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Pictorial Review

# Succinate dehydrogenase mutations: paraganglioma imaging and at-risk population screening

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Paragangliomas are rare vascular tumours of the autonomic nervous system. They can be classified as sympathetic or parasympathetic. Sympathetic paragangliomas, which include phaeochromocytomas, tend to be functional and symptomatic. Parasympathetic paragangliomas are usually non-functional and may present with mass effect. Forty percent of paragangliomas are linked to genetic syndromes, most commonly due to mutations of the succinate dehydrogenase (SDH) enzyme complex and are collectively known as paraganglioma syndromes, of which five are described. Genetic testing is recommended for all patients, and their first-degree relatives, diagnosed with paragangliomas. When SDH mutations are discovered, biochemical screening and imaging surveillance is indicated. There is currently no consensus on imaging surveillance protocols. Most advocate full-body imaging, but the choice of technique and frequency varies. If paragangliomas are demonstrated, functional imaging to look for synchronous tumours or metastases is indicated. 2-[$^{18}$F]-fluoro-2-deoxy-D-glucose ($^{18}$F-FDG) positron-emission tomography (PET)-computed tomography (CT) is the technique of choice for metastatic evaluation, but [$^{123}$I]-metaiodobenzylguanidine or [$^{111}$In]-DTPA-octreotide scintigraphy are also utilised. Current research into emerging positron-emitting radiolabelled somatostatin analogues have yielded promising results, which is likely to be reflected in future guidelines. As genetic testing becomes increasingly prevalent, the need to answer the remaining questions regarding surveillance imaging is paramount.



## Introduction

Paragangliomas are rare neuroendocrine neoplasms that arise from the autonomic nervous system. Initially thought to be sporadic, recent studies suggest approximately 40% of

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paragangliomas are associated with inherited syndromes. These include multiple endocrine neoplasia (MEN) 2A and 2B, von Hippel–Lindau syndrome, neurofibromatosis type 1, and succinate dehydrogenase (SDH) mutations. SDH mutations account for one-quarter of inherited paragangliomas,[1,2] and are the focus of this article. As well as predisposing to paragangliomas, patients with SDH mutations are at increased risk of malignant transformation and developing other neoplasms with consequent implications for screening and surveillance.

Unfortunately, there are no highly specific imaging features of inherited paragangliomas. This review summarises the current paraganglioma classification and typical imaging findings. Features that may be suggestive of inherited paragangliomas are highlighted. In view of the difficulty in identifying inherited paragangliomas, it is paramount to be aware of the subtypes of SDH mutation. We present cases demonstrating the propensity and distribution of SDH-associated paragangliomas from our cohort of patients. Finally, we discuss imaging surveillance for patients with known SDH mutations, and screening for metastatic disease when paragangliomas are discovered.

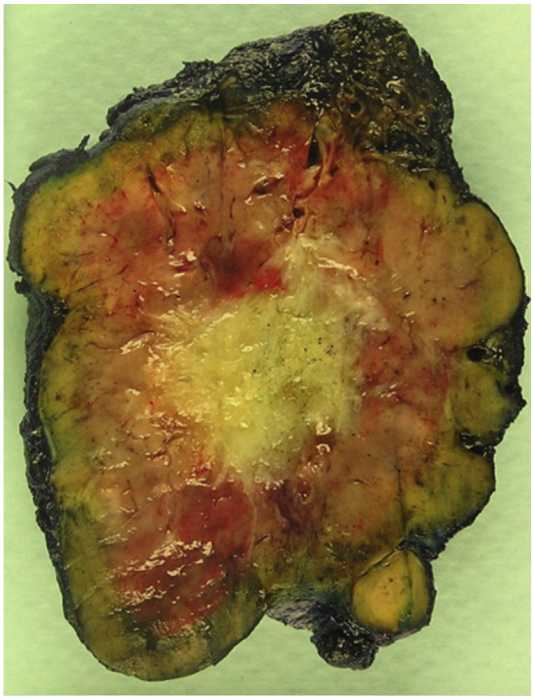
## Paraganglioma nomenclature

Paragangliomas arise from cells derived from the embryonic neural crest within the sympathetic and parasympathetic nervous system. They can be divided into sympathetic or parasympathetic subtypes. The World Health Organization (WHO) also divides paragangliomas as extra-adrenal or intra-adrenal. Extra-adrenal paragangliomas encompass both sympathetic and parasympathetic paragangliomas arising outside the adrenal gland. Intra-adrenal paragangliomas encompass all paragangliomas arising from the adrenal gland and are synonymous with phaeochromocytoma.[3] There are no intra-adrenal parasympathetic paragangliomas and therefore intra-adrenal paragangliomas will be referred to as phaeochromocytomas throughout the review.

