Surgical management of pancreatic neuroendocrine tumors
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CHAPTER 7

The additional value of somatostatin receptor scintigraphy during preoperative staging in patients with non-functioning pancreatic neuroendocrine tumors.

A clinical guidance

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ABSTRACT

Purpose: Patients with non-functioning pancreatic neuroendocrine tumors (NF-pNET) are staged with both computed tomography-scan (CT-scan) and somatostatin receptor scintigraphy (SRS). Aim was to determine the additional value of the SRS during pre-operative staging as second test after CT-scan.

Methods: All SRSs made between 2002-2013 were selected. Patients with NF-pNET were included if both CT-scan/SRS were performed during pre-operative staging. Diagnostic accuracy of CT-scan and SRS were analyzed for both detection of the primary NF-pNET as well as metastases. Altered TNM classification and changed clinical management were calculated. Changed management was defined as a change from surgical resection into palliative treatment or vice versa.

Results: Overall, 62 patients with NF-pNET were included with a mean age of 57yr. Sensitivity to detect the primary tumor with CT-scan or SRS were resp. 95 and 73%. Sensitivity and specificity for CT-scan and SRS in detection of metastases were resp. 85%-80% and 85%-90%. In 28 patients (45%), the outcome of both CT-scan and SRS was comparable. In 34 patients (55%) the outcome was not comparable between CT-scan and SRS. TNM classification altered in 14 patients (23%) after SRS and management changed in 9 patients (15%) after SRS. In patients without metastases on CT scan, SRS detected lymph node metastases in one patient.

Conclusion: In patients with NF-pNET without suspicious metastatic lesions on CT scan, the SRS has limited value. Additional SRS is indicated to detect the primary tumor, confirm suspicious lesions for NET-metastases or to image the extent of the disease in already proven metastatic patients.
INTRODUCTION

During pre-operative staging in non-functioning pancreatic neuroendocrine tumors (NF-pNET), often both standard abdominal imaging as well as nuclear imaging is performed. Almost 1-2% of all pancreatic malignancies appear to have pNET. Some NF-pNET are detected incidentally due to routine screening for other disease or in patients with atypical abdominal pain. In the diagnostic algorithm of the European Neuroendocrine Tumor Society (ENETS), a somatostatin receptor scintigraphy (SRS) has been advised after computed tomography (CT scan) or magnetic resonance imaging (MRI). However, given the high diagnostic accuracy of the CT and MRI, the additional value of SRS may be debatable in patients with resectable disease on CT/MRI during preoperative staging.

During pre-operative staging, a CT scan is performed for several reasons; first to diagnose and locate the primary lesion in the pancreas, second to find distant metastases in the abdomen and third to assess resectability of the tumor. The CT scan has a sensitivity and specificity of resp. 73% and 96% for diagnosing pNET and a sensitivity and specificity of resp. 82% and 92% for detecting liver metastases.

Compared to pancreatic adenocarcinoma, NF-pNET has a high incidence and density of somatostatin receptors on their tumor surface and these receptors can be made visible by a SRS. A radiolabeled peptide binds with varying affinity to these receptors. In patients with NF-pNET, the SRS is used for detection and localization of the primary lesion and possible metastases. Furthermore, the SRS is used for staging, follow-up and for the selection of metastatic patients for peptide receptor radionuclide therapy (PRRT). The combination of SRS and conventional CT scan attained the highest diagnostic accuracy. However, the time burden in hospital for SRS is considerable for patients since SRS is made 24 and 48h after injection of the radiopharmaceutical and patients therefore have to make multiple visits to the hospital.

