

# Well-Differentiated Pancreatic Tumor/Carcinoma: Insulinoma

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## Epidemiology and Clinicopathological Features

### *Minimal Consensus Statement on Epidemiology*

Insulinomas are the most common functioning endocrine tumors of the pancreas, with an estimated incidence of 1–3 per million per year. There is an age-specific incidence peak in the fifth decade of life and the incidence is slightly higher in women than in men. Approximately 10% are multiple, less than 10% can be malignant, and 5–10% are associated with the MEN-1 syndrome. These latter tumors are usually multiple and can be malignant in up to 25% of cases. After initial recognition of the key symptoms, careful laboratory testing, sophisticated imaging and eventually meticulous surgery follows in most cases. It is evident that a multidisciplinary team approach is required [1, 2].

### *Histopathology of Insulinomas – General*

The WHO classifies functioning endocrine tumors of the pancreas into 3 well-defined categories: [1] well-dif-

ferentiated endocrine tumors, with benign or uncertain behavior at the time of diagnosis; [2] well-differentiated endocrine carcinomas with low-grade malignant behavior, and [3] poorly differentiated endocrine carcinomas, with high-grade malignant behavior. Most insulinomas are classified as well-differentiated endocrine tumors, according to the WHO criteria (WHO 1), but occasionally they belong to the WHO 2 or 3 group [3].

### *Minimal Consensus Statements on Histopathology and Genetics – Specific*

#### *Histopathology*

A detailed description of the macroscopic, microscopic and immunohistochemical findings, in order to support the diagnosis of insulinoma and to allow for its correct classification according to the current WHO classification is indispensable. The necessary

**Table 1.** Requirements for the histopathological diagnosis of an insulinoma

Macroscopic evaluation	Microscopic evaluation	Immunohistochemistry
Tumor size (largest diameter)	Mitotic index (expressed as the number of mitoses in 10 HPF)	Chromogranin A expression (yes/no; if yes, % of cells positive) Insulin expression (yes/no; if yes, % of cells positive)
Lymph node metastases (yes/no; if yes, number and location of metastatic lymph nodes)	Angioinvasion (yes/no)	Synaptophysin expression (yes/no; if yes, % of cells positive) Insulin expression (yes/no)
Extra-pancreatic invasion (yes/no)	Perineural invasion (yes/no)	Ki-67 index (expressed in % of cells positive)
Distant metastases (yes/no/unknown)		Insulin expression (yes/no; if yes, % of cells positive)

information is listed in table 1. Evaluation of the mitotic index and Ki67 index is required. Ancillary tests include the immunohistochemical detection of chromogranin A and synaptophysin. The immunohistochemical determination of insulin expression by tumor cells is not absolutely necessary for diagnosis. Some insulinomas do not stain positively for insulin despite the correct diagnosis. This might be caused by the rapid release of insulin from the insulin-producing cells [3]. Cytology is not recommended as a standard diagnostic procedure.

#### Genetics

Germline DNA testing for hereditary tumor syndromes is only recommended in specific situations: a familial history or clinical findings suggesting MEN-1 or von Hippel-Lindau disease (VHL); the presence of multiple tumors; or the demonstration of precursor lesions in the peritumoral pancreatic tissue. Mutation analysis should be performed to test for menin or VHL mutations (following informed consent).

### Diagnostic Procedures: Clinical Assessment with Laboratory Tests, Imaging and Nuclear Medicine

#### Clinical Assessment with Laboratory Tests – General

Hypoglycemic symptoms can be grouped into those resulting from neuroglycopenia (commonly including headache, diplopia, blurred vision, confusion, dizziness, abnormal behavior, lethargy, amnesia, whereas rarely, hypoglycemia may result in seizures and coma) and those resulting from the autonomic nervous system (including sweating, weakness, hunger, tremor, nausea, feelings of warmth, anxiety, and palpitations) [4, 5]. Because symptoms occasionally are not specific and insulinoma can mimic several pathological conditions, a broad differential diagnosis should be considered but major distinction should be made between patients with insulinoma and noninsulinoma pancreatogenous hypoglycemia (NIPHS)

[6]. However, Whipple's triad remains fundamentally sound. This triad consists of:

- 1 Symptoms of hypoglycemia.
- 2 Plasma glucose level  $\leq 2.2$  mmol/l ( $\leq 40$  mg/dl).
- 3 Relief of symptoms with administration of glucose.

