BJO Online First, published on October 31, 2012 as 10.1136/bjophthalmol-2012-301977

MRI findings at baseline and after neoadjuvant chemotherapy in orbital retinoblastoma (IRSS stage III)

Venkatraman Radhakrishnan,[1] Sanjay Sharma,[2] Sreenivas Vishnubhatla,[3] Sameer Bakhshi[1]

[1]Department of Medical Oncology, All India Institute of Medical Sciences, New Delhi, India
[2]Department of Radiology, All India Institute of Medical Sciences, New Delhi, India
[3]Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India

Correspondence to
Dr Sameer Bakhshi, Department of Medical Oncology, Dr B. R. A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India; sambakh@hotmail.com

Accepted 23 September 2012

ABSTRACT

Background Published findings on MRI results in retinoblastoma patients treated with neoadjuvant chemotherapy (NACT) are lacking. The present study evaluates the role of MRI in International Retinoblastoma Staging System (IRSS) stage III retinoblastoma treated with NACT.

Methods 28 consecutive IRSS stage III retinoblastoma patients underwent MRI at baseline and after three cycles of NACT prior to enucleation. MRI films were reviewed retrospectively by an ophthalmic radiologist who was masked to patient outcome. Optic nerves were staged based on their thickness, contrast enhancement and length of involvement on MRI. Response evaluation criteria were based on optic nerve staging and changes in the size of the orbital mass on MRI after NACT.

Results The proposed staging at baseline and after NACT was able to predict event-free-survival (EFS) ($p=0.005$ and $p<0.001$, respectively) and overall survival (OS) ($p=0.002$ and $p=0.001$, respectively) using the log-rank test for trends. Patients with complete or partial response according to the proposed response evaluation criteria had significantly better EFS ($p<0.001$) and OS ($p=0.024$) than those who had stable or progressive disease.

Conclusions The proposed MRI based optic nerve staging system and response evaluation criteria were able to predict EFS and OS at baseline and after NACT.

INTRODUCTION

Published findings on MRI results in International Retinoblastoma Staging System (IRSS) stage III patients treated with neoadjuvant chemotherapy (NACT) are lacking. IRSS stage III retinoblastoma accounts for 25–40% of retinoblastoma cases in resource-poor countries; these cases are currently treated with NACT rather than with primary enucleation or exenteration.[1–6]

MRI is preferable to CT scanning for staging retinoblastoma because of the risk of secondary malignancies associated with ionising radiation. Positron emission tomography combined with CT (PET/CT) can detect distant metastasis in retinoblastoma but is associated with radiation exposure. Response Evaluation Criteria in Solid Tumors (RECIST) is commonly used to radiologically assess solid tumour response.[7] RECIST was proposed as a CT-based criteria, although it has been extended to other modalities like MRI. The use of RECIST criteria for retinoblastoma treated with NACT has not been previously reported. Tumour response assessment in retinoblastoma according to RECIST criteria is difficult due to the spherical shape of the globe, the frequently multifocal nature of the disease and the lack of clarity in assessing and measuring optic nerve involvement. The present study evaluates the role of MRI at baseline and after NACT in IRSS stage III retinoblastoma and correlates MRI findings with clinical outcome.

MATERIALS AND METHODS

Patients and treatment

Twenty-eight untreated consecutive IRSS stage III retinoblastoma patients were prospectively enrolled from May 2009 to June 2010 at our cancer centre after written informed consent was obtained. All patients underwent MRI of the orbit and brain, cerebrospinal fluid analysis, PET/CT, and bone marrow aspiration/biopsy at baseline to detect metastatic disease. The study was approved prospectively by the institute ethics committee and was conducted according to the Helsinki Declaration.

Median age was 3 years (range: 2–12 years), 17/28 patients were male, 24/28 had IRSS stage IIIA and 4/28 had IRSS stage IIIB retinoblastoma. At presentation, an overt orbital mass was seen in 23/28 patients, while 5/28 had involvement of the orbital part of the optic nerve on MRI without overt orbital mass. The median duration of symptoms was 6 months (range: 1–30 months). Seven of the 28 patients had bilateral retinoblastoma. Synchronous bilateral disease was present in six of these seven patients; one patient was previously enucleated for intraocular retinoblastoma and presented with IRSS stage III disease in the opposite eye. Five of these six patients with synchronous bilateral disease had intraocular retinoblastoma (IRSS stage 0) in the other eye, while one patient presented with bilateral stage IIIA disease.

The planned therapy for the patients included three cycles of NACT consisting of vincristine, carboplatin and etoposide, followed by enucleation and external beam radiotherapy (EBRT) for the involved orbits, and adjuvant VEC chemotherapy for nine more cycles.[8]

Post-NACT enucleation was carried out in 22/28 patients (two patients died and four patients were lost to follow-up before enucleation). EBRT was given to 19 of the 22 enucleated patients (two patients died before radiotherapy and one patient was lost to follow-up before radiotherapy). Sixteen of the 28 patients have died: 11 had central nervous system (CNS) metastasis and one had

abdominal metastasis, two died suddenly at home in complete remission and two others who had refused further therapy died due to disease progression.

