Well-Differentiated Grade 3 Neuroendocrine Tumors

Characteristics, Treatments, and Outcomes From a Population-Based Study

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Objectives: We evaluated a population-based cohort of metastatic well-differentiated grade 3 gastroenteropancreatic neuroendocrine tumors (G3 NETs) to describe their characteristics, prognosis, and treatment outcomes.
Methods: The British Columbia provincial database was queried for G3 NETs diagnosed 2004 to 2021, and charts were reviewed to describe clinical features and outcomes.
Results: Forty-one patients were identified, most were diagnosed with pancreatic (58.5%) or midgut (26.8%) primary tumor and Ki-67 was less than 55% in 68.3%. The primary was resected in 19 (46.3%) with median disease-free survival of 25.2 months. Once metastatic, patients received a median of one line of systemic therapy. Median overall survival with metastatic disease was 33.8 months. Median progression-free survival was longest in patients treated with capecitabine-temozolomide (20.6 months) or somatostatin analogs (7.9 months), while etoposide-platinum provided little benefit (2.4 months). Limited data of efficacy for targeted therapies and radionuclide therapy was available. Seven patients (17.1%) were also treated with local therapies, which were associated with improved overall survival (median not reached, hazard ratio, 0.23; *P* = 0.012).
Conclusions: Capecitabine-temozolomide and somatostatin analogs were associated with clinically meaningful benefit, and use of local therapies provided benefits in selected patients. Multidisciplinary discussion is essential to optimize individual outcomes in this heterogeneous population.

Key Words: well-differentiated, grade 3 neuroendocrine tumors, treatments, outcomes

Neuroendocrine neoplasms (NENs) of the digestive tract are a heterogeneous group of tumors with variable clinical behavior. Before 2017, the World Health Organization (WHO) classification regrouped all NENs with a Ki-67 above 20% or above 20 mitoses per high-power field into one category defined as high-grade (or grade 3) neuroendocrine carcinomas (NECs). The NORDIC NEC study[1] was the first study to show important differences in terms of prognosis and response rate to platinum-based chemotherapy among high-grade NENs. Tumors with a Ki-67 below 55% were found to have lower response rate but better prognosis compared with tumors with a Ki-67 above 55%. Subsequent reports confirmed the existence of 2 distinct subtypes among this category and identified tumor morphology (differentiation) as a predictive biomarker.[2] It is now recognized that grade and differentiation define biologically distinct entities and serve as the basis for the latest 2019 WHO classification, which now separates grade 3 tumors into well-differentiated tumors (G3 NETs) and poorly differentiated carcinomas (NECs).

The treatment of this new clinical entity defined as G3 NETs presents a challenge for clinicians. A few reports have recently been published describing their clinical characteristics, but data remain limited. G3 NETs are thought to be intermediate between G2 NETs and NECs in terms of clinical characteristics and prognosis. They originate more commonly from the pancreas (33–65%),[3–8] are usually metastatic at diagnosis (62–80%)[4,6,9–11] with liver metastases being the most common site of metastases (74–95%),[7,9,12] and are more likely to be clinically nonfunctional (75–95%)[5,6,9,10] despite being octreotide-avid on functional imaging (87–92%).[4–7,9,13] Grade 3 NETs are also frequently fluorodeoxyglucose-avid (75%) and a positive fluorodeoxyglucose-positron emission tomography does not appear to distinguish G3 NETs from NECs.[4,6,7] Ki-67 is usually lower in G3 NETs (20–50%) than NECs (60–100%)[4–7,9,10,12] and overall survival has been reported between 19 and 99 months[4,6,7,9,10] compared with 11 to 17 months for NECs.[4–6,9,10,14,15]

There are no established treatment guidelines for G3 NETs. They were excluded from landmark clinical trials establishing the role of various systemic therapies in the management of advanced well-differentiated NETs. The NORDIC study reported a low response rate to platinum-based chemotherapy for high-grade NENs with a Ki-67 < 55%, and this was subsequently confirmed in multiple small cohort studies.[1,5–7,12,13] On the other hand, alkylator-based chemotherapy is an established treatment option even for low-grade pancreatic NETs, which are regarded as chemosensitive tumors, unlike midgut NETs.[16,17] The role of surgical management and other local therapies for G3 NETs is also controversial, as it is often indicated in G1–2 NETs but contraindicated for NECs.[4,6,10,18]

Clinical decision making for this rare disease is complex and based on limited data. We aimed to contribute to the existing body of evidence by describing clinical characteristics and treatment outcomes in a population-based cohort from British Columbia, Canada.

