$^{68}$Ga-DOTATOC-PET/CT in patients with iodine- and $^{18}$F-FDG-negative differentiated thyroid carcinoma and elevated serum thyroglobulin

**Short title:** SSTR-PET/CT in iodine/FDG negative DTC

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**Word count:** 4859
ABSTRACT

This study evaluated the impact of $^{68}$Ga-DOTATOC-PET/CT in detecting recurrence or metastases in differentiated thyroid carcinoma (DTC) patients with elevated serum thyroglobulin and both negative radioiodine imaging and $^{18}$F-FDG-PET/CT.

Methods

$^{68}$Ga-DOTATOC-PET/CT (CT without contrast, low-dose) was performed on average 6 weeks after negative $^{18}$F-FDG-PET/CT (CT contrast-enhanced, full-dose) in 15 consecutive radioiodine negative DTC patients with elevated and rising thyroglobulin. Visual assessment of $^{68}$Ga-DOTATOC-PET/CT images used a 4-point-scale for classification of lesions (0=no pathological findings; 1=benign; 2=equivocal; 3=malignant). PET findings were correlated with the histological subtype of tumor, levels of serum thyroglobulin and morphological findings on full-dose CT and neck ultrasound. Histology or clinical and imaging follow-up served as reference standard. Analysis was performed on patient- and lesion-basis.

Results

$^{68}$Ga-DOTATOC-PET/CT was true positive in 5 patients (10 tumor lesions) and was false positive in 1 patient. The rate of positive $^{68}$Ga-DOTATOC-PET/CT was significantly higher in poorly differentiated/oxyphilic carcinomas (4/4 patients) than in papillary (1/5) or follicular (0/6) tumors. Thyroglobulin levels tended to be higher in patients with tumor localization on $^{68}$Ga-DOTATOC-PET/CT, but differences were not significant. In 2/5 patients with true positive findings on $^{68}$Ga-DOTATOC-PET/CT CT alone but not ultrasound identified 2/10 tumor lesions, but in both patients $^{68}$Ga-DOTATOC-PET/CT revealed further tumor lesions not detected on CT alone.
Conclusions

$^{68}$Ga-DOTATOC-PET/CT should be considered in case of negative $^{18}$F-FDG-PET/CT in radioiodine negative DTC patients with elevated and rising thyroglobulin. Imaging with $^{68}$Ga-DOTATOC appears promising especially in poorly differentiated and oxyphilic subtypes of DTC.

Key Words: differentiated thyroid carcinoma, recurrence, DOTATOC-PET/CT, SSTR, elevated thyroglobulin
INTRODUCTION

Differentiated thyroid carcinomas (DTC) have generally excellent prognosis after initial surgery and radioiodine treatment. However, tumor recurrence is quite common with a relapse rate of up to 20% (1). Even in the case of relapse or metastasis, iodine accumulating tumors can be effectively treated with radioiodine. But once DTC lose the capability to concentrate (radio)iodine, they can be challenging to treat (2). The recently established molecular targeted therapy for patients with locally advanced or metastatic radioiodine-refractory tumors was shown to extend progression-free survival, but patients failed to achieve complete remission (3).

Currently, there are no curative systemic treatment options for metastatic radioiodine-refractory tumors. As long as these tumors are locally limited, they can be removed surgically or at least controlled by external radiation. In consequence, long-term local tumor control or even cure is achievable, provided that the tumor can be localized early enough. 18F-FDG-positron emission tomography and computed tomography (PET/CT) is an established tool for detection of recurrent DTC in patients presenting with elevated and rising thyroglobulin levels after radioiodine ablation and negative radioiodine scans (1, 4). However, 18F-FDG-PET/CT fails to localize the tumor in some of these patients.

