Validation of Postinduction Curie Scores in High-Risk Neuroblastoma: A Children's Oncology Group and SIOPEN Group Report on SIOPEN/HR-NBL1

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A semiquantitative ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scoring method (the Curie score, or CS) was previously examined in the Children's Oncology Group (COG) high-risk neuroblastoma trial, COG A3973, with a postinduction CS of more than 2 being associated with poor event-free survival (EFS). The validation of the CS in an independent dataset, International Society of Paediatric Oncology European Neuroblastoma/High-Risk Neuroblastoma 1 (SIOPEN/HR-NBL1), is now reported. **Methods:** A retrospective analysis of ^{123}I-MIBG scans obtained from patients who had been prospectively enrolled in SIOPEN/HR-NBL1 was performed. All patients exhibited ^{123}I-MIBG–avid, International Neuroblastoma Staging System stage 4 neuroblastoma. ^{123}I-MIBG scans were evaluated at 2 time points, diagnosis ($n = 345$) and postinduction ($n = 330$), before consolidation myeloablative therapy. Scans of 10 anatomic regions were evaluated, with each region being scored 0–3 on the basis of disease extent and a cumulative CS generated. Cut points for outcome analysis were identified by Youden methodology. CSs from patients enrolled in COG A3973 were used for comparison. **Results:** The optimal cut point for CS at diagnosis was 12 in SIOPEN/HR-NBL1, with a significant outcome difference by CS noted (5-y EFS, 43.0% ± 5.7% [CS ≤ 12] vs. 21.4% ± 3.6% [CS > 12], $P < 0.0001$). The optimal CS cut point after induction was 2 in SIOPEN/HR-NBL1, with a postinduction CS of more than 2 being associated with an inferior outcome (5-y EFS, 39.2% ± 4.7% [CS ≤ 2] vs. 16.4% ± 4.2% [CS > 2], $P < 0.0001$). The postinduction CS maintained independent statistical significance in Cox models when adjusted for the covariates of age and *MYCN* gene copy number. **Conclusion:** The prognostic significance of postinduction CSs has now been validated in an independent cohort of patients (SIOPEN/HR-NBL1), with a postinduction CS of more than 2 being associated with an inferior outcome in 2 independent large, cooperative group trials.

Key Words: neuroblastoma; MIBG; Curie score

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Despite a multimodality approach combining chemotherapy, surgical resection, radiotherapy, autologous stem cell transplantation, and biotherapy, survival for high-risk neuroblastoma remains poor, with a 5-y event-free survival (EFS) of 30%–49% (*1–3*). The use of the anti-GD2 chimeric antibody (ch14.18, dinutuximab [Unituxin; United Therapeutics Corp.]) after transplantation in combination with granulocyte–macrophage colony-stimulating factor and intravenous interleukin-2 has led to improvements in EFS (*4*). For patients who develop relapsed disease, specifically those who relapse 6–18 mo from initial diagnosis, 5-y overall survival (OS) is less than 20% (*5*). The identification of prognostic markers of response and survival early in a patient's treatment may have a significant impact on therapy and outcome.

Metaiodobenzylguanidine (MIBG) is a guanethidine analog that has been used as a diagnostic imaging agent for neuroblastoma for over 30 y (*6–9*). Uptake is well described in marrow, osseous sites, and soft-tissue sites of disease. In 1995, a MIBG scoring system was developed to semiquantify the extent of MIBG uptake within individual patients and to serve as an imaging biomarker for outcome prediction (*10*). The role of semiquantitative MIBG scoring

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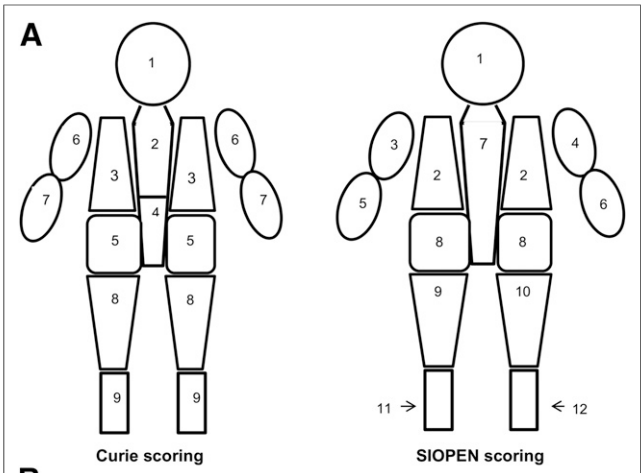

