Validation of post-induction Curie scores in high-risk neuroblastoma. A Children’s
Oncology Group (COG) and SIOPEN Group report on SIOPEN/HR-NBL1

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Running Title: Curie score in High Risk Neuroblastoma


Tables: Two

Figures: Six.
ABSTRACT

A semi-quantitative metaiodobenzylguanidine (mIBG) scoring method (Curie scoring, CS) was previously examined in the Children’s Oncology Group (COG) high risk neuroblastoma trial, COG A3973 (A Randomized Study of Purged vs. Unpurged Peripheral Blood Stem Cell Transplant Following Dose Intensive Induction Therapy for High Risk Neuroblastoma), with a post-induction CS>2 associated with poor event free survival (EFS). The validation of Curie scoring in an independent data set, High Risk Neuroblastoma1/International Society of Pediatric Oncology European Network (SIOPEN/HR-NBL1), is now reported. **Methods:** A retrospective analysis of mIBG scans obtained from patients that had been prospectively enrolled on SIOPEN/HR-NBL1 was performed. All patients exhibited mIBG avid, International Neuroblastoma Staging System stage 4 neuroblastoma. mIBG scans were evaluated at two time points, diagnosis (n=345) and post-induction (n=330), prior to consolidation myeloablative therapy. Scans were evaluated in 10 different anatomic regions, each region scored 0-3 based upon disease extent, with a cumulative Curie score generated. Cut-points for outcome analysis were identified by Youden methodology. Curie scores from patients enrolled on COG A3973 were used for comparison. **Results:** The optimal cut-point for Curie score at diagnosis was 12 in SIOPEN/HR-NBL1, with a significant outcome difference by Curie score noted [5-year EFS: 43.0 ±5.7 (CS≤12) vs. 21.4 ±3.6% (CS>12), p<0.0001]. The optimal Curie score cut-point post-induction was 2 in SIOPEN/HR-NBL1, with a post-induction Curie score >2 associated with inferior outcome [5-year EFS:39.2 ±4.7% (CS≤2) vs. 16.4 ±4.2% (CS>2), p<0.0001]. The post-induction Curie score maintained independent statistical significance in Cox models, when adjusted for the covariates of age and MYCN (V-Myc Avian Myelocytomatosis Viral Oncogene Neuroblastoma Derived Homolog) gene copy number.
**Conclusion:** The prognostic significance of post-induction Curie scores has now been validated in an independent cohort of patients (SIOPEN/HR-NBL1), with a post-induction Curie score >2 associated with inferior outcome in two independent large, cooperative group trials.

**Key words:** Neuroblastoma, MIBG, Curie Score
INTRODUCTION

Despite a multi-modality approach combining chemotherapy, surgical resection, radiotherapy, autologous stem cell transplant and biotherapy, survival for high risk neuroblastoma remains poor, with 5-year EFS 30-49% (1,2,3). The use of the anti-GD2 chimeric antibody (ch14.18, dinutuximab, Unituxin™) post-transplant in combination with GM-CSF and intravenous interleukin-2 has led to improvements in EFS (4). For patients who develop relapsed disease, specifically those who relapse 6–18 months from initial diagnosis, 5-year overall survival is <20% (5). The identification of prognostic markers of response and survival early in a patient’s treatment may have significant impact on therapy and outcome.

mIBG is a guanethidine analog that has been used as a diagnostic imaging agent for neuroblastoma for over 30 years (6-9). Uptake is well described in marrow, osseous and soft tissue sites of disease. In 1995, a mIBG scoring system was developed to semi-quantify the extent of mIBG uptake within individual patients and to serve as an imaging biomarker for outcome prediction (10). The role of semi-quantitative mIBG scoring as a prognostic indicator for high risk neuroblastoma has now been reported in both institutional and cooperative group trials, including trials within the COG and the International Society for Paediatric Oncology European Neuroblastoma Research Network (SIOPEN R-NET) (10-20). In particular, the presence of mIBG avid disease post-induction has correlated with extremely poor EFS and overall survival (OS) following consolidation therapy, including high dose chemotherapy with autologous stem cell transplant (ASCT) (11, 14-20). Likewise, mIBG scores at diagnosis have been prognostic in SIOPEN high risk neuroblastoma studies (20). Scan type, I-131 vs I-123 mIBG, has not affected outcome predictions, either at diagnosis or post-induction (21).
Two mIBG scoring methods are now commonly used, the Curie and SIOPEN scoring methods (14, 19, 20). The two scoring methods subdivide the skeleton into 9 (Curie scoring) or 12 regions (SIOPEN scoring) (Fig. 1), with Curie scoring adding an additional 10th 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 Curie (or SIOPEN) score. The Curie scoring method has been adapted for use in COG trials, including the high risk neuroblastoma trial, COG A3973 (A Randomized Study of Purged vs. Unpurged Peripheral Blood Stem Cell Transplant Following Dose Intensive Induction Therapy for High Risk Neuroblastoma) (22). The SIOPEN scoring method has been adapted for use in SIOPEN high-risk (HR) neuroblastoma trials, including the recent SIOPEN/HR-NBL1.

