Thursday, November 3, 2005

2:30 - 4:00 p. m. **Duodenal Tumor Session**
Chairman: R. Jensen, Bethesda, MD, USA

2:50 - 3:30 p. m. **Working Group Session**
Pathology and Genetics
Group leaders: G. Rindi, Parma, Italy
Questions to be answered: 13
Medicine and Clinical Pathology
Group leader: R. Arnold, Marburg, Germany
Questions to be answered: 17
Surgery
Group leader: H. Ahlman, Gothenborg, Sweden
Questions to be answered: 9
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 Duodenum

Epidemiology
The age-adjusted annual incidence is <0.1 per 100.000 individuals (5).
Clinicopathological staging
According to WHO-indications, tumours of the duodenum and upper jejunum are classified together (12).
Well-differentiated tumours – carcinoids - are the majority. Most of them are mainly but not exclusively, composed of gastrin-producing (G), somatostatin-producing (D) or serotonin-producing (EC) cells. They may be either benign and of uncertain behaviour (WHO group 1), or low-grade malignant (WHO group 2, carcinoma). G cell tumours are preferentially located in the proximal duodenum when non-functioning. When functioning, (gastrinomas) may be found at any site in the duodenum and jejunum and are usually multiple when associated with MEN-1. D cell tumours are usually non-functioning and may be associated with neurofibromatosis (Recklinghausen's disease). Serotonin cell tumours are rare. Gangliocytic paragangliomas are observed in the ampullary region, are usually benign and only exceptionally low-grade malignant with metastases composed of the epithelial component only.

Q1: Do you agree with the above statements as for epidemiology and clinical settings?
Most of the duodenal tumors are functionally inactive despite they express several hormones as determined by IHC.
Term "carcinoid" should be replaced by "endocrine tumor".

Q2: In your experience and according to the literature, what is the incidence of functioning tumors within the duodenal-ampullary and jejunal regions?
10%

Q3: In your experience and according to the literature, is there a gender and age preferential distribution?
60% are male and increase with age

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Prognosis/Survival
Five-year survival rate for localized disease is 66%, regional disease 28%, distant metastases 17% and all stages 51% (5).

Q4: Is your experience consistent with the above?
No. The overall 5 year-survival rate for localized disease is more than 60%, for gastrinomas more than 90%. Only around 5% have distant metastasis, 5 year survival in these patients is probably around 40% (no actual data available, but expert experience suggests these numbers).

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Clinical presentation
The majority of patients presenting with dyspepsia are diagnosed with duodenal ulcer. In an occasional patient, anemia may be a result of bleeding. Most patients are diagnosed incidentally.

Q5: Is your experience consistent with the above?
No. Up to 10-15% of patients with nonfunctioning duodenal tumors have complications (e.g. bleeding, jaundice) that lead to diagnosis.
Reflux disease, peptic ulcer and chronic diarrhea might be symptoms of ZES due to duodenal gastrinoma.

Q6: What are the most frequent reasons for incidental finding?
Dyspepsia most frequent finding.

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Diagnostic procedures
1. Tumour imaging
Endoscopy, EUS, contrast-enhanced CT or MRT of the abdomen, SRS scintigraphy
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.

Q7: Which procedure(s) is/are required for a minimal diagnostic approach?
No change.

Q8: Which procedure should be done first?
Endoscopy and biopsy.

Q9: Is EUS required? When is it recommended? CT/MRI? Octreotide scintigraphy?
EUS plus biopsy if possible always.
Nonfunctioning CT or MRI. No data for Octreoscan, but possibly helpful.

Q10: Please suggest your imaging/procedure flow-chart for duodenal tumors.
See Q9

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2. Biochemical diagnosis
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 von Recklinghausen's disease or ZES secondary to MEN-1 should have an extended biochemical work-up.

Q11: What are the minimal required biochemical tests in patients with non-functioning duodenal tumors?
Chromogranin A, gastrin, 5-HIAA. (minority vote: no gastrin)

Q12: What is the minimal biochemical work-up for functioning G and D cell tumors?
For both Chromogranin A, Gastrin for functioning G cell tumor, somatostatin if functioning D cell tumor suspected.

