Friday, November 4, 2005

11:00 - 12:20 a. m. **Pancreatic Tumors, Session 3**
Chairman: D. O'Toole, Clichy, France

11:20 - 11:50 a. m. **Working Group Session**
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: 17
Surgery
Group leader: W. O. Bechstein, Frankfurt/Main, Germany
Questions to be answered: 13
Imaging
Group leaders: S. Pauwels, Brussels, Belgium; D.J. Kwekkeboom, Rotterdam, The Netherlands
Questions to be answered: 4

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

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Endocrine Tumours of the Pancreas – rare functioning tumors (RFT)

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: In your experience and according to the literature, what is the average clinicopathological staging of RFTs?
The majority of patients present with metastatic disease, some with only local disease. The average age at diagnosis is 50 to 55 yrs, with equal gender distribution.

Q2: Which WHO group do RFTs 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.

Q3: Concerning RFTs, are your experience and the literature consistent with the above?
Not enough data

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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%. 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 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.

Q4: In your experience and according to the literature, what is the incidence of RFTs within PETs?
Less than 10% of all functioning tumors

Q5: As for mixed syndromes in RFTs, are your experience and the current literature consistent with the above?
Agree with the previous guideline

Q6: In your experience and according to the literature, is there a gender and age preferential distribution for RFTs? Which tumor type?

Q7: In your experience, what are the most frequent familial conditions associated with RFTs?
MEN 1

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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).

Q8: Which procedure(s) is/are required for a minimal diagnostic approach?
Refer to gastrinoma session

Q9: Which procedure should be performed initially?
Refer to the gastrinoma session

Q10: Is EUS required? When is it recommended? What is the role of CT, MRI, PET and SRS?
SRS plus CT or MRI (for localisation or if metastatic for response measurement to therapy). EUS may be used as a sequential method when CT, MRI and SRS are not conclusive, especially preoperatively. Exception: Pancreatic tumor with liver mets at presentation: EUS not necessary. Majority votes for the first line use of EUS.

Q11: Which type of PET is recommended?
[Statement missing]

Q12: Please suggest your imaging/procedure flow-chart for RFT.
See Q 10

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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). (…) 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.

Q13: What is the minimal biochemical work-up for RFTs?
Biochemical tests related to potential hormonal activity, CgA, PP, specific hormones related to the syndrome, PTH and Ca (MEN 1)

Q14: When should biochemical tests be performed?
At first visit

Q15: Is germline DNA testing recommended? Which genes? Which method?
YES, if familial history, suspicious clinical findings, multiple tumors or precursor lesions; MEN1; mutational analysis.

Q16: Is somatic (tumor) DNA testing recommended? Which genes? Which method?
NO.

Q17: When is genetic counseling recommended?
See Q15.

Q18: 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

Q19: Is histology required?
YES.

Q20: Is cytology recommended and in which clinical situations?
NO, occasionally useful in the intraoperative setting for tumor confirmation.

Q21: What are the minimal ancillary tests required to support the histological diagnosis?
IHC CgA, synaptophysin and specific hormone(s) according to clinical setting.

Q22: Is the mitotic index necessary? Which method?
YES, mitotic count.

Q23: Is the Ki-67 index necessary? Which method?
YES, to be worked out.

Q24: Is IHC required for tumor cell subtyping?
YES, see Q21.

Q25: Would you recommend IHC staining for p53?
NO.

Q26: 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 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 (…) .

Q27: Which intraoperative procedures are recommended to detect occult RFTs?
delete

Q28: When is curative surgery recommended?
Whenever feasible after careful symptomatic control of the syndrome (medical of locoregional treatments)

Q29: When is curative surgery NOT recommended for RFTs?
Always recommended

Q30: What type of surgical resection would you recommend?
Oncological resection (lymphoadenectomy). Bilateral adrenalectomy in selected cases with Cushing

Q31: What type of surgery is recommended for multicentric RFTs?
delete

Q32: Is surgery for liver metastases recommended along with elective surgery?
Yes

Q33: In advanced stages, are debulking surgical strategies recommended and to what extent?
Debulking strategies have a major role. (Bilateral adrenalectomy in selected cases with Cushing)

Q34: Which criteria should be advocated (QOL)?
Delete

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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.

Q35: What is the best treatment option for liver metastases in RFTs?
Liver resection when feasible or chemoembolization, liver transplantation

Q36: When is surgical treatment of liver metastases recommended?

Q37: Which type of palliative surgery is recommended?

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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.

Q38: When and which type of loco-regional ablative therapy is recommended for malignant RFTs?

Transarterial chemoembolization, radiofrequency ablation, PRRT

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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.

Q39: Is liver transplantation recommended for malignant RFT? In which clinical settings?

It is recommended in selected patients as long as extraepatic tumor growth is ruled out

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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). About 80-90% of patients with VIP-oma and glucagonoma improve very promptly, overcoming diarrhea and skin rash, and 60-80% have a reduction in VIP and glucagon levels. Symptomatic relief is not always related to reduction in circulating hormone levels, indicating that somatostatin analogues have direct effects on the peripheral target organ. (…) 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® 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.

Q40: Is somatostatin analog therapy recommended for RFTs? If so, when and how?
VIPomas and glucagonomas, and in selected cases based on positive Octreoscan

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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.

Q41: Is interferon therapy recommended in patients with RFTs? If so, when and how?
In selected cases.

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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

Q42: When is chemotherapy recommended in RFT patients?
Refer to gastrinoma session

Q43: Which cytotoxic agents and protocols are recommended?
Refer to gastrinoma session

Q44: Can chemotherapy be proposed in an adjuvant setting?
Refer to gastrinoma session

Q45: Can PRRT be recommended? If so, when and which type?
Yes, in inoperable metastatic disease, if the tumors are positive on SRS.

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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.

Q46: What is the scheduled follow-up for patients with RFT? Which minimal examinations are required and for how long?
Refer to gastrinoma session, but considering the different hormones