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Residual meta-iodobenzyl guanidine (MIBG) positivity following therapy for metastatic neuroblastoma: Patient characteristics, imaging, and outcome

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Abstract

Background: Meta-iodobenzylguanidine(MIBG) scans are used to detect neuroblastoma metastatic lesions at diagnosis and during posttreatment surveillance. MIBG positivity following induction chemotherapy correlates with poor outcome; however, there are reports of patients with progression-free survival despite MIBG positivity at the end of therapy. The factors distinguishing these survivors from patients who progress or relapse are unclear. FDG-positron-emission tomography (PET) scans can also detect metastatic lesions at diagnosis; however, their role in posttherapy surveillance is less well studied.

Methods: We performed a retrospective analysis of International Neuroblastoma Staging System (INSS) stage 4 patients to identify those with residual MIBG-avid metastatic lesions on end-of-therapy scans without prior progression. Data collected included age, disease sites, histopathology, biomarkers, treatment, imaging studies, and response.

Results: Eleven of 265 patients met inclusion criteria. At diagnosis three of 11 patients were classified as intermediate and eight of 11 high risk; nine of 11 had documented marrow involvement. Histologic classification was favorable for four of 10 and *MYCN* amplification was detected in zero of 11 cases. The median time with persistent MIBG positivity following treatment was 1.5 years. Seven patients had at least one PET scan with low or background activity. Biopsies of three of three MIBG-avid residual lesions showed differentiation. All patients remain alive with no disease progression at a median of 4.0 years since end of therapy.

Conclusion: Persistently MIBG-avid metastatic lesions in subsets of patients following completion of therapy may not represent active disease that will progress. Further studies are needed to determine whether *MYCN* status or other biomarkers, and/or

Abbreviations: 18-F-FDG, fluorine-18-fluorodeoxyglucose; INPC, International Neuroblastoma Pathology Classification; INRC, International Neuroblastoma Response Criteria; INSS, International Neuroblastoma Staging System; MIBG, meta-iodobenzylguanidine; NB, neuroblastoma; PET, positron-emission tomography; PR, partial response; SCT, stem cell transplant; SD, stable disease; SUV, standardized uptake values.

PET scans, may help identify patients with residual inactive MIBG lesions who require no further therapy.

KEYWORDS
MIBG, neuroblastoma, PET

1 | INTRODUCTION

Clinical and biological heterogeneity is a characteristic feature of neuroblastoma (NB) and may account for the wide range of clinical behaviors including differences in response to treatment. NB patients have clinical courses that range from spontaneous regression to widespread metastatic disease that is often resistant to intensive multimodal therapies.[1] Age, stage, and molecular-genetic features are prognostic factors that are used to classify patients into low-, intermediate-, and high-risk groups, with therapy being tailored accordingly.[2,3] Bone marrow sampling and imaging studies are used to determine stage and metastatic spread at diagnosis, as well as to monitor treatment response and surveillance following completion of therapy.[2]

Although historically bone scans with Tc-99m-methylene diphosphonate ([^{99m}TC]Tc-MDP) were commonly used to detect bone lesions for NB patients, the current standard imaging to detect metastatic spread is iodine-123 or 131 meta-iodobenzylguanidine (MIBG) scans. MIBG is a norepinephrine analog that concentrates in NB cells via uptake by the norepinephrine transporter (NET) and is a very sensitive and specific test for detecting soft tissue, bone, and bone marrow disease.[4] For the approximately 90% of tumors that are MIBG-avid, scans are further used to stage, measure response and detect relapses.[5,6] Several studies demonstrate that persistent MIBG positivity, and specifically quantitative MIBG scoring (e.g., Curie score) during and after induction chemotherapy correlate with survival; however, the impact on prognosis may depend on the timing of scans and specific therapies received.[5–9] Recent reports, mostly of patients with loco-regional and/or intermediate-risk disease, have suggested that patients with MIBG scans that are persistently positive following the end of treatment do not necessarily progress or relapse, and that MIBG positivity can be seen in tumors that mature or undergo differentiation and thus, may not require further treatment.[10–13] However, few patients with metastases and/or high-risk disease are included in these studies, and only subsets of these patients had extensive follow-up, biopsies, or alternative types of imaging.

