Original Article

Low-Dose, Low-Specific Activity ^{131}I-metaiodobenzyl Guanidine Therapy in Metastatic Pheochromocytoma/Sympathetic Paraganglioma: Single-Center Experience from Western India

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Abstract

Introduction: Radionuclide therapy is a promising treatment modality in metastatic pheochromocytoma/paraganglioma (PPGL). There is scarce data on ^{131}I-metaiodobenzyl guanidine (^{131}I-MIBG) therapy from the Indian subcontinent. Hence, we aim to study the safety and effectiveness of low-dose, low-specific activity (LSA) ^{131}I-MIBG therapy in patients with symptomatic, metastatic PPGL. **Methods:** Clinical, hormonal, and radiological response parameters and side effects of LSA ^{131}I-MIBG therapy in patients with symptomatic, metastatic PPGL were retrospectively reviewed. World health organizations' (WHO) symptomatic, hormonal, and tumor response, and response evaluation criteria in solid tumors (RECIST1.1) criteria were used to assess the response. **Results:** Seventeen (PCC: 11, sympathetic PGL: 06) patients (15 with disease progression) received low-dose LSA ^{131}I-MIBG therapy. Complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) were 18% (3/17), 24% (4/17), 18% (3/17), and 41% (7/17), respectively, for WHO symptomatic response; 20% (2/10), 10% (1/10), 30% (3/10), and 40% (4/10), respectively, for WHO hormonal response; and 19% (3/16), 6% (1/16), 31% (5/16), and 44% (7/16), respectively for tumor response based on RECIST1.1. All patients with symptomatic PD and 50% (2/4) with hormonal PD had progression as per RECIST1.1 criteria. Side effects included thrombocytopenia, acute myeloid leukemia, mucoepidermoid carcinoma, and azoospermia in 6% (1/17) each. **Conclusions:** Our study reaffirms the modest efficacy and safety of low-dose, LSA ^{131}I-MIBG therapy in patients with symptomatic, metastatic PPGL. Symptomatic, but not hormonal, progression after ^{131}I-MIBG therapy correlates well with tumor progression and should be further evaluated with imaging. In resource-limited settings, anatomic imaging alone may be used to assess tumor response to ^{131}I-MIBG therapy.

Keywords: ^{131}I-MIBG, low-specific activity, paraganglioma, pheochromocytoma

Introduction

Pheochromocytoma (PCC) and paraganglioma (PGL), collectively called PPGL, are rare tumors arising from neural crest cells of the adrenal gland and autonomic ganglia. Metastasis is observed in 2%–25% of PCCs and 2.4%–60% in PGLs with a 5-year survival of 34%–74%.[1,2] Germline mutation in the succinate dehydrogenase B (*SDHB*) gene is the most frequent genetic abnormality in metastatic PPGLs. Treatment options for metastatic and/or inoperable tumors include external beam radiation therapy (EBRT), chemotherapy, peptide receptor radionuclide therapy (PRRT), ^{131}I metaiodobenzylguanidine (^{131}I-MIBG) therapy, radiofrequency ablation, and tyrosine kinase inhibitors.

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Radionuclide therapy with ^{131}I-MIBG is a promising option for unresectable and/or metastatic disease. ^{131}I-MIBG accumulates in the neuroendocrine cells via norepinephrine transporter (NET) and emits γ and β rays. Cytotoxicity is

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caused by β rays, whereas γ rays are useful in measuring distribution.[3]

In conventional ^{131}I-MIBG therapy (used in this study), 99% of the MIBG molecules are unlabeled with ^{131}I (low-specific activity [LSA]: 3.3 mCi/mg) resulting in low levels of radioactivity delivered to the tumor per dose. This may allow unlabeled MIBG molecules to compete for NET resulting in catecholamine excess in blood. LSA ^{131}I-MIBG therapy is classified into low dose (2.96–7.4 GBq), intermediate dose (7.43–18.5 GBq), and high dose therapy (>18.5 GBq).[4] It is observed that with an increase in the dose of LSA, the efficacy as well as side effects increase.[4] Recently, the United States Food and Drug Administration (USFDA) has approved high-specific activity (HSA) ^{131} I-MIBG in which almost all MIBG molecules are tagged with ^{131}I (~2,500 mCi/mg; 92,500 MBq/mg) leading to less catecholamine surge during therapy. It results in high levels of radioactivity delivered to the tumor per dose (approximately 100–200 times higher than that of LSA-^{131}I MIBG). Among patients treated with HSA ^{131} I-MIBG (phase II trial), 25% of patients had a 50% reduction in the requirement of antihypertensive drugs, 92% had a partial response (PR), and stable disease (SD) within 12 months but side effects were higher.[5]

In a meta-analysis evaluating the efficacy of LSA ^{131}I-MIBG therapy, tumor response-based pooled proportions for complete response (CR), PR, and SD were 0.03, 0.27, and 0.52, respectively, whereas hormonal response-based CR, PR, and SD were 0.11, 0.4, and 0.21, respectively.[6] However, these do not accurately represent the real-life scenario as studies included were heterogeneous with varied treatment regimens and only four included studies used on response evaluation criteria in solid tumors (RECIST) criteria to assess tumor response. Furthermore, only one study in the meta-analysis had documented tumor progression before patient inclusion; thus treatment effect would partly be influenced by the natural course of the disease.[6]

HSA therapy is not yet available in India, moreover, data on efficacy and safety of LSA ^{131}I MIBG therapy is scant from the Indian subcontinent; hence, we aim to describe our experience on low-dose, LSA ^{131}I-MIBG therapy in patients with metastatic progressive PPGL using standardized WHO and RECIST criteria.