The aim of this study was to investigate whether all patients with NF-pNET benefit from a routine additional SRS in the pre-operative staging after initial imaging with CT. Benefit is defined as a changed management due to the SRS.
METHODS

Patient selection
SRS from the period between January 2002 and July 2013 made in the Academic Medical Center of Amsterdam (AMC) were selected. All included patients have been presented to our hospital for preoperative staging without any NET related treatment procedures before. The inclusion criteria were
- Definitive diagnosis of non-functioning pancreatic neuroendocrine tumors
- Radiologic imaging is made during pre-operative staging
- Radiologic imaging included both CT-scan and SRS

Functional pNET were excluded from the analysis because staging of functional pNET differs from staging of non-functioning pNET. Diameter of the NF-pNET was measured on radiologic imaging on CT-scan. If the CT scan was negative for the primary tumor, the tumor diameter of the endoscopic ultrasound was used. If the primary tumor was not visible on radiologic imaging, tumor size was measured in the resected specimen.

CT abdomen
In all patients a spiral CT abdomen was performed according to standard guidelines for pNET and assessed or revised by an experienced abdominal radiologist at the AMC. A Philips Brilliance 64 CT scan was made during inspiration position, with IV-contrast, 130ml Ultravist 300, 3,5 ml/sec, 64 slices and reconstructed with an imaging thickness of 2mm and 3mm.

Somatostatin receptor scintigraphy
All SRS’s were performed in the AMC and analyzed by an experienced nuclear medicine physician. In this study, the In-111-(DTPA-Phe) Octreotide (Octreoscan) was used in combination with whole body scintigraphy and whole body single-photon emission computed tomography (SPECT). The patients were injected with a median dose of 200MBq In-111-(DTPA-Phe) Octreotide. After injection of the radiopharmaceutical, the first whole body SRS was performed after 24 hours and, if necessary due to mimic pathological uptake in the gut, repeated after 48 hours, using a gamma camera (Siemens Symbia-T16), 1024 x 256 matrix, 10cm/min. Medium-energy all-purpose collimators were used with 20% energy peaks of 171-245 keV. SPECT (128x128 matrix, 30 frames, 40 seconds per frame) was performed with low-dose CT for attenuation correction and anatomical correlation.

Diagnostic accuracy
The gold standard to prove the primary tumor or metastasis was by biopsy/resection or long-term follow-up. First outcome was the detection of the primary NF-pNET and the second outcome was the detection of metastases. Specificity measured the proportion of patients without pNET but all the included patients are diagnosed with pNET. Therefore, in the detection of the primary tumor, only the sensitivity could be calculated. The diagnostic accuracy of CT-scan and SRS for detection of the primary tumor or metastases was separately compared
with the gold standard. CT scan was scored as positive if a pancreatic lesion was visible in at least one phase or if suspicious metastatic lesions were seen in which additional imaging or biopsy was required. SRS was scored as positive if there was pathological uptake was seen in the pancreas or in other suspicious lesions outside the pancreas. The European Neuroendocrine Tumor Society (ENETS) TNM classification was used. A distinction was made between an altered TNM classification and a changed clinical management. In patients with an altered TNM classification, the T, N or M stage was altered due to additional finding or suspicious lesions were not confirmed on SRS. The definition for a changed clinical management for patients was a change from surgical resection into palliative treatment or vice versa.

Statistical Analysis
IBM SPSS Statistics, version 20.0. (IBM Corp., Armonk, NY, United States) was used for statistical analysis. Continuous data were presented, dependent on their distribution, as mean and standard deviation (SD) or as median and range. Categorical data are presented as the absolute number and percentage. Data were analyzed according the chi-square test or student T-test, based on the different outcome variables. A P value of < 0.05 was considered to be statistically significant. The study has been approved by the Medical Ethics Review Committee.

RESULTS
A total of 741 patients who underwent SRS were analyzed. Only patients with pNET were selected and therefore 669 patients were excluded. In addition, 10 patients were excluded, 4 patients because radiological imaging was incomplete and 6 patients because of a functioning pNET. Finally, 62 patients were included in the study. Fifty eight CT scans (94%) were made or re-evaluated by an experienced abdomen radiologist in the medical center. The remaining 4 CT scans (6%) were performed in another hospital and only the CT report was available. The number of included patients was equally divided during the study period.