MRI protocol and image interpretation

MRI of the orbit was performed with a 1.5 T MRI scanner (Magnetom Sonata, Siemens, Erlangen, Germany) using a standard head coil. The contrast used was gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany) at a dose of 0.1 mmol/kg. Before intravenous administration, axial and sagittal T1-weighted and axial T2-weighted MR images were obtained. Post-contrast axial, sagittal and coronal T1-weighted images were obtained using frequency selective fat suppression. Spin echo sequences were employed with a slice thickness of 3 mm. Axial T1-weighted post-contrast and T2-weighted brain imaging was also carried out. Gadolinium contrast MRI of both orbits and the brain was performed at baseline and after completion of three cycles of NACT (3–3.5 months after initiation of NACT).

Although the study was conducted prospectively, literature review suggested that there are no definite staging or response evaluation criteria for orbital retinoblastoma patients treated with NACT. Therefore for this analysis, MRI images were reviewed retrospectively by an experienced radiologist (SS) with 14 years' experience in radiology. The radiologist was masked to pathology findings and patient status.

Tumours were detected on MR images as hyperintense to vitreous on T1-weighted and hypointense to vitreous on T2-weighted images, and enhanced following intravenous contrast administration. Tumour size was measured in all cases on T1-weighted post-contrast images. The optic nerve was considered as involved when it showed contrast enhancement on T1-weighted images and/or thickening. It was compared with the contralateral optic nerve in unilateral disease or age-matched controls in patients with bilateral disease. The extent of post-laminar optic nerve involvement was classified as stage 0–4 (table 1). Sclera was identified as a continuous hypointense ring outside enhancing choroids on T1-weighted post-contrast images and also T2-weighted images. Interruption of this layer was considered to be scleral invasion and frank tumour extension beyond the sclera was taken as extra-scleral extension. Choroidal invasion was considered to be present when choroidal enhancement was irregular, asymmetrically thick or nodular.

Proposed new optic nerve staging system

The proposed new staging system for optic nerve involvement (stages 0–4) to assist prognosis in IRSS stage III retinoblastoma is based on optic nerve thickening, length of involvement and contrast enhancement characteristics (table 1 and figure 1A–D). The extent of optic nerve involvement was classified as intra-orbital <5 mm, intra-orbital ≥5 mm, intra-canalicular and intra-cranial.

Table 1 Proposed new staging system based on optic nerve involvement on MRI

Stage	Optic nerve thickening	Optic nerve enhancement	Optic nerve area
0	No	No	Not applicable
1	No	Yes	Intraorbital <5 mm
2	Yes	Yes or no	Intraorbital
	No	Yes	Intraorbital ≥5 mm
3	Yes	Yes or no	Optic canal
	No	Yes	Optic canal
4	Yes	Yes or no	Intracranial
	No	Yes	Intracranial

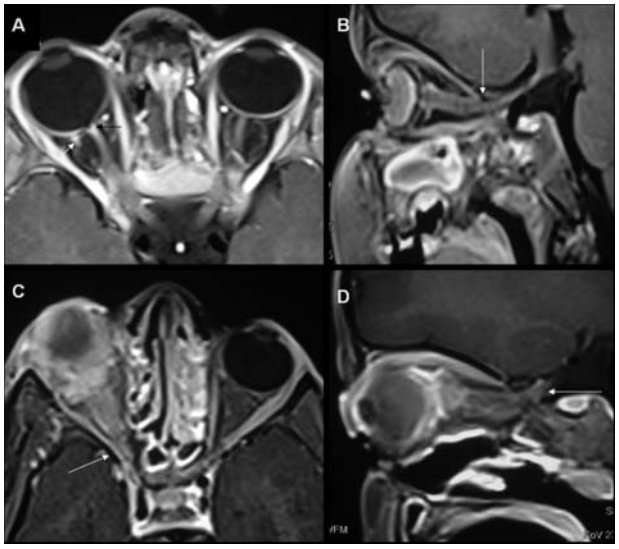

Figure 1 Post-contrast T1-weighted MRI demonstrating the proposed optic nerve based staging. (A) Stage 1: post-neoadjuvant chemotherapy (NACT) MR image (axial) showing enhancement of the most proximal right optic nerve (black arrow) for approximately 4 mm. A small linear residual tumour (white arrow) is noted temporal to the optic disc posterior to the staphylomatous globe. (B) Stage 2: post-NACT MRI (sagittal) showing enhancement of the optic nerve sparing the portion within the optic canal (arrow). Note the shrunken globe following chemotherapy. (C) Stage 3: Baseline MR image (axial) showing thickening and enhancement of the entire optic nerve including its intra-canalicular portion (arrow). (D) Stage 4: Post-NACT MR image (sagittal) showing marked thickening and enhancement of the entire optic nerve including its intra-cranial portion (arrow).

Patients with bilateral retinoblastoma with IRSS stage III retinoblastoma in both eyes were staged separately for each eye according to the proposed staging system. Patients with bilateral retinoblastoma with IRSS stage III retinoblastoma in one eye and intraocular retinoblastoma in the other eye (stage 0 or 1) underwent optic nerve staging for the eye with IRSS stage III only as optic nerve staging was not applicable to the eye with an intraocular tumour.

