

CURRENT KEY DEVELOPMENTS

Recent advances in the imaging of adrenal and neuroendocrine tumours

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The recent rapid development of imaging technology has revolutionised the detection of adrenal and neuroendocrine tumours by allowing more precise lesion characterisation and improving the staging of malignant disease. These developments are briefly reviewed below.

Adrenal tumours

Computed tomography (CT) remains the cornerstone of adrenal imaging. Masses are initially assessed without contrast medium to measure their attenuation value (Hounsfield Unit, HU). About 70% of benign cortical adenomas will contain sufficient intracellular lipid to lower the attenuation value to 10 HU. If the attenuation value is greater than 10 HU, immediate and delayed scans are performed following administration of contrast for the calculation of contrast medium washout. In general, adenomas will demonstrate greater washout than a nonadenomatous lesion. This technique has a sensitivity of 98% and a specificity of 92% in differentiating an adenoma from other adrenal tumours.¹ With the advent of multidetector CT, it is now possible to obtain exquisite reformatted images of the adrenal glands in any plane. This has proven helpful determining whether a large mass is of renal or adrenal origin, and also in depicting possible invasion into adjacent organs.

Chemical shift magnetic resonance imaging (MRI) is another powerful tool for the characterisation of adrenal lesions. It does not involve the use of ionising radiation or contrast medium and relies on the difference in resonance frequencies of protons in water and intracytoplasmic lipid. Adenomas typically lose signal on the out-of-phase images compared with the in-phase images and the loss of signal can be assessed visually. It therefore also depends on the presence of intracellular lipid and although more sensitive than unenhanced CT it is less sensitive than the CT washout techniques. The specificity of this technique is comparable to washout CT.²

Newer functional imaging techniques of the adrenal gland such as positron emission tomography (PET)-CT and single photon emission computed tomography (SPECT) combine anatomic and functional information. ¹⁸F-fluoro-deoxy-glucose positron emission tomography (¹⁸F-FDG-PET) exploits the increased metabolism of glucose in malignant lesions. PET-CT

with this tracer has a high specificity for the detection of malignant adrenal lesions but there have been reports of FDG uptake in benign lesions such as adrenal adenomas and myelolipomas.^{3,4} FDG-PET is positive in the majority of pheochromocytomas, whether benign or malignant. It is useful for the localisation of pheochromocytomas that fail to concentrate MIBG. There have been several recent studies evaluating the use of PET using ¹¹C-metomidate as a tracer.⁵⁻⁷ This technique is highly sensitive and specific for differentiating between adrenocortical lesions (both carcinomas and adenomas) and non-adrenocortical masses. It remains to be seen if the cost and limited availability of metomidate (MTO)-PET will justify its widespread use in future.

Neuroendocrine tumours

Functioning pancreatic neuroendocrine tumours are typically small at the time of presentation and their detection is often challenging. As they are characteristically intensely vascular, multidetector CT, which allows the acquisition of excellent arterial-phase imaging, has undoubtedly improved the sensitivity of CT for their detection. Similarly, modern MRI with faster gradients and improved radiofrequency coils has improved their detection. Studies comparing CT and MRI are often difficult to evaluate as the cohorts studied are small and the modalities are not at comparable stages of development. We believe, however, that their sensitivities are similar and exceed 80%.⁸ CT and MRI have the advantage of the detection of small liver metastases although they may be difficult to identify on contrast-enhanced CT and gadolinium-enhanced MRI.⁹ The use of liver-specific contrast agents such as mangafodipir-DPDP may improve their detection.¹⁰

Endoscopic ultrasound (EUS) also enables visualisation and localisation of small pancreatic neuroendocrine tumours, particularly those in the pancreatic head. It has a sensitivity of between 79–100%.¹¹ The wide variation in reported sensitivities is likely to be due to the fact that it is an operator-dependent technique. Recently, a study into the use of contrast-enhanced EUS in the characterisation of pancreatic tumours found that hypovascularity as a sign of malignancy had a sensitivity of 92% with a 100% specificity. FDG-PET has not been shown to be of benefit in the imaging of neuroendocrine tumours except for those that are dedifferentiated or have high proliferative activity.¹³ Other PET tracers such as ¹⁸F-L-Dopa and ⁶⁸Ga-octreotide have shown some promise¹³ but the role of PET in neuroendocrine tumours has yet to be defined.

References

- 1 Caoili EM, Korobkin M, Francis IR *et al*. Adrenal masses: characterization with combined enhanced and delayed enhanced CT. *Radiology* 2002;222:629–33.
- 2 Haider MA, Ghai S, Jhaveri K *et al*. Chemical shift MR imaging of hyperattenuating (>10 HU) adrenal masses: does it still have a role? *Radiology* 2004;234:711–6.
- 3 Rao SK, Caride VJ, Ponn R *et al*. F-18 Fluorodeoxyglucose positron emission tomography – positive benign adrenal cortical adenoma: imaging features and pathologic correlation. *Clin Nucl Med* 2004;29:300–2.

