

Consensus of the French Endocrine Society

Surgical treatment^{☆,◇}

Traitement chirurgical

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Following biological diagnosis of insulinoma and imaging, surgical treatment is required.

We consider it preferable to have two concordant examinations locating the insulinoma. CT and MRI are certainly the reference examinations. Cholangio-Wirsung MRI also indicates the distance between the tumour and Wirsung's duct. If either or both examinations prove negative, endoscopic ultrasound should be performed; the need for general anaesthesia is the reason why this examination is not systematically performed in first line. Tattooing the tumour by methylene blue injections is certainly helpful for laparoscopic resection.

At the present time, no nuclear imaging examinations have demonstrated particular interest; they are therefore used only when the other examinations are negative.

Venous catheterization after intra-arterial calcium stimulation is invasive and difficult to interpret. It should be performed only as a last resort, and probably only by experienced teams; it must be borne in mind that it merely "regionalises" the tumour in the pancreas.

Imaging assessment should allow the surgeon:

- to localize the tumour within the pancreas;
- to measure the distance between the tumour and Wirsung's duct so as to be able to consider enucleation;
- to check that the rest of the pancreas is normal and thus that the lesion is isolated, and;
- to check for absence of lymph nodes or metastases.

The rate of "occult" insulinoma reached 10–27% in the 1990s, but should no longer be encountered [1–3].

Given the low incidence of insulinoma, whether benign or malignant, no comparative studies or meta-analyses have been carried out. The level of evidence in favour of surgery is thus weak (level 3 or 4). Nevertheless, scientific societies have published guidelines for the management of pancreatic neuroendocrine tumour.

Several resection procedures are possible.

1. Enucleation

Macroscopically, insulinoma presents as a well-contoured, rounded, regular, hard, pink or brown lesion. It is usually surrounded by a capsule, absence of which indicates malignancy. These characteristics make enucleation the attitude of choice whenever possible. If resection is complete, the success rate exceeds 90% [4].

Enucleation is performed after thorough exploration of the pancreas, locating all lesions. Two-finger palpation of the entire gland, including head, isthmus and posterior side, and an ultrasound scan should be performed prior to any surgery [5,6]. Dissection is performed up against the tumour. Resection quality is checked by extemporaneous histologic examination and venous glycaemia and insulinaemia assay, preferably with stimulation [7–10], although assay is not mandatory. Depending on

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the depth of resection and especially on the distance between the margin and Wirsung's duct, the resection bed may be protected either by simple gluing or by a Y-shaped bow with contact drainage. Laparoscopy has not changed these principles (see Laparoscopy section).

Enucleation is indicated for all small (generally $\leq 2\text{--}3$ cm, depending on the author), superficial, pre- and peroperatively located lesions at more than 2–3 mm from Wirsung's duct and shown to be benign on extemporaneous histology [5,7,10,11]. The safety distance between insulinoma and Wirsung's duct should be checked on peroperative ultrasound, which may be coupled to Doppler to locate the large vessels [11]; if it is less than 2–3 mm, there is increased risk of pancreatic fistula [11,12]. If the dissection plane between the insulinoma capsule and the adjacent pancreatic parenchyma cannot be found, pancreas resection is advisable, as the risk of malignancy is elevated [6]; lymph-node resection should be associated [5,9].

Morbidity after enucleation is 30–50%, dominated by pancreatic fistula with associated increased risk of haemorrhage, deep sepsis and pleuro-parenchymatous complications that are always more severe in subjects with a naturally high BMI [5]. In a large majority of cases, fistula is grade A on the Bassi classification [13], not requiring invasive management [14]. The risk of fistula is increased in normal (friable) pancreatic parenchyma, by failure to respect safety margins and by Wirsung's duct lesions, and seems to be reduced by gluing [5,14]. No studies have proven the interest of new energy sources (laser) in preventing pancreatic fistula.

2. Left pancreatectomy

Left pancreatectomy consists in resecting the body and/or tail of the pancreas, not further than the right edge of the superior mesenteric vein. Splenic vessels should be spared to avoid splenectomy. Dissection of the splenic artery and vein should be in contact with them. At the splenic hilum, the tail of the pancreas may be difficult to dissect due to fatty tissue [15]. Closure may use staples, suture or a Y-shaped bow, as best suited; in laparoscopy, automatic stapling is preferred (see Laparoscopy section).