Region	Anatomic site	Curie score
1	Head	3
2	Cervical thoracic spine	3
3	Chest (ribs, sternum, scapula)	2
4	Lumbosacral spine	3
5	Pelvis	3
6	Proximal arms	3
7	Distal arms	1
8	Proximal lower extremities	3
9	Distal lower extremities	3
10	Soft Tissue	1
Total		25

FIGURE 1. (A) Anatomic regions for CS and SIOPEN score. Body is divided into 9 (CS) or 12 (SIOPEN score) skeletal regions, with CS adding 10th (soft-tissue) region. (B) Example of CS of individual patient: diffuse uptake (CS, 3) is noted in head, cervical-thoracic spine, lumbar-sacral spine, pelvis, proximal arms, proximal lower extremities, distal lower extremities, and chest (CS, 2). There is one ^{123}I-MIBG–avid soft-tissue site, involving $<$ 50% abdomen (CS, 1). Total CS = 25.

as a prognostic indicator for high-risk neuroblastoma has now been reported in both institutional and cooperative group trials, including trials within the Children's Oncology Group (COG) and the International Society of Paediatric Oncology European Neuroblastoma (SIOPEN) Research Network (*10–20*). In particular, the presence of MIBG-avid disease after induction has correlated with extremely poor EFS and OS after consolidation therapy, including high-dose chemotherapy with autologous stem cell transplantation (*11,14–20*). Likewise, MIBG scores at diagnosis have been prognostic in SIOPEN high-risk neuroblastoma studies (*20*). Scan type, ^{131}I versus ^{123}I MIBG, has not affected outcome predictions, either at diagnosis or after induction (*21*).

Two MIBG scoring methods are now commonly used, the Curie score (CS) and the SIOPEN score (*14,19,20*). The 2 scoring methods subdivide the skeleton into 9 (CS) or 12 (SIOPEN score) regions (Fig. 1), with CS adding a tenth region for evaluating soft-tissue disease in both primary and metastatic sites. Scores from each region (ranging from 0 to 3) are summed to determine a cumulative CS (or SIOPEN score). The CS method has been adapted for use in COG trials, including the high-risk neuroblastoma trial, COG A3973 (*22*). The SIOPEN score has been adapted for use in SIOPEN high-risk neuroblastoma trials, including the recent International Society of Pediatric Oncology European Neuroblastoma/High-Risk Neuroblastoma 1 (SIOPEN/HR-NBL1).

For patients treated in COG A3973, a postinduction CS of more than 2 was associated with an inferior outcome, when compared with patients with a CS of 2 or less after induction (5-y EFS, 10.5% ± 10.0% vs. 42.0% ± 5.8%, $P < 0.0001$) (*19*). Furthermore, a postinduction CS of more than 2 identified patients at high risk for an event in COG A3973, independent of other known prognostic factors, including age, *MYCN* (v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog) status, ploidy, and histologic grade (*19*).

We now report the prognostic value of the CS of ^{123}I-MIBG scans at diagnosis and at the end of induction for patients treated in the European high-risk trial (SIOPEN/HR-NBL1), with subsequent comparisons to an independent cohort of patients treated in the COG high-risk neuroblastoma protocol, COG A3973. The current study validates the role of CS as a prognostic marker of response and survival in a large, independent dataset of patients with ^{123}I-MIBG–avid, stage 4, newly diagnosed high-risk neuroblastoma.

MATERIALS AND METHODS

Patient Population

Three hundred forty-five patients with newly diagnosed stage 4, high-risk neuroblastoma (per International Neuroblastoma Staging System) (*23*) who were enrolled in SIOPEN/HR-NBL1 and had ^{123}I-MIBG–avid disease at diagnosis were examined (Table 1; Fig. 2). Determining the prognostic value of ^{123}I-MIBG scoring was a stated aim of SIOPEN/HR-NBL1, with scoring performed retrospectively, examining ^{123}I-MIBG scans obtained at diagnosis ($n = 345$) and after induction ($n = 330$).

