Review

Nuclear medicine imaging of neuroendocrine tumours

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Summary

Different tracers have been proposed in nuclear medicine to visualize neuroendocrine tumours; the majority are based on specific uptake mechanisms while some are aspecific. Among the most important gamma-emitting tracers, radiolabelled metaiodobenzylguanidine (123I or 131I-MIBG) and 111In-pentetreotide should be mentioned. In particular, good results can be obtained with 111In-pentetreotide scanning, which visualizes more than 70% of all neuroendocrine tumours and in some indications, as in gastro-entero-pancreatic (GEP) tumours, has a diagnostic sensitivity superior to that of conventional radiological imaging. Radiolabelled monoclonal antibodies have at present only a storical value, while a series of new peptides represent interesting subjects in areas currently being regarded.

Positron emission tomography (PET) is a successful modality to detect cancer and recent years have demonstrated a great diagnostic value in a large series of tumour types. 18F-deoxyglucose (FDG)-PET has also been used to diagnose tumours of neuroendocrine origin. Even if 18F-FDG has been successfully and widely employed in oncology, it has not demonstrated a significant uptake in well differentiated neuroendocrine tissues. On the contrary, other positron emitter tracers seem to be more promising. A serotonin precursor 5-hydroxytryptophan (5-HTP) labelled with 11C has shown an increased uptake in carcinoids. This uptake seems to be selective and some clinical evidence has demonstrated that it allows the detection of more lesions with PET than with CT or octreotide scintigraphy. Another radiopharmaceutical in development for PET is 11C L-DOPA, which seems to be useful in visualizing endocrine pancreatic tumours. This Review summarizes the potential of several nuclear medicine techniques in the diagnosis of neuroendocrine tumours and stresses the renewed role of nuclear medicine in the management of this disease.

Key words: neuroendocrine tumours, nuclear medicine imaging, peptide imaging, somatostatin scintigraphy

Introduction

Neuroendocrine tumours have particular characteristics that distinguish them from other malignancies including low incidence, low proliferation rate and sometimes the hypersecretion of biologically active substances. They have a particular pattern of histology due to the presence of specific secretory products and particular cytoplasmic proteins. Over the last 20 years these tumours have been the subject of research aimed at a more adequate biological classification and at the development of novel management strategies. As a result significant progress in both diagnosis and treatment has been made [1].

As for imaging procedures, technological improvements in computerized tomography (CT), magnetic resonance (MR), ultrasonography (US), intraoperative ultrasonography, angiography and nuclear medicine have greatly facilitated the evaluation of tumour extent and, in general, led to the earlier diagnosis of small tumour masses [2,3].

Nuclear medicine has become more and more involved in this topic because in recent years, many techniques have been developed, based on several different radiopharmaceuticals, and these new techniques successfully been used to visualize neuroendocrine tumours; this especially is due to the different metabolic pathways and features of neuroendocrine tissue [4,5]. Even if neuroendocrine tumours are relatively rare, in the daily practice of a nuclear medicine centre, nuclear medicine physicians are often faced with the diagnosis of neuroendocrine lesions. This Review will only consider the most important approaches in current clinical practice and describe the future perspectives rising from the ongoing experimental data.

Radiopharmaceuticals for neuroendocrine tumours imaging

Different metabolic pathways determine the choice of radiopharmaceuticals for visualisation of neuroendocrine tumours. Various tracers have been proposed in nuclear medicine; some of them are based on specific uptake mechanisms, other are non-specific probes [6]. It should be made clear that even if a specific uptake mechanisms exists, it is not selectively characteristic of a particular tumour type, as the neuroendocrine cells are distributed all over the body. In fact, from a histological point of view, neuroendocrine cells form either small...
organisms, distinct cell clusters within other tissues or a network of cells dispersed in the lung, gut, thymus and thyroid. This is the reason why each tracer can be used in different clinical indications. In this Review only the most important tracers will be considered: some of them are in current clinical use, metaiodobenzylguanidine (MIBG) and pentetreotide; others are of potential interest such as positron emitters radiopharmaceuticals, vasoactive intestinal peptides (VIP) and several new somatostatin analogues; others are of storical value such as radiolabelled monoclonal antibodies; and others are going to be abandoned such as $^{99m}$Tc (V) DMSA.

**Metaiodobenzylguanidine (MIBG)**

MIBG represents a combination of the benzyl group of bretylium and the guanidine group of guanethidine. Radiolabelled MIBG was developed in the early 1980s to visualize diseases arising from the adrenal medulla [7,8]. It shares structural features with norepinephrine. It is taken up by an active, sodium-and-energy dependent (Type 1) amine uptake mechanism in the cell membrane of sympathomedullary tissues. When it is within the cytoplasm, it is transported into the intracellular catecholamine storage vesicles. This uptake process allows MIBG to enter into neuroendocrine pathways. The prolonged storage within the vesicles is the mean component permitting the high specific uptake and imaging. MIBG can be labelled both by $^{131}$I and $^{123}$I. The injected activity in adults is 18.5–37 MBq for $^{131}$I-MIBG and 185–370 MBq for $^{123}$I-MIBG respectively [9, 10]. Theoretical considerations and clinical experience indicate that the $^{123}$I-labelled agent is the radiopharmaceutical of choice. It gives better quality images, better photon detection and a superior sensitivity. These qualities are essential to perform single photon emission tomography (SPECT). Nonetheless, $^{131}$I-MIBG is still widely employed for most routine applications, because of its lower costs, availability, longer half-life and possibility of obtaining delayed scans [11].

