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Recent Advances in Gastrointestinal Neuroendocrine Tumor Classification

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Abstract

Gastrointestinal Neuroendocrine Tumors (GI-NETs) encompass a broad spectrum of neoplasms arising from neuroendocrine cells, showcasing diverse clinical manifestations and behaviors. The evolution of GI-NET classification has been marked by advancements in histopathology, molecular biology, imaging, and biomarker discovery. Traditional classifications relied on histological features, while modern approaches integrate molecular profiling and imaging modalities to refine tumor characterization and guide personalized treatment strategies. This mini-review provides an overview of the historical progression and current landscape of GI-NET classification systems, highlighting recent breakthroughs in molecular characterization and the integration of imaging and biomarkers.

Keywords: Neuroendocrine tumor; Carcinoid; Gastrointestinal tract; Classification.

Introduction

Gastrointestinal well-differentiated Neuroendocrine Tumors (GI-NETs) represent a diverse group of neoplasms arising from neuroendocrine cells scattered throughout the GI [1-3]. Once considered rare entities, the prevalence of GI-NETs has exhibited a consistent upward trend in recent decades, likely due to improved diagnostic techniques and heightened awareness among clinicians [4-8]. Despite their heterogeneity, accurate classification of GI-NETs is paramount for guiding treatment decisions and predicting patient outcomes.

Traditionally, GI-NET classification has relied on histopathological features, such as mitotic rate, and Ki-67 proliferation index, as outlined in the World Health Organization (WHO) classification system [1-9]. While this classification scheme has served as a valuable foundation for diagnosis and prognostication, it has certain limitations, including interobserver variability and a lack of comprehensive molecular characterization.

In recent years, there has been a paradigm shift in the classification of GI-NETs, driven by advances in molecular biology, genetics, and imaging modalities [1,3,10]. These developments have led to the identification of distinct molecular subtypes and novel biomarkers that offer deeper insights into tumor behavior and potential therapeutic targets. Additionally, advanced imaging techniques, such as Positron Emission Tomography (PET) and multiparametric Magnetic Resonance Imaging (MRI), have enabled more accurate staging and localization of GI-NETs.

This mini-review aims to provide an overview of recent advances in GI-NET classification, highlighting the evolving landscape of diagnostic and prognostic markers. By synthesizing current knowledge in this rapidly evolving field, we aim to shed light on the clinical implications of these advancements and identify potential future directions for research.

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Traditional classification of GI-NETs

GI-NETs represent one of the two classes of GI Neuroendocrine Neoplasms (NENs), with the other being GI Neuroendocrine Carcinomas (NEC) [1]. According to the WHO definition, GI-NETs are well-differentiated NENs characterized by the following features [1]:

– Cytology: Clean smear, cell monomorphism, medium size, round shape, abundant eosinophilic cytoplasm, salt and pepper chromatin, and no or very few mitotic figures.

– Histology: Organoid structure (solid, trabecular, glandular, mixed), no necrosis or only spotty, highly vascularized stroma, low nuclear/cytoplasm ratio, round-oval shape, and abundant cytoplasm.

– Immunohistochemistry profiles: CK+, Chromogranin A (CgA) +, synaptophysin+, insulinoma-associated protein 1+, and Ki-67 low.

Furthermore, the WHO system categorizes GI-NETs based on mitotic rate and the Ki-67 proliferation index into three grades, reflecting their proliferative activity and histological differentiation: Grade 1 tumors typically exhibit low mitotic activity (<2 mitoses/2 mm^2) and/or Ki-67 index (<3%), while Grade 2 tumors display moderate mitotic activity (2-20 mitoses/2 mm^2) and/or Ki-67 index (3-20%). Grade 3 tumors, on the other hand, demonstrate high mitotic activity (>20 mitoses/2 mm^2) and/or Ki-67 index (>20%) and are associated with aggressive clinical behavior and poor prognosis [1,3,9].

Recent advances in GI-NET classification

Molecular landscape

Recent studies have elucidated the molecular landscape of GI-NETs, leading to the identification of distinct molecular subtypes with unique genetic alterations and clinical characteristics. Notably, chromosomal alterations affecting genes like *DAXX*, *ATRX*, *menin*, *p27*, *MEN1*, and *SSTR2/5* have been linked to specific subtypes of NETs, including GI-NETs [3,11]. Additionally, mutations in genes governing the mTOR pathway and dysregulation of genes controlling crucial cellular processes such as cell cycle regulation, apoptosis, and angiogenesis, including *p53*, *Rb*, *BCL2*, and *VEG*, have been implicated in the development of GI-NETs [12-16]. High *PD-L1* expression and microsatellite instability status in NECs and may predict responsiveness to immune checkpoint inhibitors, opening avenues for personalized treatment [17,18]. High *ALDH1A1* expression correlates with poor prognosis in GI-NECs, indicating its potential as a prognostic marker [10]. These molecular subtypes offer valuable insights into tumor biology and may serve as prognostic and pred] T=ctive markers for treatment response.

Additionally, the NETest is an advanced molecular diagnostic tool that uses a liquid biopsy to analyze a tumor's gene expression. By isolating mRNA, synthesizing cDNA, applying PCR and gene analysis, it generates a score from 0 to 100%. Demonstrating over 90% sensitivity and specificity, the NETest surpasses traditional markers like CgA in diagnosing and monitoring NETs, including GI-NETs. It can detect disease progression earlier than imaging techniques [19].

