Staging and treatment of differentiated thyroid carcinoma with radiolabeled somatostatin analogs

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In patients with progressive metastatic (or recurrent) differentiated thyroid carcinoma that either do not take up radioiodine or are unresponsive to continued radioiodine therapy, staging is difficult and treatment options are few. However, in most of these patients uptake of radiolabeled somatostatin analogs is evident on somatostatin-receptor scintigraphy (SRS). Using SRS, patients with sufficient uptake of radiolabeled somatostatin analogs can be selected for high-dose peptide receptor radionuclide therapy (PRRT) as an alternative targeted-treatment option. PRRT with the β-particle-emitting radionuclides 90yttrium (90Y) and 177lutetium (177Lu) gives the best results in terms of objective tumor response. Promising, novel, radiolabeled somatostatin analogs that have a broader receptor affinity profile and, thus, a potentially wider therapeutic range are being tested clinically.

Introduction

Standard therapy in most patients with non-medullary differentiated (papillary, follicular and Hürtle cell) thyroid carcinoma (DTC) involves either total or near-total thyroidectomy followed by ablation of the thyroid remnant with radioiodine. With a reported overall 10-year-survival rate of 75–95%, DTC is regarded as a malignancy with a relatively good prognosis [1–3]. However, tumors recur in ~20% of patients [2,3]. Long-term follow-up after initial therapy, which is based primarily on measurements of serum thyroglobulin (Tg, see Glossary) in combination with radioiodine whole-body scans (WBSs), is, therefore, obligatory. Additional treatment with radioiodine can be initiated when recurrence and/or metastases are evident and imaged by WBSs. However, radioiodine therapy is no longer an option in the 20–30% of patients who have recurrences and/or persistent metastases caused by dedifferentiation with a lack of radioiodine uptake (non-radioiodine-avid) within the tumors (4–6% of patients diagnosed with DTC) [4,5].

Patients with dedifferentiated DTC have a worse prognosis, largely because they cannot be treated with radioiodine [2,5,6]. Therefore, alternative, accurate imaging methods for diagnosis, and therapeutic modalities are of interest. Hürtle cell thyroid carcinoma (HCTC), an uncommon form of thyroid cancer that is usually classified as a variant of follicular thyroid carcinoma (FTC), is of special interest because these carcinomas rarely take up radioiodine, even at the time of diagnosis [7]. In this review, we focus on both the staging and the therapeutic potential of radiolabeled somatostatin analogs in patients with non-radioiodine-avid DTC.

Somatostatin receptor scintigraphy

Over ten years ago, we published the first results of patients with DTC who were imaged by somatostatin receptor scintigraphy (SRS) [8,9]. The potential value of SRS in patients with non-radioiodine-avid DTC was clear because, in some patients, either new or more tumor localizations were detected compared with WBS. Furthermore, in some patients with a negative WBS, SRS showed tumor uptake of the radiolabeled somatostatin analog 111indium-diethylene triamine pentaacetic acid (DTPA) octreotide (111In-octreotide). The finding that SRS visualizes tumors in patients with DTC whose tumors do not take up radioiodine has great potential for staging the disease and treating it with somatostatin analogs.

Glossary

CT: spiral computed tomography
DOTA: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
DTC: differentiated thyroid carcinoma
DTPA: diethylene triamine pentaacetic acid
EDDA: ethylene diamine diacetic acid
18F-FDG: 18F-fluorodeoxyglucose
FTC: follicular thyroid carcinoma
HCTC: Hürthle cell thyroid carcinoma
HYNIC: hydrazinonicotinyl
LAN: lanreotide
MRI: magnetic resonance imaging
NOC: Na1-octreotide
PDT: poorly differentiated thyroid carcinoma
PRRT: peptide receptor radionuclide therapy
PCT: papillary thyroid carcinoma
SPECT: single-photon emission computed tomography
SRS: somatostatin receptor scintigraphy
TATE: Tyr3-Thr8-octreotide
TSH: thyroid-stimulating hormone
Tg: thyroglobulin
TOC: Tyr3-octreotide
US: ultrasound
WBS: whole body scan
The value of SRS in clinical practice