Positron-emission tomography (PET) with fluorine-18-fluorodeoxyglucose ([^{18}F]FDG) is used for imaging and staging for MIBG-non-avid patients and several studies have also compared the sensitivity of [^{18}F]FDG-PET and MIBG scans at the time of diagnosis.[14] For INSS stages 1 and 2 patients, [^{18}F]FDG-PET was superior at determining primary disease extent and detection of residual masses; however, MIBG was more sensitive in detecting metastases in INSS stage 4 patients.[15] In addition, PET scans with a different imaging agent 3,4-dihydroxy-6-[^{18}F]fluoro-L-phenylalanine ([^{18}F]fluorodopa) may be more sensitive than [^{123}I]mIBG for staging and evaluating residual disease after chemotherapy; however, the role for further surveillance has not been studied.[16] Jarmillo et al. reported a single INSS stage 4 patient with persistent MIBG uptake who had a concurrent negative [^{18}F] FDG-PET scan. Based on the observed low metabolic activity, therapy was terminated with no evidence of disease progression detected at 3 years following completion, suggesting that persistent MIBG uptake may reflect tumor differentiation and that [^{18}F]FDG-PET-CT may inform further treatment decisions.[17]

The goal of our study was to identify patients with metastatic disease at diagnosis (INSS4) who had detectable posttherapy residual metastatic MIBG-avid lesions, describe their outcomes, and determine whether there may be characteristics predictive of MIBG-positive lesions that remain stable or eventually resolve. In addition, we describe PET scan and biopsy findings in a subset of these patients. These results may support the use of additional studies, including PET scans, to assist in identifying less-active, potentially differentiated, MIBG-avid lesions following completion of therapy.

2 | METHODS

We conducted a multicenter retrospective analysis including patients at Hospital for Sick Children, McMaster Childrens' Hospital, BC Children's Hospital, and Janeway Children's Health and Rehabilitation Centre. Research ethics boards and data sharing agreements were approved at all institutions. Eligible patients were 0–18 years old with INSS stage 4 NB diagnosed between 2002 and 2018. For the primary analytic cohort, patient eligibility was defined as those with persistent metastatic site MIBG positivity on end-of-therapy scans without evidence of progression during previous treatment and for ≥24 months post completion of their upfront regimen as defined by International Neuroblastoma Response Criteria (INRC) (stable disease [SD] or partial response [PR] without progressive disease).[14] Patients with lesions limited to radiation fields were ineligible. Data collected included age at diagnosis, primary tumor site, *MYCN*-amplification status, histopathological classification (favorable, unfavorable), ploidy (DNA index = 1 or >1), 1p and/or 11q loss of heterozygosity (LOH) status, surgical reports detailing resection extent (complete or partial), treatment (chemotherapy, radiation and/or stem cell transplant [SCT], immunotherapy), INRC response, and imaging reports (CT, MRI, MIBG, PET scans). Biomarker and histology status were reported as per the International Neuroblastoma Risk Group (INRG) and International Neuroblastoma Pathology Classification (INPC) definitions, respectively.[14,18] In

addition to reports, all available MIBG and [^{18}F]FDG-PET images were re-reviewed centrally by two nuclear medicine radiologists and Curie scores, and standardized uptake values (SUVmax) were calculated. PET studies were considered positive if there was a focal activity more than the background liver uptake that could not be explained by the physiologic FDG activity. Descriptive statistics were used for demographic characteristics. Means and standard deviations were reported for continuous data; medians and quartiles for nonnormal continuous data; and count and percentages for categorical data. Statistical analyses were performed using SPSS statistical software.[19] Data were also collected for a second patient cohort with persistent MIBG-avid metastases on end-of-therapy scans who did progress within 24 months ("progressors").

3 | RESULTS

3.1 | Patient characteristics

3.1.1 | Stage and age

Records for all confirmed INSS[20] stage 4 newly diagnosed patients (2002–2018) were reviewed ($N = 265$) to identify eligible patients with residual MIBG-avid metastatic lesions following treatment (44/265) (Figure S1). Of these 44 patients, 32 had ≥1 MIBG-avid lesion not in the radiation field. Eleven of 32 patients did not have evidence of prior progression (primary or metastatic disease) or further progression for ≥24 months after end-of-therapy scans and form the main analytic cohort (consort diagram, Figure S1). Patient characteristics are summarized in Table 1. The median age was 29 months and included seven females and four males. Diagnostic bone marrow aspirates and/or biopsies were positive for neuroblasts in nine of 11 patients, and all had elevated urinary catecholamines. In addition, of the 32 patients with residual lesions on end-of-therapy MIBG scans, a second cohort of 19 were identified who *did* progress within 24 months ("progressors," Table 2).

