Role of PET/CT in Staging and Evaluation of Treatment Response After 3 Cycles of Chemotherapy in Locally Advanced Retinoblastoma: A Prospective Study

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The present study prospectively evaluated the role of ^{18}F-FDG PET/CT for staging, neoadjuvant chemotherapy response evaluation, and final outcome assessment in International Retinoblastoma Staging System (IRSS) stage III retinoblastoma. **Methods:** Twenty-five consecutive IRSS stage III patients, with a median age of 3 y, were prospectively enrolled after ethics approval. All patients received neoadjuvant chemotherapy followed by enucleation, radiotherapy, and adjuvant chemotherapy. PET/CT was performed at baseline (PET/CT-1) and after 3 cycles of neoadjuvant chemotherapy (PET/CT-2). All 25 patients underwent PET/CT-1, and 21 of 25 patients underwent PET/CT-2. PET/CT-1 was compared with routine staging, and response on PET/CT-2 was assessed by criteria from the European Organization for Research and Treatment of Cancer response. Event-free survival (EFS) and overall survival (OS) were calculated using Kaplan–Meier survival analysis, and differences between the groups were compared using log-rank test. A P value of 0.05 or less was considered significant. **Results**: Increased ^{18}F-FDG uptake was noted in primary extraocular tumor in all patients, except 5 with bilateral retinoblastoma (one eye with advanced and the other eye with intraocular disease) in whom the intraocular tumor did not show ^{18}F-FDG uptake. Five of 22 IRSS stage IIIA patients with clinically negative cervical lymph node involvement were found to have uptake in cervical lymph nodes on PET/CT-1, and 2 of 3 IRSS stage IIIB patients with pathologically confirmed cervical lymph node involvement did not show any uptake in the involved lymph nodes. No significant difference in EFS and OS was seen between IRSS stage IIIA and IIIB patients using routine staging or PET/CT staging ($P \geq 0.05$); however, there was a trend toward better OS in patients with IRSS stage IIIB disease on PET/CT ($P = 0.065$). There was no significant discordance between routine staging and PET/CT staging ($P = 0.256$). The 8 patients with optic nerve uptake had lower EFS ($P = 0.0001$) and OS ($P = 0.0009$) than did 17 patients without optic nerve uptake on PET/CT-1. The 17 patients with complete response or partial response had better EFS ($P = 0.042$) and OS ($P = 0.026$) than did the 4 patients with progressive disease on PET/CT-2. **Conclusion:** Optic nerve uptake at baseline on PET/CT and response after neoadjuvant chemotherapy according to criteria from the European Organization for Research and Treatment of Cancer are strong predictors of EFS and OS in IRSS stage III retinoblastoma.

Key Words: oncology; retinoblastoma; PET/CT; chemotherapy

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Locally advanced retinoblastoma, also referred to as orbital retinoblastoma or extraocular retinoblastoma, denotes retinoblastoma that has spread either microscopically or macroscopically beyond the confines of the ocular globe (*1*). Patients with locally advanced retinoblastoma are at high risk for developing metastatic disease; this risk is evident from the reported overall survival (OS) rates of 20%–70% (*2,3*). In the recently proposed International Retinoblastoma Staging System (IRSS), microscopic locally advanced disease detected in primarily enucleated specimens is classified as stage II (*4*). Overt clinical or radiologically diagnosed extraocular disease is classified as stage III, and patients with metastatic disease are classified as stage IV (*4*).

CT or MRI of the orbit and brain are the standard imaging modalities used for diagnosing and evaluating disease extent in retinoblastoma (*5*). To the best of our knowledge, the role of ^{18}F-FDG PET/CT in retinoblastoma has not been reported in the published literature. There has been only 1 previous report on the use of ^{18}F-FDG PET alone without CT in 4 patients with retinoblastoma (*6*). In developing countries, 25%–40% of all retinoblastoma patients belong to IRSS stage III, because of delayed presentation and diagnosis (*7,8*). We estimate that around 7,000–10,000 IRSS stage III children are diagnosed every year in developing countries, and more than half of them would die because of the disease. Therefore, we studied the role of ^{18}F-FDG PET/CT in retinoblastoma and specifically IRSS stage III retinoblastoma.

The present study prospectively evaluates the role of ^{18}F-PET/CT for staging, neoadjuvant chemotherapy response evaluation, and final outcome assessment in IRSS stage III retinoblastoma treated with a uniform protocol.

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MATERIALS AND METHODS

Study Population

Approval from the institute ethics committee was obtained before initiation of the study. Twenty-five IRSS stage III patients were prospectively enrolled in the present study at our cancer center from May 2009 to June 2010. All patients with locally advanced retinoblastoma at our cancer center undergo gadolinium-enhanced MRI of orbits and brain, bone marrow aspiration and biopsy, cerebrospinal fluid examination, and fine-needle aspiration cytology (FNAC) of any significantly enlarged lymph nodes at baseline. Patients with bone marrow metastasis, positive cerebrospinal fluid examination, MRI showing involvement of the brain or optic nerve beyond the optic canal, and FNAC-positive lymph nodes other than cervical or preauricular were diagnosed as having metastatic disease (IRSS stage IV) and excluded from the present study. Patients with clinically overt or MRI evidence of extraocular extension without preauricular or cervical lymph node involvement were diagnosed as having IRSS stage IIIA disease, and patients with FNAC-positive cervical or preauricular lymph node were diagnosed as having IRSS stage IIIB disease (*4*).