Left pancreatectomy with splenic sparing is indicated for any insulinoma in the tail of the pancreas in contact with Wirsung's duct or the splenic vessels, or if malignancy is suspected pre- or peroperatively (indurated, adherent lesion, dilation of upstream Wirsung's duct, suspect adenopathy, peripancreatic tissue invasion) [5,9,11]. So far as possible, the spleen should be spared, to limit the risk of infectious and thromboembolic complications [16,17]. Baring the splenic vessels incurs a risk of haemorrhage secondary to vessel wall erosion, usually induced by postoperative fistula, and of splenic infarction due to vessel torsion, although these two complications are exceptional [15]. Extemporaneous examination of the section and possibly venous insulin assay proceed as in enucleation.

Blind left pancreatectomy is no longer recommended [3,7,9,11]. If no lesions are found on painstaking pre- and peroperative exploration associating two-finger palpation of the whole gland, including uncus and posterior face, and peroperative

ultrasound, no surgery should be performed on the pancreas and the patient should be referred to a reference centre to rule out any other aetiology of hyperinsulinism, repeat the stimulation tests and complete the location examinations [7,18,19].

Morbidity following left splenopancreatectomy is dominated by the high rate of pancreatic fistula, which ranges, depending on the author and the definition, from 0 to more than 40%. Several well-conducted randomised trials comparing staple versus suture closure and laparoscopy versus laparotomy and two meta-analyses failed to single out one approach or closure method [20–22]. A meta-analysis [23] and a randomised study [24] identified three factors for pancreatic fistula: BMI superior to 27, extensive pancreatic resection (≥ 8 cm), and heavy blood loss (> 150 mL).

3. Pancreaticoduodenectomy (PD)

Pancreaticoduodenectomy is reserved for pancreatic head insulinoma non-amenable to enucleation due to deep location in contact with the principle pancreatic duct.

This is the heaviest form of pancreatic resection: mortality is about 3–4% and morbidity 30–40%, dominated by pancreatic fistula (15–25% of cases) and associated infectious or haemorrhagic complications [25–28]. Fistula is especially frequent in case of soft friable parenchyma or narrow Wirsung's duct, which are usually found with endocrine tumours, where pancreatic fistula following PD is especially frequent [29].

No comparative studies have reliably assessed the respective roles of PD and other treatments in this indication. However, the particularly high surgical risk for a benign condition calls for precise risk/benefit estimation taking account of physiological status and comorbidity. PD is a debateable option and, so far as possible, more limited resection, such as enucleation or central pancreatectomy, is preferable.

4. Medial pancreatectomy (MP)

Certain tumours, notably of the isthmus, where the pancreas is narrow, lie very close to Wirsung's duct, preventing safe enucleation. To avoid extensive resection of the pancreas for an insulinoma of the isthmus or body, medial pancreatectomy has been recommended. It is curative, resecting the entire tumour without risk of long-term sequelae such as exocrine or endocrine pancreatic insufficiency.

MP was first described in 1984 [30], and fully described in 2000 [31,32]. After a laparotomy or laparoscopy approach [33,34], the rear epiploic cavity is opened and the anterior side of the pancreas is exposed. Peroperative ultrasound confirms tumour location, checks that the tumour is isolated and determines its relations with Wirsung's duct (thus ruling out enucleation as an option). The superior mesenteric veins are released from the posterior side of the pancreas. The superior edge of the pancreas is dissected to isolate the splenic pedicle, which ideally should be spared. Once the pancreas has been released on either side of the tumour, it is sectioned with a margin of about 1 cm. In case of doubt, extemporaneous inspection of the section is useful.

There are no series in the literature specifically devoted to insulinoma managed by MP. Reported morbidity is thus for all types of tumour: 48% (range, 0 to 92%) for 539 observations reported between 2001 and 2009, mainly pancreatic fistula (mean, 31.6%; range, 0–63%) [35]; most resolved spontaneously, as the rate of revision surgery was only 4.2%. Surgical mortality was 0.7%; median hospital stay was 11 days. Two recent studies [33,34] reported initial experience of laparoscopic MP: morbidity was 33% and 44%, with fistula rates of 33% and 22%. Another recent study [36], comparing MP and left pancreatectomy, showed a significantly lower rate of postoperative diabetes with MP (24% versus 50%); likewise, no cases of preoperative diabetes were worsened by MP, versus 18%; there was no difference with respect to postoperative endocrine function. These findings are confirmed elsewhere [37,38]. Recurrence after MP mainly concerned papillary or mucinous pancreatic duct tumour, where extemporaneous section inspection could have allowed surgery to be modified [37–40]. Two cases were not endocrine tumours: one gastrinoma [33] and one tumour of uncertain malignancy [41].

