

## Thursday, November 3, 2005

4:30 - 6:00 p. m. **Pancreatic Tumors, Session 1**  
*Chairman: W. de Herder, Rotterdam, The Netherlands*

4:50 - 5:30 p. m. **Working Group Session**  
**Pathology and Genetics**  
*Group leaders: J.-Y. Scoazec, Lyon, France*  
*Questions to be answered: 13*  
**Medicine and Clinical Pathology**  
*Group leader: K. Öberg, Uppsala, Sweden*  
*Questions to be answered: 21*  
**Surgery**  
*Group leader: B. Niederle, Vienna, Austria*  
*Questions to be answered: 12*  
**Imaging**  
*Group leaders: S. Pauwels, Brussels, Belgium; D.J. Kwekkeboom, Rotterdam, The Netherlands*  
*Questions to be answered: 5*

### Color Codes

 Pathology and Genetics  Medicine and Clinical Pathology  Surgery  Imaging

ENETS Guidelines Neuroendocrinology 2004;80:394-424

## Endocrine Tumors of the Pancreas - insulinoma

### *Epidemiology*

The incidence of clinically detected tumours has been reported to be 4-12 per million inhabitants, which is much lower than that reported from autopsy series (about 1%) (5,13).

### *Clinicopathological staging (12, 14, 15)*

Well-differentiated tumours are the large majority of which the two largest fractions are insulinomas (about 40% of cases) and non-functioning tumours (30-35%). When confined to the pancreas, non-angioinvasive, <2 cm in size, with <2 mitoses per 10 high power field (HPF) and <2% Ki-67 proliferation index are classified as of benign behaviour (WHO group 1) and, with the notable exception of insulinomas, are non-functioning.

Tumours confined to the pancreas but > 2 cm in size, with angioinvasion and /or perineural space invasion, or >2mitoses >2cm in size, >2 mitoses per 20 HPF or >2% Ki-67 proliferation index, either non-functioning or functioning (gastrinoma, insulinoma, glucagonoma, somastatinoma or with ectopic syndromes, such as Cushing's syndrome (ectopic ACTH syndrome), hypercalciemia (PTHrpoma) or acromegaly (GHRHoma)) still belong to the (WHO group 1) but are classified as tumours with uncertain behaviour. The presence of unquestionable signs of malignancy like metastases or invasion of nearby structures identifies low grade malignant carcinomas (WHO group 2).

**Q1:** Do you agree with the above statements regarding epidemiology and clinical settings?

Agree for insulinoma. Incidence 1 to 3 per million, symptomatology has to be specified

**Q2:** In your experience and according to the literature, what is the average clinicopathological staging of insulinoma?

NF, more than 40%;

**Q3:** Which WHO group do insulinomas most frequently belong to?

Group 1

*Prognosis/Survival*

The five-year survival rate was reported to be 60-100% for localized disease, 40% for regional disease, 29% for distant metastases, and 80% for all stages (5, 13). In a publication from 1993 (16), the 5-year survival rate for advanced EPT was approaching 60 months from diagnosis.

**Q4:** Is your experience consistent with the above?

Not agree. Insulinomas, localized disease has almost 100% 5 years survival, for distant metastases is approaching 50%

**Q5:** What, in your opinion, and according to peer review is the frequency of malignant insulinoma?

Between 10 and 15% of all insulinomas

*Clinical presentation*

Endocrine pancreatic tumours are classified according to clinical symptoms into functioning and non-functioning tumours. The non-functioning tumours (17), i.e., the hormonally silent tumours, constitute the largest group, about 50%. Next in incidence are the insulinomas (18, 19) and gastrinomas (20, 21), constituting about 25% and 15%, respectively. VIP-omas (22, 23), glucagonomas (24, 25), somatostatinomas (26, 27) constitute the remaining 15%. Patients with malignant tumours may present with mixed syndromes, or the tumours may change clinically over time.

Endocrine pancreatic tumours can occur at any age with an equal sex distribution. About 15-30% of patients have MEN-1. In MEN-1-patients, multiple tumours occur either syn- or metachronously (1). MEN-1 pancreatic tumours are usually non-functioning in early ages and then after the age of 40 may turn into gastrinomas or other functioning tumours. In von Hippel-Lindau's disease the endocrine pancreatic tumours are usually non-functioning.

**Q6:** What in your experience and according to the literature is the incidence of insulinoma within the overall endocrine pancreatic tumor group? What is the incidence within functioning pancreatic tumors?

Skip see Q5

**Q7:** As for mixed syndromes in malignant insulinoma, is your experience and the current literature consistent with the above?