Methods

A retrospective evaluation of patients with metastatic PPGLs registered between January 2004 and March 2020 at a tertiary care center from western India was performed. Patients with progressive and/or symptomatic metastases with avid uptake on ^{131}I-MIBG scan and who had received at least one cycle of ^{131}I-MIBG therapy with at least 3 months of follow-up after the first cycle were included in the study. The study was approved by Institutional Ethical Committee (EC/OA-171/2018) with a waiver of consent.

Diagnosis of PPGL was based on histopathology (HP) in those who underwent surgery (n = 13) and when HP was not available (n = 4), the diagnosis was based on biochemical, anatomical (contrast-enhanced computed tomography [CECT]), and functional imaging (^{68}Ga-dodecanetetraacetic acid–DPhe1-Tyr3-octreotate positron emission tomography CT [^{68}Ga-DOTATATE – PET/CT], and ^{131}I-MIBG scintigraphy). Metastasis was defined as the presence of lesions at nonchromaffin sites distant from the primary tumor (lymph node, bones, liver, lung, brain, and others) and further subclassified as synchronous (concurrent metastasis with primary lesion) and metachronous (metastasis detected after 3 months of diagnosis of the primary).[1,7]

Baseline clinical, biochemical, and radiological characteristics were reviewed. The biochemical evaluation included plasma-free nor-metanephrine (PFNMN) and metanephrine (PFMN) and/or 24h-vanillyl mandelic acid (VMA). PFNMN and PFMN were measured using an enzyme immunoassay commercial kit manufactured by Labour Diagnostic (Nord GmbH, Nordhorn, Germany); 24-h urinary VMA was measured by radioimmunoassay.[8,9] CECT was performed in two phases (plain and enhanced) from 2004 to 2012 and from 2013 onward four phases were used (unenhanced phase and 20 s, 1 min, and 15 min after contrast injection).[10] Genetic information was recorded whenever available.

MIBG Treatment Protocol

Scan protocol

All patients received 100 mg of a saturated solution of potassium iodide (SSKI) from 2 days before to 5 days after the injection of ^{131}I-MIBG to protect the thyroid and salivary glands. The whole body ^{131}I-MIBG scan was performed 48 to 72 h after intravenous injection of 37 MBq (1 mCi) of the radiopharmaceutical. Whole body views were acquired in anterior and posterior projections. Spot views of known or suspected lesions were also acquired. Images were independently interpreted by two experienced nuclear medicine physicians who were blinded about patient information. Any disagreement in interpretation was resolved after mutual discussion and consensus. All scans were stored on a mass storage device (Seagate, Cupertino, CA, USA) and analyzed by connecting to a picture archiving and communication system (PACS).

^{131}I-MIBG therapy protocol

All patients were administered 100 mg of SSKI from 48 h before to 2 weeks after ^{131}I-MIBG therapy. The blockade was done by α-blocker prazosin with adequate salt, water intake, and β-blocker for heart rate control before the therapy. A total of 5.55 to 7.4 GBq (150 to 200 mCi) of ^{131}I-MIBG was administered by an intravenous infusion lasting for 1–2 h using a lead-shielded infusion system. Vital signs were monitored before and at regular intervals during (every 30 min) and after (every 2 h) the infusion. Prophylactic antiemetic (ondansetron) was administered during the initial

2 days of therapy. Patients were isolated and monitored daily until their radiation burden was within the permissible limit to be discharged (usually within 1 week). At the time of discharge, a posttherapy scan was done in all patients to look for tracer uptake in the known lesions as well as additional areas of involvement.

Assessment of efficacy

Clinical and biochemical responses were evaluated as per the World Health Organization (WHO) criteria. WHO daily defined dose (DDD) criteria were used to assess the change of antihypertensives following therapy. Morphological responses to ^{131}I-MIBG therapy were assessed based RECIST criteria1.1 and WHO criteria.[11–13] The WHO and RECIST criteria1.1 have been detailed in the supplementary table.

Safety assessment: Common terminology criteria for adverse events (CTCAE, version 5), was used for reporting side effects.[14]

Statistical analysis

Categorical variables were expressed in actual numbers and percentages. Continuous variables were expressed as means ± standard deviation or median and range as appropriate. Chi-square test or Fisher's exact test were used to compare dichotomous variables, whereas the *t*-test or Mann–Whitney test was used for continuous variables as appropriate. Progression-free survival (PFS) and overall survival (OS) were determined by using Kaplan–Meier analysis and survival curves were compared using the log-rank test. All the statistical analyses were done using SPSS (version 23, IBM, Armonk, NY) and MedCalc (Version 19.1.6, Ostend, Belgium).

Results

Seventeen patients (13 males) with metastatic symptomatic PPGL (PCC: 11, sPGL: 06, HNPGL: 0) were included [Table 1]. They received a median of 3 (1–7) cycles of LSA ^{131}I-MIBG with a median cumulative dose of 19 (5.55–42.92) GBq. The indication of therapy was disease progression in 88% (15/17) and symptomatic metastases in 12% (2/17). The participants were followed up for a median period of 20 (3–31) months. Baseline characteristics are described in Table 2.

