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# The Ultrasonic Detection of Insulinomas During Surgical Exploration of the Pancreas

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**The sensitivity of preoperative imaging was evaluated for the localization of insulinomas in 2 series of 54 and 17 patients, respectively. In the first series, diagnosis was obtained with ultrasonography (US) in 14.8%, with computed tomographic (CT) scan in 60%, and with arteriography and/or angio CT scan in 75% of patients. In the second series, US, CT scan, and arteriography were performed preoperatively showing a sensitivity of 53% of one or more of the imaging techniques. The last 17 patients all underwent intraoperative pancreatosonography, and the insulinoma was localized in each.**

**Considering the high reliability of intraoperative ultrasonography, and the high costs and low benefits of other current diagnostic techniques, a new management plan is suggested for patients with a definite laboratory diagnosis of insulinoma.**

Insulinomas were the first endocrine tumors to be described 60 years ago [1]. Although that first report referred to a case of carcinoma, 90% of insulinomas are benign [2]. The incidence is low (1 case/year per million people): females are more often affected than males; and the age of onset is 30–60 years. Organic hyperinsulinism is most often caused by an insulinoma [3] and at present its diagnosis is based on clinical and biochemical data [4, 5]. Microadenomatosis and β-cell hyperplasia are extremely rare, the incidence reported being lower than 10% of patients with hyperinsulinism [6].

Preoperative localization of the tumor by currently employed diagnostic means has a poor sensitivity [7–11]. Presurgical ultrasonography is positive in only 30% of patients and is limited by the retroperitoneal location of the pancreas [8]. Computed tomography (CT) is effective for the diagnosis of insulinoma in no more than 20–30% of patients [8, 12]. Angio CT scan and selective angiography are diagnostic only in 60–70% of patients [7, 12–15].

Better results can be obtained by transhepatic portal venous sampling (THPVS) along the pancreatic vein [16–21]. Nevertheless, this technique may not allow the evaluation of small hormone gradients as they are observed in microadenomatosis, nesidioblastosis, and β-cell carcinomas [16]. Transhepatic percutaneous venous sampling does not provide precise localization of the tumor, and if no tumor is found on exploration, enucleation is impossible and blind segmental resection must be performed based on the site of the insulin gradient [11]. This technique is also quite complicated. The therapy of choice for insulinomas is surgical resection, and it is curative in 90% of patients.

Precise location of the tumor avoids blind resection which is considered an unacceptable procedure by some authors [11]. Some clinicians prefer a second look after 1 or 2 years (if the first exploration was negative for tumor) especially if the symptoms are manageable with medical treatment [5, 22, 23]. The surgeon must decide in favor of enucleation or resection, carefully avoiding any injury to the Wirsung duct or its branches [12].

Intraoperative glucose monitoring represents an interesting alternative. Perioperative portal venous sampling with quick immunoreactive insulin (IRI) assays [24] can localize tumors less than 1 cm in size, but it prolongs the operation and is not devoid of false-positives [25]. Intraoperative ultrasonography (US) with a high-frequency scanner, directly applied on the pancreas surface, opens new prospectives. Its high resolution allows thorough exploration of pancreatic parenchyma and the definition of focal lesions a few millimeters in diameter, even those located deeply within the pancreas [10, 26, 27].

Intraoperative US permits fine-needle aspiration with cytologic diagnosis or Tru-cut® biopsy in doubtful cases [28]. This article presents the results of a joint research study on the use of intraoperative US for the localization of insulinomas, carried out at the universities of Rome and Padua. Intraoperative US provides accurate information about the site of β islet-cell tumors, facilitating enucleation of the insulinoma instead of blind distal resection [11].