For patients treated on COG A3973, post-induction Curie scores >2 were associated with inferior outcomes, when compared to patients with Curie scores ≤2 post-induction (5-year EFS: 10.5±10.0% vs. 42.0±5.8%, p<0.0001) (19). Furthermore, a post-induction Curie score >2 identified patients at high risk for an event on COG A3973, independent of other known prognostic factors, including age, MYCN status, ploidy, and histologic grade (19).

We now report the prognostic value of Curie scoring of mIBG scans at diagnosis and end induction for patients treated on the European high risk trial (SIOPEN/HR-NBL1), with subsequent comparisons to an independent cohort of patients treated on the COG high-risk neuroblastoma protocol, COG A3973. The current study validates the role of Curie scoring as a prognostic marker of response and survival in a large, independent data set of patients with mIBG avid, stage 4, newly diagnosed high-risk neuroblastoma.
MATERIALS AND METHODS

Patient Population

Three hundred and forty-five patients with newly diagnosed, stage 4 high-risk neuroblastoma (per International Neuroblastoma Staging System) (23) enrolled on SIOPEN/HR-NBL1, with mIBG avid disease at diagnosis were examined [Table 1, Fig. 2]. The prognostic value of mIBG scoring was a stated aim of SIOPEN/HR-NBL1, with scoring performed retrospectively, examining mIBG scans obtained at diagnosis (n=345) and post-induction (n=330).

Treatment

SIOPEN/HR-NBL1 (NCT00030719) is a randomized, multicenter study, for patients < 21 years of age with biopsy proven high-risk neuroblastoma (patient enrollment 2002-2010) (3). Inclusion criteria included patients with stage 2-4 disease with MYCN amplification (any age), or patients with stage 4 over one year of age. Only the cohort with mIBG avid stage 4 disease was used for purposes of the current evaluation. Therapy on SIOPEN/HR-NBL1 included 8 cycles of an intensively timed induction regimen (Rapid COJEC), surgical resection of residual disease (post-induction) followed by mIBG scanning, high dose chemotherapy (HDC) with ASCT, local radiotherapy and subsequent maintenance therapy with isotretinoin, as previously published [Fig. 3](2,3,24,25). Rapid COJEC (Cisplatin-Vincristine-Carboplatin-Etoposide-Cyclophosphamide) consisted of repetitive courses of vincristine-carboplatin-etoposide (cycle A), vincristine-cisplatin (course B), and vincristine-etoposide-cyclophosphamide (course C). Immunotherapy with an anti-GD2 monoclonal antibody (ch14.18) ± subcutaneous interleukin-2 was given to patients enrolled from 2007 onward. Only patients in complete or partial remission with ≤ 3 mIBG avid sites upon
completion of induction and >50% reduction of mIBG avid osseous lesions were eligible to proceed to ASCT. Patients who failed to meet these criteria, received two additional courses of topotecan, vincristine, and doxorubicin (TVD) pre-HDC and surgery was postponed till a better metastatic response was achieved. Transplant was performed using either a busulfan-melphalan (BuMel) or carboplatin-etoposide-melphalan (CEM) conditioning regimen. Written informed consent (approved by local ethics boards) was obtained from patients (or legal guardians) prior to entry onto SIOPEN/HR-NBL1. The trial was registered at Clinicaltrials.gov (NCT00030719), International Society of Pediatric Oncology-Europe-High Risk-Neuroblastoma-1 (SIOP-Europe-HR-NBL-1), CDR0000069191, European International Society of Pediatric Oncology (ESIOP), EU-20148), and at EudraCT (European Clinical Trials Database 2006-001489-17-eudrac.uk.eva.eu).

