

Saturday, November 5, 2005

8:30 - 10:30 a. m. **Poorly Differentiated Endocrine Carcinomas**
Chairman: E. Van Cutsem, Leuven, Belgium

9:00 - 9:30 a. m. **Working Group Sessions**
Pathology and Genetics
Group leaders: O. Nilsson, Gothenborg, Sweden
Questions to be answered: 12
Medicine and Clinical Pathology
Group leader: M. Caplin, London, UK
Questions to be answered: 12
Surgery
Group leader: A. Sauvanet, Clichy, France
Questions to be answered: 6
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

ENETS Guidelines Neuroendocrinology 2004;80:394-424

Poorly Differentiated Endocrine Tumors of foregut Origin

Epidemiology

Stomach

Na: define (not available)

Duodenum

na define (not available)

Pancreas

na define (not available)

Clinicopathological staging

Stomach

Poorly differentiated tumors are highly malignant and belong to WHO group 3, i.e. poorly differentiated, small cell, endocrine carcinomas (PDEC). They are relatively rare and account for less than 5% of endocrine tumors. They are probably underestimated since they may resemble undifferentiated carcinomas. A positive staining for synaptophysin may be the only indicator of endocrine differentiation.

Duodenum

Poorly differentiated carcinomas belonging to WHO group 3 (small cell, poorly differentiated endocrine carcinomas) are relatively rare, highly malignant carcinomas of the ampullary region.

Pancreas

Poorly differentiated, small cell carcinomas are rare high-grade malignant carcinomas (WHO group 3), presenting with distant metastases, and display solid structure with necrosis, high mitotic and Ki-67 proliferation indices and frequent hyperexpression/accumulation of p53.

Q1: What is the current knowledge regarding the epidemiology and clinical settings of foregut PDECs?

Less than 2 % of gastric carcinomas are PDEC, less than 3 % of duodenal carcinomas

Q2: In your experience and according to the literature, what is the average clinicopathological staging of PDECs?
Not enough data.

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Prognosis/Survival

Stomach

In the same series type 3 tumors had a mean survival of 28 months and poorly differentiated only 7 months. (reference)

Duodenum

Na (define: not available)

Pancreas

Na (define: not available)

Q3: Are your experience and the literature consistent with the above? Is there data available concerning prognosis/survival for duodenal or pancreas PDECs?
Survival 6-12 months in treated patients with metastatic disease.

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Diagnostic procedures

1. Tumor imaging

Stomach

Gastroscopy/EUS, abdominal ultrasound, contrast-enhanced CT or MRT of the abdomen and SRS.

Comments:

Gastroscopy with multiple biopsies from tumor and non-tumor tissue is essential for histopathological diagnosis to distinguish between the different types of gastric tumors and also indicating the size and location of the primary tumor. It is also important to exclude infection with *Helicobacter pylori*. CT/MRT and SRS are important for staging of the disease in type 3 and poorly-differentiated tumors.

Duodenum

Endoscopy, EUS, contrast-enhanced CT or MRT of the abdomen, SRS

Comments:

Endoscopy with biopsy is essential for histopathological diagnosis to distinguish between the different types of duodenal tumors also indicating the size and location of the primary tumor. CT/MRT and SRS are important for staging.

Pancreas

1. Tumour imaging

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

Comments:

EUS 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).

Q4: Which procedure(s) is/are required for a minimal diagnostic approach in each individual tumor type (gastric, duodenal and pancreatic)?

Gastroscopy, CT or MRI.

According to the clinical situation.

Q5: Which procedure should be initially performed?

Q6: Is EUS required? When is it recommended?

Q7: What is the role of CT, MRI, and SRS? Are there limitations to be considered for PDECs of the foregut?

No data for the impact of SRS on diagnostic evaluation. It cannot be recommended, but should be evaluated in a clinical setting.

Q8: Is there a role for PET in PDECs? If so, which type?

FDG- PET: Yes for diagnosis (primary) and staging.

Q9: Please suggest your imaging/ procedure flow-chart for PDECs.

Depends on clinical situation (CT, endoscopy with biopsy or EUS, and FDG-PET)

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2. Biochemical diagnosis

Stomach

Chromogranin A, Gastrin, Histamine metabolites in urine (with appropriate diet). It is also important to determine the presence of parietal cell antibodies. MEN-1 should be excluded by determining ionized calcium, PTH and possibly also pituitary hormones.

Duodenum

Chromogranin A, further determination according to the clinical picture: gastrin, calcitonin, somatostatin, urinary 5-HIAA twice (24-h) with appropriate diet.

Comments:

Chromogranin A is the most reliable tumor marker in endocrine duodenal tumors. The levels of other tumor markers will vary depending on the type of tumor. Patients with suspected Recklinghausen's disease or ZES secondary to MEN-1 should have an extended biochemical work-up.

Pancreas

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. For genetic testing, see introduction.

Q10: What is the minimal biochemical work-up for PDECs?

