Rare Cause of Severe Hypertension in a Young Woman

Colin G. Perry, E. Marie Freel, Patrick O’Dwyer, Ernesto L. Schiffrin, Garry L. Jennings, Anna F. Dominiczak, Marc De Buyzere

Presentation of Case
An asymptomatic 20-year-old woman was seen at a preoperative assessment clinic before elective orthopedic surgery. She had a blood pressure of 240/110 mm Hg in both arms and was referred for urgent medical opinion. On examination, her phenotype was unremarkable. She had bilateral papilledema with normal cardiovascular examination other than her blood pressure. Renal function and urinalysis were normal.

The patient had a normal renal ultrasound, plain computed tomography of brain, and computed tomography cerebral venogram. Renin and aldosterone were normal with a normal ratio and potassium was within the normal range. She commenced amiodipine and an angiotensin-convertase enzyme inhibitor with blood pressure falling to 151/112 mm Hg.

Dr Colin Perry: I would ask our experts, what would they do next?

Dr Ernesto Schiffrin: I think in a young person you have to consider secondary hypertension. And of course, with very severe elevated blood pressure I would have liked to know whether she is very pale, does she not have headaches? One would start to think of pheochromocytoma in a young person like this.

Dr Perry: That is why I think the history is very important at this stage, because she did not complain of recent headaches when seen initially in the emergency department. She was always rather pale.

Dr Schiffrin: I think that is important because I always tell the medical students that if the patient has a flushed face it is not pheochromocytoma. Pallor is almost an inevitable element.

Dr Marie Freel: Would there have been an argument that an MR angiogram of renal vessels might still have been appropriate in a young girl with malignant-phase hypertension because you can still have a fairly normal aldosterone renin ratio in that circumstance?

Dr Perry: I think that is entirely justifiable.

Discussion of Investigation
Dr Perry: Can I ask then, what test would you do for pheochromocytoma?

Dr Schiffrin: We usually measure urinary metanephrines.

Prof Garry Jennings: This lady did not have it, but when you have episodic hypertension with a pheochromocytoma, that is when your plasma measurement can be absolutely definitive. If they are not elevated and their blood pressure is up, they have not got a pheochromocytoma.

Dr. Schiffrin: Just going back to the history, simply because I have seen some of these patients, I would have inquired about family history, about thyroid surgery in the family.

Dr. Perry: I agree, however at this stage, she has not been to the specialist center. So, in fact you are correct. She does have headaches and if you really explore the history, she gives a good story of headaches. Eighty percent of patients with pheochromocytoma will give a history of headaches when asked specifically.

Twenty-four-hour urinary metanephrines and catecholamines were measured and were reported as elevated, with 24-hour urinary normetanephrine 11374 nmol/24 hour (normal range <900 nmol/24 hour) and 24-hour urinary free normetanephrine 16365 nmol/24 hour (normal range <650 nmol/24 hour).

Computed tomography scan of chest, abdomen, and pelvis revealed a left para-aortic mass and a smaller mass on the right, along with sclerotic vertebral and rib deposits (Figure 1). 123I metaiodobenzylguanidine (mIBG) scintigraphy confirmed widespread 123I mIBG avid disease (Figure 2).

Initial Management
Dr Perry: At this stage, what would you suggest in terms of treatment given the extensive nature of this young woman’s disease?

Dr. Schiffrin: Debunking.

Dr Perry: Would anyone not operate at this point? Or do you think the right thing to do is to debulk as much disease as we can?

All heads nod.
After α- and β-blockade she underwent debulking surgery where a 80x40x22 mm tumor adjacent to left adrenal was resected along with affected lymph nodes.

Dr. Schiffrin: Perhaps for those who are not used to treating these patients, can you explain why you proceed with the phenoxybenzamine first and introduce the β-blocker shortly after?