Proposed new response evaluation criteria

The proposed new response evaluation criteria incorporate the proposed new optic nerve staging system and a decrease in tumour size according to RECIST criteria (table 2). Response in the proposed criteria was defined as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). If there was discordance between the response of the orbital tumour and optic nerve stage on MRI in a patient, final response was then assigned according to the worse response seen in the orbital tumour or optic nerve stage. For example, if a patient had resolution of orbital mass consistent with CR but worsening of optic nerve stage consistent with PD, final response was then assigned as PD. Overall response in the patient with bilateral IRSS stage III disease was assigned according to the least response in one of the eyes. For survival analysis, patients with CR and PR were combined together and analysed against patients with SD and PD combined together.

Table 2 Proposed new response evaluation criteria based on MRI findings after neoadjuvant chemotherapy

Response	Orbital tumour	Stage of optic nerve
Complete response (CR)	Resolved or phthisical globe	Stage 0 or 1
Partial response (PR)	At least a 30% decrease in the sum of diameters of orbital mass	Down-staged
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD	No change
Progressive disease (PD)	At least a 20% increase in the sum of diameters of orbital mass or appearance of new lesions or metastasis	Up-staged

If there was discordance in response between the orbital tumour and optic nerve stage, the final response was assigned according to the least response seen.

Statistical analysis

All data analyses were performed using the statistical software package STATA 9 (StataCorp, College Station, Texas, USA). Patients without an event or death were censored at last known follow-up or 1 January 2012. Event-free-survival (EFS) was defined as time from presentation to disease progression or death due to any cause. Overall survival (OS) was measured from the date of presentation to the date of death from any cause. Patients who were lost to follow-up or abandoned treatment were also included for EFS and OS analysis; outcomes in these patients were confirmed by telephonic contact.[9] Measurement of EFS and OS for MRI findings after NACT, started at 3 months after initiation of NACT. EFS and OS were calculated using Kaplan–Meier analysis and 95% CI. Differences between groups were analysed using the log-rank test. For staging of the optic nerve, survival was calculated using the log-rank test for trends. A p value of ≤ 0.05 was considered significant.

RESULTS

Table 3 provides demographic details, MRI findings and outcome in study patients. EFS for all patients was 33.33% (CI 16.77 to 50.86) and OS was 40.74% (CI 22.53 to 58.21) at a follow-up of 30.93 months.

Baseline MRI findings and outcome

All 28 patients underwent baseline MRI. No significant correlation was seen between globe perforation, anterior chamber, choroid, scleral or extra-scleral involvement on MRI and EFS or OS (table 4). Optic nerve thickening at baseline significantly predicted EFS ($p=0.002$) and OS ($p=0.005$) (table 4).

Table 3 Demographic characteristics, baseline and post-NACT proposed optic nerve staging, proposed response evaluation criteria, outcome and follow-up of study patients

Patient	Age (years)/sex	Bilateral	IRSS stage	Enucleation	RT	Chemotherapy cycles (NACT and adjuvant)	Baseline optic nerve stage	Post-NACT optic nerve stage	MRI response as per proposed criteria	Relapse site	Final outcome
1	3/M	Yes	IIIA	Yes	Yes	7	3	3	SD	CNS	Died at 10.43 months
2	2.5/M	No	IIIA	Yes	Yes	12	0	0	CR	NA	Alive at 30.93 months
3	3/F	No	IIIA	Yes	No	4	0	3	PD	NA	Died at 7.2 months (LFU)
4	4/M	Yes	IIIA	Yes	No	3	0	3	PD	CNS	Died at 5.73 months
5	4/F	No	IIIA	No	No	3	2	NA	NA	CNS	Died at 7.67 months (LFU)
6	2/F	Yes	IIIA	Yes	Yes	12	1	1	PD	NA	Alive at 27.87 months
7	2/M	No	IIIA	Yes	Yes	8	2	3	PD	Abdomen	Died at 11.03 months
8	3/F	No	IIIA	Yes	Yes	11	3	2	PR	CNS	Died at 15.73 months
9	4/F	No	IIIA	Yes	Yes	7	2	2	PR	NA	Died at 11.2 months (unknown cause)
10	2/M	No	IIIA	Yes	Yes	10	3	4	PD	CNS	Died at 13.77 months
11	3/M	No	IIIA	Yes	Yes	12	1	1	PR	NA	Alive at 26.8 months
12	3/M	No	IIIA	Yes	Yes	12	2	0	CR	NA	Alive at 26.47 months
13	3/F	No	IIIA	No	No	3	0	NA	NA	NA	Alive at 2.23 months (LFU)
14	2/M	Yes	IIIA	Yes	Yes	10	2	3	PD	CNS	Died at 12.33 months
15	5/F	No	IIIA	No	No	3	3	NA	NA	NA	Died at 5.13 months (LFU)
16	3/M	Yes	IIIA	Yes	No	4	3	3	SD	CNS	Died at 5.3 months
17	3/M	No	IIIA	Yes	Yes	12	1	0	CR	NA	Alive at 24.23 months
18	4/M	No	IIIA	Yes	Yes	12	2	2	SD	NA	Alive at 23.7 months
19	3/M	No	IIIA	No	No	4	1	0	CR	CNS	Died at 9.83 months (LFU)
20	11/F	No	IIIA	Yes	Yes	12	0	0	CR	NA	Alive at 22.97 months
21	12/M	No	IIIB	Yes	Yes	6	1	0	CR	NA	Alive at 22.73 months (LFU)
22	4/F	No	IIIB	Yes	Yes	12	1	0	CR	NA	Died at 16.43 months (unknown cause)
23	4/M	No	IIIB	Yes	Yes	12	2	3	PD	NA	Alive at 21.57 months
24	5/F	No	IIIA	Yes	Yes	10	2	1	SD	CNS	Died at 16.87 months
25	6/F	No	IIIA	Yes	Yes	12	1	0	CR	NA	Alive at 21.57 months
26	3/M	No	IIIA	Yes	Yes	10	1	1	CR	NA	Alive at 21.37 months (LFU)
27	2/M	Yes	IIIB	No	No	3	2	2	PD	CNS	Died at 4.33 months
28	2/M	Yes	IIIA	No	No	2	3	NA	NA	CNS	Died at 4.43 months

