99mTc-EDDA/HYNIC-Tyr(3)-octreotide for staging and follow-up of patients with neuroendocrine gastro-entero-pancreatic tumors

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Aim. To evaluate the use of 99mTc-EDDA-hydrazinonicotinyl-Tyr3-octreotide (Tc-TOC) for staging and follow-up of neuroendocrine gastro-entero-pancreatic (GEP) tumors with special focus on the acquisition protocol including single photon emission computed tomography (SPECT).

Methods. Eighty-eight patients (37 female, 51 male; age range: 16 to 81 years; mean age: 56.3 years) were studied: 42 patients for staging after initial histological confirmation and 46 patients during post-therapy follow-up. An average activity of 400 MBq of the radiopharmaceutical was injected. All tumors originated from neuroendocrine tissue of the gastroenteropancreatic tract. Whole body scintigrams at 4 h postinjection and SPECT of the abdomen were obtained in all patients. Additional planar images of the abdomen were acquired at 2 h after injection in 68 patients.

Results. The Tc-TOC scan result was true-positive in 56 patients, true-negative in 17, false-negative in 14, and false-positive in 1 patient. The false-positive finding was caused by a colonic adenoma. Overall, a scan sensitivity of 80% (56/70 patients), specificity of 94.4% (17/18 patients) and accuracy of 82.9% (73/88 patients) were calculated on patient basis. In total, Tc-TOC detected 357 foci in 69 patients. In 7 patients equivocal findings were observed in the bowel at 4 h postinjection without corresponding tracer uptake in the scan 2 h earlier, meaning that these abnormal findings were correctly classified as non-malignant. In addition to planar views, SPECT revealed further 62 lesions.

Conclusion. Tc-TOC with one-day, dual-time acquisition protocol is an accurate staging procedure in patients with neuroendocrine GEP tumors. SPECT shows high sensitivity for detection of abdominal lesions, while earlier images improve the reliability of abnormal abdominal findings.

KEY WORDS: Technetium-99m – Tyrosine(3)-octreotide – Scintigraphy – Neuroendocrine gastroenteropancreatic neoplasms.

Any publications describe the value of somatostatin receptor (SSTR) scintigraphy for detection of neuroendocrine gastro-entero-pancreatic (GEP) tumors and their metastases as well as for patient management. To date, SSTR scintigraphy with 111In-DTPA-D-Phe1-Octreotide (OctreоСcan, Mallinckrodt; Medical, Petten, The Netherlands; In-Oct) is considered one of the standard procedures for staging and evaluating treatment efficacy, since neuroendocrine GEP tumors contain high-affinity binding sites for somatostatin and their analogs. However, the high costs of the 111In-label and the two-day acquisition protocol create a need for improved radiopharmaceuticals.

Recently, the clinical efficacy of 99mTc-EDDA-hydrazinonicotinyl-Tyr3-octreotide (Tc-TOC) was compa-
red with that of In-Oct in a series of patients, who were very heterogeneous in terms of underlying pathology. The results showed that sensitivity when using Tc-TOC for the detection of tumor sites is similar. The clinical results were confirmed by semi-quantitative evaluation showing higher tumor-to-organ ratios for the technetium labeled compound. However, many patient studies showed a matching pattern of uptake assuming that both tracers have a similar binding behavior for SST receptors used to image subtypes 2 and 5. The high clinical value is based on the advantages of technetium labeling since the physical characteristics of this isotope are more adapted to the energy detection ability of gamma cameras and gamma probes. A higher dosage can be administered, thus producing better image quality at lower radiation burden and the pharmacokinetics of the radiolabelled peptide provides faster tumor visualization (one-day imaging protocol). However, more false-positive findings were observed in the abdomen with Tc-TOC as compared to In-Oct for a single acquisition with imaging at 4 h after injection.

The aim of this study was to evaluate the efficacy of scintigraphy using Tc-TOC for initial staging and follow-up in patients with neuroendocrine GEP tumors. The Tc-TOC results were compared with other imaging procedures and further course of disease. Attention was especially focused on the acquisition protocol, with imaging at 2 h and 4 h after injection, and on the use of single photon emission computed tomography (SPECT).