MATERIALS AND METHODS

The BC Cancer provincial database was queried for all G3 NENs (Ki-67 > 20%) diagnosed from 2004 to 2021. Identified cases underwent expert pathology review to assess tumor differentiation and confirm Ki-67 above 20%. Confirmed cases with metastatic gastroenteropancreatic G3 NETs according to the WHO 2019 classification were included in the final analysis. Electronic

medical records were reviewed and patient demographics, tumor characteristics, treatments received and outcomes were extracted. Outcomes included disease-free survival (DFS) (time from primary tumor resection to disease recurrence), progression free survival (PFS) (time from date of treatment initiation to progression or death) and overall survival (OS) (time from date of pathologically confirmed diagnosis of metastatic disease to date of death). The date of progression was assessed using radiological reports documenting progression and/or clinical notes indicating a change of treatment due to progressive disease, whichever occurred first. Imaging was not reviewed and response rates were not assessed. Patients were censored if there was no progression, if they were rendered no evaluable disease with local therapy, or if they were lost to follow-up. The study was approved by the Institutional Review Board, informed consent requirements were waived because of the retrospective nature of the study. All data were deidentified and encrypted.

Basic patient demographic data were summarized as frequencies (%) for categorical variables and as medians with range for continuous variables. Median DFS, PFS, and OS were calculated according to the Kaplan-Meier method. Treatment groups were compared using a log-rank test and univariate Cox proportional hazard model to generate hazard ratios (HRs) with corresponding 95% confidence intervals (CIs), with *P* value less than 0.05 considered significant. The number of events did not allow for multivariate analysis.

Statistical analysis was performed using IBM SPSS version 28 (IBMI, Armonk, NY).

RESULTS

We identified 756 patients diagnosed with a GI NET between 2004 and 2021 and available for clinical and pathologic review. Of these, 139 (18.0%) corresponded to the former "high-grade NEN" category according to the 2010 WHO classification. Ninety-eight (13.0%) were reclassified as NECs according to the WHO 2019 classification and 41 (5.0%) were reclassified as G3 NETs and included in the final analysis (Fig. 1).

Baseline characteristics are presented in Table 1. Median age was 60 years (interquartile range, 52–71 years) and Ki-67 was below 55% in 68.3% of patients. Pancreatic tumors were the most frequent (58.5%), followed by midgut (26.8%), unknown (9.8%) and rectal primary (4.9%). Tumor was octreotide-avid on functional imaging in 24 patients (58.5%) and 10 (24.4%) had elevated urinary 5-hydroxyindoleacetic acid. Nearly half of patients (46.3%) presented initially with localized disease and had resection of their primary tumor with a median DFS of 25.2 months.

