Original Article

Tumor mutation burden in gastro-entero-pancreatic-neuroendocrine neoplasms

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Background: As rare tumors, there are limited treatment options for neuroendocrine neoplasms (NENs). Recently, microsatellite instability (MSI) and tumor mutation burden (TMB) have been emerging as potential biomarkers in various tumors. However, there is a lack of research on the use of these biomarkers in gastro-entero-pancreatic (GEP)-NENs.

Methods: We analyzed 31 patients diagnosed with GEP-NEN between 2013 to 2022. The TMB and MSI analyses using next-generation sequencing (NGS) were performed for all patients. The TruSightTM Oncology 500 assay from Illumina was used as the NGS panel.

Results: Out of the 31 patients analyzed, the most frequent primary origin was the pancreas (12 patients, 38.7%), followed by the stomach (4 patients, 12.9%), gallbladder (4 patients, 12.9%), rectum (7 patients, 22.6%), small bowel (2 patients, 6.5%), and bile duct (1 patient, 3.2%). Among these patients, 19 (61.3%) were diagnosed with well-differentiated neuroendocrine tumors, with grade 2 being the most common (15 patients, 48.4%), followed by grade 3 (3 patients, 9.7%) and grade 1 (1 patient, 3.2%). Neuroendocrine carcinoma was confirmed in 12 patients (38.7%). The median number of metastases was 2.0 [interquartile range (IQR), 1.0–3.0], and the liver was the most common site of metastasis (23 patients, 74.2%). The median TMB was 4.7 (IQR, 3.1–6.3) mutations/Mb, and all tumors were classified as microsatellite stability (MSS). Only one patient had a high TMB (266.4 mutations/Mb), which was a grade 3 neuroendocrine tumor originating from the pancreas. The TMB value did not vary depending on the primary tumor site or World Health Organization (WHO) grade.

Conclusions: This analysis showed that, despite very low incidence, there are GEP-NENs with high TMB. For precision medicine, testing for MSI and TMB is needed for this tumor type.

Keywords: Tumor mutation burden (TMB); neuroendocrine tumor (NET); neuroendocrine carcinoma (NEC); gastro-entero-pancreatic neuroendocrine neoplasm (GEP-NEN)

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Introduction

Neuroendocrine neoplasm (NEN) is a rare malignancy, with a 0.02% incidence (1). NENs can arise in almost every organ of the body. Although they share similar morphologic and immunophenotypic features, the primary anatomic site is an important classification criterion (2). The gastrointestinal tract (62–67%) and lung (22–27%) are the most common sites (1). Gastro-entero-pancreatic NENs (GEP-NENs) are classified according to the grading system based on proliferation assessed by mitotic rates and Ki-67 labeling; well-differentiated neuroendocrine tumor (NET) grades 1, 2, and 3 and poorly differentiated neuroendocrine carcinoma (NEC) (3). The prognosis of GEP-NENs is very poor, with a 5-year overall survival of 13%. More than 60% of patients with newly diagnosed GEP-NENs experience distant metastasis (4); however, the efficacy of systemic chemotherapy for GEP-NENs is limited (5).

The introduction of immune checkpoint inhibitors (ICIs) has changed the treatment strategies for various tumors. ICIs also showed promising results in some tumors with NEN features, such as small-cell lung cancer (6) and Merkel cell carcinoma (7). However, in GEP-NENs, the results were less promising. Because various biomarkers have been used to select patients who can benefit from ICIs, microsatellite instability (MSI) and tumor mutation burden (TMB) are novel biomarkers in various tumor types (8-10). However, these novel biomarkers have not been well studied in GEP-NENs.

Herein, we evaluated MSI status and TMB in patients with GEP-NENs. We present this article in accordance with the MDAR reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1190/rc).

Highlight box

Key findings

- This analysis showed that, despite very low incidence, there are GEP-NENs with high TMB. For precision medicine, testing for MSI and TMB is needed for this tumor type.