### Materials and methods

#### Patients

Eighty-eight patients (51 males, 37 females; age range: 16 to 81 years; mean age ±SD, 56.3 ±14.6 years) with neuroendocrine GEP tumors were studied. Forty-two patients underwent SSTR scintigraphy for initial staging during first admission, whereas 46 patients were studied during post-therapy follow-up. All tumors originated from neuroendocrine tissue of the gastrointestinal tract: stomach (n=8), pancreas (n=29), small bowel (n=34), liver metastases from unknown primary (n=6), rectum (n=4), appendix (n=3), colon (n=2), cecum (n=1) and the papilla vateri (n=1), (Table I). Definitive diagnosis of GEP tumors was established on the basis of specific biological symptoms and secretion pattern, when present, and by histopathology and immunohistochemical analysis. Overall, 59 patients with clinical and biochemical signs of secreting tumors and 29 patients with non-functional GEP tumors were included.

In patients referred for restaging during follow-up (n=46) various therapeutic procedures were performed prior to scintigraphy. Most patients were treated by surgery (n=38), alone (n=6) or in combination with drug therapy (n=32): 27 patients received chemotherapy, 8 cold somatostatin analogs and 5 both modalities. Eighteen patients were consecutively treated with 90-yttrium labelled or 177-lutetium-labelled somatostatin analogs if lesions showed enhanced tracer accumulation and were refractory to conventional strategies. The patients were followed over a minimum of 6 months, during which further localization procedures were performed to confirm or refute the additional tumor sites found by scintigraphy.

Administration of Tc-TOC to patients was approved by the Ethics Committee of the Innsbruck Medical University. All patients gave written informed consent before scintigraphy.

#### Radiopharmaceutical and imaging

Tc-TOC was prepared using a kit formulation as recently described, showing a radiochemical purity of >95%. Each patient received an average activity of 400 MBq i.v. of the radiopharmaceutical. Whole-body imaging was performed with a double-headed camera (Elscint HELIX, Haifa, Israel). For the 99mTc whole-body studies the camera was equipped with a low-energy all-purpose parallel-hole collimator, window
setting 140 keV, width 10%. Whole-body scintigrams were obtained at 4 h postinjection in all patients, and earlier images, at 2 h postinjection, in 68 patients. In the remaining 20 patients earlier imaging was not performed because of the poor patient conditions in 6 patients, of technical reason in 5 patients and 9 patients were late for their schedule and could only be imaged 4 h postinjection. For SPECT acquisition, the same double-headed gamma camera was used. Acquisition parameters were: 60 projections, 25 s/projection, matrix: 64×64, zoom: 1. For SPECT analysis raw data were transferred to a HERMES system (Nuclear Diagnostics, London, UK) and filtered (Wiener filter) before reconstruction. SPECT of the abdomen was performed in all patients, of the chest in 61 patients and of the head in 12 patients. Whole-body views and SPECT images were interpreted by two nuclear medicine physicians.

**Image and data analysis**

Any focal tracer accumulation exceeding normal regional tracer uptake was rated a pathological finding (tumor uptake). Linear, non-focal limited intestinal uptake with moderate intensity was rated an equivocal finding. Patients with liver metastases were initially classified in two groups: patients with resectable metastases, and patients with non-resectable metastases considering that patients with limited liver disease without other tumor lesions might have a better prognosis after resection. All patients had undergone at least 2 of 3 CI modalities (CT, MR and ultrasound). A positive CI diagnosis was based on specific appearance of malignant disease derived from neuroendocrine tumors as described elsewhere.\(^1^6\) Additionally, it was evaluated if the scan result has an impact on patient management, meaning that unexpected scintigraphic findings, initially not detected by conventional imaging methods, influenced further therapeutic decision.