Treatments received are detailed in Table 2. Patients received a median of one line of therapy and received a variety of treatments: somatostatin analogs (SSAs) or capecitabine-temozolomide (CAPTEM) in 16 patients each (39.0%), followed by platinum- etoposide (EP) in
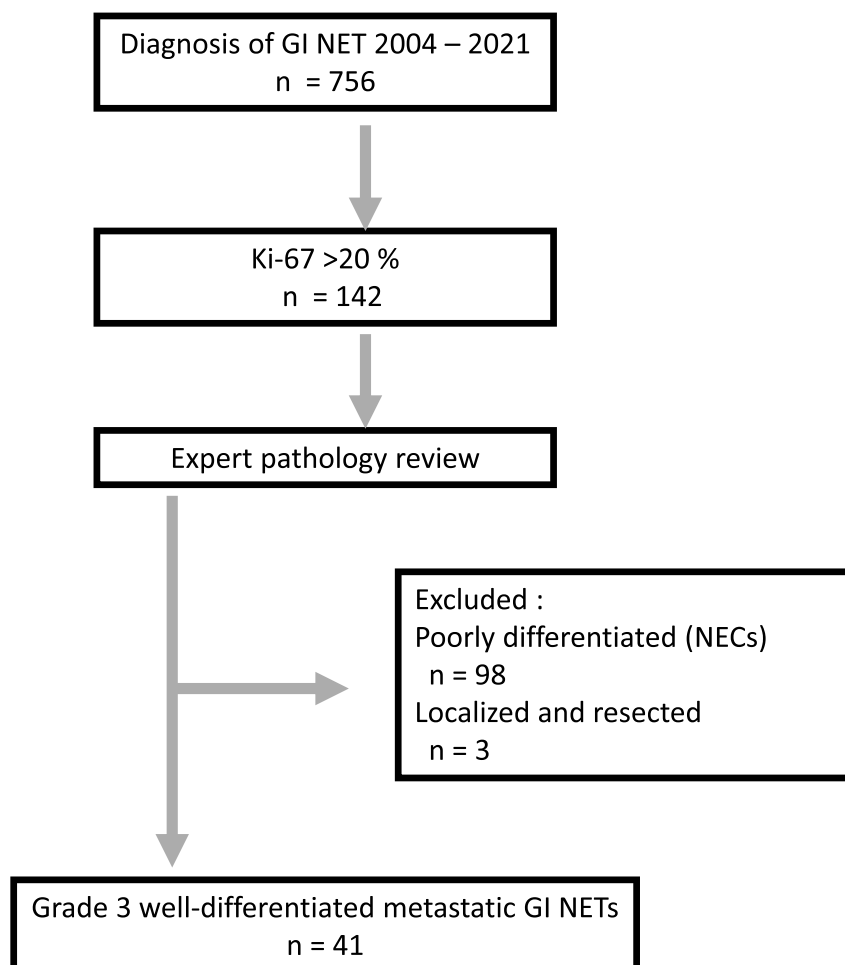

FIGURE 1. Study overview.

TABLE 1. Baseline Characteristics

	n = 41
Sex, n (%)	
Female	25 (61.0)
Male	16 (39.0)
Age at diagnosis, median (range), y	60 (15–80)
Date of diagnosis, n (%)	
2004–2010	20 (48.8)
2011–2021	21 (51.2)
Primary tumor location, n (%)	
Midgut	11 (26.8)
Pancreas	24 (58.5)
Colorectal	2 (4.9)
Unknown	4 (9.8)
Ki-67, n (%)	
20–55%	28 (68.3)
>55%	7 (17.1)
Octreotide-avid, n (%)	
Yes	24 (58.5)
No	6 (14.6)
Unknown	11 (26.8)
Functional tumor (clinically), n (%)	
Yes	15 (36.6)
No	26 (63.4)
Elevated urinary 5-HIAA, n (%)	
Yes	10 (24.4)
No	16 (39.0)
Unknown	15 (36.6)

5-HIAA indicates 5-hydroxyindoleoacetic acid.

13 (31.7%), streptozocin-doxorubicin or everolimus in 5 patients each (12.2%), and peptide receptor radionuclide therapy (PRRT) in 2 (4.8%). Resection of the primary tumor was required for obstruction in 5 of 9 patients with metastatic midgut NET and primary in situ. Local therapies aimed at tumor debulking were used for 7 patients (17.1%) after a median of 19.2 months from diagnosis of metastatic disease. Local therapies consisted of 10 surgeries, 1 liver transplant, 1 radiofrequency ablation and 2 Ytrium-90 radioembolizations. The use of local therapies aimed at tumor debulking in the metastatic setting was associated with improved OS (median, not reached; HR, 0.23; P = 0.012) on univariate analysis.

Median follow-up was 66.7 months from diagnosis of metastatic disease and median OS was 33.8 months (Fig. 2). Among all therapies, use of CAPTEM was associated with the longest PFS (20.6 months) and OS (73.8 months) and was well-tolerated, with only 1 of 16 patients discontinuing therapy for toxicity after 30 months of treatment (fatigue and cytopenias). The majority of patients (12/16) treated with CAPTEM had pancreatic primary tumor. Median follow-up for patients treated with CAPTEM was shorter than for the whole cohort (12.6 months for PFS analysis and 41.5 months for OS analysis) and a high proportion of patients were censored at data cutoff (68.8% for OS analysis and 37.5% for PFS analysis).

