Radiolabelled somatostatin analogue(s) for peptide receptor scintigraphy and radionuclide therapy

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Summary

Background: Peptide receptor scintigraphy with the radioactive somatostatin analogue, [111In-DTPA]octreotide, is a sensitive and specific technique to show in vivo the presence and abundance of somatostatin receptors on various tumours.

Aim: With this technique primary tumours and metastases of neuroendocrine cancers as well as of many other cancer-types can be localised. This technique is currently used to assess the possibility of peptide receptor radionuclide therapy (PRRT) with repeated administrations of high doses of [111In-DTPA]octreotide. 111In emits Auger and conversion electrons having a tissue penetration of 0.02–10 μm and 200 to 500 μm, respectively.

Patients and methods: Thirty end-stage patients with mostly neuroendocrine progressing tumours were treated with [111In-DTPA]octreotide, up to a maximal cumulative patient dose of about 74 GBq, in a phase I trial.

Results: There were no major clinical side effects after up to two years treatment, except that in a few patients a transient decline in platelets counts and lymphocyte subsets occurred. Promising beneficial effects on clinical symptoms, hormone production and tumour proliferation were found. Of the 21 patients who received a cumulative dose of more than 20 GBq, eight patients showed stabilisation of disease and six other patients a reduction in size of tumours. There is a tendency towards better results in patients whose tumours have a higher accumulation of the radioligand.

Conclusions: PRRT is feasible, also with 111In as radionuclide. Depending on the homogeneity of distribution of tumour cells expressing peptide receptors and the size of the tumour, β-emitting radionuclides, e.g., 90Y, labelled to DOTA-chelated peptides, are also attractive candidates for PRRT. The first PRRT trials with [90Y-DOTA],[Tyr3]octreotide started recently.

Key words: octreotide, peptide, radionuclide, scintigraphy, somatostatin, therapy

Introduction

The inhibitory effect of somatostatin on hormone secretion of various glands led to the concept of beneficial effects of somatostatin in the treatment of diseases, based on gland hyperfunction or overproduction of hormones by endocrine-active tumours. However, the tetradecapeptide SS14 itself is unsuitable for routine treatment, because of its very short half-life of ≈ 3 minutes in man after intravenous injection due to rapid enzymatic degradation and because of its diversity of action, such as lowering insulin levels. Successful efforts have been undertaken to synthesise somatostatin analogues that are more resistant to enzymatic degradation. Introduction of D-amino acids and shortening of the molecule to the bioactive core sequence resulted in the eight amino acids-containing somatostatin-analogue octreotide (Figure 1).

Somatostatin receptors are structurally related integral membrane glycoproteins. Recently, five different human somatostatin receptor types have been cloned. All subtypes bind SS14 and SS28 (a polypeptide of 28 amino acids with SS14 making up the C-terminus) with high affinity, while the affinity of numerous somatostatin analogues for the five different subtypes differs considerably [1–3]. Octreotide binds with high affinity to the sst2 (human somatostatin receptor subtype 2), while this analogue has a relatively low affinity for sst3 and sst5 somatostatin.

Figure 1. Structures of octreotide, [Tyr3]octreotide, DTPA and DOTA.
and shows no binding to sst1 and sst4 [1–4]. Octreotide scintigraphy is, therefore, based on the visualisation of (an) octreotide-binding somatostatin receptor(s), most probably the sst2 and sst5.

Peptide receptor scintigraphy with the radioactive somatostatin analogue, \[^{111}\text{In-DTPA}^\circ\text{octreotide}\] (Figure 1), is a sensitive and specific technique to show in vivo the presence and abundance of somatostatin receptors on various tumours. In general, mapping of the presence of various peptide receptors on the cell membrane by peptide receptor scintigraphy (PRS) may become an attractive, non-invasive, harmless, easy-to-perform tool for an individual therapeutic approach of the cancer patient [5–8]. Also the detection of heterogeneous metastases (with regard to the expression of different peptide receptors or the accumulation of other radiolabeled ligands) becomes possible if a combination of radiolabeled peptides or of radiolabeled peptides with other radioligands (all labelled with different radionuclides) can be used. At the moment, examples of this approach are the use of 1) octreotide and MIBG scintigraphy in patients with metastasised pheochromocytoma and 2) octreotide and radiiodine scintigraphy in patients with metastasised differentiated thyroid cancer. One of the therapeutic options for patients with endocrine cancers is the use of non-radioactive peptide receptors (antagonists) but application of radiolabeled peptides for therapeutic use, possibly in combination with other radiolabeled ligands (e.g., MIBG or radioiodine) may become a new alternative or adjunct as well.