3.1.2 | Tumor characteristics and risk groups

Genetic markers (Table 1) for the nonprogressors included zero of 11 with MYCN amplification; hyperdiploidy (DNA index >1) was detected in four of 10, and diploidy (DNA index 1) in six of 10. Among six of 11 patients with available LOH data, 11q and 1p LOH was detected in four and two tumors, respectively. Favorable INPC histology classification was reported for four of 10 patients who underwent biopsy at diagnosis. Of the individual histologic components used to determine INPC, the mitotic karyorrhexis index (MKI) was low for two of 10, intermediate for six of 10, and high for two of 10 patients. At diagnosis, poor differentiation was present for the majority (7/10) and three of 10 were differentiating. Based on age, histology, and *MYCN* status, three patients were classified as intermediate and eight as high risk according to the COG classification.[20]

3.2 | Response and therapies

At diagnosis, patients received initial chemotherapy according to their assigned COG risk group, with three receiving intermediate-risk type therapy on or as per protocol ANBL0531 and the remaining seven were started on high-risk treatment on or according to the induction chemotherapy regimens for COG A3973, ANBL0532, or ANBL12P1.[21–24] Table 1 summarizes details of initial chemotherapy and radiation therapy received. In addition, most patients received further therapies for persistent MIBG-avid metastases (Table 1). All patients had a documented PR (7/11) or SD (4/11) after initial chemotherapy (either five to six cycles of high-risk induction chemotherapy or four to eight cycles of intermediate-risk chemotherapy) and surgical resection (Table 3). At the end of therapy, nine of 11 achieved PR, and all patients had normal urinary catecholamines and bone marrow assessments, with the exception of one patient who had rare differentiated cells detected on marrow biopsy. All three patients who were initially classified as intermediate risk were escalated to high-risk protocols.

For the nonprogressor main analytic cohort, six of 11 patients underwent myeloablative chemotherapy with SCT and five of six received additional therapies following SCT for persistent disease. The four of 10 patients who did not undergo SCT received additional chemotherapies and investigational agents. Therapies received by the nonprogressor ($N = 11$) and progressor ($N = 19$) cohorts were compared. All patients received cis-retinoic acid, and although a higher percentage of the nonprogressors received anti-GD2 immunotherapy (six of 11 vs. five of 19, nonprogressors vs. progressors), the difference was not statistically significant (Fischer's exact test, data not shown). No significant difference was detected for autologous SCTs (six of 11 vs. 16/19). These differences also remained nonsignificant when only including the eight high-risk nonprogressor subset in the analysis.

3.3 | Surgical resection and histology

As previous reports have suggested that residual or poorly responsive MIBG-avid primary tumors post chemotherapy may have differentiated histology, we reviewed postchemotherapy surgical and pathology reports (Table 3). Nine of 11 patients underwent resection during or at end of therapy and seven of nine histology reports included either ganglioneuroma or ganglioneuroblastoma, differentiation, and/or low MKI. Four patients had biopsies of residual MIBG-avid lesions. Three revealed differentiated NB; one was necrotic with fibrotic changes (Table 3).

3.4 | MIBG and PET scan surveillance

Among all 11 patients with MIBG-persistent positivity at the end of therapy, Curie scores decreased during their course; three of 11 scans eventually became negative despite no further therapy (Figure 1,

TABLE 1 Characteristics of patients with residual MIBG-avid metastases without progression (nonprogressors)