More recently, circulating tumor DNA (ctDNA), Circulating Tumor Cells (CTC), and microRNAs (miRNA) have emerged as promising biomarkers for non-invasive monitoring of disease progression and treatment response [19-21].

miRNAs are small, noncoding RNA molecules (about 22 nucleotides long) that regulate gene expression post-transcriptionally. Discovered in 1993, their clinical significance has only recently been recognized. In GI-NETs, over 100 miRNAs have shown altered expression. miR-21 and miR-133a are present in both blood and tumor tissues of GI-NETs [22]. Other miRNAs, such as miR-375, hold potential as biomarkers to distinguish between different types of pancreatic and gastrointestinal tumors, thereby aiding in diagnosis and prognosis [23].

CTCs are cells that detach from a tumor and circulate in the bloodstream, potentially causing metastasis. Technologies to detect CTCs emerged in the late 20th century, and the FDA approved the first CTC analysis device in 2004. A study noted that 43% of midgut NETs had detectable CTCs, particularly in metastatic cases [24] and it has been proven that the presence of CTCs is linked to a worse prognosis [25].

ctDNA consists of tumor-derived DNA fragments in the bloodstream, offering insights into tumor-specific genetic changes. Detected first in 1948, ctDNA provides a non-invasive alternative to tissue biopsies. In GI-NETs, ctDNA levels correlate with tumor characteristics and prognosis. For example, tumors with liver metastases or high proliferative indices often show higher ctDNA concentrations [26].

Imaging techniques

Advanced imaging modalities play a crucial role in the accurate staging and localization of GI-NETs. Somatostatin receptor-based PET imaging, utilizing radiolabeled somatostatin analogs, allows for the detection and characterization of somatostatin receptor-positive tumors with high sensitivity and specificity [27]. Functional MRI techniques, such as diffusion-weighted imaging and dynamic contrast-enhanced MRI, provide valuable information on tumor perfusion and vascularity, aiding in the differentiation of benign and malignant lesions. Furthermore, molecular imaging techniques, including Peptide Receptor Radionuclide Therapy (PRRT), offer targeted therapeutic options for patients with somatostatin receptor-positive tumors [28].

Artificial intelligence in image analysis

The integration of Artificial Intelligence (AI) and machine learning algorithms into image analysis holds great promise for improving the accuracy and efficiency of GI-NET classification [29]. AI-based approaches can analyze large volumes of imaging data to identify subtle patterns and features indicative of tumor biology and behavior. Deep learning algorithms trained on multi-parametric imaging datasets have demonstrated superior performance in lesion detection, segmentation, and characterization, offering potential tools for automated image interpretation and decision support in clinical practice [30].

Integration of multi-omics data

The integration of multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, holds the key to a

comprehensive understanding of GI-NET biology and classification. Integrative analysis of multi-omics data allows for the identification of molecular signatures and dysregulated pathways driving tumor development and progression [31,32]. Furthermore, systems biology approaches, such as network analysis and pathway modeling, enable the elucidation of complex interactions within the tumor microenvironment and the identification of potential therapeutic targets [31,32].

Challenges and future directions

While recent advances in GI-NET classification have significantly enhanced our understanding of tumor biology and clinical management, several challenges and opportunities for further research and improvement remain.

Tumor heterogeneity: One of the key challenges in GI-NET classification is the inherent heterogeneity of these tumors, both within individual patients and across different anatomical sites. Tumors may exhibit diverse histological, molecular, and clinical characteristics, making accurate classification and treatment selection challenging. Future research efforts should focus on elucidating the drivers of tumor heterogeneity and developing robust classification systems that account for intra-tumoral diversity.

Biomarker validation: While numerous biomarkers have been proposed for GI-NET classification, their clinical utility and reproducibility require further validation in large, multicenter cohorts. Standardization of biomarker assays and interpretation criteria is essential to ensure consistency and comparability across studies. Additionally, longitudinal studies are needed to assess the dynamic changes in biomarker expression over time and their predictive value for treatment response and prognosis.

Integration of multi-omics data: The integration of multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, holds great promise for advancing our understanding of GI-NET biology and classification. However, challenges remain in integrating and analyzing large-scale omics datasets, as well as in interpreting the complex interactions within the tumor microenvironment. Development of bioinformatics tools and computational algorithms capable of integrating multi-omics data and predicting clinical outcomes is crucial for translating omics-based discoveries into clinical practice.

Imaging challenges: Despite the advancements in imaging techniques for GI-NET characterization, challenges such as lesion detection, characterization of indeterminate lesions, and differentiation of benign and malignant lesions persist. Furthermore, the cost and availability of advanced imaging modalities may limit their widespread adoption in clinical practice. Future research should focus on addressing these challenges through the development of novel imaging probes, quantitative imaging biomarkers, and artificial intelligence-based image analysis algorithms.

Therapeutic resistance: While targeted therapies have shown promise in the treatment of GI-NETs, therapeutic resistance remains a significant challenge, particularly in the setting of advanced or metastatic disease. Resistance mechanisms, such as activation of alternative signaling pathways, clonal evolution, and tumor microenvironment-mediated immune evasion, pose obstacles to treatment efficacy. Future research efforts should aim to elucidate the molecular mechanisms underlying therapeutic resistance and identify strategies to overcome or prevent resistance development.

Patient-centered outcomes: In the era of personalized medicine, it is essential to prioritize patient-centered outcomes, including quality of life, symptom control, and treatment tolerability, in addition to traditional clinical endpoints such as progression-free survival and overall survival. Incorporating patient-reported outcomes and preferences into treatment decision-making and trial design is crucial for optimizing patient care and enhancing treatment adherence and satisfaction.

Conclusion

GI-NET classification has evolved significantly, integrating advances in histopathology, molecular biology, imaging, and biomarker discovery. From histological to molecular profiling, the landscape has expanded to enable personalized approaches to diagnosis and treatment. Recent advances have reshaped patient management and clinical trial design, offering promise for improved outcomes.

Conflicts of interest: The author declare no conflict of interest in relation to this study.

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