A new and fascinating application is the use of radiolabeled peptides for PRRT. The success of the therapeutic strategy relies upon the amount of radioligand, which can be concentrated within tumour cells and the rates of internalization, degradation and recycling of both ligand and receptor will among other things determine this. Binding of several peptide hormones to specific surface receptors is generally followed by internalization of the ligand receptor complex via invagination of the plasma membrane [9, 10]. The resulting intracellular vesicles, termed endosomes, rapidly acidify, which causes the ligand to dissociate from the receptor. The ligand may be delivered to the lysosome [11] and the receptor recycles back to plasma membrane. The whole process takes approximately 15 min [9], and a single receptor can deliver numerous ligand molecules to the lysosomes. We have studied internalization and degradation of [DTPA\(^\circ\)]octreotide in the somatostatin receptor positive rat pancreatic tumour cell lines CA20948 and AR42J and in the somatostatin receptor negative human anaplastic thyroid tumour cell line ARO. We detected internalization of the radiopharmaceutical in vitro, in accordance with the findings of Andersson et al. [12], and found that this process was receptor specific and temperature dependent [13]. Receptor-mediated internalization of \[^{111}\text{In-DTPA}^\circ\text{octreotide}\] will most probably result in degradation to \[^{111}\text{In-DTPA-D-Phe}\], this metabolite is not capable passing the lysosomal membrane(s) [11].

For radiotherapeutic applications several radionuclides have been proposed and investigated for coupling to [DTPA\(^\circ\)]octreotide. \[^{90}\text{Y}\], a suitable \(\beta\)-emitting radionuclide, shows dissociation from this chelated peptide in serum. \[^{111}\text{In}\] labelled [DTPA\(^\circ\)]octreotide has an appropriate distribution profile in humans for PRS and PRRT [14, 15]. \[^{111}\text{In}\] emits Auger- and conversion-electrons and can therefore be used to investigate its antiproliferative effect in cancer.

**Scintigraphy with \[^{111}\text{In-DTPA}^\circ\text{octreotide}\]**

The efficacy of PRS with \[^{111}\text{In-DTPA}^\circ\text{octreotide}\] was evaluated in a European multicenter trial (EMT) in 350 patients with a histologically or biochemically proven GEP tumour [7]. Tumour sites were detected by conventional imaging methods (CIM) in 88%, whereas somatostatin receptor scintigraphy was positive in 80%. The highest success rates of somatostatin receptor scintigraphy were observed with glucagonomas (100%), vipomas (88%), carcinoids (87%) and non-functioning islet cell tumours (ICT; 82%). The low detection rate (46%) noted for insulinomas is related to the lower incidence of sst2 somatostatin receptors on insulinoma cells. However, the overall 80% sensitivity found is somewhat lower than the 88% obtained at the Erasmus University Rotterdam (EUR) in 130 patients with GEP tumours. This may be related to important differences in scanning procedures such as the amount of radioligand administered (minimal dose of \[^{111}\text{In}\] of 200 MBq and at least 10 \(\mu\)g of peptide at EUR), the duration of the acquisition and the use of single photon emission computed tomography (SPECT, with a triple head camera at EUR). The fact that abdominal SPECT was not systematically performed in all patients of the EMT may explain that only 73% of gastrinoma patients had a positive scan compared to the 90%–100% sensitivity reported in other studies. In the EMT, a total of 388 sites were visualized with CIM in 308 out of the 350 patients. In addition to 297 known localisations, somatostatin receptor scintigraphy revealed another 166 unsuspected lesions. Forty percent of these unsuspected lesions were subsequently confirmed as true positive findings based on the results of additional imaging procedures or histology obtained during the one-year follow-up period. The clinical relevance of detecting additional tumour localizations is very dependent on the clinical status of the patient. The demonstration of an unsuspected lesion in a patient with known metastatic spread usually has little impact on the management. In contrast, the detection of unsuspected tumour sites in patients with a single known lesion or without any known lesion is important in that it may affect the selection for curative surgery, which remains the treatment of choice of patients with this type of tumours. In the cohort of 350 patients studied, 42 had no lesion detected by CIM and 178 were known to have a single tumour localisation prior to the study. Somatostatin receptor scintigraphy was positive in 11 of the 42 patients (25%) and 12 of 16 lesions revealed by somatos-
tatin receptor scintigraphy were further confirmed as true positive. Somatostatin receptor scintigraphy demonstrated multiple tumour sites in 62 of the 178 patients (35%), 60% of these lesions were confirmed by follow-up (one year) procedures. A reply to an impact questionnaire was obtained for 235 patients. Overall, the scintigraphic findings led to management changes in 40% of the 235 patients.