Pt #	Age (months)	Gender	Primary tumor site	COG risk group[a]	MYCN	Histology	DNA index (DI)	MKI	LOH1p/11q	Urine cate-cholamines	Initial protocol chemotherapy (COG)	SCT	Radiation therapy	Immuno-therapy, Cis-RA	Other therapy
1	46	M	Paraspinal	High	NA	UH; poorly differentiated, SP	DI = 1	Intermediate	ND	+	ANBL0532	Bu/Mel	Residual primary tumor, R humerus	Yes/yes	None
2	60	M	Paraspinal	High	NA	UH; poorly differentiated, SP	DI = 1	High	No; yes	+	ANBL0532	Bu/Mel	Paraspinal primary tumor	No/yes	Topo-cyclo. TMZ/irino Pracinostat. Vorinostat
3	48	F	Abdomen	High	NA	UH; poorly differentiated, SP	DI > 1	Intermediate	ND	+	ANBL0532	Bu/Mel	No	Yes/yes	TMZ/irino, MIBG therapy
4	18	F	Adrenal	High	NA	FH; 5% ganglionic differentiation	DI > 1	Intermediate	Yes; ND	+	ANBL12P1	No	No	Yes/yes	TVD
5	17	F	Adrenal	High	NA	UH; poorly differentiated; SP	DI = 1	High	No; no	+	ANBL0531 (1 cycle pre-risk group) ANBL0532	Single CEM	R abdomen, R iliac, femurs	Yes/yes	None
6	48	F	Adrenal	High	NA	UH	DI = 1	Intermediate	No; ND	+	A3973	Single CEM	L abdomen	No/yes	TMZ/irino, ABT-751
7	24	M	Abdomen	High	NA	FH; differentiating; SP	DI > 1	Low	Yes; yes	+	ANBL0532	No	No	Yes/yes	TMZ/irino, MIBG therapy, TVD, MLN8237, cyclo
8	36	F	RP	High	NA	ND (marrow only)	DI = 1	NA	ND	+	A3973	Bu/Mel	No	No/yes	Topo/Cyclo, MIBG therapy
9	9	F	RP	IR	NA	FH; differentiating, SP	DI = 1	Low	No; yes	+	ANBL0531 (4 cycles); ANBL0532 (2 cycles)	No	RP tumor	No/yes	TMZ/irino, vinblastine /rapamycin
10	4	F	Adrenal	IR	NA	FH; poorly differentiated, SP	ND	Intermediate	No; yes	+	ANBL0531	No	No	No/yes	Surgical resection
11	12	M	RP	IR	NA	FH; poorly differentiated	DI > 1	Intermediate	ND	+	ANBL0531 (4 cycles); ANBL0532	No	No	Yes/yes	TMZ/irino

Note: Rows describing patients initially classified as IR are the final three (#9-11).

Abbreviations: Cis-RA, cis-retinoic acid; dx, diagnosis; FH, favorable histology; IR, intermediate risk; NA, non-amplified; NB, neuroblastoma; ND, not done; RP, retroperitoneal; SCT, stem cell transplant; SP, stroma poor; TMZ/Irino, temozolomide and irinotecan; top-cyclo, topotecan + cyclophosphamide; TVD; topotecan-vincristine-doxorubicin; UH, unfavorable histology; XRT, radiation.

[a]Risk stratification per COG.

TABLE 2 Characteristics of patients with residual MIBG-avid metastases who progressed (progressors)

Pt #	Age (months)	COG risk group[a]	MYCN	INPC	LOH1p/11q	SCT	Immuno-therapy/Cis-RA	Post Rx (Curie)	Additional therapies	Time to progression post end-of-therapy MIBG scan(months)	Alive/dead disease status
12	37	HR	NA	UH	No/yes	Yes	No/yes	2	At relapse: topo-cyclo, TMZ/irino, I131-MIBG, palliative RT	6	Dead
13	40	HR	NA	UH	ND	Yes	No/yes	1	At relapse: topo-cyclo, VP16 and focal RT	6	Alive NED >2 years off therapy
14	116	HR	NA	ND	Yes/yes	Yes	Yes/yes	1	Oral VP16 at end of therapy	10	Dead
15	49	HR	NA	UH	No/yes	Yes	Yes/yes	10	At relapse: topo-cyclo, chemoimmunotherapy	7	Dead
16	46	HR	NA	ND	ND	Yes	No/yes	4	Never stopped therapy	13	Dead
17	157	HR	NA	UH	No/yes	Yes	No/yes	2	Never stopped therapy	6	Dead
18	65	HR	NA	UH	No/no	No	No/yes	19	Did not stop therapy until 4 years Post diagnosis	12	Alive w/ disease (Curie 17) >2 years off all Rx
19	156	HR	NA	UH	Yes/yes	No	No/yes	19	MIBG, ALK TKI	6	Dead
20	36	HR	NA	UH	Yes/ND	Yes	No/yes	12	At relapse: topo-cyclo	23	Dead
21	48	HR	NA	UH	Yes/ND	Yes	Yes/yes	2	At relapse: topo-cyclo	6	Dead
22	72	HR	NA	UH	Yes/ND	Yes	Yes/yes	4	Never stopped therapy	3	Dead
23	28	HR	AMP	UH	Yes/ND	Yes	No/yes	5	Never stopped therapy (chemotherapy, MIBG)	14	Dead
24	27	HR	NA	UH	No/no	Yes	No/yes	9	Topo-cyclo	3	Dead
25	72	HR	NA	UH	Yes/ND	Yes	No/yes	8	Topo-cyclo, aurora kinase inhibitor (never stopped therapy)	14	Dead
26	60	HR	NA	UH	No/no	Yes	No/yes	5	VP16	3	Dead
27	30	HR	AMP	UH	No/no	Yes	No/yes	7	Progression post BMT	3	Dead
28	12	HR	NA	FH	No/ND	Yes	No/yes	5	Progression post BMT	3	Dead
29	36	HR	NA	UH	ND/ND	Yes	Yes/yes	3	Chemoimmunotherapy	12	Alive (on Rx) 12 months since progression
30	36	HR	NA	UH	ND/ND	No	No/yes	11	RT, topo-cyclo, TMZ/irino	8	Dead

