Management of metastatic phaeochromocytoma and paraganglioma: use of iodine-131-meta-iodobenzylguanidine therapy in a tertiary referral centre

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Summary

Background: Phaeochromocytoma (phaeo) and paraganglioma (PGL) are rare conditions, which are malignant in up to 30%. Optimal treatment is controversial, but in patients with metastatic iodine-131-meta-iodobenzylguanidine (123I-MIBG) avid tumours, we offer 131I-MIBG therapy. We summarize response rates, survival and safety in a cohort of such patients treated with 131I-MIBG in our centre from 1986 to 2012.

Design/Methods: Retrospective analysis of the case notes of patients with metastatic phaeo/PGL who received 131I-MIBG was undertaken; patients underwent clinical, biochemical and radiological evaluation within 6 months of each course of 131I-MIBG therapy.

Results: Twenty-two patients (9 males) were identified, 12 with metastatic PGL and 10 with phaeo. Overall median follow-up time after first dose of 131I-MIBG was 53 months. In total, 68 doses of 131I-MIBG were administered; average dose was 9967 MBq (269.4 mCi). After the first dose, >50% of patients demonstrated disease stability or partial response; progressive disease was seen in 9%. A subset of patients underwent repeated treatment with the majority demonstrating partial response or stable disease. No life-threatening adverse events were reported, but three patients developed hypothyroidism and two developed ovarian failure after repeated dosing. Five-year survival after original diagnosis was 68% and median (+inter quartile range) survival from date of diagnosis was 17 years (7.6–26.4) with no difference in survival according to diagnosis (P < 0.1).

Conclusions: 131I-MIBG is well tolerated and associates with disease stabilization or improvement in the majority of patients with metastatic phaeo/PGL. However, stronger conclusions on treatment effectiveness are limited by lack of a directly comparable ‘control group’ as well as an alternative ‘gold standard’ treatment.

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Introduction

Phaeochromocytomas (phaeos) are tumours arising from the chromaffin cells of the adrenal medulla. Paragangliomas (PGLs) also arise from extra-adrenal tissue, mainly along the sympathetic (chromaffin derived) and parasympathetic (non-chromaffin origin) chains. Both tumours are extremely rare; their combined incidence is ~8 per 100,000 patient years. However, the incidence at post mortem is higher, suggesting that these tumours are under diagnosed.

The majority of phaeos and PGL are sporadic, although it is recognized that an increasingly significant proportion arises due to underlying germline mutations within RET (multiple endocrine neoplasia type 2), VHL (von Hippel–Lindau), NF1 (neurofibromatosis type 1) and SDH (succinate dehydrogenase) genes. It is likely that many other genetic causes of phaeo/PGL are to be identified and very recently, two further genetic mutations have been identified in familial phaeo (FP/TMEM127 and MAX genes).

Although most cases of phaeo/PGL are benign, ~17% of phaeos and up to 30% of PGL are malignant; risk of malignancy is higher in subjects with SDH mutations (especially succinate dehydrogenase B). The only dependable indicator of malignant disease is the presence of metastatic disease in non-chromaffin tissues (e.g. liver, bone, lung and lymph nodes). Therefore, it remains a challenge to recognize the malignant potential of tumours where metastases have not been identified at the time of diagnosis although recent evidence suggests that the size and location of primary tumours may be helpful.

There is no ‘gold standard’ algorithm for the optimal management of malignant disease although several guidelines exist. While surgical debulking of metastatic deposits is still advocated for palliation of symptoms, if patients are asymptomatic with stable disease then close surveillance with no active treatment may be appropriate for a period of time. For other patients with symptomatic or progressive disease, not amenable or appropriate for surgery, then additional systemic therapy is required. Our local practice in such circumstances is to offer iodine-131-meta-iodobenzylguanidine (131I-MIBG) therapy. 131I-MIBG is structurally similar to noradrenaline and accumulates more rapidly in phaeo or PGL than normal tissue and, since 1983, has been used in the treatment of malignant phaeo/PGL in patients with 131I-MIBG-avid disease.

The aim of this study was, therefore, to describe our experience of the use of 131I-MIBG therapy in patients with metastatic phaeo/PGL in a single tertiary referral centre. We evaluated treatment by symptomatic, hormonal or tumour (radiological) response over a prolonged period of follow-up. In addition, we aimed to assess outcome and survival of our patient cohort as well as tolerability and safety of 131I-MIBG therapy.