**Curie score determinations**

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

**Statistical Analysis**

Patients were categorized by Curie score (0 vs. >0; ≤ optimum cut-off vs. > optimum cut-off) and compared with respect to survival (EFS and OS) at each time point. The optimum cut-off was determined by maximizing the Youden index with respect to how well the Curie score 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 Curie score (26,27). Survival comparisons were drawn at each individual site by score (0 vs. >0 only). The percent change in Curie score from diagnosis to post-induction scan for patients with both sets of mIBG scan readings was stratified based on 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 event were censored at the time last known date of contact. For OS, death was the only event considered. At post-induction, time to event was calculated from the date of the post-induction mIBG scan. Patients who had an event between the date of diagnosis and the date of post-induction mIBG scan (n=15) were considered to have gone off-study and hence were not included in the analysis at post-induction. Survival
analyses were performed 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 event times were fit to determine the Curie score cut-off at which the hazard ratio was maximized, as well as the prognostic strength for survival of the Curie score in the presence of age (<18 months vs. ≥18 months) and MYCN gene copy number (non-amplified vs. amplified). P-values less than 0.05 were considered statistically significant.

RESULTS

Three hundred and forty-five patients had mIBG scans available at diagnosis, with post-induction scans available in 330 patients, and both sets of images evaluable in 329 patients (Table 1). The median Curie score at diagnosis was 19 (range 1-30), with 149 patients (43.2%) exhibiting a Curie score >20 at diagnosis (Fig. 4a). The median score post-induction was 1.5 (range 0-27), with only 14 patients (4.2%) exhibiting a Curie score >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.

Curie Scores at Diagnosis and Outcome

The 5-year EFS and OS for the 345 patients with 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 Curie score of 12. Five-year EFS was 43.0 ±5.7% for patients with a Curie score ≤12 (n=126) versus 21.4±3.6% for those with a score >12 (n=219) at diagnosis, p<0.001 [Table 2; Fig. 5]. Differences in OS were likewise noted, with 5-year OS 53.9±5.6% vs. 32.7 ±4.0% for patients with Curie scores ≤12 vs. >12, p=0.001. The Cox proportional hazard
model found Curie scores to be predictive of EFS and OS after adjusting for MYCN and age, as explained below. Patients with Curie score >12 had an increased risk of 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 mIBG avid soft tissue disease at diagnosis, and 35 patients (10.1%) exhibiting avidity in >1 soft tissue site. The presence of mIBG avid soft tissue disease at diagnosis did not impact EFS, with 5-year EFS 29.2 ± 3.3% vs. 29.4 ± 10.1% for patients with (or without) mIBG avid soft tissue disease at that time point (p=0.64).

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

Post-Induction Curie Scores and Outcome

The 5-year EFS and OS for the 330 patients with mIBG scans post-induction were 30.1±3.4% and 40.6±3.5%, respectively. The optimum cut-point post-induction was a Curie score of 2. In addition, Cox proportional hazard models indicated that a Curie score of 2 post-induction corresponded to the largest significant hazard ratio (1.710, 95% CI: 1.314, 2.226), when compared to other potential cut-points. Patients with a Curie score ≤2 (n=198, 60%) had significantly better 5-year EFS when compared to patients with a Curie score >2 (n=132) post-induction, 39.2±4.7%
vs. 16.4±4.2%, p<0.001 [Table 2; Fig. 6]. Likewise, there was a significant improvement in 5-year OS for patients with Curie scores ≤2 vs. >2 post-induction, 48.0±4.7% vs. 29.5±5.1%, p<0.001. Outcome comparisons with a cut-off of 0 were also performed, yielding statistically significant differences for EFS, but not for OS.

The median post-induction soft tissue score was 1 (range: 0-3), with 137 patients (41.5%) exhibiting no mIBG avid soft tissue disease at that time point. Improved 5-year EFS was noted in patients without mIBG avid soft tissue disease present post-induction, 37.8±6.1% (CS =0) vs. 25.2±3.9% (CS >0), p=0.04. If soft tissue scores (region 10) were excluded from the analysis, the optimum cut-point was a Curie score of 0 post-induction (5-year EFS 41.1±4.9% vs. 17.7±4.5%, CS=0 vs. >0).

The Cox models showed that Curie score was predictive of EFS and OS after adjusting for MYCN and age. Patients with Curie score >2 had an increased risk of event and death of 1.791 and 1.769, respectively.