The response to therapy is detailed in Table 3. WHO symptomatic response-based CR, PR, SD, and progressive disease (PD) were observed in 3/17 (18%), 4/17 (24%), 3/17 (18%), and 7/17 (41%) patients, respectively. Of the 14 patients who were on antihypertensive drugs before ^{131}I-MIBG therapy, >50%, 10%–50%, and <10% decrease in DDD were observed in 5/14 (37%), 3/14 (21%), and 1/14 (7%), respectively, whereas 2/14 (14%) had no change in their DDD and 2/14 (14%) had an increase in their DDD by >10%. WHO hormonal response-based CR, PR, SD, and PD were present in 2/10 (20%), 1/10 (10%), 3/10 (30%), and 4/10 (40%) patients, respectively.

WHO tumor response-based CR, PR, SD, and PD were seen in 2/10 (20%), 1/10 (10%), 4/10 (40%), and 3/10 (30%) patients, respectively. Based on RECIST 1.1 criteria CR, PR, SD, and PD were observed in 3/16 (19%), 1/16 (6%), 5/16 (31%), and 7/16 (44%) patients, respectively. In patients treated for disease progression and assessed on RECIST1.1 ($n = 14$), CR, PR, SD, and PD were seen in 3/14 (21%), 1/14 (7%), 3/14 (21%), and 7/14 (50%) patients, respectively. Among patients who had PD on RECIST1.1, all of them had symptomatic PD whereas 50% (2 of 4) had hormonal PD. All 10 patients with tumor responses based on WHO criteria had concordant responses on RECIST1.1. ^{131}I-MIBG therapy resulted in numerically, but statistically insignificant, a higher rate of CR (18% vs. 0%, $P = 0.5$) and a lower rate of PD (36% vs. 60%, $P = 0.6$) in patients with PCC than those with sPGL. Figure 1 depicts one such patient with CR on MIBG therapy.

The overall survival rate was 76.5%, whereas the median OS was not reached [Figure 2]. Mortality was seen in 4/17 (24%) patients. The median (range) PFS following ^{131}I-MIBG therapy based on RECIST1.1 criteria was 37 (3–131) months [Figure 2]. The median (range) progression-free time (PFT) after ^{131}I-MIBG therapy for the symptomatic response was 37 (3–131) months and the median PFT for the hormonal response was not reached. The median (range) PFS was longer in ^{131}I-MIBG-treated PCC patients than those with sPGL (115 months vs. 37 months, $P = 0.42$) [Figure 2].

One patient [case: 10, Table 1] had transient grade 2 thrombocytopenia. One [case no 2, Table 1] had severe bone marrow toxicity with pancytopenia after 123 months of ^{131}I-MIBG therapy (7 cycles, cumulative dose 42.2 GBq). Bone marrow biopsy and flow cytometry led to the diagnosis of acute myeloid leukemia (AML) with a deletion of chromosome 7. Another patient [case 1, Table 1] was diagnosed with mucoepidermoid carcinoma (MEC) of the parotid gland after 115 months of ^{131}I-MIBG therapy, which was treated with surgical excision. None of these above three patients had received prior systemic therapy. One [case: 8, Table 1] with primary infertility was found to have the mild elevation of follicle-stimulating hormone (FSH) (13.74 mIU/mL), low inhibin B level (100 pg/mL), and azoospermia suggestive of Sertoli and germ cell dysfunction. This patient had received ^{131}I-MIBG therapy at an early age (18 years) and three cycles of cytotoxic chemotherapy (cisplatin/etoposide) at 21 years of age.

Discussion

We describe modest efficacy and minimal toxicity in Asian Indian patients with symptomatic metastatic PPGL (88% [15/17]) with disease progression who received low-dose LSA ^{131}I-MIBG therapy from a single center in western India. We also describe symptomatic and hormonal response using WHO criteria, and tumor response by both WHO and RECIST1.1 criteria in our ^{131}I-MIBG-treated PPGL cohort. All patients with symptomatic PD and 50% (2/4) with hormonal PD had PD on RECIST1.1 criteria.

In our patients, symptomatic response (CR + PR) was observed in 42% (7/17), whereas worsening of symptoms (PD) was

Table 1: Patient characteristics of the study cohort

Patient	Sex/Age at starting MIBG therapy, yrs	ECOG status before MIBG therapy	Primary tumor	Site of metastasis	Follow-up (months)	Size cm	PFNMN/PFMN, pg/mL	Previous therapy	Indication for MIBG therapy	Intensity of uptake on MIBG scan
1		1	PCC	Intra-abdominal	19	5		Surgery	M, P, S	++
2	M/51	1	PCC	Lung	15	4		Surgery	M, P, S	++
3*	M/31	2	PCC	Lung, Liver, Skeletal	27	2.5	317/143	Surgery, PRRT	M, P, S	++
4	F/62	3	sPGL	Liver, Bone	34	9.8	5392/39.2	Surgery	M, P, S	++
5	M/52	2	PCC	Lung, Mediastinal lymph node	38	11.4	256/-	Surgery	M, P, S	+
6	M/61	2	PCC	Liver	105	10.8	9922/173	Surgery, PRRT	M, P, S	+
7	F/36	1	PCC	Abdominal Lymph node	25	9	559/-		M, P, S, I	++
8	M/18	1	PCC	Liver	180	3	1591/-	Surgery, Chemotherapy	M, P, S	+
9*	M/19	3	PCC	Abdominal Lymph node	41	15		Chemotherapy, Angioembolization	M, P, S, I	+
10	M/44	2	PCC	Lung, Skeletal	21	8.4	984/79	Surgery, EBRT	M, P, S	++
11	M/53	2	PCC	Skeletal	20	5.6	1348/-	EBRT	M, P, S	+
12	F/58	3	sPGL	Liver, Skeletal	4	3.8	1281/-	Surgery	M, P, S	++
13	M/38	2	PCC	Lung, abdominal Lymph nodes	56	2.6	1957/-	Surgery	M, P, S	++
14	M/24	2	sPGL	Abdominal Lymph nodes	19	7.6	437/-	Surgery	M, S	+
15	M/38	2	sPGL	Left iliac mass and lymph nodes	16	5	2146/-	Surgery	M, P, S, I	+
16*	M/32	1	sPGL	Intraabdominal lymph nodes	37	8.7	-/23.5		M, S, I	++
17	F/35	2	sPGL	Abdominal Lymph node	5	5	5176/-	Surgery, Chemotherapy	M, P, S	++