Dr Perry: So, the danger in a patient like this would be that if they are given unopposed β-blockade you may have profound α-mediated vasoconstriction and precipitate a crisis and that can be fatal. So, there is a real danger of giving the wrong agent in the wrong order. The options would be phenoxybenzamine and doxazosin. Phenoxybenzamine is long-acting and
noncompetitive and is only inactive once the receptor becomes internalized. So that may be a safer approach to $\alpha$-blockade preoperatively than doxazosin, although there are more symptoms associated with it and long-term phenoxybenzamine is not a particularly pleasant medication to take.

Surgery Overview

Prof Patrick O’Dwyer: We did a laparoscopic resection. We removed all her para-aortic and paracaval lymph nodes from the iliacs right up to the diaphragmatic crus, removing this, as you can see, with the vein. We divided the left renal vein. We removed it all laparoscopically and she was in hospital for 24 hours postoperatively with a noneventful recovery.

Dr. Schiffrin: During the manipulation of the tumor, were there any arrhythmias?

Prof O’Dwyer: No. We have done >100 pheochromocytomas or paragangliomas and we have not had a serious event in anyone. No arrhythmias. This is because the laparoscopy is so gentle on these tissues.

Pathological examination of the resected tumor revealed infiltrating islands of solid cellular sheets of tumor cells, which had round vesicular nuclei and eosinophilic granular cytoplasm. The tumor’s immunohistochemical staining was positive for chromogranin and synaptophysin. The Ki-67 proliferation index was variable, being <1% in some areas and between 2% and 3% in others. Infiltration into fat, vascular invasion, and involvement of local lymph nodes was evident.

Postoperative Management

The panel were asked about their suggestions for further treatment, with the patient having undergone debulking surgery though with disease still present.

Dr Schiffrin: mIBG treatment.

Dr Perry: Would anyone consider chemotherapy at this stage?

No response

Dr Perry: Would anyone watch and wait?

Heads shaking “No”

Since her surgery 20 months ago she has had 3 courses of $^{131}$I mIBG (10,000 MBq on each occasion) and has tolerated this well, allowing her to return to her studies. Her disease is stable in terms of biochemistry and disease bulk, with most recent 24-hour urinary norepinephrine being recorded at 987 nmol/24 hour and 24-hour free normetanephrine 4198 nmol/24 hour. Despite there being no clear family history of neuroendocrine tumors, genetic testing revealed a pathogenic mutation in the succinate dehydrogenase B ($SDHB$) gene, which is predicted to affect the normal splicing of exon 1. This was later found in other members of her paternal family.

Further Discussion

Dr Schiffrin: I would like to hear a little bit more about genes and mutations and pheochromocytoma.

Dr Perry: I think it is important here to consider the approach to genetic testing. You may consider screening for most of the known genetic mutations, looking in particular for $RET$, $SDHB$, $SDHD$, von Hippel-Lindau ($VHL$); however in this patient I think you would predict that a mutation in the $SDHB$ gene would be the most likely genetic predisposition to pheochromocytoma. This is based on her having abdominal disease with metastatic spread, rather than it being multicentric, and the biochemical phenotype was norepinephrine, rather than epinephrine, secreting. I think that takes you more toward an $SDHB$ mutation than $SDHD$ and away from $RET$; it is less likely to be a $VHL$ mutation as there are no other associated features or relevant family history. As would be applicable to any other investigation, I think that there is value in identifying the most appropriate initial investigation, rather than a broad approach to screening for all the genetic
abnormally. And if it were not a SDHB or SDHD mutation, you can start to think of other possibilities.

Dr Schiffrin: The association with thyroid cancer and the RET gene mutations?

Dr Perry: There was no history in the family or the patient to suggest multiple endocrine neoplasia type 2, or features of medullary thyroid cancer.

Dr Schiffrin: Is there any reason for looking at the armpits of patients who have pheochromocytoma or possible pheochromocytoma?

