateral disease was 6 months, and among those with unilateral disease it was 7·2 months (Table 6). In 4 patients with bilateral disease tumour was seen in the second eye at an average of 10·7 months (range 3 to 18 months) after enucleation of the first eye. This delay in appearance of the tumour in the second eye has already been noted by Reese (1963), Jensen (1965), and Aherne and Roberts (1975) and indicates the importance of regular observation of the second eye.

Table 5 *Review of age at enucleation and duration of symptoms in retinoblastoma*

	Average age at enucleation, in months	*Average age when symptoms appeared, in months*	*Average length of symptoms in months*
Duke-Elder (1940) reviewing other authors	24		
Falls and Neal (1951)	25·4	19·9	5·5
Herm and Heath (1956) excluding 6 year+	26·6	21·7	4·9
Carbajal (1958)	23·2	17·1	6·1
Reese (1963)	13	10	3
Howard and Ellsworth (1965)	20	16	4
Taktikos (1966)	25		
Bedford *et al.* (1971)		12	
Present series	35·9	29	6·9

As stated previously, it is generally accepted that the mortality for retinoblastoma increases with increasing invasion of the optic nerve (Brown, 1966) and that the prognosis becomes significantly worse once the tumour has extended beyond the lamina cribrosa (Carbajal, 1958; McKenzie in Zimmerman, 1961; Brown, 1966) (Table 7). The present series shows that, provided the resection line of the nerve is free, invasion of the optic nerve carries 100% survival for 25 patients, 6 of whom had invasion beyond the lamina cribrosa, allowing for the treatment technique utilised and provided also that tumour invasion does not go beyond the choroid.

It is also generally accepted that choroidal

Table 6 *Average age at enucleation and duration of symptoms in 95 retinoblastoma patients*

	3 years+ survivors	*Dead*	*Bilateral*	*Unilateral*
Average age at enucleation, in months	31·6	43·7	17·3	42·8
Average duration of symptoms, in months	5·4	7·9	6	7·2

Table 7 *Review of survival related to progressive invasion of the optic nerve in retinoblastoma*

Involvement of nerve	*Percentage survival*			
	Carbajal (1958), 72 patients	*McKenzie in Zimmerman (1961), 300 patients*	*Brown (1966), 204 patients*	*Present series, 64 patients*
No involvement		91·6	72·4	100
Invasion anterior to or in lamina cribrosa	83	85·2	84	100
Invasion posterior to lamina cribrosa—resection line free	33	55·6	37	100
Invasion as far as resection line		36	19	23

Table 8 *Review of survival related to choroidal involvement in retinoblastoma*

	Carbajal (1958), 72 patients	*McKenzie in Zimmerman (1961), 236 patients*	*Brown (1966), 204 patients*	*Redler and Ellsworth (1973), 42 patients*	*Present series, 74 patients*
Number of patients with choroidal involvement	26	128	85	26	15 (N3, N?, C3, C4 patients excluded)
	Percentage survival				
Superficial choroidal involvement	57	78	87·5	81	100
Full thickness choroidal involvement	0	36	40		100

invasion carries a bad prognosis (Herm and Heath, 1956; Carbajal, 1958; McKenzie in Zimmerman, 1961; Brown, 1966; Miron *et al.*, 1966; Taktikos, 1966; Duke-Elder, 1967; Sevel *et al.*, 1974), although Redler and Ellsworth (1973) found that choroidal invasion was both more common and less dangerous than previously believed (Table 8). The present series shows that whether tumour invasion of the choroid is superficial or full thickness, provided it does not penetrate the sclera, ciliary body, or iris, and provided the resection line of the nerve is free, the survival is 100% for 15 patients. The prognosis becomes considerably worse once the sclera or anterior uvea is involved in addition to the choroid.

The poor prognosis associated with involvement of the iris has previously been noted by Sevel *et al.* (1974), but it would seem that iris involvement reflects advanced disease, and it is the latter factor that is associated with haematogenous dissemination.

The incidence of choroidal invasion varies with different authors—Jensen (1965) 17%, Taktikos (1966) 20%, Reese (1963) 25%, Walton and Grant (1968) 28%, Herm and Heath (1956) 34·5%, Carbajal (1958) 36%, Brown (1966) 41·6%, McKenzie in Zimmerman (1961) 54%, Redler and Ellsworth's (1973) serial sections 62%, Miron *et al.* (1966) 83%. The incidence here of invasion of the choroid without extension into the sclera is 32·4%. Invasion of the choroid together with extension into or through the sclera occurred in a further 43·2% of patients. It is not entirely clear whether the other authors' figures for choroidal invasion included those in whom the sclera was involved in addition to the choroid (with the exception of Miron *et al.*, 1966, see below).