## Material and Methods

The sensitivity and the specificity of various preoperative diagnostic tools have been compared with special regard to ultrasonography, CT scan, angio CT, and arteriography in 54

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**Table 1.** Islet-cell tumor localization in 17 patients with hyperinsulinism.

| Patient no. | Preoperative localization (echography, CT, angiography) | Surgical localization |
|---|---|---|
| 1 | + | + |
| 2 | + | + |
| 3 | + | + |
| 4 | − | + |
| 5 | − | − |
| 6 | + | + |
| 7 | − | + |
| 8 | − | + |
| 9 | + | + |
| 10 | + | + |
| 11 | + | + |
| 12 | − | − |
| 13 | − | − |
| 14 | + | ++[a] |
| 15 | − | − |
| 16 | − | + −[b] |
| 17 | − | + |

[a] Two insulinomas were present, both located surgically.
[b] Two insulinomas were present, but only 1 was visible.

cases of hyperinsulinism observed in the Department of Endocrinology of the University of Rome from 1968 to 1986.

Intraoperative pancreatic sonography was performed on a second series of 17 patients observed in the Department of Surgery of the University of Rome and the University of Padua from 1982 to 1986. Ultrasonography, CT scan, and arteriography were carried out preoperatively after a $\beta$ islet-cell tumor had been diagnosed on the basis of laboratory studies. The accuracy of intraoperative US, the ultrasound imaging, the localization and size of tumor, the operative procedure, and the late outcome were all analyzed, evaluating the sensitivity of preoperative investigations and the significance of intraoperative US (Tables 1, 2).

All patients were studied with a 5, 7.5, and 10 MHz real-time scanner (High-Stoy SR 100B; SAL-35A Toshiba). The probes were gas-sterilized or, when possible, immersed in the sterilizing fluid glutaric-dialdehyde (Cidex®). (The use of this substance is permitted in Italy. The probe is thoroughly rinsed with sterile saline before use.) As an alternative, the probe can be enclosed in a sterile bag filled with gel to improve acoustic coupling.

The head of the pancreas was widely mobilized by a Kocher maneuver while the epiploic retrocavity was opened by a small omental incision and colon epiploic detachment. The mobilization of the pancreas is necessary for the ultrasonic exploration of its posterior aspect. A small quantity of lukewarm saline was introduced in the operative field in order to have a good acoustic window.

The exploration of the pancreas was systematically carried out with longitudinal scans, from right to left, in order to detect the relation of possible focal lesions with the choledochus, the mesenteric-portal axis, and the superior mesenteric artery. Then, a series of cranio-caudal scannings followed, after a 90° rotation of the transducer in order to find the course of the splenic vessels and the Wirsung duct, and to define their relation to possible nodular overgrowths.

## Results

Preoperative US was performed in 28 of 54 patients observed in the Department of Endocrinology with positive results in only 4 cases, appearing as the least sensitive (14.8%) study for the localization of insulinomas. CT scan was positive in 12 of 20 patients (sensitivity rate, 60%). Arteriography and angio CT scan was positive in 75% of patients (21 of 28 patients). With arteriography, 3 cases were false-positives, and 2 were partially positive (multiple adenomatosis). In 2 patients the study offered no information. The size of the tumor varied from 5 mm to 6 cm. Surgical exploration was negative in 7 (13%) of the 28 patients.

In the second series of 17 patients who underwent US, CT scan, and arteriography preoperatively, positive results were obtained in 8 patients with a sensitivity of this pool of investigations of 47%. The lowest sensitivity is attributed to US and the highest to arteriography. The rate of false-negatives was 53%. On positive selective arteriograms the neoplasias appeared as areas of hyperconcentration of contrast medium, with highly developed vascularity.

On surgical exploration of the pancreas, a typical ovoidal, small-sized mass was visible and palpable in 14 patients, sometimes emerging on the surface of the gland. In 4 patients the tumor was localized to the tail, in 2 to the head, and in 3 to the body. Two insulinomas were detected in 1 patient: 1 in the head and 1 in the body. In a second patient with 2 insulinomas, only the one located in the tail was visible. In 1 patient the tumor had a body-isthmic location. In another patient only a cephalic area of increased consistency was palpable and it demonstrated a malignant tumor. The sensitivity of surgical exploration in this series was 74% with a false-negative rate of 26%. On the other hand, intraoperative ultrasonography confirmed all clinical diagnoses demonstrating, in the absence of a true nodular lesion, a well-circumscribed area with a different echodensity, often located deeply in the parenchyma.