Median PFS with platinum-based chemotherapy was 2.4 months, and 3 of 10 patients treated with first-line EP died within 3 months. Among 4 patients with Ki-67 above 55%, EP achieved a PFS varying from 0.13 to 4.1 months. One patient with Ki-67 > 55% was treated

with adjuvant EP with a DFS of 11.7 months. Forty percent of patients treated with EP had a Ki-67 > 55%, compared with 20% of patients treated with CAPTEM (P = 0.43).

Somatostatin analogs also yielded a clinically significant PFS of 7.9 months in the first-line setting for patients with Ki-67 < 55%, SSAs were not used for patients with Ki-67 > 55%. A variety of other systemic therapies were also used in multiple lines of treatment, but the numbers are too low to draw firm conclusions. Figure 3 summarizes the course of each patient with all treatments received and Figure 4 provides details about first-line PFS.

Univariate Cox analysis was performed to assess for potential differences in outcomes according to clinical characteristics (Table 3). We could not perform reliable multivariate analysis because of the low number of events. There was no impact of primary site, Ki-67 (only 7 patients had a Ki-67 > 55%) or year of diagnosis on outcome, although there was a trend toward improved outcomes in patients diagnosed after 2010. Interestingly, the only significant finding was a worse first-line PFS in patients younger than 50 years, that did not translate into a difference in OS. There were only 7 patients younger than 50 years, 5 of them had pancreatic primary and 3 of them had Ki-67 above 55%. They were treated with first-line EP (4), streptozocin-doxorubicin (2) or everolimus (1).

DISCUSSION

In this retrospective cohort of metastatic G3 NETs, we found that CAPTEM and the use of local therapies were associated with improved outcomes, unlike platinum-based chemotherapy.

TABLE 2. Treatments Received

	n (%)	1st Line, n	2nd Line, n	+3rd Line, n
Resection of primary tumor				
Yes	19 (46.3)			
No	22 (53.7)			
Median DFS after resection, mo	25.2			
Local therapies				
Surgery for bowel obstruction	5 (12.2)			
Palliative surgical debulking	4 (9.8)			
Surgical debulking + Y90/RFA	3 (7.3)			
None	31 (75.6)			
Systemic treatments				
Somatostatin analogs	16 (39.0)	14	2	0
IV chemotherapy	22 (53.7)	13	7	2
CAPTEM	16 (39.0)	7	4	5
Targeted therapies	7 (17.1)	3	3	2
PRRT or I131 mIBG	3 (7.3)	0	1	2
Lines of treatment				
0	4 (9.8)			
1	20 (48.8)			
2	10 (24.4)			
3	5 (12.2)			
More than 3	2 (4.9)			

IV chemotherapy: etoposide–platinum (n = 13), streptozocin–doxorubicin (n = 5), irinotecan (n = 3), gemcitabine (n = 1).

Targeted therapies: everolimus (n = 5), sunitinib (n = 1), lenvatinib (n = 1).

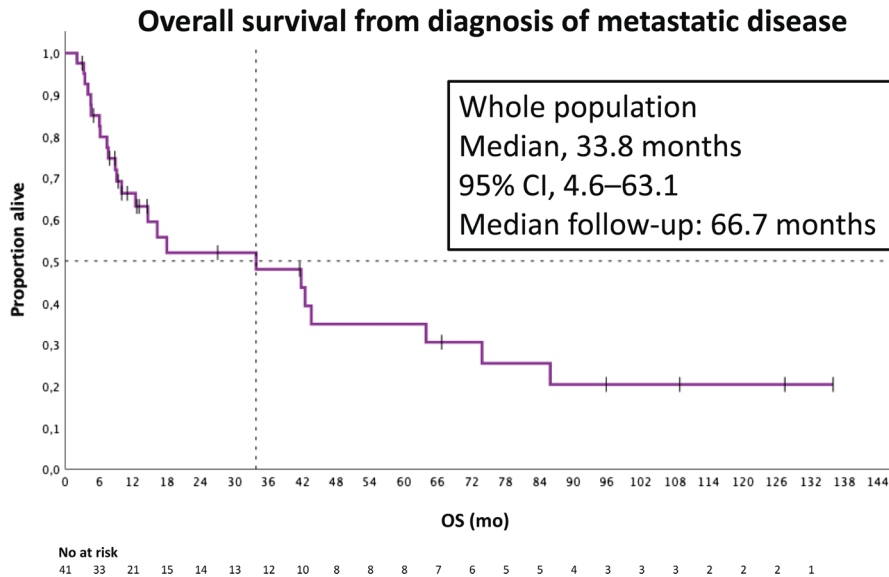I131 mIBG indicates iodine-131 metaiodobenzylguanidine.

