Friday, November 4, 2005

2:30 - 4:00 p. m. **Pancreatic Tumors, Session 4**
Chairman: M. Falconi, Verona, Italy

2:50 - 3:30 p. m. **Working Group Sessions**
Pathology and Genetics
Group leaders: J.–Y. Scoazec, Lyon, France
Questions to be answered: 12
Medicine and Clinical Pathology
Group leader: K. Öberg, Uppsala, Sweden
Questions to be answered: 19
Surgery
Group leader: W. O. Bechstein, Frankfurt/Main, Germany
Questions to be answered: 11
Imaging
Group leaders: S. Pauwels, Brussels, Belgium; D.J. Kwekkeboom, Rotterdam, The Netherlands
Questions to be answered: 3

Color Codes
Pathology and Genetics **Medicine and Clinical Pathology** **Surgery** **Imaging**

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Endocrine Tumors of the Pancreas – non-functioning tumors (NFT)

Epidemiology
The incidence of clinically detected tumours has been reported to be 4-12 per million inhabitants, which is much lower than what is 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), hypercaliemia (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 as for epidemiology of NFTs?
The paragraph is not consistent with the novel data. It should be rewritten tacking into account several new aspects in both epidemiology and clinicopathological staging. The incidence is higher, about 45-50%. Diagnosis is made incidentally, however, peak incidence could be set around 50. Pain is the major presenting symptom, followed by weight loss (20%), and 60-75% of patients show metastases already at diagnosis. In MEN 1 patients NFT are quite common and are diagnosed earlier than sporadic cases (more benign course of the disease).

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

Q3: Which WHO group does NFT belong to more frequently?
Group 2

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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 and the literature consistent with the above?
Overall 5 year survival of 60%.
80% for localized disease; 40-50% for distant metastasis.

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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%. (…)
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.

Q5: In your experience and according to the literature, is there a gender and age preferential distribution for either benign or malignant NFTs?
There is no gender difference. Peak incidence could be set around 50 yr.

Q6: In your experience, what are the most frequent familial conditions associated with NFTs?
MEN-1, followed by VHL

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Diagnostic procedures
1. Tumour imaging
Ultrasonography, endoscopic 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).

Q7: Which procedure(s) is/are required for a minimal diagnostic approach?
Multi slice-CT plus SRS, US guided biopsies. (SPECT CT). EUS may be of value in MEN-1 patients.

Q8: Which procedure should be initially performed?
Combined with Q7

Q9: Is EUS required? When is it recommended? What is the role of CT, MRI and SRS?
Upper Abdominal CT or MRI including MRCP plus SRS always for staging
EUS may be useful in localized disease in conjunction with biopsy.
Imaging techniques may be needed to guide biopsy if histology is required.
Follow-up: CT and if initially positive SRS.

Q10: Is PET useful? If so, which type of PET is recommended?
NO: NFT is detected, never occult.

Q11: Please suggest your imaging/procedure flow-chart for NFTs.
See Q9.

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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. (…) 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.

Q12: What is the minimal biochemical work-up for NFTs?
CgA, (optional PP and other markers)

Q13: When should biochemical tests be performed?
At first visit

Q14: Is germline DNA testing recommended? Which genes? Which method?
YES, if familial history, suspicious clinical findings, multiple tumors or precursor lesions;
MEN1, VHL; mutational analysis.

Q15: Is somatic (tumor) DNA testing recommended? Which genes? Which method?
NO.

Q16: When is genetic counseling recommended?
See Q15.

Q17: Would you recommend collecting a consensus statement for genetic testing?
See Q15.

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3. Histopathology (14, 36, 37)
Hematoxylin-eosin, chromogranin A, synaptophysin, specific hormones (insulin, gastrin etc), Ki-67
Comments: see previous chapter

Q18: Is histology required?
Not required but recommended for preoperative diagnosis, according with the clinicians' requirement. Required for definitive diagnosis

Q19: Is cytology recommended and in which clinical situations?
Not recommended, but needed in absence of tissue specimen.

Q20: What are the minimal ancillary tests required to support the histological diagnosis?
IHC CgA, synaptophysin, additional markers according to differential diagnosis

Q21: Should the mitotic index be assessed? If so, which method?
YES, mitotic index

Q22: Is the Ki-67 index necessary? Which method?
YES, see previous sessions.

Q23: Is IHC required for tumor cell subtyping and, if so, when?
Whenever appropriate after additional clinical evidence

Q24: Would you recommend IHC staining for p53?
NO

Q25: Would you recommend IHC for SSR2A receptor?
NO; may be useful e.g. OCTscan not available.