DTC were shown to express somatostatin receptors (SSTR) (5-10). In consequence, several imaging studies using radiolabeled SSTR-analogues like 111In-pentetreotide or 99mTc-depreotide were performed in DTC to date (11-19). However, the patient populations investigated in these studies were heterogeneous and only few studies have investigated the impact of SSTR scintigraphy in DTC patients with elevated thyroglobulin, indicating disease recurrence, and negative radioiodine imaging (11-13, 16, 19). Controversial results were reported about SSTR scintigraphy compared with 18F-FDG-PET/CT in iodine positive and iodine negative DTC (12, 14, 16). PET has several advantages over planar scintigraphy or even single photon emission computed tomography (SPECT) like better spatial resolution allowing for the detection of smaller lesions. In recent years, SSTR binding PET tracers like 68Ga-DOTATOC were established in
clinical routine. To our knowledge, only three studies have compared the diagnostic performance of 68Ga-labeled SSTR-analogues (DOTATOC-, DOTANOC-, DOTALAN-PET/CT) with 18F-FDG-PET/CT in the staging of iodine negative DTC so far (20-22). Padhy et al. reported about their initial experience of 68Ga-DOTATATE-PET/CT in identifying non-iodine avid/ non-18F-FDG avid disease in patients with DTC (23). However, studies having focused on the usefulness of 68Ga-labeled SSTR-binding PET tracers in DTC patients with elevated thyroglobulin and both negative radiiodine imaging and 18F-FDG-PET/CT have yet not been reported.

The aim of this study was to evaluate the impact of 68Ga-DOTATOC-PET/CT in detecting recurrence or metastases in radiiodine negative DTC patients with elevated serum thyroglobulin and negative 18F-FDG-PET/CT.

MATERIALS AND METHODS

Patients

This retrospective study included 15 consecutive DTC patients with negative radiiodine and 18F-FDG imaging as well as elevated and rising serum thyroglobulin levels (7 women and 8 men; mean age at the time of initial surgery 57 years, range 19-76 years). Tumor histology was papillary thyroid carcinoma in 5 patients, follicular thyroid carcinoma in 6 patients, poorly differentiated carcinoma in 3 patients and oxyphilic (Hürthle cell) thyroid carcinoma in 1 patient. Most patients presented initial with locally advanced tumor stage (T3 or T4 according to the Union Internationale contre le cancer (UICC), 7th edition 2010; 11 patients) and/or lymph node metastases (5 patients). After total thyroidectomy, all patients were treated with at least one radiiodine therapy (median cumulative activity 8 GBq 131I, range 3-11 GBq) 1-19 years (median 7 years) ago. In addition to radiiodine therapy one patient underwent re-surgery and external radiation therapy. Follow-up care routinely included high-resolution ultrasound of the neck (iU22,
Philips) and determination of the tumor marker serum thyroglobulin (SELco Tg, Medipan) under thyroid stimulating hormone (TSH)-suppressive treatment with L-thyroxine or under TSH-stimulation. Thyroglobulin recovery testing was performed for detecting interference in serum thyroglobulin measurement. Additionally, interfering thyroglobulin antibodies (Anti-TG, Siemens) were determined.

All patients presented with elevated and rising thyroglobulin levels during follow-up. Consecutive whole body radiiodine imaging ($^{131}$I-whole body scan in 8 patients and $^{124}$I-PET/CT in 7 patients) under endogenous TSH stimulation (TSH >30mU/L) was assessed as negative in all patients by two experienced nuclear medicine physicians in consensual diagnosis. All patients followed a low iodine diet for 4 weeks prior to radiiodine imaging and measurement of iodine urinary concentration excluded iodine excess.

Patient characteristics and the corresponding results of $^{68}$Ga-DOTATOC-PET/CT are summarized in Table 1.

The study has been approved by the local ethics committee and all patients signed an informed consent form.