Overall survival from diagnosis of metastatic disease

FIGURE 2. Overall survival from time of metastatic diagnosis.

Clinical characteristics and overall survival in this cohort are similar to previously published reports,[3,5–8,19] with a Ki-67 below 55% in a majority of cases, 58.5% of pancreatic primaries and median survival of 33.8 months.

Capecitabine-temozolomide was associated with a first line PFS of 20.6 months translating into a median survival of 73.8 months. Other retrospective studies focusing on G3 NETs reported improved outcomes with CAPTEM, but PFS is usually shorter than in our cohort. For example, Liu et al[7] analyzed treatment outcomes in a cohort of 30 patients and reported a median PFS of 10.3 months in the first-line setting compared with 4.4 months in second line. Similarly, Apostolidis et al[19] reported a first-line PFS of

12.0 months and second-line PFS of 7.7 months among 42 patients, and Rogowski et al[20] reported a PFS of 15.3 months in 20 patients. Our results may be overestimated because of the shorter follow-up and high proportion of patients censored at data cutoff, but CAPTEM remains nevertheless the only systemic therapy showing a statistically significant improvement in both PFS and OS in univariate analysis. In our cohort, 12 of 16 patients treated with CAPTEM had pancreatic tumors. This regimen is used traditionally to treat advanced G1–2 pancreatic NETs, based on the study by Strosberg et al[16] reporting high and durable response in these patients with a median PFS of 18 months and the prospective study by Kunz et al[21] with a PFS of 22.7 months. Midgut NETs
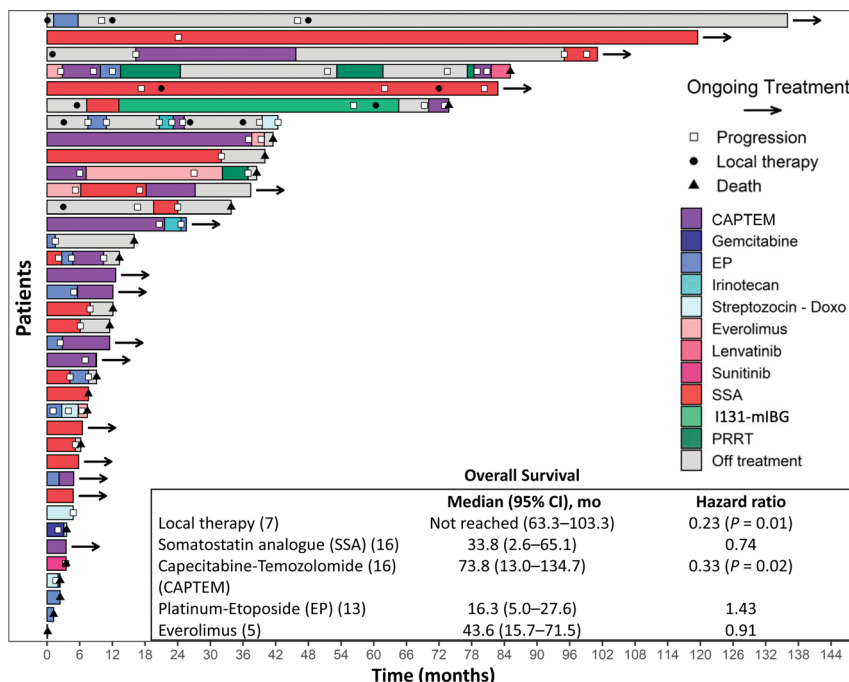

