Intraoperative Ultrasound and Preoperative Localization Detects All Occult Insulinomas

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Hypothesis: Preoperative invasive localization procedures with intraoperative ultrasound (IOUS) can result in successful surgical treatment of occult insulinomas when noninvasive imaging study results are equivocal or negative.

Design: Prospective study.

Setting: Tertiary care university hospital.

Patients: Thirty-seven consecutive patients with a biochemical diagnosis of insulinoma without multiple endocrine neoplasia (MEN).

Intervention: All patients underwent portal venous sampling (PVS) (n=22) or calcium angiogram (n=15) followed by surgery with palpation and IOUS (n=37).

Main Outcome Measure: Portal venous sampling, calcium angiogram, palpation, and IOUS were compared for accurate localization of insulinoma.

Results: All patients were cured of hypoglycemia after surgery. Portal venous sampling correctly localized tumors in 17 (77%) of 22 patients. Calcium angiogram was correct in 13 (87%) of 15 patients. Palpation identified 24 (65%) of 37 tumors, and IOUS found 35 (95%) of 37 tumors. The 2 tumors missed by IOUS were located in the tail of the pancreas and were resected based on regional localization alone.

Conclusions: Intraoperative ultrasound is the single best localization study, but it will miss some tumors that regional localization can identify. Combining both modalities allowed surgical cure of all insulinomas in our study. Therefore, we recommend both IOUS and regional localization for insulinoma when preoperative imaging studies are equivocal.

Arch Surg. 2001;136:1020-1026

Hypoglycemia caused by an insulinoma is not well controlled by medical therapy, and surgery is the only potentially curative treatment. Since insulinomas are generally benign, simple enucleation of the tumor is the goal, with preservation of the normal pancreas and adjacent tissue. Precise preoperative localization of tumors facilitates successful surgical therapy and minimizes the risk of complications that may be associated with blind pancreatic resections. In addition, many tumors are small, making precise operative localization difficult.

Conventional imaging studies such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) fail to reveal the majority of insulinomas. Somatostatin receptor scintigraphy (SRS) has become the noninvasive imaging study of choice for neuroendocrine tumors, as most gastrinomas and carcinoid tumors are detected based on receptor density. However, insulinomas are rarely imaged with SRS because of a low density of type 2 somatostatin receptors. Pancreatic arteriography alone, which is the single best imaging study for insulinomas, is invasive and detects only 50% of tumors. Since insulinomas are uniformly distributed throughout the pancreas, regional localization indicating the region of the pancreas (ie, head, body, or tail) with tumor is helpful. Studies that are designed to provide regional localization, such as portal venous sampling (PVS) for insulin concentrations and intraarterial stimulation of insulin secretion with calcium, are much more sensitive than noninvasive studies, and can guide successful surgery. However, these procedures are invasive, technically complicated, and expensive. Furthermore, with the 90% to 96% sensitivity of intraoperative ultrasound (IOUS), it may be that invasive preoperative localization studies are not necessary at all. The purpose of this study was to examine the results.
PATIENTS AND METHODS

Between 1982 and the present, 37 consecutive patients with a biochemical diagnosis of insulinoma without MEN were treated at a tertiary care referral center by the same surgeon (J.A.N.). The cases of some of these patients have been previously reported.\textsuperscript{2,6,7} All patients were referred because they either had unsuccessful surgery or equivocal noninvasive imaging studies (i.e., ultrasonography, CT, and/or MRI). Each patient had the diagnosis of insulinoma based on symptomatic hypoglycemia (<50 mg/dL) and concomitant hyperinsulinism (>5 µU/mL) during a 72-hour fast. All patients had undergone preoperative invasive localization studies with either PVS (n=22) or intra-arterial calcium stimulation (n=15) followed by open surgical exploration with palpation, IOUS, and insulinoma resection.

PORTAL VENOUS SAMPLING

The first 22 patients in this series underwent percutaneous transhepatic PVS with selective vein sampling for insulin concentrations. The technique was first described by Gothlin et al\textsuperscript{8} and has been modified by Miller et al.\textsuperscript{9} Initial access to the portal vein is achieved using a right transhepatic approach. An angiographic catheter is then advanced into the main portal vein, and selective catheterization of the branches of the portal venous system is performed to include the main portal vein, superior mesenteric vein, splenic vein, inferior mesenteric vein, transverse pancreatic vein, and the anterior and posterior superior pancreaticoduodenal veins. Blood samples are obtained from each venous branch, and contrast injection is performed to document catheter position. Samples are placed in prechilled numbered tubes, stored on ice, and subsequently assayed for insulin concentration by radioimmunoassay. The anatomic location of each blood sample is carefully annotated on a standardized anatomic diagram.

The insulin gradient, expressed as a percentage of the simultaneous peripheral sample, was calculated as insulin gradient = 100 \times [(\text{maximal selective insulin concentration} - \text{simultaneous peripheral insulin concentration})/ (\text{simultaneous peripheral insulin concentration})]. An insulin gradient of 50% or more was interpreted as localizing the insulinoma regionally to the head, body, or tail of the pancreas. Between 20 and 30 samples were obtained from each patient for insulin concentration.

CALCIUM ANGIOGRAM

The subsequent 15 patients underwent intra-arterial stimulation of tumor insulin secretion with a calcium gluconate angiogram. The technique of selective intra-arterial injection of calcium gluconate to locate insulinomas was first described by Dopman et al\textsuperscript{10} and has been replicated by others, including Pereira et al.\textsuperscript{11} A catheter was positioned in the right hepatic vein using a right internal jugular venous approach. Blood samples were obtained through the hepatic vein catheter after selective injection of calcium into the arteries that supply various regions of the pancreas.

RESULTS

Demographic results are summarized in Table 1. The size distribution of tumors in our study is demonstrated in Figure 4.

PORTAL VENOUS SAMPLING

In the 22 patients who underwent PVS, the region of the pancreas with tumor was correctly identified in 17 patients (77%). There were no false-positive results. The identified tumors ranged in size from 0.6 cm to 4.0 cm. Portal venous sampling missed tumors in 5 patients: 2 in the head, 2 in the body, and 1 in the tail of the pancreas. Tumors were palpable in 13 (59%) of 22 patients and visualized by IOUS in 20 (91%) of 22 patients. Intraoperative ultrasound missed 2 tumors located in the tail of the pancreas. One patient initially had imaging studies and a preoperative PVS study that were negative for lesions. No tumor could be detected intraoperatively, either by palpation or IOUS. A resection was not done.
Pancreatic arteriography is performed using a right femoral approach. Selective injection of the nonionic contrast agent is performed in the splenic, proper hepatic, gastroduodenal, and superior mesenteric arteries. Following each selective arteriogram, 10% calcium gluconate (Lyphomed, Rosemont, Ill), at a dose of 0.01 to 0.025 mEq Ca\(^{2+}\)/kg, is diluted in 3 mL of normal saline and rapidly injected through the selective catheter. Blood samples are then obtained through the hepatic vein catheter. Five-milliliter samples are obtained just prior to the injection, and then at intervals of 0.5, 1.0, 1.5, 2.0, and 3.0 minutes after the injection of calcium. Samples are frozen and stored until the insulin assay is performed.

A positive localization is indicated by a 2-fold elevation of hepatic vein insulin levels in the 0.5-minute or 1.0-minute sample (or both) following calcium injection. A 2-fold rise in insulin levels following injection into the gastroduodenal or superior mesenteric artery localizes the tumor to the pancreatic head and uncinate process; a 2-fold rise following injection into the splenic artery localizes the insulinoma to the body and tail. Figure 1 shows the selective catheterization of the gastroduodenal artery and the subsequent tumor “blush” in the head of the pancreas. Figure 2 graphically demonstrates the rise in insulin levels after intraarterial calcium injection in a patient with an insulinoma.

**OPERATIVE EXPLORATION AND ULTRASOUND**

All operations were performed in a similar manner. The pancreas was exposed by an extended Kocher maneuver and entering of the lesser sac. To facilitate palpation of the body and tail, the inferior border of the pancreas was divided, and the spleen and pancreatic tail were elevated out of the retroperitoneum. Systematic palpation of the entire pancreas was performed. An insulinoma feels like a firm nodule within the softer pancreatic parenchyma. Following palpation, IOUS was performed using a near-field real-time high-resolution 7.5- to 10-MHz transducer. The pancreas was routinely scanned in the longitudinal plane by passing the probe from the pancreatic head, across the body, and to the tail. Several parallel passes were necessary for complete examination of the pancreas. Intraoperative ultrasound was considered positive for an insulinoma if a sonolucent mass lesion could be detected in both transverse and longitudinal imaging planes. Figure 3 shows an IOUS image of an insulinoma in the tail of the pancreas.

Biopsies were performed on all abnormal lesions identified by palpation or IOUS. In the pancreatic head, suspected tumors were enucleated. In the pancreatic body and tail, enucleation was performed unless tumors were adjacent to the pancreatic duct, in which case they were resected by a distal pancreatectomy. Blind resections of the pancreas were not performed. If an insulinoma could not be identified by intraoperative maneuvers, a pancreatic resection was performed only if an insulin gradient suggested a region to resect. Results of intraoperative localization procedures (palpation and IOUS) were compared with those of the preoperative invasive localization studies as well as with the final pathological proof of an insulinoma.

Finally, prior to a third operation, a calcium angiogram was performed, which demonstrated a peak in insulin secretion when the splenic artery was injected. At the time of the third operation, neither palpation nor IOUS identified the tumor. However, a curative distal pancreatic resection was performed based on the information obtained with the calcium angiogram. Intraoperative ultrasound also missed a 3-mm tumor in the tail of the pancreas. That patient underwent a curative distal pancreatectomy based solely on the PVS gradient.

Palpation did not detect any tumors that IOUS missed. Intraoperative ultrasound was particularly helpful in identifying nonpalpable tumors in the head of the pancreas (6 nonpalpable tumors in the head of the pancreas were identified by IOUS). Portal venous sampling missed 2 tumors in the head of the pancreas that were found by IOUS.

Two patients in this group each had a previous exploration for insulinoma prior to referral. One patient underwent a laparotomy at an outside institution; no tumor was found and no resection of the pancreas was performed. Another patient had a blind subtotal pancreatectomy at an outside institution, but no tumor was found. Both of these patients had undergone PVS that correctly localized an insulinoma in the head of the pancreas, and surgical cure based on IOUS results was achieved.

There were 4 postoperative complications, including a pseudocyst requiring percutaneous drainage, an incarcerated hernia at a drainage site requiring emergent reoperation, and an intraabdominal abscess treated by open drainage. One patient had a pancreatic fistula and...
required parenteral nutrition and a prolonged hospital stay. The pancreatic fistula eventually healed without long-term sequelae. There were no deaths.

**CALCIIUM ANGIOGRAM**

Tumor localization was correct in 13 (87%) of 15 patients who underwent a calcium angiogram. These tumors ranged in size from 1.0 to 2.5 cm. There was one false-positive result that localized the tumor to the head of the pancreas; on operative exploration, a 1-cm tumor was found in the body of the pancreas. One calcium angiogram was false-negative since a 1-cm tumor was found in the body of the pancreas on operative exploration.

Palpation identified 11 (73%) of 15 tumors in this group, but missed 4 tumors located in the head of the pancreas, which were 1.0, 1.0, 1.2, and 2.5 cm in diameter, respectively. Intraoperative ultrasound correctly localized all tumors in these 15 patients. In 1 patient, a 1-cm tumor was localized to the tail of the pancreas and enucleated. Intraoperative ultrasound then revealed a ductal injury, and a distal resection was performed (*Figure 5*).

One patient had a blind distal pancreatectomy prior to referral. Both calcium angiogram and IOUS localized a 1-cm tumor in the head of the pancreas, which was then successfully enucleated. There were no surgical complications in this group. No patients became diabetic or had permanent morbidity or death from surgery. No patients had recurrent hypoglycemia after surgery. The combined results of these studies are presented in *Table 2.*

**OUTCOME**

Using the 2-tailed Fisher exact test, there was no significant difference between PVS and calcium angiogram in correct tumor localization (*P* = .68). Intraoperative ultrasound was significantly better than palpation alone (*P* = .003) but not significantly better than either PVS (*P* = .09) or calcium angiogram (*P* = .57). Overall, the postoperative complication rate for the entire study was 4 (11%) of 37. The hypoglycemia cure rate was 100%, but 1 patient required 3 operations. No other patient required more than 1 operation. There were no deaths. There was neither long-term diabetes requiring insulin nor pancreatic insufficiency requiring enzyme replacement in any patient.

**COMMENT**

Controversy exists regarding the best tests to use for preoperative localization of insulinoma and whether these studies are even necessary since intraoperative palpation with IOUS will detect most tumors.3-5,12,13 Conventional imaging studies such as CT and MRI have a role in the preoperative evaluation for malignant insulinomas or identification of metastatic disease to the liver. However, these studies are not very useful in localizing small tumors, as was seen in our study (32/37 tumors were ≤2 cm). The sensitivity of these tests increases as tumor size increases; however, when tumors are larger than 3 cm, most are easily palpable by the surgeon intraoperatively. With small tumors, many are not
palpable (35% in this study), and other localization studies are needed.

The 2 preoperative invasive localization procedures that we used in our study were PVS and calcium angiogram. The initial 22 patients received PVS. In the subsequent 15 patients, we changed to calcium angiogram. Although PVS is sensitive, it is invasive, expensive, and tedious, requiring multiple small vein samples. It is more difficult than the calcium stimulation test and requires specific skill and experience with percutaneous transhepatic catheterization. In addition, it is associated with a slight but significant morbidity from bleeding at the liver puncture site. For these reasons, we switched to using intra-arterial injections of calcium to stimulate the release of insulin during pancreatic arteriography. This procedure is less painful and less invasive, yet it provides the same information and sensitivity as PVS.

The current study revealed a 77% sensitivity rate for PVS and an 87% sensitivity rate for calcium angiogram, which is consistent with results of previous reports. portal venous sampling missed tumors uniformly distributed throughout the entire pancreas. The limitation of calcium angiogram is in localizing tumors in the body of the pancreas, which was demonstrated in our study. This may occur because it is difficult to inject an exact single artery that perfuses only the body of the pancreas, as can be done for the head and tail. The surgeon should know that an uninformative study with calcium angiogram suggests that the tumor may be in the body. Furthermore, insulinomas in the body are usually readily detected by palpation and/or IOUS. Calcium angiogram detected all tumors in the tail of the pancreas, which is the most problematic area for IOUS.

The best single modality for identifying insulinomas is IOUS. Intraoperative ultrasound alone identified 95% of all tumors in our study, which is consistent with results of other studies. It is a critical element in any surgery for insulinoma. No procedures for resection of insulinomas should be performed without the use of IOUS. Intraoperative ultrasound identified all tumors that were found on intraoperative palpation, and palpation did not identify any tumors that IOUS missed. The 2 tumors that IOUS missed were located in the tail of the pancreas. One tumor had preoperatively been identified using PVS, and surgical resection was guided by these results. The other tumor was finally identified by calcium angiogram after 2 unsuccessful operations and PVS studies. Although IOUS alone identifies the majority of tumors, it does not identify them all. One hundred percent of the tumors in this study were found by combining the use of an invasive localization study with IOUS, which suggests that the use of these studies can improve the outcome of patients who are operated on with involvement of IOUS alone.

Prior to their referral to a tertiary care center, all of the patients in this study had previously been extensively evaluated. Each patient had clear signs and symptoms of insulinoma with biochemical proof of tumor but without identifiable tumor. All had inconclusive noninvasive conventional imaging studies, including abdominal US, CT, MRI, and/or SRS. Four patients even had previous operations that failed to remove the insulinoma. In this setting, the surgeon is faced with the conundrum of operation without exact knowledge of the tumor location. Furthermore, the surgeon is also concerned because standard palpation, a tried and true operative maneuver, will miss a large number of these tumors. The major issue is whether to proceed directly to surgery with IOUS or to try to use a study like calcium angiogram that will provide regional localization. Although IOUS will detect the majority of insulinomas, it will miss some tumors (5%-10%), resulting in an unsuccessful operation. Since medical therapy is ineffective for long-term control of symptoms from the insulinoma, and reoperative surgery makes identification of the insulinoma even more difficult, we recommend the combined use of both preoperative calcium angiogram and IOUS for all patients with insulinoma who are referred to tertiary care centers and who have inconclusive conventional imaging studies or prior failed operations. This strategy should result in a high likelihood of cure with a low probability of long-term complications or death.

**Presented at the 72nd Annual Meeting of the Pacific Coast Surgical Association, Banff, Canada, February 19, 2001.**

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Table 2. Comparison of Preoperative to Intraoperative Localization Studies

<table>
<thead>
<tr>
<th>Modality</th>
<th>Correct No. (% of Tumors Localized)</th>
<th>Location of Tumors Missed</th>
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<tbody>
<tr>
<td>PVS</td>
<td>17/22 (77)</td>
<td>2 Head, 2 body, 1 tail</td>
</tr>
<tr>
<td>Ca^{++} angiogram</td>
<td>13/15 (87)</td>
<td>2 Body</td>
</tr>
<tr>
<td>Intraoperative palpation</td>
<td>24/37 (65)</td>
<td>10 Head, 1 body, 2 tail</td>
</tr>
<tr>
<td>IOUS</td>
<td>35/37 (95)</td>
<td>2 Tail</td>
</tr>
</tbody>
</table>

*PVS indicates portal venous sampling; Ca^{++} angiogram, calcium-stimulated angiogram; and IOUS, intraoperative ultrasound.*
DISCUSSION

Lawrence W. Way, MD, San Francisco, Calif: The diagnosis of insulinoma can be made with virtual certainty, but pinpointing the tumor within the pancreas remains something of a challenge. Conventional CT, ultrasound, and MR imaging exhibit a sensitivity hovering around 25%, and arteriography, the first invasive test for this purpose, detects only 50% of lesions, with a bias in favor of those easiest to find at surgery (ie, the largest). Portal venous sampling in search of regional hot spots of insulin production was introduced over 20 years ago. Invasive, complex, and expensive, PVS eventually gave way about 10 years ago to the simpler regional pancreatic stimulation with calcium via selective arterial injection (ASVS). In addition to these tests, which are thoroughly discussed in the article, dual-phase spiral CT scanning and endoscopic ultrasound have recently vied for a place in the preoperative diagnostic regimen.

With such a plethora of tests, expenses would be excessive if all were to be obtained in every patient. Furthermore, to be justified, such tests require evidence that individually they would truly affect patient management. The interesting problem when developing a diagnostic strategy for this disease is that almost 95% of insulinomas can be found at surgery by thorough inspection, palpation, and direct ultrasonographic (IOUS) inspection of the pancreas. Preoperative localization may not be all that important.

Consequently, an extensive battery of preoperative studies would ultimately affect the care of very few patients. A hundred thousand dollars or more might have to be spent to find each of the uncommon elusive tumors. While Dr Norton's experience demonstrated that ASVS coupled with IOUS found nearly all insulinomas, his arguments in favor of routine ASVS are incompletely developed, for they do not address the cost-benefit aspect. Furthermore, the article does not conclude with a contemporary algorithm for preoperative testing that integrates ASVS, the newer less invasive tests, and the diagnostic ramifications of laparoscopic treatment, which appears to many to be the preferred approach, into one comprehensive scheme.

In other words, the discussion of diagnostic testing does not culminate in a specific diagnostic plan.

There is also a caveat to mention regarding ASVS. Although there was no example in the present series, an occasional test points incorrectly to the head of the gland as the insulin source when the tumor is actually located in the neck. This would complicate a decision for resection based on ASVS alone in the complete absence of corroborating localizing information. Thus, ASVS is afflicted to some extent by the vagaries that affect some of the other vascular stimulation-secretion studies.

Several reports have shown that EUS can locate as many as 85% of insulinomas, missing a few, predominantly in the tail of the gland. Spiral CT also seems to be outperforming conventional CT scans by as much as a 2-to-1 margin. Thus, noninvasive tests are gradually filling the gap. Nevertheless, there is still reason to debate whether one should obtain ASVS in all cases where preoperative tests have not localized the tumor, or whether it should be kept in reserve for the rare case in which the tumor could not be found at surgery. The authors argue here in favor of the former approach; other experts, considering the same data, prefer the latter. And in another recent publication (B J Surg. 2000;87:385), Dr Norton seemed to take a stance different from the one in this article.

Therefore, I would like to ask whether the authors can integrate their observations with data on the value of EUS and spiral CT scans into recommendations for an efficient diagnostic scheme for this disease?

Quan-Yang Duh, MD, San Francisco: I enjoyed the paper and I have a couple of comments. The calcium angiogram was originally developed by Dr Alfred Cuschieri and Dr Michel Gagner, and subsequently by many others, including us.

The easiest ones to resect laparoscopically are those that can be localized preoperatively and are anteriorly located. Using intraoperative ultrasound, many of these tumors can be found and can be removed easily, especially with the help of a harmonic scalpel. Even for those that cannot be preoperatively localized, one can start with an initial diagnostic laparoscopy followed by intraoperative laparoscopic ultrasound and then if needed, followed by hand assistance. This is done by making an incision that is the same size as your glove, for example, a 7.5-cm incision for someone who wears a size 7.5 glove. This will enable you to palpate the pancreas.

So basically we can now reproduce almost everything we do in an open operation laparoscopically. If we follow this algorithm, one would imagine the majority of insulinomas could be removed laparoscopically. What is the role of laparoscopic procedures, and what are the contraindications?

Haile T. Debas, MD, San Francisco: I also rise to congratulate the speaker. He has enormous experience in the field of endocrine surgery, but I think we are trying to bring him out of the NIH rarified atmosphere into the reality of clinical practice in managed care, and I think Dr Way's comments are appropriate. I would have to say that percutaneous transhepa-

REFERENCES


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tic venous sampling is a very complicated procedure. It's a very expensive, long, time-consuming procedure, and we have seen patients who go into hypovolemia because of the amount of blood removed during the procedure. So that being the case, and with the advances in endoscopic ultrasound and intraoperative ultrasound, shouldn't that procedure be delegated as a last-resort localizing technique?

I would like to ask Dr Norton what his relative indications would be for removing a tumor in the tail of the pancreas: enucleation vs distal pancreatectomy, and what would be the indications for each?

Finally, I would like for him to finally relegate into history books the practice of blind distal pancreatectomy when the insulinoma cannot be found at operation. Of course, the chance of not finding insulinomas is becoming very, very small. But perhaps that is the place for percutaneous transhepatic sampling.

Orlo H. Clark, MD, San Francisco: Jeff, when we do certain tests we must justify the reasons for these tests. My specific question is, with the changing approach to patients with insulinoma by using laparoscopic procedures, should we do more preoperative localizing studies, specifically transgastric ultrasound? When the tumor is identified, it could be removed laparoscopically, thus avoiding a laparotomy.

The second question, which Dr Debas also asked, is should we do a different preoperative evaluation depending on whether patients are going to have an initial operation or a reoperation? Also, should we use a different approach for patients who have sporadic disease or MEN-I and familial disease? Dr Debas suggested one should not do a distal pancreatectomy. This, however, is a controversial subject, since when the insulinoma cannot be found one should consider whether the patient might have nesidioblastosis. How would you make this diagnosis in the operating room?

Dr Norton: In reply to Dr Way, I agree with you. The critical element in the evaluation of a patient with an insulinoma is the fast, which needs to be a 72-hour fast to unequivocally make the diagnosis. Once I was a visiting professor at Duke, and they mentioned. In response to Dr Duh, actually Dr Imamura described the secretin angiogram for detecting gastrinomas. We described the calcium angiogram. We used Imamura's study and translated it to insulinomas. We had done studies that showed that calcium was a provocative drug for insulin secretion in insulinomas.

The laparoscopic method is a real method and a very useful method for removing insulinoma. It may be the initial method of choice. However, one case that I presented was actually done laparoscopically at another hospital, and they didn't find the tumor. So there may be pitfalls related to laparoscopic surgery for insulinomas.

In response to Dr Debas, portal venous sampling is definitely not indicated in any patient. Endoscopic ultrasound is probably the best study. The surgery for insulinoma is pancreas-preserving surgery. These tumors are benign, and it's really just a matter of removing the insulinoma. But occasionally if the tumor is right near the duct, one may need a distal pancreatectomy, and that can be usually done without splenectomy.

In response to Dr Clark, first of all I actually don't think adult nesidioblastosis exists. I know there is controversy about the diagnosis. Once I was a visiting professor at Duke, and they presented a case which was diagnosed as adult nesidioblastosis. I had the slides reviewed at the AFIP, and they said unequivocally that it was not nesidioblastosis. So it is a controversial diagnosis. I personally haven't seen it in any patient. The laparoscopic approach is going to change the way we manage insulinomas. These more invasive studies will be used in reoperations as you suggest.