Patient	Number of MIBG cycles	Cumulative dose of MIBG (GBq)	Response to MIBG therapy					Survival time (Months)			Outcome	Genetics
			DDD	WHO symptomatic response	WHO hormonal response	WHO tumor response	Best tumor response (RECIST criteria)	Since diagnosis	Since metastasis	Since MIBG Therapy		
1	5	30.5	−100%	CR	CR	NA	CR	403	115	115	Alive	NA
2	7	42.92	−11%	PD	NA	PD	PD	159	123	123	Alive	NA
3*	4	19.09	0	PD	NA	PD	PD	27	27	14	Died	RET M918T, MEN 2B
4	3	19	+33%	PD	PD	NA	PD	34	34	20	Died	NA
5	3	21.20	0	CR	CR	CR	CR	42	42	28	Alive	NA
6	1	5.66	−74%	SD	SD	SD	SD	105	24	5	Alive	Neg
7	2	12.98	−78%	PR	PD	SD	SD	25	25	23	Alive	NA
8	6	38.48	−100%	CR	PR	CR	CR	180	132	131	Alive	Neg
9*	6	42.73	0	SD	SD	PR	PR	119	119	117	Alive	NA
10	3	21.09	−14%	PR	SD	NA	PD	21	21	19	Alive	NA
11	2	15.65	−24%	SD	PD	SD	SD	37	37	20	Alive	NA

Contd...

Table 1: Contd...

Patient	Number of MIBG cycles	Cumulative dose of MIBG (GBq)	Response to MIBG therapy					Survival time (Months)			Outcome	Genetics
			DDD	WHO symptomatic response	WHO hormonal response	WHO tumor response	Best tumor response (RECIST criteria)	Since diagnosis	Since metastasis	Since MIBG Therapy		
12	1	5.55	NA	PD	NA	NA	PD	4	4	3	Died	NA
13	3	28	+74%	PD	PD	PD	PD	150	102	52	Alive	NA
14	2	12.83	−59%	SD	PD	SD	SD	19	19	10	Alive	Neg
15	2	14.8	NA	PD	NA	NA	PD	16	13	13	Died	NA
16*	1	7.4	0	PR	NA	NA	SD	85	85	37	Alive	NA
17	1	7.4	−2%	PR	NA	NA	NA	11	6	5	Alive	NA

*Normotensive. PCC: pheochromocytoma, sPGL: sympathetic paraganglioma, M: metastasis, S: symptomatic, P: progressive, I: inoperable primary, PD: progressive disease, SD: stable disease, PR: partial remission, CR: complete remission, DDD: daily defined dose, MIBG: metaiodobenzylguanidine, NA: not available, EBRT: external beam radiotherapy, ECOG: Eastern cooperative oncology group performance score, PFNMN: plasma-free normetanephrine, PFMN: plasma free metanephrine. Pretherapy urinary metanephrine levels were available in five patients (Patient No. 8, 9,11,12, and 14 with levels 304 µg/24 h, 107 µg/24 h, 86 µg/24 h, 119 µg/24 h, and 132 µg/24 h, respectively). Pretherapy urinary nor-metanephrine levels were available in two patients (Patient No. 11 and 12 with levels 386 µg/24 h and 4297 µg/24 h, respectively)

Figure 1: Response to LSA ^{131}I- MIBG therapy in patient number 5 A. Baseline imaging (Nov 2016) showing 11.4 cm left pheochromocytoma, A1 MIBG scan, A2 FDG fusion image, A3 CT scan B. Postoperative scan (June 2017) showing metastasis in cervical, lung and vertebrae, B1 MIBG scan, B2 FDG PET MIP image, B3 FDG fusion C. Post MIBG therapy (Mar 2018) showing complete remission, C1 MIBG scan, C2 FDG fusion, C3 CT scan

observed in a considerable proportion (41%) of patients. Although a recent study by Thorpe *et al*.[15] (n = 125) showed a higher rate (75%) of initial symptomatic response (CR + PR); 62% of these experienced symptomatic

