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Racial disparities in the anatomic distribution of gastrointestinal neuroendocrine tumors

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RACIAL DISPARITIES IN THE ANATOMIC DISTRIBUTION OF GASTROINTESTINAL NEUROENDOCRINE TUMORS

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ABSTRACT

Neuroendocrine tumors (NETs) are a rare type of malignancy, however, their incidence and prevalence have markedly increased over the past several decades. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), NETs of the gastrointestinal (GI) tract, account for the majority of these tumors. Data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI), as well as from multiple cancer registries in Canada and Europe, indicate that the small intestine is one of the most common primary sites of GEP-NET development in Caucasian populations. Smaller studies from Asian countries, however, report a significantly lower proportion of small intestinal NETs (SI-NETs) in those countries' populations. Interestingly, this finding persists in a study of Asians living in the United States, which, therefore, may suggest that genetics, and not environment, play a predominant role in driving this difference.

Multiple studies exploring the genetics of SI-NETs in Caucasians have been published and have identified several genetic alterations implicated in tumorigenesis. However, the most consistently reported finding is chromosome 18 loss of heterozygosity (chr18 LOH), which has been detected in 61-78% of SI-NETs. Unfortunately, these studies have yet to be performed in a strictly Asian cohort. The proposed study, therefore, is a multicenter, cross-sectional study that will compare the proportion of SI-NETs with

chr18 LOH in Asian versus Caucasian populations by performing a fluorescence in-situ hybridization (FISH) analysis of SI-NET tissue from both Asian and Caucasian samples. Overall, the results of this study may help to identify possible mechanisms driving the difference in proportion of SI-NETs between Asians and Caucasians, which in turn, may help to better characterize the genetic events leading into SI-NET tumorigenesis.

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LIST OF ABBREVIATIONS

5-HIAA	5-Hydroxyindoleacteic Acid
AI/AN	American Indian/Alaskan Native
CgA	Chromogranin A
CNV	Copy Number Variance
DFCI	Dana-Farber Cancer Institute
ERG	End Results Group
FGF	Fibroblast Growth Factor
FISH	Fluorescence In-Situ Hybridization
FOLFIRI	Folinic Acid, 5-Fluorouracil, Irinotecan
FOLFIRINOX	FOLFIRI, Oxaliplatin
GEP-NET	Gastroenteropancreatic Neuroendocrine Tumor
GI-NET	Gastrointestinal Neuroendocrine Tumor
IRB	Institutional Review Board
MEN-1	Multiple Endocrine Neoplasia Type 1
mTOR	Mammalian Target of Rapamycin
NCI	National Cancer Institute
NET	Neuroendocrine Tumor
NSE	Neuron-Specific Enolase
PDGF	Platelet-Derived Growth Factor
PI	Pacific Islander
pNET	Pancreatic Neuroendocrine Tumor

PRRT.. Peptide Receptor Radionuclide Therapy

SEER..Surveillance, Epidemiology, and End Results

SI-NET...Small Intestinal Neuroendocrine Tumor

SNP .... Single Nucleotide Polymorphism

SSA ....Somatostatin Analog

TNCS .... Third National Cancer Survey

UCSF...University California San Francisco

VEGF .... Vascular Endothelial Growth Factor

VHL ....von-Hippel-Lindau

VIP ....Vasoactive Intestinal Peptide

INTRODUCTION

Background

Neuroendocrine tumors (NETs) are a rare type of malignancy, however, their incidence and prevalence have markedly increased over the past few decades.[1] Neuroendocrine cells, which can transform into NETs, are found throughout the body and, therefore, these tumors can arise in most organ systems, though the gastrointestinal (GI) tract and the bronchopulmonary system are the most common sites of development.[2] Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), NETs of the GI tract, account for the majority (70%) of these tumors.[2] NETs of this class include tumors arising from the esophagus, stomach, pancreas, liver, gall bladder, biliary tract, duodenum, jejunum, ileum, colon, rectum, and anus. Tumors within the GI tract can be further classified based on embryonic origins, including the foregut (esophagus, stomach, pancreas, duodenum), midgut (jejunum, ileum, proximal colon), and hindgut (distal colon, rectum, anus).[3] Data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI), as well as from multiple cancer registries in Europe, indicate that the small intestine is one of the most common primary sites of GEP-NET development in Caucasians.[2,4–10] Conversely, smaller studies from Asian countries report a significantly lower proportion of small intestinal NETs (SI-NETs) in Asian populations.[11–19] The mechanisms driving this difference remain unknown, however, several genomic alterations have been identified in SI-NETs, including various chromosomal gains and losses, cell cycle inhibitor mutations, and epigenetic dysfunction.[20–22]

