Imaging phaeochromocytoma

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Abstract

The phaeochromocytoma (pheochromocytoma) is a hormonally active tumour of neuroendocrine origin. This article reviews the embryology, anatomy, nomenclature and pathology as it relates to the imaging of phaeochromocytomas and paragangliomas. The imaging findings and the role of different imaging modalities are emphasised. The application of multidetector computed tomography (MDCT), magnetic resonance imaging (MRI) and nuclear medicine imaging techniques are discussed and illustrated by multiple images. Since the accurate diagnosis and localisation of phaeochromocytoma is critical to patient management, it is important for all physicians to understand the strengths and weaknesses of different imaging modalities during the work-up of a patient. Radiologists must be familiar with both the common and uncommon imaging characteristics of these lesions to diagnose and localise these lesions accurately.

Introduction

The phaeochromocytoma is a hormonally active tumour of neuroendocrine origin first described by Frankel in 1886. The pathophysiological manifestations of the tumour are usually responsible for the patient’s presentation, albeit not always. The biochemical evaluation of a patient with suspected phaeochromocytoma is central to patient management; however, the role of imaging should also be emphasised, as patients suspected of having such a tumour invariably need advanced imaging techniques to localise and confirm the diagnosis.

Embryological considerations

The embryological basis for the possible distribution of the phaeochromocytoma and the paraganglioma is worthy of consideration. During the fifth developmental week, neuroblasts migrate from the neural crest and lead to the formation of the sympathetic chain and the preaortic ganglia. During the seventh developmental week, chromaffin cells migrate from the neural crest to form the adrenal medullae. However, some of the chromaffin cells also reach the sympathetic ganglia and the vagus nerve, and also become associated with the carotid arteries and the aorta. Extra-adrenal chromaffin cells are also found in the urinary bladder, the prostate, perihepatically, near the renal hilum, perirectally and in the gonads. It is postulated that the first migration of neuroblasts are the precursors of neuroblastomas and ganglioneuromas, and the second migration of chromaffin cells are the cells that ultimately may lead to the development of phaeochromocytomas and paragangliomas.¹

Nomenclature

The use of the terms paraganglioma and phaeochromocytoma are not uniform in the literature. Pathologically, phaeochromocytomas contain chromaffin cells, which are paraganglia that contain secretory granules storing usually catecholamines, but also sometimes other hormones such as steroids or peptides. These chromaffin-positive tumours are called phaeochromocytomas. Extra-adrenal chromaffin-positive tumours are thus often called extra-adrenal phaeochromocytomas. The term paraganglioma is preferred for tumours arising from extra-adrenal paraganglia. The two main distinctions within this group pertain to whether the tumour is related to the sympathetic
nervous system (paravertebrally) or the parasympathetic nervous system (aortico-pulmonary). The tumours with sympathetic connections are chromaffin positive, and about 50% of these tumours elaborate catecholamines. The tumours related to the parasympathetic system, including the paragangliomas of the head and neck, are chromaffin negative, and infrequently release catecholamines. However, because there are no microscopic discriminatory factors between paragangliomas of various locations, what name they are called by is of little relevance per se, as long as everybody involved in the care of the patient understands that the tumour is a paraganglioma and whether it secretes hormones or not.

Clinical background
Catecholamine release and hypertension are the main causes of presenting symptoms. The triad of palpitations, headache and diaphoresis is classic. However, some patients with phaeochromocytoma will not have hypertension or other symptoms. The hypertension may be paroxysmal and labile, but many patients present with sustained chronic hypertension. It is important to be aware of the possibility that other hormones, such as ACTH and growth hormone, may also be secreted by phaeochromocytomas.

Pathology
The macroscopic appearance of phaeochromocytomas and paragangliomas is important, as it has direct bearing on the appearance of the tumour on imaging. The tumours are often solid, but larger lesions often undergo cystic, necrotic or haemorrhagic changes. Calcifications are sometimes noted and the presence of fibrosis and lipid degeneration has also been reported. The microscopic appearance of all paragangliomas and phaeochromocytomas is remarkably uniform. The histological hallmark is nests of chief cells enclosed by trabeculae of a fibrous and vascular network. This pattern is referred to as “zellballen”. Histological differentiation of benign versus malignant tumours is difficult. Tumours with benign histology may metastasise or invade locally, and tumours with bizarre features may be benign. Extra-adrenal tumours are more commonly malignant. It is important to note that no single histological feature can reliably predict clinical behaviour. The definitive diagnosis of malignancy can only be made on the grounds of metastases to non-chromaffin tissues.