Even if there is some overlap in neoplasms that can be detected with radiolabelled MIBG and also with $^{111}$In-pentetreotide, most of the studies suggest that the indications may be different, depending on the type of tumour and clinical setting. In our opinion, MIBG scintigraphy, at present, represents a first-choice modality in functioning pheochromocytomas, paragangliomas and neuroblastomas [11, 12]. It has a complementary role in other neuroendocrine tumours such as carcinoids, medullary thyroid carcinomas and non-functioning paragangliomas [11].

**DTPA-D-Phe-octreotide (pentetreotide)**

Somatostatin (SST) is a small multifunctional cyclic peptide synthesised in neuroendocrine and other cells present in many districts and organs [13]. SST receptors (sstr) have been identified on many cells and tumours of neuroendocrine origin [14]. Molecular studies revealed the existence of five distinct somatostatin receptor types with different tissue distribution. These receptors have been cloned and chronologically termed sstr1, sstr2 (with two splice variants sstr2A and sstr2B), sstr3, sstr4, sstr5 [15]. As naturally occurring SST has a very short half-life (1–3 min) and causes rebound hypersecretion on withdrawal, it is not the ideal tracer to use in imaging. A synthetic analogue first developed was octreotide-acetate; the major drawbacks were the cumbersome labelling of the radiopharmaceutical, the limited availability, the high cost and the high intestinal radioactivity. Therefore a new tracer has been developed by binding the ethylene-triamine-penta-acetic acid (DTPA) with octreotide, resulting in the DTPA-octreotide (Pentetreotide). This tracer was labelled with $^{123}$I and after with $^{111}$In [19].

$^{111}$In-labelled pentetreotide specifically binds to sstr2 [16–18]. Clinical studies have clearly shown that this receptor radiopharmaceutical is effective in diagnosis and staging tumours and their metastases, due to its ability to bind to sstr2, which are present in many cellular membranes of neuroendocrine tumours [20].

In spite of the efforts from the research in developing more specific radioligands, at present $^{111}$In-pentetreotide remains the radiopharmaceutical of first choice for imaging neuroendocrine tumours. The injected activity in adult is 110–220 MBq of $^{111}$In-pentetreotide; approximately 80% of i.v. administered radiolabelled $^{111}$In-pentetreotide is eliminated via urinary system. Even if somatostatin receptors are expressed in a wide spectrum of tumours, $^{111}$In-pentetreotide has its main indication as a diagnostic agent in the localization of primary sites and metastases of GEP-tumours (carcinoids, islet cell tumours, gastrinomas, insulinomas, glucagonomas, VIPomas). Many other tumours have been visualized using $^{111}$In-pentetreotide and they include: medullary thyroid carcinoma (MTC), small-cell lung cancer (SCLC), pheochromocytoma, pituitary tumours, CNS tumours; also breast carcinoima and renal tumours have a high incidence of somatostatin receptors. However the utility of $^{111}$In-labelled pentetreotide scanning in patients with these tumours has not been thoroughly demonstrated [5].

**Other somatostatin-analogue peptides**

As five types of somatostatin receptors have been discovered, other analogues with different affinity for these receptors are under study [21]. Various experimental clinical trials are ongoing in order to evaluate the selectivity of localization of these new diagnostic analogues, which can be used also as therapeutic agents. Among these, $^{111}$In-DOTA lanreotide (MAURITIUS) is a conjugate of DOTA coupled directly to the N-terminus of lanreotide [22]. The tracer can be stably labelled with a variety of radionuclides. $^{111}$In/$^{99m}$Tc DOTA, lanreotide is presently applied at several centres in Europe to prove the concept of receptor-mediated therapy controlled by dosimetry using the same ligand.

Although clinical results with $^{111}$In-pentetreotide have
been excellent, extensive efforts have been made in preparing and evaluating peptides labelled with $^{99m}\text{Tc}$. The advantages of using $^{99m}\text{Tc}$ as a label are well known in nuclear medicine. $^{99m}\text{Tc}$-Depreotide (P829) has been identified as a suitable somatostatin receptor ligand that binds to sst2, sst3 and sst5 with high affinity [23, 24]. $^{99m}\text{Tc}$ Vapreotide (RC-160) is another somatostatin analogue developed for oncological applications. This peptide binds to sst2 and sst5 with high affinity and to sst3 and sst4 with moderate activity.