Rarely patients with malignant insulinomas develop mixed syndrome

**Q8:** In your experience and according to the literature, is there a gender and age preferential distribution for insulinoma (for either benign or malignant)?

Female preponderance for benign insulinomas, equal for malignant tumors

**Q9:** Which are the most frequent familial conditions associated with insulinoma?

MEN-1, 5 to 10%

*Diagnostic procedures*

1. Tumour imaging

Ultrasonography, EUS, contrast-enhanced CT or MRT of the abdomen, MR-angiography for surgical decision-making, SRS.

**Comments:**

Endoscopic ultrasonography combined with biopsies in experienced hands is the most sensitive method to detect pancreatico-duodenal tumours (28). US, CT and MRI can also be used to detect the primary tumours and metastases (29). SRS is a routine investigation for both primary tumours and metastases (30, 31). However, smaller tumours especially insulinomas can be difficult to visualize with this method and intraoperative ultrasonography is still the most sensitive method (32).

(...) The sensitivities for detection of histopathologically proven liver metastases with the different methods are the following: US 46%, CT 42%, MRI 71%, angiography 62% and SRS 92%, respectively. (For detection of intra and extrahepatic lesions: US 19%, CT 38%, MRI 45%, angiography 40% and SRS 70%). In conclusion, SRS has a sensitivity that exceeds the combination of the others (31). PET with 5-HTP or L-DOPA can be an option for detection of small tumours (33).

**Q10:** Which procedure(s) is/are required for a minimal diagnostic approach?

The biochemical diagnosis should be established first, then three phase CT and EUS. SRS cannot be considered as first approach in insulinomas

**Q11:** Which procedure should be initially performed?

skip

**Q12:** What are the limitations in detecting small occult insulinomas? To what extent should diagnostic procedures be pursued?

Intraoperative US and Ca stimulation test

**Q13:** Is EUS required? When is it recommended? What is the role of CT, MRI, PET and SRS?

EUS yes, always. MRI including MRCP/ upper abdominal CT for primary and/or liver mets. PET no.

**Q13a:** Do you agree with the above-reported sensitivity of SRS for benign and malignant insulinoma?

SRS only if metastatic disease.

SRS sensitivity for benign disease 40 to 50%. For metastatic disease 90 to 100%.

**Q14:** Which type of PET is recommended?

None

**Q15:** Please suggest your imaging/procedure flow-chart for insulinoma.

See Q13.

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##### 2. Biochemistry

Chromogranin A, insulin, C-peptide, pro-insulin, gastrin, VIP, glucagon, calcitonin, somatostatin.

##### **Comments:**

Chromogranin A is a general tumour marker, which is increased in almost all different types of endocrine pancreatic tumours (13). Another general tumour marker is PP, which can be elevated in non-functioning tumours but also in functioning tumours. For each tumour type characteristic clinical symptoms should lead to measurement of specific markers such as gastrin, insulin, VIP, glucagon, and somatostatin (13). To establish the diagnosis of insulinoma a 12-72-hour fast is recommended; a glucagon test may also be informative (18, 19). (...) Determination of pituitary hormones, ionized calcium and PTH is included in MEN-1-screening (35). For early detection of pancreatic involvement in MEN-1, a meal stimulation test with measurements of PP and gastrin can be performed.

**Q16:** What is the minimal biochemical work-up for insulinoma?

Blood glucose below 2 mmol/l, spontaneously or after 72 hr fasting, inappropriate serum insulin levels, if insulin levels inconclusive measurement of C pep and/or proinsulin levels

**Q17:** When should biochemical tests be performed?

When there is a clinical suspicion

**Q18:** Is germline DNA testing recommended? Which genes? Which method?

YES, if familial history, suspicious clinical findings, multiple tumors or precursor lesions; MEN1, very rarely other (e.g. VHL and NF1)

**Q19:** Is somatic (tumor) DNA testing recommended? Which genes? Which method?

NO

**Q20:** When is genetic counseling recommended?

YES see Q18

**Q21:** Would you recommend collecting a consensus statement for genetic testing?

YES see Q18

**ENETS Guidelines** Neuroendocrinology 2004;80:394-424

3. Histopathology (14, 36, 37)

Hematoxylin-eosin, chromogranin A, synaptophysin, specific hormones (insulin, gastrin etc), Ki-67

**Comments:** see previous chapter (eventually defined page...)

**Q22:** Is histology required?

YES

**Q23:** Is cytology recommended and in which clinical situations?

Not useful in preoperative setting in a symptomatic pt..