During the study period, 110 retinoblastoma patients presented to our cancer center and 28 of 110 patients were diagnosed as having IRSS stage III disease. All 28 IRSS stage III patients were eligible for enrollment in the present study after written informed consent was given by the guardian. However, only 25 of 28 IRSS stage III patients were finally enrolled in the present study because 3 patients could not undergo baseline ^{18}F-FDG PET/CT due to procedural anxiety and apprehension.

Sixteen of 25 patients were males (64%) and 9 of 25 patients were females (36%); the median age of patients was 3 y (mean, 3.9 y; SD, ±2.53 y; range, 2–12 y). The median duration of symptoms before presentation to our hospital was 6 mo (mean, 6.7 mo; SD, ±6.4 mo; range, 1–30 mo). Twenty-two of 25 (88%) patients belonged to IRSS stage IIIA, and 3 of 25 (12%) patients belonged to IRSS stage IIIB. Bilateral disease was present in 5 of 25 (20%) patients. Twenty of 25 (80%) study patients presented with fungating proptotic masses and had MRI evidence of extraocular extension, whereas 5 of 25 (20%) patients were diagnosed as having IRSS stage III disease on the basis of MRI evidence of extraocular extension only.

Treatment

The current standard of care in IRSS stage III retinoblastoma is neoadjuvant chemotherapy, followed by enucleation, and then external-beam radiotherapy and adjuvant chemotherapy. All patients received 3 cycles of vincristine, etoposide, and carboplatin (VEC) consisting of vincristine (0.05 mg/kg) (≥3 y, 1.5 mg/m^2) and carboplatin (25 mg/kg) (≥3 y, 750 mg/m^2) on day 1 and etoposide (5 mg/kg) (≥3 y, 150 mg/m^2) on days 1 and 2 every 4 wk, followed by surgical excision of the involved eye, external-beam radiotherapy (40 Gy) to the involved eye, and adjuvant VEC chemotherapy for 9 more cycles.

Response assessments were done clinically every 4 wk and by gadolinium-enhanced MRI after completion of 3 cycles of neoadjuvant chemotherapy before surgical intervention. Patients also underwent examination under anesthesia of the unaffected eye at baseline and every 3 mo to detect bilateral disease.

The median number of chemotherapy cycles including neoadjuvant and adjuvant therapy received by study patients was 10 (mean, 8.1; SD, ±3.8; range, 2–12). Enucleation was performed in 20 of 25 (80%) patients; 2 patients were lost to follow-up, and 3 patients died before enucleation could be performed. Radiotherapy after enucleation was given in 17 of 25 (68%) patients; 3 patients were lost to follow-up, and 5 patients died before radiotherapy could be given. Events were recorded in 13 of 25 patients; 8 of 13 patients had central nervous system (CNS) relapse, 3 had local site progression, 1 had local relapse followed by abdominal relapse, and 1 died of an unknown cause. Ten of 25 study patients have died: 9 died because of disease progression and 1 of an unknown cause. Four of 25 patients were lost to follow-up: 2 before enucleation, 1 before radiotherapy, and 1 while on adjuvant chemotherapy. Three of 4 patients lost to follow-up did not have an event at the last visit.

PET/CT Protocol

PET/CT was used as an investigative modality in our study, and the PET/CT results were not used for staging, response assessment, or therapeutic decision making. Whole-body PET/CT was performed at baseline (PET/CT-1) and after completion of 3 cycles of neoadjuvant chemotherapy (PET/CT-2). PET/CT-2 was performed after a minimum of 4 wk after the third cycle of chemotherapy, which means 3–3.5 mo after treatment initiation.

The PET/CT scans were performed with a dedicated PET/CT scanner (Biograph 2; Siemens). Patients were kept fasting for at least 4-h before the PET/CT scan. Blood glucose less than 140 mg/dL was a prerequisite for performing the scan. ^{18}F-FDG was injected intravenously at a dose of 5.9–6.6 MBq/kg (0.16–0.18 mCi/kg; minimum, 3 mCi), 45–60 min before the scan, and patients rested in a quiet room. Triclofos (syrup pedicloryl, 500 mg/5 mL; Dr. Reddy's Lab, Hyderabad, India) (20–30 mg/kg orally) was given 30 min before the scan for sedation in children who could not cooperate with the PET/CT. CT images were acquired on a spiral dual-slice CT scanner, with a slice thickness of 4 mm and pitch of 1, using a matrix of 512 × 512 pixels and pixel size of 1 mm. Three-dimensional PET images were acquired for 2–3 min per bed position using a matrix of 128 × 128 pixels, with a slice thickness of 1.5 mm, after the CT images were acquired. CT-based attenuation correction of the emission images was used. PET images were reconstructed by iterative ordered-subset expectation maximization (2 iterations and 8 subsets). After CT acquisition, PET acquisition of the same axial range was started with the patient in the same position on the table. After completion of the PET acquisition, the reconstructed attenuation-corrected PET images, CT images, and fused images of matching pairs of PET and CT images were available for review in axial, coronal, and sagittal planes, as well as in maximum-intensity projections, 3-dimensional cine mode. In addition to the routine base-of-skull-to-mid-thigh acquisition, a spot view of head and neck regions was taken separately.

All 25 patients underwent PET/CT-1, and 21 of 25 (84%) patients underwent PET/CT-2 (2 patients died because of progressive disease and 2 patients were lost to follow-up before PET/CT-2).