Table 2: Baseline characteristics

Variable	*n*=17
Males, *n* (%)	13 (76)
Age at diagnosis (years) (mean±SD), median (range)	36.5±17, 35 (14-60)
Age at initiation of 131I-MIBG therapy (years) (mean±SD), median (range)	41.1±14, 38 (18-62)
Median (range) follow-up after therapy (months)	20 (3-131)
Mode of presentation, *n* (%)	
Catecholaminergic symptoms	9 (53)
Incidental	7 (41)
Symptoms of metastasis	1 (6)
Triad (headache, palpitation, sweating), *n* (%)	2 (12)
Symptoms	
Headache, *n* (%)	9 (53)
Sweating, *n* (%)	7 (41)
Palpitations, *n* (%)	9 (53)
Hypertension, *n* (%)	14 (82%)
Daily defined dose (DDD) of antihypertensive, median (range)	3 (0-12.66)
Diabetes mellitus, *n* (%)	5 (29)
Biochemistry	
Median (range) PFNMN (*n*=13), pg/ml	1348 (256-9922)
Median (range) PFMN (*n*=6), pg/ml	62 (23.5-173)
Median (range) 24-h urinary VMA (*n*=6), mg/24 h	20.16 (4.6-92.5)
Secretory phenotype (*n*=15), *n* (%)	
Normetanephrine secreting	11 (74)
Metanephrine secreting	2 (13)
Non secretory	2 (13)
Location (PCC/PGL), *n* (%)	11/6
Right PCC	5
Left PCC	6
Organ of Zuckerkandl (OOZ)	2
Infradiaphragmatic (other than OOZ)	4
Maximum tumor size (cm), mean±SD, median (range)	6.89±3.56, 5.6 (2.5-15)
Metastasis, *n* (%)	
Synchronous	17 (100)
Metachronous	10 (59)
Site	7 (41)
Lung	3 (18)
Liver	3 (18)
Bone	4 (23)
Lymph node	7 (41)
Treatment	
^{131}I MIBG therapy	
First-line therapy, *n* (%)	2 (12)
Second-line therapy, *n* (%)	9 (53)
Third-line therapy, *n* (%)	6 (35)
Other modalities, *n* (%)	
Surgery	13 (76)
Chemotherapy	3 (18)
EBRT	2 (12)
PRRT	2 (12)
Angioembolization	1 (6)

EBRT: external beam radiotherapy, MIBG: metaiodobenzyl guanidine, PCC: pheochromocytoma, PGL: paraganglioma, PFMN: plasma-free metanephrine, PFNMN: plasma-free normetanephrine, PRRT: peptide receptor radionuclide therapy, VMA: vanillyl mandelic acid

progression over a mean period of 1.8 years reducing the long-term symptomatic response to 28%. Notably, all our patients with symptomatic progression had tumor progression on RECIST1.1, which warrants evaluation for tumor progression by imaging in patients with symptomatic progression.

Pooled hormonal response-based CR, PR, and SD in the meta-analysis were 0.11 (0.05–0.22), 0.4 (0.28–0.53), and

Table 3: Characteristics of ^{131}I-MIBG therapy and response evaluation

^{131}I-MIBG Cycles, median (range)	3(1-7)			
^{131}I-MIBG dose GBq, median (range)	19 (5.55-42.92)			
Indication for ^{131}I-MIBG, *n* (%)				
Metastatic, symptomatic	2 (12%)			
Metastatic, symptomatic, progressive disease	15 (88%)			
Response-evaluation				
Change in the DDD (*n*=14), *n* (%)	Reduction by >50%: 5 (37) Reduction by 0-50%: 3 (21) Reduction by <10%: 1(7) Increased by >10 % : 2 (14) No change:2(14) NA: 1(7)			
Response by WHO/RECIST Criteria	**CR**	**PR**	**SD**	**PD**
WHO Symptomatic response (*n*=17), *n* (%)	3 (18)	4 (24)	3 (18)	7 (41)
WHO Hormonal response (*n*=10), *n* (%)	2 (20)	1 (10)	3 (30)	4 (40)
WHO Tumour response, (*n*=10), *n* (%)	2 (20)	1 (10)	4 (40)	3 (30)
RECIST 1.1 tumour response, (*n*=16), *n* (%)	3 (19)	1 (6)	5 (31)	7 (44)
MIBG complications, *n* (%)				
Transient thrombocytopenia (Grade 2 CTCAE)	1 (6)			
AML (Grade 4 CTCAE)	1 (6)			
MEC (Grade 3 CTCAE)	1 (6)			
Hypergonadotropic hypogonadism (Grade 2 CTCAE)	1 (6)			

AML: Acute myeloid leukemia, CR: Complete remission, CTCAE: Common terminology criteria for adverse events, DDD: Daily defined dose, MEC: Mucoepidermoid carcinoma of the parotid gland, MIBG: Metaiodobenzylguanidine, PD: Progressive disease, PR: Partial remission, RECIST: Response evaluation criteria in solid tumors, SD: Stable disease, WHO: World health organization