Most reported studies on SRS focus on the clinical value of this imaging modality in patients with non-radioiodine-avid DTC with progressive disease. Tenenbaum et al. [10] studied four patients with DTC of whom three showed no uptake on WBS. Two patients, one with papillary thyroid carcinoma (PTC) and one with poorly differentiated thyroid carcinoma (insular; PDTC), showed $^{111}$In-octreotide uptake on SRS. In a larger study of 25 DTC patients (16 with radioiodine-negative tumors and nine with radioiodine-positive tumors), 20 out of 25 (80%) showed uptake during SRS with $^{111}$In-octreotide [11]. In the patients with radioiodine-negative tumors, 12 out of 16 (75%) showed uptake on SRS. All patients had elevated serum levels of Tg, which reflected the presence of disease. It was concluded that SRS is a useful, additional image and staging modality for follow-up in patients with elevated serum Tg levels and negative WBS. Several studies have confirmed these findings and reported uptake of $^{111}$In-octreotide in either non-radioiodine-avid metastatic or recurrent disease in 74–100% of patients (Table 1) [12–15]. By contrast, Garin et al. [16] reported a positive $^{111}$In-octreotide scan in only three out of 16 patients (19%) in whom no radioiodine uptake could be demonstrated. Valli et al. [17] reported similar results and concluded that octreotide scintigraphy has a lower diagnostic accuracy than conventional imaging modalities, including chest x-ray, ultrasound (US) of the neck, spiral computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy. However, the administration of a low dose of $^{111}$In-octreotide and a short acquisition time compared with the other studies might account for the discrepancy in sensitivity observed.

Giammarile et al. [18], who performed $^{111}$In-octreotide scintigraphy with the largest group of patients with no detectable radioiodine uptake and elevated serum Tg levels, reported an overall sensitivity of 51% which was clearly lower than that of both conventional imaging, such as US of the neck and abdomen, CT and/or MRI, and bone scintigraphy, and the relatively new technique of positron emission tomography (PET) using $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG). With the large number of patients studied, factors that might influence diagnostic accuracy of SRS, were discussed. The first of these is the anatomical localization of the tumors. The sensitivity of SRS was high for the detection of mediastinal lesions (93%), whereas most false-negative results were observed in patients who, at follow-up, were proved to have had undetectable, small, neck and lung metastases at the time of SRS.

In addition to anatomical location, a high serum Tg level (>50 ng ml$^{-1}$) in patients who had thyroxine substitution therapy (Tg-on) was associated with significantly increased sensitivity. Furthermore, Görges et al. [19] reported a clear distinction between the detected lesions within the group of patients with low serum Tg-on levels (<10 ng ml$^{-1}$, n = 11) and those from the group with high serum Tg-on levels (>10 ng ml$^{-1}$, n = 39). In the latter group, 85% of patients had a positive SRS whereas in the group with low serum Tg-on levels only 27% of patients had a positive SRS. Garin et al. [16] reported that all their studied patients with a positive SRS had a serum Tg-on level > 5 ng ml$^{-1}$. Patients without uptake had low serum Tg-on levels (<5 ng ml$^{-1}$). These results indicate a positive correlation between the serum Tg level and/or thyroid-stimulating hormone (TSH) and visualization on SRS. To test this hypothesis Haslinghuis et al. [13] studied whether withdrawal of thyroxine therapy and the subsequent increase in TSH and serum Tg levels might optimize the information obtained with SRS. Direct comparison of SRS before and after withdrawal of thyroxine therapy was performed in six patients. Essentially, the same clinical information was obtained after withdrawal of thyroxine, and it was concluded that there is no need to withdraw patients from thyroxine to perform SRS. In the case of SRS for purely diagnostic purposes, this conclusion is fair and the benefit for patients is that they do not have to suffer the burden of thyroxine withdrawal before SRS. However, although the same information was obtained, higher pathological uptake was observed in at least two patients in whom thyroxine-substitution therapy was withdrawn temporarily [13]. In view of therapy with radiolabeled somatostatin analogs (see later), increased uptake in the