In 1 patient US was negative and blind resection of the body and tail was performed on the basis of laboratory data and symptoms. Histologic findings revealed $\beta$-cell microadenomatosis. In 15 of our patients the insulinomas appeared, on ultrasonography, as sonolucent, sometimes multilobulated lesions with a posterior accentuation of the echoes (Fig. 1). Two cases (1 with functional and laboratory characteristics of malignancy) appeared as a well-circumscribed area with increased echogenicity (Fig. 2). An insulinoma has, however, never presented as an isoechogenic tumor to the surrounding parenchyma.

The characteristic sonographic image of an insulinoma seems to be related to the scant stromal framework and the high cellularity which confers a strongly homogeneous aspect to the tumor. We believe that the 2 reported cases of hyperechogenic insulinomas may be due to their rich vascularity. The diagnostic sensitivity of intraoperative US for organic hyperinsulinism was 95%; for insulinomas it was 100%.

Six islet-cell tumors were located in the tail, 6 in the body, and 5 in the head. One was body-isthmic. The size varied in this series from 0.5 mm to 4 cm.

Because of intraoperative ultrasonography, 8 patients were managed with simple enucleation of the tumor. Six patients were treated with caudal pancreatectomy. In 2 patients a

**Table 2.** Clinical findings and surgical management in 17 patients with hyperinsulinism.

| Patient no. | Intraoperative echography | Echographic features | Site | Histological findings | Surgical management |
|---|---|---|---|---|---|
| 1 | + | Hypoechogenic | Tail | Insulinoma | Distal pancreatectomy |
| 2 | + | Hypoechogenic | Body | Insulinoma | Enucleation |
| 3 | + | Hyperechogenic | Head | Malignant insulinoma | Enucleation |
| 4 | + | Hypoechogenic | Head | Insulinoma | Enucleation |
| 5 | – | – | – | Microadenomatosis | Distal pancreatectomy |
| 6 | + | Hypoechogenic | Head-body | Insulinoma | Enucleation |
| 7 | + | Hypoechogenic | Body | Insulinoma | Enucleation |
| 8 | + | Hypoechogenic | Body | Insulinoma | Distal pancreatectomy |
| 9 | + | Hypoechogenic | Tail | Insulinoma | Distal pancreatectomy |
| 10 | + | Hypoechogenic | Tail | Insulinoma | Distal pancreatectomy |
| 11 | + | Hyperechogenic | Head | Insulinoma | Duodenocephalopancreatectomy |
| 12 | + | Hypoechogenic | Tail | Insulinoma | Enucleation |
| 13 | + | Hypoechogenic | Head | Insulinoma | Enucleation |
| 14 | + | Hypoechogenic | Head-body | 2 insulinomas | Duodenocephalopancreatectomy |
| 15 | + | Hypoechogenic | Body | Insulinoma | Enucleation |
| 16 | + | Hypoechogenic | Body-tail | 2 insulinomas | Distal pancreatectomy |
| 17 | + | Hypoechogenic | Tail | Insulinoma | Distal pancreatectomy |