PET/CT Interpretation

The PET/CT scans were reviewed prospectively by 2 qualified nuclear medicine specialists in consensus, who had more than 5 y of experience in reading PET/CT. The nuclear medicine specialists were unaware of the MRI findings. The areas of ^{18}F-FDG uptake were localized anatomically on nonenhanced CT. ^{18}F-FDG uptake was considered abnormal if there was an area of ^{18}F-FDG uptake greater than that of the mediastinal blood pool. Regions of interest were drawn over the tumor lesion for quantitative analysis. For calculating tumor maximum standardized uptake value (SUVmax), multiple

TABLE 1
Demographic Characteristics, IRSS Stage, PET/CT Findings, and Outcome in Study Patients

Patient no.	Age (y)	Sex	Standard staging (IRSS)	PET/CT staging (IRSS)	PET ON-1	SUV max1	SUV max2	Change in SUV (%)	PET response (EORTC)	Event	Outcome/ follow-up
1	2.5	M	IIIA	IIIB	No	1.2	0.5	58.33	PR	No	Alive at 24.3 mo
2	3	F	IIIA	IIIB	No	1.3	0.7	46.15	PD	Yes	Alive at 7.2 mo (lost to follow-up)
3	4	M	IIIA	IIIA	Yes	4.3	6.8	−58.14	PD	Yes	Died at 5.7 mo
4	2	F	IIIA	IIIB	No	1.4	NA	NA	NA	Yes	Alive at 21.2 mo
5	2	M	IIIA	IIIA	Yes	1.3	0.3	76.92	PR	Yes	Died at 11.0 mo
6	3	F	IIIA	IIIA	No	2	0	100	PD	Yes	Died at 15.7 mo
7	4	F	IIIA	IIIA	No	1.2	0	100	CR	Yes	Died at 11.2 mo
8	2	M	IIIA	IIIA	Yes	1.5	0	100	CR	Yes	Died at 13.8 mo
9	3	M	IIIA	IIIB	No	2	1.5	25	PR	No	Alive at 20.1 mo
10	3	M	IIIA	IIIA	No	1.7	0	100	CR	No	Alive at 19.8 mo
11	3	F	IIIA	IIIB	No	2.4	NA	NA	NA	No	Alive at 2.2 mo (lost to follow-up)
12	2	M	IIIA	IIIA	No	1.3	0.6	53.85	PR	Yes	Died at 12.3 mo
13	5	F	IIIA	IIIA	Yes	2.3	1.5	34.78	PR	No	Alive at 3.0 mo (lost to follow-up)
14	3	M	IIIA	IIIA	Yes	1.2	0.3	75	PD	Yes	Died at 5.3 mo
15	3	M	IIIA	IIIA	No	1.2	0.7	41.67	PR	No	Alive at 17.6 mo
16	4	M	IIIA	IIIA	No	1.4	0.5	64.29	PR	No	Alive at 17.0 mo
17	3	M	IIIA	IIIA	Yes	1.9	NA	NA	NA	Yes	Died at 9.8 mo
18	11	F	IIIA	IIIA	No	6.6	0.6	90.91	PR	No	Alive at 16.3 mo
19	12	M	IIIB	IIIA	No	1.9	0.3	84.21	PR	No	Alive at 16.1 mo (lost to follow-up)
20	4	M	IIIB	IIIB	Yes	4.5	0.5	88.89	PR	Yes	Alive at 14.9 mo
21	5	F	IIIA	IIIA	No	3.3	0.9	72.73	PR	No	Alive at 15.0 mo
22	6	F	IIIA	IIIA	No	3.4	0.6	82.35	PR	No	Alive at 14.9 mo
23	3	M	IIIA	IIIA	No	5.7	0.6	89.47	PR	No	Alive at 14.7 mo
24	2	M	IIIB	IIIA	No	3.2	0.5	84.38	PR	Yes	Died at 4.3 mo
25	2	M	IIIA	IIIA	Yes	4.1	NA	NA	NA	Yes	Died at 4.4 mo

PET ON-1 = optic nerve uptake on PET/CT at baseline; NA = not available.

circular regions of interest covering the tumor were drawn over the length of the tumor. The SUVmax calculation was done via the default method by body weight: SUV = mean region-of-interest activity (MBq/g)/injected dose (MBq)/body weight (g).

The difference in SUVmax for PET/CT-1 (SUVmax1 [SUVmax at baseline]) and PET/CT-2 (SUVmax2 [SUVmax after 3 cycles neoadjuvant chemotherapy]) was calculated using the formula ([SUVmax1 − SUVmax2]/SUVmax1) × 100.

Patients with PET/CT uptake limited to the orbital tumor and intraorbital part of the optic nerve were classified as having IRSS stage IIIA disease. Patients with uptake in the preauricular or cervical lymph nodes in addition to the orbital mass were classified as having IRSS stage IIIB disease. Patients with nonphysiologic uptake in sites other than those mentioned were diagnosed as having IRSS stage IV disease.

Response on PET/CT after 3 cycles of neoadjuvant chemotherapy was defined using the metabolic criteria of the European Organization for Research and Treatment of Cancer (EORTC) (*9*). Complete response (CR) was defined as a decrease in SUVmax by 100%, with no evidence of tumor metabolic activity. Partial response (PR) was defined as a decrease in SUVmax of more than 25% but less than 100%. Stable disease was defined as an increase or decrease in SUVmax by less than 25%. Progressive disease (PD) was defined as an increase in SUVmax by more than 25% or the appearance of a new nonphysiologic metabolically active lesion.