Abbreviations: AMP, amplified; dx, diagnosis; FH, favorable histology; INPC, International Neuroblastoma Pathology Classifcation; NA, not amplified; NB, neuroblastoma; ND, not done; NED, no evidence of disease; Pt, patient; Rx, therapy; SCT, stem cell transplant; TMZ/irino, temozolomide and irinotecan; topo-cyclo, topotecan + cyclophosphamide; UH, unfavorable histology; XRT, radiation.

[a] Risk stratification per COG.

TABLE 3 Surgical resection, postchemotherapy histology, and posttherapy response

	Post induction/post cycles 4–8			Post ASCT	End of therapy	
Pt #	Overall response(INRC)	Resection extent	Pathology (primary tumor, post chemotherapy)	Overall response	Overall response	Pathology of persistent MIBG-avid lesion (location)
1	PR	Partial	5% Tumor nonviable, 85% viable 60% SP, poorly differentiated subtype with MKI <2% and 25% GNB	PR	PR	NA
2	SD	Partial	SP, GN, differentiating NB, lymphovascular space invasion present	PR	PR	NA
3	PR	Complete	Predominately GN-like intermixed with GN-like differentiating	SD	SD	GN (primary tumor)
4	SD	Complete	<15% Necrosis, SP, differentiating NB, anaplasia present	NA	NA	NA
5	PR	Complete	SP, poorly differentiated NB	PR	PR	NA
6	PR	Complete	SP, GNB, differentiating NB	PR	PR	NA
7	SD	Partial	<5% Necrosis, poorly differentiated	NA	PR	Schwannian stroma and ganglion cells (liver)
8	PR	No resection	NA	PR	PR	NA
9	SD	Partial	SP, differentiating NB, minor component of ganglioneuroblastomatous differentiation	SD	PR	NA
10	PR	Complete	Residual NB w/ ganglion cell differentiation, SP	NA	PR	Residual GNB with a nidus of maturing NB (liver)
11	PR	No resection	NA	PR	PR	Fibrosis (R temporal bone)

Abbreviations: GN, ganglioneuroma; GNB, ganglioneuroblastoma; GNB-intermixed, ganglioneuroblastoma intermixed; NA, not applicable; NB, neuroblastoma; NEG, negative; POS, positive; PR, partial response; Pt, patient; SD, stable disease; SP, stroma poor.