CNS, central nervous system; CR, complete response; F, female; IRSS, International Retinoblastoma Staging System; LFU, lost to follow-up; M, male; NA, not available; NACT, neoadjuvant chemotherapy; PD, progressive disease; PR, partial response; RT, radiotherapy; SD, stable disease.

Table 4 EFS and OS according to baseline MRI findings estimated by Kaplan–Meier survival analysis and comparison using the log-rank test*

Parameter (n)	EFS†	95% CI	p value*	OS†	95% CI	p value*
Perforation						
Yes (19)	33.33	13.65 to 54.54	0.99	38.89	17.49 to 59.96	0.56
No (9)	33.33	7.83 to 62.26		44.44	13.59 to 71.93	
Anterior chamber						
Yes (24)	34.78	16.63 to 53.71	0.45	39.12	19.34 to 57.69	0.53
No (4)	25.00	0.89 to 66.53		50.00	5.78 to 84.49	
Choroid						
Yes (21)	30.00	12.25 to 50.14	0.43	40.00	19.28 to 60.05	0.43
No (7)	42.86	9.78 to 73.44		42.86	9.78 to 73.44	
Sclera						
Yes (18)	35.29	14.48 to 57.04	0.91	41.18	18.58 to 62.64	0.63
No (10)	30.00	7.11 to 57.79		40.00	12.27 to 67.02	
Extra-scleral						
Yes (12)	27.27	6.52 to 53.89	0.68	36.36	11.18 to 62.68	0.51
No (16)	37.50	15.42 to 59.77		43.75	19.81 to 65.56	
Optic nerve thickening						
Yes (14)	7.14	0.45 to 27.52	0.002	14.29	2.32 to 36.55	0.005
No (14)	61.54	30.83 to 81.84		69.23	37.34 to 87.18	
Proposed optic nerve stage						
Stage 0/1 (13)	58.0	27.01 to 80.09	0.005	66.7	33.70 to 85.97	0.002
Stage 2 (9)				33.3		
Stage 3 (6)	22.2	3.37 to 51.31		0.00	7.83 to 62.26	
Stage 4 (0)	0.00	–		–	–	

†Percent of patients alive at the end of follow-up.
EFS, event free survival; n, number of patients; OS, overall survival.

Baseline optic nerve staging and outcome

There was no significant difference in EFS (p=0.45) or OS (p=0.26) between stage 0 and stage 1 patients. Therefore, stage 0 and 1 were combined and this new optic nerve stage significantly predicted EFS (p=0.005) and OS (p=0.002) (table 4 and figure 2).

Post-NACT MRI findings and outcome

Twenty-four of the 28 patients underwent post-NACT MRI (one patient died due to disease and three patients were lost to follow-up before post-NACT MRI). A notable clinical reduction was seen in the orbital mass of all patients after NACT. MRI showed phthisis in 17/24 (70.8%) patients.

