Treatment of Gastric Neuroendocrine Tumors

The Necessity of a Type-Adapted Treatment

Martin Schindl, MD; Klaus Kaserer, MD; Bruno Niederle, MD

Background: Gastric neuroendocrine (or gastric carcinoid) tumors have recently been classified into 3 types that differ in biological behavior and prognosis. Although the necessity of type-adapted treatment is widely accepted, it seems inconsistently used in daily practice.

Hypothesis: Diagnostic differentiation into various biological types is necessary for an adequate treatment of gastric neuroendocrine tumors.

Design: Retrospective study.

Setting: University hospital department of surgery.

Patients: Twenty-seven patients with a histologically verified gastric neuroendocrine tumor.

Main Outcome Measures: A univariate analysis of survival rates with respect to tumor type, tumor biological parameters, and treatment performed was accomplished by applying the Kaplan-Meier estimation method. The log-rank test was used to evaluate the level of significance.

Results: The 16 type 1 (59%) and 11 type 3 (41%) gastric neuroendocrine tumors differ in tumor size, histopathologic characteristics, and biological behavior. Nine (56%) of 16 type 1 gastric neuroendocrine tumors were treated by local excision, 8 of these (89%) had persistent atrophic gastropathy during the follow-up period. Five-year cumulative survival of patients with type 1 gastric neuroendocrine tumor was 100% without any progression into malignant phenotype. In contrast, 4 (44%) of 9 locally advanced type 3 gastric neuroendocrine tumors were treated radically by extended resection with a 5-year cumulative survival of 75%.

Conclusions: Differentiation into 3 biologically distinct tumor types for gastric neuroendocrine tumors is important with respect to therapeutic strategy and prognostic consideration. Correct diagnosis is attainable by using endoscopy, histopathologic characteristics, and laboratory chemical analysis and should precede any treatment. Extended radical surgery of high-risk type 3 tumors is indicated when definitive healing is achievable, whereas type 1 tumors are best treated by endoscopic removal and long-term follow-up.

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From the Department of Surgery, Division of General Surgery (Drs Schindl and Niederle), and the Institute of Clinical Pathology (Dr Kaserer), University of Vienna, Austria.

G RIGORI1 in 1985 was the first to divide gastric carcinoid tumors into 2 clinicopathologically distinct groups on the basis of the serum gastrin level. Although serotonin-producing enterochromaffin cells are rare in these tumors, the term gastric carcinoid is historically used in its nomenclature. Recently, gastric neuroendocrine tumors (gastric carcinoids) have been classified on the basis of pathogenesis and histomorphologic characteristics into 3 types differing in biological behavior and prognosis.2-8 Enterochromaffinlike (ECL) cells are the main endocrine cell types in type 1 and type 2 gastric neuroendocrine tumors and are highly susceptible to gastrin trophic stimulus. Under circumstances that cause hypergastrinemia, such as chronic atrophic gastritis (CAG) in pernicious anemia (type 1) or gastrin-producing neoplasms in Zollinger-Ellison syndrome (ZES)/multiple endocrine neoplasia (MEN) 1 (type 2), multiple ECL cell carcinoids occur in the oxyntic corpus and fundus mucosa of the stomach. Gastric neuroendocrine tumor types 1 and 2 are usually considered benign with a low risk of malignancy. Type 3 gastric neuroendocrine tumors are composed of different endocrine cells, including poorly differentiated endocrine and exocrine cells, which grow sporadically, irrespective of gastrin in an otherwise normal mucosa. Most of these tumors show a low- to high-grade malignant transformation, already metastasizing at the time of diagnosis.
PATIENTS AND METHODS

PATIENTS

The medical documentation of 27 consecutive patients (12 men and 15 women; mean±SD age, 60.0±11.6 years [range, 34-77 years]) with a histologically verified gastric neuroendocrine tumor was retrospectively reviewed. The study, with a prospective follow-up period, included patients treated over the last 2 decades. Information concerning preoperative history, endoscopic examination (macroscopic tumor manifestation, topographical localization, evidence of multiplicity), laboratory data, and treatment performed was obtained from patients’ reports. Special emphasis was placed on tumor pathologic characteristics (size, local wall invasion, and differentiation), localization within the stomach, preoperative serum basal gastrin level and evidence of regional and distant tumor growth.