Gibril et al. compared in a prospective study the sensitivity of somatostatin receptor scintigraphy with that of CT, MRI, ultrasonography and selective angiography in the detection of primary and metastatic gastrinomas [16]. Their conclusion is that somatostatin receptor scintigraphy is the single most sensitive method for imaging either primary or metastatic liver lesions in patients with Zollinger–Ellison syndrome. The same group studied the effect of somatostatin receptor scintigraphy on clinical management based on the data of this comparative study [16, 17]. Since this technique altered management of 47% of the patients, they concluded that somatostatin receptor scintigraphy should be the initial imaging modality for patients with gastrinomas, also because of its superior sensitivity, high specificity, simplicity and cost-effectiveness. Furthermore, “it is likely that the conclusion drawn from this study can also be extended to other pancreatic endocrine tumour syndromes except insulinomas” [17].

**PRRT with \(^{111}\text{In-DTPA}\)octreotide**

After internalization of the radiopharmaceutical in tumour cells, the radioactive ligand is close to the nucleus. Since \(^{111}\text{In}\) emits not only gamma-rays, which are visualized during PRS, but also short-ranged Auger-electrons, an effect on tumour cell proliferation could be expected, as the radiotoxicity of Auger electrons is very high if their target, the DNA of the cell, is within the particle range [18–20].

**Preclinical**

We performed PRRT studies in rats using \(^{111}\text{In-DTPA}\)octreotide. To investigate receptor dependence of the therapeutic effects, we compared the effect of PRRT in animals inoculated with the somatostatin receptor positive CA20948 tumour cells in the portal vein of the liver and the somatostatin receptor negative CC531 tumour cells. Other groups of rats were co-injected with 1 mg octreotide, to investigate the effect of excess unlabeled peptide. All rats were sacrificed 21 days after inoculation of tumour cells and tumour growth was determined by counting the number of metastases on the surface of the liver lobes.

**Clinical**

The side-effects and antiproliferative effect of high, multiple radiotherapeutic doses of \(^{111}\text{In-DTPA}\)octreotide, using the Auger- and conversion-electrons emitted by \(^{111}\text{In}\), are being investigated in patients and reported here preliminarily [14, 15, 21]. In this phase 1 study of therapy with \(^{111}\text{In-DTPA}\)octreotide we included end-stage patients with mainly a high tumour load of progressing neuroendocrine tumours.

**Patients and methods**

\[^{111}\text{In-DTPA}\]octreotide and \(^{111}\text{InCl}_3\) (DRN 4901, 370 MBq/ml in HCl, pH = 1.5–1.9) were obtained from Mallinckrodt Medical BV (Petten, The Netherlands). \[^{111}\text{In-DTPA}\]octreotide was labelled with \(^{111}\text{In}\) as has been described previously [22].

**Preclinical**

Rats in the experimental groups were injected with 370 MBq (0.5 \(\mu\)g) \[^{111}\text{In-DTPA}\]octreotide i.v. on day 1 and/or 8 after injection of tumour cells into the portal vein. Tumour inoculated rats in the control groups were injected with 0.5 \(\mu\)g unlabeled \[^{111}\text{In-DTPA}\]octreotide i.v. according to the same schedule.