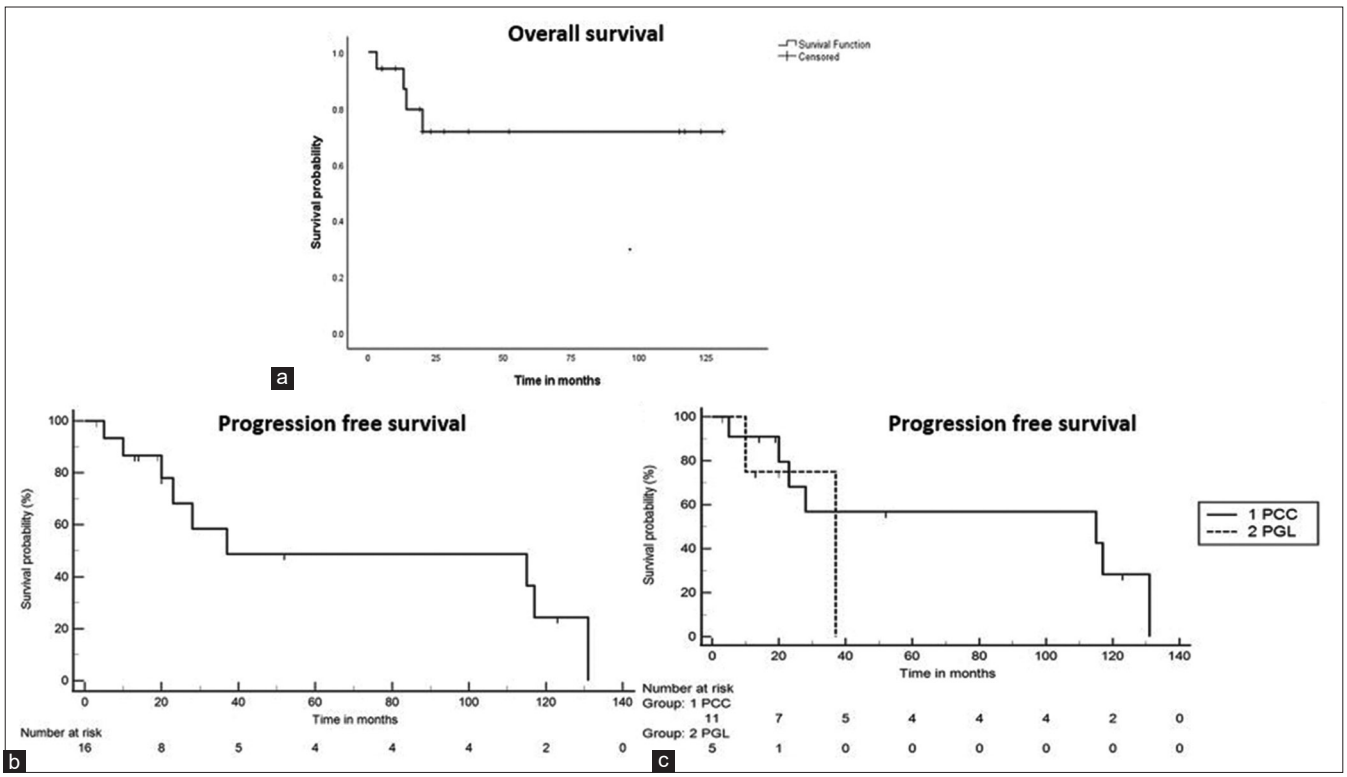

Figure 2: (a) Overall survival of patients treated with ^{131}I- MIBG therapy (b) Median progression free survival of patient with pheochromocytoma/paraganglioma treated with ^{131}I-MIBG therapy (c) Comparison of progression free survival between pheochromocytoma (PCC) and paraganglioma (PGL) in patients treated with ^{131}I-MIBG therapy

0.21 (0.1–0.4). In contrast, hormonal-based response (CR + PR) was less frequent (30%) in our study.[6] In Thorpe *et al*.[15] the study, the initial hormonal response was observed in 59%, which was subsequently reduced to 30% on follow-up. Unlike those with symptomatic progression, only 50% (2/4) of patients with hormonal progression had PD on RECIST1.1 suggesting hormonal progression as a poor predictor of tumor progression on RECIST1.1. In studies that have used WHO criteria for tumor response evaluation, CR, PR, and SD were 0%–38%, 17%–83%, and 0%–35%, which are in concurrence with our cohort (CR [20%, 2/10], PR [10%, 1/10], SD [40%, 4/10]).[6]

The literature on the efficacy of LSA based on RECIST criteria is summarized in Table 4.[15–21] Most of the studies used low-dose, LSA ^{131}I-MIBG therapy except Gonias *et al*. (30.26 GBq).[16] The median dose in low-dose studies ranged from 5.5 to 7.4 GBq, which was similar to our study (6.7 GBq) with a total cumulative dose ranging from 11.4 to 118 GBq. In previous studies, RECIST1.1-based CR, PR, SD, and PD were seen in 0%–9%, 0%–33%, 0%–83%, and 11%–100%. In our cohort, CR was slightly higher (19%, 3/16), whereas PR (6%, 1/16), SD (31%, 5/16), and PD (44%, 7/16) were similar to those reported previously. The reason for this variation in response is not known; however, the stage of disease at presentation, genomic makeup of tumors, and response to MIBG therapy are some of the hypotheses, which could have affected the response, long-term prospective studies would help further our understanding. There was a 100% concordance with tumor response based on WHO criteria, which includes both functional and anatomical imaging findings, and RECIST1.1 criteria, which includes only anatomical imaging findings. Although this observation is based on a small number of subjects, anatomical imaging alone may be used to assess tumor response-based PD, especially in resource-limited settings.