Statistical Analysis

Event-free survival (EFS) was defined as the time from presentation to disease progression clinically or on MRI or death due to any cause. OS was measured from the date of presentation to the date of death from any cause. Patients without an event or death were censored at the time of the last known follow-up or June 15, 2011. EFS and OS were calculated using Kaplan–Meier analysis along with 95% confidence interval (CI) and SE, and the difference between groups was analyzed using log-rank test. Exact symmetry testing was used to compare routine staging and PET/CT staging. A P value of 0.05 or less was considered significant. Mean, median, range, and SD were calculated for continuous variables. A receiver-operating-characteristic (ROC) curve was drawn to determine the cutoff value of SUVmax at which sensitivity and

specificity were highest. All data analyses were performed using the statistical software package STATA 9 (StataCorp).

RESULTS

Table 1 gives the demographic characteristics, staging, PET/CT findings, SUVs, and outcome of study patients. The median follow-up of study patients was 15.4 mo (mean, 13.4 mo; SD, ±5.9 mo; range, 2.2–24.3 mo). The EFS for study patients was 41.85% (95% CI, 21.3–61.3; SE, 10.7), and the OS for study patients was 53.03% (95% CI, 29.6–71.8; SE, 11.2) at a median follow-up of 15.4 mo.

Baseline PET Staging (PET/CT-1)

Twenty-two of 25 patients had IRSS stage IIIA disease, and 3 of 25 patients had IRSS stage IIIB disease per the routine staging work-up described at baseline. Three patients had a cervical or preauricular lymph node more than 1 cm at baseline, and all 3 had positive findings on lymph node FNAC and were therefore classified as having IRSS stage IIIB disease.

Five of 22 IRSS stage IIIA patients with clinically negative cervical lymph node involvement were found to have uptake in cervical lymph nodes on PET/CT-1, and 2 of 3 IRSS stage IIIB patients with pathologically confirmed cervical lymph node involvement did not show any uptake in the involved lymph nodes. The 5 patients with IRSS stage IIIA on routine staging but IRSS stage IIIB on PET/CT staging did not have cervical lymph node enlargement on follow-up. There was no significant discordance between routine staging and PET/CT staging ($P = 0.256$).

PET/CT and Bilateral Disease

Bilateral retinoblastoma was present in 5 of 25 (20%) patients at baseline. All 5 patients had intraocular retinoblastoma in the opposite eye, which was diagnosed on ophthalmoscopic examination and MRI. None of the intraocular tumors was visualized on PET/CT. Four of 5 patients with bilateral disease had clinical stage IIIA disease, and 1 had clinical stage IIIB disease. On PET/CT staging, 4 of 5 patients with bilateral disease had stage IIIA disease, and 1 had stage IIIB disease (not the same patient with clinical stage IIIB).

PET/CT Staging and Outcome

No significant difference was seen between IRSS stage IIIA and stage IIIB patients on routine staging for EFS ($P = 0.607$) and OS ($P = 0.876$) at a median follow-up of 15.4 mo (Table 2). Similarly, no significant difference was seen between IRSS stage IIIA and stage IIIB patients on PET/CT staging for EFS at a median follow-up of 15.4 mo ($P = 0.940$) (Table 2). However, there was a trend toward better OS in patients with IRSS stage IIIB than in patients with IRSS stage IIIA on PET/CT-1 ($P = 0.065$) at a median follow-up of 15.4 mo (Table 2).

Baseline SUVmax and Outcome

The mean SUVmax1 was 2.49 (median, 1.9; SD, ±1.51; range, 1.2–6.6). An SUVmax1 of 1.5 or less as determined by ROC analysis was taken as a cutoff value for EFS (sensitivity, 53.8%; specificity, 75%; area under ROC curve, 0.606) and OS (sensitivity, 50%; specificity, 66.67%; area

TABLE 2
EFS and OS Estimated by Kaplan–Meier Survival Analysis and Comparison Using Log-Rank Test

	EFS				OS			
Parameter (*n*)	EFS	SE	CI	*P**	OS	SE	CI	*P**
Overall (25)	41.85	10.7	21.3–61.3	NA	53.03	11.2	29.6–71.8	NA
Routine staging								
IIIA (22)	42.9%	11.6	20.4–63.6	0.607	51.1%	12.0	26.4–71.3	0.876
IIIB (3)	33.3%	27.2	0.9–77.4		66.7%	27.2	5.4–94.5	
PET/CT staging								
IIIA (19)	41.7%	12.4	18.1–63.8	0.940	41.6%	12.4	18.1–63.8	0.065
IIIB (6)	40.0%	21.9	5.2–75.3		100%	—	—	
SUVmax1								
≤1.5 (10)	30.0%	14.5	7.1–57.8	0.358	45.0%	16.6	13.9–72.4	0.687
>1.5 (15)	49.2%	15.4	18.5–74.2		55.4%	16.1	21.3–79.8	
Optic nerve uptake at baseline								
Yes (8)	0.0%	—	—	0.0001	14.3%	13.2	0.7–46.5	0.0009
No (17)	60.2%	12.9	31.2–80.1		71.4%	12.4	39.8–88.4	
PET/CT response								
CR/PR (17)	62.5%	12.1	34.9–81.1	0.042	68.7%	11.6	40.5–85.6	0.026
PD (4)	0.0%	—	—		0.0%	—	—	
SUVmax2								
≤0.5 (11)	36.4%	14.5	11.2–62.7	0.337	43.6%	15.5	14.7–69.9	0.236
>0.5 (10)	66.7%	15.7	28.2–87.8		76.2%	14.8	33.2–93.5	

n = number of patients; NA = not applicable.
*Log-rank test.

under ROC curve, 0.6). No significant difference in EFS ($P = 0.358$) or OS ($P = 0.687$) was seen for an SUVmax1 of 1.5 or less or an SUVmax1 of greater than 1.5 at a median follow-up of 15.4 mo (Table 2).