**Clinical**

Since 1995, the typical doses per administration are 6000–7000 MBq \(^{111}\text{In}\) incorporated in 40–50 \(\mu\)g \[^{111}\text{In-DTPA}\]octreotide within 24 hours after production of \(^{111}\text{In}\). It is given with at least two weeks intervals between administrations and a total of eight administrations is aimed at with extensions to 12–14 administrations. PRRT with \[^{111}\text{In-DTPA}\]octreotide was applied after witnessed informed consent by the patient and approval by the medical ethics committee of our hospital. The following measurements, carried out prior to and between all administrations, served as parameters of possible side-effects: the usual hematological and chemical analyses of bone-marrow, liver, kidney and endocrine pancreatic glucose or Hb A1c) function. Pituitary function (Free T4, post-menopausal women: LH and FSH, men: testosterone) was assessed prior to and after weeks 4, 8th and 8th administration of \[^{111}\text{In-DTPA}\]octreotide: at these time points also possible effects on 1) the endocrine activity of the tumours and/or their production of specific serum markers, and 2) tumour-size (CT or MRI) were investigated. Pituitary-adrenal-axis function testing (metyrapone tests) prior to and after eight administrations as well as long-term follow-up with three to four months' intervals was also investigated, if feasible.

**Dosimetry of \[^{111}\text{In-DTPA}\]octreotide accumulation**

Scoring of tumour radioactivity uptake in patients prior to the start of treatment with \[^{111}\text{In-DTPA}\]octreotide was done visually by using scintigrams obtained 24 hours after injection of a diagnostic dose (220 MBq) of \[^{111}\text{In-DTPA}\]octreotide. The scoring grades used were 4 = intense, 3 = clear (higher than liver uptake), 2 = clear but faint (lower than or equal to liver uptake), 1 = equivocal and 0 = no accumulation.

Patients were also scanned three and seven days after each administration of the radiotherapeutic dose. Percentage uptake of the administered dose in total body and in the most prominent tumour was calculated (data not shown). Uptakes decreased slowly or remained the same if the interval between the successive administrations was less than one month. In patients who had 6 or more administrations of 6000 to 7000 MBq of \[^{111}\text{In-DTPA}\]octreotide with intervals of maximally one month between administrations, uptake in the tumour was still clearly visible after the last administration. Typical radiation doses to tissues with administered doses of 6000-7000 MBq \[^{111}\text{In-DTPA}\]octreotide are: kidneys 300 – 1400 (depending on the relative biological effectiveness (RBE 1–20) for Auger electrons) cGy, spleen 200 cGy, liver 50 cGy, bone marrow 15 cGy (target organ for gamma photons), thyroid gland 25 cGy and pituitary 70 cGy [23]. Thus the critical organs are kidneys and spleen. With these administered doses the estimated tumour radiation doses are for a 10 gram tumour (assumptions: 1% uptake; effective half-life is equal to the physical half-life) 1700 and 6700 cGy (RBE for Auger electrons 1 and 20, respectively) and for a 100 gram tumour (1% uptake) 250 and 750 cGy, respectively.
Results and discussion

Preclinical
PRRT with administrations of 370 MBq $[^{111}\text{In-DTPA}]$-octreotide on day 1 and/or day 8 induced a significant ($p < 0.01$) decrease in the number of hepatic metastases 21 days after intraportal injection of CA20948 pancreatic somatostatin receptor positive tumour cells. PRRT in rats with somatostatin receptor-negative liver metastases did not induce a difference in the number of liver tumour colonies. Furthermore, pre-treatment with 1 mg octreotide, resulting in a saturation of somatostatin receptors, led to a diminished therapeutic effect of PRRT. The results of these experiments indicate that the effect on tumour growth be due to specific binding of the radiolabel to somatostatin receptors (manuscript submitted for publication).

Clinical
Thirty end-stage patients with mainly neuroendocrine tumours have been treated with $[^{111}\text{In-DTPA}]$-octreotide in Rotterdam [29] and Brussels [1] (Table 1). Twenty-one out of these thirty patients received a total cumulative dose of at least 20 GBq $[^{111}\text{In-DTPA}]$-octreotide. Of the nine patients treated with a total dose lower than 20 GBq, seven had to stop prematurely because of too severe adverse effects. 

