

G3 Neuroendocrine Neoplasms (G3 NENs) with Deceptively Well-Differentiated Histologic Features Have a Poor Outcome

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Background: The 2010 WHO classification stratifies NENs into 3 tiers based on cellular proliferation. The G3 NENs (mitotic count >20/10 HPF and/or Ki-67 index >20%) are classified as neuroendocrine carcinomas (NECs). G3 NENs and poorly-differentiated NECs (PDNECs) are categorized the same. PDNECs exhibit small cell (SC) or large cell (LC) morphology with severe nuclear atypia, necrosis and high mitotic activity. G3 NENs may show features similar to well-differentiated NENs, except for high Ki-67 index. This study evaluates the clinicopathological features of G3 NENs with well-differentiated histology (G3-WD).

Methods: Gastroenteropancreatic G3-WD and PDNECs were retrieved from the anatomic data base from 2000 to 2011. Outcome data was obtained from the tumor registry.

Results: 9 cases of G3-WD (6 pancreatic, 3 gastrointestinal) were identified. The tumor cells were uniform and largely arranged in an organoid pattern. None could be classified as NEC of SC or LC type. 3 had oncocytoid appearance; 5 had focal higher grade cytologic features; 4 had prior diagnosis or current foci of low or intermediate grade NEN. 5 PDNECs (all gastrointestinal with SC morphology) were used as controls. Patient demographics, tumor characteristics and follow-up are as follows:

Categories	Mean age	M:F	Mean (range) of mitoses/10 HPF	Mean (range) of Ki-67 (%)	Distant metastases (%)	Mean follow-up (months)*	AWD/AWOD/DOD **
G3 NEN (n=9)	51	2:7	7 (1-20)	34 (24-46)	100	19	2/1/6
PDNECs (n=5)	65	3:2	> 50	85 (80-90)	100	11	1/0/4

* Mean follow-up in both groups from time of high grade tumor diagnosis

** AWD=alive with disease; AWOD=alive without disease; DOD= died of disease

Conclusion: G3-WD have a poor clinical outcome, although fare slightly better compared to PDNECs. G3-WD may represent transformation from prior low or intermediate grade NENs. When such transformation occurs, aggressive treatment may be warranted.