**Vasointestinal peptide (VIP)**

Molecular cloning of human somatostatin receptors and VIP receptors has recently provided new insight into the biology and interaction of SST and VIP. Over recent years a cross-reactivity has been observed between VIP and SST analogues binding VIP proteins and vice-versa [25]. In support of the significant role of these receptors in oncological imaging, sst3 has been demonstrated to be the site of this interaction, and expression of binding sites for both VIP and SST on tumour cells has been shown [26–29]. VIP is a 28-aminoacid neuroendocrine mediator with a broad range of biological activities in various cells and tissues (vasodilatory substance, growth and proliferation promoter). VIP scintigraphy uses naturally occurring VIP labelled with $^{125}\text{I}$. Although the results obtained thus far suggest $^{125}\text{I}$ VIP to be a promising tumour tracer with the potential to provide additional information to supplement conventional imaging, there are still shortcomings which hamper widespread clinical use of this compound. Attempts have been made to label VIP with $^{99m}\text{Tc}$, since $^{125}\text{I}$ VIP is not easily available and costly to obtain [29].

$^{99m}\text{Tc}(V)$ dimercaptosuccinic acid (DMSA)

This radiopharmaceutical was initially developed as a general tumour-seeking agent. It rapidly became clear that its main clinical use was in patients with medullary thyroid cancer (MTC). Several clinical trials on patients with primary and recurrent MTC reported a sensitivity ranging from 50% to 80% [30]. The SPECT imaging of the neck regions and mediastinum improves the sensitivity of tumour detection. The most important role of $^{99m}\text{Tc}(V)$ DMSA in the clinical management of patients with MTC seems to be as a diagnostic tool in the follow-up treatment of patients after surgery [31, 32]. Unfortunately the commercial production of this radiopharmaceutical is going to be stopped.

**Monoclonal antibodies**

Controversial results have been reported regarding the utility of monoclonal antibody imaging in neuroendocrine tumours. Nonetheless some interesting findings have been described with anti-CEA and anti-chromogranin A in MTC, anti-UJ13A and anti-GD2 antibodies in neuroblastoma patients [33–36]. However the available data are limited and the clinical experiences are very heterogeneous. Therefore these reports only have value as experimental studies, since the clinical use of radiolabelled monoclonal antibodies in the diagnosis of neuroendocrine tumours has not been currently adopted in any clinical routine.

**Positron-emitters radiopharmaceuticals for PET**

$^{18}\text{F}$-FDG, which allows the study of glucose metabolism, is the most commonly used tracer in oncology because of its favourable half-life of $^{18}\text{F}$ (110 min) compared with other positron emitters. Cancer cells demonstrate increased glucose metabolism, due in part to increased number of glucose transporter proteins and increased intracellular enzyme levels of hexokinase and phosphofructokinase, among others, both of which promote glycolysis [37]. On this basis, FDG-PET can be used to exploit the metabolic differences between benign and malignant cells for imaging purposes. Although variations in uptake are known to exist among tumour types, elevated uptake of FDG has been demonstrated in various malignant primary tumours [38]. The administered activity in the adult is 350–750 MBq in a patient fasting for at least four hours to diminish physiologic glucose utilization and to reduce serum insulin levels to near basal levels, and thus diminish FDG uptake by organs such as the heart. In spite of this common finding, some evidence demonstrates that $^{18}\text{F}$-FDG is not a good tracer for neuroendocrine tumours, as FDG-PET imaging of a number of GEP tumours revealed increased glucose metabolism only in less differentiated GEP tumours with high proliferative activity and in metastasising MTC associated with rapidly increasing CEA levels [39, 40]. This is the reason why some authors developed new radiopharmaceuticals based on different precursors, namely $5$-hydroxytryptophan (5HTP) and L-DOPA labelled with $^{11}\text{C}$ [41, 42]. The first tracer has been used to detect the endocrine pancreatic tumours, the second one to visualize endocrine pancreatic tumours.

**Clinical applications of nuclear medicine imaging**

**Gastroenteropancreatic tumours (GEP)**

Neuroendocrine GEP tumours include a series of neoplasms that originate with the neuroendocrine cells distributed in in the gastro-intestinal tract epithelium (carcinoids, islet cell tumours, gastrinomas, insulinomas, glucagonomas, VIPomas). The overall results from the literature and the current experience at our Institute indicate that $^{111}$In-pentetreotide scintigraphy is particularly useful for patients who have small-bowel carcinoids that may be difficult to localise via conventional methods [43–45]. SPECT imaging can visualize more lesions than planar imaging or radiological procedures [46], so it is mandatory in cases of clinical doubt. Imaging of carcinoids is independent of tumour site or hormonal
Figure 1. Whole body imaging 24 hours after the injection of 120 MBq of $^{111}$In-pentetreotide. An abdominal lesion in the left upper quadrant and many liver metastases can be clearly seen. The patients were soon after operated on, and histology demonstrated a diffuse carcinoid.

hypersecretion, and may show distant metastases on whole body scanning (Figure 1). Due to its high sensitivity, SST receptor imaging may be particularly useful for localising a tumour site when surgery is planned.

Islet cell tumours arise from endocrine pancreatic cells and are named according to their secreted hormone (gastrinoma, VIPoma, insulinoma); 15% of these tumours are not associated with the hypersecretion syndrome. Gastrinoma is the most prevalent form of islet cell tumour, accounting for 10% of all GEP tumours. Clinical evidence demonstrates that somatostatin receptors appear in high concentrations in most malignant islet cell carcinoma (Figures 2a and 2b). Reported data on the sensitivity of $^{111}$In-pentetreotide scintigraphy vary from 70% to 90%, and part of the discrepancy is likely due incorrect scanning techniques and failure to perform SPECT studies [47, 48].

