Value of endoscopic ultrasonography and somatostatin receptor scintigraphy in the preoperative localization of insulinomas and gastrinomas

Experience with 54 cases

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SUMMARY

Aim — The classic morphological techniques for the localization of insulinomas and gastrinomas are of limited value. Endoscopic ultrasonography and somatostatin receptor scintigraphy have shown high sensitivity for the detection of gastroenteropancreatic endocrine tumors. The aim of the study was to evaluate the sensitivity of endoscopic ultrasonography and that of somatostatin receptor scintigraphy in the localization of insulinomas and gastrinomas.

Patients and methods — This retrospective study concerned 54 patients with insulinoma (n = 29) or gastrinoma (n = 26) operated on between March 1991 and March 2000 and who had at least one among the two tested examinations. Forty-two patients had scintigraphy (17 with insulinoma, 25 with gastrinoma), 47 had endoscopic ultrasonography (28 with insulinoma, 17 with gastrinoma). One of the ten patients with MEN 1 had both tumors. All diagnosis were confirmed by histologic examination.

Results — The sensitivity of scintigraphy for the localization of insulinomas was 47%. There was one false positive. Sensitivity of endoscopic ultrasonography for insulinomas was 85%. The sensitivity of scintigraphy in the detection of gastrinomas was 65% for the tumor in the duodenopancreatic area, 20% for the tumors in the pancreatic tail and 71% for metastasis. The sensitivity of endoscopic ultrasonography was 46% for duodenal tumors, 75% for pancreatic tumors and 57% for lymph node metastasis. The combination of both localization studies increased sensitivity to 94%.

Conclusion — Endoscopic ultrasonography and somatostatin receptor scintigraphy are the gold standard for localization of gastrinomas. Association of both examinations increases the sensitivity. Scintigraphy for the detection of insulinomas should be performed when endoscopic ultrasonography is negative.


Endocrine tumors of the duodenum and pancreas are uncommon (annual incidence 1/100,000). The most frequently encountered functional endocrine tumors are insulinoma and gastrinoma. These tumors may occur sporadically or in patients with multiple endocrine neoplasia type 1 (MEN 1); 5 to 10% of insulinomas and 25 to 40% of gastrinomas are found in patients with MEN 1 [1-4]. Zollinger-Ellison syndrome is the first sign of MEN 1 in 13% of the cases [4]. Diagnosis is suggested by clinical signs and laboratory findings and is confirmed at histology when possible. Initially, symptomatic treatment is necessary but the only hope for cure is surgery. It is often however difficult to precisely localize the tumor and identify distant dissemination before surgical resection [4-9]. The diagnostic yield of conventional non-invasive imaging techniques (transcutaneous ultrasound, computed tomography, magnetic resonance imaging) has not been particularly satisfactory both for the primary tumor and to a lesser degree for non-nodal metastatic dissemination. Sensitivity has ranged from 30 to 60% [5, 7, 9-11]. Transhepatic venous sampling for gastrin or insulin after secretin or calcium stimulation can improve sensitivity [10, 12, 13]. This is however an invasive method requiring arterial catheterization (usually the femoral artery) to inject gastrin or calcium, and a venous catheterization to collect blood from the hepatic veins [10]. Moreover, revision procedures render the test difficult to interpret due to modifications in anatomic venous drainage. Early in the 90s, two non-invasive methods became available for preoperative exploration of suspected insulinoma and gastrinoma [11, 1-4]: endoscopic ultrasonography (EUS) and somatostatin receptor scintigraphy (SRS). Although peroperative exploration remains the best method for localizing gastrinomas and insulinomas [13], surgery should be limited to patients without metastasis or with resectable metastatic dissemination. So surgery cannot be the only examination for localization. Several groups have demonstrated the importance of localizing gastrinomas preoperatively, demonstrating a significant impact on the management decisions in 17 to 50% of the patients with sporadic or genetically associated (MEN-1) dis-

ABBREVIATIONS :