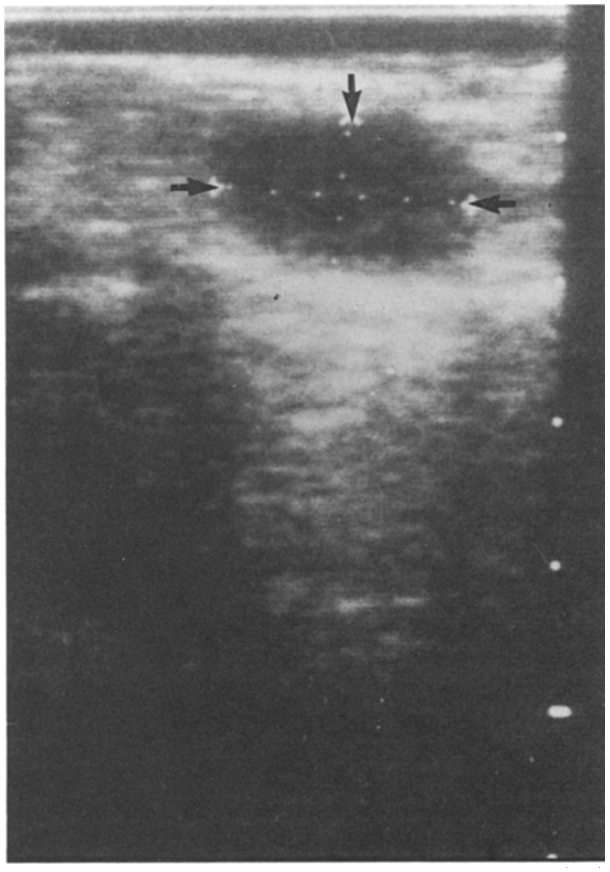

**Fig. 1.** Ultrasonographic patterns (*arrows*) of insulinoma: hypoechogenic mass of pancreatic body.

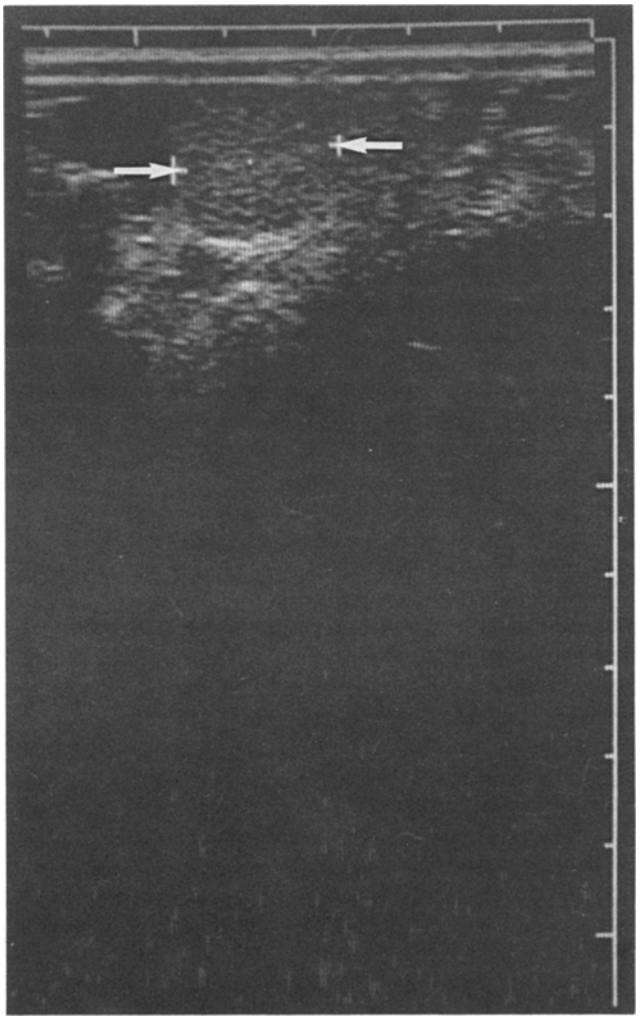

**Fig. 2.** Ultrasonographic patterns (*arrows*) of insulinoma: hyperechogenic mass of pancreatic head.

duodenal-cephalopancreatectomy was performed and only 1 patient underwent blind distal resection. Postoperative follow-up has demonstrated favorable results with 100% survival rate and recovery from hypoglycemic symptoms.

