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Is There a Role for Surgical Resection of Grade 3 Neuroendocrine Neoplasms?

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BACKGROUND

Grade 3 (G3) gastroenteropancreatic (GEP) neuroendocrine neoplasms (NENs) are aggressive tumors with poor survival outcomes for which medical management is usually recommended. This study sought to evaluate outcomes of surgically treated G3 GEP-NEN patients.

METHODS

A single-institutional prospective NEN database was reviewed. Patients with G3 GEP-NENs based on World Health Organization (WHO) 2019 definitions included well-differentiated neuroendocrine tumors (G3NET) and poorly-differentiated neuroendocrine carcinomas (G3NEC). Clinicopathologic factors were compared between groups. Overall survival from G3 diagnosis was assessed by the Kaplan-Meier method.

RESULTS

Surgical resection was performed for 463 patients (211 G1, 208 G2, 44 G3), including 276 from small bowel, 157 from pancreas, and 30 from stomach/duodenum/right colon. Most had metastatic disease at presentation (54% G1, 69% G2, 91% G3; p<0.001). The G3 cohort included 39 G3NETs and 5 G3NECs, 22 of pancreatic and 22 of midgut origin. Median overall survival (mOS; in months) was 268.1 for G1NETs, 129.9 for G2NETs, 50.5 for G3NETs, and 28.5 for G3NECs (p<0.001). Over the same period, 31 G3 patients (12 G3NETs, 19 G3NECs) were treated non-surgically, with mOS of 19.0 for G3NETs and 12.4 for G3NECs. On multivariable cox-analysis grade and TNM-stage correlated with survival, with better survival in resected than non-resected G3NETs (Table).

Table: Overall Survival in 463 Surgically Resected GEP-NEN Patients and 31 Non-resected G3 Patients

WHO Classification (n)	Median OS (months)	HR (95% CI)	p-value*
G1NET (n = 211)	268.1	Reference	-
G2NET (n = 208)	129.9	1.89 (1.27 to 2.81)	0.002
G3NET (n = 39)	50.5	4.70 (2.42 to 9.11)	<0.001
G3NEC (n = 5)	28.5	7.99 (2.42 to 26.4)	<0.001
G3NET- No resection (n = 12)	19.0	15.2 (6.93 to 33.5)	<0.001
G3NEC- No resection (n = 19)	12.4	21.8 (12.0 to 39.4)	<0.001

WHO = World Health Organization; OS = Overall Survival; HR = Hazard Ratio; CI = Confidence Interval;
* Using multivariable cox proportional hazards model adjusting for grade and T, N, M-stage

CONCLUSIONS

Surgical resection of G3 GEP-NENs remains controversial due to poor prognosis, and surgical series are rare. This large, single-institutional study found significantly lower mOS in patients with resected G3NENs than those with G1/G2 tumors, reflecting more aggressive tumor biology and a higher proportion with metastatic disease. The mOS for resected G3NETs and G3NECs exceeded historical non-surgical G3NEN series (mOS 11-19 months), suggesting surgery should be considered in carefully selected patients with G3NENs, especially those with well-differentiated G3NETs.

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