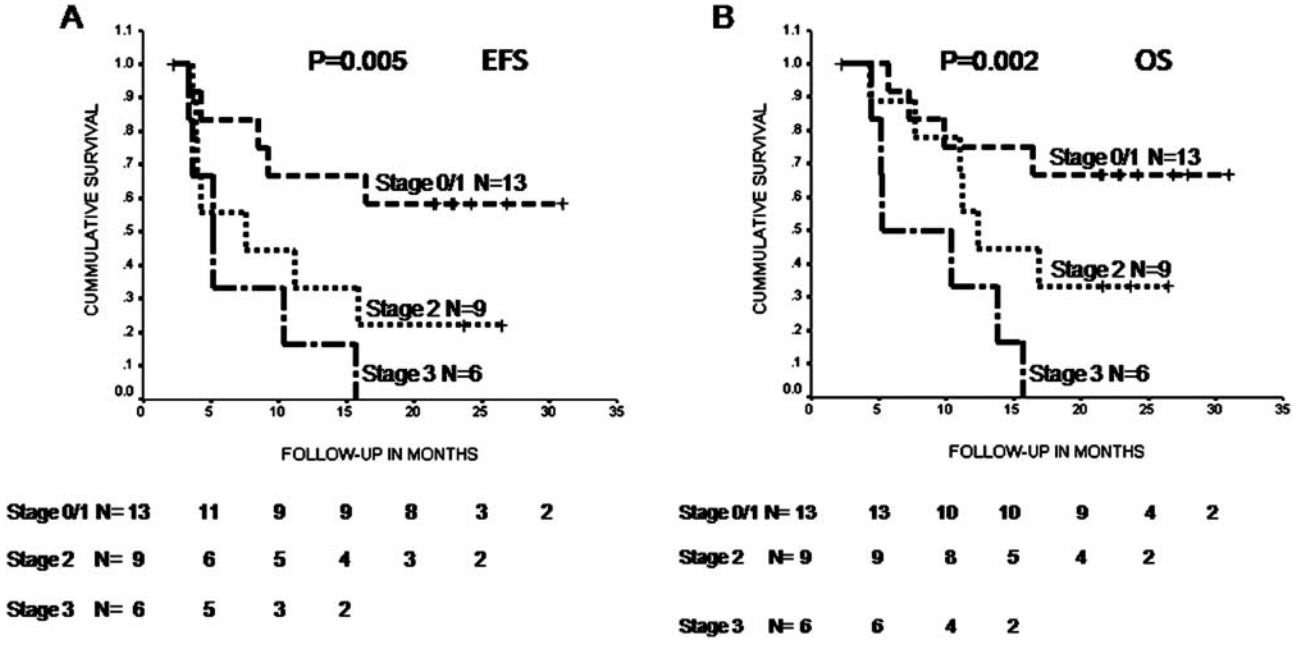

Figure 2 Kaplan–Meier survival curves for the proposed optic nerve staging based on MRI findings. (A) Event-free survival (EFS) according to the proposed optic nerve stage at baseline. (B) Overall survival (OS) according to the proposed optic nerve stage at baseline.

As marked distortion of intraocular structures was noticed in phthisical eyes on MRI after NACT, involvement of the choroid, anterior chamber and sclera could not be assessed. However, interpretation of extra-scleral and optic nerve involvement was not affected by post-NACT phthisis. Patients with extra-scleral disease after NACT had significantly worse EFS (p=0.004) but not OS (p=0.13) (table 5). Optic nerve thickening after NACT significantly predicted worse EFS (p<0.001) and OS (p<0.001) (table 5).

Post-NACT optic nerve staging and outcome

There was no significant difference in EFS (p=0.39) and OS (p=0.9) between stage 0 and stage 1 patients. Therefore, stages 0 and 1 were combined and the proposed new MRI stage after NACT significantly predicted EFS (p<0.001) and OS (p=0.001) (table 5 and figure 3).

Proposed new response evaluation criteria and outcome

Of 24 patients who underwent response assessment, nine achieved CR, three PR, four SD and eight PD. One patient with PD died due to disease and one patient with CR was lost to follow-up and therefore could not undergo enucleation.

Twenty-two patients underwent enucleation (8/9 CR patients, 3/3 PR patients, 4/4 SD patients and 7/8 PD patients) and at last follow-up 7/8 patients with CR, 1/3 patients with PR, 1/4 patients with SD and 2/7 with PD are alive.

EFS in patients with CR and PR after NACT according to the proposed new response evaluation criteria, was significantly better than in patients with SD and PD (66.7% vs 8.3%, respectively; p<0.001) (figure 4A). OS in patients with CR and PR after NACT was significantly better than in patients with SD and PD (66.7% vs 25.0%, respectively; p=0.024) (figure 4B).

Analysis after exclusion of patients who abandoned treatment

Twenty-one of the 28 patients persisted with treatment (table 3). In this cohort, the proposed new staging system at baseline significantly predicted EFS (p=0.01) and OS (p=0.003). Further in this cohort, after NACT, the proposed new staging system significantly predicted EFS (p<0.001) and OS (p=0.003) and the proposed new response criteria significantly predicted EFS (p=0.001) and OS (p=0.049).

DISCUSSION

Studies on MRI in retinoblastoma are predominantly of intraocular retinoblastoma with a few cases of extraocular retinoblastoma.[10–18] In extraocular disease, studies on MRI have focused on proximal post-laminar optic nerve enhancement and most such cases would have been suitable for primary enucleation, unlike the situation in this study where all patients required NACT.[15] In the present study, MRI findings of globe perforation and involvement of the anterior chamber, choroid, sclera and extra-scleral tissue did not correlate with EFS or OS, suggesting that involvement of these structures may not be prognostic in IRSS stage III retinoblastoma, unlike the situation in intraocular retinoblastoma.