The SST scintigraphy revealed also high accuracy in detecting VIPomas and glucagonomas, where the sensitivity is about 75%. The sensitivity of $^{111}$In-pentetreotide imaging for the detection insulinomas is generally lower than that found for other islet cell tumours; this is probably due to a reduced number of somatostatin receptors that bind pentetreotide [45].

A large study on 160 patients with GEP tumours emphasises that SST scintigraphy can modify classification of patients and change the post-operative strategy (following surgery) in 25% of them. This trial confirms also that the sensitivity of $^{111}$In-pentetreotide imaging for localizing insulinomas was not as good as for other GEP tumours [48]. In our Institute, we studied 131

Figure 2. (a) Whole body imaging acquired 24 hours after the injection of 120 MBq of $^{111}$In-pentetreotide, showing increased uptake in the pancreas body due to an endocrine pancreatic tumour. This examination demonstrated the absence of distant sites of metastasis. (b) CT scan of the pancreatic lesion demonstrated by the whole body scan with $^{111}$In-pentetreotide. Morphologic imaging clearly defines the topographic location of the tumour and the relationships with the surrounding organs.
Table 1. Results of 111In-pentetreotide scintigraphy (SSTS) and other diagnostic modalities (US, CT, MR) in detecting primary and metastatic lesions of neuroendocrine GEP tumours at the Istituto Nazionale Tumori Milano.

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>SSTS (%)</th>
<th>US (%)</th>
<th>CT (%)</th>
<th>Other (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.62</td>
<td>0.36</td>
<td>0.43</td>
<td>0.45</td>
</tr>
<tr>
<td>Liver metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.90</td>
<td>0.88</td>
<td>0.78</td>
<td>0.71</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.97</td>
<td>0.95</td>
<td>0.93</td>
<td>0.81</td>
</tr>
<tr>
<td>Accuracy</td>
<td>0.97</td>
<td>0.84</td>
<td>0.86</td>
<td>0.75</td>
</tr>
<tr>
<td>Other soft tissue lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.90</td>
<td>0.47</td>
<td>0.66</td>
<td>0.61</td>
</tr>
<tr>
<td>Specificity</td>
<td>1.00</td>
<td>0.71</td>
<td>0.98</td>
<td>0.97</td>
</tr>
<tr>
<td>Accuracy</td>
<td>0.98</td>
<td>0.83</td>
<td>0.83</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Table 2. Results of SST imaging in patients studied only by qualitative evaluation.

<table>
<thead>
<tr>
<th>Sites</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>SN (%)</th>
<th>SP (%)</th>
<th>ACC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>41</td>
<td>1</td>
<td>29</td>
<td>100</td>
<td>0.59</td>
<td>0.99</td>
<td>0.82</td>
</tr>
<tr>
<td>Liver</td>
<td>86</td>
<td>3</td>
<td>8</td>
<td>74</td>
<td>0.91</td>
<td>0.96</td>
<td>0.94</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>47</td>
<td>6</td>
<td>9</td>
<td>109</td>
<td>0.84</td>
<td>0.95</td>
<td>0.91</td>
</tr>
<tr>
<td>Bone</td>
<td>12</td>
<td>2</td>
<td>2</td>
<td>155</td>
<td>0.86</td>
<td>0.99</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Abbreviations: TP – true positive result; FP – false positive result; FN – false negative result; TN – true negative result; SN – sensitivity; SP – specificity; ACC – accuracy.

Table 3. Results of SST imaging in patients studied by qualitative and semi-quantitative evaluation.

<table>
<thead>
<tr>
<th>Sites</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>SN (%)</th>
<th>SP (%)</th>
<th>ACC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>46</td>
<td>3</td>
<td>1</td>
<td>32</td>
<td>0.98</td>
<td>0.91</td>
<td>0.99</td>
</tr>
<tr>
<td>Liver</td>
<td>20</td>
<td>0</td>
<td>1</td>
<td>61</td>
<td>0.95</td>
<td>1.00</td>
<td>0.99</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>79</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Bone</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: TP – true positive result; FP – false positive result; FN – false negative result; TN – true negative result; SN – sensitivity; SP – specificity; ACC – accuracy; PPV – positive predictive value; NPV – negative predictive value.

consecutive patients affected by neuroendocrine GEP tumours: 51 were examined for staging purposes and 80 during the follow-up [49]. Whole body and SPECT images were obtained in all patients who were examined also with CT, US and other conventional procedures. Tumours were classified according to their site of origin: 39 pancreas, 32 ileum, 16 stomach, 9 appendix, 5 duodenum, 5 jejunum, 3 rectum, 2 biliary tract, 2 colon, 1 caecum, 15 liver metastases from unknown primary, and 2 widespread metastases from unknown primary. The results are summarised in Table 1. This study demonstrates the important role of SST scintigraphy in the management of GEP tumours. 111In-pentetreotide scintigraphy proved to be the first diagnostic method able to detect many previously unknown lesions that were confirmed afterwards in 37 of the 131 patients (28%).

