

Mechanisms Underlying Gastroenteropancreatic Neuroendocrine Tumors

Shereen Ezzat, MD, FRCP, FACP
Professor of Medicine & Oncology
Princess Margaret Hospital & Mount Sinai Hospital
University of Toronto

Tumours of the dispersed endocrine system represent a range of neoplasms from small benign incidental findings to functional hormone-secreting neoplasms to aggressive malignancies. These tumours arise from endocrine cells that are dispersed throughout the gastroenteropancreatic (GEP) tract as well as lung and more rarely prostate and ovary. The term “carcinoid” was originally introduced to describe well differentiated neuroendocrine tumours as well as to tumours that result in the clinical syndrome of systemic serotonin hypersecretion. The use of this terminology, however, causes great confusion because of the wide diversity of hormone activity and biological behaviour that cannot be conveyed by this classification. Since many of these neoplasms ultimately prove to be malignant, this terminology has fallen out of favor. GEP tumors may be clinically silent in terms of hormone function, but they are almost always found to express peptide hormones. Some elaborate hormones that give rise to dramatic clinical syndromes of hormone excess; the pattern of hormone production may be eutopic to the tissue of origin or ectopic, reflecting derepression of genes that are expressed in related cells.

The current approach to the classification of these lesions is based on three principles: (i) microscopic features including immunohistochemical survey of candidate peptides, (ii) differentiated cell type and site of origin, and (iii) biological behaviour extending from benign, low grade malignant and to the high grade malignant lesions; the latter include poorly differentiated endocrine carcinomas and the so-called small cell or oat cell carcinomas.

The wide spectrum of clinical symptomatology associated with these lesions can be partially attributed to the numerous peptide hormones that can be elaborated by the cells of the diffuse endocrine system. The pathological diagnosis of these lesions rests on the identification of markers of neuroendocrine differentiation with a minimum assessment of neuron-specific enolase (NSE), synaptophysin and chromogranins as well as localization of the putative hormone product by immunohistochemistry. The determination of malignant potential is based primarily on architectural and cytologic features, the location and hormone content of individual lesions is of importance, especially in the classification of tumours of histological low grade malignancy, the well differentiated endocrine carcinoma where these additional information may aid in predicting metastatic behaviour.

Recent advances in molecular biologic approaches have provided some insight into both heritable and sporadic neoplasms. In general, a single genetic defect or mutation is not sufficient to initiate tumourigenesis but other events including alterations in angiogenesis, telomerase activity, gain of survival signals, and loss of cell adhesion all contribute to the phenotype that we recognize as carcinoma. While many of operative mechanisms responsible for human neoplasia probably apply to neuroendocrine tumourigenesis, considerably less is known about the molecular events resulting in these lesions.

This update will highlight some of the cellular and genetic defects that have thus far been identified in neuroendocrine carcinomas of the GEP system and their implications for classification, diagnosis, and management.