Treatment

SIOPEN/HR-NBL1 (NCT00030719) is a randomized, multicenter study for patients less than 21 y old with biopsy-proven high-risk neuroblastoma (patient enrollment, 2002–2010) (*3*). Inclusion criteria were stage 2–4 disease with *MYCN* amplification (any age) or stage 4

TABLE 1
Characteristics at Diagnosis in Patients with ^{123}I-MIBG–avid, Stage 4 Disease

Characteristic	*n*
Total patients	345
Sex	
Male	212 (61%)
Female	133 (39%)
Age	
Median age	2.9 (range, 0.2%–16.1%)
Age $<$ 18 mo	48 (14%)
Age $\geq$ 18 mo	297 (86%)
MYCN status	
Amplified	122 (35%)
Nonamplified	182 (53%)
Unknown	41 (12%)
ASCT	261 (76%)
Chimeric antibody	23 (7%)

ASCT = autologous stem cell transplantation, which was performed if patient was in CR/PR with $\leq$ 3 ^{123}I-MIBG–avid sites and $>$ 50% reduction of ^{123}I-MIBG–avid osseous lesions.

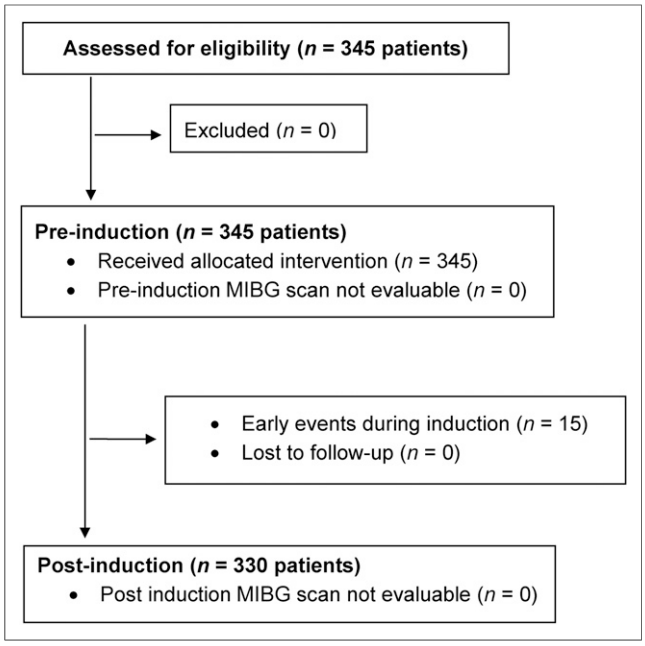

FIGURE 2. CONSORT (consolidated standards of reporting trials) diagram: CS analysis of SIOPEN/HR-NBL1.

disease in patients older than 1 y. Only the cohort with ^{123}I-MIBG–avid stage 4 disease was used for the current evaluation. Therapy on SIOPEN/HR-NBL1 included 8 cycles of an intensively timed induction regimen (Rapid COJEC, which consisted of repetitive courses of vincristine-carboplatin-etoposide [cycle A], vincristine-cisplatin [course B], and vincristine-etoposide-cyclophosphamide [course C]), surgical resection of residual disease (after induction) followed by ^{123}I-MIBG scanning, high-dose chemotherapy with autologous stem cell transplantation, local radiotherapy, and subsequent maintenance therapy with isotretinoin, as previously published (Fig. 3) (*2,3,24,25*). Immunotherapy with an anti-GD2 monoclonal antibody (ch14.18) with or without subcutaneous interleukin-2 was given to patients enrolled from 2007 onward. Only patients in complete (CR) or partial remission (PR) with no more than 3 ^{123}I-MIBG–avid sites on completion of induction and more than a 50% reduction in ^{123}I-MIBG–avid osseous lesions were eligible to proceed to autologous stem cell transplantation. Patients who failed to meet these criteria received 2 additional courses of topotecan, vincristine, and doxorubicin before high-dose chemotherapy, and surgery was postponed until a better metastatic response was achieved. Transplantation was performed using either a busulfan-melphalan or a carboplatin-etoposide-melphalan conditioning regimen. Written informed consent (approved by local ethics boards) was obtained from patients (or legal guardians) before entry into SIOPEN/HR-NBL1. The trial was registered at Clinicaltrials.gov (NCT00030719, SIOP-Europe-HR-NBL-1, CDR0000069191, ESIOP, EU-20148) and at EudraCT (2006-001489-17).