What is known and what is new?

- GEP-NENs are tumors with low TMB and MSS, which indicates the limited efficacy of ICIs in GEP-NENs, as found in previous clinical trials
- However, although very few, there are GEP-NENs with high TMB.

What is the implication, and what should change now?

- A test for MSI status and TMB is needed in this type of tumor for precision medicine.

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board (IRB) of Samsung Medical Center approved this study (No. 2022-10-077-001). This study is a retrospective analysis. Therefore, the requirement for informed consent to this study was waived.

Patients selection

We selected patients diagnosed with GEP-NEN between 2013 and 2022 based on MSI status and TMB status, which were assessed using next-generation sequencing (NGS). The following patient clinicopathologic characteristics were analyzed: age, gender, pathologic diagnosis, site of metastasis, number of metastases, TMB, and MSI status. Pathologic diagnosis was re-reviewed by the pathologist according to the 2017 World Health Organization (WHO) classification of NENs (11).

Next-generation sequencing

Tumor samples were obtained at the time of initial diagnosis or progression, and. formalin-fixed paraffin-embedded (FFPE) material was used. The Qubit dsDNA HS Assay (Thermo Fisher Scientific, Waltham, MA, USA) on the Qubit 2.0 Fluorometer (Thermo Fisher Scientific) was used to quantify the 40 ng of DNA. The Covaris E220 Focused-ultrasonicator (Woburn, MA, USA) and the 8 microTUBE-50 Strip AFA Fiber V2 were used for shearing. The treatment time was optimized for FFPE material, and the treatment settings were as follows: peak incident power, 75 W; duty factor, 15%; cycles per burst, 500; treatment time, 360 s; temperature, 7 ℃; water level, 6. We used the TruSight™ Oncology 500 Kit (Illumina Inc., San Diego, CA, USA) for DNA library preparation and enrichment, following the manufacturer's instructions. The post-enriched libraries were quantified, pooled, and sequenced on a NextSeq 500 (Illumina). The quality of the NextSeq 500 (Illumina) sequencing runs was assessed with the Illumina Sequencing Analysis Viewer (Illumina). TruSight Oncology 500 Local App Version 1.3.0.39 (Illumina) was used to analyze the sequencing data. The TruSight™ Oncology 500 is a comprehensive tumor profiling assay designed to identify various tumor biomarkers, including small variants, splice variants, and fusions. It also measures TMB and MSI, features that are

Table 1 Basic patient characteristics

Characteristics	Total number (n=31)
Male	18 (58.1)
Age (years)	61.7 (53.5–68.9)
Pathology	
Well-differentiated neuroendocrine tumor	19 (61.3)
Grade 1	1 (3.2)
Grade 2	15 (48.4)
Grade 3	3 (9.7)
Neuroendocrine carcinoma	12 (38.7)
Primary tumor site	
Stomach	4 (12.9)
Small bowel	2 (6.5)
Pancreas	12 (38.7)
Bile duct	1 (3.2)
Gallbladder	4 (12.9)
Liver	1 (3.2)
Rectum	7 (22.6)
Number of metastases	2.0 (1.0–3.0)
Site of metastasis	
Liver	23 (74.2)
Lung	5 (16.1)
Pancreas	2 (6.5)
Pleura	1 (3.2)
Peritoneum	3 (9.7)
Adrenal gland	2 (6.5)
Lymph node	16 (51.6)
Bone	2 (6.5)
Survived at the time of analysis	18 (58.1)
TMB (mutations/Mb)	4.7 (3.1–6.3)
MSI status	
MSS	31 (100.0)

Data are presented as median interquartile range or n (%). TMB, tumor mutation burden; MSI, microsatellite instability; MSS, microsatellite stability.

potential key biomarkers for immunotherapy.

TMB was reported as mutations per megabase (Mb) sequenced. Although there is no consensus on the definition of the high TMB in NET, we use the cutoff of 10 mutations/Mb as a high TMB (12).