#### Minimal Consensus Statements Clinical Assessment – Specific

The diagnosis of insulinoma can be absolutely established using the following 6 tight criteria [4, 5]:

- Documented blood glucose levels  $\leq 2.2$  mmol/l ( $\leq 40$  mg/dl).
- Concomitant insulin levels  $\geq 6$   $\mu$ U/l ( $\geq 36$  pmol/l;  $\geq 3$   $\mu$ U/l by ICMA).
- C-peptide levels  $\geq 200$  pmol/l.
- Proinsulin levels  $\geq 5$  pmol/l.
- $\beta$ -Hydroxybutyrate levels  $\leq 2.7$  mmol/l.
- Absence of sulfonylurea (metabolites) in the plasma and/or urine.

Further controlled testing includes the 72-hour fast, which is the gold standard for establishing the diagnosis of insulinoma [7]. When the patient develops symptoms and the blood glucose levels are  $\leq 2.2$  mmol/l ( $\leq 40$  mg/dl), blood is also drawn for C-peptide, proinsulin and insulin. Failure of appropriate insulin suppression in the presence of hypoglycemia substantiates an autonomously secreting insulinoma [4, 5, 8].

#### Imaging and Nuclear Medicine – General

The spectrum of endogenous hyperinsulinism not only includes insulinoma, but also NIPHS/nesidioblastosis. Nesidioblastosis affects approximately 4% of adults with hyperinsulinemic hypoglycemia [9]. The role of imaging is first to detect and provide precise anatomical localization and second to stage the tumor prior to surgery. Insulinomas are usually solitary and the majority is intra-pancreatic in location. They are characteristically small with ap-

proximately two thirds being  $\leq 2$  cm at presentation, making them notoriously difficult to localize radiologically. What is the ideal imaging modality for insulinoma evaluation? The three most useful modalities are: gadolinium-enhanced dynamic magnetic resonance imaging (MRI); 3-phase computed tomography (CT), and endoscopic ultrasound. Invasive techniques such as selective celiac and mesenteric arteriography, venography and venous sampling are progressively being abandoned, and together with somatostatin receptor imaging and positron emission tomography (PET) with  $^{11}\text{C}$ -5-hydroxytryptophan (5-HTP) as tracer (HTP-PET) or  $^{11}\text{C}$ -I-DOPA (DOPA-PET) should be considered as complementary techniques for specific indications. A strikingly wide discrepancy with regard to the results for localization between different centers for each of these techniques presumably reflects the specialist expertise and the availability of equipment. Still, no single modality is 100% effective. Any proposed imaging algorithm should take into account cost, sensitivity, availability and local expertise [1].

### *Minimal Consensus Statements on Imaging and Nuclear Medicine – Specific*

#### *Transabdominal Ultrasound*

Like in many other abdominal disorders, transabdominal ultrasound yields the widest range of success and failure of all preoperative localization tests. It is noninvasive, free of radiation exposure, readily available, relatively inexpensive, and anatomically precise. Key major drawbacks include its extreme dependence on operator expertise and limitations based on patient habitus, which usually is unfavorable in this setting since most of insulinoma patients are obese.

#### *Computed Tomography (CT)*

As the majority of benign insulinomas tend to be small at presentation and, therefore, seldom alter the contour of the pancreas, 3-phase CT should be used to maximize detection. Insulinomas are typically hypervascular and their appearance is that of a hyperattenuating lesion in both the arterial and portal venous phases. Liver metastases also tend to be hypervascular and, therefore, the arterial phase shows the number and size of liver metastases better than the venous phase. Spread to regional nodes is best seen during the arterial phase. The reported sensitivity of CT for the detection of insulinomas is in the range of 30–85%, depending on tumor size [10]. Combined 3-phase CT and endoscopic ultrasound may further increase this sensitivity up to 100% [11].

#### *Magnetic Resonance Imaging (MRI)*

MRI techniques have reported high sensitivities, ranging from 85 to 95%, in the detection of insulinomas and for determining the presence of metastatic disease. As compared to CT, MRI is superior in the detection of small lesions. The enhancement pattern of these tumors on MRI is due primarily to their hypervascularity. Insulinomas are low in signal intensity on fat-

suppressed  $T_1$ -weighted images and moderately high in signal intensity on fat-suppressed  $T_2$ -weighted images, although variations do exist. Small metastases, like the primary tumor, exhibit homogenous enhancement [12–16].

#### *Endoscopic Ultrasound*

In experienced hands, endoscopic ultrasound (EUS) is currently considered the best preoperative procedure to localize insulinomas with a reported sensitivity of 94%. The high spatial resolution of this technique allows the detection of very small lesions and their precise anatomical localization. The sensitivity of this technique is the highest for lesions located in the head and body of the pancreas as compared to localization in the tail. Combined with 3-phase CT, the sensitivity rises to 100%. Endoscopic ultrasound imaging is also able to identify patients that qualify for laparoscopic, minimal invasive surgery [17, 18].