Anatomy and location
Up to 90% of phaeochromocytomas originate from the adrenal medulla (Figure 1). The most common region of extra-adrenal phaeochromocytomas is in the abdomen, in close association with the aorta. The organs of Zuckerkandl are the second most common site from which phaeochromocytomas originate. They are located near the aorta, on both sides of the origin of the inferior mesenteric artery (Figure 2). As is already clear from the embryological discussion, these tumours may originate anywhere where residual paraganglia cell rests may be found. Thus, less common, but important sites to be aware of are the heart, pericardium, bladder and testis.

Furthermore, the well-known “rule of 10s” is a useful way to remember the following pertinent facts about phaeochromocytomas: 10% are extra-adrenal, 10% of nonfamilial adrenal phaeochromocytomas are bilateral (in familial syndromes, this figure approaches 70%), 10% of adrenal phaeochromocytomas are biologically malignant, 10% of adrenal phaeochromocytomas occur in childhood. Traditionally, it was also thought that 10% of phaeochromocytomas are familial, but recent evidence suggest that up to 25% are hereditary. Nonfamilial tumours usually occur between 40–60 years of age and with a slight female preponderance. The childhood tumours are usually familial and have a prominent male preponderance.

The following syndromes have been described as either having phaeochromocytomas as part of their definition, or as being associated with these tumours: multiple endocrine neoplasia 2A and 2B, Von-Hippel Lindau syndrome, neurofibromatosis type 1, Sturge-Weber syndrome, Carney’s triad (pulmonary chondroma, extra-adrenal phaeochromocytoma and gastric gastrointestinal stromal tumour) and nonsyndromic familial phaeochromocytoma.

Pathophysiology
The pathophysiological manifestations of phaeochromocytoma are very important from a clinical perspective, but may also manifest and have bearing on the imaging of the patient. The main factor is the alpha-1-adrenergic receptor stimulation which leads to increased systemic vascular resistance with subsequent increased myocardial workload, ischaemia, left ventricular hypertrophy and even cardiac failure. The possible sequelae of hypertension are intravascular volume depletion, renal failure and cerebral haemorrhage. Other factors to keep in mind are the presence of underlying catecholamine-induced cardiomyopathy and hyperglycaemia. Beta-1-adrenergic receptor stimulation leads to increased cardiac automaticity and ventricular ectopy. Preoperative blood pressure control is achieved by initiation of alpha-receptor blockade and, later on, the addition of a beta-blocking agent. The order
Figure 1a: Axial T1-weighted (T1W) MR image demonstrating a well-defined right sided adrenal phaeochromocytoma with isointense signal compared to other solid organs.

Figure 1b: Axial T2-weighted (T2W) MR image reveals isointense signal in the lesion.

Figure 1c: Gadolinium-enhanced T1WI with fat saturation shows that the tumour enhances avidly and homogenously in a fashion characteristic of a phaeochromocytoma.

Figure 1d, 1e: Chemical shift MR imaging with in-phase (1d) and opposed-phase (1e) images showing no loss of signal on the opposed phase images, indicating that the lesion does not contain intravoxel lipid, and is thus not an adenoma.

Figure 1f: I123 MIBG scintigraphy at 24 hours demonstrates characteristic and specific avid uptake in the phaeochromocytoma.

Figure 2a: Composite ultrasonographic image (left – sagittal, right – axial), demonstrating an isoechoic tumour lying just above the aortic bifurcation and between the IVC and the aorta in a child.

Figure 2b: Axial contrast enhanced multidetector CT (MDCT) image and (2c) coronal reconstruction confirms the position of the avidly enhancing tumour at the origin of the inferior mesenteric artery. This position and appearance is characteristic of an extra-adrenal phaeochromocytoma of the organ of Zuckerkandl.
of the administration of these drugs must not be reversed, because initial beta-blockade may lead to unopposed alpha stimulation.

Laboratory investigation
The measurement of plasma-free and urinary fractionated metanephrines has 99% and 97% sensitivity respectively. Subsequently, the diagnosis of phaeochromocytoma is often strongly suspected before the patient is referred for imaging. This information will help the radiologist to select the most appropriate imaging modality to use for investigating a specific patient. It is also reassuring to the radiologist to know that a mass of undetermined aetiology is most likely not a phaeochromocytoma based on the laboratory analysis, before performing an image-guided intervention like a biopsy, which may precipitate a hypertensive crisis if the lesion is an undiagnosed phaeochromocytoma.