Statistical analysis

Descriptive statistics were used to summarize the characteristics of patients and tumors, MSI status, TMB, and treatment history. The data did not follow a normal distribution, and numerical variables were evaluated using the Mann-Whitney *U* test. All P values were two-sided, and statistical significance was set at P value <0.05. The statistical analyses were performed using IBM PASW version 25.0 software (SPSS Inc., Chicago, IL, USA).

Results

Clinical features

Between 2013 and 2022, 31 patients with GEP-NEN were evaluated for MSI status and TMB. We retrospectively review the medical records of those patients. The median age at the time of diagnosis was 61.7 [interquartile range (IQR), 53.5–68.9] years, and 18 (58.1%) patients were male (*Table 1*). According to the 2017 WHO classification of NENs, 1 (3.2%) patient was diagnosed with a grade 1 tumor, 15 (48.4%) patients with grade 2 tumors, and 3 (9.7%) patients with grade 3 tumors. NEC was diagnosed in 12 (38.7%) patients. The primary sites were as follows: 22 (71.0%) foregut-derived NET including stomach (4, 12.9%), pancreas (12, 38.7%), bile duct (1, 3.2%), gallbladder (4, 12.9%), liver (1, 3.2%); 2 (6.5%) midgut-derived NET [small bowel (2, 6.5%)]; and 7 (22.6%) hindgut-derived NET [rectum (7, 22.6%)]. The median number of metastases was 2.0 (IQR, 1.0–3.0; range, 0–4), and the most common metastatic sites were liver (23, 74.2%), lymph node (16, 51.6%), and lung (5, 16.1%).

Tumor mutational burden and MSI

The median TMB score was 4.7 mutations/Mb (IQR, 3.1–6.3; range, 0.8–266.4; *Figure 1*) among 31 patients. Only 1 patient had a tumor with high TMB (266.4 mutations/Mb),