MYCN status was available in 290 of 330 patients with post-induction Curie scores. Patients with Curie scores >2 post-induction had inferior survival, independent of MYCN status. For patients with MYCN amplified disease, a significant outcome difference existed by post-induction Curie score, with 5-year EFS 38.0±7.0% (CS ≤2) vs. 13.8 ±12.8% (CS >2), p=0.001. For patients with MYCN non-amplified disease, a significant outcome difference likewise existed by post-induction Curie score, with 5-year EFS 38.4 ±6.7% (CS≤2) vs. 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 non-amplified tumors.
Relative scores: Change in Curie score from Diagnosis to Post-Induction

None of the outcome comparisons by % reduction in Curie scores were statistically significant [Table 2]. Specifically, no differences in survival were noted in patients with ≥50% versus < 50% reduction in Curie scores between diagnosis and post-induction. Likewise, no outcome differences were noted in patients with ≥75% (versus < 75%) reduction in scores.

DISCUSSION

The prognostic impact of post-induction Curie scores in the COG study, COG A3973 has been previously reported (19). We now validate the utility of post-induction Curie scores in an independent data set, SIOPEN/HR-NBL1. In both SIOPEN/HR-NBL1 and as reported in COG A3973 (19), a post-induction Curie score >2 was associated with extremely poor outcome, with 5-year EFS 16.4±4.2% (SIOPEN) and 10.5±10.0% (COG A3973) respectively. In contrast, patients with a post-induction Curie scores ≤2 had improved EFS in both SIOPEN/HR-NBL1 and COG A3973, with 5-year EFS 39.2 ± 4.7% (SIOPEN) and 42.0±5.8% (COG A3973) (19). This suggests that patients with Curie scores ≤2 post-induction benefit from ASCT and consolidation therapy, but that patients with higher Curie scores 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, ASCT, radiotherapy to the primary tumor site, and maintenance therapy with isotretinoin, with receipt of immunotherapy (chimeric antibody, ch14.18) in a small sub-set of patients (<20%). Eligibility criteria approximated each other, though SIOPEN/HR-NBL1 included infants (<12 months) with MYCN amplified disease, and COG A3973 included infants (<18 months) with unfavorable biology (MYCN amplification, unfavorable histology, and/or a tumor
DNA index=1). There were distinct differences in the two trials, however. Induction consisted of six cycles of therapy, including two anthracycline and two cisplatin based cycles in COG A3973, compared with 8 induction cycles (at 10 day intervals, no anthracycline, 4 cycles cisplatin) of Rapid COJEC administered on SIOPEN/HR-NBL1(3,22). Patients on SIOPEN/HR-NBL1 were randomized to receive either BuMel or CEM for transplant, with unpurged stem cells the donor source. Patients on COG A3973 were randomized to receive purged or unpurged autologous grafts, with patients receiving CEM for transplant conditioning. A major difference was the timing of second-look surgery in the two studies. Whereas surgical resection was performed post-induction in SIOPEN/HR-NBL1, patients treated on COG A3973 underwent surgical resection of their primary tumor prior to completion of induction therapy. In contrast to the COG A3973 cohort, >50% of all patients in the SIOPEN study had mIBG avid soft tissue disease present at the time of the post induction mIBG scan, prior to their surgical resection. Despite these differences, our Curie scoring analyses came to the same conclusion in each trial, with post-induction Curie scores >2 associated with inferior outcomes.

The prognostic significance of Curie scores at the time of initial diagnosis remains unclear. In SIOPEN/HR-NBL1, a cut-point of 12 (at diagnosis) was able to differentiate patients who had a subsequent event from those that did not. In COG A3973, higher Curie scores at diagnosis were also associated with inferior outcome, though the outcome difference did not reach statistical significance (19). Differences in the two induction regimens may help explain these findings, with a “modified N7” regimen used in COG A3973 and a Rapid COJEC regimen used in SIOPEN/HR-NBL1.
There are several limitations with our analysis. The conclusions are derived from a treatment protocol under which patients received a single transplant (BuMel or CEM) followed by local radiotherapy. The impact of post-induction Curie scores in other scenarios, including receipt of tandem transplant, is not yet established. The prognostic significance of post-induction Curie scores in patients receiving immunotherapy is likewise unclear, with only 18% (COG A3973) and 7% (SIOPEN/HR-NBL1) of patients receiving immunotherapy in our Curie score analysis. In COG A3973, immunotherapy with ch14.18 was recommended, but not mandatory. In SIOPEN/HR-NBL1, patients were only assigned to receive immunotherapy in the latter portion study, from 2007 onward. The impact of post-induction Curie scores in large groups of patients who receive immunotherapy may become available upon completion of current COG high risk trials, including ANBL12P1 (NCT01798004).