CS Determinations

CS was determined from diagnostic ^{123}I-MIBG scans as previously reported (*14,19*). Planar images were acquired 24 h after administration of ^{123}I-MIBG, with scans obtained at diagnosis and after induction (before surgery). Patient scans were evaluated for ^{123}I-MIBG avidity at 10 different sites (*19*). Skeletal sites were individually scored 0–3 (0, no ^{123}I-MIBG–avid lesions; 1, one ^{123}I-MIBG–avid lesion; 2, more than one ^{123}I-MIBG–avid lesion; and 3, ^{123}I-MIBG uptake in >50% of an individual skeletal site). Soft-tissue lesions were also scored 0–3 (0, no ^{123}I-MIBG involvement; 1, one ^{123}I-MIBG–avid soft-tissue lesion; 2, more than one ^{123}I-MIBG–avid soft-tissue lesion in one or more regions; and 3, ^{123}I-MIBG avidity in a soft-tissue lesion that occupied >50% of the chest or abdomen). Both the primary and the metastatic soft-tissue lesions were included to create a composite soft-tissue score. A patient's overall CS was calculated as the sum of scores over all 10 individual sites, with a maximum possible CS of 30. The ^{123}I-MIBG scans were centrally reviewed by 4 pediatric nuclear medicine physicians from the COG diagnostic imaging committee, with reviewers masked to clinical or radiographic reports. The reviewers scored each scan as a collective group, to establish a consensus CS for each case. Two of the 4 reviewers had previously reviewed all ^{123}I-MIBG scans from COG A3973 (*19*).

Statistical Analysis

Patients were categorized by CS (0 vs. >0; ≤optimum cutoff vs. >optimum cutoff) and compared with respect to survival (EFS and OS) at each time point. The optimum cutoff was determined by maximizing the Youden index with respect to how well the CS differentiated patients who had and did not have an event. The Youden index is the maximum of [sensitivity + specificity − 1] over all threshold values (0–30) of the CS (*26,27*). Survival comparisons were drawn at each individual site by score (0 vs. >0 only). The percentage change in CS from diagnosis to postinduction scan for patients with both sets of ^{123}I-MIBG scan readings was stratified on the basis of score reduction (≥50% reduction vs. <50%, and ≥75% reduction vs. <75%), with survival compared between groups.

For EFS, time to event was defined as the time from diagnosis until the time of first occurrence of relapse, progressive disease, secondary malignancy, or death or until the time of last contact if no event occurred. Patients who were alive without an event were censored at the last known date of contact. For OS, death was the only event considered. After induction, time to event was calculated from the date of the postinduction ^{123}I-MIBG scan. Patients who had an event between the date of diagnosis and the date of postinduction ^{123}I-MIBG scan (n = 15) were considered to have gone off-study and hence were not included in the analysis after induction. Survival was analyzed using the methods of Kaplan and Meier, with standard errors per the methods of Peto et al. (*28,29*). Survival curves were compared using a log-rank test. Cox proportional hazards models with the Efron model of handling tied events were fit to determine the CS cutoff at which the hazard ratio was maximized, as well as the prognostic strength for survival of the CS in the presence of age (<18 mo vs. ≥ 18 mo) and *MYCN* gene copy number (nonamplified vs. amplified). P values of less than 0.05 were considered statistically significant.

RESULTS

Three hundred forty-five patients had ^{123}I-MIBG scans available at diagnosis, with postinduction scans available in 330 patients and

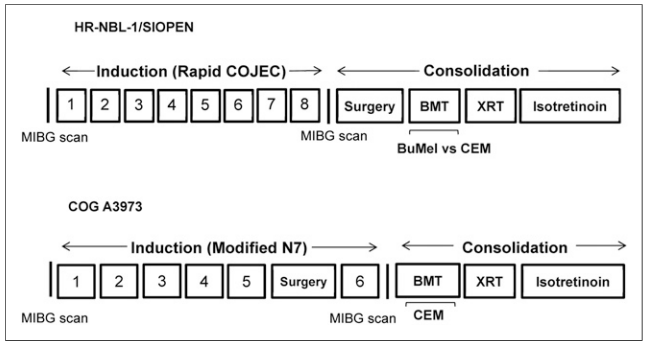

FIGURE 3. Schematic overview of SIOPEN/HR-NBL1 (*2*) and COG A3973 (*22*) therapy. Biotherapy = isotretinoin ± anti-GD2 chimeric antibody; BMT = bone marrow transplant; BuMel = busulfan-melphalan; CEM = carboplatin-etoposide-melphalan; XRT = radiotherapy.