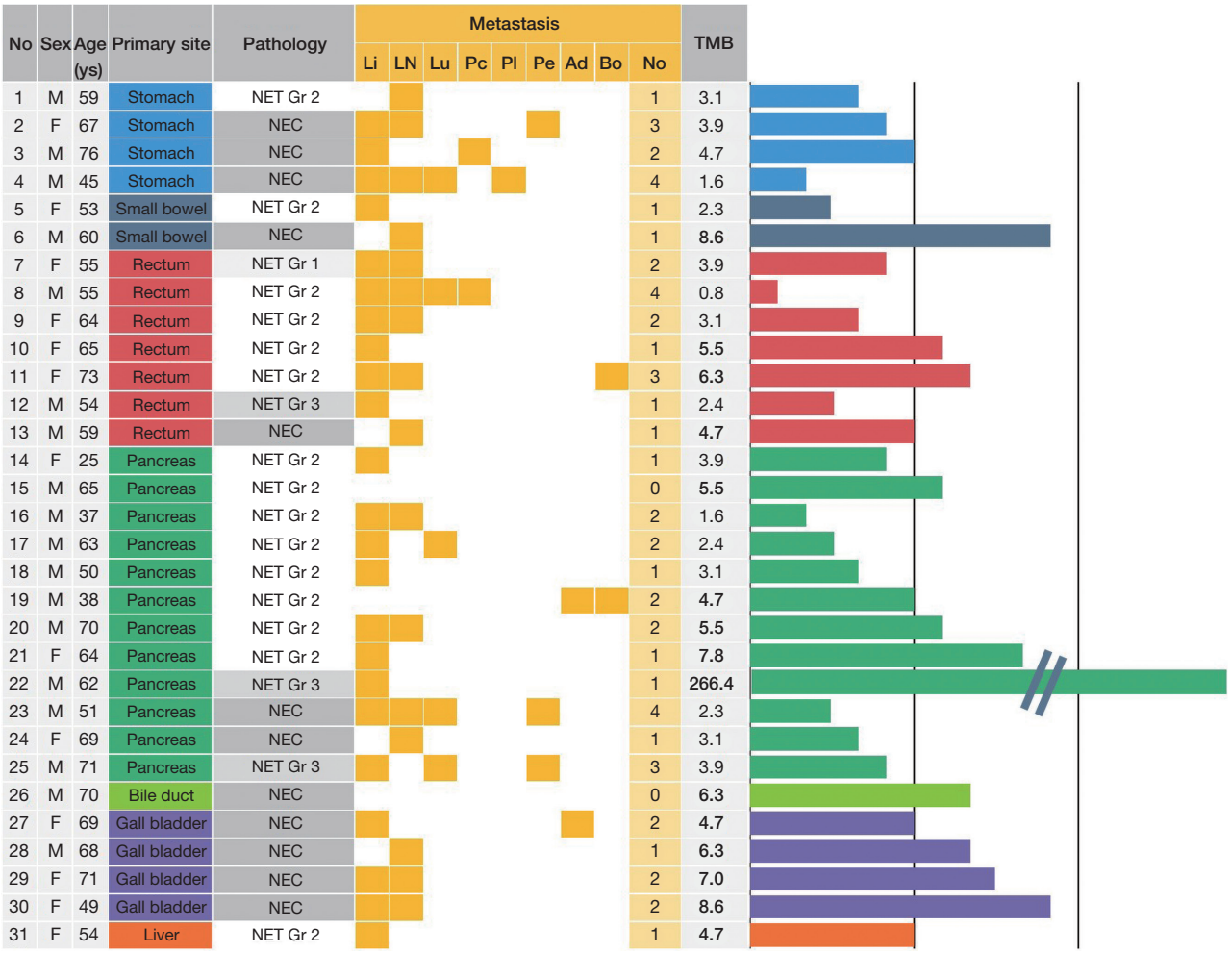

Figure 1 Summary of the 31 patients in the study. TMB higher than the median (4.7 mutations/Mb) is emphasized in bold letters. No, number; ys, years; Li, liver; LN, lymph node; Lu, lung; Pc, pancreas; Pl, pleura; Pe, peritoneum; Ad, adrenal; Bo, bone; TMB, tumor mutation burden; M, male; F, female; NET, neuroendocrine tumor; Gr, grade; NEC, neuroendocrine carcinoma.

and the tumor was classified as grade 3 NET with the pancreas as the primary tumor site. The patient received octreotide as the first-line, everolimus as the second-line, sunitinib as the third-line, and capecitabine plus temozolomide as the fourth-line treatment. The best tumor response was partial remission with capecitabine plus temozolomide (*Figure 2*). The duration of the response was 3 months. After progression, this patient was treated with 5-fluorouracil, irinotecan, and leucovorin combination therapy until the time of analysis.

A statistically significant difference was not observed in the TMB score between well-differentiated NET (grade 1, 2, and 3) and poorly differentiated NEC (median: 3.9 *vs.* 4.7, P=0.232). In addition, the TMB score did not differ based on the primary tumor site (pancreatic NEN *vs.* other primary NEN; median: 3.9 *vs.* 4.7, P=0.646).

All 31 patients had tumors with microsatellite stability (MSS). The tumor with high TMB (266.4 mutations/Mb) was also an MSS tumor.

Discussion

In this analysis, 31 patients diagnosed with GEP-NEN had a median TMB of 4.7 mutations/Mb (IQR, 3.1–6.3; range, 0.8–266.4). The TMB value did not differ based on WHO grade or primary tumor site. Only 1 among 31 patients had a