Dr Perry: It is always worth considering the phenotype of neurofibromatosis type 1 (NF-1), looking for café au lait patches and axillary freckling. NF-1 is very interesting because I think if you have NF-1 and a pheochromocytoma, the chance, we are told, of malignancy is higher than were it to be a sporadic pheochromocytoma. Perhaps as many as 6% of NF-1 patients develop pheochromocytomas, depending on which series you look at. The interesting question is how best to identify disease early; many NF-1 patients are only screened by asking them whether they have high blood pressure. That may not be sufficient.

Prof Dominiczak: I have an additional question. She is now 22. You have done debulking. You have done the treatment. She is likely to come to your clinic in a year or 2 to ask you, “Doctor, should I become pregnant?” What are you going to say?

Dr Perry: I think there is a danger in a future pregnancy and we would be concerned were she to plan this. We have had at least 1 VHL patient whose disease accelerated in the context of pregnancy. There would have to be a careful discussion of the associated risks.

Prof. Dominiczak: Another related question. We had a patient with this mutation discovered during her first pregnancy and this was a new mutation. This must be very rare in this genetic presentation. In your looking through the literature, have you seen many new mutations in SDHB?

Dr Perry: We have several families with the same SDHB mutation and the reason I think we are accumulating considerable experience locally is that we seem to have an SDHB founder mutation in the West of Scotland.

Mr Marc de Buyzere: In older literature, we learn when you have syndromic paragangliomas there was a kind of association possible with hemangioblastomas. Are there still arguments today that there is still an association?

Dr. Perry: There is no doubt that carriers of the VHL mutation could develop both pheochromocytoma and hemangioblastoma. I have seen a similar presentation in a young man with VHL and bilateral pheochromocytoma and again a noradrenaline secreting phenotype in association with hemangioblastomas and renal cell carcinoma. There are of course also ocular manifestations. So, I think a full history is undoubtedly appropriate and in someone like this you may be guided toward the test for the most likely mutation.

Overview

Pheochromocytomas are tumors arising from the chromaffin cells of the adrenal medulla. Paragangliomas also arise from chromaffin cells but in extra-adrenal tissue, mainly along the sympathetic and parasympathetic chains. Both tumors are extremely rare; their combined incidence is ≈8 per 100,000 patient years,1 whereas the prevalence of pheochromocytoma and paraganglioma in patients with hypertension in outpatient clinics varies between 0.2% and 0.6%.2–4 However, the incidence at postmortem is higher suggesting that these tumors are under diagnosed; undiagnosed tumors may be found in 0.05% to 0.1% of patients.5–7 A recent Endocrine Society Clinical Practice Guideline provided clear guidance on diagnosis and treatment of these rare tumors.8

The majority of pheochromocytoma and paraganglioma are sporadic; however, a significant proportion arise because of underlying germline mutations. For example, recent studies estimate that between 30% to 50% of paragangliomas and up to 20% of pheochromocytomas may be associated with an inherited syndrome.9 Hereditary pheochromocytomas are associated with multiple endocrine neoplasia type 2, VHL syndrome, and NF-1. The estimated frequency of pheochromocytomas in these disorders is 10% to 20% in VHL, 50% in multiple endocrine neoplasia type 2, and 0.1% to 6% in NF-1.10,11 Hereditary paragangliomas are most often associated with mutations in genes encoding or stabilizing the SDH enzyme complex (SDHB, SDHD, SDHC, and SDHA), which forms the mitochondrial complex 2 and links the Krebs cycle to electron transport,12 whereas mutations in other genes that have been identified as predisposing to pheochromocytoma and paraganglioma include SDHAF2, MAX, and TMEM127.13

Overall, the risk of malignancy, defined as the presence of metastases in nonchromaffin tissue, is relatively low, with prevalence between 10% and 17%.1,4,12 The incidence of malignancy in patients with mutations in the B subunit of SDH is reported as 17%, with disease presenting most often as abdominal noradrenaline-secreting paraganglioma; SDHD mutations are more frequently manifest as multifocal paraganglioma, often in the head and neck, and may be less frequently associated with malignancy.16

