

Thursday, November 3, 2005

8:30 - 10:30 a. m. **Gastric Tumors, Session 1**
Chairman: P. Ruszniewski, Clichy, France

9:00 - 9:30 a. m. **Working Group Sessions**
Pathology and Genetics
Group leaders: G. Rindi, Parma, Italy
Questions to be answered: 11
Medicine and Clinical Pathology
Group leader: R. Arnold, Marburg, Germany
Questions to be answered: 16
Surgery
Group leader: H. Ahlman, Gothenborg, Sweden
Questions to be answered: 4
Imaging
Group leaders: S. Pauwels, Brussels, Belgium; D.J. Kwekkeboom, Rotterdam, The Netherlands

Color Codes

 Pathology and Genetics  Medicine and Clinical Pathology  Surgery  Imaging

ENETS Guidelines Neuroendocrinology 2004;80:394-424

Endocrine tumors of the Stomach – Type 1 and Type 2

Epidemiology

The yearly age-adjusted incidence of gastric neuroendocrine tumors has been reported to be around 0.2 per 100, 000 population (5). The tumors are probably under-diagnosed.

Clinicopathological staging

As in other sites of the gastrointestinal tract, neuroendocrine tumors of the stomach are categorized into well-differentiated or poorly differentiated tumors (6,7).

Well-differentiated tumors are the majority. Besides the extremely rare gastrin-producing (G), somatostatin-producing (D), or serotonin-producing (EC) cell tumors, most well differentiated tumors are mainly, but not exclusively, composed of enterochromaffin-like (ECL) cells and are most frequently located in the acidopeptic mucosa. They are also called ECL-cell carcinoids or ECL-omas and three subtypes of well-differentiated ECL cell tumors are recognised (6,7)

Type 1 is the most common NE neoplasm in the whole stomach with a relative incidence of 70-85%, and is frequently small, polypoid, often multiple and usually benign (WHO group 1). Is secondary to hypergastrinemia, related to atrophic gastritis (also includes microcarcinoidosis) and is always associated with ECL-cell hyperplasia.

Type 2 is a rare tumor associated with primary hypergastrinemia as a manifestation of Zollinger-Ellison syndrome (ZES) as part of MEN-1. Type 2 tumors appear mostly as multiple benign polyps (WHO group 1), and are only in exceptional cases metastatic (WHO group 2, endocrine carcinoma).

Q1: Do you agree with the above statements concerning the epidemiology and clinical settings?
Yes, in addition
Type 2 up to 35 % metastatic

Q2: In your experience and according to the literature, is there a gender and age preferential distribution?
Yes, there is a gender pref. Distribution for type 1 gastric carcinoids with women 70-80% of patients affected in their 50s and 70s; however due to extensive use of endoscopy some patients may be younger and belong to multiple autoimmune disease.

Q3: Is the clinical subtyping of ECL cell tumors effective in patient management?
yes

Q4: Does the above reported incidence for type 1 and 2 tumors correspond to your experience?
yes

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Prognosis/Survival

Type 1 occurs most often in women, with no tumor-related death at an overall mean follow-up of 53 months (8). Among type 2 tumors there was one tumor-related death (49 months after diagnosis) and an overall mean survival of 84 months.

Q5: Is your experience consistent with the above?
Yes for sentence 1, first part, ..” with rare tumor-related death at follow-up”. Among type 2 death due to metastatic gastric carcinoid is exceptional.

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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.

Q6: Is your experience consistent with the above?
Very rarely instead of occasionally . . . ; first sentence: incidentally in patients with atrophic gastritis

Q7: What proportion of type 1 or type 2 patients present the “atypical carcinoid syndrome”?
Less than 1%

Q8: In your experience, are “functioning” tumors metastatic to the liver? If so, in what proportion?
Delete question

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Diagnostic procedures

1. Tumor imaging

Gastroscopy/Endoscopic ultrasonography (EUS), abdominal ultrasound, contrast-enhanced CT or MRT of the abdomen and somatostatin receptor scintigraphy (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.

Q9: Which procedure(s) is/are required for a minimal approach?
Gastroscopy, antral (2 biopsies) and fundic biopsies (4 biopsies) in addition to biopsies of the largest polyps

Q10: Which procedure should be initially performed?
Delete question (see Q9)

Q11: For type 1/type 2 tumors, is EUS required? When is it recommended? Are CT/MRI and SRS required? If so, under what circumstances?

Type 1, small type 2 tumors: endoscopy and biopsy suffices. Follow-up: if steady do nothing. If growth (bigger than 1 cm), EUS. If lymphnode positive, invasion (on EUS): FNA plus MRI or CT (upper abdomen) together with OctreoScan (no data)

For type 1/type 2 tumors EUS should be performed in tumors above 1 cm in size. CT, MRI, SRS are not required with the exception of larger tumors and invasive tumors at the EUS.

Q12: Please suggest your imaging/procedure flow-chart necessary in the diagnosis of type 1/type 2 tumors.

