




[¹²³I]-metaiodobenzylguanidine imaging findings and outcome in patients with metastatic neuroblastoma



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Background: [¹²³I]-Metaiodobenzylguanidine ([¹²³I]mIBG) is the agent of choice to assess for presence of metastases and therapy response in patients with neuroblastoma.

Aim: To assess [¹²³I]mIBG scan results and outcome in patients with stage 4 neuroblastoma at our institution.

Setting: Red Cross War Memorial Children's Hospital.

Methods: A retrospective review of baseline and follow-up [¹²³I]mIBG scans of patients who presented between January 2001 and May 2015. The clinical follow up extended until October 2019. The association between the baseline and post-induction Curie score (CS) and overall survival (OS) were assessed.

Results: Thirty-four patients with stage 4 disease were included. Twenty-two (65%) patients died. The median age at diagnosis for survivors was 15.5 months vs 39 months for those who died (Kruskal Wallis $\chi^2 = 4.63$, $p = 0.03$). Neither the baseline CS nor the post-induction CS predict the outcome or duration of survival. The median OS for a baseline CS ≤ 12 and CS > 12 was 19 and 26 months, $p = 0.13$. The median OS for a post-induction CS > 2 and CS ≤ 2 was 28 and 26 months, $p = 0.66$.

Conclusion: In this study, baseline, post-induction and reduction in CS did not predict OS in stage 4 neuroblastoma. Factors such as small patient numbers, less intensive treatment regimes, and possible poorly dedifferentiated disease have been identified for this finding.

Contribution: In contrast to international studies the Curie score did not predict treatment outcome in the South African setting where the vast majority of patients are treated with OPEC/OJEC OPEC/OJEC (vincristine [O], cisplatin [P], etoposide [E], cyclophosphamide [C] and carboplatin [J]) chemotherapy.

Keywords: neuroblastoma; baseline; Curie score; [¹²³I]mIBG; post-induction Curie score; overall survival.

Introduction

Neuroblastoma, a common solid tumour of childhood arises from neuro-ectodermal tissue.¹ Older age at diagnosis, presence of metastases, N-myc proto-oncogene (NMYC) amplification and an unfavourable histology portend poor prognosis.^{2,3}

[¹²³I]-metaiodobenzylguanidine is the nuclear medicine imaging agent of choice to assess for the presence of metastases and therapy response in patients with neuroblastoma.⁴

The semi-quantitative Curie scoring system was developed to assess disease burden in bone and bone marrow. Patients without disease or with low Curie score (CS) post-treatment have a good quality of life and good event free survival (EFS). The Children's Oncology Group (COG) high-risk neuroblastoma trial COG A3973 reported that the post-therapy CS > 2 after induction chemotherapy was associated with a poorer outcome compared with those with score ≤ 2 . In this cohort 73% of the patients were imaged with [¹²³I]mIBG and the rest with [¹³¹I]mIBG.⁵ A follow-up study on an independent population reported that in stage 4 neuroblastoma all imaged with [¹²³I]mIBG, patients with a CS of > 12 at diagnosis ($n = 330$) had a significantly poorer outcome than those with a CS ≤ 12 . The post-therapy CS > 2 after induction chemotherapy was associated with a poorer outcome compared with those with score ≤ 2 , 5-year EFS $39.2\% \pm 4.7\%$ versus $16.4\% \pm 4.2\%$. The post-induction CS was an independent risk factor.⁶ A relative CS (calculated as the ratio of post-therapy CS to pre-therapy CS), identifies patients with refractory neuroblastoma who are likely to benefit from [¹³¹I]mIBG therapy.⁷

This study aimed to assess the relationship between the results of [¹²³I]mIBG scan and outcome in patients with neuroblastoma at our institution.

Research methods

The authors performed a retrospective review of [¹²³I]mIBG scans and clinical, laboratory and other available imaging data of patients with stage 4 neuroblastoma who presented to their institution between January 2001 and May 2015. The images of patients with histologically confirmed neuroblastoma who had a baseline [¹²³I]mIBG scan before the start of any chemotherapy and at least one subsequent scan during or after completion of treatment were retrieved from the electronic archives of the Nuclear Medicine department. The follow-up extended until October 2019 to allow for a follow-up period of at least 53 months from presentation.