Management in such cases is challenging and there is limited clinical trial evidence to support the value of therapeutic interventions such as 131I mIBG. A recent meta-analysis of the efficacy of 131I mIBG in metastatic pheochromocytoma found values for complete response, partial response, and stable disease of 0.02, 0.27, and 0.41 for tumor volume and of 0.10, 0.43, and 0.12 for biochemical response.17 There are, however, no large randomized controlled trial data to support its efficacy. Chemotherapy may also be considered in the form of cyclophosphamide, vincristine, and dacarbazine, with a trial of 18 patients finding complete response in 11%18 and a more recent meta-analysis suggesting partial response in terms of tumor volume and catecholamine excess of ≈40%.19 There is now early experience of tyrosine kinase inhibitors such as sunitinib in the treatment of metastatic disease. The First International Randomized Study in Malignant Progressive Pheochromocytoma and Paraganglioma (FIRSTMAPP) is a randomized, double-blind, multicenter study, which aims to determine the efficacy of treatment with sunitinib in patients with malignant pheochromocytoma.

Prognosis in patients presenting with malignant disease is variable. The overall 5-year survival may be ≤50%; however, the rate of progression of disease is unpredictable; Hescot et al20 demonstrated a 50% progression-free survival at 1 year.
in asymptomatic patients presenting with metastatic pheochromocytoma who received no treatment.

Here, we describe a young woman who presented with metastatic paraganglioma in the context of an SDHB mutation, but who has responded well to a combination of debulking surgery and repeated doses of 131I mIBG. Future therapeutic options include further 131I mIBG therapy, combination chemotherapy, or experimental treatments (eg, Sunitinib); however, none will afford the possibility of cure and will require careful consideration of risks versus benefits.

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Disclosures
None.

References
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病例介绍

患者, 女性, 20岁, 无症状, 拟行择期骨科手术, 前来接受术前临床评估。测双上肢血压为240/110 mmHg, 并行急诊会诊。经检查患者无明显的临床表现。除血压外, 心血管系统检查及肾功能和尿液分析均正常, 但可见双侧颈项水肿。

该患者肾脏超声、脑普通计算机断层扫描 (Computed tomography, CT) 和脑 CT 静脉造影未见异常。肾素、醛固酮水平以及醛固酮/肾素比值和血钾均正常。患者开始氨氯地平和血管紧张素转换酶抑制剂治疗，血压降至151/112 mmHg。

Colin Perry博士: 我认为对于年轻患者, 必须要考虑继发性高血压。当然, 该患者血压正常, 我想知道是患者是否面色苍白? 是否有头痛? 像这样年轻的患者, 开始就会想到是嗜铬细胞瘤。

Perry博士: 这就是为什么我认为在这样一个阶段，病史非常重要。因为，在急诊室首诊时，并无近期头痛的主诉，但患者一直面色苍白。

Schiffrin博士: 我认为这对很重要。所以，我向医生问，患者面色苍白，不就是嗜铬细胞瘤。面色苍白几乎像是嗜铬细胞瘤必备的表现。

Marie Freel博士: 尽管醛固酮/肾素比值正常，但对于恶性高血压的年轻女性，是否需要行肾血管的核磁共振血管造影仍有争议。

Perry博士: 我认为行肾血管的核磁共振血管造影完全合理。

有关检查的讨论

Perry博士: 请问你们将会做哪些嗜铬细胞瘤的检查？
Schiffrin博士: 我们建议测定尿液的甲氧基肾上腺素。
Garry Jennings: 这位患者未做这项检查。因嗜铬细胞瘤的患者, 当血压阵发性升高时, 测定血液指标即可确诊, 若血压升高时, 尿去甲肾上腺素则升高, 则不表示嗜铬细胞瘤。
Schiffrin博士: 再去病史中, 当接诊这样一些患者时, 我会询问家族史, 询问有无甲状腺手术家族史。

