Role of interventional venous sampling in localising neuroendocrine tumours

RAD Magazine, 38, 449, 33-34

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Introduction

Neuroendocrine tumours (NETs) are a heterogeneous group of tumours arising in most organs of the body and defined by their prominent neuroendocrine differentiation. These tumours are commonly classified by their site of origin and their ability to store and secrete hormones, leading to specific clinical syndromes.

Functioning tumours are typically small and tend to present relatively early due to their associated clinical syndromes, therefore they are often difficult to localise with conventional cross-sectional imaging. Although there have been significant therapeutic advances in medical treatment of these rare tumours, surgical resection remains the gold standard in achieving cure, hence pre-operative localisation and staging is key in achieving the goal of surgical cure.

This article provides an overview of the role of interventional venous sampling in the functional localisation of selected neuroendocrine tumours (Cushing's syndrome, pancreatic neuroendocrine tumours (PNETs), hyperaldosteronism and hyperparathyroidism). The role of venous sampling in the detection of phaeochromocytomas and androgen secreting ovarian tumours remains beyond the scope of this article, but is discussed in the listed further reading material.

Cushing's syndrome

Endogenous Cushing's syndrome describes the clinical state arising from prolonged and inappropriate exposure to glucocorticoids. Cushing's disease (pituitary corticotroph adenoma) accounts for 80-90% of adrenocorticotropin hormone (ACTH)-dependent causes, the other 10-20% are due to ectopic-ATCH production or, very rarely, a corticotroph-releasing-hormone (CRH) secreting tumour.

Differentiation of pituitary-dependent Cushing's disease from ectopic ACTH secretion is key, however, despite the availability of numerous non-invasive biochemical tests, none achieve 100% diagnostic accuracy. Transphenoidal surgery is the treatment of choice in Cushing's disease, however, localisation can be problematic in these patients. MRI with gadolinium enhancement remains the initial imaging modality of choice in Cushing's disease, although sensitivity and specificity is poor, ranging from 50-75%.

A recent retrospective analysis of diagnostic performance of MRI in adult and adolescent Cushing's disease demonstrated sensitivity of 75% in adults and 55% in the adolescent groups, and similarly poor performance in the paediatric population.

Incidental pituitary lesions are seen in up to 10% of the general population, therefore detection of a pituitary lesion on MRI alone cannot be relied upon to establish a functional tumour.

Conversely, a normal MRI does not exclude a pituitary corticotroph adenoma since these lesions are often small and inconspicuous.

Bilateral inferior petrosal sinus sampling (BIPSS), originally described by Corrigan et al, is utilised as the functional localisation technique in patients with negative or discordant biochemical and imaging studies. This technique utilises the central measurement of ACTH produced by pituitary corticotroph tumour cells (native pituitary production of ACTH is suppressed by a state of hypercortisolaemia) compared with peripheral ACTH values and expressed as a ratio. Measurements are typically made before and after administration of CRH, as many corticotroph adenomas are susceptible to stimulation by CRH, which is exploited to increase the sensitivity of BIPSS. Optimal catheter placement, confirmed by demonstrating crossover flow into the contralateral petrosal sinus following contrast injection (figure 1) is vital to ensure diagnostic results and avoiding false negative outcomes. BIPSS has been shown to be both highly sensitive and specific (88-100% and 67-100% respectively) in the localisation of corticotroph secreting pituitary tumours. Its use is indicated in patients whose clinical, biochemical or radiological studies are discordant.

Localising a corticotroph adenoma within the sella may be helpful in performing selective/peripheral transspheunoidal pituitary surgery (TPSS) with the prospect of preserving anterior pituitary function. This can be difficult with microadenomas, particularly when pituitary MR imaging is negative or equivocal. Several studies have looked into the ability of BIPSS to lateralise tumours by the calculation of inferior petrosal sinus gradients from one side to another. Accuracy in BIPSS to localise tumours is variable, ranging from 50-100%.

Although BIPSS is recognised as a sensitive and specific technique in functional localisation of corticotroph adenoma, several centres have described other methods of sampling, particularly where expertise in BIPSS is not readily available. Jugular venous sampling (JVS) has been shown to be a useful, although less selective, method in the confirmation of Cushing's disease. Cavernous venous sampling is a highly selective and sensitive technique in the detection and localisation of pituitary corticotroph secreting adenomas, however, most institutions do not advocate its use due to the small but significant risk associated with it.