$^{18}$F-FDG-PET/CT Imaging

$^{18}$F-FDG-PET/CT (CT contrast-enhanced, in full-dose technique) was performed for detection of iodine refractory thyroid carcinoma in median 3 months after radiiodine imaging. PET/CT images were obtained using a Biograph mCT PET/CT scanner (Siemens Healthcare, Erlangen, Germany). Before tracer administration, a fasting period of at least 4 hours and blood glucose levels lower than 150 mg/dL were assured. After intravenous administration of 250-350 MBq (median 325 MBq) $^{18}$F-FDG, PET data were acquired 57-70 minutes (median 60 minutes) p.i. by scanning from upper thigh to head using 6-8 bed positions for 2 min each. The PET data were reconstructed using a 3D attenuation weighted ordered subsets expectation maximization algorithm with 4 iterations and 8 subsets, a 4mm post-reconstruction Gaussian filter and
attenuation image segmentation. Diagnostic computed tomography (CT) was performed after administration of oral and intravenous contrast media. Attenuation correction of the PET data was based on the acquired whole-body CT dataset. CT acquisition parameters were as follows: 100 kV, automatic mAs adjustment (max. 210 mAs), 5mm slice thickness, 5mm increment, pitch 1. 18F-FDG-PET/CT studies were evaluated by two independent, experienced nuclear medicine physicians as well as a radiologist in consensual diagnosis. Lesions were considered malignant if focal 18F-FDG-uptake was noted. 18F-FDG imaging was assessed as negative in all patients. CT revealed two pathological findings without 18F-FDG accumulation assessed as not clearly benign or malignant.

68Ga-DOTATOC-PET/CT Imaging

As no tumor site was detected on radioiodine and on 18F-FDG imaging, all patients received a 68Ga-DOTATOC-PET/CT scan. The mean interval between 18F-FDG-PET/CT and 68Ga-DOTATOC-PET/CT scan was 6 weeks (range 1-12). 68Ga-DOTATOC was synthesized in-house as previously described (24). No patients received treatment with somatostatin analogues. PET data were acquired 28-40 minutes (median 30 minutes) after intravenous administration of 60-100 (median 78) MBq 68Ga-DOTATOC from upper thigh to head using 6-8 bed positions for 2 min each. Scans were acquired using a Biograph mCT (Siemens Healthcare, Erlangen, Germany). CT data were used for attenuation-correction. The PET data were reconstructed using a 3D attenuation weighted ordered subsets expectation maximization algorithm with 4 iterations and 8 subsets, a 4mm post-reconstruction Gaussian filter and attenuation image segmentation. To minimize radiation exposure, CT was performed without contrast in low-dose technique with 15 mAs, 100 kV, slice width 5 mm, increment 5 mm and 0.85 pitch and served only for attenuation correction of the PET data and anatomical orientation.

68Ga-DOTATOC-PET/CT Data Analysis and Statistics
68Ga-DOTATOC PET studies were retrospectively evaluated by two independent, experienced nuclear medicine physicians in consensual diagnosis. Visual assessment of PET images used a 4-point-scale for classification of lesions (0=no pathological findings; 1=benign; 2=equivocal; 3=malignant). Lesions were considered malignant if marked, focal 68Ga-DOTATOC-uptake above background was noted in a location incompatible with physiological tracer uptake. If mild uptake near background level was observed, lesions were assessed as benign. Lesions were assessed as equivocal if assignment as benign or malignant was uncertain. We also measured the maximum standardized uptake value (SUVmax) of lesions, but as there is no generally accepted SUVmax threshold to define malignancy, we did not use a fixed threshold for differentiating between benign and malignant findings. Analysis was performed on patient- and lesion-basis. Findings were verified by histology or clinical follow-up including different imaging modalities.

Results of the 68Ga-DOTATOC-PET/CT were correlated with initial tumor histology (papillary, follicular and less differentiated oxyphilic/poorly differentiated carcinomas) and levels of serum thyroglobulin under TSH-suppressive therapy at the time of 68Ga-DOTATOC-PET/CT.

The PET lesions were compared with the full-dose CT of the 18F-FDG-PET/CT and were rated as “without morphologic correlate” or “with morphologic correlate”. Lesions with morphologic correlate were further classified as “inconspicuous”, “not clearly benign or malignant” or “highly suspicious of malignancy” on CT alone to define if a 68Ga-DOTATOC positive lesion was recognized as malignant on CT alone.

Additionally, high resolution ultrasound of the neck (iU22, Philips) was performed for detection of local recurrence or suspicious lymph nodes. Findings were compared with the results of 68Ga-DOTATOC-PET/CT.