**Q24:** What are the minimal ancillary tests required to support the histological diagnosis?

IHC: CgA, synaptophysin, insulin, proinsulin

**Q25:** Is the mitotic index necessary? Which method?

YES

Mitotic count

**Q26:** Is the Ki-67 index necessary? Which method?

YES, see previous statements..

**Q27:** Is IHC required for tumor cell subtyping and, if so, when?

YES if multiple tumors or MEN1 suspect or insulin and proinsulin staining is negative

**Q28:** Would you recommend IHC for P53?

NO

**Q29:** Would you recommend IHC for SSR2A receptor?

NO

**Q30:** Please see the proposal of TNM classification of pancreas tumors (Appendix 2, see below) and comment.

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*Surgical therapy*

1.1. Curative surgical therapy of primary tumours

The indications for surgery depend on clinical symptoms, tumour size and location, malignancy and metastatic spread. There is a general consensus that curative surgery should be aimed for also in metastatic disease, including “localized” metastatic disease to the liver (10). Preoperative procedures should include exploration of the whole abdominal cavity, intraoperative ultrasonography of pancreas and liver, and transillumination of the duodenum in ZES (10, 38, 39, 40). The type of surgical procedure depends on the location of the tumour: pancreatico-duodenal resection (Whipple’s operation), distal pancreatic resection, tumor enucleation, enucleation in combination with resection. If malignancy is suspected, lymph node dissection is mandatory.

**Comments:**

Since the vast majority of insulinomas are benign, patients with insulinomas can undergo surgery. Most patients are cured by enucleation or pancreatic resection. (...) The indications for surgery in MEN-1- patients are more controversial, since these patients have tumours in other endocrine organs and multiple tumours either syn- and/or metachronously in the pancreatico-duodenal area. These patients are very rarely cured of their pancreatico-duodenal tumour by surgery. Surgery is advocated to avoid later development of malignancy (tumors >2 cm) in both functioning and non-functioning cases (41). Tumours in the head of the pancreas should be enucleated if possible, distal pancreatic resection for caudally-located tumours (...).

**Q31:** At surgery, what procedures are recommended to detect occult insulinoma?

Before exploring pancreas for sporadic insulinoma disease two imaging studies are mandatory EUS and MRI/multislice CT. With these modalities around 90% of tumors may be localized. In the group of non localized tumors regionalization by selective arterial Ca stimulation and venous sampling (SAVS) may be helpful.

Occult tumors with positive OGTT-fasting test and SAVS are explored.

Intraoperative mobilisation of the pancreas with palpation and IOUS is mandatory.

**Q32:** When is curative surgery NOT recommended for insulinoma? Perhaps Q33 before 32?

If curative surgery is possible it is mandatory

**Q33:** When is curative surgery recommended?

Always if possible

**Q34:** What criteria help in surgical decision-making? Describe your recommended type of surgical resection?

Limited resection, preferable enucleation is to be applied but may not be possible in tumors with close contact to the pancreatic duct (to be determined by EUS and IOUS). Preferably preserve the spleen.

In selected cases with localized single tumors and sporadic disease minimal invasive surgery may be applied. Blind resections are not recommended.

**Q35:** Which surgery for malignant insulinoma?

As radical as possible (primary tumor plus LN plus liver-mets)

**Q36:** Which surgery for multicentric insulinoma?

Very rare situation in sporadic disease (diffuse hyperplasia) treatment as above mentioned; more common in MEN-1 patients.

In the latter MEN 1 patients multicentric neuroendocrine tumors usually require distal pancreatectomy preserving the spleen and enucleation of the remaining lesions in the pancreatic head. In some patients with specific malignant phenotype even more extensive resection up to total pancreatectomy may be required.

**Q37:** Is surgery for liver metastases recommended along with elective surgery?

Yes. The type of surgery up to liver transplantation depends on tumor distribution.

**ENETS Guidelines** Neuroendocrinology 2004;80:394–424

#### 1.2. Curative surgery of liver metastases (42)

Resection of liver metastases should always be considered both in functioning and non-functioning tumours, since progression of tumor disease can be delayed. Complete resection should be aimed for. The type of surgery depends on the location of the metastases. The following procedures can be chosen: enucleation, one or more segmental resections, hemi-hepatectomy or extended hemi-hepatectomy. Intraoperative US should be performed for detection of all liver metastases.