<table>
<thead>
<tr>
<th>Number of patients, n</th>
<th>62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)¹</td>
<td>56.9 (12.4)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>37 (60)</td>
</tr>
<tr>
<td>Tumor size in mm, median (range)</td>
<td>28 (5-180)</td>
</tr>
<tr>
<td>Final diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Resectable disease</td>
<td>38 (61)</td>
</tr>
<tr>
<td>Resectable disease but conservative treated</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Locally unresectable without metastases</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Tumor grading of resected patients ²</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>19 (54)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>14 (40)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

¹ Standard deviation. ² Tumor grading was missing in 3 patients.

Table 1. Baseline characteristics of patients with non-functioning pancreatic neuroendocrine tumor
Final diagnosis

In 53 patients (85%), the diagnosis of the primary tumor was confirmed by biopsy or pathology result of the resected specimen. The other 9 patients had their diagnosis based on radiological imaging and long-term follow-up, with a median follow-up of 34 months (IQR: 24-50). Metastatic disease was proven with histological or cytological biopsy in 71% of the patients. In 29% metastatic disease was proven by repeated visualization and increase in size and number of metastatic lesions on radiological imaging during long-term follow-up. The baseline characteristics of the included patients were listed in table 1. All patients (n=38) with resectable disease were treated by surgery. Reasons for a conservative treatment were either a small NF-pNET with a median tumor size of 13 mm (range: 8-20mm) in 5 patients or high co-morbidity in 2 patients.

Detection of primary tumor at diagnosis

The primary tumor could be detected by CT scan in all tumors except one. In comparison, SRS did not detect the primary tumor in 17 patients (27%). The sensitivity of CT-scan and SRS were respectively 95% and 73% for detection of the primary tumor. Not detected NF-pNET on SRS were significant smaller (median size of 23 mm; IQR 9-30) compared with the detected NF-pNET (median size 36 mm; IQR 22-60) P< 0.01.

Diagnostic accuracy of the detection of metastatic disease

In total, 13 patients had metastases, 12 patients had metastatic disease (M1) and 1 patient had a metastatic lymph node (N1). Of these 13 patients, 11 patients were detected on CT scan and 11 patients were detected on SRS. In 1 patient, metastatic disease was missed on both CT and SRS. In 1 patient (2%), a metastatic lymph node was missed by CT scan but detected by SRS and this metastatic lymph node was located in the resected specimen.

The CT scan was true positive in 11 patients, true negative in 39 patients, false positive in 10 patients and false negative in 2 patients. In the patients with a false negative test result, a liver metastases (M1) was missed in one patient and the second patient had a missed metastatic lymph node in the resected specimen. False positive (suspicious) lesions were observed in the liver (n=6), lymph nodes (n=2), adrenal (n=1) and peritoneal lesions (n=1). The SRS was true positive in 11 patients, true negative in 44 patients, false positive in 5 patients and false negative in 2 patients. In the 2 patients with a false negative SRS, lesions were missed in the appendix (n=1) and liver (n=1) and in the 5 patients with a false positive SRS, lesions were observed in the liver (n=2), lung (n=1), adrenal (n=1) and supraclavicular lymph node (n=1). The diagnostic accuracy of detection of metastatic disease for the two different imaging modalities is listed in table 2. The positive predictive value of both imaging modalities was moderate due to the patients with a false positive scan. In these patients, additional imaging was required. The negative predictive value was high for both modalities.
Table 2. Diagnostic accuracy of the detection of metastatic lesions during pre-operative staging

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity metastases</th>
<th>Specificity metastases</th>
<th>Positive predictive value metastases</th>
<th>Negative predictive value metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT scan</td>
<td>85%</td>
<td>80%</td>
<td>52%</td>
<td>95%</td>
</tr>
<tr>
<td>SRS</td>
<td>85%</td>
<td>90%</td>
<td>69%</td>
<td>96%</td>
</tr>
</tbody>
</table>