Imaging approach
Because of the ubiquitous nature of cross-sectional imaging in recent years, more and more phaeochromocytomas/paragangliomas are being diagnosed “incidentally”. However, ideally, a patient is first assessed by clinical and laboratory methods. When the aforementioned suggests the presence of a phaeochromocytoma, the lesion needs to be localised by imaging. Which modality to use first depends on various factors, which includes local availability and cost. However, when magnetic resonance imaging (MRI), computed tomography (CT) and metaiodobenzylguanidine (MIBG) scintigraphy are compared, MRI outperforms both CT and MIBG scintigraphy. The reported overall sensitivity for the preoperative localisation of phaeochromocytomas and paragangliomas were 98% for MRI, 89% for CT and 81% for MIBG scintigraphy. The reported sensitivity of MIBG scintigraphy has improved with the use of I 123 instead of I 131. The major advantages of MRI are the lack of ionising radiation, multiplanar imaging capabilities and superior tissue characterisation and sensitivity. Drawbacks are the longer imaging times than for CT, less widespread availability and relatively higher cost. The major advantages of CT are wide availability with short imaging times. The advent of multidetector CT (MDCT) scanners has also transformed CT into a multiplanar imaging modality. The main disadvantage of CT is the exposure of the patient to ionising radiation, which is of particular concern in children and pregnant women. MIBG scintigraphy has relatively poor sensitivity compared to CT and MRI, but has very high specificity (approaching 100%) for neuroendocrine tumours. It also exposes the patient to ionising radiation.

A cost-effective imaging strategy would probably use abdomino-pelvic MRI as a first line imaging tool. This would allow for the correct localisation of infra-diaphragmatic tumours in 98% of cases. This is especially applicable to children, young adults and pregnant women in whom the radiation burden of other modalities is most detrimental. If MRI is not readily available, MDCT is a proven and robust alternative investigation to MRI and is used as the first line imaging investigation in many institutions. If the MRI or CT scan does not localise the tumour, MIBG scintigraphy should be used to localise the extra-abdominal lesion(s). In familial cases, recurrence or with suspicion of malignancy, MIBG scintigraphy would also be able to localise any other synchronous tumours or metastatic lesions. In patients with metastatic disease, MIBG scintigraphy may be used to assess the avidity of the lesions if MIBG therapy is being considered. A CT or MRI of the extra-abdominal tumour may then be performed for more accurate anatomical
assessment. However, many centres use MIBG scanning routinely as a complementary study in all patients to detect extra-adrenal tumours. Since MIBG may not detect approximately 10–20% of phaeochromocytomas, if the lesion is still not localised after the initial abdomino-pelvic MRI/CT and the MIBG scintigraphy, a CT scan of the thorax, as well as a CT/MRI of the head and neck region are needed to localise the tumour. In such a case, other imaging options may also include alternative nuclear medicine investigations. Octreotide scintigraphy is not routinely used for imaging paragangliomas, but may be indicated in problem cases. Positron emission tomography (PET) scanning using 2-[fluorine-18] fluoro-2-deoxy-D-glucose (FDG) will often reveal these tumours to be avid, but it lacks specificity for these lesions. Special metabolites, such as 6-18F-fluorodopamine or carbon-11(11C) hydroxeyephedrine, should yield much more specific results, but these are not locally available at the moment.8-12

**Imaging characteristics**

MDCT and MRI scans reflect the macroscopic pathology of phaeochromocytomas and paragangliomas.

**MDCT**

On MDCT scans, the tumours are mostly solid and homogeneous lesions (Figure 4). However, cystic changes and a heterogeneous appearance are well-known variants. Usually these tumours will have pre-contrast administration attenuation of more than 10 Hounsfield units (HU). However, rarely, these tumours may contain sufficient microscopic lipid to have attenuation values of below 10 HU. Thus, using this criterion in isolation may lead to phaeochromocytomas being misinterpreted as lipid-rich adrenal adenomas. Rarely macroscopic fat may be visible. Since macroscopic fat is a very characteristic finding in adrenal myelolipomas, finding it in a phaeochromocytoma adds complexity to the image interpretation. The attenuation may also be relatively high in tumours that have haemorrhaged. In a case where cystic degeneration occurred, there will be hypodensitinating areas visible within the lesion.5 Calcifications, when present, are readily visible on CT, especially on unenhanced images (Figure 5).