Materials and Methods

Patients

We reviewed the case records of all patients who underwent 131I-MIBG therapy at the Beatson West of Scotland Cancer Centre from 1986 to August 2012. Patients who had a diagnosis other than PGL or phaeo were excluded. All patients with 131I-MIBG-avid disease and evidence of metastases either locally or in distant organs (bone/liver/lungs) were included. All patients had complete hormonal (24-h urinary evaluation of catecholamines and, later, fractionated metanephrines), symptomatic (blood pressure assessment and clinical history) and radiological (computerized tomography or magnetic resonance imaging with 131I-MIBG scintigraphy) evaluation immediately prior to treatment with subsequent similar evaluation performed within at least 6 months of receiving each course of 131I-MIBG therapy.

The follow-up period was defined from the date of diagnosis until either death or 1 August 2012, when case note review was completed. As this study began as an audit of clinical practice and all data, once gathered, were anonymized, it was confirmed by NHS Greater Glasgow & Clyde Ethics Committee that no ethical approval was required.

131I-MIBG protocol

131I-MIBG was purchased from commercial sources (GE Healthcare, Buckinghamshire, UK). In each case, potassium iodate was given (85 mg twice daily) 24 h prior to and 14 days after therapy to prevent uptake of 131I-MIBG by the thyroid gland. 131I-MIBG was administered as a slow intravenous infusion over a period of 60 min. A typical adult treatment dose was 7500–10 000 MBq (200–270 mCi).

All patients with malignant (i.e. distant metastases) 131I-MIBG-avid disease were given an initial course of 131I-MIBG therapy in accordance with local policy. Thereafter, subsequent 131I-MIBG was given if there was evidence of symptomatic, radiological or biochemical progression or if there was judged to be significant tumour burden by the clinical team. All patients who underwent repeated
dosing of $^{131}$I-MIBG had demonstrated either disease stabilization or partial/complete response to the previous $^{131}$I-MIBG treatment.

**Response to therapy (malignant disease cohort)**

Objective tumour response was assessed according to standard World Health Organization (WHO) criteria as outlined in Table 1.

**Statistics**

All data were analysed with IBM SPSS (version 18, NY) statistical analysis software. To evaluate response and its effect on outcome, we divided the groups into responders, including the partial and complete response patients and non-responders, including patients in the no-response and progression groups. This analysis was performed for symptomatic response, hormone response and tumour response. Kaplan–Meier statistics were performed for each group. Responders vs. non-responders were compared by use of the Wilcoxon and log rank tests. We defined statistical significance to be $P < 0.05$.

**Results**

**Summary**

**General information**

Complete clinical details were available for 22 patients with $^{123}$I-MIBG-avid disease (9 males; median age 44.5 years) treated for metastatic phaeo ($n = 10$) and PGL ($n = 12$) between 1986 and 2012. Table 2 summarizes clinical details of each of the 22 patients. Median follow-up time after the first dose of $^{131}$I-MIBG was 53 months (inter quartile range [IQR] 12.3–134.3 months).

**Dose**

In total, 68 doses of $^{131}$I-MIBG were administered; the median number of doses per patient was two (IQR: 1–5). The median time between doses for each episode of $^{131}$I-MIBG ranged from 188 to 627 days. The average dose of $^{131}$I-MIBG was 9967 MBq (270 mCi; range: 5000–11 300 MBq). The median cumulative dose of $^{131}$I-MIBG was 20 121 MBq (544 mCi; IQR: 10 000–50 667 MBq).

**Additional treatment**

In the majority of subjects, $^{131}$I-MIBG was administered after debulking surgery, but in three cases, $^{131}$I-MIBG was the primary treatment due to inoperable disease at diagnosis.

Seven patients received chemotherapy in addition to $^{131}$I-MIBG (subsequent to $^{131}$I-MIBG in five cases), two of these patients also received external beam radiotherapy to bone metastases, and one further patient received adjuvant external beam radiotherapy only to rib metastases (Table 2). The two subjects who received further $^{131}$I-MIBG after chemotherapy were excluded from further analysis of $^{131}$I-MIBG response (Table 4).