PREOPERATIVE EVALUATION AND TUMOR CLASSIFICATION

In each case diagnosis was made using findings from endoscopic examination followed by biochemical and histopathological analysis. Tumor size and the number of lesions were evaluated preoperatively using endoscopy. Additionally, local invasion and regional lymphatic spread were evaluated by endoscopic ultrasonography in 3 of 16 patients with type 1 gastric neuroendocrine tumors. Percutaneous ultrasonography, chest radiography, and computed tomography (CT) were applied to exclude distant tumor growth. Serum basal gastrin levels were measured prior to operation. Tumor specimens were stained routinely with hematoxylin-eosin. Neuroendocrine differentiation was identified by silver impregnation techniques and immunostaining for neuroendocrine markers, such as synaptophysin, neuron-specific enolase, chromogranin A, as well as for gastrin, serotonin, and glucagon. Stepwise biopsy specimens of the gastric mucosa were obtained and analyzed histomorphologically for any kind of gastropathy.

TUMOR CHARACTERISTICS

Type, Size, and Histopathologic Characteristics

By definition, the group of patients consisted of 16 (59%) with type 1 and 11 (41%) with type 3 gastric neuroendocrine tumors. No type 2 tumor in association with ZES/MEN 1 was found. All type 1 gastric neuroendocrine tumors were localized within the gastric corpus-fundus; 10 of these tumors (62%) appeared as multiple nodules. Five (45%) of 11 type 3 gastric neuroendocrine tumors were situated in the antrum; none showed multiplicity (Table 1). The distribution of tumor size varied among tumor types; type 3 gastric neuroendocrine tumors were large, with a mean±SD diameter of 41.6±33.5 mm (range, 6-90 mm) whereas type 1 gastric neuroendocrine tumors were small with a mean±SD diameter of 6.0±2.3 mm (range, 2-10 mm; *P*<.01) (Table 1).

On histomorphological examination, local invasion was evident in 9 (82%) of 11 type 3 tumors but in no type 1 tumors. In 3 patients with type 1 gastric neuroendocrine tumors, the preoperative endoscopic ultrasonographic diagnosis of submucosal growth, local wall invasion, or lymphatic spread compared well with histological findings. Tumor specimens were further examined for signs of cell and tissue atypia. Mild to moderate...
cell and nucleus polymorphism, increased mitotic activity, and atypical tissue structures were evident in 10 (91%) of 11 type 3 tumors but in no type 1 tumors (Table 2).

### Distant Growth and Classification

Nine (82%) of 11 type 3 tumors but no type 1 tumors showed either lymphatic or distant tumor spread to other organs (Table 2). Based on histopathologic findings and growth characteristics, benign tumor behavior was assumed in type 1 gastric neuroendocrine tumors, all of which were smaller than 20 mm in diameter and situated within the mucosa and/or submucosa without any evidence of lymph node and distant metastases. In contrast, 9 (82%) of 11 type 3 gastric neuroendocrine tumors were classified as malignant because of local wall invasion (100%) as well as lymph node (100%) and distant metastases (44%) (Table 2). Six (67%) of 9 tumors were larger than 20 mm. Two (18%) type 3 tumors, 6 and 7 mm in diameter, situated within the mucosa and/or submucosa behaved uncertainly at the time of diagnosis. Although without evidence of lymph node and distant metastases, both were composed of mixed endocrine cells with mild to moderate atypia in one (Table 2).