FIGURE 3. Treatments received and overall survival according to treatments.
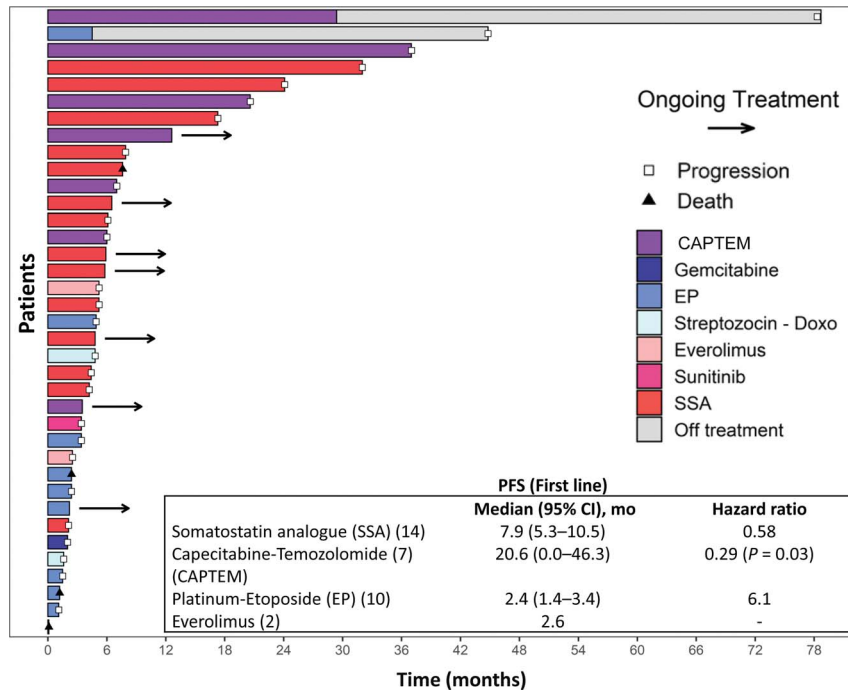
FIGURE 4. First-line progression-free survival according to treatments.

are usually not regarded as chemosensitive tumors, and it remains unknown if CAPTEM would provide similar results in G3 midgut NETs. In the study by Apostolidis et al,[19] PFS was 1.6 months in 6 patients with non-pancreatic tumor compared with 17.0 months in 16 patients with pancreatic tumor.

Platinum-based chemotherapy yielded poor outcomes in our cohort and was associated with significant toxicity. This was first demonstrated in the NORDIC-NEC study[1] and confirmed in multiple small reports since then, and was one of the arguments to review the classification of NENs in 2017. Platinum-based chemotherapy is now considered an inferior regimen and is currently not recommended in the first-line setting by the European Society of Medical Oncology and European Neuroendocrine Tumors Society guidelines,[22,23] and other therapeutic options should be favored in later lines when available. The poor outcomes associated with EP might explain why patients younger than 50 years had a worse first-line PFS in our cohort, given that most of them received EP as first-line treatment.

The use of SSAs yielded a clinically significant median PFS of 7.9 months in our study that did not reach statistical significance. There is a rationale to use SSAs in G3 NETs. As reported in ours and other's cohorts, G3 NETs frequently express somatostatin receptors on functional imaging. This has been shown to correlate with molecular expression of somatostatin receptors (SSTRs),[2,24] and expression of SSTR-2 has been associated with longer PFS and OS in patients treated with SSAs.[25] Data regarding the use of SSAs in G3 NETs is scarce and SSAs were historically not recommended for high-grade NENs. McGarrah et al[26] reported a median PFS of 4.4 months and a disease control rate of 50% in 14 patients with G3 NETs receiving single-agent SSAs in any line of therapy. They concluded SSAs may present an attractive option given their favorable side-effect profile, a conclusion that is supported by our results.