All [¹²³I]mIBG scans were acquired in accordance with the relevant guidelines of the European Association of Nuclear Medicine (EANM).^{4,8} Administered doses of [¹²³I]mIBG were in accordance with EANM guidelines.^{9,10} Images were recorded 24 h after injection of [¹²³I]mIBG (iThemba LABS, Cape Town, South Africa) using a Phillips Axis dual head camera fitted with a low energy high-resolution collimator. Baseline scans were recorded before the start of any chemotherapy and subsequent scans were performed after four, seven or after four and seven cycles of chemotherapy.

The raw data of the [¹²³I]mIBG scans of the patients were retrieved from the electronic archives. The [¹²³I]mIBG scans were anonymised so that the single observer was unaware of the patient's name and folder number or the date on which each set of images were acquired. In addition, the single observer was also blinded to the clinical information of patients other than the diagnosis of neuroblastoma. Each set of images were processed and reviewed twice on a HERMES (version V1.0, 2005, Hermes Medical Systems, Sweden) physicians' workstation. On the first occasion, the single observer was also not aware of whether images were baseline, cycle four or cycle seven scans. All the anonymised images were retrieved and re-processed. The location of each lesion, the body segment involved, and the extent of involvement in each segment were recorded according to the Curie 4-point scoring system.^{7,11} In addition, the uptake seen in bone on the [¹²³I]mIBG scan was assessed and characterised as focal or diffuse using previously described criteria.¹² Lesions identified as focal were clearly distinguishable from background. Lesions with no clearly defined margins were categorised as diffuse. The number of focal and diffuse lesions in each skeletal segment was recorded. The level of diagnostic certainty of lesions were recorded.

Three weeks after the first review, a second review of all the images was performed on matched pre- and post-treatment scans using the same criteria utilised during the first review.

After all images had been reviewed twice, the anonymisation code was opened and the clinical information of patients

was retrieved from the archived folders of the oncology department of the hospital. Patients' age, sex, date of diagnosis of neuroblastoma, site of primary tumour, disease stage, histopathology, NMYC status and bone marrow biopsy results were recorded. The details of chemotherapy were also abstracted. Disease staging was performed in accordance with the International Neuroblastoma Staging System criteria.¹³ The clinical outcome and date of each event, date of last clinic visit or known contact and duration of follow-up were noted.

Data analysis

The analysis involved assessment of clinical data for any relationships with the [¹²³I]mIBG scan findings. Clinical data are presented as frequencies and percentages. Overall survival (OS) was defined as the time from diagnosis until death or last examination for all patients including those lost to follow-up. Survival was assessed using the Kaplan-Meier life table method. Differences in OS between different groups were assessed using the log-rank test. Statistical analyses were performed using Statistica (Dell Inc. 2016). Dell Statistica (data analysis software system), version 13), IBM® SPSS® statistics for windows (version 28.0) and Microsoft Office 2013 Excel.

Ethical considerations

Approval to conduct the study was obtained from the Human Research Ethics Committee of the University of Cape Town (HREC: 716/2015).

Results

Thirty-four patients with stage 4 disease were included in the analysis. The clinical and pathological characteristics of the study participants are presented in Table 1. A total of 29 (85%)

TABLE 1: Clinical and pathological characteristics of all neuroblastoma patients.

Characteristic	All patients (N = 34)	Deceased (n = 22)	Alive at the time of analysis (n = 12)
Age at diagnosis in months			
< 12	5	2	3
12–24	9	5	4
> 24	20	15	5
Gender			
Male	18	13	5
Female	16	9	7
Site of primary tumour			
Adrenal	21	12	9
Abdomen	8	7	1
Thorax	2	1	1
Pelvis	3	2	1
NMYC amplification			
Positive	17	12	5
Negative	15	8	7
Not available	2	2	0
Bone marrow infiltration at diagnosis	28	17	11
Bone marrow infiltration at end of treatment	7	7	0

NMYC, N-myc proto-oncogene.

patients were older than 12 months and the median age at diagnosis was 34.5 months (range 6–93 months). The adrenal gland was the most common site of the primary tumours and 50% of tumours had NMYC amplification. A total of 28 (82%) patients were treated with OPEC/OJEC (vincristine [O], cisplatin [P], etoposide [E] cyclophosphamide [C] and carboplatin [J]) chemotherapy.