The role of venous sampling in the detection of ectopic (extra-pituitary) ACTH-dependent tumours is less established and limited to case reports.

Pancreatic neuroendocrine tumours

Pancreatic neuroendocrine tumours (PNETs) are rare neoplasms arising from pluripotent cells of the islet of Langerhans, accounting for 1-2% of all pancreatic neoplasms. PNETs are broadly divided into two clinical groups: functioning and non-functioning, the latter being more common. Functional tumours are classified according to the hormones they secrete, leading to specific clinical syndromes. An overview of the most common PNETs is shown in table 1.

Functioning PNETs are invariably small at presentation (<1cm in 40% and <2cm in 90% of cases) making localisation difficult. Early lesion detection with imaging is key to allowing prompt and often curative management of these tumours.

Conventional imaging with CT and/or MRI remains the
initial imaging modality of choice, with detection sensitivity up to 94%. MRI (and CT) remains superior to angiography in the detection of metastatic disease. Selective arterial stimulation with calcium and simultaneous venous sampling (ASVS) has been widely described as being highly sensitive and specific in the localisation and treatment planning of PNETs. This technique is specifically used in the diagnosis and localisation of insulinomas and gastrinomas, the commonest of the functioning PNETs.

Specific indications for use of ASVS in the diagnostic work-up of PNETs include:
1. Failure to localise functional PNET with other imaging modalities.
2. Localisation of functional tumour(s) in the presence of multiple dormant pancreatic lesions particularly associated with MEN1.
3. Allowing lateralisation of tumour within the pancreas, in relation to the superior mesenteric artery, therefore allowing surgical approach to be planned (ie laparoscopic vs open approach and enucleation vs distal pancreatectomy vs pancreatoduodenectomy). ASVS in localisation of insulinomas (and more recently gastrinomas) is based upon the injection of hyperosmolar calcium into selective arteries supplying different anatomical portions of the pancreas, leading to degranulation of tumour cells, releasing insulin into the portal vein and from there into the hepatic venous system where it is detected. Therefore, both arterial and venous catheters are required simultaneously; a venous catheter within a hepatic vein sampling insulin or gastrin and an arterial catheter injecting secretagogue (hyperosmolar calcium) into selective arteries. This correlation of the site of injection with a secondary rise in insulin or gastrin from the hepatic veins, allows diagnosis and lateralisation of tumour within the pancreas. In addition, digital subtraction angiography following selective catheterisation allows added anatomical localisation of these hypervascular tumours (figure 2).

Diagnostic performance of ASVS has been widely reported in the literature, although data is mainly limited to small powered series and case reports due to the rarity of these tumours. The majority of studies have looked at the role of ASVS in detection of insulinomas, with fewer looking at its role in gastrinomas. The National Institute of Health (NIH) conducted the largest study demonstrating its superiority in 2009, showing the superiority of combined ASVS with diagnostic sensitivity of 89% compared to CT, MR and US sensitivity of 28%, 35% and 14% respectively. An earlier study by Wiesli et al also demonstrated similar diagnostic performance of ASVS with sensitivity of 96%, versus 59% for CT/MRI. ASVS has also shown to be of significant value in localisation of tumours that were inconspicuous on US, CT, MRI, EUS and intra-operative bimanual palpation. However, a study by Druce et al showed a combined CT/MRI insulinoma localisation sensitivity of 80%, superior to that of ASVS at 64%. The authors highlight the merit of reserving ASVS to those cases where non-invasive measures are contentious/non-contributory, however, others advocate its use in all patients prior to surgical intervention.

The role of angiography and ASVS is less clear cut in the localisation of gastrinomas. Somatostatin receptor scintigraphy and EUS will detect up to 90% of gastrinomas and, therefore, ASVS should be reserved for cases where conventional imaging has failed.