Another multicentric Italian study considered a total of 253 patients, 121 from the Istituto Nazionale Tumori Milano, 50 from the Policlinico S. Orsola-Malpighi Bologna and 82 from the Azienda Ospedaliera Careggi Florence and evaluated the diagnostic effectiveness of SST scintigraphy by using two different protocols of imaging: a qualitative visual method and a semi-quantitative protocol based on the analysis of the tumour/background ratio calculated on SPECT transaxial slices acquired 4 and 24 hours after administration of the radiolabelled analogue [50]. Results are shown in Tables 2 and 3. Data are expressed on a per-lesion basis, the lesions being classified into four major groups. The use of semi-quantitative methods increased the specificity of the detection, however our overall results demonstrated that all figures of merit are excellent when imaging is accurately performed and analysed by experienced operators.

In the area of GEP tumours an interesting cost-effectiveness study found that the detection of more tumour sites in patients who present one cancer localization with conventional imaging may be vital when deciding to perform surgery. The SST scintigraphy can detect resectable tumours that would not be diagnosed
hyperfunctioning tumours [52]. On the contrary, the I-VIP scan has a lower sensitivity than \(^{111}\)In-pentetreotide for gastrinoma, phaeochromocytoma and glucagonoma.

### Phaeochromocytoma and paraganglioma

The most widely used radiopharmaceutical for the diagnosis of phaeochromocytoma is MIBG radiolabelled with \(^{123}\)I and \(^{131}\)I, showing a total sensitivity of about 90% (Table 5) [11, 53–62]. MIBG is useful to characterize and locate the intra-adrenal (phaeochromocytomas) and extra-adrenal paragangliomas. MIBG whole body scan can determine the extent of disease (staging) and allows the diagnosis of the relapses during the postoperative follow-up. The examination with MIBG has also the advantage that it is possible to select patients for the following radiometabolic therapy, based on MIBG uptake into the cancer cells [63, 64].

The sensitivity of SST scintigraphy for phaeochromocytoma detection seems to be better or comparable; however, the series of patients evaluated until now is too small to draw any final conclusions. The results depend also on tumour sites as it is well known that the adrenal lesions are difficult to visualize with \(^{111}\)In-pentetreotide due to its high renal activity.

\[^{111}\]In-pentetreotide has proven to be very accurate for paraganglioma tumours, as many unexpected additional paraganglioma localisations not detected with other conventional images can be revealed with \(^{111}\)In-pentetreotide whole body scan [6–65]. Clinical evidence has found that the sensitivity of SST scintigraphy for paraganglioma is superior to that of any other nuclear medicine tests or radiological procedures (CT, MR, US), even if MIBG imaging displays a very good specificity. In this respect, one of the major advantages of SST scintigraphy is that it provides information on potential tumour localizations in the whole body (Table 6). This provides justification for some authors who propose \(^{111}\)In-pentetreotide scintigraphy as the first diagnostic test in patients with paraganglioma, to be followed by CT scanning, MR or US of the sites at which abnormalities are found.

### Medullary carcinoma of the thyroid gland (MTC)

Many radiopharmaceuticals have been proposed for the scintigraphical visualisation of this tumour (including also the lymphofolic cation \(^{99m}\)Tc-Sesta-MIBI), moreover no experience has been permitted to have a definitive and univocal effect [66–69] (Table 7). After total thyroidectomy, the follow-up of patients is currently performed by clinical examinations and monitoring the changes in serum levels of calcitonin and/or CEA. Elevated post-surgical calcitonin and/or CEA levels indicate persistent disease, while a progressive increase after normalization means presence of relapse; in this case the clinical problem is to locate cancer. One of the most effective tech-

### Table 4. Results of \(^{123}\)I-VIP scan in neuroendocrine tumours.

<table>
<thead>
<tr>
<th>Tumours</th>
<th>No. of patients</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary or recurrent carcinoid</td>
<td>38/45</td>
<td>84</td>
</tr>
<tr>
<td>Sites of metastatic spread</td>
<td>76/92</td>
<td>82</td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
<td>4/16</td>
<td>25</td>
</tr>
<tr>
<td>Insulinomas</td>
<td>14/17</td>
<td>82</td>
</tr>
<tr>
<td>Insulinoma syndrome</td>
<td>2/5</td>
<td></td>
</tr>
<tr>
<td>VIPomas and syndrome</td>
<td>7/12</td>
<td></td>
</tr>
<tr>
<td>Primary or recurrent MTC</td>
<td>1/17</td>
<td>5</td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
<td>3/7</td>
<td></td>
</tr>
<tr>
<td>Gastrinomas and syndrome</td>
<td>2/8</td>
<td></td>
</tr>
<tr>
<td>Glucagonomas</td>
<td>0/2</td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine unclassified</td>
<td>4/12</td>
<td>33</td>
</tr>
</tbody>
</table>