Statistical analysis was performed using Prism 5 software package (GraphPad Software, La Jolla, CA, USA). Thyroglobulin values were compared between patients with positive and negative 68Ga-DOTATOC-PET/CT and between histologic subtypes using the non-parametric
Mann-Whitney test or Kruskal Wallis test followed by Dunn’s multiple comparison test. To exclude bias due to tumor progress over time, thyroglobulin levels at the time of radioiodine imaging were compared with those at $^{68}$Ga-DOTATOC-PET/CT using paired t-test. Patient-based analysis of positive findings on $^{68}$Ga-DOTATOC-PET/CT in dependence of histology was performed using Fisher’s exact test. In all analyses $p < 0.05$ was considered to indicate statistical significance.

RESULTS

$^{68}$Ga-DOTATOC-PET/CT

$^{68}$Ga-DOTATOC-PET/CT was negative for malignant lesions in 9 patients: PET was completely negative in 6/15 patients. In 2/15 patients, only benign lesions were detected. Findings were rated as equivocal in 1/15 patient. In all of these 9 patients the absence of detectable malignant lesions was confirmed during follow-up (median follow-up 22 months, range 16-40 months).

In 6/15 patients at least one lesion was considered as malignant (mean SUVmax 4.8, range 3.0-10.1). An example is given in Fig. 1. Assessment was verified as true-positive in 3/6 patients by histologic confirmation, in 1 patient by fine needle aspiration biopsy prior to external radiation therapy and in 1 patient by progressive disease during follow-up. In 1/6 patients focal uptake in a mesenteric lymph node assessed as suspicious of neuroendocrine tumor turned out to be false positive as it showed no tracer accumulation on follow-up $^{68}$Ga-DOTATOC-PET/CT. Therefore, $^{68}$Ga-DOTATOC-PET/CT allowed to localize tumor sites in 5/15 (33%) patients with elevated thyroglobulin and negative radioiodine and $^{18}$F-FDG imaging. In these patients, a total of 10 malignant lesions were detected by $^{68}$Ga-DOTATOC-PET/CT. In detail, 7 cervical (including 3 in
the cervicothoracic region), 1 axillary and 2 mediastinal tumor sites (local relapse or lymph node metastases) were identified.

**Tumor Histology and Thyroglobulin Level: Correlation with the Detection Rate on $^{68}$Ga-DOTATOC-PET/CT**

Considering the different histological tumor subtypes, the tumor detection rate on $^{68}$Ga-DOTATOC-PET/CT was 1/5 for patients with papillary carcinoma, 0/6 for follicular tumors and 4/4 for the group of poorly differentiated and oxyphilic carcinomas. Statistical analysis revealed significance between poorly differentiated/oxyphilic and papillary carcinomas ($p<0.05$) and between poorly differentiated/oxyphilic and follicular carcinomas ($p<0.01$), whereas difference between papillary and follicular carcinomas was not significant ($p=0.45$).

All patients presented with elevated and rising thyroglobulin levels under TSH-suppression (11 patients) or under TSH-stimulation (4 patients). Recovery testing was within the normal reference range in all patients. One patient was excluded from thyroglobulin analysis, because he presented, in addition to elevated and rising thyroglobulin levels, with increasing thyroglobulin antibodies during follow-up.

We found no significant differences ($p=0.40$) between unstimulated thyroglobulin levels at the time of radioiodine imaging (median 14ng/mL) and $^{68}$Ga-DOTATOC-PET/CT (median 16ng/mL), thus excluding bias due to tumor progress between radioiodine imaging and SSTR imaging.

At the time of $^{68}$Ga-DOTATOC-PET/CT, unstimulated thyroglobulin levels were significantly higher in the group of poorly differentiated/oxyphilic carcinomas (median 211ng/mL, range 32-1000) than in papillary carcinomas (median 0.4ng/mL, range 0.3-19.9), whereas we found no significant differences between poorly differentiated/oxyphilic and follicular carcinomas (median 16ng/mL, range 0.3-299) or between papillary and follicular carcinomas (Fig. 2).