Table 1. $^{111}$In-octreotide scintigraphy in non-radioiodine-avid DTC

<table>
<thead>
<tr>
<th>Study year</th>
<th>Number of patients</th>
<th>Tumor classification</th>
<th>Serum Tg level range (ng ml$^{-1}$)</th>
<th>Imaging</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>3</td>
<td>2 PTC, 1 insular TC</td>
<td>120–60 000 (3)</td>
<td>Tg-on$^a$ (number of patients)</td>
<td>2 out of 3 (67%)</td>
</tr>
<tr>
<td>1996</td>
<td>16</td>
<td>11 FTC, 5 PDTC</td>
<td>2–42 500 (16)</td>
<td>Tg-on$^a$ (number of patients)</td>
<td>12 out of 15 (75%)</td>
</tr>
<tr>
<td>1996</td>
<td>6</td>
<td>5 FTC, 1 PTC</td>
<td>NA</td>
<td>NA</td>
<td>6 out of 6 (100%)</td>
</tr>
<tr>
<td>1998</td>
<td>16</td>
<td>15 FTC, 1 vesicular TC</td>
<td>&lt;0.2–1440 (11)</td>
<td>Tg-off$^b$ (number of patients)</td>
<td>3 out of 16 (19%)</td>
</tr>
<tr>
<td>1999</td>
<td>15</td>
<td>14 FTC, 1 HCTC</td>
<td>10–65 000 (15)</td>
<td>Tg-on</td>
<td>7 out of 15 (48%)</td>
</tr>
<tr>
<td>2001</td>
<td>29</td>
<td>3 FTC, 4 PTC, 21 HCTC, 1 insular TC</td>
<td>0.48–48 300 (27)</td>
<td>1670–2030 (2)</td>
<td>19 out of 29 (68%)</td>
</tr>
<tr>
<td>2001</td>
<td>25</td>
<td>9 FTC, 16 PTC</td>
<td>&lt;1.5–14 910 (25)</td>
<td>Tg-on</td>
<td>6 out of 8 (75%)</td>
</tr>
<tr>
<td>2003</td>
<td>17</td>
<td>1 FTC, 4 PTC, 12 HCTC</td>
<td>NA</td>
<td>Tg-off$^b$ (number of patients)</td>
<td>14 out of 17 (82%)</td>
</tr>
<tr>
<td>2004</td>
<td>23</td>
<td>8 FTC, 13 PTC, 2 HCTC</td>
<td>16.6–586 000 (22)$^c$</td>
<td>NA</td>
<td>17 out of 23 (74%)</td>
</tr>
<tr>
<td>2004</td>
<td>43</td>
<td>9 FTC, 20 PTC, 8 HCTC, 6 insular TC</td>
<td>0.7–5250 (40)</td>
<td>171–5850 (3)</td>
<td>22 out of 43 (51%)</td>
</tr>
</tbody>
</table>

$^a$Tg-off, thyroglobulin levels without TSH-suppressive treatment (L-thyroxine); Tg-on, thyroglobulin levels under TSH-suppressive treatment.

$^b$Excluding one patient with serum Tg of 0.8 ng ml$^{-1}$ who was Tg-antibody-positive.

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tumors after thyroxine withdrawal might be beneficial in terms of tumor shrinkage. Such a correlation between uptake on pretherapy SRS and favorable outcome of therapy with radiolabeled somatostatin analogs was reported in patients with neuroendocrine gastroenteropancreatic (GEP) tumors [20]. Further quantitative imaging studies into the effect of thyroxine withdrawal on tumor uptake of radiolabeled somatostatin analogs are warranted to address this issue.

In view of a possible correlation of elevated serum Tg level, tumor size and SRS sensitivity, the report by Bachelot et al. [21] is of interest. This study demonstrated a close relationship between the serum Tg level after withdrawal of thyroid-hormone treatment and tumor mass/extent of disease. Thus, the reported increased SRS sensitivity in patients with elevated serum Tg levels [16,18,19] might reflect an increase in SRS sensitivity in larger tumors, rather than the elevated serum Tg level.

In summary, these studies indicate that anatomical localization and tumor size/extent of disease are important in determining the outcome of SRS in patients with non-radioiodine-avid DTC.

