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Clarifying the Diagnostic Boundaries in High-Grade Neuroendocrine Neoplasms: A Commentary on Histopathologic and Genetic Distinctions

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Abstract:

Background: High-grade neuroendocrine neoplasms (NENs) encompass well-differentiated grade 3 neuroendocrine tumors (G3 NETs) and poorly differentiated neuroendocrine carcinomas (NECs), which differ significantly in morphology, genetics, prognosis, and therapeutic response. The article reviewed by Sun et al. (Am J Clin Pathol. 2025;163(6):804–814) provides a synthesis of histopathologic, immunohistochemical, and genomic criteria to aid in distinguishing these entities. **Objective:** To critically appraise the review by Sun et al., highlighting its strengths, identifying areas needing further clarity, and suggesting directions for future research to refine diagnostic and therapeutic strategies. **Methods:** A narrative critical appraisal was undertaken, examining the review's discussion of morphology, immunohistochemistry, genetic profiling, proliferation indices, imaging modalities, and treatment implications, with reference to current literature and practice guidelines. **Key Appraisal Points: Strengths:** Comprehensive synthesis of morphologic patterns, genetic alterations (ATRX, DAXX, MEN1 in G3 NETs; TP53, RB1 in NECs), and proliferation indices. Useful incorporation of WHO classification updates and proposed diagnostic algorithms. Clear delineation of functional imaging differences (somatostatin receptor imaging for G3 NETs vs FDG PET for NECs). **Limitations:** Absence of a defined systematic review methodology (search strategy, selection criteria, quality assessment). Limited discussion on handling borderline Ki-67 indexes cases and mixed morphologic features in small biopsies. Small sample sizes in genomic profiling studies; organ-specific mutation patterns not explored. Undefined immunohistochemistry interpretation criteria for p53 and ATRX mutation status. **Clinical Relevance:** Highlights the importance of integrating histology, proliferation rate, immunohistochemistry, genetics, and imaging in diagnosis. Emphasizes differing prognoses and treatment responsiveness—PRRT, temozolomide, and somatostatin analogues for G3 NETs vs platinum-based chemotherapy and emerging immunotherapy for NECs. **Conclusions:** The review by Sun et al. makes a valuable contribution to refining diagnostic boundaries between G3 NETs and NECs. Greater methodological transparency, standardized biomarker interpretation, and larger multicentre genomic studies are needed to strengthen evidence and guide practice. Integrating proliferative indices with multimodal diagnostic algorithms holds promise for improving accuracy and patient outcomes.

Keywords: High-Grade Neuroendocrine Neoplasms, Well-Differentiated Grade 3 Neuroendocrine Tumor, Neuroendocrine Carcinoma, Histopathology, Immunohistochemistry, Genomic Profiling, Ki-67 Index, Diagnostic Algorithm.

1. Introduction

High-grade neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors comprising two biologically distinct entities—well-differentiated grade 3 neuroendocrine tumors (G3 NETs) and poorly differentiated neuroendocrine carcinomas (NECs). Accurate classification is critical, as prognosis and treatment differ markedly between these subtypes. However, the distinction is often challenging due to overlapping morphological features, variable Ki-67 proliferation indices, and limited

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biopsy material. The review by Sun et al. (2025) (1) synthesizes histopathologic, immunohistochemical (IHC), and genomic criteria aimed at refining diagnostic boundaries between G3 NETs and NECs. This commentary critically appraises their work in light of earlier publications, including those of Coriat et al. (2016) on gastroenteropancreatic (GEP) G3 NETs, the 2023 European Neuroendocrine Tumor Society (ENETS) guidance on digestive NECs (Sorbye et al.), and the narrative review by Pellat and Coriat (2020).(2-4)

2. Methods

The review by Sun et al. was evaluated for comprehensiveness, methodological transparency, and clinical relevance. The appraisal focused on the presence or absence of a defined literature search strategy, explicit inclusion criteria, and a quality assessment framework for the referenced studies. The synthesis of evidence across morphology, proliferation indices, IHC markers, genetic alterations, imaging modalities, and therapeutic approaches was examined.