**Statistical analysis**

Tc-TOC planar and SPECT images were classified as true-positive (TP), true-negative (TN), false-positive (FP), or false-negative (FN) according to the gold standard (histopathology or other imaging procedures during follow-up after scan), as described above. The sensitivity, specificity and accuracy of the detection of tumor lesions were calculated on this basis. The \(\chi^2\) test for independence was used to evaluate differences when subgroups of the patients being investigated were statistically compared (staging versus follow-up, and patients with secreting versus non-secreting tumors). The results were considered significant when \(P<0.05\) was estimated.

**Results**

Primary tumors were correctly identified with Tc-TOC in 23 patients; in 13 cases the tumor was located in the pancreas, in 7 cases in the small bowel, in 2 cases in the stomach and in 1 case in the rectum. In 6 patients residual tumor tissue was identified at the site of the resected primary tumor; in 5 cases in the pancreas and in 1 case in the jejunum. Tumor recurrence was missed in the pancreas in 1 case. Thirteen tumor sites of primary or recurrent tumors were detected by SPECT, but were missed in the whole-body planar images.

The scan result was TP in 56 patients (63.6%), TN in 17 (19.3%), FN in 14 (15.9%) and FP in 1 case (1.1%). Overall, a sensitivity of 80% (56/70 patients), specificity of 94.4% (17/18 patients) and accuracy of 82.9% (73/88 patients) were calculated on patient basis. Tc-TOC studies detected 357 abnormal findings in 69 patients, of which 356 were TP and one was FP. This finding was caused by a benign colonic adenoma as confirmed by surgery. Eighty-four lesions in 14 patients were FN; the summarized results on lesion basis are shown in Table II. Final diagnosis of the lesions was based on contemporaneous imaging modalities or follow-up controls (n=77), histopathology (n=19) and surgical exploration (n=12).

In the group of patients referred for initial staging (n=42) the scan result was TP in 31 patients, TN in 1 case after successful surgical removal of a gastric carcinoid during primary intervention, FP in 1 case and FN in 9 cases. In the second group, in which patients were investigated after therapy during follow-up (n=46), the scan result was TP in 25 patients, TN in 16 patients and FN in 5 cases. No statistically significant difference was observed between the two groups (P=0.18), as illustrated in Table III.

Patients were further categorized in 2 groups in order to evaluate the influence of functional status on detectability with Tc-TOC: those with clinical and biochemical signs of secreting tumors (n=59) and the...
se without such features (n=29). No statistically significant difference was observed when comparing both groups with a P-value of 0.34.

**Acquisition at 2 h and 4 h after injection**

Despite rapid background clearance and low hepatobiliary excretion, some non-specific accumulation in the bowel can lead to false-positive interpretation with Tc-TOC when a single-acquisition protocol is used. Adequate bowel preparation, which can be advantageous for investigations with In-Oct, does not improve accuracy of the 99mTc-studies because of the short time range available between tracer application and scanning. Thus, additional whole-body views at 2 h after injection were obtained in 68 patients (Figure 1). In 7 cases equivocal findings were found in the 4 h images, but without correlative tracer uptake in the earlier scan. These findings were classified as non-malignant, assuming unspecific tracer uptake in the bowel. Further clinical data showed no evidence of disease in these patients. Increased tracer accumulation in late images was also found in 8 patients, projecting into liver segment IV where the gallbladder is located (Figure 2). Since the earlier images were negative, these studies were also classified as non-malignant. Earlier images were not available in 3 patients showing equivocal findings in the bowel. After careful evaluation of the 4 h images by 3 experienced nuclear medicine physicians these findings were also classified as non-malignant, which was confirmed by follow-up data.

