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Original Research

Prognostic significance of neuroendocrine components in gastric carcinomas

Ji Y. Park [a], Min-Hee Ryu [b], Young Soo Park [a,*], Hye Jin Park [b], Baek-Yeol Ryoo [b], Min Gyu Kim [c], Jeong Hwan Yook [d], Byung Sik Kim [d], Yoon-Koo Kang [b]

[a] *Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-Ro 43-Gil, Songpa-Gu, Seoul 138-736, Republic of Korea*
[b] *Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-Ro 43-Gil, Songpa-Gu, Seoul 138-736, Republic of Korea*
[c] *Department of Surgery, Hanyang University Guri Hospital, 153, Gyeongchun-ro, Guri, Gyeonggi-do 471-701, Republic of Korea*
[d] *Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-Ro 43-Gil, Songpa-Gu, Seoul 138-736, Republic of Korea*

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Abstract ***Background:*** Gastric neuroendocrine carcinomas (NECs) and mixed adenoneuroendocrine carcinomas (MANECs) are aggressive tumours but the prognostic significance of a neuroendocrine component in <30% of the tumour remains unclear. Here, the implication of neuroendocrine components in gastric carcinomas was assessed according to proportion.
Methods: Surgically resected primary gastric carcinomas with neuroendocrine morphology (NEM; $n = 88$) from 2000 to 2012 at Asan Medical Center were retrospectively reviewed. Neuroendocrine differentiation (NED) was defined as immunopositivity for one of three neuroendocrine markers (synaptophysin, chromogranin or CD56) within the NEM area. To validate the prognostic significance of NED, these cases were compared with 650 randomly selected gastric adenocarcinomas without NEM from the same time period.
Results: Gastric carcinomas with NEM were reclassified as NEC (⩾70% NED, $n = 47$), MANEC (30–70% NED, $n = 10$), gastric carcinoma with 10–30% NED (GCNED, $n = 8$) and carcinoma with <10% NED ($n = 23$). The survival rates of patients with ⩾10% NED were significantly poorer than those with <10% NED but no survival difference was observed between NEC and MANEC. In univariate analyses, older age (⩾60 years), larger tumour size (⩾4 cm), advanced stage group, ⩾10% NED and lymphovascular or perineural invasion were indicative of a poor prognosis. Stage group and ⩾10% NED remained as independent prognostic factors by multivariate analysis.

* *Corresponding author:* Tel.: +82 2 3010 5608; fax: +82 2 472 7898.
E-mail address: youngspark@amc.seoul.kr (Y.S. Park).

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Conclusions: A minor proportion (10–30%) of NED should not be overlooked in gastric carcinomas with NEM. NED should be carefully evaluated to predict patient outcomes and plan optimal additional therapies.

1. Introduction

The recent 2010 World Health Organisation (WHO) classification classified neuroendocrine neoplasm of the stomach into three categories: neuroendocrine tumour, neuroendocrine carcinoma (NEC) and mixed adenoneuroendocrine carcinoma (MANEC) [1]. Neuroendocrine tumours are well-differentiated neoplasms with less than 20 mitotic counts per 10 high-power fields and/or less than a 20% Ki67 index. Grade 1 (carcinoid) and grade 2 neuroendocrine tumours are categorised in this group. NECs are poorly differentiated, high-grade malignant neopla sms that encompass small cell and large cell types. MANECs show both malignant exocrine and neuroendocrine components, with at least 30% of either component [1].

While the behaviour of neuroendocrine tumour is considered to be that of a low to intermediate malignancy [2], NECs, which account for 6–16% of all gastric neuroendocrine neoplasms [1,2], are extremely malignant [3,4].The prognosis for gastric NECs is considered to be poorer than conventional adenocarcinomas because they tend to present in advanced clinical stages and often metastasise to the lymph nodes or the liver even in the early stages of the disease [4,5]. As for the coexistence of NEC and adenocarcinoma, mixed adenocarcinoma components in NECs [5] or combined neuroendocrine components in gastric adenocarcinoma are frequently observed [1], but their documentation in the literature is uncommon [6–9]. Although the WHO defines MANEC as harbouring a more than 30% neuroendocrine component and states that a minor (<30%) neuroendocrine component should not prevent its classification as a conventional adenocarcinoma [1], the 30% cut-off is somewhat arbitrary and not enough data on the prognostic significance of the neuroendocrine component are available.

Identification of the neuroendocrine component usually depends on both histological features of neuroendocrine neoplasms and immunohistochemical (IHC) positivity for neuroendocrine markers, such as synaptophysin (SYN), chromogranin A (CGA), neuron cell adhesion molecule (NCAM or CD56), neuron-specific enolase and Leu7 (CD57) [10]. Neuroendocrine marker positivity in gastric carcinomas without regarding histological features of neuroendocrine neoplasm has been reported [11–13], but these studies do not provide enough information on whether neuroendocrine marker positivity should be considered a prognostic indicator.

In this study, we investigated the prognostic significance of the neuroendocrine component in surgically resected primary gastric carcinomas, taking its proportion into account. Clinicopathological features and IHC profiles of neuroendocrine markers in gastric carcinomas with neuroendocrine morphology (NEM) were evaluated. We compared these results with those of conventional gastric carcinomas (with no NEM), according to the proportion of neuroendocrine components, to provide a general understanding of the prognostic influence of neuroendocrine components in gastric carcinomas.

2. Patients and methods

2.1. Selection of patients

Gastrectomy cases with the word 'neuroendocrine' in the diagnosis that presented between 2000 and 2012 were retrieved from the database of the pathology department of Asan Medical Center. Only primary gastric carcinomas with no prior treatment (chemotherapy and/or radiotherapy) were primarily collected. Cases with grade 1 or grade 2 neuroendocrine components and those with distant metastasis at the time of surgery were excluded. Ki67 index was evaluated in cases with <20 mitotic counts, which were all >20%. A total of 88 cases were finally selected.

Clinicopathologic parameters including age, sex, tumour location, depth of invasion, nodal status, lymphovascular and perineural invasion, tumour necrosis, postoperative chemotherapy, recurrence and/or metastasis and survival outcome were obtained by reviewing medical records and haematoxylin and eosin (H&E) stained slides. The pathological tumour-node-metastasis (pTNM) stage was given according to the American Joint Committee on Cancer (AJCC) staging manual for gastric adenocarcinoma. This study adhered to the guidelines established by the Declaration of Helsinki and was approved by the institutional review board.

2.2. Histopathological evaluation and IHC staining

From the review of H&E slides, we were able to identify NEM in all 88 cases, as defined by the WHO classification and recent reports [1,4,5]: (1) organoid architectures such as solid nests, sheets, broad trabeculae or rosette formation; (2) nuclear features manifested by hyperchromatic nuclei with finely to coarsely granular, but evenly distributed, chromatin and (3) cytoplasmic features with a scant to moderate amount of