Perry博士: 没错, 不过在这样一个阶段, 该患者还未到专科中心就诊。所以, 你很容易对, 实际上该患者有头痛史, 如果你仔细追问, 她会讲述头痛的病史。如果认真问诊，80%的嗜铬细胞瘤患者有头痛史。

该患者24小时尿去甲肾上腺素和儿茶酚胺升。尿去甲肾上腺素水平为11,374 nmol/24 h (正常值为<500 nmol/24 h), 尿游离甲氧基去甲肾上腺素水平为16,365 nmol/24 h (正常值为<650 nmol/24 h)。

胸部、腹部和盆腔CT显示左侧主动脉旁可见一肿块, 右侧亦有一较小的肿块 (图1)。[123]碘间碘苯基 (methyl-123iodobenzylguanidine, mIBG) 软肝扫描证实存在广泛的[123]碘mIBG高摄取性病灶 (图2)。

初始治疗

Perry博士: 在这个阶段, 考虑到这位年轻女性病变广泛, 治疗上您有哪些建议？
Schiffrin博士: 切除病灶。
Perry博士: 有人认为此时不需要手术吗? 或者你们认为正确的做法是尽可能地切除病灶。

大家均点头表示赞同。

在受α和β阻滞剂治疗后, 该患者接受切除手术，切
除靠近左侧肾上腺的80×40×22 mm的肿块，同时切除受累及的淋巴结。

Schiffrin博士：对于那些不常使用治疗这样患者的医生，您能否解释一下为什么首先给予美氟苯胺治疗，随后才开始应用β受体阻滞剂?

Perry博士：因为，此类患者的危险在于，β受体阻滞剂在无拮抗情况下使用，则可能出现严重的α受体介导的血管收缩，促发危象，甚至可能致命。因此，真正的危险是以错误的顺序、使用错误的药物治疗。可以酌情给予美氟苯胺和硝酸酯，苯氧苄胺是一种长效的、非竞争性的药物，只有在受体内化后，才会失去活性。因此，尽管服用苯氧苄胺后相关症状较多，而且，长期服用也非令人愉快，但术前应用该药比多沙唑嗪更为安全。

手术概况

Patrick O’Dwyer教授：我们进行了腹腔镜切除手术。切除患者主动脉旁的全部病变和下腔静脉旁淋巴结。从髂骨直至髋肌脚、连同静脉，正如大家所见。分离了左侧肾静脉，通过腹腔镜切除了所有的淋巴结。该患者术后住院24小时，恢复顺利。

Schiffrin博士：在切除肿瘤的过程中，患者是否出现过心律失常?

Patrick O’Dwyer教授：没有。我们已经开展了100多例嗜铬细胞瘤或副神经节瘤手术，均未发生任何严重事件。没有发生心律失常，这是因为腹腔镜手术对这些组织影响很小。

Anna Dominiczak教授：即使在过去采用开放性手术时，术前准备良好、α-受体阻滞充分的患者，也不会发生心动过速、心律失常或血压升高。如果苯氧苄胺使用足量，则不会发生任何异常。

O’Dwyer教授：安娜，我们的确有此一例患者，在开放手术的过程中发生心脏骤停。

Dominiczak教授：那不是我的患者。

对切除肿瘤的病理学检查显示浸润性的，实体性团块状肿瘤细胞，核呈圆形泡状，胞浆中嗜酸颗粒，肿瘤的免疫组化染色显示嗜铬细胞蛋白和特异性阳性。Ki-67增生指数不一致，一些区域<1%，一些区域为2%~3%。脂肪、血管侵润，局部淋巴结明显受累。