**Somatostatin receptor subtypes**

Another important factor in the observed differences in uptake during SRS might be the relative expression of somatostatin receptor subtypes (sstr1–sstr5) and their density on the tumor cell surface. John et al. demonstrated that positive 111In-octreotide scintigraphy is caused mainly by sstr2, whereas sstr1, sstr3, sstr4 and sstr5 are less important. Therefore, the presence of sstr2 is essential for imaging tumors with SRS [22]. Reubi et al. [23], who used autoradiography to study the sstr profile of numerous human tumors, reported a predominance of sstr2 and/or sstr1 in neuroendocrine GEP tumors. No DTC tissue was studied. In contrast to the high concentration of sstr1 and sstr2 in GEP tumors, in vitro studies with monolayers of thyroid cancer cell lines and xenografts showed predominant expression of sstr3 and sstr5, with sstr2 mRNA detected only faintly [24]. In another report, which investigated sstr expression in biopsies of DTC tumor tissue by northern-blot analyses, sstr1, sstr3, sstr4 and sstr5 were expressed in all tumors, but sstr2 was not detected in either FTC or PTC tumors [25]. The same report demonstrated the highest tumor:background ratio and expression of high-affinity sstr2 in medullary thyroid carcinoma and Hürthle cell neoplasia, including Hürthle cell adenoma, rather than in the clinically more common, in vitro studied PTC and FTC. In Hürthle cell neoplasia, the expression of sstr2 is irregular, and tumors with high, intermediate and low expression of sstr2 were demonstrated. These findings indicate that the sstr-expression profile in DTC cells is different and more variable than in neuroendocrine GEP tumors, which might explain the variation of uptake observed during SRS (Figure 1).

**Differences in SRS protocols**

In addition to these clinical factors, differences in SRS imaging protocols must also be taken into account. Differences in the amount of injected dose and/or imaging acquisition characteristics can have a significant impact on the interpretation of scintigraphy. The methodology used is, therefore, important because this might lead to differences in the sensitivity of SRS. For optimal and standardized imaging, guidelines for SRS with 111In-octreotide were published in 2001 [26], but only three of the 10 studies in Table 2 have been performed in accordance with these. In some clinical centers, only half of the recommended dose of 222 MBq was used. Furthermore, high-speed whole-body scanning (>3 cm min−1) was performed frequently, rather than the recommended ≥ 10 min planar-spot imaging, which indicates suboptimal imaging. However, adding single-photon emission computed tomography (SPECT) imaging, which allows a more precise anatomic delineation than planar imaging, resulted in similar sensitivity to the SRS studies that followed the guidelines. This underlines the importance of SPECT and the injection of sufficient radioactive dose in SRS to obtain the best possible imaging with the lowest number of false-negative cases.

**Novel radiolabeled somatostatin analogs in DTC**

Alternative radiolabeled somatostatin analogs are under investigation for SRS [27,28]. Gabriel et al. [29] studied the use of a new radiolabeled somatostatin analog 99mTc-EDDA/HYNIC-TOC (99mTc-labeled hydrazinonicotinyl (HYNIC)-Tyr3-octreotide (TOC) coupled with ethylene...
studies are necessary to assess the affinity profile of 99mTc-receptor subtypes, this remains to be proven. Further similar affinity profile for the different somatostatin results indicate that both radiopharmaceuticals have a HYNIC-TOC scintigraphy was reported. Although these scintigraphy compared with 111In-octreotide scintigraphy, comparison of both SRS modalities was performed in eight demonstrated a positive correlation between true-positive phy in patients with DTC was reported. Furthermore, it demonstrated an equal number of lesions in radioiodine-negative and in radioiodine-positive patients. 18F-FDG PET imaging in the same patients detected fewer tumor lesions in 15 out of 18 (83%) patients.

In addition, the novel radiolabeled somatostatin analog, [111In]DOTA-1-Nal3-octreotide (111In-DOTA-NOC), which besides high affinity for sstr2, also has high affinity for sstr3 and sstr5, is of interest. Because of this affinity profile, which clearly differs from that of 111In-octreotide, this analog holds promise for better tumor imaging in patients with non-radioiodine-avid DTC.

**Therapy with radiolabeled somatostatin analogs**

Despite the differences in sensitivity, and variations in the expression of somatostatin receptor subtypes and uptake during 111In-octreotide scintigraphy, SRS has additional diagnostic value in determining either the extent of metastatic disease or recurrences in DTC. Furthermore, the uptake of 111In-octreotide in tumor sites, imaged by SRS, indicates somatostatin receptors on the tumor-cell surface, which might be a potential therapeutic target for somatostatin analogs such as octreotide in patients with DTC for whom there is no alternative treatment. However, reports on the use of these non-radioactive somatostatin analogs to treat patients with non-radioiodine-avid DTC objective response, one patient showed clear clinical improvement whereas the other experienced no change in clinical signs and symptoms. Alternative explanations for the observed reduced metabolic activity, such as inhibition of inflammatory cells and inhibition of revascularization or angiogenesis, were suggested. These early, limited studies indicate that octreotide is likely to be of limited value in the management of patients with DTC, and no further studies have been published since 2000. Recently, a novel somatostatin analog, SOM230, has been introduced. Compared with octreotide, the binding affinity of SOM230 for sstr1, sstr3 and sstr5 is 30×, 5× and 40× higher, respectively, and 2.5× lower for sstr2. In addition, the favorable elimination half-life of SOM230 (23 h), makes it suitable for clinical application. Therefore, it is of interest to study the anti-tumor effects of this somatostatin analog with a broader somatostatin receptor profile than the somatostatin analogs that are currently available.