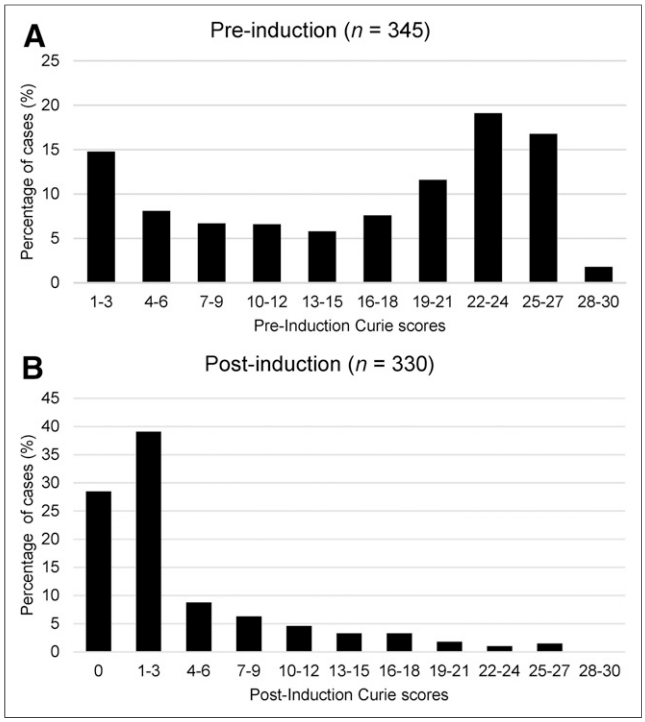

FIGURE 4. Distribution of CSs at (A) diagnosis, and (B) after induction.

both sets of images evaluable in 329 patients (Table 1). The median CS at diagnosis was 19 (range, 1–30), with 149 patients (43.2%) exhibiting a CS of more than 20 at diagnosis (Fig. 4A). The median score after induction was 1.5 (range, 0–27), with only 14 patients (4.2%) exhibiting a CS of more than 20 at that time point (Fig. 4B). Seventy-six percent of patients in the SIOPEN/HR-NBL1 cohort underwent myeloablative therapy according to SIOPEN/HR-NBL1 guidelines.

CS at Diagnosis and Outcome

The 5-y EFS and OS for the 345 patients with ^{123}I-MIBG scan reviews at diagnosis were 29.3% ± 3.2% and 40.5% ± 3.4%, respectively. The optimal cut point for analyses, as determined by the Youden index, was a CS of 12. Five-year EFS was 43.0% ± 5.7% for patients with a CS of no more than 12 (n = 126), versus 21.4% ± 3.6% for those with a score of more than 12 (n = 219) at diagnosis, $P < 0.001$ (Table 2; Fig. 5). Differences in OS were likewise noted, with a 5-y OS of 53.9% ± 5.6% versus 32.7% ± 4.0% for patients with a CS of 12 or less versus more than 12, respectively (P = 0.001). The Cox proportional hazards model found CS to be predictive of EFS and OS after adjusting for *MYCN* and age. Patients with a CS of more than 12 had an increased risk of an event and death of 1.802 and 1.765, respectively.

The median soft-tissue score (region 10) at diagnosis was 1 (range, 0–3), with 34 patients (9.9%) exhibiting no ^{123}I-MIBG–avid soft-tissue disease at diagnosis and 35 patients (10.1%) exhibiting avidity in more than 1 soft-tissue site. The presence of ^{123}I-MIBG–avid soft-tissue disease at diagnosis did not affect EFS, with 5-y EFS of 29.2% ± 3.3% versus 29.4% ± 10.1% for patients with versus without ^{123}I-MIBG–avid soft-tissue disease, respectively, at that time point (P = 0.64).

MYCN status was available in 304 (88.1%) of the 345 patients, with *MYCN*-amplified disease present in 122 cases and *MYCN*-nonamplified disease present in 182. Patients with a CS of more than 12 at diagnosis had inferior survival, independent of *MYCN* status. For patients with *MYCN*-amplified disease, a significant outcome difference existed by CS at diagnosis, with 5-y EFS of 39.3% ± 7.9% (CS ≤ 12) versus 19.1% ± 8.6% (CS > 12) (P = 0.013). For patients with *MYCN*-nonamplified disease, a significant outcome difference likewise existed by CS, with 5-y EFS of 42.8% ± 9.0% (CS ≤ 12) versus 23.4% ± 4.5% (CS > 12) (P = 0.008).