All the patients included in this study had a baseline [¹²³I] mIBG scan before the start of chemotherapy. Of the 34 patients, 22 had scans acquired after chemotherapy cycle four (cycle 4 scans) and 21 had scans after cycle seven (cycle 7 scans). Nine patients had cycle 4 and cycle 7 scans. The cycle 7 scan was used as the end of treatment scan in the patients who had both cycle 4 and cycle 7 scans.

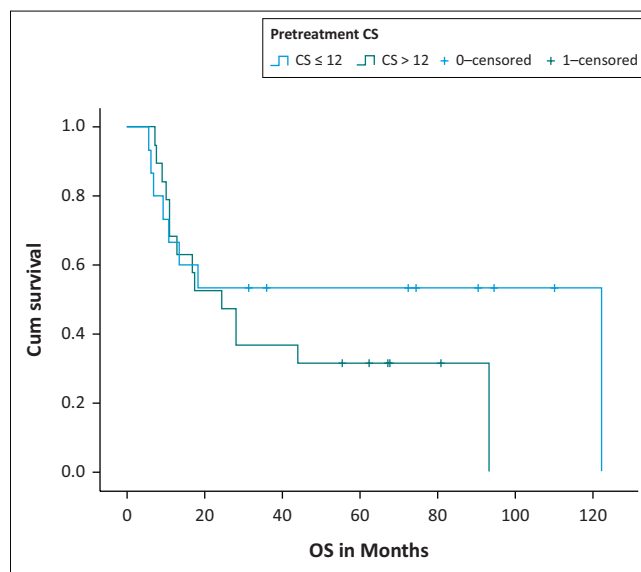
A total of 22 (65%) patients died and 12 were alive when follow-up for this study ended. Twenty (91%) of deaths occurred in patients diagnosed when older than 12 months. The median age at diagnosis for survivors was 15.5 months (range: 6–93) versus 39 months (range: 6–72) for those who died (Kruskal–Wallis $\chi^2 = 4.63$, $p = 0.03$). Of 17 patients with NMYC amplified tumours, 12 died and five were alive. Eight patients with NMYC unamplified tumours died: one was diagnosed at the age of 17 months and the other seven were ≥ 36 months at diagnosis, four patients with NMYC unamplified disease had poorly differentiated tumours and five had the primary tumour located in the adrenal gland.

The median interval from diagnosis to death was 12 months (range: 6–123 months). For survivors, the median interval from diagnosis to the last recorded follow-up for the study was 70 months (range 31–110 months).

There was one treatment-related death. This patient had an NMYC amplified primary tumour in the abdomen and died six months after diagnosis from disseminated intravascular coagulation 48 h post-surgical resection of the primary tumour. The cycle 4 scan had a CS of one.

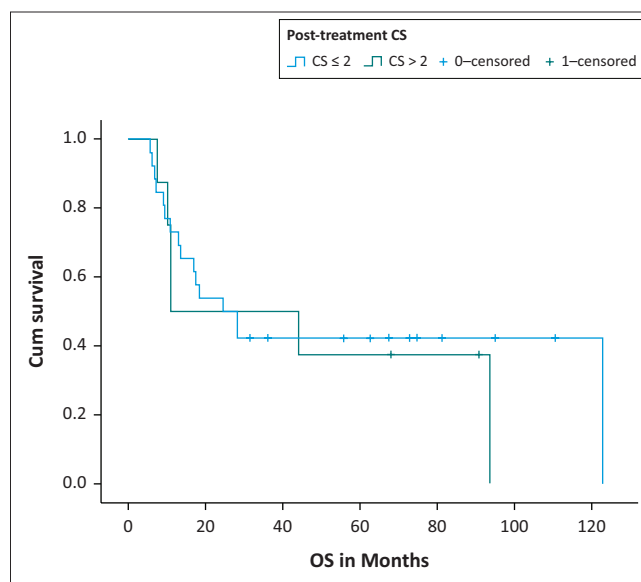
The baseline CS did not predict outcome or duration of survival. The survival of the 13 patients with baseline CS ≤ 12 was not statistically different from the 21 with CS > 12 (median OS 19 vs 26 months, $p = 0.13$), Figure 1. Seven of the patients did not have [¹²³I]mIBG uptake on the baseline scan, CS = 0.