The clinical presentation of GEP-NETs varies based on tumor type and functionality, while treatment depends on localization of disease. These tumors can be classified as either functional or nonfunctional. Functional tumors secrete hormones in excess and the hormones they secrete, such as serotonin, gastrin, insulin, or glucagon, are responsible for the clinical syndrome manifested by the patient.[23] Conversely, nonfunctional tumors do not secrete hormones and often present due to symptoms of mass effect, such as abdominal pain.[23] These tumors, therefore, are usually diagnosed in more advanced stages. In terms of treatment, surgery remains the gold standard for localized tumors. However, when tumors have metastasized, other options, such as systemic therapy, have been shown to relieve symptoms and reduce tumor burden. Somatostatin analogs (SSAs), such as octreotide or lanreotide, have been shown to significantly reduce symptoms of carcinoid syndrome, while simultaneously slowing tumor growth.[23] Other agents, such as everolimus and sunitinib, have been shown to reduce tumor size in the treatment of pancreatic NETs (pNETs).[23] Peptide receptor radionuclide therapy (PRRT) has recently been demonstrated to provide significant reductions in tumor size while minimizing cytotoxic effects.[23] Finally, liver-directed therapies, such as radiofrequency ablation and transarterial embolization, have demonstrated efficacy in reducing metastatic tumor burden.[23] Overall, treatment options for GEP-NETs are myriad and continue to advance as these tumors become increasingly more recognized and studied.

Statement of the Problem

Recent population-based data from national cancer registries in North American and European countries indicate that the small intestine is one of the most common primary sites of GEP-NET development in Caucasians.[2,4–10] This type of surveillance data, unfortunately, is lacking in Asian countries. However, there are multiple cohort studies in these countries that found a considerably lower proportion of SI-NETs in Asian populations as compared to Caucasian populations.[11–19] These studies, however, were mostly small and retrospective, primarily utilizing single-center cohorts, and, therefore, are subject to a degree of sample bias. Collectively, though, each of these studies found this same pattern and, therefore, could reflect a true difference. This pattern also persists in Asians living in the United States[4], which, therefore, may suggest that genetics, and not environment, play a major role in driving this difference.

Multiple studies have been published on the genetics of SI-NETs but only in predominantly Caucasian cohorts. These studies have identified multiple, recurrent chromosomal gains and losses, most notably chromosome 18 loss of heterozygosity (chr18 LOH). Other genetic alterations, such as *CDKN1B* mutations[21] and epigenetic dysregulation[22], have also been identified in these tumors. There is no data, however, on the genetics of SI-NETs in strictly Asian populations. Further exploration into the genetics of these tumors in Asians, therefore, can help to identify the possible mechanisms driving this difference between Asian and Caucasian populations, as well as help to explain SI-NET tumorigenesis from a genetic perspective.

Hypothesis

The proportion of SI-NETs with chr18 LOH is significantly lower in Asian populations as compared to Caucasian populations.

Objectives and Aims

The objective of this thesis is to provide a comprehensive review of the anatomic distribution of GEP-NETs in both Caucasian and Asian populations and, then, to propose a study to explore the genetic profile of Asian SI-NETs in order to better understand the mechanisms that may be driving the difference in proportion of these tumors between the two races. The specific aims of this study are:

- To review the anatomic distribution of GEP-NETs in Caucasian populations in the United States, Canada, and Europe.
- To review the anatomic distribution of GEP-NETs in Asian populations in Asia and the United States.
- To summarize the current state of genetics in Caucasian SI-NET tumorigenesis.
- To propose a multicenter, cross-sectional study that will compare the proportion of SI-NETs with chr18 LOH in Asian versus Caucasian populations by performing a fluorescence in-situ hybridization (FISH) analysis of SI-NET tissue from both Asian and Caucasian samples.