1 Somatostatin Receptor Scintigraphy

Additional value of the SRS after CT scan

In the detection of both primary tumor as metastases, CT scan and SRS were both true positive in 28 patients (45%). Of these 28 patients, 24 patients (39%) were diagnosed with only a primary NF-pNET and 4 patients (7%) had metastatic disease. In 34 patients (55%), the outcome between the CT scan and SRS was not comparable, see table 3. In 20 patients (32%), SRS was incorrect, mostly because SRS was false negative in the detection of the primary tumor in 17 patients. In the other 3 patients, SRS was false negative in 1 patient with metastatic disease and false positive in 2 patients.

In 14 patients (23%), the TNM has been altered by the SRS and in 9 patients (15%) clinical management changed after SRS, see table 3. In 1 patient (7%), the T classification changed from Tx to T2. On the CT scan, a dubious lesion was seen in the pancreatic head, but SRS showed pathological uptake in the pancreas. In 1 patient (7%), the N classification changed from N0 to N1. However, the treatment did not change since the extra lymph node was located in the resected specimen. In 9 patients (64%) the M classification changed from Mx to M0. All these 9 patients had lesions in the liver on CT scan, suspected for NET metastases, cyst, haemangioma or another differential diagnosis. The lesions were not confirmed as NET metastases on the SRS and therefore in these 9 patients (15%), management changed from potential palliative to curative surgical resection (Mx to M0). In 3 patients (21%), the M classification changed from M1 to M1+. Instead of single liver metastases, multiple bone metastases (n=1), lung metastases (n=1) and extended lymph node metastases in the mesentery (n=1) were detected. These extra findings resulted in a modified palliative treatment.
DISCUSSION

This study focused on the pre-operative staging in NF-pNET patients. CT scan is a reliable choice in detection of the primary tumor in patients with a NF-pNET with a sensitivity of 95%. The sensitivity of SRS in detection of the primary NF-pNET was 73% and the accuracy decreased in small tumors. In 23% of the patients, TNM classification has been altered after SRS due to additional findings or because suspicious lesions were not confirmed and in 15% of the patients management changed after SRS.

In our study, 45% of all the patients had comparable results on both CT scan and SRS. In these patients, SRS had no additional value. In patients without distant metastases (M0) on CT scan, no additional distant metastases were detected with SRS. In one patient, an extra lymph node was found, but this malignant lymph node was located in the resection specimen and therefore did not affect the therapeutic plan. Based on the results of this study, SRS may be omitted in patients with a primary NF-pNET without distant metastases on CT scan. The contribution of the SRS in these patients was minimal while the time burden was substantial and additional costs were made due to the extra scans and hospital visits.

In 23% of all the patients, SRS had an additional value after a CT scan. This is coherent with the literature, which described a changed TNM classification of 14-47% 7,10,11. In patients with suspicious metastatic lesions suspicious on the CT scan, SRS did not confirm these lesions. In these patients (15%), management changed from potential palliative to curative surgical resection (Mx to M0) by the additional SRS. Additional investigation was necessary in these patients and SRS was a good choice since SRS was truly negative in almost all these patients. Moreover, if suspicious metastatic lesions were octreotide positive, this may have consequences for adjuvant or palliative treatment such as peptide receptor radionuclide therapy 10.
### Table 3. Patients with a different outcome between CT scan and Somatostatin Receptor Scan

