Thursday, November 3, 2005

11:00 - 12:20 a. m. **Gastric Tumors, Session 2**
Chairman: G. Delle Fave, Rome, Italy

11:20 - 11:50 a. m. **Working Group Sessions**
Pathology and Genetics
Group leaders: G. Rindi, Parma, Italy
Questions to be answered: 12
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 Stomach – Type 3

Clinicopathological staging
Type 3 is the second most common NE gastric tumor with a relative incidence of 13-20%; it appears sporadically without predisposing factors either local (atrophic gastritis) or genetic (MEN-1: ZES). These are usually solitary and belong to WHO group 2: Ki-67 >2%, >2 cm in diameter and infiltrative growth with metastases both to regional lymph nodes and the liver. Less than 5% of these tumors can cause the so-called "atypical carcinoid syndrome" due to histamine-production.

Q1: Concerning type 3 tumors, is your experience consistent with the above statements on incidence, tumor aggressiveness and functional activity?
Well differentiated tumors show distant metastasis in less than 50%. Poorly differentiated tumors have metastasis in a higher degree.
Less than 1 % instead 5% of these tumors can cause carcinoid syndrome.

Q2: In your experience and according to the literature, is there a gender and age preferential distribution?
No data, Type III-Tm demonstrate a male predominance

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

Q3: Is your experience consistent with the above?
There are no sufficient data on prognosis, but some have the experience that survival in well differentiated type 3 tumor is longer.

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Clinical presentation
Small gastric carcinoids rarely give rise to symptoms and are diagnosed incidentally or in patients with pernicious anemia (9). Larger carcinoids may bleed. Occasionally, patients may complain of flush and present the "atypical carcinoid syndrome". The "atypical carcinoid syndrome" includes severe generalized flushing, swelling, lacrimation, asthma and diarrhoea, caused by histamine-production from a gastric endocrine tumor type 3.

Q4: Is your experience consistent with the above?
Small type 3 tumors rarely produce symptoms, very rarely patients may complain symptoms of the CS. Larger carcinoids may bleed.

Q5: Which proportion of your type 3 patients present the "atypical carcinoid syndrome"?
Delete

Q6: In your experience, do "functioning" tumors metastatize to the liver? If so, in which proportion?
Delete

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Diagnostic procedures
1. Tumor imaging
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.

Q7: Which procedure(s) is/are required for a minimal diagnostic approach?
Gastroscopy with biopsies of the tumour and antral and fundic mucosa, EUS optional, CT or MRI and SRS (see Q9)

Q8: Which procedure should be initially performed?
Delete

Q9: For type 3 tumors, is EUS required? When is it recommended? What about CT/MRI and SRS?
If PDC, no EUS is indicated. If WDC and less than 1 cm, EUS may be indicated.
Staging For PDC whole body CT. If negative CT, go for surgery, no further imaging.
WDC staging CT whole/body and Octreoscan
Follow/up use the imaging methods that was were positive.

Q10: Please suggest your imaging/procedure flow-chart for type 3 tumors.

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2. Biochemical diagnosis (9)

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.
Comments:
Chromogranin A is the most sensitive marker for detection of gastric endocrine tumors (not in type 1 and 2). Measurement of gastrin will reveal atrophic gastritis and secondary hypergastrinemia. If the patients present flush in association with a gastric endocrine tumor (type 3), measurement of urinary histamine metabolites is recommended (elevated in 33% of type 1 and 80% of type 3 gastric carcinoids).

Q11: What are the recommended biochemical tests in patients with type 3 tumors?
Chromogranin A. (Gastrin to exclude other conditions)
Delete parietal cell antibodies and MEN 1 diagnostic procedures.

Q12: Which circulating markers should be tested for?
Delete

Q13: When should biochemical tests be performed?
At diagnosis and follow-up

Q14: Is germline DNA testing recommended? Which genes? Which method?
NO

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

Q16: Is genetic counseling recommended?
Delete question

Q17: Would you recommend collecting a consensus statement for genetic testing?
Not applicable

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3. Histopathology
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 to demonstrate the proliferative capacity of the tumor. High Ki-67 (>15-20%) indicates poor prognosis.