Optic Nerve Uptake at Baseline

Optic nerve uptake was seen in 8 of 25 (32%) study patients on PET/CT-1. Patients with optic nerve uptake on PET/CT-1 had lower EFS (0% vs. 60.2%, $P = 0.0001$) (Fig. 1A) and OS (14.3% vs. 71.4%, $P = 0.0009$) (Fig. 1B) than patients without optic nerve uptake at a median follow-up of 15.4 mo (Table 2). Overall, 8 of 25 patients developed CNS relapse on follow-up, of which 5 had optic nerve uptake on PET/CT-1.

On follow-up 5 of the 8 patients with optic nerve uptake developed CNS relapse, 1 developed local progression, 1 developed abdominal metastasis, and 1 was lost to follow-up. MRI showed optic nerve involvement in 6 of the 8 patients with optic nerve uptake on PET/CT-1. The 2 patients with optic nerve uptake on PET/CT-1 but with no evidence of optic nerve involvement on MRI died because of CNS relapse.

PET/CT-2 SUVmax and Outcome

The mean SUVmax2 was 0.82 (median, 0.5; SD, ±1.42; range, 0–6.8). The mean change in SUVmax (SUVmax1 − SUVmax2) was 1.67 (median, 1.2; SD, ±1.8; range, −2.5–6). An SUVmax2 of 0.5 or less as determined by ROC curve analysis was taken as the cutoff value for EFS (sensitivity, 70%; specificity, 63.6%; area under the ROC curve, 0.686) and OS (sensitivity, 75%; specificity, 61.4%; area under the ROC curve, 0.736). No significant difference in EFS ($P = 0.337$) or OS ($P = 0.236$) was seen for an SUVmax2 of 0.5 or less or an SUVmax2 of greater than 0.5 (Table 2).

PET/CT-2 Response Assessment

Reduction in extraocular tumor mass was seen clinically in all patients after neoadjuvant chemotherapy. Of the 21 patients who underwent PET/CT-2, per EORTC criteria, CR was seen in 3 (14.3%), PR in 14 (66.7%), stable disease in 0 (0%), and PD in 4 (19%). A decrease in the SUVmax of the orbital mass was seen in 20 of the 21 (95.2%) patients, and 1 patient had an increase in SUVmax after