If they did, then it could account for the higher survival of those with choroidal invasion alone in our series. In Miron *et al.'s* (1966) series 8 of the 9 patients with choroidal invasion who died also had invasion of the emissary vessels of the sclera.

The mortality from scleral involvement (67%) is well documented by other authors—Carbajal (1958) 57%, Brown (1966) 75%; and likewise from extrascleral involvement (74%), Herm and Heath (1956) 100%, Taktikos (1966) 77%, and Brown (1966) 70%). Of the patients in this series with scleral or extrascleral involvement who died 78% (18/23) also had invasion of the optic nerve up to the resection line. In the remaining 5 patients the optic nerve was not present on the slide in 3 and the invasion did not reach the resection line in 2.

The observation that plentiful rosettes were found in the eyes of patients with an early stage of the disease and therefore indicate a good prognosis corresponds to the findings of other authors (Parkhill and Benedict, 1941; Herm and Heath, 1956; Carbajal, 1958; Brown, 1966).

The average age at enucleation among patients with many rosettes was 15 months and the average length of symptoms 4 months (Table 9). Among

Table 9 *Relationship of rosettes to age at enucleation and duration of symptoms in 69 retinoblastoma patients*

	Number of patients	*Average age at enucleation, in months*	*Average length of symptoms, in months*
Plentiful rosettes	12	15	4
Occasional rosettes	6	63·4	8·2
No rosettes	51	41·4	7·7

patients in whom no rosettes were found the average age was 41·4 months and the average length of symptoms 7·7 months. The figures in the group where occasional rosettes were seen are probably not reliable, as this was a small number of patients and included 1 child of 9 years and another of 14 years. Therefore symptoms were first noticed in patients with many rosettes at the age of 11 months and in patients with no rosettes at the age of 33·7 months.

It has been suggested that the longer the tumours are present the more undifferentiated they become, so that mortality is related to the prolonged presence of the tumour and its extension rather than the degree of differentiation (Herm and Heath, 1956; Brown, 1966). The question arises as to whether the children with undifferentiated tumours harboured their tumours for 22 months, or whether a more differentiated tumour is likely to appear in the first year or two of life.

Parkhill and Benedict (1941) distinguished two different forms of the disease—the slower-growing neuroepithelial type with rosettes, which was not usually associated with invasion beyond the nerve or orbit, and the highly undifferentiated retinoblastoma, which was associated with optic nerve and extraocular extension. Herm and Heath (1956), as mentioned above, found that the longer a tumour was present the more undifferentiated it became. Taktikos (1966) found that the degree of differentiation was unrelated to the size and therefore the age of the tumours, and suggested that well differentiated as well as less differentiated tumours seem to arise as such. Jensen (1965) noted that rosettes were found more frequently in small tumours (less than half the eyeball) than in large tumours (more than half the eyeball), although the length of history was the same for both. He suggested that the more anaplastic tumours grew at a faster rate and therefore reached a larger size before enucleation was performed. Unfortunately he does not relate the size or the degree of differentiation to the age of the patient.

Age is considered to be one of the most crucial prognostic factors in the two most common non-cerebral malignant solid tumours—Wilms's tumour and neuroblastoma (Sutow *et al.*, 1970).

The prognosis for Wilms's tumour (excluding congenital mesoblastic nephroma) is better for children under 2 years old (D'Angio *et al.*, 1976). These children are less likely to develop metastases (Sutow *et al.*, 1970), and according to Bolande (1971) metastases below the age of 1 year are rare. The degree of differentiation of the tumours is also an important factor. Anaplastic tumours are almost always found in patients over 2 years old and associated with a poor outcome (Beckwith and Palmer, 1978), whereas sarcomatous lesions are found both in the under- and over-2-year-old groups. They tend to metastasise, have a poor prognosis, and account for most of the deaths in the under 2-year-olds (Johnson *et al.*, 1967; Beckwith and Palmer, 1978).

The prognosis for neuroblastoma is also better below the age of 2 years. Metastases are less common in this age group, and although the degree of differentiation is unrelated to age those with differentiated tumours below the age of 2 years did significantly better than those with undifferentiated tumours in this age group (Sutow, 1958). After the age of 2 years the prognosis was poor for both differentiated and undifferentiated tumours.