Patients with an end of treatment CS > 2 ($n = 8$) had median OS of 28 months compared with 26 months for those with CS ≤ 2 ($n = 26$), $p = 0.66$. Ten of the 26 patients with an end of treatment CS ≤ 2 were still alive at the end of the 53-month follow-up period. The median survival of these 10 patients were 70 months. Six of the eight patients with an end of treatment CS > 2 died. The two patients with an end of treatment CS > 2 who were still alive at the end of follow-up were diagnosed at 10- and 12-months age, respectively. The Kaplan-Meier plot showed that there was no difference in the survival if the end of treatment CS ≤ 2 and CS > 2 , Figure 2.



CS, Curie score; OS, overall survival.

FIGURE 1: Overall survival compared with the baseline Curie score for scores ≤ 12 versus > 12 .

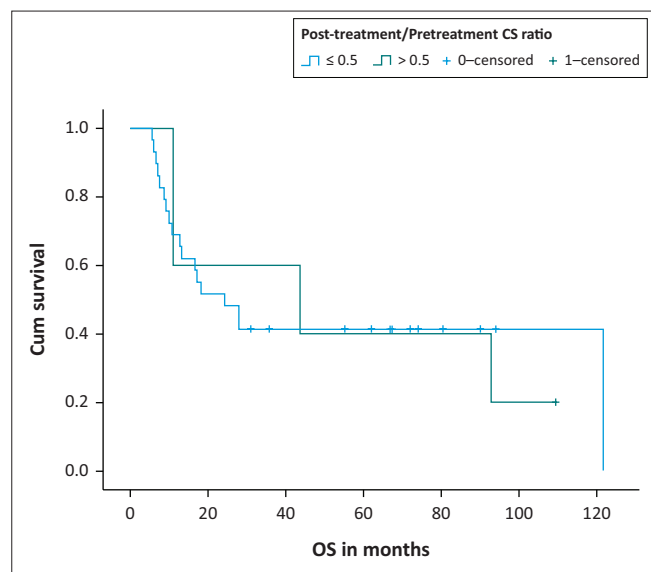


CS, Curie score; OS, overall survival.

FIGURE 2: Overall survival compared with the end of treatment Curie score for scores ≤ 2 versus > 2 .

Survivors and deceased patients had decreases in CS on the follow-up scan at cycle 4 or 7. A relative CS was calculated for each patient as the ratio of score at last follow-up scan to the baseline score. This relative CS was used as a measure of tumour response to treatment. There was no relationship between the magnitude of decrease in CS and outcome. A 50% reduction in tumour burden from baseline was calculated (relative CS > 0.5 and ≤ 0.5). There was no difference in survival between the two groups, $p = 0.55$, Figure 3.

The patients with no abnormal bone uptake on the baseline scan were excluded from the analysis of pattern of uptake and survival as there was no pattern of uptake to classify. For the survival analysis, patients with clearly defined focal uptake on the baseline scan were considered as one category.



CS, Curie score; OS, overall survival.

FIGURE 3: Overall survival by relative Curie score for score ≤ 0.5 versus > 0.5 at the end of treatment scan.

All patients with diffuse uptake, lesions with poorly defined margins at baseline were also grouped as one category. The survival of patients with focal uptake was compared with those with diffuse uptake.

Of the 12 patients who survived, four had focal uptake and eight diffuse uptake. The uptake pattern of the 22 patients who died were as follows: five had focal uptake and the remaining 17 had diffuse uptake.

There was no difference in survival between patients with focal uptake ($n = 9$) and those with diffuse uptake ($n = 25$), median survival 31.2 months versus 24.5 months ($p = 0.15$).

The authors did not have sufficient patient numbers to enable assessment of the relationship between baseline form of bone uptake and survival in patients with NYMC amplified tumours.

Discussion

The authors found that the baseline CS did not predict outcome in our cohort. This is similar to initial reports that the pre-treatment score is not a predictor of prognosis.^{5,14} In 2013, the COG reported that in 280 patients with stage 4 neuroblastoma, there was no correlation between the pre-treatment CS and treatment outcome.⁵ However, recently Yanik et al. tested the CS on an International Society of Paediatric Oncology European Neuroblastoma (SIOPEN) data set of 345 patients. They found that a baseline CS > 12 was associated with decreased EFS, 5-year EFS $43.0\% \pm 5.7\%$ for a CS of ≤ 12 versus $21.4\% \pm 3.6\%$ for a CS > 12 .⁶ It is important to observe that in this study the authors assessed the association between CS and OS and not EFS.