**Table 2. Differences in 111In-octreotide scintigraphy protocols**

<table>
<thead>
<tr>
<th>Study year</th>
<th>Diagnostic 111In-octreotide scintigraphy protocol</th>
<th>Guidelines*</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>110 WBS</td>
<td>N</td>
<td>[10]</td>
</tr>
<tr>
<td>1999</td>
<td>111 WBS, SPECT</td>
<td>N</td>
<td>[12]</td>
</tr>
<tr>
<td>2001</td>
<td>222 WBS, SPECT</td>
<td>N</td>
<td>[14]</td>
</tr>
<tr>
<td>2003</td>
<td>111 WBS, SPECT</td>
<td>N</td>
<td>[15]</td>
</tr>
<tr>
<td>2004</td>
<td>110 WBS, SPECT</td>
<td>N</td>
<td>[16]</td>
</tr>
</tbody>
</table>

*Y. 111In-octreotide scintigraphy followed the guidelines for SRS described in [26]; N, different protocol.

aThe 48-h-after-injection scan was only performed when high background uptake was present on the 24-h-after injection scan to increase the sensitivity.

**Box 1. Treatment of DTC with non-radioactive somatostatin analogs**

Zlock et al. [32] treated four patients with DTC with relatively high doses (4 mg daily) of non-radioactive octreotide subcutaneously for up to 12 months: each showed progressive disease under therapy. However, the expression of the somatostatin receptor in biopsied tumor tissue and uptake of 111In-octreotide during SRS was not evaluated, which makes it difficult to evaluate the effect of octreotide treatment in this study. In a more recent report, Robbins et al. described two patients with widely metastatic PTC who, because of failure of conventional treatment, were treated with monthly injections of a slow-release form of octreotide (Sandostatin LAR depot®) [33]. Both patients had visible uptake in the lungs on SRS. 18F-FDG PET scans before therapy and 3–4 months after the start of the monthly injections of sandostatin LAR showed a reduction of standard uptake values in both patients, which suggested octreotide-induced reduction of metabolic activity in the tumors. However, no effect on tumor size and/or serum Tg levels was reported. Despite the absence of an uptake in 17 out of 18 patients (94%). Each radioligand demonstrated an equal number of lesions in radioiodine-negative and in radioiodine-positive patients. 18F-FDG PET imaging in the same patients detected fewer tumor lesions in 15 out of 18 (83%) patients.

**References**

1. Robbins et al. [31] reported results of in vitro binding studies and SRS of two other radiolabeled somatostatin analogs; 111In-coupled to 1,4,7,10-tetraaza-cyclododecane (DOTA)-laneotide (111In-DOTA-LAN) and DOTA-D-Phe1-Tyr3-octreotide (111In-DOTA-TOC). SRS with both radioligands demonstrated tumor-related

diamine diacetic acid (EDDA) as a co-ligand in 54 patients with thyroid cancer and no radioiodine uptake during WBS. The rationale for conducting this study were the favorable characteristics of 99mTc-EDDA/HYNIC-TOC scintigraphy compared with 111In-octreotide scintigraphy, such as wider availability of the radionuclide, shorter acquisition time and higher spatial resolution [30]. A sensitivity of 66% for 99mTc-EDDA/HYNIC-TOC scintigraphy in patients with DTC was reported. Furthermore, it demonstrated a positive correlation between true-positive findings and elevated serum Tg levels. In addition, direct comparison of both SRS modalities was performed in eight patients. One discordant finding in favor of 99mTc-EDDA/HYNIC-TOC scintigraphy was reported. Although these results indicate that both radiopharmaceuticals have a similar affinity profile for the different somatostatin receptor subtypes, this remains to be proven. Further studies are necessary to assess the affinity profile of 99mTc-EDDA/HYNIC-TOC and the value of 99mTc-EDDA/HYNIC-TOC scintigraphy in clinical practice.