### SURGICAL TREATMENT

Nine (56%) of 16 patients with type 1 and 2 (18%) of 11 patients with type 3 gastric neuroendocrine tumors were treated by local excision (5 endoscopically, 6 open gastrotomies). Mean±SD tumor size was 6.0±2.3 mm (range, 4-10 mm). On histological examination no local invasion into the muscularis layer or beyond was found. All malignant type 3 tumors (n=9) and 7 (44%) of 16 patients with type 3 gastric neuroendocrine tumors, 6 and 7 mm in diameter, situated within the mucosa and/or submucosa behaved uncertainly at the time of diagnosis. Although without evidence of lymph node and distant metastases, both were composed of mixed endocrine cells with mild to moderate atypia in one (Table 2).

### FOLLOW-UP

Within the observation period, 19 patients were alive, 8 patients (30%)—1 with type 1 and 7 with type 3 tumors, respectively—died. All 27 patients were followed over time for tumor recurrence or progression.

In patients with type 1 gastric neuroendocrine tumors, no change in malignant tumor behavior was seen at any time. One of these patients (6%) developed recurrence of ECL cell type tumors in the fundic mucosa 8 months after endoscopic excision. Seven (88%) of 8 patients with type 1 tumors after local excision and 1 after partial corpus resection had persistent gastropathy (CAG, endocrine cell hyperplasia, and intestinal metaplasia), whereas all patients treated by antral resection (n=2) or total gastrectomy (n=4) were free of disease during follow-up (Table 3).

For the patients with type 3 tumors, 2 were classified as uncertain tumors and 3 (75%) of 4 patients with malignant tumors were followed after radical surgery without any recurrence of disease. Recurrence was seen in 1 patient who died 17 months after radical surgery of a mixed neuroendocrine carcinoma, which recurred locally. Four (80%) of 5 patients died in the median of 1.3 months (range, 0.3-14.5 months) after palliative surgery.

Analysis of cumulative survival (Kaplan-Meier method) showed different survival rates depending on tumor type. In patients with type 1 tumors, estimated 5-year cumulative survival was 100%, whereas 5-year survival estimation in patients with type 3 tumors was 54.5%±13% (Figure A). This difference was statistically significant (P<.01). Estimated cumulative survival of patients with type 3 tumors depended on tumor size, local invasion, and metastases. In tumors larger than 20 mm in diameter with deep gastric wall invasion and distant tumor spread, 5-year survival decreased to 33.3%±19% (P=.03), 28.6%±17% (P<.01), and 25%±22% (P=.01), respectively (Figure B-D).

### COMMENT

Gastric neuroendocrine tumors consist of a heterogeneous group of neoplasms comprising tumor types of varying pathogenesis, histomorphologic characteristics, and biological behavior.2,7,8,9-19 Effective clinical

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**Table 1. Tumor Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type 1, CAG (n = 16)</th>
<th>Type 3, Sporadic (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location, No. (%)</td>
<td>Antrum 16 (100)</td>
<td>6 (55)</td>
</tr>
<tr>
<td></td>
<td>Corpus-fundus 16 (100)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Background gastropathy, No. (%)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Elevated serum basal gastrin, No. (%)</td>
<td>16 (100)</td>
<td>2 (18)</td>
</tr>
</tbody>
</table>

* CAG indicates chronic atrophic gastritis; ellipses, none.

**Table 2. Tumor Pathologic Characteristics**

<table>
<thead>
<tr>
<th>Characteristic†</th>
<th>Type 1, CAG (n = 16)</th>
<th>Type 3, Sporadic (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local invasion</td>
<td>T1 16 (100)</td>
<td>2 (18)</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Atypia</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>M1</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Classification</td>
<td>Benign 16 (100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uncertain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malignant</td>
</tr>
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</table>

* CAG indicates chronic atrophic gastritis; ellipses, none. All values given as number (percentage).
† TNM staging system.
management of gastric neuroendocrine tumors requires a correct diagnosis and an algorithm of type-adapted treatment.\textsuperscript{15-20} Treatment protocols so far have seemed inconsistently used in daily practice. To answer the question about the effect of surgical treatment on the clinical course of different types of gastric neuroendocrine tumors, an institutional group of patients were retrospectively studied.