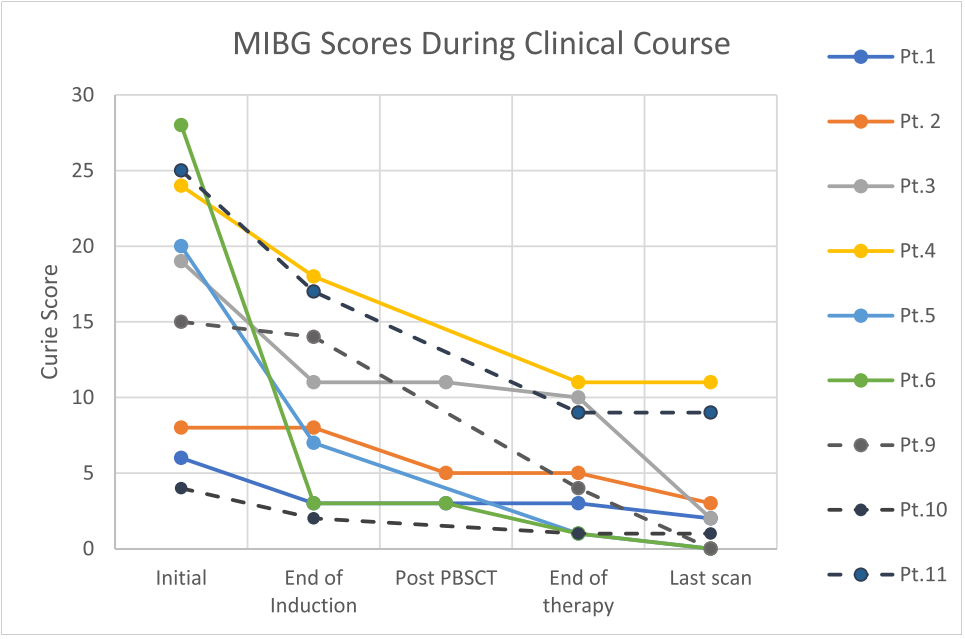

FIGURE 1 MIBG scores (Curie) During clinical course. Shown are the Curie scores for each patient at diagnosis and at the indicated time points during therapy and posttherapy surveillance. Nine of 11 patients with data included those with scans available for central review. End of therapy for intermediate-risk patients (#9, 10, 11), dotted lines, was following four to eight cycles of initial chemotherapy regimen

Tables S1 and S2). Nine patients continued to show MIBG uptake up to 6.5 years following active therapy. Eight of the 11 patients continued to demonstrate uptake in the primary tumor along with bony sites and liver on their last MIBG scan (Table S2). The Curie score and MIBG-avid lesion numbers decreased in the nine patients with scans available for central review by at least 30% (post SCT and/or end of therapy) (Figure 1, Figure S2). Seven patients had ≥1 [^{18}F]FDG-PET scan performed at time of MIBG and six of seven were considered negative for active disease at the sites corresponding to MIBG-avid lesions based on no nonphysiologic FDG activity above background liver activity. The SUVmax was <2.5 for all, and many publications suggest variable cut-offs for malignant lesions ranging between 2 and 2.5 (Table S1).[25–31]

3.5 | Outcomes for patients with and without progression

The 11 patients in the analytic cohort (nonprogressors) have been off therapy for a median of 4.0 years (range 1–8) and zero of 11 has had evidence of progressive disease and all are alive at a median of 8 years (range 2–12) from diagnosis. One patient developed myelodysplastic syndrome and underwent allogenic SCT. In contrast to the 11 patients who did not progress, 19 patients with residual MIBG-avid lesions on end-of-therapy scans did progress in the subsequent 3–24 months and 17/19 did not survive (Table 2). The majority either progressed within 6 months following end of therapy or progressed within 12–24 months while still receiving salvage treatments. Similar to the main analytic cohort who did not progress, the majority of these patients (19/21) had tumors that were *MYCN*-nonamplified and 10/15 with testing had detectable 1p or 11q LOH.

4 | DISCUSSION

MIBG scans are used to detect primary and metastatic lesions at diagnosis and during posttreatment surveillance; however, previous reports, mainly for patients with loco-regional tumors, suggested that posttherapy residual MIBG-avid lesions may not always lead to disease progression.[10–12,17] We identified a rare cohort of patients with metastatic NB (intermediate- and high-risk patients) at diagnosis who had either PR or SD with residual MIBG-avid metastatic lesions at the end of upfront therapy, and subsequently did not show progression for an additional 24 months or longer. These represented <5% of all initially diagnosed INSS4 patients. The majority (7/9) who had pathology from resected tumors or residual metastatic lesions had evidence of differentiation. Those with MIBG-avid residual lesions and concurrent PET scans had evidence of low or no FDG-PET-metabolic activity. In contrast to the three of 19 patients with persistent MIBG-avid lesions who had PD within 24 months, all 11 of the nonprogressors were long-term survivors with a median of 4 years follow-up from the end of last active therapy. These results suggest that biopsies and, in some cases, serial [^{18}F]FDG-PET scans may help discriminate active residual metastatic lesions that are potentially differentiated and less likely to progress.