## Sympathetic paraganglioma

Sympathetic paragangliomas arise anywhere along the sympathetic chain, from the skull base to pelvis. The most common presentation is a phaeochromocytoma. Extra-adrenal sites most frequently affect the organ of Zuckerkandl; the small mass of chromaffin cells between the origin of the inferior mesenteric artery and aortic bifurcation. Less frequently sympathetic paragangliomas affect the infra-diaphragmatic para-aortic region and mediastinum.[4] The majority of sympathetic paragangliomas are functional, producing catecholamines, mostly adrenaline and noradrenaline.[5] Consequently, patients often develop hypertension, which can be sustained or paroxysmal. Typical symptoms also include headache, palpitations, and sweating. Up to 10% of patients have no or minimal symptoms and paragangliomas are discovered incidentally on imaging.[6]

Macroscopically both sympathetic and parasympathetic paragangliomas are highly vascular tumours, which appear fleshy pink to red, brown and grey in colour secondary to haemorrhage and fibrosis.[7] Imaging findings correlate well with the macroscopic appearance, but other than location do not differentiate sympathetic from parasympathetic paragangliomas. Fig 1 demonstrates the macroscopic histology on



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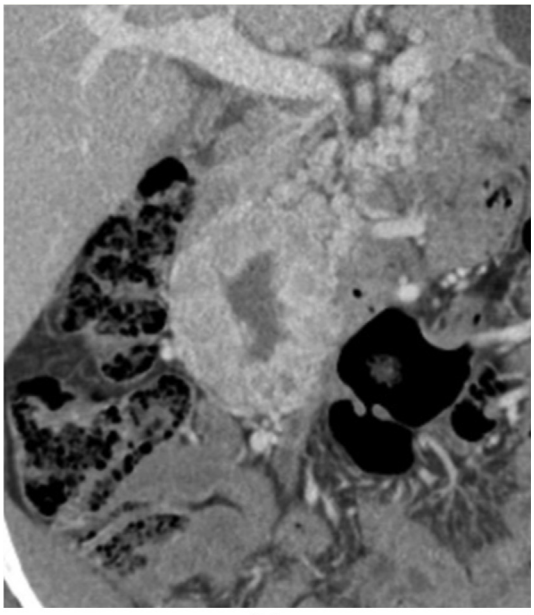


(b)

**Figure 1** (a) Macroscopic appearance of an extra-adrenal sympathetic paraganglioma. Note the fleshy red and brown colouration and central fibrosis. (b) Coronal portal venous phase CT reformat demonstrates a para-aortic avidly enhancing mass with surrounding leash of vessels and central low attenuation consistent with fibrosis or necrosis, as seen on the macroscopic histology.

an extra-adrenal sympathetic paraganglioma and corresponding appearance on computed tomography (CT). The highly vascular nature is indicated by avid enhancement, although minimal enhancement can occur rarely.[8] Cystic change, necrosis, and internal calcifications are also commonly seen.[9] On magnetic resonance imaging (MRI) both sympathetic and parasympathetic paragangliomas usually demonstrate intermediate T1 signal and high T2 signal. As well as avid enhancement, scattered focal signal voids reflect high-flow blood vessels, which is known as the "salt and pepper" appearance.[10] The typical T1 and T2 MRI characteristics of a phaeochromocytoma are demonstrated in Fig 2.

## Parasympathetic paraganglioma

Parasympathetic paragangliomas most commonly occur in the carotid body, jugular foramen, tympanic cavity, and along the vagus nerve, but have also been reported in other regions of the head and neck including, the larynx, orbit, thyroid, and tongue.[11] The common sites of parasympathetic paragangliomas and associated nomenclature are illustrated in Fig 3. Parasympathetic paragangliomas are usually non-functional, and consequently, often asymptomatic; however, depending on location, they can present with symptoms of mass effect such as pain, hearing disturbance, dysphagia, and hoarseness.[12] Examples of a vagal paraganglioma and carotid body paraganglioma are shown in Figs 4 and 5, respectively. In Fig 4 there is anterior displacement of the internal and external carotid arteries indicating the paraganglioma is arising from the vagus nerve, as opposed to the case in Fig 5 where there is splaying of the carotid arteries indicating the paraganglioma is arising from the carotid body.