Q18: Is histology required?
YES
Histological subtyping required (e.g. small cell carcinoma)

Q19: What are the minimal ancillary tests required?
Mucin staining, IHC for CgA and synaptophysin

Q20: Should the mitotic index be assessed? Which method?
YES see Type I/II

Q21: Is the Ki-67 index necessary? Which method?

YES
Standard to be defined (Method), work in progress

Q22: Is IHC required for tumor cell subtyping and, if so, when?
Delete

Q23: Would you recommend IHC staining for p53?
NO

Q24: Would you recommend IHC staining for SSR2A receptor?
NO.

Q25: Do we need a TNM classification? Please see the proposal for gastric tumors (Appendix 2, see at the end).

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Endoscopic and surgical therapy (10):
1.1. Curative therapy
Type 3 and poorly differentiated tumors: Partial or total gastrectomy with lymph node dissection as recommended for adenocarcinomas.

Q26: How does tumor multiplicity affect the therapy approach?
Inappropriate question

Q27: When is curative surgery NOT recommended in type 3 tumors?
Inappropriate question

Q28: When is minimal alternative surgery recommended?
(no data for recommendation)

Q29: When is curative surgery recommended?
(see question 30)

Q30: Which type of surgical resection would you recommend?
Partial and radical resection with lymph node dissection according to size and site as recommended for adenocarcinoma.

Q31: Should surgery for liver metastases be combined with gastric surgery? If so, under what circumstances?
It can be done, but no data for recommendation available

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Cytoreductive therapy (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 for liver metastases in gastric endocrine tumors.

Q32: When is the treatment of liver metastases recommended?
When macroscopical clearance is possible with curative intent (primary tumor excised)
Suggestion: Separate section at the end of the guidelines on surgical treatment of liver mets

Q33: What is the best treatment option for liver metastases from type 3 tumors?

Curative surgery; as optional treatment cytoreduction of tumor mass (90%) is possible using surgery, HAE and other possible ablative therapies

Q34: Which type of ablative therapy is recommended?
Depending on size, number and topographical localisation of lesions (see Suggestion Q32)

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Medical therapy
1. Biotherapy
1.1. Somatostatin analogues
In the case of multiple ECL-omas with athrophic gastritis or ZES/MEN 1, somatostatin analogues have been shown to induce regression of gastric s, type 1 and 2 (11). This scheme, however, is not recommended.
1.2. Interferon
Can be tried in disseminated type 2 and 3 tumors. Experience is limited (9).
2. Systemic chemotherapy
Chemotherapy should only be used in metastatic disease (mainly type 3 and poorly differentiated tumors). The combination of STZ plus 5-FU/doxorubicin is recommended in less aggressive tumors and cisplatin/carboplatin plus etoposide in poorly differentiated tumors. There are few reports in the literature and experience is limited.

Q35: Is somatostatin analog therapy recommended in type 3 tumor disease? If so, when and how?
Indicated in case of associated syndrome.
SSA or alpha-interferon may be considered in well differentiated growing tumors for antiproliferative reasons, the antiproliferative effect is being evaluated in prospective studies.

Q36: Is interferon therapy recommended? If so, when and how?
See Q 35

Q37: When is chemotherapy recommended?
Inoperable and progressive metastatic disease

Q38: Which cytotoxic agents and protocols are recommended?
In well differentiated tumors STZ and 5FU can be tried, but studies are missing.
In poorly differentiated tumors cisplatin and etoposide is first line treatment.

Q39: Can chemotherapy be proposed in an adjuvant setting?
No data

Q40: Can PRRT be recommended? If so, when and which type?
Refer to Q34 and 35 session 1.

Q41: What is the scheduled follow-up for patients with type 3 tumors? What are the minimal examinations required and for how long?
In well differentiated tumors and after curative resection of the tumor endoscopy, imaging (according to the initially positive study, to local experience) and chromogranin A in 6 months intervals for the first 2 years, and then yearly for 3 more years; in well differentiated metastatic tumors follow-up investigations in 3 month intervals.
In poorly differentiated tumors after curative resection in 3 months intervals for the first 2 years.