Parathyroid tumours
Primary hyperparathyroidism is most commonly associated with sporadic parathyroid adenomas, although smaller, but significant proportions are associated with familial hyperparathyroid syndromes such as MEN1, MEN2a, hyperparathyroidism-jaw tumour syndrome and familial isolated hyperparathyroidism. Surgery offers definitive cure in up to
95% of patients with low complication rates. Historically, bilateral surgical exploration had been considered to be the ‘gold-standard’, however, highly specific localisation techniques with high frequency US, MRI and, most importantly, technetium 99m sestamibi (MIBI) have increased the trend towards minimally invasive parathyroid surgery.

Pre-surgical localisation with selective venous sampling is generally not required in uncomplicated hyperparathyroidism due to the high sensitivity of MIBI and US. Selective venous sampling, however, has been shown to be a valuable utility in: 1, 2, 14, 20

1. patients who have had previous neck surgery to define extent of distorted anatomy
2. patients known or suspected to have a familial hyperparathyroid syndrome
3. cases with non-concordant or misleading functional and/or anatomical imaging, and
4. patients with evidence of multi-gland involvement or ectopic disease with MIBI.

The role of less selective venous sampling in the way of jugular venous sampling has shown favourable results, although its role in complicated hyperparathyroidism and ectopic parathyroid disease remains limited.26

Adrenal neuroendocrine tumours

Primary hyperaldosteronism is the commonest endocrine cause of hypertension, with the choice of treatment dependent upon the lateralisation of aldosterone secretion. Significant improvement or even cure of hypertension may be achieved following adrenalectomy in patients with unilateral aldosterone overproduction.

Aldosterone producing adenomas (APA) and bilateral adrenal hyperplasia (BAH) are the commonest causes of hyperaldosteronism. Rare causes include unilateral adrenal hyperplasia, adrenocortical carcinoma and familial hyperaldosteronism. Pre-surgical localisation is key in achieving a curative surgical outcome.

Conventional cross sectional imaging with CT and MRI may be highly sensitive in the detection of adrenal adenomas with sensitivities as high as 90%, however, it remains poor in allowing localisation and lateralisation of functional tumours.27

Adrenal vein sampling (AVS) is considered the ‘gold-standard’ in the pre-operative localisation of aldosterone-secreting adenomas in patients with primary hyperaldosteronism, with high accuracy rates ranging from 92-100%,28, 29

A prospective study looked at the value of AVS in those with equivocal CT findings and showed that using CT findings alone, 21.7% of patients would have been incorrectly excluded as candidates for adrenalectomy and 24.7% of patients would have had an unnecessary or inappropriate adrenalectomy.30 These findings were reinforced by Mathur et al, who showed that 50% of patients would have had inappropriate management based on CT findings alone.31

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### Summary

Interventional venous sampling continues to be a highly sensitive modality in the localisation of neuroendocrine tumours. Although significant advances in non-invasive anatomic and functional imaging modalities have reduced the reliance on this well-established technique, the latest literature continues to support its important role in the diagnostic armamentarium of these unique and rare tumours.

### Further reading


### References

3. Storr H L, Alexandraki K I, Martin L et al. Comparisons in the epidemiology, diagnostic features and cure rate by transphenoidal surgery

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<table>
<thead>
<tr>
<th>Tumour</th>
<th>Location</th>
<th>Solitary/multiple</th>
<th>Size</th>
<th>Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinoma</td>
<td>Pancreatic head or tail</td>
<td>Usually solitary</td>
<td>Small (90% are &lt;2cm)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple in MEN-1 (5-10%)</td>
<td>Large (&gt;3cm)</td>
<td>60-90%</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>90% in gastrinoma triangle</td>
<td>Multiple in up to 60%</td>
<td>Usually large (6-20cm)</td>
<td>70%</td>
</tr>
<tr>
<td>Non-functioning islet cell tumour</td>
<td>Any</td>
<td>Solitary</td>
<td>Large (mean 5-10cm)</td>
<td>80%</td>
</tr>
<tr>
<td>VIPoma</td>
<td>&gt;2/3 pancreatic body or tail</td>
<td>Solitary</td>
<td>Large (mean 6.4cm)</td>
<td>80%</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Pancreatic tail &gt;body &gt;neck</td>
<td>Solitary</td>
<td>Large (mean &gt;4cm)</td>
<td>50%</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Pancreatic head (50% in duodenum)</td>
<td>Solitary</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 1**

Overview of the most common pancreatic neuroendocrine tumours. (From original article).