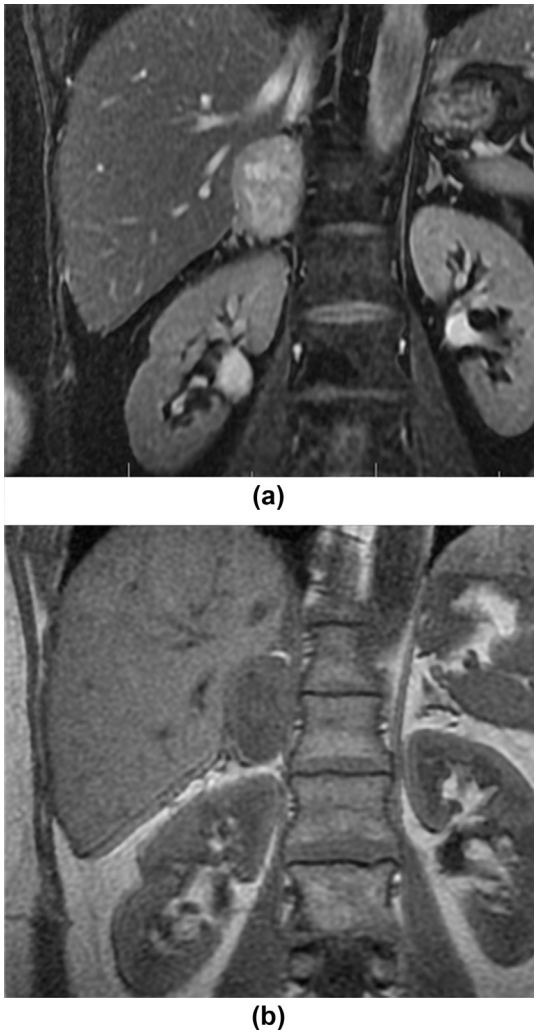



**Figure 2** (a) Coronal T2-weighed MRI appearance of a right-sided phaeochromocytoma. The mass is arising from the adrenal gland and has high to intermediate T2 signal. (b) The corresponding in-phase T1 image demonstrates intermediate T1 signal.

## Clinicoradiological features suggesting inherited paraganglioma

There are several clinicoradiological features suggesting inherited as opposed to sporadic paragangliomas; age of onset, multiplicity, malignant transformation, and atypia. Patients with SDH syndromes tend to develop paragangliomas around a decade earlier than in sporadic disease with the majority presenting by 35 years of age.[13] Multiplicity has been reported in up to 10% of sporadic paragangliomas, but as high as 87% in certain SDH syndromes.[14] There is often increased risk of malignant transformation in inherited paragangliomas.[15] Atypical presentations with relatively low T2 signal have been reported in inherited paragangliomas. The nuclear medicine imaging characteristics of paragangliomas are discussed in detail later, but