#### **Comments:**

Metastatic disease should be confined to the liver. Surgery should be undertaken only if 90% of the tumour's mass can be successfully removed. Liver surgery can be done concomitantly with surgery of the primary tumour or on a separate occasion. Specific anesthesiological procedures and perioperative somatostatin analogue infusion are indicated to avoid hormonal crises. If feasible, cholecystectomy should be performed synchronously, to prevent gallstone formation during future somatostatin analogue therapy or complications after liver embolization.

#### 2. Palliative surgery of primary tumours and/or liver metastases (42)

The indications for palliative/debulking resections of primary tumours and liver metastases have been broadened. Severe hormonal symptoms that cannot be controlled by medical treatment are indications for palliative resections. These procedures have to be individually designed for each patient.

**Q38:** What is the best treatment option for liver metastases from malignant insulinoma?

**Q39:** When is surgical treatment for liver metastases recommended?

**Q40:** Which type of palliative surgery is recommended?

**ENETS Guidelines** Neuroendocrinology 2004;80:394–424

#### *Cytoreductive therapy*

##### 1. Selective embolization alone or in combination with systemic chemotherapy

Selective embolization alone or in combination with intraarterial chemotherapy (chemoembolization) is an established procedure to reduce hormonal symptoms, as well as liver metastases (43, 44). Selective embolization of peripheral arteries is usually preferred, which induces temporary ischemia and can be repeated. The objective response rates vary between 30-70% and the duration of response is between 10-30 months. At chemoembolization, cytotoxic drugs are injected intra-arterially together with embolization material. The cytotoxic drugs most often used are 5-FU, doxorubicin and mitomycin C. It has not been established whether chemoembolization is more efficient than embolization alone.

#### **Comments:**

The procedure is accompanied by a mortality rate of 5-10% and there is significant morbidity. Minor side effects (postembolization syndrome) are fever, right upper quadrant pain, nausea, elevation of liver enzymes and a decrease in albumin and PK. Major side effects are gallbladder necrosis, hepato-renal syndrome, pancreatitis, liver abscess. To prevent hormonal crises and i.v.



infusion of somatostatin analogues is indicated. Forced diuresis to prevent hepatorenal syndrome is recommended.

## 2. Radiofrequency ablation

Radiofrequency ablation can be used to reduce the tumour mass in the liver and thereby reduce hormonal symptoms (45, 46).

### **Comments:**

The patient should not have more than 8-10 lesions in the liver. The largest diameter should be 4 cm. The morbidity rate is low, if not too many lesions are treated at the same time. Ablative surgery and RF can be combined.

**Q41:** When and which type of loco-regional ablative therapy is recommended for malignant insulinoma?

Transarterial chemoembolisation for liver metastases

**ENETS Guidelines** Neuroendocrinology 2004;80:394–424

### *Liver transplantation*

Liver transplantation may be considered in patients with no extrahepatic metastases (47, 48, 49). However, experience is limited. Most patients had recurrences within months to years, possibly because of postoperative immuno-suppressive treatment. Hence, improved methods for the detection of extrahepatic metastases are necessary before liver transplantations can be used or recommended.

### *Comments:*

Liver transplantation may be indicated for patients with tumours causing life-threatening hormonal symptoms and for patients who don't respond to medical therapy or who don't have access to other surgical interventions. Patients who have undergone Whipple's procedure or have aggressive carcinomas should be excluded.

**Q42:** Is liver transplantation recommended for malignant insulinoma? In which clinical settings?

After radical resection of primary tumor with metastases defined to liver only transplantation may be an option in selected patients.

**ENETS Guidelines** Neuroendocrinology 2004;80:394–424

### *Medical therapy*

#### 1. Biotherapy

1.1. Somatostatin analogues: Somatostatin analogues are the primary treatment for patients with hormonal symptoms of endocrine tumours (11, 50). (...) Somatostatin analogues can also be used in malignant gastrinomas and insulinomas, if they are somatostatin receptor scintigraphy positive. Caution has to be taken in insulinomas, since hypoglycemia may worsen due to a more profound suppression of GH and glucagon than tumour-produced insulin. Escape from symptomatic control can be seen quite frequently but an increase in the dose of somatostatin analogues can help temporarily. A significant reduction in tumour size has been seen in <10% of patients but stabilization of tumor growth, documented by CT, occurs in 30-50% of patients (51).

### **Comments:**

To test the tolerability in an individual patient, somatostatin analogue therapy should be initiated with short-acting substance (octreotide 100 ug subcutaneously x 2-3) for 1-2 days, then the patient can be transferred to slow-release Lanreotide-SR<sup>®</sup> i.m., Lanreotide autogel<sup>®</sup>s.c. or Sandostatin –LAR<sup>®</sup> i.m. (every 4 weeks) (52). Octreotide and lanreotide are equally effective. If one preparation is not effective or tolerated, the other can be attempted. Side-effects, including abdominal discomfort and flatulence, are usually mild and subside within a few weeks. Long-term side effects include the formation of sludge and gallstones but very few patients will develop symptoms. Some patients with long-lasting diarrhoea can develop severe hypocalcemia.