术后治疗

患者已接受肿瘤切除术，但疾病依然存在，因此，询问在座专家对该患者的进一步治疗有哪些建议。

Schiffrin博士：mIBG治疗。

Perry博士：有人大认为在这个阶段需要进行化疗吗？

无人回应。

Perry博士：有人大认为应该观察和等待吗？

大家摇头表示“不”。

该患者自20个月前接受手术以来，共进行3个疗程的131碘mIBG治疗(每次治疗剂量10,000毫克(MBq))，耐受性良好，使她能够重回她的研究工作中。根据生化指标和病情情况，提示患者病情稳定。其最近测定的尿去甲肾上腺素为987 nmol/24 h，游离甲氧基去甲肾上腺素为4198 nmol/24 h。尽管患者无明确的神经内分泌家族史，但是，遗传学检测发现琥珀酰脱氢酶B (succinate dehydrogenase B, SDHB)基因存在病理性突变，推测该突变会影响到外显子2的正常剪切。后来，在她父亲家族的其他成员中检出该突变。
进一步的讨论
Schiffin博士：我想多了解一下基因密码和细胞癌。
Perry博士：我认为在这里讨论一下基因检测的方法很重要。你可以在检查大多数已知的基因癌突变，尤其是检测RET， SDHB，SDHD和von Hippel-Lindau（VHL）基因的突变，但是，我认为对于这位患者，你应当已经检测了SDHB基因突变是钙细胞癌最可能的遗传原因。这是基于患者有腹部的广泛转移，而不是多灶性疾病。生化表型是分泌去甲肾上腺素，而不是肾上腺素。我想，这些在你更多的去考虑是SDHB突变，而不是SDHD突变，将不是RET突变，也不是VHL突变。因为没有相关的表现及家族史。当任何其他检查也适用时，我认为确定最合适的基因很重要，而不是广泛的筛查到所有遗传异常。如果没有SDHB或SDHD突变，你将考虑其他的可能性。
Schiffin博士：甲状旁腺与RET基因突变的关系？
Perry博士：该患者没有多发性内分泌腺2型的病史及家族史，亦无甲状旁腺样症状的出现。
Schiffin博士：有理由检查嗜铬细胞瘤或是可能的钙细胞癌患者的腋下吗？
Perry博士：值得注意的是，神经纤维瘤病1型（neurofibromatosis type 1, NF-1）的表型，查看有无咖啡牛奶斑和皮下斑块。NF-1非常有意思，因为同时患有NF-1和嗜铬细胞瘤，其恶性的可能性要高于散发的嗜铬细胞瘤。可能多达5%的NF-1患者发生嗜铬细胞瘤，这取决于你所观察的系列。令人感兴趣的案例是如何早期发现与识别与很多NF-1患者的筛查结果仅仅询问他们是否有高血压，这可能远远不够。
Dominiczak教授：我还有一个问题。该患者22岁，肿瘤已切除，也接受其它治疗。患者可能在一两年内来到诊室询问：“医生，我能怀孕吗？”你会如何回答？
Perry博士：我认为，未来怀孕有风险。我们会关注她是否怀孕。将至少两例VHL突变的患者在妊娠过程中病情恶化，因此，必须仔细讨论相关风险。
Dominiczak教授：另一个相关问题，我们有一例患者，她是患者的女儿，她发现自己是临床观察的SDHB基因的新突变点。
Perry博士：我们有几个同是SDHB基因突变的家族。我认为，我们在本地积累相当多的经验，是因为在苏格兰，我们发现SDHB基因的新突变点。
Marc de Burzyk先生：在早期的文献中，我们了解到，当有副神经节瘤症候群时，则与血管母细胞瘤有一种可能的关联。现在，对于二者存在关联问题还有争议吗？
Perry博士：毫无疑问，VHL突变携带者会发生嗜铬细胞癌和血管母细胞瘤。我见到过类似表现，一位VHL基因突变的年轻男性患者，双侧嗜铬细胞瘤。去双肾上腺素分泌表型，同时伴有血管母细胞瘤和肾细胞癌。当然，还有眼部表现。因此，我认为完整的病史无疑是必要的，像这样的患者，病史可能会指导你检测最有可能的突变。