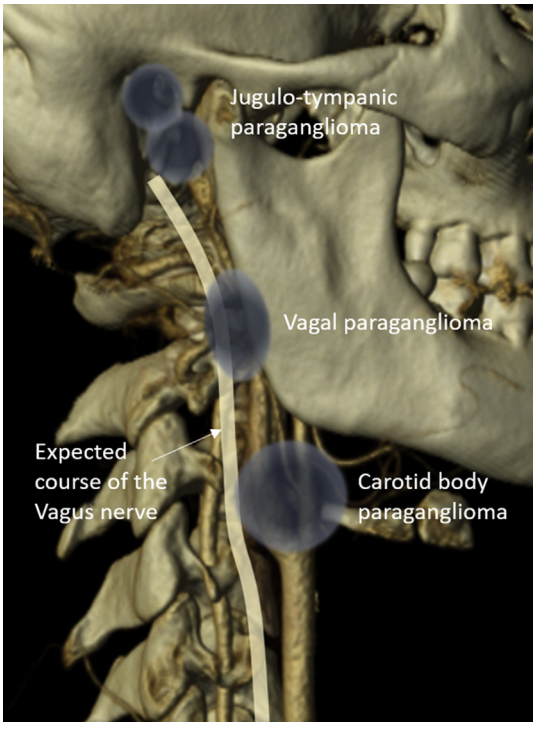



**Figure 3** Diagram illustrating the common sites of parasympathetic paragangliomas.

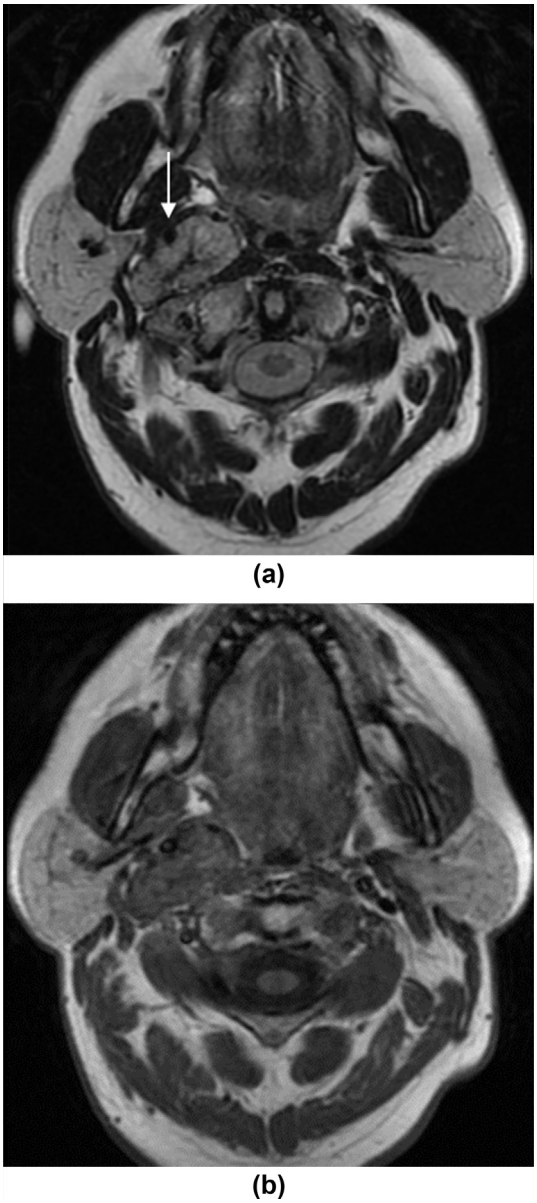



**Figure 4** (a) Axial T2-weighted MRI appearance of a right-sided vagal paraganglioma. There is moderately elevated peripheral T2 signal with central low signal indicating fibrosis. Anterior displacement of the internal carotid artery (arrow) indicating the paraganglioma is likely arising from the vagus nerve. (b) Corresponding axial T1-weighted image showing intermediate signal within the paraganglioma.

notably, at least 50% of malignant paragangliomas are associated with decreased uptake of [$^{123}$I]-meta-iodobenzylguanidine ([$^{123}$I]-MIBG), again highlighting atypical physiology and morphology.[16]

## SDH gene mutations and paraganglioma syndromes

SDH, also known as mitochondrial complex II, is a mitochondrial enzyme complex. It is the only membrane bound member of the tricarboxylic acid cycle (Krebs cycle);

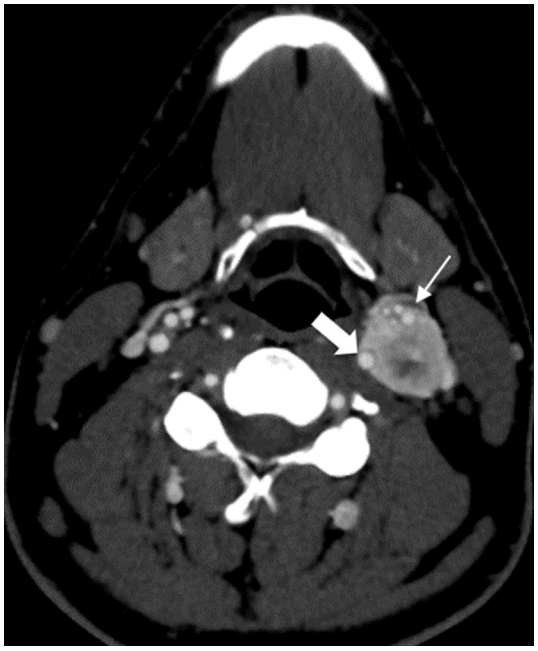


**Figure 5** Axial arterial phase CT appearance of a left-sided carotid body paraganglioma. There is avid enhancement and splaying of the internal and external carotid arteries (thick and thin arrows respectively) indicating the paraganglioma is arising from the carotid body.

its function is to catalyse oxidation of succinate to fumarate. It is also involved in the electron transfer chain transferring electrons to co-enzyme Q.[17] SDH consists of four subunits: SDHA, SDHB, SDHC and SDHD, each with a corresponding encoding gene. Two further genes have been identified in the assembly of the SDH complex: SDHAF1 and SDHAF2.[18,19] The location of SDH in the tricarboxylic acid cycle is illustrated in Fig 6.

The pathogenesis of SDH mutations and the association with paraganglioma development is incompletely understood. It is known that inactivation of SDH induces hypoxia-driven angiogenesis pathways, which likely account for the pathognomonic vascularity of these lesions.[20] Five of the SDH genes have been implicated in paraganglioma formation: SDHA, SDHB, SDHC, SDHD, and SDHAF2. No association has been established between SDHAF1 and paraganglioma formation which, however, has been linked to infantile leukoencephalopathy.[18] Correspondingly, five SDH paraganglioma syndromes are described: paraganglioma syndromes 1–5 (Table 1). All paraganglioma syndromes are inherited in an autosomal dominant pattern, but display variable penetrance.[21]

The most common mutation affects SDHD and results in paraganglioma syndrome 1. As well as being autosomal dominant, the SDHD gene is maternally imprinted. Counterintuitively, this means the maternal allele is silent and, therefore, paraganglioma syndrome 1 can only be passed on to children by their father.[21] Ninety-three percent of patients with paraganglioma syndrome 1 develop extra-adrenal paraganglioma of the head and neck, of which 84% are parasympathetic, 56% are multifocal, and 4% malignant.[15] Twenty-four percent of these patients will also develop