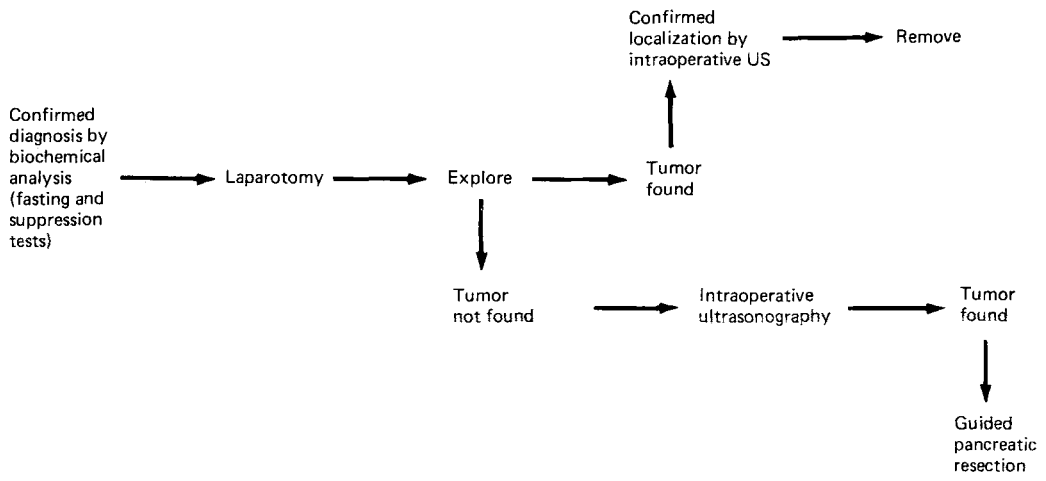


**Fig. 3.** New management plan for patients with confirmed diagnosis of insulinoma.

## Discussion

In 90% of patients, insulinomas present as solitary lesions between 1 and 2.5 cm in size; however, lesions of smaller (5 mm) and larger (15 cm and 1,500 g) size have been reported [7]. Ninety-nine percent of tumors are intrapancreatic. Possible extrapancreatic localizations in decreasing order of frequency are: the duodenal wall and the periduodenal area, the jejunum, the ileum, and the spleen [29]. Patients who present with multicentricity have a greater chance of having multiple endocrine neoplasia type I (MEN I) [10, 30, 31].

On the basis of the data available in international reports and our own experience with 54 patients with organic hypoglycemia we can state that this diagnosis can be made by: (a) neuroglycopenic symptoms during fasting, (b) hypoglycemia (< 40 mg/100 ml = 2.2 mmol/l), (c) relief of symptoms after glucose administration, and (d) determination of the glycemia/insulinemia ratio [4, 11, 32, 33]. Besides the prolonged fasting test, indications of diagnostic value can be obtained in cases of endogenous hyperinsulinism using the somatostatin and diazoxide suppression test [5, 34, 35].

The surgical management is strongly influenced by the morphological features of the tumor on the one hand and the possibilities of localization on the other [36]. Fourteen percent of these tumors have sizes less than 1 cm and cannot be visualized preoperatively, despite good diagnostic procedures [8, 11]. Ten percent of insulinomas are neither visible nor palpable on bimanual exploration of the pancreas [7, 37, 38]. These diagnostic difficulties are due to the cephalic site of the tumor and its deep location within the gland [19]. The retroperitoneal position of the pancreas, the anatomical features, and previous silent inflammatory processes contribute to the difficulty of manual exploration. These conditions, along with the presence of multiple locations, nodular hyperplasia, and microadenomatosis probably lead to a large number of invasive diagnostic procedures, exploratory laparotomies, blind distal resections, and serial caudo-cranial resections usually followed by failure or unexplained transitory improvements (45–50%) [39–41]. There is no proven evidence that postponing the surgical procedure, and managing the hyperinsulinism with diazoxide, will increase the future chances of localizing the insulinoma [7, 32].

Our second series of 17 patients confirms the above-mentioned considerations: only 45% of insulinomas were localized preoperatively, whereas the surgical examination was positive in 70% of patients.

Intraoperative ultrasonography with high-resolution scan has allowed a thorough and accurate exploration of the gland. The localization of tumors of less than 1 cm has been possible, most of which were undetected by preoperative studies as well as surgical exploration. In 1 of our patients intraoperative ultrasonography demonstrated its significance by localizing a second insulinoma that had been missed during surgical exploration. The resection became more extended but curative.