### Table 5. Results of MIBG and SST receptor imaging in phaeochromocytoma.

<table>
<thead>
<tr>
<th>Author</th>
<th>Radiopharmaceutical</th>
<th>No. of patients</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoefnagel CA</td>
<td>(^{123})I, (^{131})I-MIBG</td>
<td>1396</td>
<td>88</td>
</tr>
<tr>
<td>Fischer M et al.</td>
<td>(^{123})I-MIBG</td>
<td>129</td>
<td>95</td>
</tr>
<tr>
<td>Jakubowski W et al.</td>
<td>(^{123})I-MIBG</td>
<td>16</td>
<td>94</td>
</tr>
<tr>
<td>Troncone L et al.</td>
<td>(^{123})I, (^{131})I-MIBG</td>
<td>74</td>
<td>92</td>
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<tr>
<td>Welshik MG et al.</td>
<td>(^{131})I-MIBG</td>
<td>19</td>
<td>94</td>
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<td>Warren MJ et al.</td>
<td>(^{131})I-MIBG</td>
<td>45</td>
<td>82</td>
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<td>83</td>
</tr>
<tr>
<td>Tenenbaum F et al.</td>
<td>(^{111})In-pentetreotide</td>
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<td>100</td>
</tr>
<tr>
<td>Hoefnagel CA</td>
<td>(^{111})In-pentetreotide</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Krenning EP et al.</td>
<td>(^{111})In-pentetreotide</td>
<td>14</td>
<td>86</td>
</tr>
</tbody>
</table>

### Table 6. Results of MIBG and SST scintigraphy in paraganglioma.

<table>
<thead>
<tr>
<th>Author</th>
<th>Radiopharmaceutical</th>
<th>No. of patients</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoefnagel CA</td>
<td>(^{111})In-pentetreotide</td>
<td>38</td>
<td>97</td>
</tr>
<tr>
<td>Lamberts SW et al.</td>
<td>(^{123})I-Tyr(^3)-octreotide</td>
<td>20</td>
<td>93</td>
</tr>
<tr>
<td>Hoefnagel CA</td>
<td>(^{131})I-MIBG</td>
<td>18</td>
<td>89</td>
</tr>
</tbody>
</table>

with conventional imaging and in the meantime prevents surgery in patients with advanced metastasized tumours [51].

There is a general agreement on the statement that MIBG has only a complimentary role in the diagnosis of GEP tumours [14]. Major scientific interests have been focused on VIP, intestinal peptide that can be radio-labelled with \(^{123}\)I, and binds sstr3 [27]. Some clinical trials were carried out and the radiopharmaceutical obtained a mean sensitivity of 85% in neuroendocrine tumour imaging (Table 4).

A study carried out at the University of Vienna reported that both \(^{123}\)I-VIP and \(^{111}\)In-pentetreotide were superior to CT in the visualization of extrahepatic metastatic spread. In the same series of patients insulinomas and VIPomas were successfully visualised by both tracers, including about 25% of patients with clinical sign of hyperfunctioning tumours [52]. On the contrary, the
nique is the intra-operative venous catheterisation. This allows us to locate the mass producing calcitonin with high sensitivity and specificity, but of course the approach is an invasive approach and can be performed only in a limited number of centres. A recent study shows that scintigraphic detection of recurrent metastatic MTC with labelled anti-CEA monoclonal antibodies or $^{111}$In-pentetreotide seem to have a sensitivity superior to any other diagnostic modalities [70]. However, when analyzing the cost-effectiveness of SST imaging in patients with MTC, the results indicate that receptor scintigraphy adds little to the information obtained from other conventional imaging. In conclusion, until now the radiopharmaceutical that has been considered as the most effective and cheapest to detect MTC remains $^{99m}$Tc (V) DMSA; the problem is that its production for the market is going to be stopped. The use of MIBG scan in the clinical management of MTC has shown limited value; the diagnostic performances of this tracer are very heterogeneous depending on the author. However, MIBG uptake may be high enough to allow radio- nuclide therapy. In this setting, MIBG imaging should be performed to assess such a therapeutic possibility.

### Lung tumours

Data on small-cell lung cancer (SCLC) studied with $^{111}$In-pentetreotide scintigraphy report a sensitivity ranging from 85% to 100% in visualizing primary tumours; the sensitivity in imaging known metastases seems to be lower [71–76]. However, in different trials SST scintigraphy also found additional sites of disease, and this evidence can have a serious impact on cancer staging and treatment. In spite of this variable sensitivity of SST scintigraphy for distant metastases, probably due to the changes in the expression of SST receptors on metastatic lesions, the clinical application of this technique is able to give additional information in staging patients [77]. It goes without saying that the demonstration of unexpected cerebral metastases or the upstaging of patients from limited disease (as classified by conventional imaging) to extended disease, may affect the strategies in patient management [77, 78]. At present, the adoption of $^{111}$In-pentetreotide scintigraphy in the staging protocols of SCLC patients is still a matter of discussion. However, much clinical data and the evaluations deriving from cost-effectiveness analyses seem to conclude that the cost increase compared with the conventional work-up can be justified by the therapeutic consequences.