Alignment with the World Health Organization (WHO) classification updates and major consensus statements, including ENETS recommendations, was assessed. Particular attention was given to whether the review addressed diagnostic uncertainty in borderline cases and outlined directions for future research. Comparative analysis was undertaken with key points from Coriat et al. (2016), Sorbye et al. (2023 ENETS guidance), and Pellat & Coriat (2020). (2-4)

3. Results

The review by Sun et al. presented a structured overview encompassing histopathology, proliferation indices, genomic profiles, imaging characteristics, prognosis, and therapeutic options. Morphology and histopathology showed that G3 NETs were reported as maintaining organoid architectural patterns with relatively uniform nuclei, whereas NECs typically exhibited sheet-like growth, marked nuclear pleomorphism, necrosis, and brisk mitotic activity. These differences may be obscured in small biopsy samples or when necrosis coexists with organoid nests. The Proliferative Index of Both tumor types met the grade 3 threshold (Ki-67 > 20%), but G3 NETs generally displayed rates in the 20–50% range, whereas NECs often exceeded 55%—a cutoff supported by the NORDIC NEC study and ENETS data. G3 NETs commonly harboured ATRX, DAXX, and MEN1 mutations, typically with low tumor mutational burden (TMB). NECs frequently demonstrated TP53 and RB1 alterations. G3 NETs were often positive on somatostatin receptor (SSTR) imaging, while NECs were more likely fluorodeoxyglucose positron emission tomography (FDG PET)–avid. Median survival was reported as 41–99 months for G3 NETs versus 11–17 months for NECs.
G3 NETs were considered for peptide receptor radionuclide therapy (PRRT), temozolomide-based regimens, and somatostatin analogues (SSAs). NECs were typically managed with platinum-based chemotherapy, with emerging data on immunotherapy.

Strengths of the Review
The integration of morphological, proliferative, molecular, and imaging data was comprehensive. Practical IHC surrogates, such as p53 and ATRX staining patterns, were highlighted for differentiating subtypes. The review aligned with WHO classification updates and proposed clinically relevant diagnostic algorithms.

Limitations of the Review
No reproducible search strategy, explicit inclusion criteria, or formal quality assessment of included studies was described. Guidance for ambiguous cases, such as those with overlapping Ki-67 indices or mixed morphology, was limited. Genomic studies cited were small, and organ-specific mutational differences were not examined in detail. Standardized interpretation criteria for p53 and ATRX IHC were not proposed. Therapeutic discussions for NECs were less comprehensive compared with G3 NETs.

4. Discussion

The review by Sun et al. makes a valuable contribution to the evolving classification of high-grade neuroendocrine neoplasms (NENs). Their integration of morphological, proliferative, molecular, and imaging data reflects the multimodal approach advocated in European Neuroendocrine Tumor Society (ENETS) guidelines. However, the absence of a reproducible methodological framework limits the overall strength of evidence.

In clinical practice, ambiguous cases—particularly those with overlapping Ki-67 proliferation indices and mixed morphology—pose significant diagnostic challenges. Incorporation of proliferative indices with morphology, immunohistochemistry (IHC), and clinical context into a structured algorithm has been suggested as a potential approach to improve diagnostic accuracy. Clear definitions for IHC “wild-type” and “mutant-type” patterns, especially for p53, remain urgently needed.

Future research should be directed towards the multicentre validation of biomarker thresholds to ensure reproducibility and generalizability of diagnostic criteria across diverse populations. The development of standardized IHC interpretation guidelines

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should be undertaken to reduce inter-observer variability and improve diagnostic consistency. Further exploration of organ-specific genetic alterations is warranted to enhance understanding of tumor biology and to identify potential therapeutic targets. Prospective evaluation of combined somatostatin receptor (SSTR) and fluorodeoxyglucose positron emission tomography (FDG PET) imaging should be performed to assess its added value in diagnostic accuracy and treatment planning. In addition, subtype-stratified clinical trials should be conducted to optimize therapeutic strategies for well-differentiated grade 3 neuroendocrine tumors (G3 NETs) and poorly differentiated neuroendocrine carcinomas (NECs), thereby enabling more personalized and effective patient management.

5. Conclusion

Sun et al. provide an adept and timely synthesis of the histopathologic and genetic distinctions between G3 NETs and NECs. While their proposed algorithm aligns with current consensus recommendations, further methodological rigor, standardized biomarker interpretation, and large-scale genomic studies are needed. Such refinements will enhance diagnostic precision, inform treatment selection, and ultimately improve patient outcomes.

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