It should be pointed out that Curie scoring is based upon whole body planar images. Many centers are currently performing SPECT imaging, in addition to whole body planar imaging. mIBG avid lesions identified on SPECT imaging are not included in the Curie score, unless they are also identified on the whole body planar image.

As previously noted, two mIBG scoring methods currently exist, the Curie and SIOPEN methodologies, with Curie scoring used in COG studies and SIOPEN scoring used in SIOPEN studies. A major difference between the two methodologies is the inclusion of soft tissue scoring in the Curie method, with SIOPEN scoring limited to skeletal disease. Whereas Curie scoring is a composite of skeletal (90%) and soft tissue (10%) scores, the SIOPEN methodology is primarily based upon skeletal scores. Whether the soft tissue region should be included in Curie scoring is currently being examined in on-going analyses of COG and/or 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 (Curie and SIOPEN scoring) was performed, with COG investigators traveling to Vienna, Austria to perform Curie scoring on SIOPEN/HR-NBL1 scans, and SIOPEN investigators traveling to the COG image repository [Quality Assurance Review Center (QARC), Providence, RI] to perform SIOPEN scoring on COG A3973 scans. The unique aspect of our collective work is that both scoring methods have been cross-validated using the other’s data set, with the predictive value of the SIOPEN scoring method to be reported in a separate manuscript. Standardized mIBG scores have now been incorporated into cooperative group neuroblastoma trials. Ultimately, a consensus scoring method will be developed by COG and SIOPEN investigators, for global use by the pediatric oncology community.

CONCLUSION

We have now confirmed the prognostic significance of post-induction Curie scores in an independent data set, SIOPEN/HR-NBL1, with a post-induction Curie score >2 associated with inferior survival. Future work to develop a consensus scoring methodology between the COG and the SIOPEN groups is in progress.

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DISCLOSURE:

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REFERENCES:


FIGURE 1a. Anatomic regions for Curie and SIOPEN scoring. The body is divided into 9 (Curie scoring) or 12 (SIOPEN scoring) skeletal regions, with Curie scoring adding a 10th (soft tissue) region.

FIGURE 1b: Example of Curie scoring of an individual patient: Diffuse uptake (CS=3) is noted in the head, cervical-thoracic (CT) spine, lumbar-sacral (LS) spine, pelvis, proximal arms, proximal lower extremities (LE), distal lower extremities, and chest (CS = 2). One mIBG avid soft tissue site, involving < 50% abdomen (CS = 1). Total Curie score = 25.
Assessed for eligibility \( (n = 345 \text{ patients}) \)

\[ \rightarrow \]

Excluded \( (n = 0) \)

Pre-induction \( (n = 345 \text{ patients}) \)
- Received allocated intervention \( (n = 345) \)
- Pre-induction mIBG scan not evaluable \( (n = 0) \)

\[ \rightarrow \]

- Early events during induction \( (n = 15) \)
- Lost to follow-up \( (n = 0) \)

Post-induction \( (n = 330 \text{ patients}) \)
- Post induction mIBG scan not evaluable \( (n = 0) \)

**FIGURE 2.** CONSORT Diagram: Curie score analysis of SIOPEN / HR-NBL1.
HR-NBL-1/SIOPEN  *(Ref: J Clin Oncol 2010 Jul 20; 28(21):3516-3524)*

\[ \begin{array}{ccccccccc}
& & & & & & & & & \\
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & \\
\text{Induction (Rapid COJEC)} & \text{Consolidation} & \text{Surgery} & \text{BMT} & \text{XRT} & \text{Isotretinoin}
\end{array} \]

mIBG scan \quad \text{mIBG scan}

BuMel vs CEM

COG A3973  *(Ref: Lancet Oncol 2013 Sep; 14(10): 999-1008)*

\[ \begin{array}{ccccccccc}
& & & & & & & & & \\
1 & 2 & 3 & 4 & 5 & 6 & & & & \\
\text{Induction (Modified N7)} & \text{Consolidation} & \text{Surgery} & 6 & \text{BMT} & \text{XRT} & \text{Isotretinoin}
\end{array} \]

mIBG scan \quad \text{mIBG scan}

CEM

*Key:* BMT, bone marrow transplant; XRT, radiotherapy; Biotherapy = Isotretinoin ± Anti-GD2 chimeric antibody; BuMel, Busulfan-Melphalan; CEM, Carboplatin-Etoposide-Melphalan; Rapid COJEC, Cisplatin-Vincristine-Carboplatin-Etoposide-Cytoxan.