#### *Angiography*

Angiography combined with calcium stimulation and transhepatic portal venous sampling (THPVS) previously was considered the gold standard of insulinoma localization [19]. Angiography combines both anatomic localization of a tumor with functional information provided by THPVS, which can confirm that a visualized angiographic abnormality is an insulinoma. Additionally, in the instance in which the angiogram fails to demonstrate the tumor, THPVS will still be able to localize the tumor to a particular region of the pancreas [19]. Noninvasive imaging techniques have evolved such that angiography and THPVS should today be considered only for problem cases [19].

#### *Intraoperative Ultrasound*

Intraoperative ultrasound (IOUS) has been highly useful in localizing these small tumors. Additionally, it demonstrates the relevant operative anatomy, defining the relationship of the tumor to the pancreatic and bile ducts, and adjacent blood vessels. Intraoperative localization techniques, which include both careful palpation of the pancreas and the use of IOUS, remain the most reliable way to localize insulinomas, and to determine the correct surgical procedure (enucleation vs. middle pancreatectomy). Moreover, it is mandatory in patients in whom multiple lesions are suspected [20, 21].

#### *Laparoscopic Intraoperative Ultrasound*

Laparoscopic IOUS in experienced hands can identify >85% of insulinomas [22, 23].

#### *$^{111}\text{In}$ -Pentetreotide Scintigraphy*

$^{111}\text{In}$ -pentetreotide scintigraphy is only positive in 46% of benign insulinomas because not all insulinomas express somatostatin receptor subtypes that bind  $^{111}\text{In}$ -pentetreotide. In malignant insulinomas, the relative distribution of somatostatin receptor subtypes is different from benign tumors and a higher rate of scan-positivity with this technique can be expected [24–26].

#### *Positron Emission Tomography*

The results of  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) PET imaging of insulinomas are disappointing, presumably because of their low proliferative potential. Promising results, however, have been obtained using  $^{11}\text{C}$ -5-HTP,  $^{18}\text{F}$ -DOPA, and  $^{67}\text{Ga}$ -DOTA-DPhe $^1$ -Tyr $^3$ -octreotide ( $^{67}\text{Ga}$ -DOTATOC) [27, 28].

## Surgical Therapy

### *Minimal Consensus Statements on Surgery*

During operation, the entire pancreas is explored. In the presence of the MEN-1 genotype, multiple tumors have to be excluded. Tumor enucleation is preferred. When the tumor is located in the neck, body, or tail of the pancreas and is anatomically unsuitable for enucleation, central or distal pancreatectomy are safe and effective alternatives [29]. Blind distal resections in search of an occult insulinoma are not recommended anymore. In specific cases laparoscopic surgery seems feasible [23, 30].

## Medical Therapy

### *Medical Therapy – General*

Dietary management is designed to prevent prolonged periods of fasting. Medical management is reserved only for patients who are unable or unwilling to undergo surgical treatment, for preoperative control of blood glucose levels or for unresectable metastatic disease.

### *Minimal Consensus Statements on Medical Therapy – Specific*

Diazoxide (50–300 mg/day, can be increased up to 600 mg/day) suppresses insulin secretion by direct action on the beta cells and by enhancing glycogenolysis [31]. Diazoxide is the most effective drug for controlling hypoglycemia. However, side effects are: edema, weight gain, renal impairment, and hirsutism. Verapamil and diphenylhydantoin have also been reported to be successful in the control of hypoglycemia [32–34]. In refractory cases, glucocorticoids such as prednisolone can be effective as well. Somatostatin analogs like octreotide and lanreotide can be useful in preventing hypoglycemia in those patients with somatostatin receptor subtype 2-positive tumors, but can worsen hypoglycemia in those patients with tumors that do not express this receptor subtype [35, 36]. Interferon-alpha has been shown to be beneficial in selected cases [37].

### *Minimal Consensus Statements on Malignant Insulinomas Management*

Malignant insulinomas account for only about 5–10% of all insulinomas. The primaries are usually single and generally larger than benign insulinomas. The median disease-free survival after curative resection is 5 years, but recurrence occurs in more than 60% at a median interval of 2.5–3 years. Median survival with recurrent tumors is less than 2 years [38]. Palliative resection may prolong median survival. When surgical options to address malignancy have been exhausted, other debulking procedures such as radiofrequency thermoablation, cryotherapy, hepatic ar-

tery embolization and chemoembolization, and peptide receptor radionuclide therapy have been utilized, yielding good, but regrettably only temporary, palliation [39, 40]. Systemic chemotherapeutic options include combinations of doxorubicin and streptozocin, which can result in a significant (up to >60%) tumor regression rate, and remission from hypoglycemic symptoms can be extended up to 1.5 years [41].

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