Metastasis to the CNS, the most common site for metastases, occurs via the optic nerve, as suggested by the worse prognosis associated with the presence of post-laminar optic nerve involvement in patients who mainly underwent enucleation.[19] Therefore, any staging systems or response assessment criteria in extraocular retinoblastoma need to provide a reliable prognosis based on the extent of optic nerve involvement, optic nerve thickening and contrast enhancement. MRI has been reported to have better sensitivity than CT for detecting optic nerve involvement in retinoblastoma.[13]

Our proposed new staging system provided a reliable prognosis for patients at baseline and after NACT. However, we emphasise that our study was a pilot study with a small number of patients. Our staging system is preliminary and needs to be validated in a larger cohort of patients.

There was no significant difference in EFS and OS at baseline or after NACT between patients with no evidence of optic nerve involvement on MRI (stage 0) and patients with proximal optic nerve enhancement on MRI (stage 1). Our findings suggest that proximal optic nerve enhancement without optic nerve thickening on MRI (stage 1) may not be prognostically important. Therefore, in our study, stage 0 and stage 1 were considered negative and stages 2–4 were considered positive for

Table 5 EFS and OS according to post-neoadjuvant chemotherapy MRI findings estimated by Kaplan–Meier survival analysis and comparison using the log-rank test*

Parameter (n)	EFS†	95% CI	p value*	OS†	95% CI	p value*
Phthisis						
Yes (17)	47.1	22.96 to 67.97	0.054	47.1	22.96 to 67.97	0.977
No (7)	14.3	0.71 to 46.49		42.9	9.78 to 73.44	
Extra-scleral						
Yes (4)	0	–	0.004	25.0	0.89 to 66.53	0.135
No (20)	45.0	23.11 to 64.71		50.0	27.13 to 69.19	
Optic nerve thickening						
Yes (10)	0	–	<0.001	10.0	0.57 to 35.81	<0.001
No (14)	64.3	34.33 to 83.31		71.4	40.63 to 88.19	
Proposed optic nerve stage						
Stage 0/1 (12)	66.7	31.70 to 85.97	<0.001	75.0	40.84 to 91.17	0.001
Stage 2 (4)	25.0	0.89 to 66.53		25.0	0.89 to 66.53	
Stage 3 (7)	0.0	–		14.3	0.71 to 46.49	
Stage 4 (1)	0.0	–		0.0	–	
Proposed response evaluation						
CR+PR (12)	66.7	33.70 to 85.97	<0.001	66.7	33.70 to 85.97	0.024
SD+PD (12)	8.3	0.51 to 31.11		25.0	6.01 to 50.48	

†Percent of patients alive at the end of follow-up.
CR, complete response; EFS, event free survival; N, number of patients; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

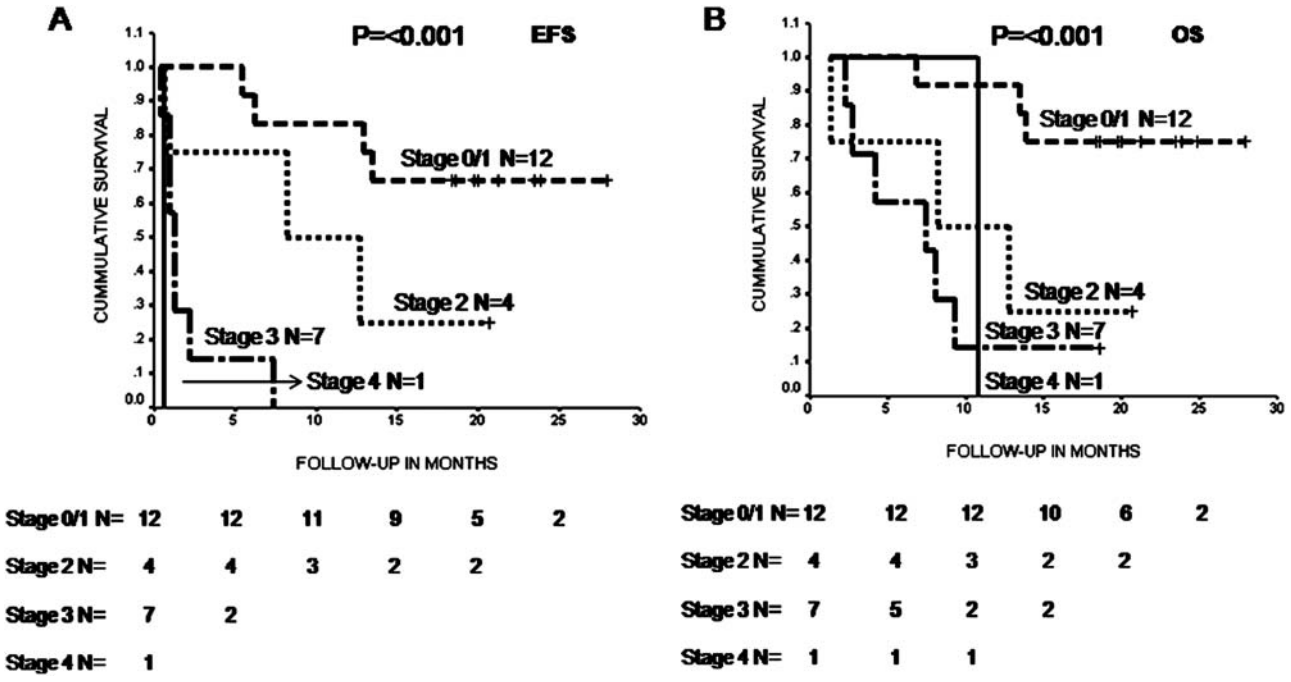

Figure 3 Kaplan–Meier survival curves for the proposed optic nerve staging based on MRI findings. (A) Event-free survival (EFS) according to the proposed optic nerve stage after neoadjuvant chemotherapy (NACT). (B) Overall survival (OS) according to the proposed optic nerve stage after neoadjuvant chemotherapy (NACT).