The diagnostic importance of intraoperative US for organic hyperinsulinism has been well proven in our series, with a 95% success rate. The only case in which intraoperative US failed was a case of diffuse $\beta$-cell microadenomatosis as demonstrated by histological examination. For the remaining patients these tumors present with peculiar echostructural appearances that permit their differentiation from other focal lesions: a hypoechoic area with posterior accentuation of echoes; while cystic formations of the pancreas are perfectly round, devoid of echoes, and with a posterior accentuation of the echoes. Tumors with characteristics of malignancy, on the other hand, often present with a reduced dyshomogeneous echogenicity and with rather irregular contours.

Endocrine tumors do not always present with the characteristic sonolucent appearance. In fact, we found 2 patients with insulinomas, 1 with suspected malignancy, who presented with an increased echogenicity.

On the basis of the above-mentioned considerations, contributions present in the literature, and our own experience, we state that the intraoperative use of ultrasonography represents a progressive step in the diagnosis of insulinoma and in the formulation of a more correct surgical strategy [10]. The demonstration of the value of intraoperative US has, on one hand, decreased the number of blind pancreatic resections and has, on the other hand, eliminated those cases in which a negative laparotomy was followed by diazoxide suppression until intol-

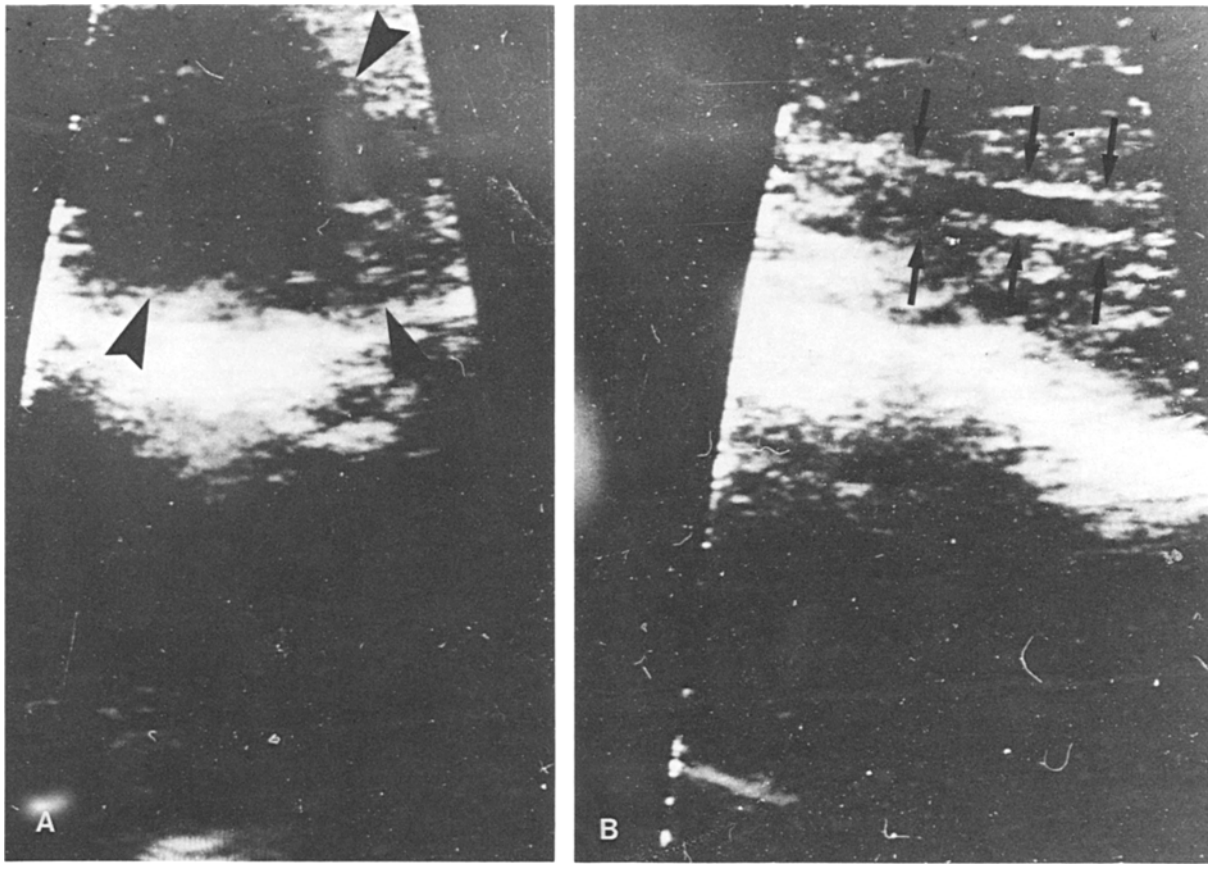


**Fig. 4.** Ultrasonographic visualization of **A.** cephalic insulinoma (*arrowheads*) and **B.** normal Wirsung duct (*arrows*).

erance to the drug made a second laparotomy, and often a blind resection, mandatory. The results of surgical management in our series are the best proof.

There is a variable discrepancy between preoperative localization and surgical exploration that other authors have also noticed [8, 42]. Adding the encouraging results achieved by us and by others [9–11, 25–27, 43] we suggest the management plan outlined in Fig. 3 for those medical centers that possess adequate facilities and competence.

Intraoperative sonography is not limited to the localization of the islet tumor. In fact, it supplies useful information on the relation of focal lesions to the pancreatic vessels and ductal system and to the choledochus, as is shown in one of our patients in whom a cephalic insulinoma was closely contiguous to an otherwise normal sized Wirsung duct (Fig. 4). These elements are of great value in directing the surgical procedure, suggesting enucleation of the tumor instead of the more extensive pancreatic resection. The economic aspect of this diagnostic technique must also be taken into account when compared with the high costs and the lesser benefits offered by the current invasive diagnostic procedures.