- 4 Ludwig V, Rice MH, Martin WH *et al.* 2-deoxy-2-[18F] fluoro-D-glucose positron emission tomography uptake in a giant adrenal myelolipoma. *Mol Imaging Biol* 2002;4:355–8.
- 5 Hennings J, Hellman P, Ahlstrom H *et al.* Computed tomography, magnetic resonance imaging and ¹¹C-metomidate positron emission tomography for evaluation of adrenal incidentalomas. *Eur J Radiol* 2007;69:314–23.
- 6 Khan TS, Sundin A, Juhlin C *et al.* ¹¹-C metomidate PET imaging of adrenocortical cancer. *Eur J Nucl Med* 2003;30:403–10.
- 7 Hennings J, Lindhe O, Bergstrom M *et al.* ¹¹-C metomidate positron emission tomography of adrenocortical tumours in correlation with histopathological findings. *J Clin Endocrinol Metab* 2006;91:1410–14.
- 8 Ichikawa T, Peterson MS, Federle MP *et al.* Islet cell tumor of the pancreas: biphasic CT versus MR imaging in tumor detection. *Radiology* 2000;216:167–71.
- 9 Bader TR, Semelka RC, Chiu VC *et al.* MRI of carcinoid tumours: spectrum of appearances in the gastrointestinal tract and liver. *J Mag Res Imaging* 2001;14:267–9.
- 10 Wang C, Ahlstrom H, Eriksson B *et al.* Uptake of mangafodipir trisodium in live metastases from endocrine tumours. *J Mag Res Imaging* 1998;8:682–6.
- 11 Rosch T, Lightdale CJ, Botel JF *et al.* Localisation of pancreatic endocrine tumours by endoscopic ultrasonography. *N Engl J Med* 1992;326:1721–6.
- 12 Dietrich CF, Ignee A, Braden B *et al.* Improved differentiation of pancreatic tumors using contrast-enhanced endoscopic ultrasound. *Clin Gastroenterol Hepatol* 2008;6:590–7.
- 13 Sundin A, Garske U, Orlefors H. Nuclear imaging of neuroendocrine tumours. *Best Pract Res Clin Endo Metab* 2007;21:69–85.

Use of mutation analysis in endocrine neoplasia syndromes

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The major benefit in the identification of gene mutations causing endocrine neoplasia syndromes has been to allow accurate and rapid diagnosis of affected family members. In particular, the focus of clinical surveillance, radiology and endocrine tests can be on only those carrying mutations.¹ It also allows testing of young individuals with apparently sporadic endocrine tumours, and many families with occult disease have been diagnosed and treated over the last 15 years.² Indeed, the original case description of pheochromocytoma by Fraenkel has been shown to be due to multiple endocrine neoplasia type 2A.³ Genetic studies have also defined new and clinically distinct endocrine neoplasia syndromes, for example: several familial paraganglioma syndromes resulting from mutations in the succinate dehydrogenase subunit genes^{4–6}; multiple endocrine neoplasia type 4,⁷ and hyperparathyroidism-jaw tumour syndrome.⁸ As a rule, genetic testing and interpretation of the results is easier in the autosomal dominant neoplasia syndromes, where one abnormal

allele is sufficient for disease. In contrast, genetic testing in inherited metabolic syndromes (for example, congenital adrenal hyperplasia) is complex and less useful. This is partly because the metabolic syndromes are often autosomal recessive conditions where both alleles are mutated and there is a high frequency of compound heterozygosity (where each allele carries a different mutation) or whole gene deletions. Furthermore, occult disease is unusual in the autosomal recessive metabolic syndromes, where biochemical tests will identify most affected individuals, in contrast to the frequent identification of occult neoplasia in asymptomatic carriers of familial endocrine neoplasia mutations.

From the clinician's view, the first major advances were in 1993. The identification of RET proto-oncogene mutations causing multiple endocrine neoplasia type 2A and familial medullary thyroid carcinoma was reported by Ponder's group.⁹ In multiple endocrine neoplasia type 2A, the mutations are usually in cysteine codons and this allows very quick diagnostic testing in families with medullary thyroid cancer, pheochromocytoma and hyperparathyroidism. Prophylactic thyroidectomy is now routine for young children carrying a RET mutation and is effective in improving the disease-free survival. RET mutation analysis has made pentagastrin-stimulation tests for the diagnosis of MEN2A obsolete (although pentagastrin-stimulation tests may still be helpful in follow-up of patients after resection of medullary thyroid carcinoma). The von Hippel-Lindau (VHL) disease tumour suppressor gene causing haemangioblastomas, retinal angiomas, renal cell carcinomas, bilateral pheochromocytomas and pancreatic cysts and neuroendocrine tumours was also reported in 1993 (10). Testing for VHL syndrome in families had involved brain, renal, pancreatic and adrenal scanning, biochemical testing and retinal examination. This burden has effectively been halved by mutational analysis. The identification of the role of the VHL disease protein in the cellular response to hypoxia promises much for future medical treatments.

Multiple endocrine neoplasia type 1 is a much more complex clinical and genetic disease with a wide range of clinical manifestations. Although primary hyperparathyroidism due to multiple adenomas is common, using serum calcium as a screening test in families was insensitive and non-specific. The disease is caused by mutations in the MEN1 gene. Genetic testing is complex because many types of mutation may affect the gene, but is important for confirming the diagnosis in patients with unusual or limited manifestations, especially the minority without hyperparathyroidism. Genetic testing also allows the possibility of identifying early pre-symptomatic hyperparathyroidism and using treatment with the calcium-sensing receptor agonist, cinacalcet, possibly avoiding extensive and repeated parathyroid surgery.

The main disappointment for clinicians is that, in general, the link between the genetic mutation and the clinical manifestations is very loose and is not useful in predicting outcome. However, genetic studies have led to much greater