Recently, Rodrigues et al. [31] reported results of in vitro binding studies and SRS of two other radiolabeled somatostatin analogs; 111In-coupled to 1,4,7,10-tetraaza-cyclododecane (DOTA)-laneotide (111In-DOTA-LAN) and DOTA-D-Phe1-Tyr3-octreotide (111In-DOTA-TOC). SRS with both radioligands demonstrated tumor-related
tumors are scarce and evidence of therapeutic benefit is limited (Box 1).

Another therapeutic approach in patients with uptake on SRS is tumor-targeted therapy with radiolabeled analogs of somatostatin. This approach, called peptide receptor radionuclide therapy (PRRT), is known to be effective in neuroendocrine GEP tumors with several radiolabeled somatostatin analogs (Reviewed in [20]).

In the first clinical PRRT study, patients with SRS-positive tumors, five of whom had DTC, were treated with high doses of $^{111}$In-octreotide [35]. PRRT resulted in stable disease in one patient whereas the other four had progressive disease. In patients with neuroendocrine GEP tumors, 2–17% had a partial remission determined by clinical imaging and/or biochemical parameters [35–37]. Although the results were promising, most PRRT studies that followed used $\beta$-particle-emitting radiouclides such as $^{90}$Y and $^{177}$Lu instead of the Auger electron emitter $^{111}$In. $\beta$-particle-emitting radiouclides have greater therapeutic potential because the emitted particle range exceeds the cell diameter [38–40]. Furthermore, the ability to irradiate neighboring cells is an advantage in tumors, which are characterized by a heterogeneous tissue distribution of somatostatin receptors, with regions of high density next to regions that do not express the receptor [41]. In addition to the introduction of $\beta$-particle-emitting radiouclides, structural changes in the analog, such as insertion of tyrosine (Tyr$^3$-OC or TOC) and replacement of the C-terminal threoninol with threonine (TATE), increased the affinity for the sstr2 [42]. As expected, clinical and pre-clinical studies in which somatostatin analogs were coupled to $^{90}$Y or $^{177}$Lu were more successful in terms of tumor shrinkage than somatostatin analogs coupled to $^{111}$In [43–46]. The results of treatment with the $\beta$-particle-emitting radiolabeled somatostatin analogs $^{90}$Y-DOTA-TOC and $^{177}$Lu-DOTA-TATE in patients with neuroendocrine GEP tumors are the most encouraging, with 24–33% of patients experiencing either complete or partial remission [20].

In addition to the use of $^{90}$Y- and $^{177}$Lu-labeled somatostatin analogs for treating patients with neuroendocrine GEP tumors, patients with non-radioiodine-avid DTC have also been treated. Recently, we have reported the results of the first patients with DTC treated with $^{177}$Lu-DOTA-TATE [47] and reviewed the available clinical PRRT studies that report the outcome of PRRT in patients with DTC [14,19,29,35,44,48,49]. Additionally, Stokkel et al. [50] reported their results of high-dose ($\sim 15$–$30$ GBq) therapy with $^{111}$In-octreotide in patients with progressive radioiodine-non-responsive thyroid cancer. Table 3 summarizes the available reports of PRRT on 62 patients with DTC. In this group, five patients (8%), including two with HCTC (Box 2), had an objective tumor response and 26 patients (42%) had stable disease. Time-to-progression data were either not available or reported for <1 year. Comparing these studies, some of which include only a few patients, is difficult because of differences in the radionuclides, somatostatin analogs and maximum doses administered. Nevertheless, it is clear that the radiolabeled analogs that have been evaluated, PRRT is less effective in DTC than in neuroendocrine GEP tumors.