### Neuroblatoma

MIBG remains a specific radiopharmaceutical for neuroblastoma as $^{123/131}$I-MIBG scintigraphy is a non-invasive modality able to establish the diagnosis of neuroblastoma in a child presenting a tumour mass of an unknown origin [79]. The overall sensitivity evaluated in a large series of 844 patients reported in the world literature shows that 91.5% of neuroblastomas concentrate MIBG, making the $^{123/131}$I-MIBG scintigraphy associated with the urinary analysis of catecholamine metabolites the most sensitive indicators of neuroblastoma [80]. Whole body scintigraphy allows the detection of metastases anywhere in the body, and this is essential for staging the disease, and frequently upgrade the stage; the number of lesion has a prognostic value [81]. After the treatment (surgery, chemotherapy or radiotherapy) $^{123/131}$I-MIBG scintigraphy is generally considered as a functional parameter of response, and its main advantage consists in the fact that is possible to evaluate the changes lesion-by-lesion [82]. The elevated concentration of $^{131}$I-MIBG at tumour masses, its limited concentration in the surrounding healthy tissues, and the relatively long half-life of $^{131}$I-MIBG enable therapy with high activities of the radiopharmaceutical [83].

Considering the primary role that MIBG has achieved in the clinical management of neuroblastoma, $^{111}$In-pentetreotide scintigraphy has, at present, no clinical relevance. However, about 90% of patients with neuroblastoma are positive to SST receptor scintigraphy [84]. Clinical evidences support the hypothesis that neuroblastoma patients whose tumour tissues express SST receptors in vitro have a longer survival than patients without such receptors [85]. This finding suggests that the presence of SST receptors can be considered as a prognostic parameter.

### Pituitary tumours

SST receptors were demonstrated in vitro in pituitary adenomas producing GH [86]. The majority of patients with pituitary adenoma are SST receptor positive, and different authors report positive scintigraphic results in patients with clinically non-functioning pituitary adenomas [87, 88]. The scintigraphy shows that the uptake of

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### Table 7 Results of different radiopharmaceuticals in MTC

<table>
<thead>
<tr>
<th>Author</th>
<th>Radiopharmaceutical</th>
<th>No. of patients</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwekkeboom et al.</td>
<td>$^{111}$In-pentetreotide</td>
<td>21</td>
<td>67</td>
</tr>
<tr>
<td>Kurtaran et al.</td>
<td>$^{131}$I-VIP</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Eising et al.</td>
<td>$^{111}$In-pentetreotide</td>
<td>24</td>
<td>63.5</td>
</tr>
<tr>
<td>Behr TM et al.</td>
<td>$^{99m}$Tc-$^{111}$In, $^{131}$I-Anti-CEA</td>
<td>16</td>
<td>86</td>
</tr>
<tr>
<td>Hoefnagel CA</td>
<td>$^{131}$I-MIBG</td>
<td>275</td>
<td>70</td>
</tr>
<tr>
<td>Baudin et al.</td>
<td>$^{111}$In-pentetreotide</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>Ugur et al.</td>
<td>$^{201}$TI</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>$^{99m}$Tc-sestamibi</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$^{99m}$Tc-DMSA(V)</td>
<td>95</td>
<td></td>
</tr>
</tbody>
</table>

---

[^99mTc]: $^{99m}$Tc
[^111In]: $^{111}$In
[^131I]: $^{131}$I
[^123I]: $^{123}$I
[^VIP]: VIP
[^MIBG]: MIBG
[^DMSA]: DMSA
[^CEA]: CEA
[^Tyr]: Tyr
[^VIP]: VIP
[^Tc]: Tc
[^SST]: SST
[^VIP]: VIP
[^123I]: $^{123}$I
[^131I]: $^{131}$I
[^VIP]: VIP
[^MIBG]: MIBG
[^DMSA]: DMSA
[^CEA]: CEA
[^Tyr]: Tyr
[^Tc]: Tc
[^SST]: SST
\(^{111}\text{In}}\text{-pentetreotide}\) is higher in patients than in control subjects, and the responses to the medical treatment are related to the scintigraphic uptake intensity. For these reasons \(^{111}\text{In}}\text{-pentetreotide}\) scintigraphy can have value as a functional test to predict and monitor the treatment response. However the diagnostic accuracy is very poor and consequently limits its clinical application.

**Intraoperative diagnosis – radioguided surgery**

Radioguided surgery is based on the use of an intraoperative radiation detector able to identify and locate cancer cells through a specific radiopharmaceutical that selectively binds to the tumours. The advantages of this techniques is its high sensitivity, as the detector probe can be applied directly in contact with the tissue, in order to find very small clusters of cancer cells. Sentinel node scintigraphy and the following intraoperative detection of sentinel node represent a classic example, that has been successful in breast cancer and in melanoma patients using radiolabelled colloids that are trapped in metastatic lymph nodes. Also the radiopharmaceuticals used for neuroendocrine tumours imaging (radiolabelled monoclonal antibodies, \(^{111}\text{In}}\text{-pentetreotide,}^{99m}\text{Tc-DMSA(V),}^{125}\text{I and}^{131}\text{I-MIBG})\) can be used for this application [89–95]. In fact several experiences from different groups demonstrated that the intraoperative detection and/or radioguided surgery of neuroendocrine tumours can help to define the exact location of tumour tissue, in obtaining a complete resection of a tumour mass, in detecting residual tumour after incomplete resection, and in searching relapses. This nuclear medicine modality can be also useful during the laparotomic staging in evidencing some occult microscopic metastatic sites. Several interesting reports are published on GEP tumours [89–92], medullary thyroid cancer [92, 93] and neuroblastoma [94, 95].

