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Grade progression in gastrointestinal neuroendocrine tumors

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BACKGROUND

Gastrointestinal neuroendocrine tumors (GI NETs) are subdivided into grades (G) G1-G3 based on Ki-67 proliferation index (%) (G1 <3%, G2 3-20%, and G3 >20%) or mitotic rate, with tumor grade informing prognosis and treatment. Grade progression (GP) over time in GI and pancreatic NETs has recently been identified, with low(G1/2)-to-high(G3) grade progression (L-to-H) the most clinically relevant form. L-to-H is associated with worse survival, yet the timeframe, incidence rate and risk factors remain largely unknown. This study aims to determine the incidence and potential predictors of L-to-H in tubal GI NETs.

METHODS

We conducted a retrospective review of the medical records of patients with stage I-IV GI or unknown primary NETs diagnosed between 2009-2023 identified from an IRB-approved NET database. Patients with low-grade (G1/2) NET at diagnosis and at least two metachronous (at least 3 months apart) tumor biopsies with Ki67 staining were included. Demographic and clinicopathologic characteristics were compared between groups using Chi-squared test and Mann-Whitney test for categorical and continuous variables, respectively.

RESULTS

Out of 354 total patients, 99 had metachronous tumor biopsies with Ki-67 staining; 82 had low-grade (G1/2) NET at diagnosis and were included in the analysis (median follow-up 5.9 yrs, median age 58 yrs, 51% female, 73% White, 17% Hispanic, 61% stage IV, 33% with functional tumor). Overall, 77 (94%) patients exhibited low-to-low (L-to-L), meaning low grade at diagnosis and on serial biopsy; 5 (6%) exhibited L-to-H. There were no differences in age, sex, race, ethnicity, follow-up time, primary tumor site, tumor functional status, or initial stage/Ki-67/grade between L-to-L and L-to-H groups.

Characteristic	Total (N=82)	L-to-L (N=77)	L-to-H (N=5)	p-value
Primary tumor site N(%): Stomach Small bowel Colon/Rectum Other Unknown	10(12) 55(67) 5(6) 2(2) 10(12)	10(13) 52(68) 4(5) 2(3) 9(12)	0(0) 3(60) 1(20) 0(0) 1(20)	0.441
Grade at diagnosis N(%): G1	52(63)	49(64)	3(60)	0.870
G2	30(37)	28(36)	2(40)	
Ki-67 at diagnosis, median(range)	2(0.1,18)	2(0.1,18)	1(1,3.2)	0.189
Subsequent Ki-67, median(range)	2.9 (0.3, 44.5)	2.4(0.3,20)	38(29.7,44.5)	<0.001

CONCLUSIONS

This single-center retrospective cohort study reveals a 6% incidence of L-to-H over time in GI NETs. Ongoing work will integrate factors such as time to 2nd biopsy, prior therapy, reasons for 2nd biopsy, and site of biopsy (primary vs. metastasis). Results of this study provide insight into the natural history of GI NETs and risk factors associated with L-to-H. Additional work is needed to understand the molecular mechanisms underlying L-to-H progression in this disease.

ABSTRACT ID 23472