**FIGURE 3.** Schematic overview of SIOPEN/HR-NBL1 and COG A3973 therapy.
FIGURE 4a.

Pre-induction (n = 345)

![Bar chart showing distribution of Curie scores at pre-induction.

FIGURE 4b.

Post-induction (n = 330)

![Bar chart showing distribution of Curie scores at post-induction.

FIGURE 4. Distribution of Curie scores at (a) diagnosis, and (b) post-induction.
**FIGURE 5.** EFS by Curie score at diagnosis, using an optimal cut-point of 12. Time to event starting from date of corresponding mIBG scan.
**FIGURE 6.** EFS by post-induction Curie score, using an optimal cut-point of 2. Time to event starting from date of corresponding mIBG scan.
Table 1. Patient Characteristics at Diagnosis.¹

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<tr>
<td>Unknown</td>
<td>41 (12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ASCT²</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>261 (76)</td>
<td></td>
</tr>
</tbody>
</table>

| Chimeric antibody     | 23 (7)  |

Key: ¹Includes only patients with mIBG avid, stage 4 disease.

²ASCT, Autologous stem cell transplant. Patients underwent ASCT if in CR/PR with ≤3 mIBG avid sites and >50% reduction of mIBG avid osseous lesions.
Table 2. EFS and OS by Curie scores at (a) Diagnosis, (b) Post-Induction and (c) % Reduction in scores.

### Diagnosis.

<table>
<thead>
<tr>
<th>Curie score</th>
<th>N (%)</th>
<th>5-yr EFS ± SE (%)</th>
<th>EFS p-value</th>
<th>5-yr OS ±SE (%)</th>
<th>OS p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 12</td>
<td>126 (37)</td>
<td>43.0 ± 5.7</td>
<td>&lt;0.001</td>
<td>53.9 ± 5.6</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt; 12</td>
<td>219 (63)</td>
<td>21.4 ± 3.6</td>
<td></td>
<td>32.7 ± 4.0</td>
<td></td>
</tr>
</tbody>
</table>

### Post-Induction.

<table>
<thead>
<tr>
<th>Curie score</th>
<th>N (%)</th>
<th>5-yr EFS ± SE (%)</th>
<th>EFS p-value</th>
<th>5-yr OS ±SE (%)</th>
<th>OS p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2</td>
<td>198 (60)</td>
<td>39.2 ± 4.7</td>
<td>&lt;0.001</td>
<td>48.0 ± 4.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>132 (40)</td>
<td>16.4 ± 4.2</td>
<td></td>
<td>29.5 ± 5.1</td>
<td></td>
</tr>
</tbody>
</table>

### Relative Curie scores.

<table>
<thead>
<tr>
<th>% Reduction¹</th>
<th>N (%)</th>
<th>5-yr EFS ± SE (%)</th>
<th>EFS p-value</th>
<th>5-yr OS ±SE (%)</th>
<th>OS p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50%</td>
<td>251 (76)</td>
<td>31.8 ± 3.9</td>
<td>0.65</td>
<td>40.6 ± 4.0</td>
<td>0.91</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>78 (24)</td>
<td>25.3 ± 6.9</td>
<td></td>
<td>41.6 ± 7.5</td>
<td></td>
</tr>
<tr>
<td>≥ 75%</td>
<td>204 (62)</td>
<td>32.3 ± 4.4</td>
<td>0.18</td>
<td>41.2 ± 4.5</td>
<td>0.39</td>
</tr>
<tr>
<td>&lt; 75%</td>
<td>125 (38)</td>
<td>26.9 ± 5.3</td>
<td></td>
<td>40.2 ± 5.8</td>
<td></td>
</tr>
</tbody>
</table>

Key: 1, % Reduction in Curie score from Diagnosis to Post-Induction.