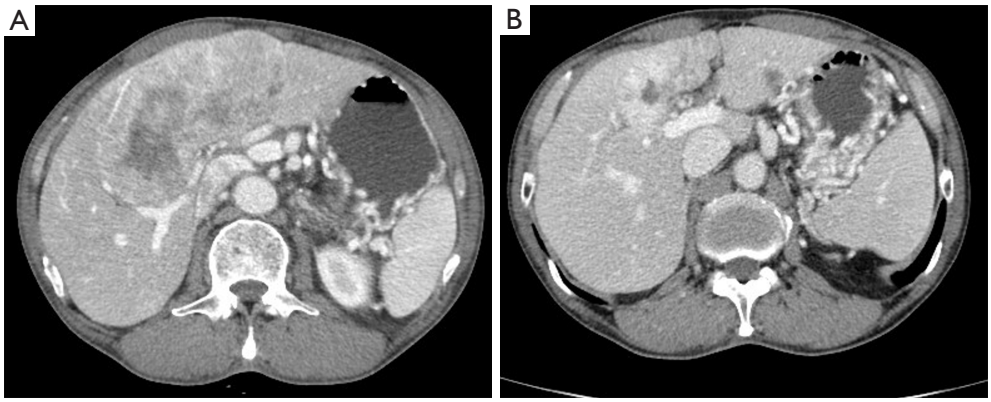

Figure 2 The CT scans of the best response of the patients with capecitabine plus temozolomide. (A) The size of the mass in segment 4 of the liver was 128 mm in February 2020. (B) After 12 cycles of capecitabine plus temozolomide, the mass decreased to 43 mm (66% reduction) in April 2022. CT, computed tomography.

tumor with high TMB (266.4 mutations/Mb); this tumor was also MSS. Although the incidence of tumors with high TMB in GEP-NENs was very low, those with high TMB were observed, indicating the need for tests for MSI and TMB.

ICIs are a promising novel therapy in cancer treatment. Regarding GEP-NENs, several agents targeting programmed death-ligand 1 (PD-L1), programmed cell death protein 1 (PD-1), and cytotoxic T-lymphocyte-associate protein 4 (CTLA-4) have been investigated over the last few years. However, the outcomes reported in clinical trials are disappointing (*Table 2*). Thus, an important challenge is to discover biomarkers to select patients who are likely to benefit from ICIs. Currently, the well-known biomarkers of ICIs are PD-L1 expression (20), TMB (8), and MSI status (9,10). In the present study, we analyzed the status of MSI and TMB in GEP-NENs.

Because NENs are rare tumors, few studies have evaluated TMB in NENs, especially GEP-NENs. Previous studies analyzing TMB in NENs with variable inclusion criteria are summarized in *Table 3*. Most studies also reported low TMB and low rate of MSI-high in NENs, which is consistent with our analysis (21,22,27).

However, in our study, there are no statistically significant differences between TMB of well-differentiated NET and poorly-differentiated NEC. One study only analyzed NEC also reported low median TMB (5.68 mutations/Mb) (22). However, another study with a large number of patients reported higher TMB in high-grade GEP-NEN than in low-grade GEP-NEN (26). This study also reported 4% of MSI-high tumors in high-grade GEP-NEN, which is a relatively high rate comparing other studies. Those studies all had different inclusion criteria, therefore, further study would be needed.

There was only one TMB-high tumor in this study. This tumor was grade 3 NET of the pancreas and the liver biopsy was done. This tumor was MSS and TMB was 266.4 mutations/Mb. Ki-67 level was 55%.

Previously, a single case of grade 3 NET of the pancreas with temozolomide-induced high TMB was reported (28). In the present analysis, 2 patients underwent the NGS test after temozolomide-based therapy and this patient with TMB-high tumor is one of the two. However, the other patient diagnosed with grade 2 NET of the pancreas did not show high TMB (7.8 mutations/Mb). Although there is the possibility of treatment options for ICIs after certain treatments, further studies are needed.