The CS after induction chemotherapy did not predict outcome in the high risk neuroblastoma cohort of this study.

Previous studies have reported on the prognostic significance of semi-quantitative score post-therapy. Katzenstein et al. studied the prognostic significance of [¹²³I]mIBG scan scores in a group of 29 neuroblastoma patients with age at diagnosis > 18 months and reported that score ≥ 3 after induction therapy was associated with a significantly worse EFS.¹⁵ The post-induction CS of the 237 patients in the COG protocol A3973 with stage 4 neuroblastoma who had post-induction imaging was a predictor of EFS. They reported that patients with a CS > 2 ($n = 52$) had decreased EFS compared with those with CS ≤ 2 ($n = 185$) after induction therapy with 3-year EFS of $15.4\% \pm 5.3\%$ versus $44.9\% \pm 3.9\%$ ($p = 0.001$).⁵ The follow-up study by the same group showed a similar pattern for 330 patients, 5-year EFS, $39.2\% \pm 4.7\%$ (CS ≤ 2) versus $16.2\% \pm 4.2\%$ (CS > 2).⁶ This COG protocol used a far more extensive treatment protocol, which included six cycles of induction chemotherapy, surgical resection of residual soft-tissue disease, autologous peripheral blood stem cell transplantation (ASCT), radiotherapy, and biotherapy.⁵ Although the pattern of results of this study is similar to previous reports, we did not find any statistically significant difference between the survival of patients with CS > 2 and those with CS ≤ 2 .^{5,15} This may be because of small numbers in this study. The authors only had eight patients who had a CS > 2 at the end of treatment. A far more likely explanation would be the difference in treatment protocols the vast majority of our patients, (82%) were treated with OPEC/OJEC chemotherapy alone.

In patients with relapsed neuroblastoma, those with relative scores ≤ 0.5 are reportedly more likely to have a complete or partial response to [¹³¹I]mIBG therapy.⁷ In the authors' series, the OS of these two groups was not significantly different. This finding is similar to a study by Andrich et al. who did not find post-therapy [¹³¹I]mIBG imaging findings to be predictive of prognosis. In that study, 8 out of 13 patients with stage 4 disease and normal post-therapy [¹³¹I]mIBG scans had disease relapse at one or more sites leading the authors to conclude that normalisation of [¹³¹I]mIBG scan after therapy was not a predictor of outcome.¹⁶ In contrast the study by Perel et al., reported that an abnormal post-induction chemotherapy [¹³¹I]mIBG/[¹²³I]mIBG scan was associated with a poor outcome: all five patients with uptake on the post-induction scan had disease relapse, while 8 of 16 patients with normal post-therapy scans were reported to be in progression-free remission.¹⁴ The COG study found that patients with $\geq 50\%$ reduction in CS from diagnosis to after induction ($n = 194$) had a much better survival when compared with those with $< 50\%$ reduction ($n = 43$) (3-year EFS: $42.9\% \pm 3.8\%$ vs $17.3\% \pm 5.9\%$, $p = 0.001$).⁵

A number of studies reported that residual mIBG avid disease on the post-induction chemotherapy scan predicts poor outcome after allogenic stem cell transplant and relapse after high-dose therapy with peripheral blood stem cell rescue, local radiotherapy, and cis-retinoic acid.^{15,17}

Recently it was reported that in patients with NMYC amplified tumours, those with focal lesions had a much

better EFS and OS than those in the other metastatic groups with a more diffuse pattern of uptake with 5-year EFS and 5-year OS of $63\% \pm 24\%$ versus $21\% \pm 15\%$, $p = 0.006$ and $81\% \pm 20\%$ versus $28\% \pm 17\%$, $p = 0.001$, respectively. The median age at diagnosis of patients in the study was similar to those in our cohort (34 months vs 32.5 months, respectively); however, that study included 84 patients with NMYC amplified disease (total number of study patients was 249) compared with 17 patients with NMYC amplified tumours in the present study.¹² Our patient numbers were too small to accurately assess the relationship between the pattern of bone uptake and survival in the NMYC amplified group.