Postinduction CS and Outcome

The 5-y EFS and OS for the 330 patients with ^{123}I-MIBG scans after induction were 30.1% ± 3.4% and 40.6% ± 3.5%, respectively. The optimum cut point after induction was a CS of 2. In addition, Cox proportional hazards models indicated that a CS of 2 after induction corresponded to the largest significant hazard ratio (1.710; 95% confidence interval, 1.314–2.226) when compared with other potential cut points. Patients with a CS of 2 or less (n = 198, 60%) after induction had significantly better 5-y EFS than patients with a CS of more than 2 (n = 132) (39.2% ± 4.7%

TABLE 2
EFS and OS by CS at Diagnosis and After Induction, and Percentage Reduction in CS

CS	*n*	5-y EFS ± SE (%)	EFS *P*	5-y OS ± SE (%)	OS *P*
At diagnosis					
≤12	126 (37%)	43.0 ± 5.7		53.9 ± 5.6	
12	219 (63%)	21.4 ± 3.6	<0.001	32.7 ± 4.0	0.001
After induction					
≤2	198 (60%)	39.2 ± 4.7		48.0 ± 4.7	
2	132 (40%)	16.4 ± 4.2	<0.001	29.5 ± 5.1	<0.001
Reduction					
≥50%	251 (76%)	31.8 ± 3.9		40.6 ± 4.0	
50%	78 (24%)	25.3 ± 6.9	0.65	41.6 ± 7.5	0.91
≥75%	204 (62%)	32.3 ± 4.4		41.2 ± 4.5	
75%	125 (38%)	26.9 ± 5.3	0.18	40.2 ± 5.8	0.39

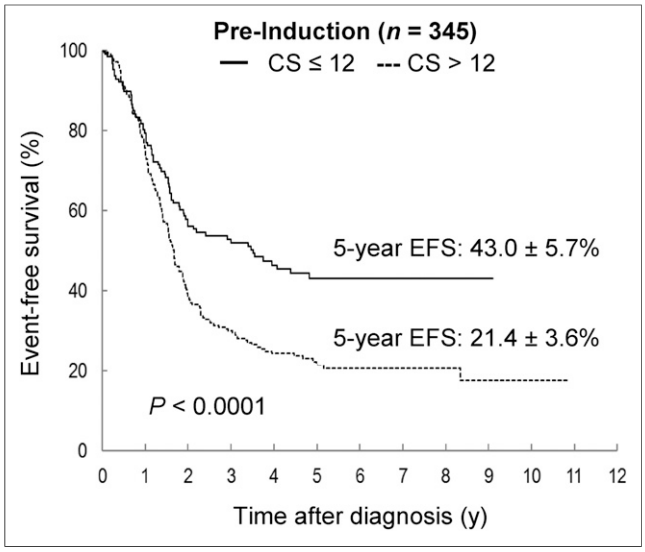

FIGURE 5. EFS by CS at diagnosis, using optimal cut point of 12: time to event starting from date of corresponding ^{123}I-MIBG scan.

vs. 16.4% ± 4.2%, $P < 0.001$ [Table 2; Fig. 6]). Likewise, there was a significant improvement in 5-y OS for patients with a CS of 2 or less after induction versus a CS of more than 2 (48.0% ± 4.7% vs. 29.5% ± 5.1%, $P < 0.001$). Outcome comparisons with a cutoff of 0 were also performed, yielding statistically significant differences for EFS but not for OS.

The median postinduction soft-tissue score was 1 (range, 0–3), with 137 patients (41.5%) exhibiting no ^{123}I-MIBG–avid soft-tissue disease at that time point. Improved 5-y EFS was noted in patients without ^{123}I-MIBG–avid soft-tissue disease after induction (37.8% ± 6.1% [CS, 0] vs. 25.2% ± 3.9% [CS, >0], $P = 0.04$). When soft-tissue scores (region 10) were excluded from the analysis, the optimum cut point was a CS of 0 after induction (5-y EFS, 41.1% ± 4.9% vs. 17.7% ± 4.5%, CS = 0 vs. >0).

