### Abstract

Long-term studies have demonstrated that cancer cells are characterised by different metabolic processes and receptor expression systems. These differences are known as cancer phenotypes. Understanding these differences is the key to the development of new diagnostic and therapeutic procedures. Recent reports indicate that some tumour cells have increased expression of receptors for somatostatin, bombesin, glucagon-like peptide 1, substance P, vasoactive intestinal peptides, or cholecystokinin.

**Key words:** PET/CT, receptor imaging, somatostatin

### Introduction

Neuroendocrine tumours (NET) belong to a heterogeneous group of cancers characterised by increased expression of somatostatin receptors. This is a prerequisite for the application of somatostatin analogues in clinical imaging. The SSTR analogue octreotide (Octerocan) labelled with indium-111 was the first agent to be used.

The increased utilisation of PET/CT in oncology has led to the introduction of positron emitting tracer-labelled SSTR analogues, of which gallium-68-1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (gallium-68-DOTA) compounds are the most widely used.

Other receptor tracers like gastrin/cholecystokinin-2, bombesin, folate, HER2 and neurotensin are being investigated in animal studies.

Tumour receptors play an important role in carcinogenesis and tumour growth. A knowledge of the overexpression of receptors such as somatostatin, bombesin, glucagon-like peptide 1, substance P, vasoactive intestinal peptides and cholecystokinin is the way forward for dedicated diagnosis and therapy. The main ideas for receptor imaging are cancer-related receptor expression, high density expression in cancer and low expression in normal tissue and stable overexpression during disease.

Labelled peptides, particularly labelled somatostatin analogues, have been used increasingly in the diagnosis and therapy of tumours expressing somatostatin receptors (SSTR) on their cell surface.

### Somatostatin receptor imaging

Somatostatin is a regulatory peptide, widely expressed in the human body. SSTRs are present in normal human tissues, such as the thyroid, spleen, liver, kidneys and pituitary gland and the bladder by renal clearance. There are 5 somatostatin receptor subtypes. Commercially available synthetic analogues have different affinities to particular subtypes.

Neuroendocrine tumours (NET) are a heterogeneous group of carcinomas characterised by overexpression of somatostatin receptors (SSTR). The indium-111 labelled SSTR analogue octreotide (Octerocan) was the first agent to be used and has demonstrated high sensitivity in the detection of NETs. Unfortunately, the unfavourable physical properties of $^{111m}$In make it unsuitable for detecting small tumour lesions, leading to false negative results. An attempt has been made to introduce somatostatin analogues labelled with $^{99m}$Tc due to the favourable physical characteristics of $^{99m}$Tc and better imaging quality; however these are not widely available in clinical practice.

The increased utilisation of PET/CT in oncology has led to the introduction of positron emitting tracer-labelled SSTR analogues, of which gallium-68-1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (gallium-68-DOTA) compounds are the most widely used.

PET imaging using the Gallium-68 (Ga-68) labelled compound-DOTATATE offers higher resolution and improved pharmacokinetics compared with SRS, with promising results in the detection of SST receptor-expressing tumours.
\[^{68}\text{Ga}\] somatostatine receptor PET/CT gives the possibility of semiquantitative analysis (SUV) which can be used for selecting patients for PRRT. The protocol of the procedure is fast (60–90 min) and patient friendly with a low radiation burden (10–12 mSv). At present \[^{68}\text{Ga}\] somatostatine receptor PET/CT is a new gold standard for in vivo SSTR receptor imaging.

The three compounds most often used in functional imaging with PET are: \[^{68}\text{Ga}\]-DOTATATE, \[^{68}\text{Ga}\]-DOTATOC and \[^{68}\text{Ga}\]-DOTANOC. These ligands have different affinities to particular subtypes of somatostatin receptors (Table 1) which may affect their efficiency in the detection of NET lesions.

Studies using these markers have a higher sensitivity in the diagnosis of primary lesions and the detection of bone and lung metastases [2, 3].

\[^{68}\text{Ga}\] DOTATATE is a somatostatin analogue that shows high affinity for somatostatin receptor subtype 2 (SSTR2) which is the most common subtype found on NETs from the GI tract. The same analogue could be labelled with \(^{18}\text{F}\)-emitters like \(^{18}\text{F}\) and \(^{177}\text{Lu}\) by the same chelators and used in targeted therapy.