In contrast to our study of patients with metastatic disease, the majority of previous series of residual posttreatment MIBG-avid

NB included non-high-risk and/or locoregional cases. Marachelian et al. reported 18 INSS stage 3 intermediate-risk patients with postchemotherapy residual or nonresponsive (SD) primary tumors.[10] Of those with MIBG scans, 10/10 were positive. Histology from postchemotherapy biopsies/resections correlated with radiologic response, with differentiation being more common in those with significant residual or stable/progressive tumors. Another retrospective study identified five of 20 intermediate-risk loco-regional patients with residual MIBG-avid masses post resection, who later became MIBG-negative during follow-up with no further treatment or progression.[11] For metastatic patients, Okamoto et al. identified four of 15 consecutively diagnosed INSS4 patients with high-risk NB and persistent positive MIBG scans post SCT who remained alive (35–100 months since diagnosis) without active disease or further chemotherapy.[12] Finally, Pinto et al. reported two intermediate-risk INSS4 NB patients with persistent MIBG uptake but SD 28 and 13 months after completion of cytotoxic treatment.[13]

The majority of INSS4 patients in our analytic cohort were high risk at diagnosis and the three of 11 that were initially classified (and treated) as intermediate risk were later treated with high-risk therapies based on poor response to initial chemotherapy. All patients also received the differentiation agent cis-retinoic acid and a higher percentage of the nonprogressors (vs. progressors) received immunotherapy. Multimodality intensive treatment, including chemotherapy, surgical resection, radiation, differentiation agents, and immunotherapy has improved survival rates for high-risk patients, but results in short- and long-term toxicities.[20,32–36] Recent trials have focused on intensifying therapy for most high-risk patients with improved outcomes reported for those with ≥PR to induction chemotherapy.[37] However, there may be subsets in which lack of PR does not predict a poor long-term outcome, especially those who initially present with intermediate-risk disease and more favorable biomarkers, a subset with EFS and OS over 80% and 90%, respectively.[38,39] Identification of these rare patients with residual MIBG-avid metastatic lesions who will not progress may enable improved ability to tailor therapy and spare potential toxicities. In particular, the rare INSS4 intermediate-risk patients with persistent lesions following upfront chemotherapy may not require SCT based on our case series (including three intermediate risk) and other reports.[10–13] Furthermore, although patients with high-risk NB with residual lesions post induction have been shown to have an inferior outcome, these results may not extrapolate to residual lesions in these rare intermediate-risk "refractory" patients or high-risk patients with persistent lesions post SCT or immunotherapy.[8]

Of the 11 patients in our analytic cohort who did not progress, eight of 11 were classified as high risk. Optimal therapy for this rare subset is unknown, but given that they were initially classified as high risk or reclassified following suboptimal metastatic response and treated as high risk, the majority (8/11) received additional therapies for refractory/persistent NB. Review of these patients revealed findings suggestive of potentially less aggressive disease such as normalized urine catecholamine levels and previous or current biopsies with evidence of differentiation. Furthermore, Curie scores during and post treatment continued to decrease for the majority, and for the subset with PET scans metabolic activity was low. Interestingly, although 20% of patients (and 40% of high risk) have tumors that harbor *MYCN* amplification, zero of 11 patients in our analytic cohort without progression and two of 19 in the cohort with progression had tumors with *MYCNA*.[40] This finding may be supported by two recent publications suggesting that *MYCNA* is more commonly detected in tumors from patients who have either CR or PD following/during induction chemotherapy and appear to be distinct from our cohort with upfront PR and SD.[37,41]

Diploidy (DNA index of 1) and segmental chromosomal aberrations (SCA), including 11q deletion, 1p deletion, and 17q gain, are prognostic in some patient subsets.[42–44] Six of 11 patients had diploid tumors and of the patients with available data five of six had 1p and/or 11q LOH (four of six with 11q LOH and two of six with 1p LOH). LOH at 11q has been previously identified as an adverse prognostic feature in subsets of patients with NB and is often found in *MYCN*-nonamplified NB tumors.[42] A recent study by Pinto et al. suggested that high-risk patients with 11q loss respond less favorably to induction chemotherapy and that absence of 11q LOH was independently associated with an end induction response of PR or better.[37] Although our analytic cohort is small, these results suggest that lack of *MYCNA*, and potentially 11q loss, may represent potential biomarkers for patients with poor upfront chemotherapy response. Identification of biomarker determinants of this indolent or quiescent disease pattern, in contrast to poor upfront response, will require larger studies to identify and validate specific segmental chromosome aberrations, alterations in telomere maintenance (including ATRX alterations), or novel signaling pathways.[45–47]