The Cox models showed that CS was predictive of EFS and OS after adjusting for *MYCN* and age. Patients with a CS of more than 2 had an increased risk of an event and death of 1.791 and 1.769, respectively.

MYCN status was available in 290 of 330 patients with a postinduction CS. Patients with a CS of more than 2 after induction had inferior survival, independent of *MYCN* status. For patients with *MYCN*-amplified disease, a significant outcome difference existed by postinduction CS, with a 5-y EFS of 38.0% ± 7.0% (CS ≤ 2) versus 13.8% ± 12.8% (CS > 2) ($P = 0.001$). For patients with *MYCN*-nonamplified disease, a significant outcome difference likewise existed by postinduction CS, with 5-y EFS of 38.4% ± 6.7% (CS ≤ 2) versus 18.7% ± 5.3% (CS > 2) ($P = 0.01$). Outcome comparisons were not statistically significant using a cut point of 0 for *MYCN*-amplified or -nonamplified tumors.

Relative Scores: Change in CS from Diagnosis to Postinduction Time Points

None of the outcome comparisons by percentage reduction in CS were statistically significant (Table 2). Specifically, no differences in survival were noted in patients with a 50% or greater reduction in CS versus a reduction of less than 50% between diagnosis and the postinduction time point. Likewise, no outcome differences were noted in patients with a 75% or greater reduction in score (vs. <75%).

DISCUSSION

The prognostic impact of postinduction CS in the COG A3973 study has been previously reported (*19*). We now validate the utility of postinduction CS in an independent dataset, SIOPEN/HR-NBL1. Both in SIOPEN/HR-NBL1 and as reported in COG A3973 (*19*), a postinduction CS of more than 2 was associated with an extremely poor outcome, with 5-y EFS of 16.4% ± 4.2% (SIOPEN) and 10.5% ± 10.0% (COG A3973), respectively. In contrast, patients with a postinduction CS of 2 or less had improved EFS in both SIOPEN/HR-NBL1 and COG A3973, with 5-y EFS of 39.2% ± 4.7% and 42.0% ± 5.8%, respectively (*19*). This finding suggests that patients with a CS of 2 or less after induction benefit from autologous stem cell transplantation and consolidation therapy but that patients with a higher CS may need alternative therapy to improve remission status.

COG A3973 and SIOPEN/HR-NBL1 treated a similar cohort of patients, specifically those with newly diagnosed, high-risk neuroblastoma (*3,22*). Each trial shared a common backbone, with induction therapy, autologous stem cell transplantation, radiotherapy to the primary tumor site, and maintenance therapy with isotretinoin, with receipt of immunotherapy (chimeric antibody, ch14.18) in a small subset of patients (<20%). Eligibility criteria approximated each other, though SIOPEN/HR-NBL1 included infants (<12 mo) with *MYCN*-amplified disease, and COG A3973 included infants (<18 mo) with unfavorable biology (*MYCN* amplification, unfavorable histology, or a tumor DNA index of 1). There were distinct differences between the two trials, however. Induction consisted of 6 cycles of therapy, including 2 anthracycline- and 2 cisplatin-based cycles in COG A3973, compared with 8 induction cycles (at 10-d intervals, no anthracycline, 4 cycles of cisplatin) of Rapid COJEC administered in SIOPEN/HR-NBL1 (*3,22*). Patients in SIOPEN/HR-NBL1 were randomized to receive either busulfan-melphalan or carboplatin-etoposide-melphalan for transplantation, with unpurged stem cells being the donor source. Patients in COG A3973 were randomized to receive purged or unpurged autologous grafts, with patients receiving carboplatin-etoposide-melphalan for transplantation conditioning. A major difference was the timing of second-look surgery between the two

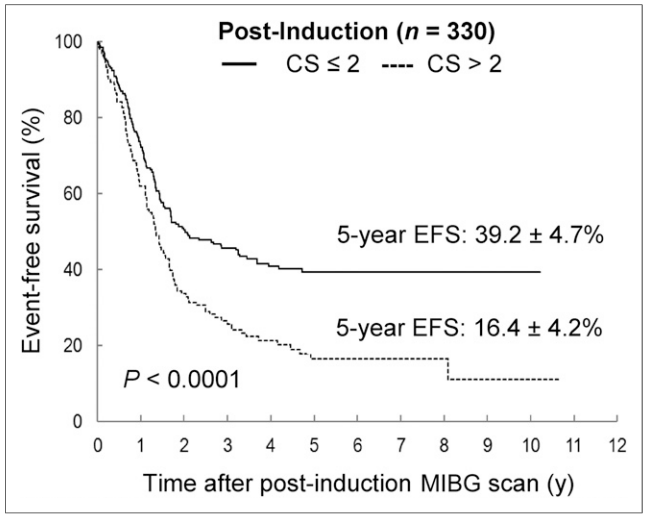

FIGURE 6. EFS by postinduction CS, using optimal cut point of 2: time to event starting from date of corresponding ^{123}I-MIBG scan.