**Q43:** Is somatostatin analog therapy recommended for insulinoma? If so, when and how?  
Not routinely for benign insulinomas, whereas for malignant insulinomas, SSA should be first tested in-house. Alternatively, diazoxide should be considered, also combined with SSA.

**ENETS Guidelines** Neuroendocrinology 2004;80:394-424

1.2. Interferon: The cytokine alpha-interferon exerts direct effects on tumour cells by inhibiting protein and hormone synthesis, blocking the tumor cells' cycles in G1/S-phase, and it also indirectly stimulates the immune system. It has been shown to reduce circulating hormone levels in 30-60% of patients with endocrine GI tumours, thereby improving symptoms (53-56). Significant tumour reduction is seen in 10-15% of patients but tumour stabilization is achieved in 40-60% of patients. Combination of alpha-interferon and somatostatin analogs can be given (57, 58).

**Comments:**

The usual dose is 3-5 million units 3-5 times per week subcutaneously. There are new long-acting formulations of pegylated alpha-interferon. The exact doses have not been established yet. The most severe and dose-limiting toxicities are chronic fatigue, mental depression and autoimmune phenomena (SLE, myositis, vasculities), which may necessitate withdrawal of treatment. Most patients will have a reduction in blood counts and an increase in liver enzymes but these side-effects can be handled by dose adjustments.

**Q44:** Is interferon therapy recommended for insulinoma? If so, when and how?  
No indication in benign insulinomas, it can be considered in selected cases of malignant tumors.

**ENETS Guidelines** Neuroendocrinology 2004;80:394-424

2. Systemic chemotherapy

Systemic chemotherapy is indicated in patients with metastatic endocrine pancreatic tumours and streptozocin (STZ) in combination with 5-fluorouracil (5-FU) or doxorubicin is still first-line treatment (59, 60). Biochemical responses are seen in >50% of patients with a median duration of more than 2 years. Significant tumour shrinkage (>50%) is seen in 20-35%. All types of EPT respond.

**Comments:**

At initiation STZ plus 5-FU/doxorubicin may induce a hormonal crisis. For example, in VIP-oma patients somatostatin analogues should be administered for protection. The major side-effects, nausea and vomiting, can be avoided by 5-HT<sub>3</sub>-receptor blockers. The dose-limiting toxicity is nephrotoxicity and hydration is important to protect the kidneys. In *poorly-differentiated* neuroendocrine tumours (Ki-67 >15-20%), the combination of cisplatin/carboplatin plus etoposide can induce objective remission in 55-80% of patients (61-63). Median duration of responses has been reported to be 8-11 months.

Also this regimen can induce hormonal crises in the patients. The toxicity is significant with alopecia, bone-marrow depression, nephrotoxicity and neuropathy being major side-effects. Nausea and vomiting can be handled by 5-HT<sub>3</sub>-receptor blockers

**Q45:** When is chemotherapy recommended in patients with insulinoma?  
In inoperable malignant insulinomas

**Q46:** Which cytotoxics and what regimens are recommended?  
STZ and dox or 5FU

**Q47:** May chemotherapy be proposed in an adjuvant setting?  
No



**Q48:** Can PRRT be recommended? If so, when and which type?

If octreoscan positive and inoperable and uncontrollable syndrome with medical therapy. Y or Lu labeled analogues are preferred.

**ENETS Guidelines** Neuroendocrinology 2004;80:394-424

*Follow-up during/ after treatment*

1. Patients with liver metastases

Ultrasonography or MR/CT and biochemical markers, including those initially elevated every 3 months. Diagnosis of bone metastases (if clinical signs are present?) by Octreoscan and/or bone scan and MR

2. Patients without liver metastases

Long-term follow-up because of the possibility of late recurrences. If curative surgery has been performed, Octreoscan or PET should be done after 6 months.

**Q49:** What is the scheduled follow-up for benign insulinoma patients? What are the minimal examinations required and for how long? What postoperative procedures do you recommend? According to treatment including routine surgical follow/up and long/term follow/up in rare case of switch from benign to malignant course

**Q50:** What is the scheduled follow-up for patients with malignant insulinoma? What are the minimal examinations required and for how long? According to the treatment