In our cohort, disease control rate (CR + PR + MR + SD) (63% vs. 40%, $P = 0.6$) and CR (27% vs. 0%, $P = 0.51$) were apparently higher (statistically insignificant) in PCC than in sPGL; however, the sample size was small between the groups. In the meta-analysis, though the proportion of CR (1% vs. 4%) and PR (28% vs. 30%) was slightly lower among patients with PCC than PGL, SD was largely higher in PCC than PGL (50% vs. 28%). Similarly, ^{131}I-MIBG therapy resulted in apparently longer PFS among patients with PCC than those with sPGL (statistically insignificant). This may be attributed to higher avidity to ^{131}I-MIBG in PCC than sPGL; hence, the higher uptake and better response. The more favorable response of PCC to ^{131}I-MIBG therapy is a promising observation because of the recently reported poorer outcomes in PCC to ^{177}Lu-PRRT.[22] However, this finding needs to be viewed with caution and lack of generalizability due to the small sample size between the groups. Large-scale prospective trials are needed to confirm this observation.[6,23,24]

Studies on LSA ^{131}I-MIBG are heterogeneous with fewer studies using RECIST criteria for response. It has been seen that intermediate dose achieved faster radiological responses (ORR: 38%, CR: 10%–15%, PR: 20%–23%) but higher rates of bone marrow suppression. High-dose LSA ^{131}I MIBG showed an overall response rate of 22%, ORR in 57%, 35% had progression at 1 year; however, a high percentage of patients had toxicity (bone marrow toxicity [80%], lethal myelodysplasia [2%], hypertension during infusion [10%]).[4,16,25,26] Few cases with mild exacerbation of catecholamine excess symptoms have been reported after LSA ^{131}I-MIBG therapy.[17,21,27] In comparison to the above, our cohort showed fewer side effects but PD was higher. None of our patients had an acute catecholaminergic crisis during or after therapy, which is generally expected with LSA. In a phase II trial, HSA ^{131}I-MIBG therapy resulted in a higher response rate (CR + PR) of 68% and a median overall survival of 36.5 months that led to the approval of the drug by the USFDA. However, overall side effects were higher with HSA ^{131}I-MIBG therapy; 98% had at least one treatment-related side effect with severe adverse effects (SAE) in 29%. Further head-to-head trials comparing the two agents are needed to assess the superiority of one over the other.[5]

The side effect profile of ^{131}I-MIBG therapy is usually tolerable as also noted in our study. The hematological system was the most commonly involved, thrombocytopenia being observed more frequently than leukopenia and appears to be a dose-dependent phenomenon.[16] Secondary malignancies reported include myelodysplastic syndrome (MDS) and acute myelocytic leukemia (AML).[25] One of our patients had AML with chromosome 7 deletion after receiving 7 cycles of ^{131}I-MIBG and being treatment naïve for other systemic therapy. His hemogram was normal prior to ^{131}I-MIBG therapy and he had only lung metastases. To our knowledge, eight patients have been reported with MDS/AML (especially loss of chromosome 5 and 7) following ^{131}I-MIBG therapy in the literature and might be associated with a higher dose of ^{131}I-MIBG administered.[16,28] Hypogonadism has been reported in five ^{131}I-MIBG-treated patients in the literature (2 males). Women developed ovarian failure after 3–12 months, whereas men presented with features of hypergonadotropic hypogonadism (testicular failure) after 6 months to 6 years of therapy with a cumulative dose of 37–67 GBq.[16,29] In our cohort, one patient (case 08) who had received ^{131}I MIBG therapy at a younger age (18 years) developed Sertoli and germ cell failure, which may be due to germ cell damage by radioactive iodine. Hence, sperm banking may be considered in males desiring future fertility before administering ^{131}I-MIBG therapy. We report the first case (case 01) of MEC of the parotid gland in association with ^{131}I MIBG therapy, which may hypothetically be a chance phenomenon or may represent the common underlying genetic (not evaluated) factors. Although the patient was pretreated with Lugol's iodine, the salivary uptake of free radioactive iodine leading to malignant transformation cannot be ruled out.

The strengths of our study include data from a single center, a large proportion of patients with homogenous treatment and

Table 4: Comparison of studies with low specific activity ^{131}I metaiodobenzylguanidine (MIBG) therapy in pheochromocytoma/paraganglioma (PPGL) using RECIST criteria for response evaluation

Study	N (PCC, PGL)	Age years	Progressive	^{131}I MIBG therapy details			Follow-up months	RECIST criteria tumor response, *n* (%)				Overall survival/PFS months	Side effects
				Dose per cycle GBq	Cumulative dose GBq	Number of cycles		CR	PR	SD	PD		
Gonias 2009	49*(15,34)	42.6 (10.3-64.4)	n.r	30.3 (18.2-42.9)	18.2-118	1 (1-3)	24 (1.2-180)	4 (9) 2 (17)	8 (18) 4 (33)	24 (53) 3 (25)	9 (20)$^{\$}$ 3 (25)$^{@}$	64%, 5 year/n.r.	N 87% (gr 3-4), T 83% (gr 3-4), A 8% (gr 3-4), MDS 2 ARDS 2, BOOP 2, acute HTN 7, HG 4, PE 1, Infection 1, Hyperthyroidism 3
Shilkrut 2010	10 (7,3)	48 (5.2)	3 (30%)	5.4 (0.2)	11.6 (1.6)	2 (1-4)	18 (6-48)	0	3 (30)	5 (50)	2 (20)	n.r./17.5 (2-47)	T 1 (gr 1), Subclinical hypothyroidism (2), Vomiting (2)
Szalat 2011	6 (1,5)	35.8 (5.2)	n.r.	n.r.	n.r	2 (1-4)	n.r.	0	0	5 (83)	1 (17)	n.r/n.r	n.r
Fishbein 2012	5 (0,5)	34.6 (4)	n.r	0.08 per kg	n.r	2 (1-4)	n.r	0	0	0	5 (100)	n.r.	n.r.
Agnieszka 2018	18 (10,8)	43.6 (11-84)	5 (28%)	Mean 7.3	33.1	n.r	78 (7-197)	2 (11)	1 (6)	13 (72)	2 (11)	87%, 5 year/85	Le 6% (gr 1) 11% (gr 2), T 11%(gr 1) 6% (gr 3), Hypothyroidism 4 (22%), HG 1 (6%), Azoospermia & Infertility 1 (6%), HTN 1 (6%), Nausea vomiting 1 (6%)
Wakabayashi 2019	20 (13,7)	51.2 (21-76)	n.r	5.6-7.4	11.4 (5.7)	1-3	5	10%	0	65%	15%	100%, 6 months/PFS 80% at 6 months	T 15 (75%), Ly 13 (65%), Le 1 0 (50%) Nausea 11 (55%), Loss of appetite 14 (70%)
Mathew Thorpe 2019	125 (73,52)	50 (41-61)	n.r	n.r.	18.8 (18.4-19)	n.r	n.r	1%	33%	53%	13%/51%	Median survival 11.5+2.4 yrs/n.r	GI 15%, fatigue 5%, Xerostomia 2%, OI 2%
Our cohort	17 (11,6)	36.5 (17)	15 (88%)	6.7 (4.8-9.3)	19 (5.6-42.9)	3 (1-7)	20 (1-131)	3 (19)	1 (6)	5 (31)	7 (44)	76.4%/37	T 1 (6%) (Gr 2), AML 1 (6%) MEC 1 (6%), HG 1 (6%)