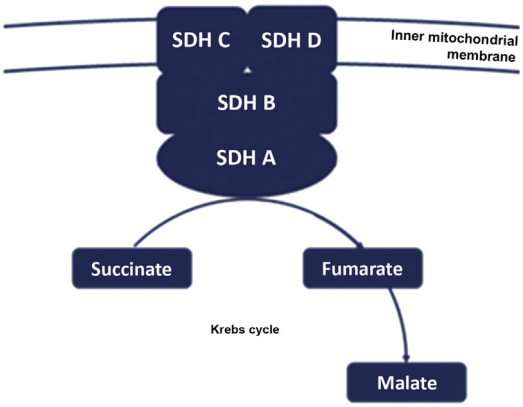
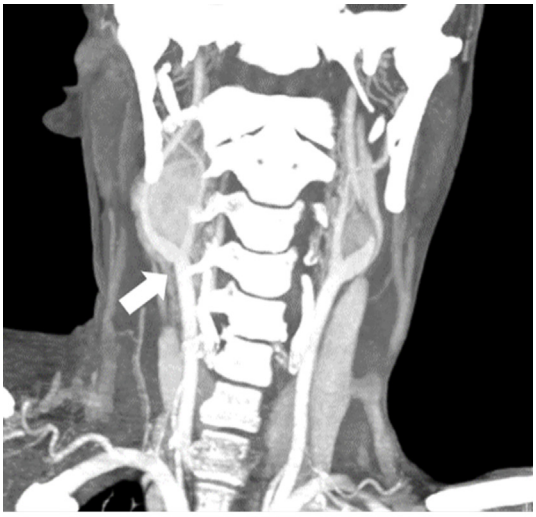



**Figure 6** Diagram illustrating the location of SDH in the tricarboxylic acid cycle.

phaeochromocytoma.[12] A rare association with gastrointestinal stromal tumours is also reported.[22] The mean age of presentation is 35 years with penetrance reported in up to 43.2% by 60 years.[15,23] An example of a 44-year-old woman with paraganglioma syndrome 1 and bilateral carotid body paragangliomas is shown in Fig 7. Fig 8 demonstrates T1 and fluid attenuated inversion recovery (FLAIR) images from a 46-year-old woman with paraganglioma syndrome 1 and known left carotid body paraganglioma, who on follow-up developed a right jugulo-tympanic paraganglioma. Jugulotympanic paragangliomas arise from the nerves of Arnold or Jacobson, which are branches of the vagus and glossopharyngeal nerves, respectively. They can arise solely within the tympanic cavity over the cochlear promontory, or within the jugular fossa, or start in the jugular fossa and extend cranially into the middle ear.

The second most common mutation affects SDHB and results in paraganglioma syndrome 4. The mean age of onset is 33 years and penetrance is reported in up to 21.8% by 60 years.[12,23] It is predominantly associated with extra-adrenal paragangliomas, with 78% of patients developing intra-thoracic or intra-abdominal extra-adrenal sympathetic paragangliomas; however, 25% of patients will also develop phaeochromocytoma.[12] There is higher morbidity



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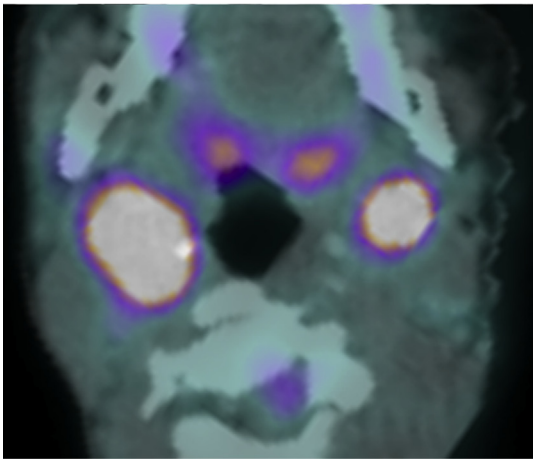

(b)

**Figure 7** (a) MIP coronal arterial phase CT image of a 44-year-old woman with paraganglioma syndrome 1 and bilateral carotid body paragangliomas. Note the splaying of the carotid arteries (arrow) which is known as the "lyre sign". This was classically described on angiography, but can be seen on coronal and sagittal reformats. (b) [$^{123}$I]-MIBG SPECT CT demonstrating avid uptake within the bilateral carotid paragangliomas.

**Table 1**
Summary of paraganglioma syndromes.

| | | |
|---|---|---|
| Paraganglioma syndrome 1 | SDH D mutation | Most common<br>Associated with parasympathetic paragangliomas which are often multiple<br>Approximately 25% develop phaeochromocytoma<br>Rarely malignant |
| Paraganglioma syndrome 2 | SDH AF2 Mutation | Very rare<br>Associated with parasympathetic paragangliomas<br>No metastatic disease described |
| Paraganglioma syndrome 3 | SDH C mutation | Rare<br>Associated with parasympathetic paragangliomas which are multiple in up to 17%<br>Rarely malignant |
| Paraganglioma syndrome 4 | SDH B mutation | Second most common<br>Associated with sympathetic paragangliomas with higher risk of malignant transformation<br>Approximately 25% develop phaeochromocytomas |
| Paraganglioma syndrome 5 | SDH A mutation | Very rare<br>Associated with both paragangliomas and phaeochromocytomas<br>No multiplicity or metastatic disease described |