The majority of studies to date have analyzed [^{18}F]FDG-PET sensitivity at diagnosis but not for long-term surveillance for metastatic NB, and direct comparisons of MIBG with [^{18}F]FDG-PET scan sensitivity and specificity during surveillance has not been reported.[15–17] The only study that evaluated PET scan utility for diagnosis and follow-up was reported by Kushner et al. in 2001[48] who compared multiple imaging modalities (CT, MIBG, PET) and marrow assessments for sensitivity in detecting metastatic disease in 51 high-risk patients. They concluded that [^{18}F]FDG-PET with bone marrow aspirates were optimal for surveillance monitoring. They also proposed that [^{18}F]FDG-PET may provide insight into proliferative activity and malignant potential of lesions. Although it was not apparent whether this cohort may have included patients with posttherapy residual MIBG-avid lesions or patients with PET and MIBG scan discordance, the rare subset we identified represented only 5% of all patients with distant metastases (INSS4) at diagnosis. Our findings in this small patient subset with residual MIBG-avid lesions support using [^{18}F]FDG-PET scans as an additional way to help identify quiescent MIBG-avid lesions; however, larger studies are needed to confirm PET scan utility in this context. Finally, other PET radiotracers (e.g., [^{68}Ga]DOTATATE) have roles in NB diagnosis and prognosis, especially for MIBG non-avid lesions; however, further studies are required to compare [^{68}Ga]DOTATATE and [^{18}F]FDG-PET, especially in the context of residual disease imaging.[49–51]

The role of biopsy of residual MIBG-avid lesions is not well studied; however, three patients with informative posttreatment biopsies showed differentiation. The majority of patients who underwent earlier tumor resections also had pathology with evidence of maturation similar to the previous report of loco-regional MIBG-avid posttherapy residual tumors with differentiation.[10] Thus, biopsies are likely to help in deciding whether residual avid primary tumor or metastatic lesions contain active nondifferentiated disease. Importantly, biopsies of residual and recurrent tumors are increasingly performed in the setting of recurrent or refractory NB to identify targetable genetic alterations and thus, may provide clinicians with informative histology.[38] Furthermore, many early-phase trials for NB patients now recommend or require biopsies of residual MIBG-avid lesions in patients in first response to determine differentiation status for trial eligibility.

Limitations of our study include the small patient cohort who all received different therapies. Many also received therapy that exceeded the doses and types usually used for patients with intermediate- or even high-risk NB and it is difficult to determine which, if any, of these therapies might have influenced the resolution of MIBG-avid lesions and/or survival. However, importantly our patients all remained stable or improved based on repeat Curie scores over 24 months and have been off treatment for median of 4 years. In contrast, only two of 19 patients who progressed are still alive. The upfront risk groups, tumor features, and therapies received by the 11 nonprogressor patients were heterogeneous and not all patients had [^{18}F]FDG-PET scans or underwent biopsy. Further prospective studies of larger subsets of these patients are needed to identify clinical or biological characteristics at diagnosis or subsequent therapies associated with lack of progression of residual MIBG-avid lesions and long-term survival.

In summary, this study demonstrates that in some patients with INSS4 NB, persistently positive MIBG-avid metastatic lesions at end of therapy may not always portend disease progression and may instead indicate tumor maturation. [^{18}F]FDG-PET scans and serial biopsies may further help to identify these patients and should be performed prior to using additional therapies, especially in patients who initially had more favorable features classified as intermediate risk and/or lacking *MYCN* amplification. These studies may thus identify patients with differentiated residual metastatic tumor following SCT and immunotherapy who may not require additional experimental therapies and can be monitored closely with surveillance imaging that should include PET scans. Identification of this rare patient subset with nonactive residual MIBG-avid metastases and potential biomarkers will enable more precise tailoring of therapy and sparing of additional short- and long-term side effects.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Meredith S. Irwin and Nida Usmani developed the study concept. Nida Usmani, Carol Portwine, Rebecca J. Deyell, Paul C. Moorehead, Mateo Farfan, and Thuvaraha Vanniyasingam collected data. Reza Vali and Amer Shammas reviewed MIBG scans. All authors participated in the writing and editing of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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