optic nerve involvement on MRI. The findings of Armenian *et al* corroborate our assertion, as they observed that all nine patients in their study with proximal optic nerve enhancement (<5 mm) are alive and well after receiving NACT.[15]

No significant difference in EFS and OS was seen between patients with and without phthisis on MRI after NACT. This finding is intriguing as it suggests that a significant reduction in tumour bulk and good clinical response as defined by RECIST criteria do not necessarily correlate with better outcome in IRSS stage III retinoblastoma. As mentioned above, optic nerve involvement is of prognostic value in retinoblastoma. However, RECIST criteria do not incorporate optic nerve findings and therefore are inadequate for response assessment in retinoblastoma. We therefore combined optic nerve findings according to our proposed new staging system and reduction in tumour size according to RECIST criteria to develop new response evaluation criteria in IRSS stage III retinoblastoma. The proposed new response evaluation criteria significantly predicted EFS and OS after NACT in IRSS stage III retinoblastoma.

In the current IRSS staging, overt orbital extension and/or radiology showing optic nerve involvement is staged as stage

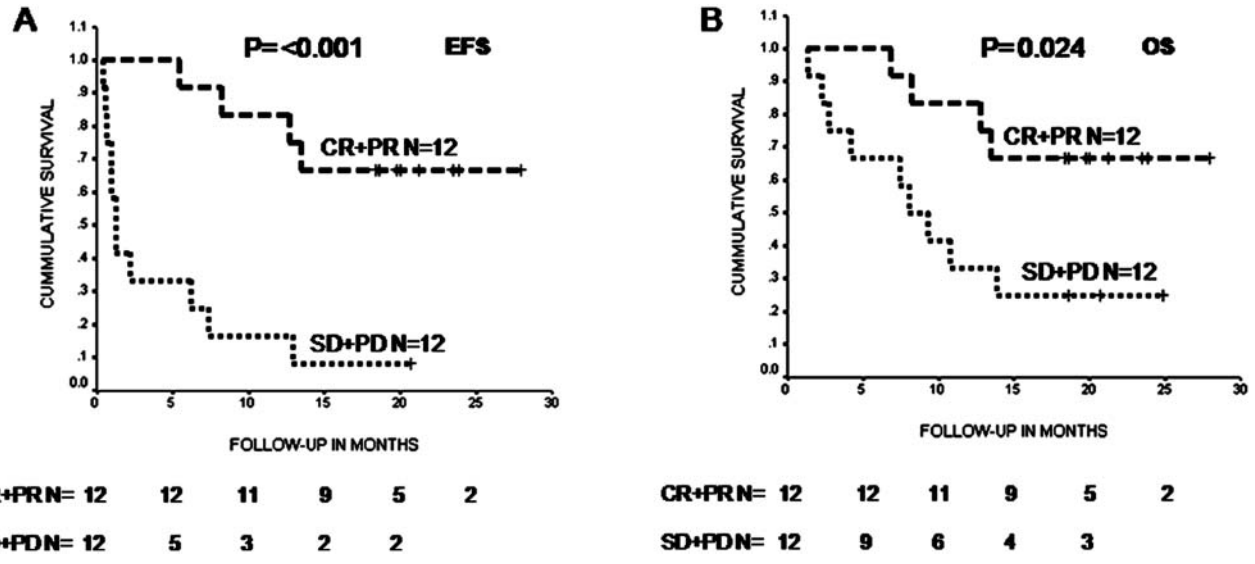

Figure 4 Kaplan–Meier survival curves for the proposed response evaluation criteria after neoadjuvant chemotherapy based on MRI findings. (A) Event-free survival (EFS) according to the proposed response evaluation criteria. (B) Overall survival (OS) according to the proposed response evaluation criteria.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

IIIA.[2] Our study shows that IRSS stage III patients with optic nerve thickening (stage 2 and above in our staging) have worse outcome when compared to IRSS stage III patients with either globe perforation, extrascleral extension or proximal optic nerve enhancement without optic nerve thickening.

Treatment abandonment is a reality in the management of retinoblastoma in developing countries.[20] We included all patients for final survival analysis as suggested by the position statement of the International Society of Pediatric Oncology.[9] When patients who abandoned treatment were excluded, the proposed staging system and response criteria continued to show statistical significance. As mentioned above, our staging system is preliminary and needs to be validated in a larger cohort of patients because the majority of patients with stage 2 and beyond had optic nerve thickening with or without enhancement. In fact, only one patient at baseline and two patients after NACT had isolated distal optic nerve enhancement (>5 mm) without thickening. Therefore, in patients with the proposed stages 2–4 disease, the importance of distal optic nerve enhancement without thickening cannot be ascertained from our study.