Based on gastrin dependency and the evidence of background mucosal pathologic characteristics, gastric neuroendocrine tumors are divided into 3 types of varying biological behavior and prognosis: Type 1 gastric neuroendocrine tumors are composed of ECL cells, the main endocrine cell type of gastric corpus-fundus mucosa, which is highly sensitive to gastrin trophic stimulus. Tu-

Table 3. Surgical Treatment of Gastric Carcinoid Tumors and Follow-up Results*  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tumor Type 1, Benign (n = 16)</th>
<th>Uncertain (n = 2)</th>
<th>Malignant (n = 9)</th>
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</thead>
<tbody>
<tr>
<td>Surgical treatment, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local excision</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Partial resection</td>
<td>1 (Corpus); 2 (Antrum)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total gastrectomy</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>1 (Local excision)</td>
<td></td>
<td>1 (Total gastrectomy)</td>
</tr>
<tr>
<td>Died of disease</td>
<td></td>
<td></td>
<td>1 (Total gastrectomy); 4 (palliation)</td>
</tr>
<tr>
<td>Gastropathy</td>
<td>8 (Local excision); 1 (partial resection, corpus)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p Ellipses indicate none.

Cumulative survival by the Kaplan-Meier method of patients with gastric neuroendocrine tumors. A, Survival of different tumor types. B, Tumor size 20 mm or smaller vs larger than 20 mm. C, Local infiltration: T1 mucosa/submucosa, T2 muscularis propria, T4 perivisceral infiltration. D, Distant tumor growth, N0 M0 no metastases, N1 M0 lymph node, and N1 M1 distant metastases. Number of patients at risk is indicated below the curves. Local infiltration (T1, T2, and T4) and distant tumor growth (N and M) refer to the TNM staging system.
mors of this type are small; 88% were smaller than 10 mm in diameter, limited to the mucosa and/or submucosa layer (100%), and are benign with a tendency to distant tumor spread of less than 5%.26-30

Endoscopic polypectomy or open surgery with tumor excision by gastrotomy is the treatment of choice in small, solitary type 1 tumors.24-25 Nine (56%) of 16 patients with type 1 gastric neuroendocrine tumors were treated by local excision. Hypergastrinemia and background mucosal pathologic characteristics were observed in all of them during follow-up, but recurrence of multiple ECL tumors in the fundic mucosa occurred in only 1 patient 8 months after undergoing polypectomy. We nevertheless found neither progression into malignant phenotype nor disease-related death in any of type 1 gastric neuroendocrine tumors.

In cases of diffuse tumor multiplicity or tumor recurrence, definitive healing from gastrin pathogenetic stimulus was achieved by extending the surgical procedure in 6 (38%) of 16 patients with type 1 tumors. Elimination of gastrin-producing cells seems the only technique with curative intent in type 1 gastric neuroendocrine tumors. Although regression of neoplastic and hyperplastic ECL cell foci in the stomach mucosa was clearly explained partly by a gastrin autocrine pathway that was discovered after malignant transforma-

tion.32 Activation of gastrin genes together with the expression of a gastrin/cholecystokinin receptor B (CCKB) receptor on carcinoid cells result in an independent tumor growth. Nevertheless, 2 patients in our series were treated by antrectomy and followed over time, having normal serum basal gastrin levels and gastric mucosa. Total gastrectomy, performed in 4 patients, was advised when tumor regression failed, but with rare exceptions it is usually not warranted for disease control in patients with type 1 tumors. Type 2 gastric neuroendocrine tumors, occurring as a result of a gastrin-secreting neoplastic tissue in ZES, behave similarly to the former type. Seventy percent to 80% are smaller than 15 mm in diameter, 90% are limited to the mucosa and/or submucosa, and the risk of metastases and tumor-related death is lower than 5% according to the literature.6,14,17 In our series, no patients with this tumor type were included.