The use of local therapies aimed at tumor debulking and symptom control was traditionally contra-indicated for high-grade tumors because of the poor prognosis associated with NECs. In our cohort of G3 NETs, the use of local therapies was associated with significantly improved overall survival in selected patients. Although such an analysis is flawed by obvious selection bias, the use of local therapies can be considered for carefully selected patients with G3 NETs after multidisciplinary discussion, as suggested by European Society of Medical Oncology guidelines.[22]

Patients in our cohort also received a variety of other treatments, including everolimus, sunitinib, PRRT and streptozocin-doxorubicin. It was not possible to draw conclusions regarding the use of these treatments given the low number of patients receiving each treatment. No patient was treated with oxaliplatin-based chemotherapy, which recently yielded the highest response rate (56.4%) in one report[19] and the longest PFS in another report (13.0 months),[7] compared retrospectively with other therapies including CAPTEM, EP, PRRT, everolimus, and streptozocin-doxorubicin.

Our study has several limitations that need to be considered when interpreting the results. It is a retrospective study and patient numbers in treatment groups were low, especially in the second-line setting and beyond. For this reason, we were not able to draw conclusions regarding treatment sequencing, and multivariate analysis could not be performed because of the low number of events. Differences in patients' characteristics could potentially account for the observed outcomes among treatment groups, but we did not find any impact in univariate analysis. All cases underwent expert pathology review, and we are confident our cohort represents "true" G3 NETs, even though molecular data was not available. Imaging was not reviewed, hence we do not provide response rates and PFS was defined according to archival radiological reports and clinical notes. Despite this, PFS correlates with OS in our analysis and our results are similar to recently reported data. As mentioned earlier, a significant proportion of patients were censored at data cutoff. Absolute PFS and OS may be overestimated at the present time, but this should not affect the observed trends, and we plan to update the results at a later timepoint.

TABLE 3. Univariate Cox Analysis

	Months (95% CI)	HR (95% CI)	*P*
OS			
Year of diagnosis (n)			
2004–2010 (20)	14.6 (6.1–23.2)		
2011–2021 (21)	43.6 (39.5–47.7)	0.55 (0.24–1.29)	0.17
Age, y (n)			
<50 (8)	85.9 (17.6–154.3)	0.55 (0.19–1.63)	0.28
50–70 (19)	33.8 (2.8–64.8)	1.37 (0.61–3.11)	0.45
>70 (13)	14.6 (8.0–21.3)	1.12 (0.44–2.88)	0.82
Ki-67 (n)			
21–55% (28)	41.8 (0–84.3)	1.1 (0.36–1.37)	0.87
>55% (6)	85.9 (0–207.9)		
Primary site (n)			
Midgut (11)	41.8 (0–84.3)	0.66 (0.27–1.72)	0.37
Pancreas (24)	16.3 (10.7–21.9)	1.20 (0.52–2.78)	0.67
Colorectal (2)	6.1 (0–12.4)	2.44 (0.55–10.8)	0.24
PFS			
Year of diagnosis (n)			
2004–2010 (18)	4.8 (3.2–6.3)		
2011–2021 (19)	7.4 (3.2–11.5)	0.61 (0.29–1.28)	0.19
Age, (n)			
<50 (7)	2.6 (2.3–2.9)	4.0 (1.4–11.4)	0.01
50–70 (17)	5.2 (2.8–7.7)	1.1 (0.52–2.4)	0.79
>70 (13)	7.6 (5.5–9.7)	0.5 (0.18–1.12)	0.09
Ki-67 (n)			
21–55% (28)	7.4 (4.0–10.8)	0.33 (0.97–9.06)	0.06
>55% (6)	2.5 (2.2–2.7)		
Primary site (n)			
Midgut (10)	17.3 (2.7–31.9)	0.6 (0.26–1.39)	0.23
Pancreas (22)	4.8 (1.3–8.2)	1.5 (0.66–3.33)	0.34
Colorectal (1)	0.13		

In summary, CAPTEM, SSAs, and local therapies were all associated with clinically meaningful benefit. Outcomes with EP were disappointing, while limited data of efficacy for targeted therapies and PRRT was available. More data are needed to guide clinicians in the management of this newly defined and rare tumor, including predictive biomarkers of response and appropriate combination and sequencing of therapies. Multidisciplinary discussion remains essential to optimize individual outcomes in this heterogeneous population.

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