studies. Whereas surgical resection was performed after induction in SIOPEN/HR-NBL1, patients treated in COG A3973 underwent surgical resection of their primary tumor before completion of induction therapy. In contrast to the COG A3973 cohort, more than 50% of all patients in the SIOPEN study had ^{123}I-MIBG–avid soft-tissue disease at the time of the postinduction ^{123}I-MIBG scan, before their surgical resection. Despite these differences, our CS analyses came to the same conclusion in each trial, with a postinduction CS of more than 2 being associated with an inferior outcome.

The prognostic significance of CS at the time of initial diagnosis remains unclear. In SIOPEN/HR-NBL1, a cut point of 12 (at diagnosis) could differentiate patients who had a subsequent event from those who did not. In COG A3973, a higher CS at diagnosis was also associated with an inferior outcome, though the outcome difference did not reach statistical significance (*19*). Differences between the two induction regimens may help explain these findings, with a "modified N7" regimen being used in COG A3973 and a Rapid COJEC regimen being used in SIOPEN/HR-NBL1.

There were several limitations to our analysis. The conclusions were derived from a treatment protocol under which patients received a single transplant (busulfan-melphalan or carboplatin-etoposide-melphalan) followed by local radiotherapy. The impact of postinduction CS in other scenarios, including receipt of a tandem transplant, is not yet established. The prognostic significance of postinduction CS in patients receiving immunotherapy is likewise unclear, with only 18% (COG A3973) and 7% (SIOPEN/HR-NBL1) of patients receiving immunotherapy in our CS analysis. In COG A3973, immunotherapy with ch14.18 was recommended but not mandatory. In SIOPEN/HR-NBL1, patients were assigned to receive immunotherapy in only the latter portion of the study, from 2007 onward. The impact of postinduction CS in large groups of patients who receive immunotherapy may become known on completion of current COG high-risk trials, including ANBL12P1 (NCT01798004).

CS is based on whole-body planar images. Many centers are currently performing SPECT imaging in addition to whole-body planar imaging. ^{123}I-MIBG–avid lesions identified on SPECT imaging are not included in the CS unless they are also identified on whole-body planar imaging.

Two ^{123}I-MIBG scoring methods currently exist, the CS and the SIOPEN score methodologies, with CS being used in COG studies and SIOPEN score being used in SIOPEN studies. A major difference between the two methodologies is the inclusion of soft-tissue scoring in the CS method, with the SIOPEN method being limited to skeletal disease. Whereas CS is a composite of skeletal (90%) and soft-tissue (10%) scores, the SIOPEN score is based primarily on skeletal scores. Whether the soft-tissue region should be included in CS is currently being examined in ongoing analyses of the COG and SIOPEN trials.

Our analysis is a testimony to the tremendous collaboration between investigators in two large, cooperative groups, COG and SIOPEN. Cross validation of each scoring method (CS and SIOPEN score) was performed, with COG investigators traveling to Vienna, Austria, to determine the CS on SIOPEN/HR-NBL1 scans and SIOPEN investigators traveling to the COG image repository (Quality Assurance Review Center) to determine the SIOPEN score on COG A3973 scans. The unique aspect of our collective work is that both scoring methods have been cross-validated using the other's dataset, with the predictive value of the SIOPEN score method to be reported in a separate article. Standardized ^{123}I-MIBG scores have now been incorporated into cooperative group neuroblastoma trials. Ultimately, a consensus scoring method will be developed by the COG and SIOPEN investigators for global use by the pediatric oncology community.

CONCLUSION

We have now confirmed the prognostic significance of the postinduction CS in an independent dataset, SIOPEN/HR-NBL1, with a postinduction CS of more than 2 being associated with inferior survival. Future work to develop a consensus scoring methodology between the COG and the SIOPEN groups is in progress.

DISCLOSURE

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