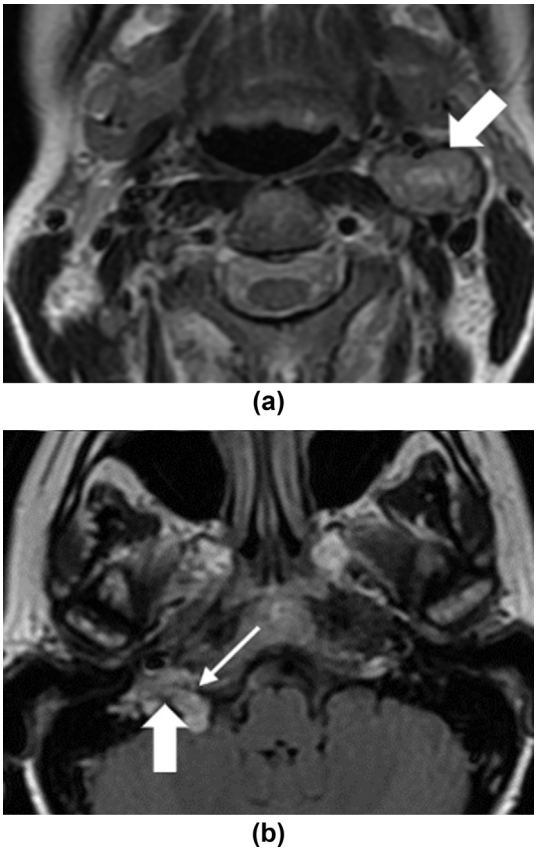

**Figure 8** (a) Axial T2 MRI image of 46-year-old woman with paraganglioma syndrome 1 and known left carotid paraganglioma. (b) Follow-up axial IR MRI image now demonstrating a right jugulotympanic paraganglioma. Note the heterogeneous T2 hyperintensity and expansion of the jugular foramen (thin arrow).

and mortality than other paraganglioma syndromes with up to 79% reported to metastasise.[24] Paraganglioma syndrome 4 is also associated with early onset renal cell cancer, papillary thyroid carcinoma, and gastrointestinal stromal tumours.[25] Fig 9 shows ultrasound and CT images of a 26-year-old man who presented with hypertension and was found to have a para-aortic paraganglioma. His young age of presentation is suggestive of an inherited syndrome and subsequent genetic testing revealed SDHB mutation.

The remaining paraganglioma syndromes 2, 3, and 5 are less common. Paraganglioma syndrome 2 results from SDHAF2 mutation and has only been described in two families.[26,27] The studies reported parasympathetic paragangliomas, which were multiple in 87% of cases. Metastatic disease was not observed.[12]

Paraganglioma syndrome 3 results from SDHC mutation. This syndrome is thought to be rare, although one study reported SDHC mutation in up to 4% of patients with parasympathetic paragangliomas.[28] It is associated with head and neck paragangliomas, and less commonly, sympathetic paragangliomas and phaeochromocytomas. The paragangliomas are often multiple with very low malignant potential.[29]

Paraganglioma syndrome 5 results from SDHA mutation. It is again considered to be very rare, identified in only six

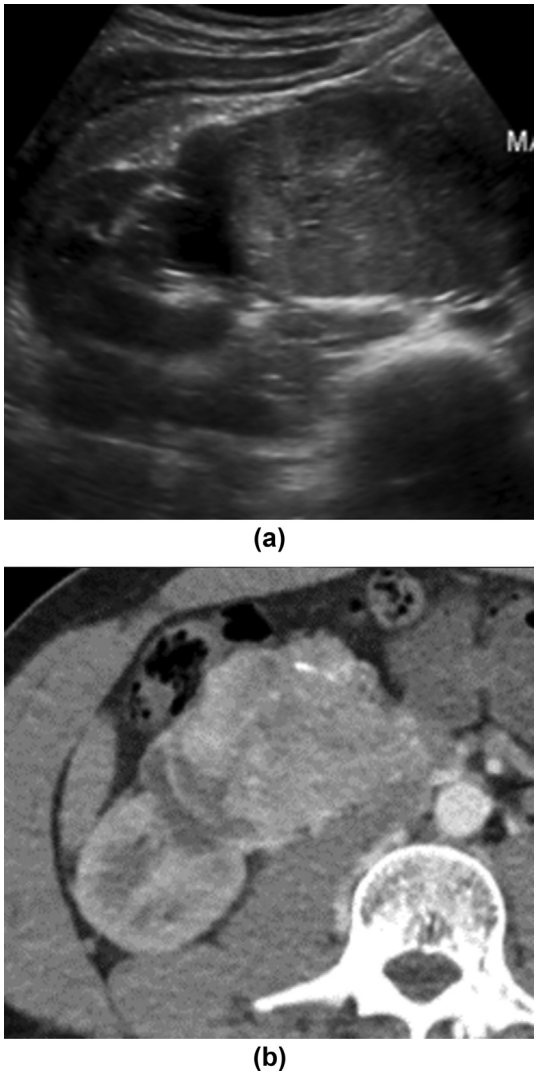

**Figure 9** (a) Ultrasound image of a 26-year-old man with paraganglioma syndrome 4 showing a large heterogeneous right pararenal mass with areas of echogenicity likely indicating calcification. (b) Axial arterial phase CT image demonstrating the same para-aortic paraganglioma. Again, note the heterogeneous appearance and regions of calcification.