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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:
(…) In the other tumor types, radical surgery is the only treatment for cure, although it is rarely possible at the time of diagnosis (10, 38, 39, 40).
The indications for surgery in MEN-1- patients are more controversial, since these patients have tumours in other endocrine organs and multiple tumours 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 >3 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 (…).

Q26: When is curative surgery recommended in NFTs?
If the tumour is larger than 2 cm, and if MEN1 is ruled out, and if curative surgery is feasible, it should be performed.
In small NFTs below 2 cm, a follow-up strategy may be acceptable, particularly if the lesion would require a Whipple-procedure.

Q27: When is curative surgery NOT recommended?
In NFTs below 2 cm of size, with the exception of easily accessible lesions (local resection or left pancreatic resection).

Q28: Which type of surgical resection would you recommend?
Depending on tumour localization and size and level of suspicion for malignancy:
Local resection in small, easily accessable tumors, unsuspicious for malignancy.
Larger resections may be required (panceaticoduodenectomy or left pancreatic resection) if the tumour is located intrapancreatically and if a carcinoma is suspected.
Staging lymphadenectomy is always recommended.

Q29: What surgical strategies are recommended for multicentric NFTs?
Very rare, see Q28.

Q30: Is surgery for liver metastases recommended along with elective surgery?
See flow chart on liver metastases.

Q31: In advanced stages, are debulking surgical strategies recommended and to what extent?
In case of non-resectable liver metastases, removal of the primary tumour may be indicated as a palliative approach in order to prevent complications from local tumour growth (and to focus treatment on the liver).

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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.

Q32: What is the best treatment option for liver metastases from NFTs?

See flow chart

Q33: When is surgical treatment of liver metastases recommended?
See flow chart

Q34: Which type of palliative surgery is recommended?
See Q 31

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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 and liver abscess. To prevent hormonal crises 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.

Q35: When and which type of loco-regional ablative therapy is recommended for malignant NFT?
Not recommended

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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.

Q36: Is liver transplantation recommended for patients with malignant NFTs? In which clinical settings?
In very few, individually selected cases this may be an option.

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Medical therapy
1. Biotherapy
1.1. Somatostatin analogues: Somatostatin analogues are the primary treatment for patients with hormonal symptoms of endocrine tumours (11, 50). (…) 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® i.m., Lanreotide autogel® s.c. or Sandostatin–LAR® 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.

Q37: Is somatostatin analog therapy recommended for NFTs? If so, when and how?
It may be indicated for progressive slowly growing (if possible, proliferating index, Ki67) tumors after positive SRS. *Majority voted for SSA therapy in well differentiated NF pancreatic tumor.* A controlled randomized trial is ongoing.

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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.

Q38: Is interferon therapy recommended for NFTs? If so, when and how?
It may be indicated in slowly growing tumors with low proliferating index (cut-off of 2%). Should be confirmed in RCT.

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2. Systemic chemotherapy
Systemic chemotherapy is indicated in patients with metastatic endocrine pancreatic tumours and streptotozocin (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/doxorubucin 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-HT3-receptor blockers. The dose-limiting toxicity is nephrotoxicity and hydration is important to protect the kidneys. In poorly differentiated endocrine 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.

Comments:

Also this regimen can induce hormonal crises in the patients. The toxicity is significant with alopecia, bone-marrow depression, nephrotoxocity and neuropathy being major side-effects. Nausea and vomiting can be handled by 5-HT3-receptor blockers

Q39: When is chemotherapy recommended in patients with NFTs?
It is of value in metastatic patients and where locoregional approaches are not feasible, or patients with progressive tumors or bulky disease.

Q40: Which cytotoxic agents and protocols are recommended?
STZ plus 5-FU and/or doxorubicin

Q41: Can chemotherapy be proposed in an adjuvant setting?
No, but it should be further studied

Q42: In the absence of disease progression, what are your treatment recommendations?
It depends on symptoms and tumor load

Q43: Can PRRT be recommended? If so, when and which type?
It can be recommended in cases with highly positive SRS

Q43: Can PRRT be recommended? If so, when and which type?
If SRS positive and inoperable.

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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.

Q44: What is the scheduled follow-up for patients with benign NFT? What are the minimal examinations required and for how long?
In cured patients biochemical assessment first, if no evidence of disease no further imaging.

Q45: What is the scheduled follow-up for patients with malignant NFT? What are the minimal examinations required and for how long?

The follow up depends on the current treatment. CgA, CT after 3 to 6 months, whereas SRS after 1 yr, if positive in the initial investigation. After curative resection of malignant tumor follow up as already discussed for functioning tumors.