CONCLUSION

This study addresses the lack of response assessment criteria in locally advanced retinoblastoma by proposing a new staging system based on optic nerve involvement and new response assessment criteria. A decrease in tumour bulk alone (phthisical eye) after NACT was unable to predict EFS or OS. However, the proposed new staging system and new response evaluation criteria significantly predicted EFS and OS at baseline and after NACT.

Acknowledgements We are thankful to Ms Deepa Dhawan for assisting in statistical analysis.

Contributors VR and SB: study design, data collection and analysis, and manuscript writing; SS: data collection and analysis, and manuscript writing; SV: data analysis.

Competing interests None.

Ethics approval This study was approved by the AIIMS Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Hurwitz RL,** Shields CL, Shields JA, *et al*. Retinoblastoma. In: *Principles and practice of pediatric oncology*. 5th edn. Pizzo PA, Poplack DG. Philadelphia, PA: Lippincott Williams & Wilkins, 2006:865–88.
2. **Chantada G,** Doz F, Antoneli CB, *et al*. A proposal for an international retinoblastoma staging system. *Pediatr Blood Cancer* 2006;**47**:801–5.
3. **Honavar SG,** Singh AD. Management of advanced retinoblastoma. *Ophthalmol Clin North Am* 2005;**18**:65–73.
4. **Chantada G,** Fandiño A, Casak S, *et al*. Treatment of overt extraocular retinoblastoma. *Med Pediatr Oncol* 2003;**40**:158–61.
5. **Chantada GL,** Guitter MR, Fandiño AC, *et al*. Treatment results in patients with retinoblastoma and invasion to the cut end of the optic nerve. *Pediatr Blood Cancer* 2009;**52**:218–22.
6. **Chantada GL.** Retinoblastoma: lessons and challenges from developing countries. Ellsworth Lecture 2011. *Ophthalmic Genet* 2011;**32**:196–203.
7. **Eisenhauer EA,** Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;**45**:228–47.
8. **Radhakrishnan V,** Kashyap S, Pushker N, *et al*. Outcome, pathologic findings, and compliance n orbital retinoblastoma (International Retinoblastoma Staging System Stage III) treated with neoadjuvant chemotherapy: A Prospective Study. *Ophthalmology* 2012;**119**:1470–7.
9. **Mostert S,** Arora RS, Arreola M, *et al*. Abandonment of treatment for childhood cancer: position statement of a SIOP PODC Working Group. *Lancet Oncol* 2011;**12**:719–20.
10. **Schueler AO,** Hosten N, Bechrakis NE, *et al*. High resolution magnetic resonance imaging of retinoblastoma. *Br J Ophthalmol* 2003;**87**:330–5.
11. **de Graaf P,** Barkhof F, Moll AC, *et al*. Retinoblastoma: MR imaging parameters in detection of tumor extent. *Radiology* 2005;**235**:197–207.
12. **Barkhof F,** Smeets M, van dV, *et al*. MRimaging in retinoblastoma. *Eur Radiol* 1997;**7**:726–31.
13. **Brisse HJ,** Guesmi M, Aerts I, *et al*. Relevance of CT and MRI in retinoblastoma for the diagnosis of postlaminar invasion with normal-size optic nerve: a retrospective study of 150 patients with histological comparison. *Pediatr Radiol* 2007;**37**:649–56.
14. **de Graaf P,** Moll AC, Imhof SM, *et al*. Retinoblastoma and optic nerve enhancement on MRI: not always extraocular tumour extension. *Br J Ophthalmol* 2006;**90**:800–1.
15. **Armenian SH,** Panigrahy A, Murphree AL, *et al*. Management of retinoblastoma with proximal optic nerve enhancement on MRI at diagnosis. *Pediatr Blood Cancer* 2008;**51**:479–84.
16. **Wilson MW,** Rodriguez-Galindo C, Billups C, *et al*. Lack of correlation between the histologic and magnetic resonance imaging results of optic nerve involvement in eyes primarily enucleated for retinoblastoma. *Ophthalmology* 2009;**116**:1558–63.
17. **Lemke AJ,** Kazi I, Mergner U, *et al*. Retinoblastoma—MR appearance using a surface coil in comparison with histopathological results. *Eur Radiol* 2007;**17**:49–60.
18. **Galluzzi P,** Cerase A, Hadjistilianou T, *et al*. Retinoblastoma: abnormal gadolinium enhancement of anterior segment of eyes at MR imaging with clinical and histopathologic correlation. *Radiology* 2003;**228**:683–90.
19. **Honavar SG,** Singh AD, Shields CL, *et al*. Postenucleation adjuvant therapy in high-risk retinoblastoma. *Arch Ophthalmol* 2002;**120**:923–31.
20. **Kivelä T.** The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. *Br J Ophthalmol* 2009;**93**:1129–31.

MRI findings at baseline and after neoadjuvant chemotherapy in orbital retinoblastoma (IRSS stage III)

Venkatraman Radhakrishnan, Sanjay Sharma, Sreenivas Vishnubhatla and Sameer Bakhshi

Br J Ophthalmol published online October 31, 2012