See Q11

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2. Biochemical diagnosis (9)

Chromogranin A, Gastrin, Histamine metabolites in urine (with appropriate diet). It is also important to perform an autoimmune screening (parietal cell and intrinsic factor 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). MEN-1 should be confirmed in gastric endocrine tumors type 2.

Q13: What are the minimal required biochemical tests in type 1/type 2 patients?
Serum gastrin and chromogranin A (majority); minority vote: gastrin only

Q14: Is chromogranin A measurement recommended in type 1/type 2 patients?
yes

Q15: When should biochemical tests be performed?
At diagnosis (majority), minority vote: CgA for f/u

Q16: Is germline DNA testing recommended? Which genes? Which method?
Delete question

No.

a) If family history positive or if multiple tumors are present in the absence of atrophic gastritis in the rare instances when MEN-1 diagnosis has not been done previously.

b) MEN1

c) Mutational screening and sequencing allowing the analysis of the entire coding gene and splice sites.

Q17: Is somatic (tumor) DNA testing recommended? Which genes? Which method?
NO.

Absence of information about relevant genes.

Q18: When is genetic counseling recommended?

In case of suspicion of familial syndrome

Q19: Would you recommend collecting a consensus statement for genetic testing?
YES, informed consent is mandatory

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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.

Q20: Is histology required?
YES.

Histology is necessary for diagnosis. Cytology may be helpful, but should be confirmed by histology.

Q21: What are the minimal ancillary tests to be done to support the histological diagnosis?
Immunohistochemistry: chromograninA, synaptophysin.

Q22: Should the mitotic index be calculated? If so, by which method?

- a) YES
- b) Mitotic count in 10 HPF (2 square mm)

Q23: Is the Ki-67 index necessary? If so, which method?

- a) YES
- b) IHC technical and counting standards must be worked out.

Q24: Is IHC required for tumor cell subtyping and, if so, when? Delet the question

YES, if the clinicians ask for it (possibly in academic setting)

If necessary for the management of the patient and highly recommended.

Q25: Would you recommend IHC staining for p53?

NO

Q26: Would you recommend IHC for SSR2A receptor in type 1/type 2 patients' samples?

NO

Q27: Do we need a TNM classification? Please see the proposal for gastric tumors (Appendix 2, see at the end).

YES

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Endoscopic and surgical therapy (10):

1.1. Curative therapy

Type 1 and 2 tumors (atrophic gastritis or MEN 1)

Polyps <1 cm in size: surveillance annually; One to 6 polyps and >1 cm in size, endoscopic resection after EUS and surveillance; more than 6 polyps and >1 cm in size, extension to muscularis and/or repeated recurrences: alternatively surgical resection or antrectomy (reduces gastrin stimulation from antral G-cells).

Malignant development or recurrence despite local surgical resection: partial or total gastrectomy with lymph node dissection.

Recommendations refer to polyps (i.e. macroscopic lesions, microcarcinoidosis does not require specific intervention)

Q28: How does tumor multiplicity affect therapeutic management?

It does not influence surgical decision. See question 29

Q29: In the case of local endoscopic ablation, specify aspects in decision-making. What type of endoscopic resection is recommended? (Majority agrees to the below, undecided: 15, disagree: 5) Lesions below 1cm undergo surveillance. Before local endoscopic ablation EUS should be performed and EMR is recommended for lesions close to and above 1cm but without invasion. With invasion and positive margins of EMR antrectomy + local resection is performed in type 1 ECLoma. In type 2 only local excision is recommended.

Q30: When is curative surgery recommended in type 1/type 2 patients?

Q31: Which type of surgical resection would you recommend? Is antrectomy an effective option? Antrectomy is effective in most patients (Type I, >80%) and more radical surgery is required in LN positive tumors.

Flow chart to be added

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Medical therapy

1. Biotherapy

1.1. Somatostatin analogues

In the case of multiple ECL-omas with atrophic gastritis or ZES/MEN 1, somatostatin analogues have been shown to induce regression of gastric , type 1 and 2 tumours (11). This scheme, however, is not recommended due to lack of sufficient data.

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.

Q32: Is biotherapy recommended in patients with type 1 and 2 tumors? Which regimen?

No except in functioning tumors and in type 2 if indicated for the underlying tumor disease

In the exceptional case of metastatic tumor disease referral to specialized center for further therapy options is recommended. (see also Q33)

Q33: When is chemotherapy recommended? Specify the active and appropriate regimens.

NO indication (see Q32)

Q34: May peptide receptor radionuclide therapy (PRRT) be recommended and in what circumstances?

Only if distant metastasis and there are no other treatment options; and if the OctreoScan shows sufficient uptake. (No data). Treatment is compassionate use based or academic initiated trial.

Q35: What type of PRRT should be employed?

Preferably Y-90 or Lu-177 labeled analogues.

Q36: What is the scheduled follow-up for patients with type 1 and 2 tumors? What are the minimal examinations required and for how long?
Gastroscopy every 2 years in (type 1), yearly if type 2.