Thyroglobulin levels under TSH-suppressive therapy tended to be higher in patients with positive $^{68}$Ga-DOTATOC-PET/CT (median 36ng/mL, range 0.3-1000) than in patients with
negative $^{68}$Ga-DOTATOC-PET/CT (median 3ng/mL, range 0.3-299), but differences were not significant ($p=0.16$) (Fig. 3).

**Pathological Findings on CT and Ultrasound of the Neck**

On full dose CT, 8 of the 10 tumor lesions detected on $^{68}$Ga-DOTATOC-PET/CT showed a morphologic correlate. But only 2 of these 8 CT lesions could be categorized as pathological on CT alone. In detail, the 2 SSTR-positive lesions with pathological finding on CT presented as local relapse with little contrast enhancement in the thyroid bed (lesion 1) and as mediastinal lymph node that slightly exceeded size criteria but showed no contrast enhancement and could not be clearly differentiated from benign reactive lymphadenopathy (lesion 2). Both lesions were assessed as “not clearly malignant, but needs to be closely monitored”. Considering the remaining 6 PET positive lesions with correlate but no pathological findings on CT, we found 4 SSTR-positive lymph nodes that did not exceed the size criteria to suspect malignancy and 2 lesions in the thyroid bed that could not be differentiated from postoperative changes on CT alone.

The 2 SSTR-positive lesions with pathological finding on CT were found in 2 patients who presented with at least one further $^{68}$Ga-DOTATOC-positive tumor lesion that would not have been characterized as malignant on CT alone. From the other 3 patients with SSTR-positive tumor sites, 1 patient did not show any morphologic correlate on CT. To summarize, in all 5 patients with tumor detection on $^{68}$Ga-DOTATOC-PET/CT, at least one tumor site would not have been identified on CT alone. Moreover, we did not find any suspicious lesions on CT that were $^{68}$Ga-DOTATOC negative.

Ultrasound of the neck did not categorize any of the 10 $^{68}$Ga-DOTATOC positive lesions as malignant. The enlarged lymph node found on CT could not be detected by ultrasound because of its mediastinal location. The local relapse with contrast enhancement on CT was assessed as
postoperative change by ultrasound. The remaining tumor sites identified on $^{68}$Ga-DOTATOC imaging were classified as benign reactive lymph nodes or could not be detected.

**DISCUSSION**

This study demonstrates the capability of $^{68}$Ga-DOTATOC-PET/CT to localize tumor relapse or metastases in DTC patients who were unsuccessfully re-staged before. Thus, we could localize tumor lesions in 5/15 patients who had negative findings on ultrasound, radiiodine imaging and $^{18}$F-FDG-PET/CT. Considering the ineffective preceding imaging effort, a detection rate of 33% is substantially high and emphasizes the diagnostic value of $^{68}$Ga-DOTATOC-PET/CT in iodine and $^{18}$F-FDG negative DTC with elevated and rising thyroglobulin.

Compared with SSTR PET/CT, $^{18}$F-FDG-PET/CT was reported to be more sensitive in detecting tumor lesions in previous studies. Yet, in accordance with our results some lesions were only detected with SSTR PET/CT (20-22). Differences in lesion detection between $^{18}$F-FDG and SSTR PET/CT may be the result of different DTC subtypes being studied:

Binding of SSTR-analogues and in consequence tumor detection rates on SSTR imaging appear to differ between histological subtypes of DTC. In our study, $^{68}$Ga-DOTATOC-PET/CT identified tumor relapse in all patients with poorly differentiated tumors (3 patients) and oxyphilic carcinoma (1 patient). Whereas SSTR scintigraphy was reported to be a promising tool in oxyphilic carcinoma in several studies before (6, 9, 12, 19, 25), reports about SSTR imaging in poorly differentiated thyroid carcinomas are rare (14, 26). Although almost all oxyphilic and poorly differentiated tumors were shown to express SSTR in these studies, $^{18}$F-FDG-PET/CT was superior to SSTR scintigraphy in most cases. Studies having performed more sensitive SSTR PET reported about 2/4 SSTR positive oxyphilic carcinomas (22) or included only papillary and follicular carcinomas (20, 21). In the latter two DTC subtypes, variable proportions of SSTR positive tumors were described before. However, even compared with studies having performed less sensitive scintigraphy (12, 14, 15, 25, 26), the rate of SSTR-positive findings on
\(^{68}\text{Ga-DOTATOC-PET/CT}\) was considerably low in patients with papillary (tumor localized in 1/5 patients) and follicular (no tumor localized in 6 patients) tumors in our cohort. This discrepancy to previous studies may be due to different patient or tumor characteristics; for example, other studies also included iodine positive DTC.

As follicular cells of the thyroid express SSTR, one would expect tumors of follicular origin to express SSTR. Loss of SSTR expression may indicate a lower grade of differentiation as observed in other tumor entities. Yet, it remains unclear whether SSTR expression in DTC is associated with tumor behavior and in consequence patient outcome. Reporting SSTR-expression in both iodine positive and negative DTC as well as in \(^{18}\text{F-FDG positive and negative DTC}\), previous studies revealed no correlation between SSTR expression and differentiation degree of DTC. These observations speak against a flip-flop-phenomenon between SSTR expression and iodine accumulation or \(^{18}\text{F-FDG uptake}\) as suggested by Feine et al. and Rodrigues et al. \((17, 27)\), respectively.

Higher thyroglobulin levels are supposed to enhance detectability of tumors on SSTR imaging. Thyroglobulin levels tended to be higher in patients with positive findings on \(^{68}\text{Ga-DOTATOC-PET/CT}\) than in those with negative findings, but differences were not significant. However, results were different with regard to DTC subtypes: Thyroglobulin levels were significantly higher in the group of poorly differentiated/oxyphilic carcinomas than in papillary tumors. Yet, differences in thyroglobulin levels were not significant between poorly differentiated/oxyphilic carcinomas and follicular carcinomas. Consequently, factors other than the tumor burden affect the detectability on SSTR imaging.

Nonetheless, according to ATA guidelines a \(^{18}\text{F-FDG-PET}\) may be performed if the thyroglobulin level is >10ng/mL. This cutoff-value might not be applicable to SSTR PET as the lowest thyroglobulin value in a patient with confirmed tumor localization on \(^{68}\text{Ga-DOTATOC-PET/CT}\) was 0,3ng/mL. Furthermore, we found a wide range of overlapping thyroglobulin values between patients with positive and negative findings on \(^{68}\text{Ga-DOTATOC-PET/CT}\).
Early detection of tumor relapse on $^{68}$Ga-DOTATOC-PET/CT and in consequence early therapy may prevent the tumor to progress from locally limited to widespread metastatic disease and thus improve patient outcome. In our cohort, 3 of the 5 patients with positive findings on $^{68}$Ga-DOTATOC-PET/CT presented with tumor lesions that all could be removed surgically, in 1 patient local tumor control was obtained by external radiation therapy and in 1 patient mediastinal tumor rendered local therapy impossible. $^{68}$Ga-DOTATOC-PET/CT may be useful also in patients with distant metastases for evaluation of peptide receptor radionuclide therapy, thus offering a systemic treatment option with considerably mild adverse effects in case of SSTR expressing tumors. However, in the patient with mediastinal tumor peptide receptor radionuclide therapy was not performed because of relatively low tumor uptake.

Whereas several studies have shown that $^{18}$F-FDG-PET/CT is superior to morphological imaging like CT in iodine-negative DTC (28-30), studies about that issue have yet not been reported for SSTR PET/CT in DTC. In gastroenteropancreatic neuroendocrine tumors higher sensitivity of SSTR PET/CT compared with CT alone was reported (31). Consistently, CT identified only 2/10 SSTR positive tumor lesions in 2 patients in our study, but in both patients $^{68}$Ga-DOTATOC-PET revealed further tumor sites not detected on CT. Our results confirm the advantage of functional imaging especially in small lymph node metastases and in differentiating local tumor relapse from postoperative changes. However, for achieving better anatomical correlation we recommend to perform full dose CT in PET/CT particularly if surgery is intended.