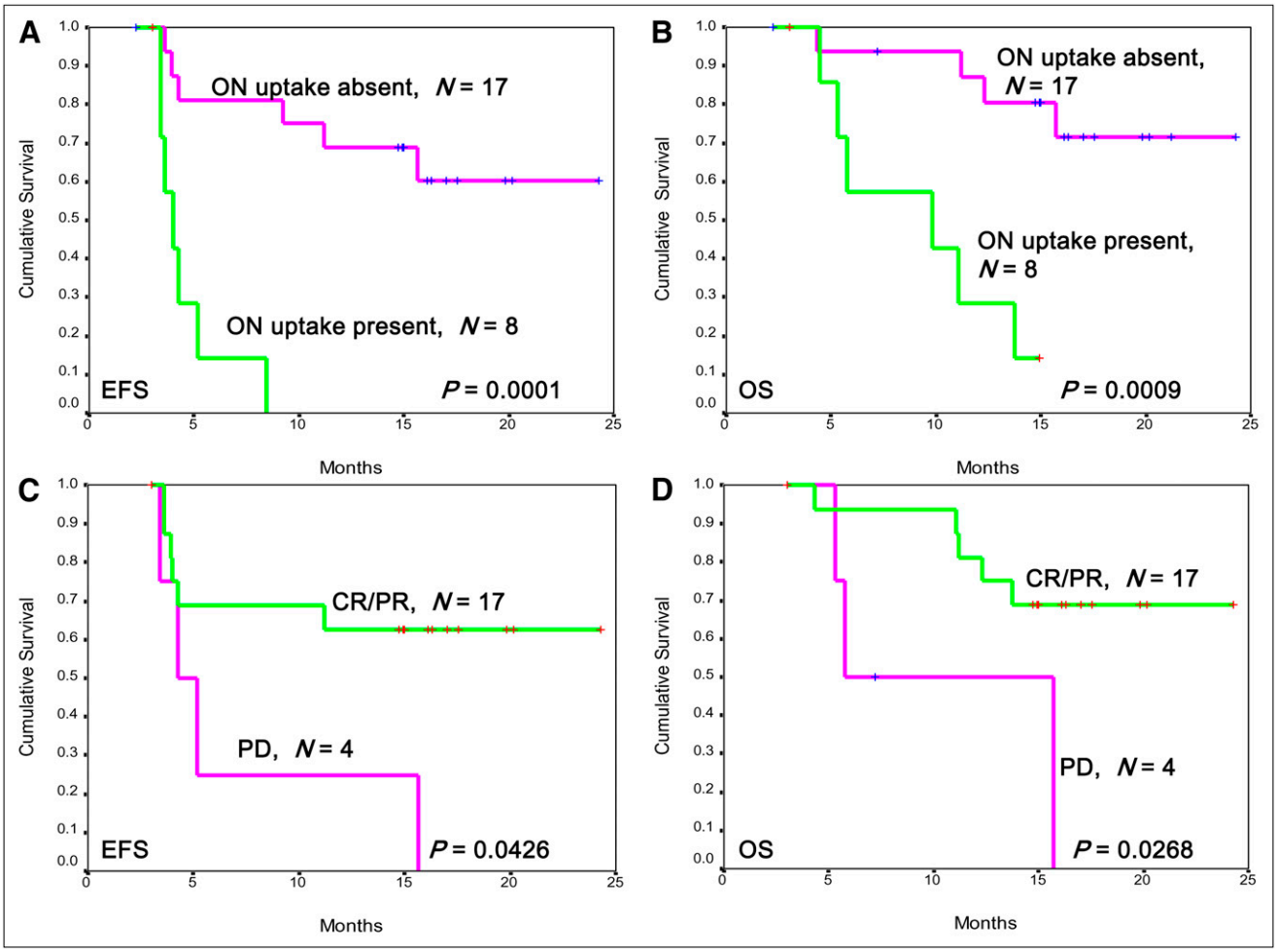

FIGURE 1. Kaplan–Meier survival curves depicting EFS and OS: EFS for PET/CT optic nerve uptake at baseline (A), OS for PET/CT optic nerve uptake at baseline (B), EFS for PET/CT response to neoadjuvant chemotherapy (C), and OS for PET/CT response to neoadjuvant chemotherapy (D). ON = optic nerve.

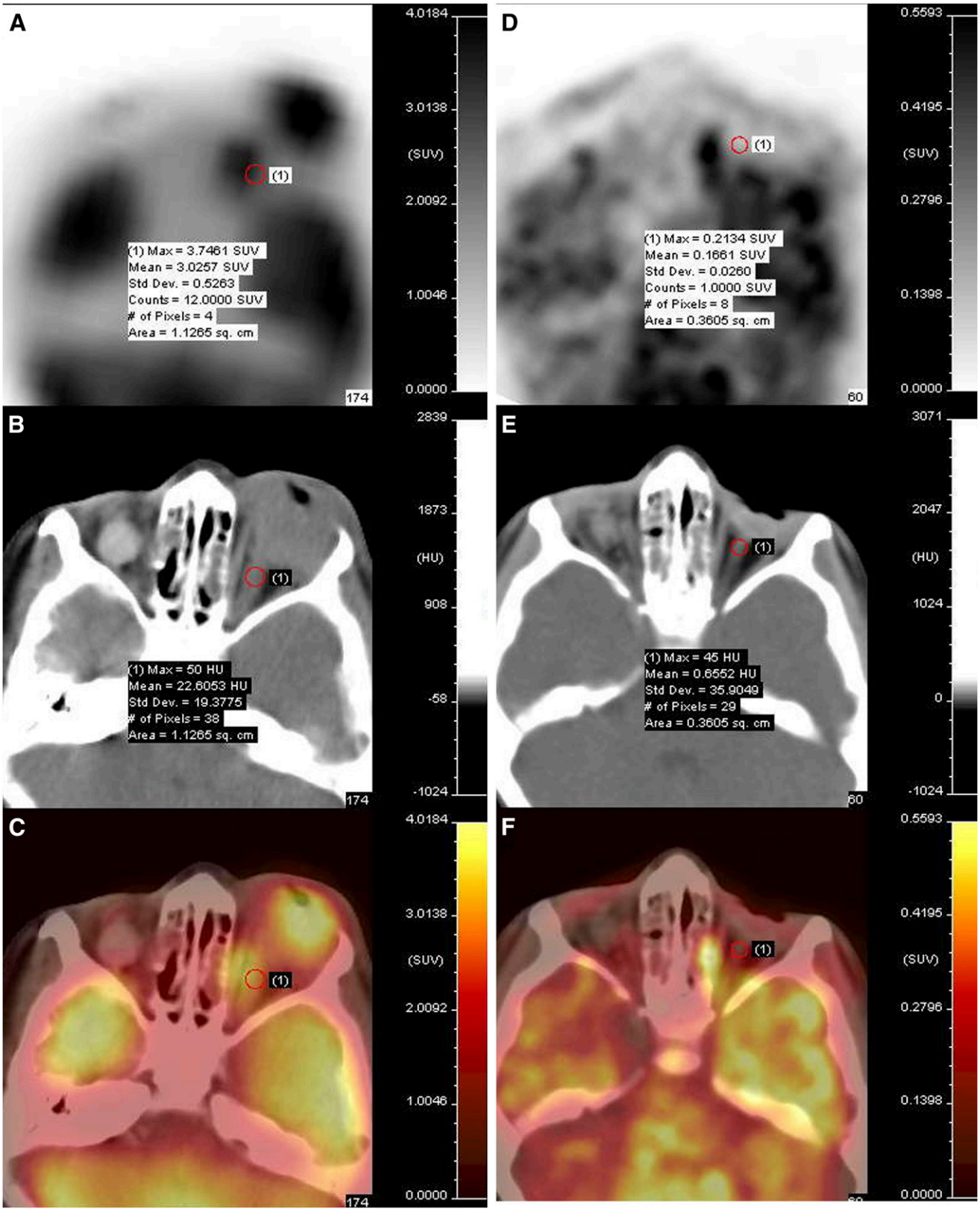

FIGURE 2. Baseline PET, CT, and fused PET/CT images (A–C) showing prosthesis in right eye and large extraocular tumor in left eye, with optic nerve thickening and uptake. After 3 cycles of neoadjuvant chemotherapy, PET, CT, and fused PET/CT images (D–F) show decrease in size of left orbital tumor and optic nerve uptake. Patient died because of brain metastases. Poor anatomic correlation of nasal or paranasal ^{18}F-FDG uptake is due to misregistration of medial rectus muscle ^{18}F-FDG uptake, which is physiologic.