**The future of PRRT in DTC**

Most of the radiolabeled somatostatin analogs that are used for diagnostic and therapeutic purposes bind with high affinity to sstr2 and with lower affinity for the other receptor subtypes. In DTC, studies indicate that the expression of the different somatostatin receptor subtypes is more variable than in neuroendocrine GEP tumors in which sstr2 is expressed predominantly. The ongoing development of somatostatin-based radiogandis with a broader receptor subtype profile is, therefore, of interest [51]. Wild et al. [28] reported the first preclinical data on the novel radiolabeled ($^{111}$In and $^{90}$Y) somatostatin analog DOTA-NOC that has high affinity for sstr2, sstr3 and sstr5. They briefly mentioned excellent image quality in the first scintigraphy studies with $^{111}$In-DOTA-NOC in patients with thyroid cancer. It is assumed that DOTA-NOC labeled with either $^{90}$Y or $^{177}$Lu will have similar favorable binding properties and, therefore, might become available to treat patients with DTC. Preliminary results

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**Table 3. Peptide receptor radionuclide therapy in 62 patients with DTC**

<table>
<thead>
<tr>
<th>Study year</th>
<th>n</th>
<th>Tumor classification</th>
<th>Progressive disease before PRRT</th>
<th>Radiopharmaceutical</th>
<th>Cumulative dose (GBq)</th>
<th>Response</th>
<th>TTP in months</th>
<th>Refs</th>
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<tbody>
<tr>
<td>2001</td>
<td>3</td>
<td>3 FTC, 4 FTC, 4 FTC</td>
<td>2/3</td>
<td>$^{90}$Y DOTA TOC</td>
<td>1.7–6.6</td>
<td>1 SD (21), 2 PD</td>
<td>[18]</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>7</td>
<td>7 FTC, 7 FTC, 4 FTC</td>
<td>2/2</td>
<td>$^{90}$Y DOTA TOC</td>
<td>1.7–14.8</td>
<td>2 SD (8.8), 5 PD</td>
<td>[48]</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>2</td>
<td>2 FTC</td>
<td>2/2</td>
<td>$^{90}$Y DOTA TOC</td>
<td>&gt; 7.4</td>
<td>NA</td>
<td>[49]</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>5</td>
<td>1 FTC, 1 FTC, 1 FTC</td>
<td>2/5</td>
<td>$^{111}$In DOTA TOC</td>
<td>29.5–83.2</td>
<td>4 PD, 1 SD (NA)</td>
<td>[35]</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>25</td>
<td>25 unclassified TC</td>
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<td>$^{90}$Y DOTA LAN</td>
<td>0.9–7.0</td>
<td>3 MR (NA), 11 SD (NA)</td>
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<tr>
<td>2003</td>
<td>1</td>
<td>1 FTC</td>
<td>1/1</td>
<td>$^{90}$Y DOTA TOC</td>
<td>5.6–7.6</td>
<td>5 SD (5)</td>
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<td>9</td>
<td>9 FTC, 9 FTC, 9 FTC</td>
<td>9/9</td>
<td>$^{111}$In DOTA OC</td>
<td>22.4–39.1</td>
<td>1 PR (22+), 1 MR (43), 2 SD (18, 24+), 1 PD (4)</td>
<td>[47]</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: NA, not available; TC, unclassified thyroid carcinoma; TTP, time to progression.*

*SD, stable disease, $< 25\%$ reduction or increase in tumor size; PD, progressive disease, $> 25\%$ increase in tumor size; MR, minor remission, between 25% and 50% reduction in tumor size; PR, partial remission, $> 50\%$ reduction in tumor size.*

*Patient had progressive disease before therapy.*

*One patient had progressive disease before therapy.*

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of SRS and PRRT with $^{111}$In and $^{177}$Lu-DOTA-NOC, respectively, are encouraging [52].

Concluding remarks

In patients with recurrent and/or metastatic non-radioiodine-avid DTC, SRS can demonstrate tumor sites in a substantial percentage of patients. Therefore, SRS is useful for imaging and to localize tumor sites in patients in whom disease is suspected because of elevated serum Tg level but who are without apparent uptake during post-radioiodine therapy WBS. Localization with SRS might be helpful in the further management of these patients. The sensitivity of SRS is likely to depend on the tumor size, the extent of disease and the expression of the different somatostatin receptor subtypes.

In patients with uptake on SRS who have no alternative therapeutic options, SRS can select potential candidates for PRRT. When conventional treatment is no longer an option and SRS shows sufficient uptake of $^{111}$In-octreotide during SRS, PRRT should be considered as an alternative therapy.

Research into radiolabeled somatostatin analogs that have high binding affinity to the different sstr subtypes is underway. This might introduce more receptor-subtype-specific SRS and, thereby, more effective PRRT for patients with DTC in the future.

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