There are some limitations of this study: First, the sample size was relatively small due to strict inclusion criteria. Thus, our study included only patients who were unsuccessfully re-staged before. In addition, our study was retrospective in nature. Finally, although the detection of tumor relapse on $^{68}$Ga-DOTATOC-PET/CT offered a therapy option, the relevance for patient outcome remains unclear and requires long-term follow-up in usually slowly progressive DTC.
To sum up, $^{68}$Ga-DOTATOC-PET/CT could localize the tumor relapse in 5/15 DTC patients and offered a treatment option in 4/15 patients.

CONCLUSION

$^{68}$Ga-DOTATOC-PET/CT is a promising tool in DTC patients with elevated thyroglobulin and negative radiiodine imaging and should be considered especially in poorly differentiated and oxyphilic subtypes of DTC if $^{18}$F-FDG-PET/CT fails to localize the tumor relapse.

DISCLOSURE

The authors disclose any conflict of interest - financial or otherwise - that may directly or indirectly influence the content of the manuscript submitted.
REFERENCES


FIGURE 1. Patient no 8 (according to Table 1) with an oxyphilic thyroid carcinoma who presented with elevated Tg (32ng/mL). Tumor relapse was detected neither on $^{124}$I-PET/CT (A) nor on ultrasound or on $^{18}$F-FDG-PET/CT (B), whereas $^{68}$Ga-DOTATOC-PET/CT revealed a small tumor lesion on the right side of the neck (C, see arrow). Patient refused surgery at the time of $^{68}$Ga-DOTATOC-PET/CT. Progressive, but still locally limited disease was diagnosed 15 months later (D, see arrow).
FIGURE 2. Serum thyroglobulin (Tg) levels in different subtypes of DTC (pap= papillary carcinoma, foll= follicular carcinoma and pd/ox= poorly differentiated/oxyphilic carcinoma). Statistical significance was found between poorly differentiated/oxyphilic and papillary carcinomas.

The box plot illustrates the 25th and 75th percentile (box), the median (middle bar in the box) and the range (whiskers).
FIGURE 3. Thyroglobulin (Tg) levels in patients with positive and negative findings on $^{68}$Ga-DOTATOC-PET/CT. The box plot illustrates the 25th and 75th percentile (box), the median (middle bar in the box) and the range (whiskers).
TABLE 1: Patient Characteristics and Results of $^{68}$Ga-DOTATOC-PET/CT

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<th>No</th>
<th>Sex*</th>
<th>Age (yrs)</th>
<th>Histology</th>
<th>TNM† (initial)</th>
<th>$^{\sum}$dose $^{131}$I (GBq)</th>
<th>$^{131}$I or $^{124}$I imaging</th>
<th>Tg‡ (ng/ml)</th>
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<td>1</td>
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<td>m</td>
<td>61</td>
<td>follicular</td>
<td>T3 N1</td>
<td>8 $^{131}$I</td>
<td>0.3$^{\S}$</td>
<td>negative</td>
<td></td>
</tr>
</tbody>
</table>

* f=female, m=male  
† TNM: all patients initial M0  
‡ For comparison, thyroglobulin (Tg) levels under TSH-suppression are given at the time of $^{68}$Ga-DOTATOC-PET/CT.  
§ The Tg values were borderline under TSH-suppression, but elevated and rising under TSH-stimulation.  
# The patient was excluded from Tg analysis, because he presented, in addition to elevated and rising Tg-levels, with increasing Tg antibodies (TgAb) during follow-up.
68Ga-DOTATOC-PET/CT in patients with iodine- and 18F-FDG-negative differentiated thyroid carcinoma and elevated serum thyroglobulin

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J Nucl Med.
Published online: March 31, 2016.
Doi: 10.2967/jnumed.115.171942

This article and updated information are available at:
http://jnm.snmjournals.org/content/early/2016/03/30/jnumed.115.171942

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The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

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