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**Table 1**  WHO tumour response criteria

<table>
<thead>
<tr>
<th></th>
<th>Complete response</th>
<th>Partial response</th>
<th>No response (stable disease)</th>
<th>Disease progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic response</td>
<td>Absence of pre-therapy symptoms</td>
<td>Subjective decrease in intensity and frequency of symptoms</td>
<td>No change in symptoms</td>
<td>Subjective decrease in intensity and frequency of symptoms or appearance of new symptoms</td>
</tr>
<tr>
<td>Hormonal response</td>
<td>Normalization of previously elevated urinary-free catecholamine or metanephrine levels and plasma metanephrine levels where relevant</td>
<td>50% or greater reduction from pre-therapy level of hormones</td>
<td>No change in hormonal status</td>
<td>25% or greater increase from pre-therapy levels of hormones</td>
</tr>
<tr>
<td>Tumour response</td>
<td>Complete regression of all clinical evidence of tumour including radiological abnormalities and a negative diagnostic MIBG scan</td>
<td>50% or greater reduction of all measurable tumour or re-calcification of lytic bone lesions</td>
<td>No change</td>
<td>Appearance of new lesions or an increase of 25% or more in tumour size</td>
</tr>
</tbody>
</table>
Genetic testing

Eight patients underwent genetic testing for mutations within genes known to predispose to PGL/phaeo (SDH-B/D, VHL and RET oncogene). Of these, four demonstrated no genetic abnormality, and four were found to have a mutation in the SDHB gene. No genetic testing information was available for one patient (patient 5), six others died before genetic screening was routinely offered and the other six were above the age (50 years) at which we routinely offered genetic screening at that time (upper age limit to longer applies to genetic screening of PGL patients).

Response

Table 3 outlines symptomatic, hormonal and tumour (radiological) response, according to WHO criteria, assessed within 6 months after the initial dose of $^{131}$I-MIBG.

Table 4 summarizes symptomatic, hormonal and tumour response within 6 months after subsequent doses of $^{131}$I-MIBG. Response was not assessed beyond four doses because of very small patient numbers receiving more than four doses of $^{131}$I-MIBG (1–4 subjects per dose) preventing meaningful analysis.

Tolerability

Nausea and vomiting were the commonest side effects, occurring in 37 treatment episodes (54%). The true incidence of haematological side effects was hampered by missing full blood count data for the majority (44) episodes. Of the 24 episodes where information was available, transient
myelosuppression developed on nine occasions (38%). One event required a blood transfusion, but the remaining haematological events were self-limiting; no case required stem cell rescue therapy.

Two patients (patients 16 and 20) developed ovarian failure (ages 36 and 32 years, respectively); however, this was after repeated doses of \(^{131}\text{I}-\text{MIBG}\) resulting in cumulative radiation exposure of 70 200 MBq (1900 mCi; 6 doses) and 50 539 MBq (1366 mCi; 5 doses), respectively.

Three patients developed hypothyroidism, again after repeated \(^{131}\text{I}-\text{MIBG}\) therapy despite potassium iodate blockade; in one case hypothyroidism developed after two doses (mean cumulative dose of 20 000 MBq [540 mCi]), in another after three doses (mean cumulative dose of 31 921 MBq [862 mCi]) and in the final case, hypothyroidism developed after five doses (mean cumulative dose of 33 289 MBq [900 mCi]).

### Table 3 Clinical response 6 months after first dose of \(^{131}\text{I}-\text{MIBG}\) (n = 22)

<table>
<thead>
<tr>
<th>Response</th>
<th>Symptoms</th>
<th>Hormonal</th>
<th>Tumour bulk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>4 (18%)</td>
<td>1 (5%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13 (59%)</td>
<td>11 (50%)</td>
<td>13 (59%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>3 (14%)</td>
<td>3 (14%)</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>Not known</td>
<td>1 (5%)</td>
<td>6 (27%)</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

### Table 4 Summary of clinical response after two, three and four doses of \(^{131}\text{I}-\text{MIBG}\)

<table>
<thead>
<tr>
<th>Response (second dose, n = 13)</th>
<th>Symptoms</th>
<th>Hormonal</th>
<th>Tumour bulk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>2 (15%)</td>
<td>1 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>2 (15%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6 (45%)</td>
<td>10 (77%)</td>
<td>10 (77%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>2 (15%)</td>
<td>0</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Not known</td>
<td>1 (8%)</td>
<td>3 (23%)</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response (third dose, n = 6)</th>
<th>Symptoms</th>
<th>Hormonal</th>
<th>Tumour bulk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>2 (33%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (66%)</td>
<td>4 (66%)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>0</td>
<td>1 (17%)</td>
<td>0</td>
</tr>
<tr>
<td>Not known</td>
<td>0</td>
<td>2 (33%)</td>
<td>1 (17%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response (fourth dose, n = 5)</th>
<th>Symptoms</th>
<th>Hormonal</th>
<th>Tumour bulk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1 (20%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>1 (20%)</td>
<td>1 (20%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3 (60%)</td>
<td>3 (60%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not known</td>
<td>0</td>
<td>2 (40%)</td>
<td>0</td>
</tr>
</tbody>
</table>

### Survival

On completion of the study (August 2012), nine patients (41%) were still alive. Of the 13 patients who had died, 11 had died as a direct consequence of metastatic disease. Five-year survival after original diagnosis was 68%. The median (+IQR) survival of all patients from date of diagnosis was 17 years (7.6–26.4) and was 11.1 years (0–22.7) after first dose of \(^{131}\text{I}-\text{MIBG}\) (Figure 1a,b).