Twenty of the 22 patients in our series who died were older than 12 months at diagnosis, 12 of them had NMYC amplified tumours while only five patients with NMYC amplified tumours survived. Nine patients who died had poorly differentiated tumours compared with three in the survivor group. This is similar to previous reports of older age at diagnosis, presence of NMYC amplification and poor tumour differentiation being associated with a worse prognosis in neuroblastoma.^{2,3}

Usually decreased uptake is associated with good disease response. Decreased [¹²³I]mIBG avidity has also been described when a tumour differentiates into a more benign pathology such as ganglioneuroma, 30% of which do not take up [¹²³I]mIBG.¹⁸ In a second group of patients it may be an indication of a worse prognosis because of tumour dedifferentiation especially if there is discordance between the [¹²³I]mIBG and 2-[¹⁸F]fluoro-2-deoxy-D-glucose (2-[¹⁸F]FDG) uptake. Higher 2-[¹⁸F]FDG have been found to have association with poorer prognostic markers such as N-MYC amplification.¹⁹ The authors postulate that some of their patients may have decreased uptake on the post-therapy scans in the setting of more aggressive and dedifferentiated disease.

While the international recommendations regarding the use of [¹²³I]mIBG in staging and response assessment of neuroblastoma are clear, there are challenges in the local South African (and probably entire African) setting that impact the use. [¹²³I]mIBG is cyclotron produced and the authors rely on a local producer for supply. For several months each year, the radiopharmaceutical is unavailable for use as the production plant is shut down for maintenance. This shutdown impacts patient management and also makes it more difficult to establish the beneficial value of [¹²³I]mIBG imaging in neuroblastoma in this setting.

This retrospective study may have had the biases usually associated with such designs. However, this study attempted to reduce the influence of bias by abstracting the clinical data only after all [¹²³I]mIBG scans had been reviewed. The small number of patients included in this study is another limitation. The patients were treated with less intensive treatment regimes than described in the

international studies this probably have also impacted the results of this study.

A larger follow-up study in a patient population who are treated with a standard protocol is needed to assess the impact of the CS in our setting.

Conclusion

In this study, the baseline CS, post-induction CS and magnitude of reduction in CS did not predict OS in stage 4 neuroblastoma. A number of factors such as small patient numbers, less intensive treatment regimes, and possible poorly dedifferentiated disease have been identified for this finding.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

Y.A.A. and A.B. were responsible for the design, data collection, analysis and writing the first draft of the manuscript. Senior review, expert consultation and final documentation approval was carried out by A.v.E., Y.A.A. and A.B. The authors alone are responsible for the content and writing of this article.

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Data availability

Data supporting the findings of this study are available from the corresponding author, Y.A.A., on request.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