There are some limitations to our study. First, due to the rarity of this disease, this study was based on a small sample size. Second, this was a retrospective study that only included the patients who had NGS. Therefore, there are

Table 2 Summary of the previous trials of immunotherapy in patients with NET

Drug name	Study phase	Total enrollment (n)	Inclusion	Diagnosis	Biomarker	ORR	Reference
Pembrolizumab	I	41	Advanced PD-L1 (+) pNET or carcinoids	pNET (n=16)	PD-L1	PD-L1 (+) pNET: 6.3% (95% CI: 0.2–30.2%)	(13)
Pembrolizumab	II	107	W/D & M/D NET	Pancreas (n=40), SB (n=25), other GI (n=18)	PD-L1	Overall: 3.7% (n=107); PD-L1 (+): 0% (95% CI: 0.0–19.5%) (n=17); PD-L1 (–): 4.8% (95% CI: 1.3–11.9%) (n=83)	(14)
Pembrolizumab	II	29	G3 NET	Pancreas (n=10), non-pancreatic GI (n=14)	PD-L1	1 (3.4%)	(15)
Toripalimab	I	40	NEN	Pancreas (n=9), GI (n=23)	PD-L1, TMB, MSI	20% (n=14); better with PD-L1 (+), TMB-H, MSI-H	(16)
Nivolumab and Ipilimumab	II	32	Nonpancreatic NEN	GEP (n=15)	–	25% (95% CI: 13–42%)	(17)
Nivolumab and Ipilimumab	II	29	Advanced NET	GEP (n=10)	–	24% (n=7/29)	(18)
Spartalizumab	II	32	W/D NET or GEP-NEC	W/D NET (n=95), GI (n=32), pancreatic (n=33), GEP-NEC (n=21)	PD-L1	NET: 7.4% (95% CI: 3.0–14.6); NEC: 4.8% (95% CI: 0.1–23.8)	(19)

NET, neuroendocrine tumor; PD-L1, programmed death-ligand 1; pNET, pancreatic neuroendocrine tumor; CI, confidence interval; W/D, well-differentiated; M/D, moderately-differentiated; SB, small bowel; GI, gastrointestinal; NEN, neuroendocrine neoplasm; TMB, tumor mutation burden; MSI, microsatellite instability; TMB-H, high TMB; MSI-H, high MSI; GEP, gastro-entero-pancreatic; NEC, neuroendocrine carcinoma.

Table 3 Published studies of TMB in NETs

Diagnosis	Total enrollment (n)	TMB (mutations/Mb)			MSI-H	PD-L1 (+)	Reference
		Median	IQR	Range			
GEP-NET	31	4.7	3.1–6.3	0.8–266.4	0	–	Our data
Pancreatic NET	75	Average: 5.8	–	–	0	2/70 (2.9%)	(21)
GI NEC	29	5.68	–	0.57–11.75	0	9/31 (29.0%)	(22)
Metastatic and locally advanced NEN	85	5.45	3.84–8.85	–	–	–	(23)
Pulmonary NET	48	0.31	0.22–0.67	–	–	–	(24)
NET	164	5.2	2.6–10.4	–	–	–	(25)
High-grade GEP-NEN	135	Average: 9.5	–	–	4%	6%	(26)
Low-grade GEP-NEN	335	Average: 5.1	–	–	0%	1%	(26)

TMB, tumor mutation burden; NET, neuroendocrine tumor; IQR, interquartile range; MSI-H, high microsatellite instability; PD-L1, programmed death-ligand 1; GEP, gastro-entero-pancreatic; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm.

possibilities that patients with the more advanced stage were included. Further studies with large and various samples would be needed in the future.

Conclusions

In conclusion, GEP-NENs are tumors with low TMB and MSS, which indicates the limited efficacy of ICIs in GEP-NENs, as found in previous clinical trials (*Table 2*). However, although very few, there are GEP-NENs with high TMB. A test for MSI status and TMB is needed in this type of tumor for precision medicine.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1190/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1190/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1190/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1190/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board (IRB) of Samsung Medical Center approved this study (No. 2022-10-077-001). This study is a retrospective analysis. Therefore, the requirement for informed consent to this study was waived.

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