neoadjuvant chemotherapy (patient 3). Three of 4 patients (patients 2, 6, and 14) with PD had a decrease in the SUVmax of the orbital mass; however, they had new metabolically active lesions. Patient 2 had uptake in multiple bilateral cervical, axillary, and mediastinal lymph nodes; patient 6 had bilateral cervical and mediastinal lymph node uptake; and patient 14 had bilateral uptake in multiple cervical lymph nodes. Patient 3 also had the appearance of metabolically active relapse in the opposite eye, which had been previously enucleated for intraocular disease and bilateral cervical and left axillary lymph nodes in addition to an increase in SUVmax after neoadjuvant chemotherapy. Optic nerve uptake was not seen in any patient on PET/CT-2.

PET/CT-2 Response and Outcome

The EFS for patients with response (CR and PR) versus patients with PD on PET/CT-2 was 62.5% (95 % CI, 34.9–81.1; SE, 12.1) and 0%, respectively, at a median follow-up of 15.4 mo ($P = 0.042$) (Fig. 1C). The OS for patients with response (CR and PR) versus patients with PD was 68.7% (95 % CI, 40.5–85.6; SE, 11.6) and 0%, respectively, at a median follow-up of 15.4 mo ($P = 0.026$) (Fig. 1D).

Figure 2 shows CT, PET, and PET/CT images of patient 3 at baseline (Figs. 2A–2C) and after 3 cycles of neoadjuvant chemotherapy (Figs. 2D–2F).

The sensitivity, specificity, positive predictive value, and negative predictive value of PET/CT-2 response for event and outcome are given in Table 3. PET/CT-2 response had high specificity but low sensitivity for predicting EFS and OS.

DISCUSSION

The role of PET/CT in pediatric cancers, unlike in many adult cancers, remains investigational (*10*). PET/CT, compared with contrast-enhanced CT and MRI, of the orbit and brain has the potential to detect additional metastatic sites and thereby upstage retinoblastoma patients. In our study, no patient had IRSS stage IV disease using PET/CT staging. PET/CT was falsely negative in 2 of 3 IRSS stage IIIB patients because these 2 patients had FNAC-proven disease in their lymph node. We did not perform FNAC for the 5 patients who were upstaged on PET/CT from IRSS stage IIIA to IRSS stage IIIB because they did not have clinically significant lymph node enlargement on follow-up. In advanced retinoblastoma, there was no significant difference between PET/CT staging and routine staging. Similarly, there was no significant difference in EFS and OS between routine staging and PET/CT staging. However, there was a trend toward better OS in patients who had IRSS stage IIIB on PET/CT ($P = 0.065$). The trend toward better OS in patients with IRSS stage IIIB disease, when compared with IRSS stage IIIA, on PET/CT may not be a true reflection. Five of 6 patients with stage IIIB on PET/CT were falsely upstaged using this modality as they had had no clinical lymph node enlargement. The false-positive lymph node uptake on PET/CT in these patients may have been due to upper respiratory tract infections, which are common in children less than 5 y of age.

Moll et al. examined the role of ^{18}F-FDG in 4 intraocular retinoblastoma patients who underwent primary enucleation; they found uptake in 2 of 4 patients (*6*). They opined that ^{18}F-FDG PET may not have a role in retinoblastoma (*6*). In our study, 5 of 25 patients had bilateral retinoblastoma, with IRSS stage III retinoblastoma in one eye and intraocular retinoblastoma in the opposite eye. Intraocular retinoblastoma was not metabolically active in any of the 5 patients, and thus it appears that PET/CT does not have a role in intraocular retinoblastoma. The number of patients with bilateral disease is too small to do a meaningful subgroup analysis for survival or discordance between clinical and PET/CT staging for patients with bilateral disease.

An interesting observation in our study was that patients with optic nerve uptake on baseline PET/CT had significantly inferior EFS and OS; in fact, all patients with optic nerve involvement progressed, and OS was only 14%. CNS is the

TABLE 3
Sensitivity, Specificity, PPV, and NPV for PET/CT Response After Neoadjuvant Chemotherapy to Predict EFS and OS

Outcome PET/CT	Relapse	Disease-free	Total	Sensitivity	Sensitivity, 95% CI	Specificity	Specificity, 95% CI	PPV	PPV, 95% CI	NPV	NPV, 95% CI
EFS				4/10 (40.0)	17.5–40.0	11/11 (100)	79.5–100	4/4 (100)	43.7–100	11/17 (64.7)	51.5–64.7
PD	4	0	4								
CR/PR	6	11	17								
Total	10	11	21								
OS				3/8 (37.5)	12.0–49.3	12/13 (92.3)	76.6–99.6	3/4 (75.0)	23.9–98.7	12/17 (70.6)	58.6–76.2
PD	3	1	4								
CR/PR	5	12	17								
Total	8	13	21								

PPV = positive predictive value; NPV = negative predictive value.
Data in parentheses are percentages.

most common site of metastasis in retinoblastoma, and metastasis to CNS occurs through the optic nerve (*1,5*). Five of the 8 study patients who developed CNS metastasis on follow-up had optic nerve uptake on PET/CT at baseline. Therefore, optic nerve uptake at baseline PET/CT suggests these patients have a high potential for developing metastatic disease.