patients, of which five had extra-adrenal paragangliomas and one had a phaeochromocytoma.[12] No multiplicity or metastatic disease has been described. SHDA mutation has been found in healthy controls suggesting paraganglioma syndrome 5 has a low penetrance.[30]

## Screening and imaging surveillance in paraganglioma syndromes

Early identification of paragangliomas is important as surgical resection represents the treatment of choice for many patients. For non-operable patients, options include chemotherapy, radiotherapy, and radionucleotide therapy.[31] As a number of paragangliomas are asymptomatic, screening and imaging surveillance is paramount for early detection and optimal management.

Currently, genetic testing is recommended for all patients diagnosed with paraganglioma.[32] In those who are found to have an SDH mutation, screening can also be undertaken for their first-degree relatives.[32] When an SDH mutation is identified, biochemical and imaging surveillance are indicated, which consists of annual biochemical screening for metanephrines and surveillance imaging for detection of asymptomatic or non-functional paragangliomas.[33]

There is no consensus on appropriate technique or frequency to image patients with SDH mutations.[34] Most authors advocate full-body imaging for all paraganglioma syndromes, but suggest slight variations for specific syndromes due to the different clinical presentations. The highest sensitivity for detection of paragangliomas is reported with the combination of head and neck MRI angiogram; CT thorax, abdomen and pelvis; and somatostatin receptor scintigraphy[35]; however, the extensive radiation exposure of this protocol makes its suitability for surveillance imaging debatable. Cross-sectional imaging has a higher sensitivity for detecting primary tumours than functional imaging.[35] One study found rapid sequence whole-body (skull base to pelvis) MRI in SHD mutation carriers to have a sensitivity of 87.5% and specificity of 94% for detection of paragangliomas.[36]

Different intervals for surveillance imaging are suggested. One study of 60 patients found 6.6% developed <1 cm lesions on annual follow-up, consistent with paragangliomas. The authors concluded that scanning at longer intervals may miss opportunities for early intervention.[37] At our institution, we perform MRI neck, thorax, and abdomen every 3 years in patients over 10 years old with paraganglioma syndromes 1, 3, and 4. Patients in the 8–10-years-old cohort only undergo biochemical screening. From the age of 25, patients with paraganglioma syndrome 4 also undergo kidney ultrasound in the years intervening their MRI studies. This is due to the increased risk of early onset renal cancer. Due to their rarity, we do not have a protocol for paraganglioma syndromes 2 and 5. Fig 10 shows an example of a 42-year-old man with paraganglioma syndrome 4 who had a vagal paraganglioma demonstrated on imaging surveillance.

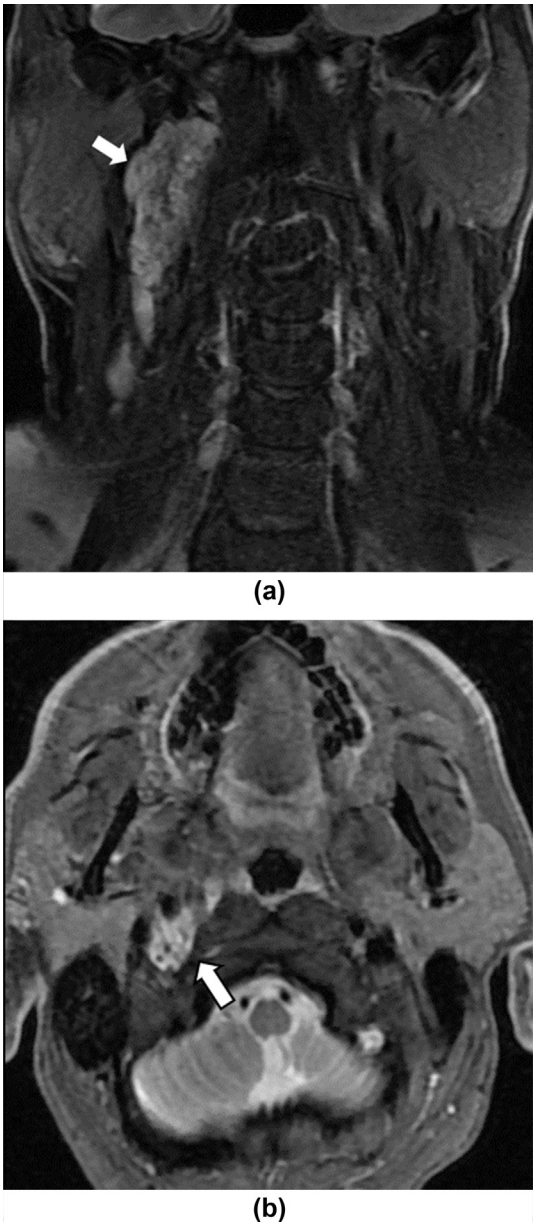


**Figure 10** (a) Coronal T2 fat saturation MRI image of 42-year-old man with paraganglioma syndrome 4 undergoing surveillance imaging demonstrating a right vagal paraganglioma (arrow). (b) Axial T2 MRI image showing the vagal paraganglioma tracking along the carotid sheath towards the jugular foramen.