To sum up, medial pancreatectomy is effective in insulinoma of the body or isthmus of the pancreas. It involves a risk of fistula that is comparable to or not much higher than in left pancreatectomy. It conserves functional pancreatic parenchyma, thereby limiting the endocrine impact of pancreatectomy.

5. Role of laparoscopy in the treatment of sporadic insulinoma

5.1. Existing literature

In all, 16 original articles and one study comparing laparotomy performed by a specialised team to the laparotomy results in the literature were retrieved [5,42–57]. The total number of laparoscopy patients for the 16 original articles was 274. Five single-centre [5,45,46,50,52] and two multicentre studies [43,54] had series of 20 or more. Three original articles and a review of the literature compared laparoscopy and laparotomy [5,53,54,57].

5.2. Relevance of the question

There are at present no prospective randomized studies comparing laparoscopic and laparotomic pancreatectomy. However, the best indications for laparoscopy seem to be benign or weakly malignant tumour requiring pancreatic resection without reconstruction (left pancreatectomy or enucleation).

Sporadic insulinoma, being benign, single and less than 2 cm in 90% of cases, is perfectly suited to laparoscopy.

The advantages of laparoscopy are, in principle:

- aesthetic (especially in case of enucleation, where the small size of insulinomas usually allows removal via the trocar opening);
- fewer non-specific complications and;
- shorter hospital stay.

The drawbacks are:

- the difficulty of locating the lesion, especially if not located preoperatively, as manual palpation is not available;
- technical difficulties, especially in tumours of the head of the pancreas.

5.3. Methodological comment

Pancreatic resection studies that covered all types of lesion or of endocrine tumour were not selected for the present study even if they included insulinomas, as there was no means of analysing results for insulinoma alone.

5.4. Early findings

In the 16 original articles, laparoscopic resection of insulinoma was scheduled in 274 patients; crossover was necessary in 62 (22.6%); crossover rates ranged from 0 to 44%. The seven studies with at least 20 patients made up 70% ($n = 194$) of the total number of laparoscopy patients; crossover was necessary in 43 (22%), with rates ranging from 5% to 41%.

Thirteen studies (58 patients) provided reasons for crossover: mainly, impossibility of locating the tumour under laparoscopy in 27 cases (46.5%) and technical difficulties (cephalic location, vascular contact) in 24 (41%).

In the four studies comparing laparoscopy and laparotomy, surgery time did not differ. Richards et al. [53], comparing the results in the Mayo Clinic series of insulinoma resected by laparotomy ($n = 215$) to a review of the literature on resection by laparoscopy, reported surgery times of 258 min for laparotomy and 318 min for laparoscopy, a non-significant difference. Overall, mortality was zero; overall morbidity ranged from 17% to 78% and specific morbidity (pancreatic fistula, effusion) from 14% to 78%. In two studies, overall and specific morbidity did not significantly differ between laparoscopy and laparotomy [5,57], whereas Richards et al. [53] found a significantly lower rate of specific morbidity in laparotomy (15% versus 27% for laparoscopy; $P < 0.05$), although this was comparing single-centre laparotomy results versus cumulative results for literature series in laparoscopy.

Mean hospital stay ranged from one to 17 days. Roland et al. [54] reported significantly shorter stays with laparoscopy (13.4 ± 4 versus 19.1 ± 4.3 for laparotomy; $P = 0.02$); two other studies reported no such difference [53,57].

In conclusion, several procedures are available to insulinoma surgery. For benign lesions, pancreas-sparing techniques are preferable. The type of surgery depends on tumour location.

Malignant insulinoma is dealt with in another chapter. One problem arising is that of large (> 3 cm) insulinoma, for which lymph-node sampling and extemporaneous analysis is recommended so as not to overlook metastatic nodes and neglect lymph-node resection.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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