NSE may be helpful

Q11: When should biochemical tests be performed?

At diagnosis, in patients with elevated NSE at diagnosis also in the follow-up

Q12: Is germline DNA testing recommended? Which genes? Which method?

No role for genetic testing except in cases with positive family history

Q13: Is somatic (tumor) DNA testing recommended? Which genes? Which method?

No

Q14: When is genetic counseling recommended?

See Q 12

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

See Q 12

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3. Histopathology

Stomach

Hematoxylin-eosin, Chromogranin, Synaptophysin, Ki-67

Comments:

...If the diagnosis of a well-differentiated or poorly differentiated endocrine tumor is established by routine histopathology including the staining for chromogranin A and synaptophysin, additional staining for Ki-67 should always be performed....

Duodenum

Hematoxylin-eosin, chromogranin A, synaptophysin, S-100 (gangliocytic paragangliomas only), Ki-67, gastrin, somatostatin, serotonin or other hormones, if required by the clinical setting.

Comments:

The diagnosis of an endocrine tumor should be demonstrated by routine histopathology including stainings for chromogranin A and synaptophysin. The staining for specific hormones will help to establish the type of duodenal tumor and the determination of Ki-67 the proliferation rate.

Pancreas

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

Comments: see previous chapter.

Q16: Is histology required?

Yes

Q17: Is cytology recommended and in which clinical situations?

Not recommended but may be useful.

Q18: What are the minimal ancillary tests to be done to support the histological diagnosis?

Chromogranin A, synaptophysin, NSE, additional neuroendocrine and non-neuroendocrine markers may be useful.

Q19: Should the mitotic index be assessed? Which method?

Yes.

Q20: Is the Ki-67 index necessary? Which method?

Yes. Standard procedure will be worked out

Q21: Is IHC required for tumor cell subtyping?

No

Q22: Would you recommend IHC staining for p53?

Optional (May be useful for diagnostic purposes).

Q23: Would you recommend IHC for SSR2A receptor?

No

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Endoscopic and surgical therapy (10):

Stomach

1.1. Curative therapy

Type 3 and poorly differentiated tumors: Partial or total gastrectomy with lymph node dissection as recommended for adenocarcinomas.

Duodenum

2.1. Curative surgical therapy:

...Patients with larger tumors should undergo pancreatico-duodenal resection (Whipple's procedure). Tumors located in the distal duodenum should be removed by duodenal resection.

2.2. Palliative surgery

Similarly as in other types of endocrine tumors, debulking of liver metastases should be considered.

Pancreas

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). (...)

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, (...).1.2. Curative surgery of 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.

Q24: When is curative surgery recommended in PDEC?

Whenever possible in localized disease.

Q25: When is curative surgery NOT recommended?

See Q 24

Q26: What type of surgical resection would you recommend?

Radical resection, but low risk

Q27: Is surgery for liver metastases recommended along with elective surgery?

Usually not.

Q28: In advanced stages, are debulking surgical strategies recommended and to what extent?

No.

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Cytoreductive therapy

Stomach

(type 3 and poorly differentiated tumors)

There are very few reports about the results with liver embolization (not recommended in histamine-producing tumors) and RF-ablation in gastric endocrine tumors.

Duodenum

Research on cytoreductive therapy in endocrine duodenal tumors are sparse but should be performed in accordance with principles applied in other endocrine gastrointestinal tumors. Ablative therapy may be considered.

Pancreas

1. Selective embolization alone or in combination with intra-arterial 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.

Q29: Is locoregional ablative therapy recommended for liver metastasis secondary to PDEC? If so, which type?

TACE may be indicated in selected patients.

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Stomach

Medical therapy

2. Systemic chemotherapy

...cisplatin/carboplatin plus etoposide in poorly differentiated tumors. There are few reports in the literature and experience is limited.

Duodenum

2. Systemic chemotherapy

... cisplatin/carboplatin plus etoposide in poorly differentiated tumors.

Pancreas

...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.

Q30: When should chemotherapy be employed for patients with PDEC?

If adequate organ function and performance status.

In inoperable disease.

Q31: Which cytotoxic agents and protocols are recommended?
Cisplatin and Etoposide as first line treatment.

Q32: Can chemotherapy be proposed in an adjuvant setting?
Can be considered, but needs to be studied further.

Q33: Is there a role for somatostatin analog or interferon therapy?
No.

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All locations

Follow-up during/ after treatment

Poorly differentiated tumours: close follow-up every 2-3 months with US/CT/MRT or other radiological methods depending on affected organs. In other cases – check-up at least once per year with clinical examination, efficacy of symptomatic treatment, measurement of initially elevated markers, including chromogranin A, US, CT, MRT of liver/pancreas.

Q34: What is the scheduled follow-up for patients with PDEC? Which minimal examinations are required and for how long?
Follow-up all 2-3 months.
Markers positive at initial diagnosis; delete “including chromogranin A”

Q35: Is there a role for PRRT?
If SRS strongly positive PRRT may be considered