EUS : endoscopic ultrasonography
MEN 1 : multiple endocrine neoplasia type 1
SRS : somatostatin receptor scintigraphy
access the completeness of the surgical resection, following the previously
peroperative exploration (SRS) and histological proof of the endocrine tumor. Preoperative
SRS was performed with 111-indium-pentetreotide (Octreoscan®,
Mallinkrodt, Bondoufle, France). The injected dose ranged from 111 to 185 MBq. Anterior and posterior planar images of the thorax, the abdomen and the pelvis were acquired at 24h. Acquisition time was 10 minutes per planar image. EUS was performed under general anesthesia by a well-experienced operator using an ultrasound probe with 12 or 7.5 Hz frequencies. The EUS findings were reported as presence or absence of tumor in duodenal wall (for gastrinoma), pancreas, lymph nodes in the duodeno-
pancreatic region (insulinomas and gastrinomas). For SRS, we searched for strong uptake in the “gastrinoma triangle” (periduodenal region and head of the pancreas) and the left pancreas to localize primary tumors. SRS was considered to be a true positive when at least one region of identified uptake corresponded to a tumor peroperatively. Positive images that were not confirmed at peroperative exploration and at histology were considered to be false positives. SRS was considered to be a false negative if a tumor identified peroperatively had not been detected on the preoperative scintigrams. The sensitivity of EUS and SRS was calculated with a 95% confidence interval [Cl] in case of 5 or more patients. Sensitivity was also calculated per patient. Outcome was assessed one year after surgery except for the most recent patients. Patients free of clinical signs and with normal laboratory tests at one year were considered to be cured.

All patients were medically treated for their hypersecretion syndrome before surgery. Diazoxide (Proglycem®) was given to control blood glucose and proton-pump inhibitors to control acid secretion. The operative exploration has been described elsewhere for insulinoma [18] and gastrinoma [19]. Briefly, the infrarenalectomy space was explored for a Meckel diverticulum (ectopic pancreas) followed by exploration of the supramesocolic space and the liver. The lesser peritoneal cavity was opened from the right to left colic flexures. Kocher’s maneuver was performed. The posterior aspect of the tail of the pancreas was mobilized following and by manual palpation of the entire gland and peroperative ultrasoundography. All insulinomas were resected by enucleation when possible (when peripherically located and at a distance from pancreatic ducts), or by segmental pancreatic resection. Lymph node clearance in the “gastrinoma triangle” was performed in patients with gastrinoma. In addition, patients with gastrinomas underwent peroperative endoscopy with transillumination of the duodenum was performed before duodenal man mistomy for intraluminal palpation. All detected tumors (potential gastrino-
mas) were removed. Peroperative hormone assays were obtained to assess the completeness of the surgical resection, following the previously described protocol [6, 18, 19].

Patients and methods

Between 1980 and March 2000, 168 patients underwent surgery for resection of duodenopancreatic tumors in the General and Endocrine Surgery Unit of the Lille University Hospital Center. The diagnosis was insulinoma in 72 and gastrinoma in 57. The present study included 54 of these patients, operated on between March 1991 and March 2000. These 54 patients had had at least one of the explorations (EUS and/or SRS) and histological proof of the endocrine tumor. Preoperative diagnosis was based on blood glucose and insulin levels for insulinoma and on basal and secretin-stimulated acid and gastrin levels for gastrinoma. Histological proof (hematein-eosin-safran stain, HES) was obtained on surgical specimens in all cases. Immunohistochemistry using anti-chromogranin A and anti-synaptophysin antibodies demonstrated the endocrine nature of the specimens.

Results

Mean age at surgery was 44.8 years (range, 12-77). There were 34 men and 20 women. Endocrine tumors were sporadic in 44 patients (26 women) whose mean age was 46.2 years (range, 12-77). MEN 1 was present in 10 patients (8 women) whose mean age was 39.3 years (range, 15-76). Insulinoma was confirmed histologically in 29 patients and gastrinoma in 26. One of the MEN 1 patients had both an insulinoma and gastrinoma. Forty-seven patients (28 with insulinoma and 19 with gastrinoma) underwent EUS exploration and 42 had SRS (17 with insulinoma and 25 with gastrinoma). Preoperative EUS and SRS was available for 16 patients with insulinoma and 18 with gastrinoma.

Insulinomas

Two patients underwent surgery for recurrent malignant insulinoma. The first (patient n° 21) had undergone a left pancreatectomy 6 years earlier for a 24 x 17 mm tumor in the pancreatic tail. The pancreatectomy was extended at the second operation where 6 metastatic nodes were removed. A 30 x 20 mm insulinoma in the tail of the pancreas had been resected three years earlier in the second patient (n° 26). At the second operation, the tumor had infiltrated the pancreatic area and adjacent nodes. Hepatic metastases that had not been identified preoperatively were discovered. This is the only case of unsuccessful surgical cure of insulinoma in this entire series (including both sporadic and MEN 1 tumors).

Peroperatively identified tumor localizations (confirmed at histology), results of EUS and SRS, and surgical procedures performed are presented for sporadic insulinomas in table I and for MEN 1 insulinomas in table II. The sensitivity of SRS in detecting insulinomas was 47% (8/17) [Cl 95: 24-70%]. Eight tumors were not identified on scintigraphy: 2 nodal extensions of recurrent insulinoma (patients n° 21 and 26), 4 caudal tumors measuring 12-25 mm, and a tumor in the pancreatic body measuring 15 mm situated next to the aorta and another single lesion in the pancreatic head measuring 14 mm. There was one false positive SRS: scintigraphy showed uptake at the hepatic flexure (patient n° 25). Preoperative computed tomography and peroperative manual exploration both failed to identify a lesion corresponding to this area of uptake. The sensitivity of EUS for insulinomas was 84.6% (22/26) [Cl 95: 70.8-98.4%]. EUS detected metastatic nodes in two patients with malignant insulinomas (n° 21 and 26). Four sporadic insulinomas were not visualized, one in the ampulla, two pediculated tumors located on the superior and inferior borders of the pancreatic body, and one found in a nodule of pancreatitis (this latter patient had been previously operated on). These undetected tumors measured 8 to 20 mm.

Gastrinomas

The number of tumors resected and their localization as well as the number of patients with nodal and/or hepatic metastasis and results of laboratory tests and surgery are given in table III for sporadic gastrinomas and in table IV for gastrinomas associated with MEN 1. Sensitivity of SRS for tumors of the “gastrinoma triangle” and the left pancreas was 65% and 20%, respectively (table V). The sensitivity of EUS was 46% for duodenal tumors, 75% for pancreas tumors (head, body, tail) and 57% for nodal metastasis in the periduodenopancreatic area (table VI).

Eight patients had a single gastrinoma (6 duodenal, 2 nodal). There were 16 duodenal gastrinomas in 14 patients, two patients

having two duodenal tumors (one with sporadic disease and one with MEN 1). The mean size of duodenal gastrinomas was 12.3 mm (range, 3-25). Eight patients had nodal metastasis and two of these also had hepatic metastasis. Pancreatic gastrinomas were in the left portion of the pancreas in 4 cases and measured a mean of 17.5 mm (range, 10-20); one patient had multiple tumors disseminated in the pancreas. This last patient also had a duodenal localization. Lymph node metastasis was found in all patients with pancreatic gastrinomas.

Three of the 19 patients with nodal tumors exhibited primary nodal gastrinomas (no primary tumor found in the duodenum or pancreas): one node was involved in 2 patients and 6 nodes in

Table I. – Operative findings, surgery, results of preoperative exams for sporadic insulinomas.

<table>
<thead>
<tr>
<th>No.</th>
<th>Primary tumor</th>
<th>Size, mm</th>
<th>Metastases (n)</th>
<th>Surgery</th>
<th>EUS</th>
<th>SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left pancreas</td>
<td>10</td>
<td>None</td>
<td>Enucleation</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>Head</td>
<td>11</td>
<td>None</td>
<td>Enucleation</td>
<td>–</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>Head</td>
<td>15</td>
<td>None</td>
<td>Enucleation</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Left pancreas</td>
<td>20</td>
<td>None</td>
<td>Distal pancreatectomy</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>Head</td>
<td>5</td>
<td>None</td>
<td>Enucleation</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td>Left pancreas</td>
<td>15</td>
<td>None</td>
<td>Enucleation</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>Left pancreas</td>
<td>8</td>
<td>None</td>
<td>Enucleation</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>Head</td>
<td>14</td>
<td>None</td>
<td>Enucleation</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>11</td>
<td>Left pancreas</td>
<td>15</td>
<td>None</td>
<td>Distal pancreatectomy</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>Left pancreas</td>
<td>11</td>
<td>None</td>
<td>Enucleation</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>13</td>
<td>Left pancreas</td>
<td>20</td>
<td>None</td>
<td>Enucleation</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>15</td>
<td>Left pancreas</td>
<td>10</td>
<td>None</td>
<td>Enucleation</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>16</td>
<td>Head</td>
<td>10</td>
<td>None</td>
<td>Enucleation</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>17</td>
<td>Left pancreas</td>
<td>8</td>
<td>None</td>
<td>Distal pancreatectomy</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>18</td>
<td>Head</td>
<td>14</td>
<td>None</td>
<td>Enucleation</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>20</td>
<td>Left pancreas</td>
<td>15</td>
<td>Nodes (3)</td>
<td>Distal pancreatectomy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>21</td>
<td>Left pancreas in 1992</td>
<td>25</td>
<td>Nodes (6)</td>
<td>Distal pancreatectomy, extended nodal dissection</td>
<td>+ (node)</td>
<td>–</td>
</tr>
<tr>
<td>23</td>
<td>Head</td>
<td>5</td>
<td>None</td>
<td>Enucleation</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>26</td>
<td>Left pancreas in 1996</td>
<td>30</td>
<td>Nodes (3)</td>
<td>Splenectomy left pancreatectomy</td>
<td>+ (node)</td>
<td>–</td>
</tr>
<tr>
<td>27</td>
<td>Left pancreas</td>
<td>16</td>
<td>None</td>
<td>Distal pancreatectomy</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>28</td>
<td>Pancreatic body</td>
<td>15</td>
<td>None</td>
<td>Enucleation</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>29</td>
<td>Left pancreas</td>
<td>20</td>
<td>None</td>
<td>Distal pancreatectomy</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

H: hepatic metastases, Head: head of the pancreas, nd: not done, EUS: endoscopic ultrasonography, SRS: somatostatin receptor scintigraphy.

Table II. – Operative findings, surgery, results of preoperative exams for patients with insulinomas and MEN I.

<table>
<thead>
<tr>
<th>No.</th>
<th>Operative findings</th>
<th>Size, mm</th>
<th>Metastases (n)</th>
<th>Surgery</th>
<th>EUS</th>
<th>SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>Head + left pancreas</td>
<td>12</td>
<td>Node (1)</td>
<td>Enucleation Distal pancreatectomy</td>
<td>nd</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>Head</td>
<td>20</td>
<td>None</td>
<td>Enucleation</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>left pancreas</td>
<td>12</td>
<td>None</td>
<td>Enucleation</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>19</td>
<td>Head + left pancreas</td>
<td>5</td>
<td>None</td>
<td>Enucleation Distal pancreatectomy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>22</td>
<td>left pancreas</td>
<td>20 and 10</td>
<td>None</td>
<td>Distal pancreatectomy</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>24</td>
<td>Head + left pancreas</td>
<td>16</td>
<td>None</td>
<td>Enucleation Distal pancreatectomy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>25</td>
<td>Body + left pancreas</td>
<td>25</td>
<td>None</td>
<td>Extended distal pancreatectomyb</td>
<td>+</td>
<td>(fp +)</td>
</tr>
</tbody>
</table>

*a This patient also had a gastrinoma. b Resection of the isthmus, body and tail. Head: head of the pancreas; fp+: false positive; EUS: endoscopic ultrasonography; SRS: somatostatin receptor scintigraphy; MEN1: multiple endocrine neoplasia type 1.
the third. Five patients had multiple hepatic metastases, two others had one and two metastases.

Node dissection was performed in the “gastrinoma triangle” in all patients except 4 with diffuse hepatic metastasis. Partial hepatectomy was required in two patients (one and two metastases) and biopsies were obtained in two others (1 with MEN 1). One patient required liver transplantation associated with duodenopancreatectomy for multiple metastases. Surgical findings are presented in tables III and IV.

SRS did not detect tumors in the “gastrinoma triangle” in 8 patients; 5 duodenal gastrinomas (2 with nodal metastasis) and 3 nodal gastrinomas. These undetected duodenal tumors measured...
a mean of 12.2 mm (range, 6-20) and one had nodal metastasis. The mean size of duodenal tumors detected by SRS was 12.3 mm (range, 3-25). However, only one of the detected tumors was unique, the others (measuring 3, 4, 6, 11 mm) consisted of two tumors or were associated with nodal metastasis in the “gastri-

oma triangle.” SRS visualized only one 20-mm tumor among the 5 pancreatic gastrinomas. Three of the undetected tumors were in the left pancreas (10-20 mm) and one involved diffuse pancreatic dissemination. Multiple hepatic metastases were not visualized in 2 patients. We had 2 false positive metastases at SRS: 1 false hepatic uptake corresponding to inflammation of the gallbladder and one false pulmonary uptake that could not be confirmed by any other morphology exploration.

Nine duodenal gastrinomas in 7 patients were not detected by EUS despite their size (mean of 11.7 mm: range, 3-25). Duodenal tumors detected by EUS measured a mean of 11 mm (range, 4-20). Six patients had nodal invasion not detected by EUS: 4 in the gastrinoma triangle, 2 along the splenic artery. We had 2 false positives for pancreatic gastrinomas. For the first (MEN1 patient), EUS visualized numerous tumors that were other endocrine tumors and not gastrinomas. In the second patient, EUS identified a 6-mm tumor in the body which could not be found at open palpation or peroperative ultrasonography.

In combining SRS and EUS, the detection rate of at least one tumor was 94% for insulinoma (15/16) and 94% for gastrinoma (17/18). Two patients had an insulinoma non-visualized by EUS that was detected by SRS (patients n° 3 and 8). Among the patients with gastrinoma who had had both EUS and SRS, only EUS was positive preoperatively in 5 (including one false positive) and only SRS in 2.

The sensitivity of EUS to detect pancreatic tumors (insulinoma or gastrinoma) was 80%. The false-negative EUS explorations had been performed early in this series; there were no false negatives among the last 17 patients with gastrinomas and the last 21 with insulinomas.

Discussion

This retrospective analysis confirms the important and complementary contribution of EUS and SRS to preoperative localization of gastrinomas. The key exploration for insulinoma is EUS. Exceptionally, SRS can detect insulinomas not visualized at EUS.

In this series, unlike other series of gastrinomas [8, 16, 20], all tumor localizations were confirmed at surgical exploration and all diagnoses were proven histologically.

Although SRS can visualize small tumors (4 mm in our series), the sensitivity of SRS depends on tumor size [7, 22]. In our patients, size was not a determinant factor, but undetected tumors were associated with nodal extension less often; uptake was thus weaker than for multiple tumors or tumors with satellite nodes. SRS only detected 1 out of 5 (20%) gastrinomas in the left pancreas. This is unusual since in the literature pancreatic tumors are generally larger than duodenal tumors and therefore localized more readily [22]. The sensitivity of SRS was lower for multiple tumors or tumors with satellite nodes. Venous assays should be reserved for patients with non-localized tumors (mainly insulinomas) in order to avoid empiric pancreatic resection [3] that provides only 50% cure rate [26]. Furthermore, despite 75% sensitivity, venous assay can only identify the region of the tumor based on arterial vascular supply [10, 12].

All these different methods used to localize tumors before surgery cannot replace rigorous peroperative exploration, especially for gastrinoma. Endoscopic transillumination of the duodenum [29] and duodenotomy [30] should always be performed in light of the weak sensitivity of EUS in detecting duodenal gastrinomas. Nodal dissection of the “gastri- noma triangle” and careful palpation and peroperative pancreatic ultrasonography are also required, even after resection of a duodenal tumor. For sporadic insulinomas, manual exploration of the pancreas may be necessary if the complete preoperative work-up (computed tomography and/or magnetic resonance imaging, EUS, SRS) favors a unique tumor. This would probably be the only situation where laparoscopy could be proposed [31]. Peroperative laparoscopic ultrasonography should be performed before resection [32].

Peroperative isotopic detection of tumors is another possibility currently under evaluation. Ohrall et al. [33] reported their experience in Upptslas. These authors were able to detect all tumors measuring > 5 mm while preoperative SRS only correctly detected those measuring > 9 mm. These promising results have not been confirmed by others [34]. Hepatic and biliary noise (the main bile duct must be clamped) and accumulation of the tracer in the colonic lumen limit the performance of this technique. In addition, tumors with few type 2 receptors cannot be detected. We have to date not evaluated this technique.

In our opinion, EUS and SRS should be combined for the preoperative exploration of patients with gastrinoma. Despite its low sensitivity, we believe that SRS should be performed for patients with an insulinoma non-localized by EUS. Computerized tomography and magnetic resonance imaging contribute to the search for liver metastasis.
REFERENCES