Figure 2 shows the course of blood cells and platelets counts. PRRT with $[^{111}\text{In-DTPA}]$-octreotide may (transiently) effect the number of white blood cells and to an even higher extent that of platelets.

Renal function was monitored by measurements of serum creatinine and creatinine clearance (Figure 3). If there is any effect on the kidney function it is of no clinical relevance so far. Remarkable is that the average kidney function of the seven patients with creatinine clearances between 21 and 80 ml/min prior to the start of PRRT did not significantly change after administrations of cumulative doses of 20 to 30 GBq ($n = 4$) and 50 to 60 GBq ($n = 3$) with a maximum follow up period of two years.

It is well known that the pituitary and pancreatic islet cells express somatostatin receptors. Endocrine parameters of pituitary and pancreatic function during treatment cycles and follow up after treatment with $[^{111}\text{In-DTPA}]$-octreotide did not change either (data not shown).

Impressive, though in a number of patients temporary because of end-stage disease, effects on the clinical condition of the patient and on hormone or tumour marker production (overall data not shown; Figure 4) were observed after administration of multiple, high doses of $[^{111}\text{In-DTPA}]$-octreotide. Also, anti-proliferative effects have been noticed (Figures 5 and 6). All twenty-one patients who received a total cumulative dose of at least 20 GBq $[^{111}\text{In-labelled DTPA}]$-octreotide, had progressive disease, i.e., unequivocal increase in tumour volume according to CT or MRI prior to the

### Table 1. Characteristics of patients treated with $[^{111}\text{In-DTPA-D-Phe}]$-octreotide.

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>$n$</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>10</td>
<td>1 (P)</td>
<td>6 (2*, P, 2S, R)</td>
<td>3 (2*, S)</td>
</tr>
<tr>
<td>NE tumour</td>
<td>7</td>
<td>1 (R)</td>
<td>3 (2*, P)</td>
<td>3 (P, S, R)</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>1</td>
<td></td>
<td>1 (S)</td>
<td></td>
</tr>
<tr>
<td>Vipoma</td>
<td>1</td>
<td></td>
<td></td>
<td>1 (R)</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>1</td>
<td></td>
<td></td>
<td>1 (R)</td>
</tr>
<tr>
<td>Med.-thyroid cancer</td>
<td>4</td>
<td>4 (1*, 2P, S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>2</td>
<td>2 (1*, S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiomysarcoma</td>
<td>1</td>
<td></td>
<td></td>
<td>1 (R)</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>(+9*)</td>
<td>(+3*)</td>
<td>(+4*)</td>
</tr>
<tr>
<td>Pos effect (S + R)</td>
<td>67%</td>
<td>50%</td>
<td>67%</td>
<td>86%</td>
</tr>
</tbody>
</table>

* Abbreviations: P = progression; S = stable; R = reduction in tumour size.

* $< 20$ GBq and/or no FU

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Course of haemoglobulin and blood cells during peptide receptor radionuclide treatment with the indicated cumulative doses of $[^{111}\text{In-DTPA}]$-octreotide. $N$ is number of patients (M ± SEM).
start of $^{111}$In-DTPA$^9$octreotide therapy. In eight patients this treatment resulted in stable disease and in another six patients in actual tumour shrinkage. Thus, six out of 21 patients with progressive disease, who received an adequate dose of at least 20 GBq $^{111}$In-DTPA$^9$octreotide, showed an antiproliferative effect. So far, it can be concluded that a response to treatment with $^{111}$In-DTPA$^9$octreotide, based on antiproliferative effects and a lowering of tumour markers in serum and/or urine, has been obtained if 1) the cumulative therapeutic dose of $^{111}$In-DTPA$^9$octreotide was at least about 20 GBq and 2) tumour uptake was at least grade 2 in order to get a stabilisation of disease and grade 3 or 4 for reduction in size of tumours (Table 1).

The observed responses to this PRRT are in agreement with internalization of $^{111}$In-DTPA$^9$octreotide into tumour cells [because of the abundance of Auger and conversion electrons with a (very) short particle range or tissue penetration] and, with an antiproliferative effect induced by these electrons. Since it is at present not exactly known to what extent the radionuclide is localised intracellularly after administration of high amounts of $^{111}$In-DTPA$^9$octreotide, measurements of the actual radiation doses are not possible.