There was no significant difference in survival according to original diagnosis (P < 0.1; Figure 1c). For the purposes of survival analysis, \(^{131}\text{I}-\text{MIBG}\) symptomatic, hormonal and radiological (tumour) response was divided into three sub-groups: responders, stable disease and non-responders (disease progression). Using this sub-classification, a log rank test of significance demonstrated that patients who responded radiologically to the first dose of \(^{131}\text{I}-\text{MIBG}\) demonstrated improved overall survival (P < 0.04; Figure 1d). However, hormonal or symptomatic response to first dose of \(^{131}\text{I}-\text{MIBG}\) did not influence overall survival (P < 0.3 in both cases).

### Discussion

This retrospective review of the use of \(^{131}\text{I}-\text{MIBG}\) as adjuvant therapy in the management of metastatic phaeo/PGL supports a role for therapeutic \(^{131}\text{I}-\text{MIBG}\) in these circumstances with 19% of patients demonstrating complete or partial tumour (radiological) response and a further 59% demonstrating stable disease 6 months after an initial dose. Several patients underwent repeated \(^{131}\text{I}-\text{MIBG}\) therapy if previous evidence of \(^{131}\text{I}-\text{MIBG}\) response and subsequent clear progression of disease or large tumour burden at baseline. Encouragingly, there continues to be evidence of effectiveness of recurrent \(^{131}\text{I}-\text{MIBG}\) in this carefully selected group with the majority demonstrating stable disease or at least partial response at least 6 months after therapy.

We appreciate that the value of \(^{131}\text{I}-\text{MIBG}\) is difficult to assess accurately within our cohort due to lack of a ‘control’ group of similar patients who did not undergo \(^{131}\text{I}-\text{MIBG}\) therapy; without such a comparison, it is always difficult to know whether any impact on the natural history of this disease has been made. In particular, we acknowledge that, although the majority of patients demonstrated ‘stable disease’ after therapy, it is difficult to comment as to whether this was genuine or simply representative of a slow ‘natural history’ of the disease (although the majority did demonstrate...
biochemical or radiological progression prior to treatment). This is highlighted by a recent study exploring the natural history of malignant phaeo/PGL in a cohort of 90 subjects from multiple centres in France. Fifty-seven of these patients had not previously undergone active treatment and yet demonstrated a mean progression free survival at 1 year of 46%. Therefore, surveillance of disease progression in the first instance is also a valid treatment approach in this circumstance. This fact, as well as ethical concerns and the relative rarity of the condition, means that there has never been a randomized placebo-controlled study of the use of $^{131}$I-MIBG in suitable patients with metastatic phaeo/PGL.

One major advantage of our long follow-up period is that we were able to demonstrate a median survival from time of diagnosis of 17 years and 11.1 years from time of first dose of $^{131}$I-MIBG. The overall 5-year survival was 68%. This further demonstrates that the prognosis for metastatic phaeo/PGL, while highly variable, tends to be better than that for other metastatic malignancies with several patients demonstrating stable disease for prolonged periods (over 20 years in two cases). Although numbers were small in each cohort, there was no significant difference in median survival between phaeo or PGL patients; however, there was a trend towards improved survival in the phaeo group. Moreover, tumour (radiological) response to first dose of $^{131}$I-MIBG does appear to impact favourably on survival. In a similar retrospective review of 33 patients with metastatic phaeo ($n=22$) and PGL ($n=11$) treated over a 10-year period, median survival after $^{131}$I-MIBG administration was 56 months. In common with our data, there was a trend towards increased survival in patients who demonstrated a measurable response to therapy.