### Table 1. Affinities of DOTA-peptides (IC50) to subtypes SSTR1-5 (IC50 nmol/l) [1]

<table>
<thead>
<tr>
<th>SSTR 1</th>
<th>SSTR 2</th>
<th>SSTR 3</th>
<th>SSTR 4</th>
<th>SSTR 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>[^{68}\text{Ga}]-DOTANOC</td>
<td>&gt; 10000</td>
<td>1.9 ± 0.4</td>
<td>40.0 ± 5.8</td>
<td>260 ± 74</td>
</tr>
<tr>
<td>[^{68}\text{Ga}]-DOTATOC</td>
<td>&gt; 10000</td>
<td>2.5 ± 0.5</td>
<td>613 ± 140</td>
<td>&gt; 10000</td>
</tr>
<tr>
<td>[^{68}\text{Ga}]-DOTATATE</td>
<td>&gt; 10000</td>
<td>0.20 ± 0.04</td>
<td>&gt; 1000</td>
<td>300 ± 140</td>
</tr>
</tbody>
</table>

### Table 2. Radiopeptide imaging and therapy in Europe [4]

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Receptor</th>
<th>Disease indication</th>
<th>Radiopeptide probe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin</td>
<td>sst2</td>
<td>NETs</td>
<td>(^{111}\text{In})-DTPA-octreotide* (^{111}\text{In})-DOTA-landeotide (^{111}\text{In})-(^{90}\text{Y})/(^{177}\text{Lu})/(^{68}\text{Ga})-DOTATOC (^{177}\text{Lu})-[^{68}\text{Ga}]-DOTATATE (^{111}\text{In})-DOTA-BASS** (^{99m}\text{Tc})-HYNIC-TOC/-TATE (^{99m}\text{Tc})-N4-TATE [^{18}\text{F}]-deoxyfructosyl-TATE [^{68}\text{Ga}]-DOTANOC</td>
</tr>
<tr>
<td>Bombezin</td>
<td>sst2/sst3/sst5</td>
<td>Prostate cancer, Breast cancer, Gastrointestinal stromal tumor</td>
<td>(^{99m}\text{Tc})-RP527 [^{68}\text{Ga}]-BZH3 [^{68}\text{Ga}]-[^{111}\text{In}] DOTAGA-substance P</td>
</tr>
<tr>
<td>Cholecystokinin/gastrin</td>
<td>Cholecystokinin 2</td>
<td>Medullary thyroid cancer</td>
<td>(^{111}\text{In})-DTPA- D-Glu-minigastrin [^{99m}\text{Tc}]-demogastrin2</td>
</tr>
<tr>
<td>RGD peptides</td>
<td>(\alpha_{B_{3}}) integrin</td>
<td>Various</td>
<td>[^{18}\text{F}]-galacto-RGD [^{18}\text{F}]-RGD-K5 [^{18}\text{F}]-AH111585</td>
</tr>
<tr>
<td>Substance P</td>
<td>Neurokinin 1</td>
<td>Glioblastoma</td>
<td>[^{211}\text{Bi}]-DOTA-substance P [^{111}\text{In}]-[^{90}\text{Y}] DOTAGA-substance P [^{111}\text{In}]-([^{18}\text{F}]-DTPA[NH2]-exendin-4 [^{111}\text{In}]-([^{18}\text{F}]-DOTA[NH2]-exendin-4</td>
</tr>
<tr>
<td>GLP-1/exendin</td>
<td>GLP-1 receptor</td>
<td>Insulinomas</td>
<td>[^{111}\text{In}]-[Lys40(Ahx-DTPA)NH2]-exendin-4 [^{111}\text{In}]-[Lys40(Ahx-DOTA)NH2]-exendin-4</td>
</tr>
</tbody>
</table>

### Other receptor imaging

In contrast to other NETs, insulinomas — neuroendocrine tumours derived from pancreatic beta-cells, are characterised by relatively low incidence of somatostatin receptors. The sensitivity of SRS for detecting insulinomas is only 40–60%. These tumours present high incidence (> 90%) and high density of the glucagon-like peptide 1 receptor (GLP-1R). GLP-1 is rapidly degraded in vivo: this is the reason why for clinical use the more stable agonist \[^{68}\text{Ga}\]-DOTA-exendin-3 is used instead (Table 2).

Other receptor tracers like gastrin/cholecystokinin-2, bombezin, folate, HER2 and neurotensin are being investigated in animal studies.

### Conclusion

The recent introduction of PET imaging with gallium-68 has a major bearing on current and future clinical practice. Its labelling with DOTA compounds has cleared the way for somatostatin recep-
tor imaging with a viable PET agent, with all its inherent imaging advantages compared to single photon imaging. The clinical application of this technique has been successful in a variety of tumours, particularly NETs, and its labelling with other ligands and molecules will improve the management of other tumours and the assessment of infection. Pre-clinical research in the use of this tracer, in its various possible radiopharmaceutical preparations, has started recently and will undoubtedly have a large impact on its clinical use.

Conflicts of interest

None.

References