**Table II.—Scintigraphic findings with 99mTc-TOC revealed by SPECT and whole-body scans; analysis per lesion and comparison with other imaging modalities, histopathology and follow-up data, i.e. the gold standard.**

<table>
<thead>
<tr>
<th></th>
<th>Localized liver lesions</th>
<th>Extensive liver lesions</th>
<th>Upper abdomen</th>
<th>Lower abdomen</th>
<th>Chest</th>
<th>Bone</th>
<th>Other*</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT (no. of patients)</td>
<td>10 (9)</td>
<td>202 (37)</td>
<td>75 (44)</td>
<td>24 (12)</td>
<td>19 (8)</td>
<td>25 (5)</td>
<td>2 (2)</td>
<td>357</td>
</tr>
<tr>
<td>WB scans (no. of patients)</td>
<td>8 (7)</td>
<td>184 (37)</td>
<td>38 (24)</td>
<td>24 (12)</td>
<td>19 (8)</td>
<td>20 (5)</td>
<td>2 (2)</td>
<td>295</td>
</tr>
<tr>
<td>Gold standard (no. of patients)</td>
<td>10 (9)</td>
<td>263 (46)</td>
<td>92 (50)</td>
<td>25 (13)</td>
<td>25 (10)</td>
<td>25 (5)</td>
<td>2 (2)</td>
<td>440</td>
</tr>
</tbody>
</table>

**Table III.—99mTc-TOC: staging versus follow-up.**

<table>
<thead>
<tr>
<th></th>
<th>Staging (no. of patients)</th>
<th>Follow-up (no. of patients)</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>77.5% (31/41)</td>
<td>83.3% (25/30)</td>
</tr>
<tr>
<td>Specificity</td>
<td>50% (1/2)</td>
<td>100% (16/16)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>76.1% (32/42)</td>
<td>89.1% (41/46)</td>
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</table>

**Whole-body imaging versus SPECT**

From the clinical point of view SPECT was superior for localizing pathological sites in the abdomen as compared to whole-body planar views, i.e. further 62 lesions were detected with SPECT that were not seen in the whole-body images (Figure 3). The difference in detection rate between whole-body planar images and SPECT was predominant in the upper abdomen. In this area SPECT detected 37 additional lesions in 20 patients. Overall, 62 lesions were additionally detected with SPECT, but were missed in the whole-body scans, so that sensitivity increased from 66.8% for whole-body scans to 80.9% for SPECT on lesion basis. The difference on patient basis is shown in Table IV.

**Impact on clinical management**

Additional scintigraphic findings prompted changes to be made in clinical management in 11 of the 88 patients (9.6%) not initially detected by conventional imaging techniques. In one patient who was investigated with CT of the chest and abdomen after successful therapy of a glucagonoma Tc-TOC imaging revealed a lesion in the head. This lesion turned out to be a meningeoma that was surgically removed, but there was no evidence of disease recurrence with regard to the GEP tumor. In 2 patients unnecessary surgical treatment was avoided by detecting previously unknown systemic tumor spread to the bone not detected by CT. Chemotherapy was administered instead of surgery in both cases as well as in 3 other cases, where recurrence of disease that was not accessible to surgery was detected. These lesions could not be discriminated from scar tissue after surgery by CT and ultrasound. Surgical treatment was performed or modified in 5 patients following positive scan result. A solitary metastasis of the liver was detected in 2 patients initially missed by CT (Figure 4). Recurrent tumor growth was also observed in 2 patients (in one
beside the initial diagnosis of neuroendocrine GEP tumors in the case of clinical or biochemical suspi-
SSTR scintigraphy is also an important clinical tool for staging and restaging during follow-up after histological confirmation. The results of our evaluation for this indication with an overall sensitivity of 80% confirm that Tc-TOC enables accurate diagnostic imaging of neuroendocrine GEP tumors when comparing it with results of the OctreoScan. Additionally, the positive scan result provided the basis for therapy with radiolabelled SST-analogs in 18 patients, since the scans have demonstrated useful activity in tumor lesions. Promising results have recently been obtained using the same technetium-labeled somatostatin analog, Tc-TOC, in patients with a variety of tumor entities. Although many of these presented with tumors in the chest showing good image results, we feel that an optimized acquisition protocol should be used to obtain the best results in the abdomen, where higher unspecific background activity can be expected. In this area lesions of neuroendocrine GEP tumors are common findings. The results of our investigation underline that a protocol including imaging at different times is very helpful in distinguishing malignant from non-malignant abnormal findings in the abdomen, as was shown in 7 patients when using a dual-time imaging protocol. The highest tumor-to-background ratio can be observed at 4 h postinjection, but earlier imaging provides sufficient specific uptake to clearly identify SSTR-positive tumors. In 8 patients enhanced uptake was also found in the gallbladder, which may present a pitfall, even with SPECT. SPECT/CT fused images are able to provide additional anatomical information that improves the accuracy of SPECT interpretation to define the focal uptake in the area overlapping the gallbladder. But without image fusion the different pattern of uptake, when comparing 2 h and 4 h images, can also be used to discriminate non-malignant from malignant disease.

