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Multicenter Real-World Study of Treatment Patterns in Well-Differentiated Grade 3 (G3) Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

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BACKGROUND

The 2017 WHO classification established well-differentiated G3 NETs as a distinct pathologic entity. However, their rarity and heterogeneity have hindered the definition of standard treatment strategies. Hereby, we present a multicenter real-world experience from the Mayo Clinic to inform clinical practice.

METHODS

Clinical data were collected across the three Mayo Clinic sites (Minnesota, Arizona, and Florida) including patients (pts) with histologically confirmed GEP-NETs G3 between 2017and 2025. Primary endpoints included ORR, DCR, PFS, and OS. Prognostic factors were analyzed with a multivariate Cox regression.

RESULTS

76 pts, median age 62 years (range, 23–83), with either ab inizio (88%) or transformed (12%) G3 GEP-NETs.The most common primary sites were pancreas (60%), small bowel (17%) and rectum (5%). The median Ki-67 was 35% (range, 20–90). Most cases were non-functional (70%). Among functional tumors, carcinoid syndrome and hypoglycemia were the most common presentations (each 11.8%). Overall, median plasma 5-HIAA level was 35.5 ng/mL (range, 5–1394). 85% had de novo metastatic disease and 18% recurrent disease. Metastatic sites included liver (91%), lymph nodes (32%), bone (22%), lung and peritoneum (each 8%). The median number of metastatic sites was 1 (range, 0–5). The median number of systemic lines was 2 (range, 0–8). Across all lines, the most frequent treatments were CAPTEM (23%), PRRT with lutetium-177 DOTATATE (14%), lanreotide (11%), octreotide (8%), carboplatin-etoposide (7%), sunitinib (5%), and everolimus (5%). Efficacy outcomes were reported in Table 1 for the three most common regimens based on radiology reports. At a median follow-up of 26.4 months, mOS of the overall population was 56.2 months (95% CI, 42.9–69.5). Insulin-producing tumors (HR 6.07, 95% CI 1.33–27.5; p=0.02) and ≥2 metastatic sites (HR 3.53, 95% CI 1.55–8.05; p=0.003) were independently associated with poor survival.

CONCLUSIONS

Overall survival for malignant insulinoma can be several years with appropriate therapy. Systemic treatment with PRRT, CAPTEM, or mTOR inhibitor is very effective for hypoglycemic control.

Table 1: Efficacy of the three most common regimens.

	CAPTEM	**PRRT Lu-177**	**Lanreotide**
Line of therapy, n (%)			
First	24 (61.5)	3 (12.5)	11 (57.9)
Second	7 (17.9)	9 (37.5)	8 (42.1)
Third or further	24 (61.5)	12 (50.1)	0 (0)
DCR	62.9	94.7	50
ORR	37.1	57.9	11.1
mPFS, months (95% CI)	6.7 (1.8-11.5)	11.2 (0-27.0)	3.4 (2.0-4.2)
mOS, months (95% CI)	50.6 (15.5-85.7)	76.1 (8.2-143.9)	NR

Pooled efficacy outcomes across treatment lines.

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