*1 Patient lost to follow-up, $^{\$}$ response after first dose, @ response after second dose. n.r.: not reported, PCC: pheochromocytoma, PGL: paraganglioma, GBq: giga Becquerel, CR: complete remission, PR: partial remission, SD: stable disease, PD: progressive disease, RECIST: response evaluation criteria in solid tumors, PFS: progression free survival, Side effect Hematological - T: thrombocytopenia, N: neutropenia, A: anemia, AML: acute myeloid leukemia, MDS: myelodysplastic syndrome, Le: Leukopenia, Ly: Lymphopenia, ARDS: acute respiratory distress syndrome, BOOP: bronchiolitis obliterans organizing pneumonia, PE: pulmonary embolism, HG: Hypogonadism, HTN: hypertension, GI; gastrointestinal, OI: opportunistic infections, MEC: mucoepidermoid carcinoma of parotid gland, gr: grade

response evaluation (RECIST1.1 criteria) in a resource-limited setting. The ^{131}I-MIBG-treated cohort predominantly consisted of patients progressing on first-line or second-line therapy. This feature of the cohort suggests that the observed positive outcomes represent the result of the therapy rather than the natural course of the disease.

The major limitations were the small sample size, retrospective design (with its inherent issues), and possible selection bias. The genetic evaluation was not available in several patients hence, the effect of ^{131}I-MIBG therapy in genotypes-based subgroups could not be assessed. The median duration of follow-up (20 months) was shorter and was not adequate to reach the median OS following therapy. However, the follow-up duration was comparable with the previously published cohorts (24–64 months).[6] Our study did not have a control arm to compare the effect of ^{131}I-MIBG therapy on PFS and OS. However, such a study setting may not be feasible due to ethical issues.

Conclusion

Our study reaffirms the modest efficacy and safety of low-dose, LSA ^{131}I-MIBG therapy in patients with symptomatic, metastatic PPGL. Symptomatic, but not hormonal, progression after ^{131}I-MIBG therapy correlates well with tumor progression and should be further evaluated with imaging. In resource-limited settings where functional imaging facilities are unavailable, anatomic imaging alone may be used to assess tumor response to ^{131}I-MIBG therapy. LSA ^{131}I-MIBG remains a preferred form of ^{131}I-MIBG therapy in resource-limited settings. However, head-to-head trials comparing the cost-effectiveness of LSA and HSA ^{131}I-MIBG therapies in such settings are warranted.

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Conflicts of interest

There are no conflicts of interest.

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WHO and RECIST 1.1 Criteria for Assessment of Efficacy:

WHO criteria (1)

Symptomatic response	
Complete response	Absence of pretherapy symptoms
Partial response	Subjective decrease in intensity and frequency of symptoms
Stable disease	No change in symptoms
Progressive disease	Subjective increase in intensity and frequency of symptoms or appearance of new symptoms
Hormonal response	
Complete response	Normal levels of estimated catecholamine derivatives
Partial response	50% or greater reduction in pretherapy levels of hormones
Stable disease	Decrease of less than 50% or an increase of less than 25% in hormonal levels
Progressive disease	25% or greater increase in pretherapy levels of hormones
Tumor response	
Complete response	complete regression of all imaging evidence of the tumur (including radiological and ^{131}I-MIBG scan
Partial response	50% or greater reduction in all measurable tumors or recalcification of lytic bone lesions and no appearance of new lesions
Stable disease	decrease in less than 50% or an estimated increase of less than 25% of the tumor
Progressive disease	the appearance of new lesions or an increase of 25% or more in tumor size

RECIST 1.1 (2)

Complete response	complete disappearance of all target lesions and pathologic lymph nodes<1 cm on short-axis
Partial response	at least 30% decrease in the sum of diameters of target lesions (relative to baseline sum)
Minor response	smaller size reductions not meeting partial response (10% to 30% decrease in maximum diameter of target lesions)
Stable disease	as not enough tumor shrinkage to qualify as MR and not enough tumor growth to qualify as progression
Progressive disease	at least 20% increase in the sum of diameters of target lesions (relative to the smallest sum) with an absolute increase of at least 5 mm, or appearance of any new lesions

Target lesions more than one cm were used to define response criteria in RECIST version 1.1

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