A similar situation appears to apply to retinoblastoma, those under the age of 1 or 2 years having a better prognosis than those appearing in subsequent years. If this is so, it could account for the low mortality in a series with a younger age group, such as that of Bedford *et al.* (1971) and the higher mortality in our series, where a large proportion of tumours were in older children.

The presence of rosettes may be associated with a better prognosis *per se* or it may be merely an incidental finding in the disease in younger children who have a better prognosis anyway.

The site of metastases and their frequency has been well documented by Merriam (1950), Carbajal (1959), Taktikos (1966), and Wintersteiner in Duke-Elder (1967). Merriam (1950) in his analysis of 17 necropsies reported that retinoblastoma was by no means a purely local and cranial disease. In his series 8 patients (47%) died with disease confined to the head and/or spinal cord. The other 9 patients (53%) had distant metastases in addition to those present within the skull. This observation was confirmed by the 24 cases he collected from the literature in which the figures were 45·8% and 54·2% respectively. Carbajal (1959) found a higher incidence of intracranial and spinal spread (75%), and conversely Taktikos (1966) found that spread was more frequently by way of the blood stream, only 29% having CNS involvement. In the present series the disease was confined to the intracranial contents, structures of the orbit, or spinal cord in 12 patients

(48%). There were distant metastases in 13 patients (52%).

Merriam (1950) found that the choroid was involved in all cases with haematogenous metastases. Leber in Merriam (1950) agreed that the most logical and frequent site of vascular invasion was the choroid, and Wintersteiner and Nattini in Merriam (1950) proved that cells grow in the thin-walled choroidal vessels. Carbajal (1959) and Taktikos (1966) both had cases in which choroidal invasion alone must have been responsible for haematogenous dissemination. In this series there are only 2 cases (C2, N3; C2, N1) with haematogenous metastases, where the full thickness of the choroid was involved, without penetration of the sclera. In all the other patients with haematogenous metastases (11), although the choroid was involved the tumour had extended either into or through the sclera and probably involved the iris in 8 cases. None of the remaining 22 patients with choroidal invasion alone developed haematogenous metastases despite full-thickness invasion in 11 cases.

The site of metastases in relation to optic nerve and scleral/extrascleral extension is not clear-cut. The C2, N3 patient mentioned above died of haematogenous metastases. Another patient (N1, C4*b*) developed CNS as well as haematogenous metastases. There is a greater proportion of CNS to distant metastases in both N3 (87·5% : 50%) and C3 and 4 groups (71% : 52%), although the proportion is less in the latter group. The percentage of local disease is greater in the C3 and 4 groups than in the N3 group (81% and 62·5%). Once the disease has passed the N2, C2 stage the risk of developing metastases at either site or recurrent local disease is greatly increased.

Table 10 compares the various systems which are used to stage retinoblastoma. The system of Reese and Ellsworth (1963) is a clinical staging based on the findings in the eye, and prognosis for vision is related to the various stages. To this Bedford *et al.* (1971) had added group VI, which includes extra-ocular extension of the tumour through either the nerve or sclera. The systems of McKenzie in Zimmerman (1961), Carbajal (1958), and Brown (1966) are histological classifications of the nerve and choroid separately. We feel that the Cape Town staging embraces the whole spectrum of the disease and can be used as a guide to prognosis and treatment.

Stage I includes those lesions amenable to local therapy—Reese and Ellsworth's (1963) groups I to IV. In a recent article Merriam (1978) advised enucleation in group V, and this would therefore be included in the Cape Town stage II. While agreeing with Reese and Ellsworth's classification in principle, we should mention that site is an important factor as well as size. A small lesion overlying the optic disc, fully or partially, can be treated only with external beam therapy, and if there is any doubt as to its complete regression enucleation is indicated. Aherne and Roberts (1975) found that there was a poor prognosis with tumours at this site. A small lesion situated anywhere other than the optic disc or macula is readily accessible to an I^{125} radioactive plaque (Sealy, 1977), and therefore anterior lesions do not necessarily carry the poor prognosis originally ascribed to them. Reese and Ellsworth (1964) noted that with more thorough examination of the ora serrata and by using means other than external beam therapy, which probably missed these lesions while they were trying to spare the lens, anterior lesions had a more favourable prognosis.

Stage II is a histological staging of those lesions unsuitable for conservative local therapy but still ostensibly confined to the eye and orbit. The substages of stage II can offer a fairly reliable prognosis for survival and a guide to the essential modality of treatment, whether external irradiation or chemotherapy, or both. In substages N0, N1, C0, C1 no further treatment is required and the prognosis for life is excellent. Substages N2 and C2 require additional therapy to enucleation and the prognosis is still very good. The prognosis becomes considerably worse in substages N3, C3, and C4, and it is these stages which require recognition and aggressive prophylactic therapy if a cure is to be obtained.