REVIEW OF THE LITERATURE

Overview

Epidemiology of GEP-NETs

Neuroendocrine tumors (NETs) are rare and account for only 0.5% of newly diagnosed malignancies.[24] Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), however, are the second most common gastrointestinal cancer.[4] Recent data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) suggest that NETs are increasing in incidence and prevalence in the United States. Dasari et al.[1] reported that the age-adjusted incidence rate for NETs has increased 6.4-fold from 1973 (1.09 per 100,000) to 2012 (6.98 per 100,000), a trend found across all sites, stages, and grades.[1] Conversely, the collective incidence of all malignant neoplasms has declined during this same time period. This discrepancy, however, is most likely due to advances in diagnostic technique for NETs, which has led to an overall increase in diagnosis of early-stage tumors.[1] Furthermore, the prevalence of NETs in the United States has also increased from 0.006% in 1993 to 0.048% in 2012,[1] which can most likely be attributed to improvement in therapy options for NETs, leading to improved survival in these patients.[1]

Using the SEER database, Sackstein et al. 2018[2] reported that the most common primary sites of GEP-NETs in the United States are the rectum (17.5%), small intestine (12.4%), pancreas (8.9%), colon (6.1%), stomach (4.7%), and appendix (3.9%)[2]. Interestingly, Yao et al. 2008[4], which published a similar study a decade prior, found the small intestine to be the most common site of GEP-NET development in the United

States. This shift from small intestine to rectum can potentially be attributed to the 20% increase in colonoscopies performed between 2000 and 2010.[25] Large, population-based studies from European countries found comparable anatomic distributions to the United States.[5–8] Unfortunately, data of this scale has yet to be collected in Asian countries. Multiple, retrospective cohort studies from these countries, however, have reported considerable differences in the anatomic distribution of GEP-NETs as compared to the populations of the United States and European countries, which raises the question as to whether or not race affects NET tumorigenesis.

Further contributing to this possibility, Yao et al. 2008[4] found that the anatomic distribution of GEP-NETs in the United States varied significantly by race and sex.[4] This study described a higher proportion of small intestinal NETs (SI-NETs) in Caucasian and African-American patients than in Asian/Pacific Islander (PI) and American Indian (AI)/Alaskan Native (AN) patients.[4] In contrast, rectal NETs were found in a higher proportion among non-Caucasian patients than Caucasian patients.[4] This study also found a higher proportion of NETs of the stomach, appendix, and cecum in females, while the same was true for NETs of the small intestine, pancreas, and rectum in males.[4] Overall, the mechanisms driving these differences remain unknown but varying genetic and/or environmental factors may be contributing to their development.

Pathophysiology of GEP-NETs

Neuroendocrine cells, which derive from multipotent gastrointestinal stem cells, occur throughout the length of the digestive tract and are the largest group of hormone-producing cells in the body.[26] These cells produce a variety of bioactive peptides or amines, such as serotonin, somatostatin, histamine, and gastrin, which help to regulate bowel motility and hormone secretion.[27] Once produced, these substances are stored in either large, dense-core or small, synaptic-like vesicles. Proteins that constitute these vesicles, such as chromogranin A and synaptophysin, can be used as biomarkers in the identification of neuroendocrine cells.[28] Secretion from the vesicle is regulated by G-protein coupled-receptors, ion-gated receptors, and receptors with tyrosine-kinase activity.[27] Enterochromaffin cells, the major neuroendocrine cell type of the small intestine, secrete various hormones in response to mechanical and chemical stimuli.[27] Secretion is activated by various chemical mediators, such as adenylyl cyclase, beta-adrenoreceptors, and pituitary adenylate cyclase-activating polypeptide. Conversely, somatostatin, acetylcholine, and gamma-aminobutyric acid are inhibitors of secretion.[29] These cells also contain serotonin receptors, which when activated, mediate downstream effects throughout the body, such as proliferation of epithelial cells and contraction of intestinal smooth muscle.[27] Rapid inactivation of serotonin, therefore, is crucial to cell vitality and can be achieved through absorption into enterochromaffin cells, followed by intracellular degradation.[29]

While the pathophysiology of tumor development in neuroendocrine cells remains largely unknown, multiple, predisposing genetic alterations have been described. First, mutations of the mammalian target of rapamycin (mTOR) gene are found in the majority of NETs[23] but most commonly in pancreatic NETs (pNETs).[30] Second, SI-NETs have been shown to harbor chromosomal gains and losses, such as chromosome 18 loss of heterozygosity (chr18 LOH)[20], as well as extensive epigenetic dysregulation.[22] Third, SI-

NETs have also been found to contain a mutation of the *CDKN1B* gene[21], which encodes p27, a cell cycle inhibitor. This mutation, however, has only been isolated in 10% of SI-NETs.[21] Finally, NETs are known to be highly vascularized tumors and tumor angiogenesis is pivotal to the progression of tumor size.[23] Multiple proangiogenic factors have been described as also driving NET vascularization, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF).[31]

In addition to genetic alterations, family history and hereditary syndromes have also been associated with an increased risk for NET development. Patients with a family history of NET in a first-degree relative have been found to have a 3.6-fold increased risk of disease.[8] