Localization of Insulinomas

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Hypothesis: Intraoperative ultrasonography is more sensitive than preoperative and other intraoperative techniques for localizing insulinoma.

Design: Retrospective review.

Setting: A tertiary referral center.

Patients: All patients with a biochemical diagnosis of organic hyperinsulinism who were referred to University of California, San Francisco, from 1975 to 1998.

Methods: Sensitivities of the localization techniques for insulinoma were evaluated.

Results: The sensitivities of tumor localization with arteriography, computed tomography, preoperative ultrasonography, magnetic resonance imaging, magnetic resonance imaging with gadolinium, transhepatic venous sampling, palpation, and intraoperative ultrasonography were 47%, 24%, 50%, 30%, 40%, 55%, 76%, and 91%, respectively. Nine of the 11 nonpalpable and nonvisible tumors at operation were localized by intraoperative ultrasonography.

Conclusion: The currently available preoperative localization tests are not reliable enough to be recommended when intraoperative ultrasonography is available.

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A variety of procedures have been advocated for detecting insulin-secreting tumors, but there is little consensus about the best method or combination of methods. After the diagnosis of insulinoma is established, most endocrinologists, surgeons, and patients would prefer preoperative localization if a reliable and cost-effective test were available. Selective arteriography was formerly used for preoperative localization of insulinoma but is usually no longer recommended because it only, at best, identifies about 60% of the tumors, and these are the larger tumors that the surgeon can usually easily identify. Arteriography is also invasive and expensive. Other localization studies have been used, including preoperative ultrasonography, transgastric endoscopy, computed tomography (CT), magnetic resonance (MR) imaging, radionuclide scanning, transhepatic venous catheterization, and calcium-stimulated angiography with catheterization of hepatic veins. Despite the many attempts aimed at localizing insulinomas, the tumors remain undetected in about 40% of patients. The purpose of this study was to review the results of the localization techniques in 66 consecutive patients who were surgically treated for insulinomas at University of California, San Francisco, from 1975 to 1998. This period was chosen for patient review because new noninvasive localization techniques became available beginning in 1975.

RESULTS

TUMOR SIZE AND SITE

The average diameter of the 50 solitary tumors in our patient cohort where this information was documented was 1.8 cm. Thirteen patients had tumors less than 1 cm in diameter. One patient had a benign tumor larger than 6 cm. The size distribution of the insulinomas is shown in Figure 3.

Thirty-four percent of the insulinomas were situated in the head of the pancreas, 38% in the body, and 28% in the tail. One female patient may have had an ectopic tumor, because no primary tumor was identified even after a total pancreatectomy including Whipple procedure (Figure 4).

The number of tumors of the 5 patients with multiple tumors ranged from...
PATIENTS AND METHODS

From January 1, 1975, to December 31, 1998, 66 patients (24 male and 42 female) with a biochemical diagnosis of organic hyperinsulinism were referred for assessment and surgical treatment (Figure 1). The age of our patients ranged from 2 weeks to 85 years, with a mean age of 43.9 years. The peak incidence occurred in the fifth decade of life (Figure 2).

The diagnosis was confirmed by documenting fasting hypoglycemia with an inappropriately elevated insulin level, an elevated or inappropriately high C-peptide level, and negative results of a test for urinary sulfonylurea or insulin antibody in most patients as these tests became available.7 A total of 63 operations were performed; 32 were primary and 11 were reoperations (8 first and 3 second reoperations). Seven of these patients underwent their initial pancreatic explorations elsewhere and were referred to University of California, San Francisco, because of persistent or recurrent insulinoma. None of our patients had ectopic tumors, although 1 patient remained hypoglycemic after Whipple operation.

Eight (12%) of the entire cohort of 66 patients had multiple endocrine neoplasia type 1 (MEN 1). There were 4 men and 4 women with a mean age of 41 years (age range, 28-73 years). Four patients (50%) with MEN 1 had multiple tumors and 13% (1 patient) of the MEN 1 group had malignant insulinoma. Four of these patients with MEN 1 were previously described by Demeure et al.8 Other endocrine tumors in patients with MEN 1 were hyperparathyroidism (7 patients), pituitary adenomas (3 patients; 2 of the 5 tumors were prolactinomas), gastrinoma (3 patients), thymoma (1 patient), papillary carcinoma of thyroid (2 patients), hyperaldosteronism (1 patient), and hypotestosteronism (1 patient).

LOCALIZATION

Preoperative studies were done in 64 of the 66 patients (Figure 5). The tumor detection rates of arteriography, transhepatic portal venous sampling (THPVS), CT, MR imaging, MR imaging with gadolinium, and preoperative and intraoperative ultrasonography among our patients and the sensitivities of tumor localization were 47%, 55%, 24%, 30%, 40%, 50%, and 91%, respectively. Transgastric ultrasonography was done in 1 patient, and the result was positive for tumor. The frequency of use of all the above studies has changed during the years because of the availability of new localization procedures.

The trends of use of arteriography, CT, preoperative and intraoperative ultrasonography, MR imaging, and THPVS techniques are shown in Figure 5).

Selective angiography was first used at University of California, San Francisco, in 1965. The first CT was performed 6 years later, in 1971; transabdominal ultrasonography was introduced in 1976; gadolinium-gated MR imaging in 1987; and intraoperative ultrasonography in 1985. Intraoperative ultrasonography before or after a careful mobilization of the pancreas, in combination with intraoperative palpation, gave the best results. It identified 15 (88%) of 17 tumors in patients with sporadic disease and solitary tumors. It is currently the only localization technique we recommend for patients who have not had previous pancreatic operations. Our success rate of using intraoperative palpation was 76% vs 91% for intraoperative ultrasonography. Among the 20 tumors identified by intraoperative ultrasonography, there were no false-positive diagnoses. Nine patients had insulinomas that were not detected by the surgeon. Five of these tumors were located in the head of the pancreas, 2 were in the tail, and 3 had occurred in patients who were undergoing reoperation. These tumors ranged from 0.5 to 3 cm in size. All of these patients had successful operations and had normal glucose levels. Thus, in 9 (39%) of the 23 patients in whom intraoperative ultrasonography was used, the information obtained substantially influenced the surgical management. Ultrason-
ography also documents the position of the insulinoma in relation to the pancreatic duct and thus helps with removal.

The accuracy of preoperative localization techniques depends on the tumor size, position, firmness, and vascularity as well as the equipment and experience of the physician doing the investigation. Some of these tumors are quite soft, making them more difficult to identify even by palpation. The accuracy of MR imaging, MR imaging with gadolinium, CT, and preoperative ultrasonography increased as the size of the tumor increased. Thus, MR imaging accuracy increased from 0% to 75% as the tumor size increased from less than 1 cm to around 2 cm. The accuracy of MR imaging with gadolinium increased from 0% to 50% and then to 100% as the tumor size increased from 1 cm to 2 and 3 cm, respectively. The sensitivity of the CT scanning increased from 21% to 40% to 100% as tumor size increased from 1 cm to 3 and 6 cm, respectively. Currently, however, CT scanning in our institution is primarily used for screening patients for malignant insulinomas with liver metastases rather than for localization of insulinomas. Arteriography did not demonstrate improved sensitivity with increased tumor size. This is probably because the vascularity of the tumor is as important as tumor size for successful detection. The results of transhepatic portal venous sampling for insulin, as expected, did not depend on tumor size. Intraoperative ultrasonography gave excellent results for all tumor sizes. Twenty of 22 tumors were localized by this technique. The 2 tumors that were not detected were 1 cm and 2 cm in diameter. The 1-cm tumor was situated in the hilum of the spleen and was identified during a spleen-preserving distal pancreatectomy. The other missed tumor was in the tail of the pancreas.

Computed tomography, arteriography, and MR imaging gave false-negative results in 76%, 53%, and 70%, respectively. Other techniques shown in Figure 6 had a false-negative result rate of less than 50%. Tumor location did not appreciably influence the success rate of the various localization procedures (Table).

Two of 7 patients with multiple tumors (1 with a malignant insulinoma) had to undergo reoperations because the additional tumors were missed during the first surgical exploration in 1 patient. The other patient, who also had malignant gastrinomas with hepatic metastases, was cured after 3 operations involving total pancreatectomy, subtotal gastrectomy, and hepatic resection.
Intraoperative Ultrasonography
Palpation
THPVS
Preoperative Ultrasonography
Arteriography
MR Imaging With Gadolinium
MR Imaging
CT

Figure 6. Sensitivities of localization techniques. THPVS indicates transhepatic portal venous sampling; MR, magnetic resonance; and CT, computed tomography.

No localization technique identified all of the tumors in the 7 patients with MEN 1 and multiple pancreatic neoplasms.

SURGICAL PROCEDURES AND OUTCOME

Sixty-two (94%) of the 66 patients were successfully treated. Among the 4 patients who were not successfully treated, 1 had extensive metastatic insulinoma and did not undergo an operation, 1 patient with MEN 1 and multiple tumors remained hypoglycemic after subtotal pancreatectomy, and 1 leucine-sensitive child remained hypoglycemic after subtotal pancreatectomy. One patient died 17 days after her initial exploration and gastrectomy because of metastatic insulinoma. Among our patients the following surgical procedures were performed: enucleation of the insulinoma in 38 patients, distal pancreatectomy in 12, subtotal pancreatectomy in 9, Whipple procedure and total pancreatectomy in 1, and only exploration when no insulinoma was detected in 2. Overall, during all the operations, splenectomy was performed in 21% (n = 13) of all patients and in 11 (52%) who had distal or subtotal pancreatectomy. Forty-six (90%) of our surviving patients were cured after the first exploration (51 primary operations). Of the 6 patients not cured after the first exploration, 2 had hyperplasia or nesidioblastosis, 1 had multiple tumors, and 1 had a benign tumor embedded deeply in the tail of the pancreas. Two of these patients who were not cured had MEN 1. Eight patients underwent a first reoperation. In 7 of these patients, additional tumors were found, and 6 (75%) were successfully treated. One of these patients developed diabetes mellitus. Of the 2 patients (67%) cured after the third exploration, diabetes mellitus developed in 1 patient after a total pancreatectomy.

COMMENT

Insulinoma can usually be accurately diagnosed and successfully treated. Analysis of our cases documents a success rate (94%) similar to that reported by others,2-4 and the best localization procedure is intraoperative ultrasonography and palpation by an experienced surgeon.2-4 There continues to be debate about what localization procedure or combination of localization procedures should be used for the preoperative identification of insulinomas. Our study, although involving a limited number of patients, suggests that CT, MR imaging, MR imaging with gadolinium, and preoperative ultrasonography are not accurate enough to be recommended for most patients. Similar results have been reported in most but not all other medical centers.4-6 Radionuclide scanning with octreotide has been reported to be moderately useful9 or not useful10 for localization of insulinomas. Results of such scanning were negative in 7 of 7 of our patients. Although the sensitivities of the techniques listed increases, with a sensitivity of 70% to 100% for tumors larger than 3 cm, these tumors are almost always easy to identify by a surgeon during the operation. Also, most insulinomas are small, with an average diameter of 1.8 cm among our patients, which limits the value of these techniques. In one series, 90% were less than 2 cm in diameter and 50% were less than 1.3 cm.11 We recommend CT or MR imaging for preoperative evaluation of the liver to detect hepatic metastases, or large and possibly malignant insulinomas in the head of the pancreas.

The results of THPVS and arteriography did not depend on tumor size. The detection of the tumor by arteriography depends on both tumor vascularity and tumor size. Arteriography may therefore be a useful localization procedure in selected patients12 but is used infrequently today in our medical center for this purpose. The sensitivity of arteriography for detection of tumors less than 1 cm in diameter among our patients in this series was 71%. Unfortunately, our overall sensitivity for arteriography was only 47%. The use of THPVS detected 66% of the tumors less than 1 cm in diameter, with an overall detection rate of 53%. The drawback of the THPVS is that it is invasive, is uncomfortable for the patient, and could potentially result in complications. This procedure has been replaced by a variation of the Imamura procedure.13 We recommend the Imamura-Doppman procedure for patients with persistent or recurrent insulinoma.
Intraoperative ultrasonography identifies insulinomas with 90% to 100% sensitivity, and 91% were identified among our patients. Some experts have suggested that this procedure eliminates the need for other preoperative localization procedures. The low false-positive rate makes this method more valuable because it does not allow a false diagnosis of adenoma in a nodular-feeling pancreas. This is especially critical in the pancreas after surgery, where nodularity and scarring may lead to unnecessary dissection. In addition, intraoperative ultrasonography provides assistance in visualizing the anatomical details during the operation, such as the relationship of the insulinoma to the pancreatic duct, thus helping to guide the surgeon and to decrease the risk of a postoperative fistula. Intraoperative palpation was 76% accurate, being second in sensitivity to intraoperative ultrasonography.

One reason for the increased sensitivity of intraoperative ultrasonography is that some insulinomas are soft or of a consistency similar to that of the pancreas, thus making the tumor difficult to palpate. Another reason is that some insulinomas are also situated deeply within the pancreas. There also was a correlation between sensitivity of palpation and the size of the tumor. Thus, for tumors less than 1 cm in diameter, the sensitivity of palpation was 69%, whereas for tumors in the range of 1.2 to 3 cm it was 79%. Intraoperative ultrasonography helped identify 9 palpable tumors, thus preventing unsuccessful operations. Intraoperative ultrasonography also decreases the risk of missing multiple tumors even after 1 tumor is identified. Intraoperative ultrasonography in combination with intraoperative palpation after careful mobilization of the pancreas gives the best results, and we and others recommend this approach for patients who have not had previous pancreatic operations.

For patients requiring reoperation, however, we recommend gadolinium-gated MR imaging scanning and the Imamura procedure after reconfirming the diagnosis and reviewing the operative notes and histological findings. Intraoperative ultrasonography is also useful during reoperations and is recommended because small differences in texture between the normal tissue and the tumor may be obscured by scars and inflammation from the first procedure.

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REFERENCES

In your next patient with an occult tumor, not localized by intraoperative ultrasonography, would you be prepared to do a spleen-saving limited distal pancreatectomy? This excellent paper will become an important reference in clinical pathways to localize these tumors, saving both patients and society expense and inconvenience.

Hernan Vargas, MD, Torrance, Calif: Would you comment on whether the success of the surgery was measured by postoperative euglycemia? My second question is: recently octreotide scan has been used for localization of neuroendocrine tumors of the pancreas. Do you have any recent experience with this study specifically for insulinomas?

Ronald Weigel, MD, Stanford, Calif: Could you specifically comment on how intraoperative ultrasound correlates with preoperative endoscopic ultrasound?

Maria Allo, MD, San Jose, Calif: Do you do intraoperative hormonal assay to document that the lesion is actually the insulinoma, particularly in your MEN patients?

Edward Phillips, MD, Los Angeles: Have you attempted laparoscopic intraoperative ultrasonography and laparoscopic excision of insulinomas?

Dr Clark: Dr Passaro, we did not analyze our data before and after ultrasound was introduced and probably should do that. I would assume from my own experience that ultrasound makes a difference. Most insulinomas are fairly firm and you can feel them quite clearly, but there are some, as Ms Bouchman mentioned, that are the same consistency as the pancreas. One therefore cannot feel them. Dr Allen E. Siperstein has participated during many of these operations. He is a superb ultrasonographer and surgeon. To emphasize the importance of intraoperative ultrasonography, there was a patient with a possible insulinoma in the head of the pancreas. Although we suspected the site of the insulinoma by this study, the soft tumor could not be palpated. The ultrasound findings certainly avoided a failed operation in this patient.

Who should do the ultrasound examination? I do not believe that it matters whether a radiologist or surgeon does the study, but you want a good ultrasonographer or you want to become one yourself so that you can trust the results. Initially we had radiologists’ help, but now we do it ourselves. We did not have any false positives, but there are a lot of nodes around the pancreas, and they have a slightly different pattern than an insulinoma and could result in a false-positive study.

Does ultrasound identify the insulinoma or just confirm its position? Well, it is both. Sometimes one feels the tumor right away. One can often palpate a suspected insulinoma by palpating the pancreas through the transverse mesentery.

In response to the question about the 2 insulinomas that were missed by ultrasonography, 1 was my patient. I could not find the tumor either by palpation or by ultrasonography. I therefore decided to do a subtotal pancreatectomy or hemipancreatectomy, thinking that the patient may have nesidioblastosis or a small or soft and therefore difficult to identify insulinoma. I started to mobilize the distal pancreas and found a small insulinoma just off the end of the tail right in the hilum of the spleen. This site is difficult to examine because the probe head does not fit well in this area. I am not sure why the other ultrasonogra examination missed a tumor in the tail of the pancreas, as it was not my patient.

It is controversial whether to do a “blind” distal pancreatectomy when the insulinoma cannot be found. We do know that 99% of insulinomas are situated in this pancreas. Pediatric surgeons do distal or subtotal pancreatectomies all of the time, because nesidioblastosis is much more common in newborns than in adults.

Is it necessary to do intraoperative ultrasonography if preoperative transgastric ultrasonography is available? Dr Weigel mentioned there is some enthusiasm for preoperative transgastric ultrasonography of the pancreas. Most believe that this procedure is probably the best preoperative study to identify small tumors in the pancreas. Our experience is limited with transgastric ultrasonography, and we only had several patients where that was done. It was useful, but our experience is still too small to adequately evaluate it.

Octreotide scanning is not very helpful for localizing insulinomas, since fewer than 30% of insulinomas are identified by this expensive study. In my opinion, it is a waste of money to use octreotide scans in patients with insulinomas.

Dr Allo asked if we did the Doppman-Imamura procedure to identify this site of the insulinomas. We use this study rather than doing transhepatic catheterization of the splenic vein and pancreatic veins, as we formerly did; this is because the Doppman-Imamura procedure is a less invasive procedure. This test is useful, but we only use it in patients who have persistent or recurrent disease.

Dr Phillips, to date we have limited experience with laparoscopic removal of insulinomas. It makes sense to try it in patients whose tumor can be localized preoperatively or perhaps during a laparoscopic procedure. Dr Siperstein and Dr Mulvihill have done a few patients laparoscopically. If a patient had a transgastric ultrasound and an insulinoma was identified, laparoscopic removal would be useful. This would not be of benefit in patients with multiple endocrine neoplasia, because these patients usually have multiple tumors.