<table>
<thead>
<tr>
<th>Additional Value SRS</th>
<th>N = 14</th>
<th>Changed management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Correct outcome SRS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>True positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detection primary tumor (Tx to T1)</td>
<td>1 (7)</td>
<td>No</td>
</tr>
<tr>
<td>Detection NET lymph node (N0 to N1)</td>
<td>1 (7)</td>
<td>No</td>
</tr>
<tr>
<td>Detection extensive metastatic disease (M1 to M1+)</td>
<td>3 (21)</td>
<td>No</td>
</tr>
<tr>
<td><strong>True Negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspicious metastatic lesions not confirmed (Mx to M0)</td>
<td>9 (64)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

In our study, sensitivity and specificity for the detection of metastases on CT scan were resp. 85% and 80%. These results were comparable with the sensitivity and specificity in the literature, respectively 66-100% and 80-98% [12-14]. A strength of this study is the strict inclusion criteria, only non-functional pNET were included. Other studies included different origins of neuroendocrine tumors, both functional and non-functional pNET and/or the numbers of included NF-pNET was often limited.

Besides Octreoscan, the gallium-68 labelled somatostatin analogues (ex.DOTA-d-Phe¹-Tyr³-octreotide (DOTATOC)) positron emission tomography (⁶⁸Ga PET) scan can be used during the pre-operative staging[1]. This relatively new technology has several advantages compared to Octreoscan. First, the ⁶⁸Galium labelled ligand showed a higher affinity for the somatostatin receptor, resulting in a higher tumor uptake[15]. Secondly, the ⁶⁸Ga-DOTATOC PET can be performed on the same day as the tracer injection. Finally, the ⁶⁸Ga-DOTATOC PET is better in the detection of small NET lesions[16,17] with a sensitivity between the 81-97% and a specificity between 90-100%[18-22]. Consequently, the ⁶⁸Ga-DOTATOC PET seems more promising than the Octreoscan[19]. Downside of this new technique may be the false positive rates of lesions in the pancreatic head area. The additional value of the ⁶⁸Ga-DOTATOC PET in staging non-metastatic NF-pNET is unclear and its effectiveness has to be demonstrated. Furthermore, the suggested diagnostic algorithm of the ENETS, the hepatocyte-specific MRI is also indicated in the detection of suspected lesions[1,23]. For the future, it is interesting which modality has the most additional value in non-metastatic NF-pNET, the ⁶⁸Ga-DOTATOC PET or the hepatocyte-specific MRI during preoperative staging.

A limitation of this study is its retrospective origin. In 6% of the included patients only had a CT report available. Furthermore, not all the CT scans were made in our center and during the 11 year study period, different types of CT scans have been used. CT scan characteristics
such as thickness of the slices or type of IV contrast may not be performed according to our standard pancreas protocol and this protocol changed over the years. However, in daily practice, the CT scan will not be remade if the CT scan is recent and of sufficient quality. Also the quality of the CT scan has become better during the study period. In addition, this study introduced a selection bias by selecting all patients with a CT scan and SRS, the diagnostic accuracy of the CT scan for the primary tumor was skewed. In general, patients will more often undergo SRS if a (dubious) lesion was seen on the CT scan. This results in a high sensitivity in the detection of the primary tumor on CT scan. It was beyond this study to investigate the role of the SRS during follow-up or in palliative setting the patient selection for PRRT.

In conclusion
Optimal radiological imaging sequence of pre-operative staging for NF-pNET consists of a CT scan, followed by SRS in case of suspicious liver lesions detected on this initial CT scan. Patients without suspicious metastatic lesions on CT scan, may not benefit from a routine additional SRS. Our proposal would be to adjust the ENETS algorithm and include SRS selectively and not as a standard after CT scan (figure 1). In patients with suspicious metastatic lesions, additional imaging with SRS is still required, wherein the available modality and experience with this modality will also be important.

Ethical Statement
The authors declare that they have no conflict of interest. Sources of financial support: funding PhD candidate by Ipsen. The study was performed according the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its comparable ethical standards. For this type of study formal consent is not required.
Figure 1. Suggested algorithm of the pre-operative staging in patients with a non-functional pancreatic neuroendocrine tumor.
REFERENCES