It is to be expected that the radiotherapeutic use of radionuclides, such as $^{90}$Y, emitting the higher energies of $\beta$-particles, coupled to (small) DOTA-chelated peptides, leads to higher radiation doses in a larger part of the tumour, also because of their more appropriate particle ranges or tissue penetration [24, 25]. In contrast to $^{90}$Y-DTPA$^9$octreotide, $^{90}$Y labelled to [DOTA$^9$Tyr$^3$]octreotide shows no dissociation from this DOTA chelated peptide in serum. The first two PRRT trials with $^{90}$Y-DOTA$^9$Tyr$^3$octreotide started recently [26; Krenning, Kvols, Pauwels in Novartis B151 trial]. Based on the same assumptions as in section 3.1. and a similar biodistribution ($^{111}$In and $^{90}$Y labelled peptide) the estimated tumour radiation dose after an administered dose of 3.7 GBq $^{90}$Y-labelled peptide will be 16,500 cGy (10 g, 1% uptake) and 1800 cGy (100 g, 1% uptake). Estimated tissue doses are 2400 cGy for the kidneys, 150
**Figure 6.** Effects of PRRT with $[^{111}\text{In-DTPA}]$octreotide in a patient with a hepatic metastasis of a neuroendocrine tumour treated according to the described protocol. The upper panel shows transversal CT scans, except on 11/96 (MRI), and the lower panel illustrates transversal slices of $[^{111}\text{In-DTPA}]$octreotide SPECT images. The decline in tumour size (300 cc) was after seven treatment courses 30% and after 11 courses 65%. After the effect of 11 treatment-courses the option of hemi-hepatectomy became feasible and this procedure was carried out, leaving in situ a lesion of 9 mm diameter (MRI) at the cutting-edge.

cGy for the liver, and 1400 cGy for the spleen. Thus, tumours with an inhomogeneous distribution of cells expressing peptide receptors may then respond in a favourable way to this kind of treatment because of the better cross-fire.

A problem during PRRT may be caused by the high uptake of $^{90}$Y-labelled peptide in the kidneys; small peptides in the blood plasma are filtered through the glomerular capillaries in the kidneys and subsequently reabsorbed almost completely (≥90%) by the proximal tubular cells by carrier-mediated endocytosis. After the subsequent degradation process that takes place in the lysosomes of the tubular cells, their labeled degradation products are ‘trapped’ in the lysosomes [11]. This will cause a high dose of radioactivity in the kidneys, thereby reducing the possibilities for PRRT. We showed that the renal uptake of $[^{111}\text{In-DTPA}]$octreotide in rats could be reduced about 50% by single intravenous administration of 400 mg/kg L- or D-lysine [27, 28]. The membranes of renal tubular cells contain negatively charged sites, to which positively charged residues of peptides or proteins are thought to bind [29]. An inhibition of this binding process may explain the effects by administration of the positively charged amino acid lysine (both D- and L-lysine) on $[^{111}\text{In-DTPA}]$octreotide re-uptake [28].

The high tissue penetration of $^{90}$Y localised in tubular cells may affect the glomeruli and eventually induce a glomerular fibrosis. Measures have to be taken in order to decrease the renal accumulation of beta-emitting peptides when used for PRRT, e.g., with lysine infusions [27, 28]. In this study, in which $[^{111}\text{In-DTPA}]$octreotide was used, no special precautions were taken to lower renal uptake.

In this phase I study of therapy with $[^{111}\text{In-DTPA}]$octreotide we only included end-stage patients with (neuroendocrine) tumours expressing a (rather) homogeneous distribution of somatostatin receptors and preferably high or modest accumulation of the radioligand. Based on our results with $[^{111}\text{In-DTPA}]$octreotide scintigraphy and given a relatively high accumulation of the radioligand in the tumour it is anticipated that patients with the following tumours might be candidates for this kind of treatment: most of (metastasised) GEP-tumours and paragangliomas, and 30% and 40% of malignant lymphomas and small-cell lung cancers, respectively.

**References**

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