**Diagnostic application of positron emission tomography (PET)**

Over the last five years PET has demonstrated significant benefits for patient diagnosis and management, particularly in oncology. The reason for the great success of PET as a clinical tool includes the high sensitivity and resolution of this sophisticated technology, the ability to perform whole body scans, the fact that PET gives functional images and the possibility to quantify the tracer uptake. PET imaging is based on the individual characteristics of cancer tissue (proliferative activity, viability, other biological parameters). In other words PET provides metabolic images that complement the conventional morphological images produced by RX, US, CT and MR. For this reason, PET has the potential to use a variety of metabolic tracers in order to assess different tissue functions [96]. Unfortunately the most widely used radiopharmaceutical for PET, \(^{18}\text{F}}\text{-FDG,}\) fails in visualizing the well differentiated tumours with a low proliferative rate [40]. Increased uptake of FDG (reflecting increased glucose metabolism) can only be seen in a less differentiated neuroendocrine tumours without SST receptors and with high proliferative activity. Therefore, this examination provides opposite information to that from \(^{111}\text{In}}\text{-pentetreotide or}^{123/131}\text{I-MIBG,}\) which is related to the tissue differentiation. This concept has been stressed by other authors, who confirmed that the most clinically aggressive neuroendocrine tumours have shown an intense uptake of FDG. In fact, the sensitivity of FDG-PET in these malignancies with a poor prognosis seems to be higher than in SST receptor scintigraphy. Of course, in those patients with neuroendocrine tumours in whom the \(^{18}\text{F}}\text{-FDG}\) uptake is evident, FDG-PET is able to detect some metastatic lesions, that are not revealed by other conventional modality techniques. Several authors have proposed FDG-PET as a diagnostic tool for staging and monitoring medullary thyroid carcinomas, phaeochromocytomas and paraganglioma [97–100]. The evidence that \(^{18}\text{F}}\text{-FDG}\) is not a tracer fully suitable for the neuroendocrine tissue led the group at Uppsala University to develop some alternative positron emitter radiopharmaceuticals based on different precursors, namely 5-hydroxitriptophan (5HTP) and L-DOPA labelled with \(^{11}\text{C}\) [40, 41]. Since increased serotonin synthesis is one of the diagnostic criterion for carcinoid syndrome, the choice was focused on a labelled precursor of serotonin. The \(^{11}\text{C}}\text{SHTP}\) was successful in visualising neuroendocrine GEP tumours: increased uptake of the tracer was shown both in primary tumours and in metastases. Besides this, \(^{12}\text{C}}\text{L-DOPA}\) was applied as a tracer for dopamine synthesis, and it was successfully used to detect both functioning and non-functioning endocrine pancreatic tumours [39].

**Conclusions**

At present there are a number of tracers available for imaging neuroendocrine tumours. Their uptake is dependent upon the different biological mechanisms that characterise the biology of this particular neuroendocrine system: the capacity to take up and store amines, the expressions of receptors on their surface, the enhanced glycolytic metabolism and the capacity to take up some metabolic precursors. The choice of radiopharmaceuticals to be adopted in clinical practice should be guided by various considerations. The first point to be considered is the frequency of the presence of specific pathway shared by the majority of endocrine cells. In this regard, MIBG is a suitable radiopharmaceutical for those tumours characterised not only by the uptake of amines but also the presence of specific storage vesicles, such as phaeochromocytoma. SST receptors are expressed on almost all neuroendocrine cells. As a consequence, \(^{111}\text{In}}\text{-pentetreotide}\) scintigraphy has shown a high sensitivity for the diagnosis of both...
primary and metastatic tumour lesions. However, somatostatin receptors are expressed with different degrees of intensity; high levels are mainly found in GEP tumours, while in other cancer there is a weaker expression (e.g., medullary thyroid tumours). The antigen structures may be displayed by all neuroendocrine tissues, but in this case a limitation is the poor bioavailability of the immunological detection probes, which do not exhibit any relevant clinical utility in this setting. The metabolic activity of neuroendocrine tumour cells does not seem very great, compared with that of the normal counterparts, and for this reason FDG-PET has not yet been as extensively applied as other oncological indications. This is the reason why FDG-PET positivity is considered a prognostic parameter of aggressiveness, and the FDG-PET indications are limited only in a less-differentiated neuroendocrine tumours without SST receptors and with high proliferative activity. The study of alternative positron emitter radiopharmaceuticals is in development exploring other metabolic pathways than glucose. In this area, promising results have been obtained with 11C 5HTP and 11C L-DOPA.

From these biological observations, the evidence is that 111In-pentetreotide and 123I/131I-MIBG remain the tracers currently used and most effective for neuroendocrine tumour scintigraphy. We can also consider that, besides the mechanisms of uptake, other factors can be taken into account for the choice of radiopharmaceuticals, including dosimetry, cost-effectiveness, radioisotope availability, patient preparation, methodological aspects, and instrumentation facilities. In this overview, we tried to give the essential information that, in our opinion, should be kept in mind for a practical routine.

Acknowledgements

This work has been partially supported by a Grant from the Ministry of Public Health and by the CNR Progetto Ponte (Rome, Italy). The authors are grateful to Ms Annaluisa De Simone Sorrentino for her editorial help in preparing this manuscript.

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