![Figure 4a: Axial contrast enhanced MDCT image of a large right sided supra-renal phaeochromocytoma (yellow arrow), that at first glance appears adrenal in origin, but a normal right adrenal gland is clearly depicted separately from the lesion (red arrow). The tumour is solid and homogeneous in consistency and enhances avidly, although not as avidly as normal renal parenchyma.](image)

![Figure 4b: Sagittally reconstructed MDCT image shows the location of the tumour separate from the right kidney. Thus it is an extra-adrenal, but supra-renal phaeochromocytoma.](image)

![Figure 4c: Sagittal reconstruction of a fused MIBG SPECT-CT (single photon emission computed tomography - (co-registered with) CT) image to help localise the MIBG uptake anatomically.](image)
The intravenous contrast washout characteristics of adrenal lesions have been widely researched. However, phaeochromocytomas may not obey the 60% absolute and 40% relative washout rules commonly used to evaluate adrenal lesions. Contrast washout of more than these percentages on delayed imaging (15 minutes) are used to diagnose a lipid-poor adrenal adenoma, and retention of contrast is indicative of a non-adenoma. Since a phaeochromocytoma may do either, it should not be excluded on the basis of washout characteristics (Figure 6).10

Characteristically, the solid portions of phaeochromocytomas and paragangliomas enhance avidly with intravenous iodinated contrast. This reflects the capillary rich nature of the tumour.

There is a persistent perceived risk regarding the possibility of a hypertensive crisis being triggered by the administration of intravenous iodinated contrast agent. Based on recent literature, and provided the newer non-ionic contrast media are used, there does not seem to be evidence to support the withholding of non-ionic contrast from patients with phaeochromocytoma. Alpha-blocking agents may be used, though, but are apparently not required before imaging these patients with non-ionic contrast enhanced CT.13

MRI

Classically these tumours demonstrate hypointense signal on T1-weighted imaging (T1WI) and hyperintense signal on T2-weighted imaging (T2WI). If a short-tau inversion recovery (STIR) sequence is used, any macroscopic fat in the image should be of low signal and since the sequence is effectively T2-weighted, the tumour would also be hyperintense. Similarly to CT, phaeochromocytomas and paragangliomas demonstrate avid contrast enhancement after the administration of intravenous gadolinium-based agents (Figure 1c).

However, true to their nature, there is significant variation in...
the MRI appearance of these lesions. In the first instance, these lesions quite commonly do not demonstrate T2 hyperintensity (Figure 1b), making this finding unreliable as a differentiating factor. Conversely, other lesions such as metastases can also have T2 hyperintense signal. The use of opposed-phase MRI or chemical shift MRI is also not useful in trying to differentiate these tumours from other lesions. This is because of the possible presence of intracellular lipid leads to overlap between adrenal adenomas and phaeochromocytomas using this technique (Figures 1d, 1e).

As mentioned before, degeneration of these tumours may lead to the presence of fat or blood in the lesions. Fat is essentially always hyperintense on T1WI. The signal of blood is variable depending on the age of the blood products involved, but is often found to be hyperintense on T1WI. When T1 hyperintensity is noted in a lesion, a STIR sequence or a sequence utilising spectral fat signal saturation clearly differentiates between the two substances. With cystic degeneration present, striking T2 hyperintensity and avid enhancement of the solid areas are expected findings (Figure 7).

The salt-and-pepper appearance is often mentioned in discussions about paragangliomas. Punctate areas of hyperintensity noted on T1-weighted imaging due to haemorrhage give the salt appearance, while low-signal foci due to vascular flow voids are the origin of the pepper appearance. When seen together, this salt-and-pepper appearance is characteristic of a paraganglioma, even though it may not be a common finding (Figure 8).

**MIBG scintigraphy**

The merits and indications of MIBG scintigraphy have already been discussed. Both I123 and I 131 labelled MIBG can be used to localise phaeochromocytomas. However, I123 is preferred because of better image quality, lower radiation dose to the patient, the ability to utilise single photon emission computed tomography (SPECT) and a shorter time interval (24 hours) between injection and image acquisition when compared to I131. The only disadvantage of I123 is that it is more expensive than I 131. Lesions usually demonstrate MIBG uptake as focal areas of intense photon concentration, or so-called “hot spots”. It is important to be aware that drugs such as labetolol, reserpine, calcium antagonists and some tricyclic antidepressant drugs may interfere with the uptake of MIBG. Thus such agents should be discontinued for 3–4 days before the scan to prevent false negative results.10,11
Figure 8: MR imaging of a patient with multiple paragangliomas and thyroid carcinoma (MEN-2 syndrome) demonstrating the salt-and-pepper appearance.