总结
嗜铬细胞瘤是起源于肾上腺髓质嗜铬细胞的肿瘤。副神经节瘤也起源于嗜铬细胞，但位于肾上腺以外的组织。主要沿交感和副交感神经分布。这两种肿瘤都非常罕见，其总患病率大约为8-100,000患者年[10]，而门诊高血压患者的嗜铬细胞瘤副神经节瘤的患病率为0.2%~0.6%不等[11,12]。
然而，尸检显示两者总患病率更高，可能有0.05%~0.1%的患者未被诊断[13]。最近内分泌学会临床实践指南对这两种罕见肿瘤的诊断和治疗提出明确的指导意见[14]

大多数嗜铬细胞瘤和副神经节瘤是散发性的，但是，很大一部分肿瘤源于潜在的遗传原因。例如，近期的研究估计大约30%~50%的副神经节瘤和多达20%的嗜铬细胞瘤可伴有遗传综合征[15]。遗传性嗜铬细胞瘤可能与多发性内分泌腺2型，VHL综合征和NF-1有关。估计嗜铬细胞瘤的患病率在VHL为10%~20%，多发性内分泌腺腺病2型为50%，NF-1为1.5%~6%[16,110,111]。遗传性副神经节瘤最常见SDHβ亚基复合物（SDHD，SDHB，SDHC和SDHA）编码或稳定基因的突变，SDHβ复合物构成线粒体复合物2，并连接三羧酸循环和电子传递[12]，而确认的其它嗜铬细胞瘤和副神经节瘤易感性相关的突变基因包括SDHA,2, MAX和TME8和TME122[13]。

总体来看，这些肿瘤的恶性程度（定义为具有非嗜铬组织的转移）比较低，其发生率为10%~17%[14,15]。据报道，SDHβ亚基B亚单位突变的患者，恶性肿瘤比例为17%，最常见的表现为腹部分泌去甲肾上腺素的副神经节瘤，SDHD突变更常表现为多发性的副神经节瘤，通常可见于颈部以及部位，可能恶性少见[10,102]

此类疾病的治疗具有挑战性。支持33碘MBG等肿瘤干预治疗价值的临床试验结果有限。最近，一项33碘MBG治疗转移性嗜铬细胞瘤疗效的荟萃分析结果显示该治疗很有价值，依肿瘤体积指标，完全缓解，部分缓解和疾病稳定的比例分别为0.02, 0.27和0.41，依生化指标，完全缓解，部分缓解和疾病稳定的比例分别为0.10, 0.43和0.12[113,137]。不过，还没有大型随机对照试验的数据支持33碘MBG的疗效。化疗可以考虑使用环磷酰胺，长春新碱和达卡巴嗪。
一项纳入18例患者的试验发现化疗的完全缓解率为11%[141]。新近开展的一项荟萃分析显示，依肿瘤体积指标，卡铂酰胺异常指标，部分缓解率为40%[139]。现有舒尼替尼和酶酰胺酶抑制剂治疗恶性嗜铬细胞瘤和副神经节瘤的初步
经验。嗜铬细胞瘤和副神经节瘤恶性进展的首个国际随机试验（First International Randomized Study in Malignant Progressive Pheochromocytoma and Paraganglioma, FIRSTMAPP）是一项随机、双盲、多中心研究，旨在明确恶性嗜铬细胞瘤患者应否施用舒尼替尼的疗效。

恶性嗜铬细胞瘤和副神经节瘤患者的预后并不一致。5年总生存率可能低于50%；不过，疾病发展速度无法预测。Hescox等（2001）证实，未经治疗的无症状的转移性嗜铬细胞瘤患者，1年无进展生存率为50%。

本文介绍一例有SDHopathy突变，表现为转移性副神经节瘤的女性患者，其对肿瘤切除术联合重复剂量的^{131}I碘MBG治疗，反应良好。未来的治疗选择，包括进一步的^{131}I碘MBG治疗，联合化疗或试验性治疗（如舒尼替尼）；但是，没有治愈的可能性，并需要仔细权衡治疗的风险和获益。

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利益声明

无。

参考文献