In stage III the lesion has spread beyond the orbit but has not undergone haematogenous spread. This may be detected clinically or by cytological examination of the CSF, brain scan, and computerised axial tomographic scan.

In stage IV haematogenous spread has occurred and may be detected clinically or by skeletal survey, bone scan, and examination of the bone marrow together with a trephine biopsy.

It can be seen that accurate staging of retinoblastoma patients, clinically, histologically, and with the tests that are available, not only gives a reliable prognosis but provides a guide to the minimum necessary effective treatment, an important factor in growing children, and offers more hope for those patients in stage II N3, C3, or C4, if the seriousness of their disease is appreciated and prophylactic treatment instituted. The design of treatment related to this staging will be subject to a further communication.

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Table 10 *Comparison of present systems of staging retinoblastoma*

Cape Town		*Reese and Ellsworth (1963)*	*Bedford* et al. *(1971)*
Stage I. Lesions amenable to local therapy		Group I (*a*) Solitary tumour less than 4 dd in size — at or behind the equator (*b*) Multiple tumours none over 4 dd in size — at or behind the equator Group II (*a*) Solitary lesion 4 to 10 dd in size — behind the equator (*b*) Multiple tumours 4 to 10 dd in size — behind the equator Group III (*a*) Any tumour anterior to the equator (*b*) Solitary tumour larger than 10 dd behind the equator Group IV (*a*) Multiple tumours, some larger than 10 dd (*b*) Any lesion extending anterior to the ora serrata	Group I–V as Reese and Ellsworth
Stage II. Lesions unsuitable for conservative local therapy, but still ostensibly confined to the eye and orbit		Group V (*a*) Massive tumours involving over half the retina (*b*) Vitreous seeding	
Nerve	*Choroid*		
N0 No invasion	C0 No invasion		
N1 Invasion up to or in lamina cribrosa	C1 Involvement of superficial layers of choroid up to half its thickness		
N2 Invasion beyond lamina cribrosa. Resection line free			
	C2 Full thickness of choroid		
N3 Nerve involved up to resection line			Group VI. Optic nerve involvement
	C3 Scleral involvement (*a*) ± ciliary body (*b*) Ciliary body, iris and anterior chamber involved		
	C4 Extra-scleral involvement (*a*) ± ciliary body (*b*) Ciliary body, iris and anterior chamber (*c*) Total destruction of eye by tumour		Extra-scleral extension Residual orbital disease
Stage III. Lesions which have spread beyond the orbit but not yet undergone haematogenous metastases G1 Pre-auricular node G2 Other nodes B1 Positive brain scan or malignant cells in CSF. No clinical sign of disease B2 Clinical malignant meningitis B3 Relapsing intracranial disease			
Stage IV. Lesions which have undergone haematogenous metastases M1 Bone marrow M2 Clinical or radiological bone involvement M3 Liver M4 Multiple organs involved			

cKenzie in Zimmerman (1961)		*Carbajal (1958)*		*Brown (1966)*		
erve	*Choroid*	*Nerve*	*Choroid*	*Nerve*		*Choroid*
tage 0 lo invasion	None	No involvement		I. Not involved		No involvement Grade 0. Tumour internal to pigment epithelium Grade 00. Tumour external to pigment epithelium
tage I. Anterior to but not beyond lamina cribrosa	Slight	Anterior-optic cup anterior to lamina cribrosa	Grade I. Confined to choriocapillaris Grade II. Invasion of large vessels but not entire thickness	II. Nerve involved (*A*) Anterior to lamina cribrosa 1. Optic cup 2. Anterior to or including lamina cribrosa		Grade I Grade II } As Carbajal
tage II. Beyond lamina cribrosa but not as far as resection line	Moderate to marked	Posterior Nerve axis only Vaginal sheath only	Grade III. Entire choroidal layers	(*B*) Posterior to lamina cribrosa 1. Nerve axis only 2. Vaginal sheath only	(*D*) Cells do not cross line of transection	Grade III Grade IV Only supra-choroidal space involved
tage III. Involvement at plane of surgical transection		Both nerve axis and vaginal sheath		3. Both nerve axis and vaginal sheath	(*C*) Cells do cross line of transection	
			Scleral involvement			Scleral involvement
						Epibulbar involvement

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