Figure 8a: Axial T1W MR image demonstrating a large carotid body paraganglioma that displaces the internal and external carotid arteries, and narrows the oropharyngeal airway. The tumour has areas of focal T1-hyperintense signal (arrow).

Figure 8b: Axial T2W MR image demonstrates small focal hypointensities (arrow) due to the flow voids of tumour vessels.

Figure 8c: Gadolinium enhanced and fat-saturated axial T1W MR image shows avid and characteristic enhancement of the paraganglioma.

Figure 8d: Coronal T2W MR image reveal three tumours in this patient. The tumours located at the carotid bifurcation and the thoracic inlet, were paragangliomas (yellow arrows). The tumour in the middle (white arrow) arises from the left thyroid lobe (red arrow), and was a thyroid carcinoma.

Figure 8e: Gadolinium enhanced and fat-saturated coronal T1W MR image demonstrates avid enhancement in all three lesions.
Figure 9a, 9b: Axial contrast enhanced MDCT images of a largely solid, but heterogenous left phaeochromocytoma. The tumour has displaced the left kidney inferiorly. Medially there is invasion of the left psoas muscle (arrow).

Figure 9c: Axial contrast enhanced MDCT 5 years after surgical removal demonstrates recurrence and advanced local invasion of the vertebral column, the spinal canal and the paravertebral muscles.

Figure 9d: Axial T2W MR image confirms the spinal canal invasion (yellow arrow) and demonstrates dural sac compression with subsequent obliteration of the cerebrospinal fluid signal in the dural sac (red arrow).

Figure 9e: Sagittal T1W MR image demonstrates multilevel vertebral body destruction with relative sparing of the intervertebral discs, which is typical for neoplastic aetiologies.
Malignant phaeochromocytoma and paraganglioma

Malignant lesions may be evident at the time of diagnosis, but patients may only develop metastatic lesions a few years after diagnosis and surgical removal of the primary lesion. Local aggressive behaviour should not be equated to malignancy disease. Aggressive local invasion may be seen in a lesion without metastatic spread, and thus the diagnosis of a malignant lesion should be reserved for cases with evidence of metastases to non-chromaffin tissues2,3 (Figure 9). However, it is important for the radiologist to report on any signs of local soft tissue or vascular invasion, since it is a contraindication to laparoscopic adrenalectomy.1

Metastatic spread to bone, liver, lung, brain and lymph nodes are well described (Figures 10, 11). Metastases may mimic the imaging characteristics of the primary lesion, but may also have a non-specific appearance. Phaeochromocytoma metastases are a known cause of expansile bone lesions.12

Currently there is no cure for malignant phaeochromocytomas, and therapy is usually directed at blood pressure control and tumour debulking. If tumours are MIBG avid, I131 MIBG therapy can be used as a palliative measure to decrease tumour bulk and to improve symptoms.14

Figure 10a,b: Axial contrast enhanced MDCT images demonstrate a malignant phaeochromocytoma with a hypervascular liver metastasis in segment 8 of the liver (yellow arrow) (10a) and local recurrence of tumour in the left adrenal bed (red arrow) (10b).

Figure 10c: Axial contrast enhanced MDCT image 1 year later reveals necrotic lymphadenopathy (long arrows).

Figure 11a: Sagittal reconstruction of a MDCT image using bone windows demonstrating extensive sclerotic changes, but also lytic bone destruction, due to metastatic spread of a malignant paraganglioma to the vertebra (arrows).

Figure 11b: Sagittal reconstruction of a contrast enhanced MDCT image using soft tissue windows reveal an avidly enhancing metastases to the orbital roof (arrow).
Conclusion

Since the accurate diagnosis and localisation of phaeochromocytoma is critical to patient management, it is important for all physicians to understand the strengths and weaknesses of different imaging modalities during the work-up of a patient. Radiologists must be familiar with both the common and uncommon imaging characteristics of these lesions to diagnose and localise these lesions accurately. The preferred cost-effective imaging strategy in patients with suspected phaeochromocytoma starts with abdomino-pelvic MRI. An alternative strategy may start with abdomino-pelvic MDCT. MIBG scintigraphy may be reserved for specific indications, or it may be used as a routine adjunct in all patients with suspected phaeochromocytoma. Any extra-abdominal tumours detected by MIBG scintigraphy should be imaged by either MDCT or MRI as appropriate.

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