Figure 4.—This 54-year-old patient was investigated because of increasing tumor marker. Tc-TOC detected a solitary liver metastasis, as confirmed by contrast-enhanced CT (A). SPECT clearly delineated the small hepatic lesion (B-D), see arrow, which was consecutively resected.
Despite a higher tumor-to-background ratio for liver metastases as compared to In-Oct, 61 liver lesions escaped detection in 9 patients. Widespread metastatic liver disease is sometimes difficult to identify, which might be related to almost equal uptake in tumor and liver tissue in some patients with reduced tumor-to-organ contrast. However, in the case of limited metastatic liver disease Tc-TOC performed very well, i.e. 10 lesions in 9 patients were identified, which gave in a sensitivity of 100% in this category. Dedicated spiral CT was found to be superior to SSTR scintigraphy for the detection of liver metastases from neuroendocrine GEP tumors. Our results show that at present Tc-TOC cannot be recommended alone for the exclusion of hepatic metastases, but that positive findings can be used to confirm abnormalities detected by radiological techniques as being metastatic in origin, which supports the importance of combined imaging in detecting liver metastases from GEP tumors.

It has been shown that SPECT significantly improves the sensitivity of SSTR scintigraphy, which agrees with the results of our investigation. In particular, SPECT proved valuable in the upper abdomen, i.e. 37 further lesions not seen in the whole-body scans were detected in 20 patients, so that abdominal SPECT is generally recommended.

Whole-body screening also seems very important for the early detection of distant metastases. In this setting SSTR scintigraphy proves valuable in determining the resectability of disease and allows scanning of a larger volume than is possible with computed tomography without additional radiation dose. In this study population, 24 previously unknown distant metastases from GEP tumors were detected in 17 patients, meaning that unnecessary surgical treatment could be avoided in 2 patients. But if surgery is considered the intervention can be improved by the use of intraoperative gamma probes. Tc-TOC might be useful for this procedure with regard to physical characteristics and availability of the isotope. In this context it should be mentioned, that the radiation burden of the Tc-label is considerably lower as compared to the In-label, meaning that higher activities of Tc-TOC can be administered for imaging purpose.

Further improvement in the diagnosis of neuroendocrine tumors might be obtained with PET. However, Tc-TOC with a one-day acquisition protocol, as shown in this larger series of patients, is a reliable and cost-effective procedure for clinical routine, because 99mTc labelling reduces costs and improves availability.

The retrospective analysis performed in this study suffers from some limitations (lacking intrapatient comparison with other SSTR derivatives, no full pathological confirmation in all cases), so that further studies are warranted to confirm the value of Tc-TOC in comparison to other tracers for SSTR imaging in neuroendocrine GEP tumors.

Conclusions

Tc-TOC with one-day, dual-time acquisition protocol offers high diagnostic quality for SSTR scintigraphy. Whole-body images display lesions of neuroendocrine tumors in different body regions with high accuracy. SPECT shows additional value, especially for detection of abdominal lesions, whereas earlier planar images are necessary to improve the reliability of abnormal abdominal findings. Therefore, an acquisition protocol including acquisitions at 2 h and 4 h postinjection and abdominal SPECT is generally recommended for staging of neuroendocrine tumors.

References


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