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Transformation of Low-Intermediate Grade Neuroendocrine Tumors into High Grade Morphology

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BACKGROUND

Low- (G1) and intermediate-grade (G2) neuroendocrine tumors (NET) are defined by lower mitotic rates and genetic mutations that rarely cause transformation to high-grade (G3) neoplasm. Yet a proportion of patients with de novo low-grade NETs progress to G3 disease or even neuroendocrine carcinoma (NEC). We aimed to highlight cases of low-grade G1 and G2 NETs that eventually transformed to G3 pathology on repeat biopsy and describe characteristics that portend high-grade transformation.

METHODS

We conducted a retrospective study of patients with de novo pathology-proven G1/G2 NETs who eventually transformed to G3 NET after treatment at the Mayo Clinic from 1999 to 2022. Patients were identified by search of pathology reports in the electronic medical record and confirmed to meet WHO criteria. In order to minimize the risk of biopsy sampling error and case misclassification, at least one-month time difference was required between collection of the two biopsy specimens. Data analysis was conducted with RStudio for tests of statistical significance including chi-square and Pearson correlation coefficient testing.

RESULTS

Twenty-five patients were identified with initial G1/G2 NET who subsequently progressed to either G3 NET or NEC. 17/25 (68%) were pancreatic primaries. Median age at diagnosis was 55 years (IQR 42-64) and 11 were male (44%). 16/19 (84%) of patients with G3 NET on follow up had a G2 NET on initial diagnosis and 3/6 of patients with poorly-differentiated NEC (60%) on follow up had a G2 NET on initial diagnosis. Median Ki-67 at initial diagnosis was 8.0 (IQR 4.3-14) and median Ki-67 after transformation was 28.5 (IQR 22-32.9). Median time from initial diagnosis to diagnosis of all high-grade pathology was 7.1 months (IQR 1.2-20.9). Median time from initial diagnosis to diagnosis of poorly differentiated NEC was 1.3 months (IQR 0.9-9.5) and median time from initial diagnosis to well-differentiated G3 NET was 8.1 months (IQR 1.6-23.7). Median length of follow up was 51 months (IQR 30.1-73.5). 11/25 (44%) patients had died by follow-up. 1-year disease specific survival was 83% (CI=0.69-1.0) from initial diagnosis and 5-year disease survival was 55% (CI=0.38-0.88).

CONCLUSIONS

Patients with G1/G2 NET on initial biopsy can have G3 NET and NEC on future biopsy signifying either high grade transformation or combined low- and high-grade heterogeneity. Patients who have low-grade to high-grade neuroendocrine transformation are more likely to have G2 pathology on initial diagnosis. When low-grade to high-grade transformation does occur, outcomes are poorer than for patients with low grade morphology.

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