Q13: When should biochemical tests be performed?
At diagnosis and if positive in the follow-up.

Q14: Is germline DNA testing recommended? Which genes? Which method?
YES according to family history and multiplicity of tumors in MEN-1 gene

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

Q16: When is genetic counseling recommended?
See Q14

Q17: Would you recommend collecting a consensus statement for genetic testing?
See Q14

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3. Histopathology
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 tumour 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 tumour and the determination of Ki-67 the proliferation rate.

Q18: Is histology required?
YES

Q19: Is cytology recommended and in which clinical situations?
NO

Q20: What are the minimal ancillary tests to be done to support the histological diagnosis?
Chromogranin A, synaptophysin, S-100 (gangliocytic paragangliomas only), gastrin and/or other hormones if required by the clinical setting. (MINORITY VOTE: ADD SOMATOSTATIN, SEROTONIN)

Q21: Is the mitotic index necessary? Which method?
YES
Mitotic count

Q22: Is the Ki67 index necessary? Which method?
YES
Working on standardization

Q23: Is IHC required for tumor cell subtyping and, if so, when?
YES, if required by the clinical setting (how do we know that it is a NF tumor?)

Q24: Would you recommend IHC staining for p53?
NO

Q25: Would you recommend IHC for SSR2A receptor?
NO

Q26: Please see the proposal of TNM classification of duodenal tumors (Appendix 2, see at the end) and comment.

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Surgical therapy
2.1. Curative surgical therapy:
Small duodenal tumors may be locally resected by endoscopy or surgery. 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.

Q27: When is curative surgery NOT recommended?
Small duodenal tumors (D1-D4) less than 1cm in size may be locally resected by endoscopy, if we have no sign of LN metastases. If the tumor is located close to the papilla surgery may be required.
Larger tumors or tumors with suspected positive LN metastases require surgery. D1 and D4 tumors without LN can be handled by local excision or resection. D2 and D3 tumors are usually treated by pancreatoduodenectomy even in the absence of lymph node metastases (due to local complications and occult LN metastases).

Q28: When is local tumor ablation (e.g., endoscopic) or minimal alternative surgery recommended?
Local regional treatment (transarterial chemoembolisation, hepatic resection, ablative procedures) may be compromised by prancreatoduodonectomy

Q29: When is curative surgery recommended?
See above Q27

Q30: Which type of surgical resection would you recommend?
See above Q27

Q31: Is surgery for liver metastases recommended along with elective surgery?

Q32: Which type of palliative surgery is recommended?

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Cytoreductive therapy
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.

Q33: What is the best treatment option for liver metastases from duodenal tumors?

Q34: When is surgical treatment for liver metastases recommended?

Q35: Which type of loco-regional ablative therapy is recommended?

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Medical therapy
1. Biotherapy
1.1. Somatostatin analogues: Somatostatin analogues can be used in patients with hormonal symptoms. Experience is limited.
1.2. Interferon: Interferon can be attempted in patients with disseminated disease. However, experience is limited.
2. Systemic chemotherapy
Chemotherapy should only be used in metastatic disease (depending on tumor proliferation). The combination of STZ and 5-FU/doxorubicin is recommended in tumors with low to moderate proliferation and cisplatin/carboplatin plus etoposide in poorly differentiated tumors.
In gastrin-producing tumors, proton pump inhibitors should be used to control acid-related symptoms.

Q36: Is somatostatin analog therapy recommended? If so, when and how?

Q37: Is interferon therapy recommended? If so, when and how?

Q38: When is chemotherapy recommended?

Q39: Which cytotoxic agents and protocols are recommended?

Q40: Can chemotherapy be proposed in an adjuvant setting?

Q41: Can PRRT be recommended? If so, when and which type?
Metastatic and inoperable disease if no other treatment options and sufficient uptake on the OctreoScan.

Q42: What is the scheduled follow-up for patients with duodenal tumors? What are the minimal examinations required and for how long?
In case of completely endoscopically removed non-functioning tumor follow-up endoscopy, abdominal ultrasound or CT scan and chromogranin A are recommended after 6, 24 and 36 months.
Gastrinomas discussed later.