References

1. Mueller S, Matthay KK. Neuroblastoma: Biology and staging. *Curr Oncol Rep*. 2009;11:431–438. <https://doi.org/10.1007/s11912-009-0059-6>
2. Matthay KK, Villablanca JG, Seeger RC, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-*cis*-retinoic acid. *N Engl J Med*. 1999;341(16):1165–1173. <https://doi.org/10.1056/NEJM199910143411601>
3. Shimada H, Stram DO, Chatten J, et al. Identification of subsets of neuroblastomas by combined histopathologic and N-myc analysis. *J Natl Cancer Inst*. 1995;87(19):1470–1476. <https://doi.org/10.1093/jnci/87.19.1470>
4. Bombardieri E, Giammarile F, Aktolun C, et al. ¹³¹I/¹²³I-metaiodobenzylguanidine (mIBG) scintigraphy: Procedure guidelines for tumour imaging. *Eur J Nucl Med Mol Imaging*. 2010;37(12):2436–2446. <https://doi.org/10.1007/s00259-010-1545-7>
5. Yanik GA, Parisi MT, Shulkin BL, et al. Semiquantitative mIBG scoring as a prognostic indicator in patients with stage 4 neuroblastoma: A report from the children's oncology group. *J Nucl Med*. 2013;54(4):541–548. <https://doi.org/10.2967/jnumed.112.112334>
6. Yanik GA, Parisi MT, Naranjo A, et al. Validation of postinduction curie scores in high-risk neuroblastoma: A children's oncology group and SIOPEN group report on SIOPEN/HR-NBL1. *J Nucl Med*. 2018;59(3):502–508. <https://doi.org/10.2967/jnumed.117.195883>
7. Messina JA, Cheng SC, Franc BL, et al. Evaluation of semi-quantitative scoring system for metaiodobenzylguanidine (mIBG) scans in patients with relapsed neuroblastoma. *Pediatr Blood Cancer*. 2006;47(7):865–874. <https://doi.org/10.1002/pbc.20777>
8. Olivier P, Colarinha P, Fettich J, et al. Guidelines for radioiodinated MIBG scintigraphy in children. *Eur J Nucl Med Mol Imaging*. 2003;30:B45–B50. <https://doi.org/10.1007/s00259-003-1138-9>
9. Lassmann M, Biassoni L, Monsieurs M, Franzius C, Jacobs F. The new EANM paediatric dosage card. *Eur J Nucl Med Mol Imaging*. 2007;34(5):796–798. <https://doi.org/10.1007/s00259-007-0370-0>
10. Lassmann M, Treves ST. Pediatric radiopharmaceutical administration: Harmonization of the 2007 EANM paediatric dosage card (version 1.5.2008) and the 2010 North American consensus guideline. *Eur J Nucl Med Mol Imaging*. 2014;41:1636. <https://doi.org/10.1007/s00259-014-2817-4>
11. Matthay KK, Edeline V, Lumbroso J, et al. Correlation of early metastatic response by ¹²³I-metaiodobenzylguanidine scintigraphy with overall response and event-free survival in stage IV neuroblastoma. *J Clin Oncol*. 2003;21(13):2486–2491. <https://doi.org/10.1200/JCO.2003.09.122>
12. Bleeker G, Van Eck-Smit BL, Zwinderman KH, et al. MIBG scans in patients with stage 4 neuroblastoma reveal two metastatic patterns, one is associated with MYCN amplification and in MYCN-amplified tumours correlates with a better prognosis. *Eur J Nucl Med Mol Imaging*. 2015;42(2):222–230. <https://doi.org/10.1007/s00259-014-2909-1>
13. Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol*. 1993;11(8):1466–1477. <https://doi.org/10.1200/JCO.1993.11.8.1466>
14. Perel Y, Conway J, Kletzel M, et al. Clinical impact and prognostic value of metaiodobenzylguanidine imaging in children with metastatic neuroblastoma. *J Pediatr Hematol Oncol* [serial online]. 1999;21(1):13–18. <https://doi.org/10.1097/00043426-199901000-00004>
15. Katzenstein HM, Cohn SL, Shore RM, et al. Scintigraphic response by ¹²³I-metaiodobenzylguanidine scan correlates with event-free survival in high-risk neuroblastoma. *J Clin Oncol*. 2004;22(19):3909–3915. <https://doi.org/10.1200/JCO.2004.07.144>
16. Andrich MP, Shalaby-Rana E, Movassaghi N, Majd M. The role of 131 iodine-metaiodobenzylguanidine scanning in the correlative imaging of patients with neuroblastoma. *Pediatrics* [serial online]. 1996 [cited 2021 Jun 28];97(2):246–250. Available from: www.aappublications.org/news
17. Ladenstein R, Philip T, Lasset C, et al. Multivariate analysis of risk factors in stage 4 neuroblastoma patients over the age of one year treated with megatherapy and stem-cell transplantation: A report from the European Bone Marrow Transplantation Solid Tumor Registry. *J Clin Oncol*. 1998;16(3):953–965. <https://doi.org/10.1200/JCO.1998.16.3.953>
18. Samim A, Tytgat GAM, Bleeker G, et al. Nuclear medicine imaging in neuroblastoma: Current status and new developments. *J Pers Med*. 2021;11(4):270. <https://doi.org/10.3390/jpm11040270>
19. Liu CJ, Lu MY, Liu YL, et al. Risk stratification of pediatric patients with neuroblastoma using volumetric parameters of 18F-FDG and 18F-DOPA PET/CT. *Clin Nucl Med* [serial online]. 2017 [cited 2022 Oct 17];42(3):e142–e148. Available from: https://journals.lww.com/nuclearmed/Fulltext/2017/03000/Risk_Stratification_of_Pediatric_Patients_With.31.aspx