**Résumé**

La sensibilité de l'imagerie pré-opératoire permettant la localisation des insulinomes a été étudiée dans 2 séries de 54 et 17 sujects. Dans la première série le diagnostic fut posé par l'échographie dans 14.8% des cas, par la tomodensitométrie dans 60% des cas, par l'artériographie et/ou l'angiotomodensitométrie dans 75% des cas. Dans la seconde série, l'échographie, la tomodensitométrie et l'artériographie furent pratiquées avant l'intervention avec une sensibilité de 53% pour l'une ou pour plusieurs techniques. Chez les 17 derniers malades l'échographie opératoire fut systématiquement pratiquée et permit la localisation de la tumeur dans 100% des cas.

Considérant la haute fiabilité de l'échographie opératoire, le coût élevé et les faibles résultats des autres techniques de diagnostic, un nouveau plan d'investigation est proposé pour explorer les malades qui présentèrent certains signes biologiques d'insulinome. Il repose sur la localisation per-opératoire de la tumeur par l'échographie, méthode qui peut être pratiquée dans des centres spécialisés.

**Resumen**

La sensibilidad de la imagenología preoperatoria para la localización de insulinomas fue evaluada en 2 series de 54 y 17 pacientes respectivamente. En la primera serie, el diagnóstico fue logrado con ultrasonografía en 14.8%, con escanografía computadorizada en 60%, y con arteriografía y/o angiografía con escanografía computadorizada en 75% de los casos. En la segunda serie, la ultrasonografía, la escanografía computadori-

zada, y la arteriografía fueron realizadas preoperatoriamente demostrando una sensibilidad de 53% en una o más de las técnicas de imagenología. En los últimos 17 pacientes se realizó pancreatosonografía, la cual permitió la localización del tumor en 100% de los casos.

En consideración a la elevada confiabilidad de la ultrasonografía intraoperatoria, y los altos costos y bajo rendimiento de las técnicas corrientes de diagnóstico, se sugiere un nuevo plan de manejo para pacientes con un diagnóstico de laboratorio certero de insulinoma. Se fundamenta en la localización ultrasonográfica intraoperatoria del tumor, la cual puede ser aplicada en los más comprensivos centros médicos.

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