$^{131}$I-MIBG was first used for the treatment of malignant phaeo in 1983, and since then, there have been several case series reported using various therapeutic protocols. Our data compare favourably with other studies within this small

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**Figure 1.** Kaplan–Meier survival curves illustrating: (a) overall survival, (b) survival after first dose of MIBG, (c) phaeo vs. PGL and (d) radiological response to first dose of MIBG.
patient group. In the largest and most comprehensive series to date (116 patients), investigators, using the WHO response criteria, demonstrated tumour response in 30%, stable disease in 57% and disease progression in 13%. Subsequently, at an EANM Radionuclide Therapy Committee workshop on 131I-MIBG therapy in 1999, the results of treatment of a cohort malignant phaeo (n = 77) and PGL (n = 34) patients were reported; the objective tumour response rates were 51 and 48%, respectively, in these patients with a significant (>50%) reduction in catecholamine excretion in 68 and 51%, respectively. The largest UK case series to date contained only 15 patients with malignant phaeo/PGL who underwent a median of three doses of 131I-MIBG. Again, using the same WHO criteria employed in our study, they demonstrated a symptomatic response rate of 100%, complete or partial hormonal response in eight of nine patients and tumour reduction in 7 of 13 patients (54%).

Finally, a very recent meta-analysis (17 studies comprising 243 patients) exploring 131I-MIBG use in this patient population resulted in stable tumour volume in 50% of subjects; again, this is comparable with our findings.

To date, there has only been one prospective phase 2 study of 131I-MIBG therapy in metastatic phaeo/PGL. In this study of 50 patients, higher doses of 131I-MIBG (18 000–43 000 MBq) were utilized, but response rates were comparable with our experience; 22% of subjects demonstrated complete or partial response to therapy and 35% demonstrated progressive disease 1 year after treatment.

The standard treatment protocol employed in our centre utilizes an ‘intermediate’ dose of 131I-MIBG of ~10 000 MBq (270 mCi) each time. This was well tolerated in our patient cohort; transient nausea and vomiting were seen in 37% of treatment episodes, whereas temporary myelosuppression was found in 38%. Although meaningful interpretation of our results is hampered by incomplete data collection, our rate of haematological side effects seems to be comparable with that described in a recent study by Sze et al. In this retrospective case series, which included 14 phaeo/PGL subjects, haematological sequelae occurred in six patients (43%).

Predictably, ovarian failure developed in two women within our cohort after repeated dosing with a large cumulative dose of 131I-MIBG. Hypothyroidism developed in three patients despite use of potassium iodate therapy. However, we have only recently included assessment of thyroid and ovarian function as part of our routine follow-up of patients who have received 131I-MIBG therapy, and so our data may underestimate the rate of ovarian and/or thyroid failure.

There has been considerable debate over the optimal dosage regimens to confer benefit while not exposing the patient to an unacceptable risk of haematological toxicity. In the previous case series described by Safford et al., there was a suggestion that patients who underwent high-dose initial therapy >18 500 MBq (>500 mCi) demonstrated an improvement in survival albeit with an increased risk of bone marrow suppression. In a subsequent small study of 12 patients administered high dose of 131I-MIBG ranging from 14 300–31 820 MBq (386–866 mCi), a complete response was seen in three patients, two of who had skeletal and soft tissue metastases at the time of treatment. Unsurprisingly, haematological complications were common in this cohort, with significant neutropenia in 79% of treatment episodes and requirement for stem cell infusion in one case. In addition, the rate of haematological sequelae in the prospective study of 131I-MIBG therapy in which larger doses were utilized was relatively high with grade 3/4 neutropenia seen in 87%. The data from our series, in common with others, support a multiple intermediate dose 131I-MIBG regimen with better evidence of efficacy as well as safety and tolerability.

Strengths of our study include patient numbers, which, although small, represent a reasonably sized cohort of a rare disease. Another major strength is the duration of follow-up allowing robust information on survival and outcomes for a prolonged period after 131I-MIBG therapy. The major limitation of this study is the retrospective collection of data, which, at times, was beyond 25 years resulting in incomplete information for some patients. Our policy of offering 131I-MIBG therapy to all patients with 123I-MIBG-avid metastatic disease has also meant that we cannot comment accurately on the ‘natural history’ of disease for many patients; this is particularly important given the recent data illustrating 49% progression free survival with no treatment at 1 year after diagnosis of malignant phaeo/PGL. In addition, the lack of control group to allow comparison of outcomes with subjects with metastatic disease who did not undergo 131I-MIBG has been acknowledged as a weakness; however, the rarity of this condition makes randomized, placebo-controlled or direct comparator studies extremely challenging.

In summary, these data support the concept that therapy with 131I-MIBG has a definite role in the management of subjects with metastatic phaeo/PGL. Our study demonstrates that 131I-MIBG therapy in malignant disease provides sustained benefit particularly in terms of symptomatic relief.
and reducing tumour burden. This benefit can be maintained in selective individuals with repeated dosing. Importantly, $^{131}$I-MIBG at modest doses (average 10 000 MBq or 270 mCi) is safe and well tolerated even when administered on multiple occasions.

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**Conflict of interest:** None declared.

**References**