## Screening for metastatic disease

Currently, there are no molecular, cellular, or histological markers to indicate whether a paraganglioma is malignant.[3,32] Malignancy is therefore defined as the presence of distant metastases with the most frequent sites involving the lymph nodes, skeleton, liver, and lungs.[38] Functional imaging is the recommended screening tool for metastatic disease and targets paragangliomas and phaeochromocytomas acting via different mechanisms. [$^{123}$I]-MIBG and [$^{18}$F]-fluorodopamine ([$^{18}$F]-FDA) target catecholamine pathways.[39,40] [$^{18}$F]-fluoro-2-deoxy-D-glucose ([$^{18}$F]-FDG) enters the cells via the glucose transporters.[41] [$^{111}$In]-DTPA-octreotide targets somatostatin receptors which, similar to neuroendocrine tumours, are expressed on paragangliomas.[42]

Multiple studies have shown that [$^{18}$F]-FDG PET-CT is superior to [$^{123}$I]-MIBG scintigraphy for detecting metastases,[43–45] especially in patients with SDHB mutations,[43] and is currently the technique of choice in this clinical scenario.[32] The main limitation of [$^{123}$I]-MIBG scintigraphy is its high false-negative rate particularly in malignant paragangliomas due to dedifferentiation resulting in lack of the norepinephrine transport system.[16] Fig 11 shows an example of a phaeochromocytoma in a 46-year-old man with SDHB mutation with no uptake on [$^{123}$I]-MIBG scintigraphy. Current guidelines suggest that [$^{123}$I]-MIBG scintigraphy also has a role in the identification of disease,

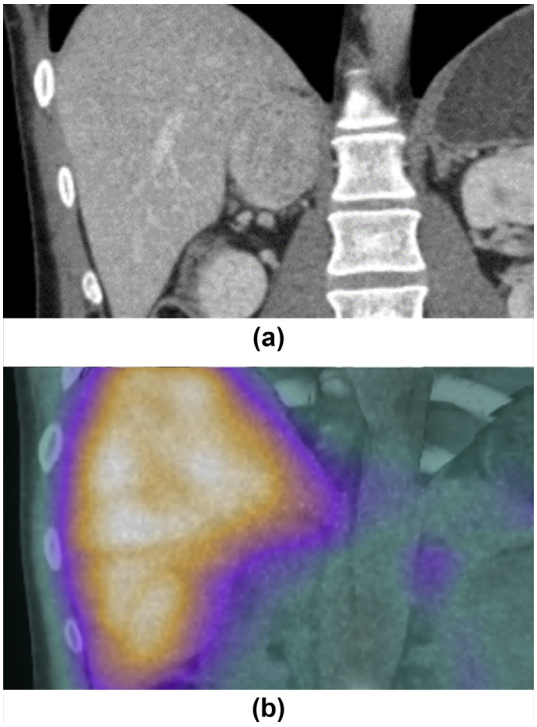


**Figure 11** (a) Coronal enhanced CT image showing right phaeochromocytoma in a 46-year-old man with SDHB mutation. (b) Corresponding [$^{123}$I]-MIBG study showing no increased uptake in the region of the known phaeochromocytoma.

which can be treated with [$^{131}$I]-MIBG.[29] [$^{111}$In]-DTPA-octreotide scintigraphy does not feature in the guidelines, but has on occasion been recognised to pick up sites of disease not evident on [$^{18}$F]-FDG PET.[43]

Several newly developed positron-emitting radiolabelled somatostatin analogues are undergoing evaluation for paraganglioma detection. These include DOTA peptides, such as DOTA(0)-Tyr(3)-octreotate (DOTATATE) and DOTA(0)-Phe(1)-Tyr(3)-octreotide, which bind somatostatin receptors much more efficiently than [$^{111}$In]-DTPA-octreotide. One study has demonstrated the superiority of DOTATATE PET/CT in localization of SDHB-associated metastatic phaeochromocytomas and paraganglioma, and it is likely this will be reflected in future guidelines.[46]

## Conclusion

Although there are no highly specific imaging features to suggest inherited paragangliomas, knowledge of the distribution of paragangliomas and associated lesions in the different SDH mutations can help recognition. Despite the association between SDH mutations and paragangliomas being well established, there is no consensus on surveillance imaging in asymptomatic carriers. Questions remain regarding technique, age, and frequency of imaging. There are clinical guidelines for the use of functional imaging in detecting metastases, but these may change in the near future due to new positron-emitting radiolabelled somatostatin analogues. With ever-increasing genetic testing, there will likely be an increase in the number of individuals undergoing surveillance imaging, making the need to answer the remaining questions paramount.

## Conflict of interest

The authors declare no conflict of interest.

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