In contrast to the former types, type 3 gastric neuroendocrine tumors consist of different mucosal endo-

crine cells, growing sporadically without the evidence of surrounding mucosal pathologic characteristics or hypergastrinemia. This type of tumor behaves more aggressively; 55% were larger than 20 mm in diameter, 64% showed advanced local invasion, and 82% had regional or distant metastases at the time of diagnosis. Forty-five percent of these patients died of tumor-related disease. In adaptation to local growth characteristics, extended radical surgery, including gastric resection and regional lymphadenectomy, is the treatment of choice in malignant type 3 tumors. In our series, 4 (44%) of 9 patients were treated radically despite locally advanced type 3 tumors with a 5-year survival expectancy of 75%. Locoregional recurrence of a malignant type 3 gastric neuroendocrine tumor was observed in 1 patient 8 months after surgery. Patients treated with palliative intent died after a median of 1.8 months postsurgery.

Observations in the literature indicate that some cases may escape the tumor type predicted behavior in up to 10%,6,11,17 Rindi et al33 recently published 15 clinicopathologic variables by which individual tumor biology is predictable with a higher accuracy than would have been the case by differentiation into 3 tumor types. Judging from this, the clinicopathologic type together with tumor size, Ki 67 proliferation index, histomorphologic grading, mitotic activity, and angiogenesis showed the highest accuracy. With the exception of tumor size, histomorphological parameters will only become known after a definitive histopathological analysis. Rerading of disease influences only the adjuvant treatment.

By retrospectively analyzing the diagnostic pathway of patients with gastric neuroendocrine tumors, we found simple criteria that may be used for immediate diagnoses. With the help of blood sampling, upper gastrointestinal tract endoscopy, endoscopic ultrasonography, and biopsy, a reliable diagnosis may be made promptly in most circumstances (Table 4). The macroscopic tumor manifestation within the stomach (size, site, and multiplicity) together with tumor and mucosa histopathologic characteristics and gastrin serum levels provide information allowing correct identification of individual tumor types. All type 1 tumors in our series were smaller than 10 mm and proved benign during follow-up. Tumor regrading on the basis of histomorphologic characteristics of surgical specimens in any case would not have changed the preoperative treatment strategy. In rare cases of type 1 tumors 15 mm to 20 mm in size or

<table>
<thead>
<tr>
<th>Disease Characteristic</th>
<th>Type 1</th>
<th>Type 3</th>
<th>Diagnostic Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor morphology</td>
<td>Size &lt;10 mm, no wall invasion, lymphatic nodes not enlarged</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Surrounding gastric mucosa</td>
<td>Chronic atrophic gastritis, foveolar hyperplasia, intestinal metaplasia</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Serum basal gastrin levels</td>
<td>Elevated (&gt;250 pg/mL)*</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Appearance</td>
<td>Multiplicity</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Localization</td>
<td>Nonantral</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Normal range of serum basal gastrin level, 25-115 pg/mL.
larger, with or without atypical histological features, a more aggressive behavior has to be supposed, thus warranting adaptation of treatment to malignant lesions.

It is obvious that surgical treatment of gastric neuroendocrine tumors influences the individual prognosis and the patient’s quality of life. Overtreatment of type 1 tumors by extended gastric resection will impair personal well-being unnecessarily without any advantage for an otherwise benign disease. Simple polypectomy of an invasive type 3 tumor implies a considerable risk of recurrence and progression of disease with lethal prognosis in certain cases. It was shown that gastric neuroendocrine tumors behave significantly divergent with respect to local invasion and distant spread, with the highest risk in type 3 tumors. Individual, type-adapted treatment is based on this knowledge, and any physician treating patients with gastric neuroendocrine tumors is responsible for its correct application.

Corresponding author and reprints: Bruno Niederle, MD, Department of Surgery, Division of General Surgery, Section Endocrine Surgery University of Vienna Medical School, Waehringer Guertel 18-20, A 1090 Vienna, Austria (e-mail: Bruno.Niederle@akh-wien.ac.at).

REFERENCES