Bone scans are routinely obtained as a part of the baseline staging work-up in locally advanced retinoblastoma to detect bone metastasis. PET/CT scans have higher sensitivity than bone scans to detect bone metastasis (*11*). Therefore, PET/CT at baseline can probably replace bone scans for the staging work-up of locally advanced retinoblastoma, with the added advantage of baseline prognostication.

Clinical, pathologic, and radiologic risk factors and response criteria in IRSS stage III patients treated with neoadjuvant chemotherapy have not been identified. There are no standard radiologic or pathologic criteria to assess response to neoadjuvant chemotherapy in IRSS stage III retinoblastoma.

Response Evaluation Criteria in Solid Tumors (RECIST) are the most widely accepted criteria to define chemotherapy response in solid tumors (*12*). RECIST are based on CT findings. The use of MRI for assessing response per RECIST is controversial and difficult in retinoblastoma because the tumor is not easily measurable because of the spheric nature of the ocular globe, multifocal nature of the disease, and difficulty in assessing and measuring optic nerve involvement.

The present study showed that EORTC criteria for PET/CT response significantly predicted EFS and OS (Table 1) and are highly specific (Table 2). Significant clinical reduction in the proptotic mass was seen in all patients after receiving neoadjuvant chemotherapy. This finding is corroborated by the PET/CT finding of a decrease in SUVmax in 21 of 22 patients. Three of 4 patients who had PD after neoadjuvant chemotherapy showed a decrease in SUVmax, suggesting primary tumor response; however, their diagnosis of PD was based on the appearance of new metabolically active lesions. Also, none of the 21 patients had optic nerve uptake on PET/CT-2. This observation is significant, because it suggests that progression in stage III retinoblastoma can occur despite a good response in the primary site.

Survival rates in extraocular retinoblastoma over the last 2 decades have improved from less than 20% to 60%–70% with the advent of multimodality management. Therapeutic options for most patients who progress or relapse are limited; however, some patients with relapsed or metastatic disease can be effectively treated with autologous stem cell transplantation (*13,14*). At baseline, PET/CT can identify patients at high risk for relapse, and similarly during response assessment PET/CT can identify disease progression before it manifests clinically. These patients can therefore be offered autologous stem cell transplantation up front or during early relapse, thereby improving their outcomes.

In IRSS stage III retinoblastoma, the current practice is to do either CT or MRI of the orbit and brain for response assessment. CT or MRI of the orbit and brain can miss non-CNS metastasis, unlike PET/CT, and it is likely that good response of the primary tumor on CT or MRI can still be associated with poor outcome due to distant metastasis, as was observed with PET/CT in our study. Our study did not compare PET/CT response against MRI response, because we feel that these 2 modalities are complementary and because the response assessment by MRI in IRSS stage III disease is not the gold standard and has its own limitations.

CONCLUSION

The present study prospectively evaluated the role of PET/CT in retinoblastoma. Optic nerve uptake at baseline of PET/CT and response after neoadjuvant chemotherapy according to EORTC criteria was a strong predictor of EFS and OS in IRSS stage III retinoblastoma. Therefore, PET/CT may play a role in baseline prognostication and response assessment in IRSS stage III retinoblastoma.

DISCLOSURE STATEMENT

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

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REFERENCES

1. Honavar SG, Singh AD. Management of advanced retinoblastoma. *Ophthalmol Clin North Am.* 2005;18:65–73.
2. Bakhshi S, Meel R, Mohanti BK, Hasan Naqvi SG. Treatment and outcome of nonmetastatic extraocular retinoblastoma with a uniform chemotherapy protocol. *J Pediatr Hematol Oncol.* 2010;32:e42–e45.
3. 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;52:218–222.
4. Chantada G, Doz F, Antoneli CB, et al. A proposal for an international retinoblastoma staging system. *Pediatr Blood Cancer.* 2006;47:801–805.
5. Chintagumpala M, Chevez-Barrios P, Paysse EA, Plon SE, Hurwitz R. Retinoblastoma: review of current management. *Oncologist.* 2007;12:1237–1246.
6. Moll AC, Hoekstra OS, Imhof SM, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography (PET) to detect vital retinoblastoma in the eye: preliminary experience. *Ophthalmic Genet.* 2004;25:31–35.
7. Canturk S, Qaddoumi I, Khetan V, et al. Survival of retinoblastoma in less-developed countries impact of socioeconomic and health-related indicators. *Br J Ophthalmol.* 2010;94:1432–1436.
8. Chantada GL, Qaddoumi I, Canturk S, et al. Strategies to manage retinoblastoma in developing countries. *Pediatr Blood Cancer.* 2011;56:341–348.
9. Young H, Baum R, Cremerius U, et al. Measurement of clinical and subclinical tumour response using (^{18}F)-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. *Eur J Cancer.* 1999;35:1773–1782.
10. Lucignani G, De Palma D. PET/CT in paediatric oncology: clinical usefulness and dosimetric concerns. *Eur J Nucl Med Mol Imaging.* 2011;38:179–184.
11. Cheran SK, Herndon JE, 2nd, Patz EF Jr. Comparison of whole-body FDG-PET to bone scan for detection of bone metastases in patients with a new diagnosis of lung cancer. *Lung Cancer.* 2004;44:317–325.
12. 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;45:228–247.
13. Palma J, Sasso DF, Dufort G, et al. Successful treatment of metastatic retinoblastoma with high-dose chemotherapy and autologous stem cell rescue in South America. *Bone Marrow Transplant.* May 23, 2011 [Epub ahead of print].
14. Dunkel IJ, Aledo A, Kernan NA, et al. Successful treatment of metastatic retinoblastoma. *Cancer.* 2000;89:2117–2121.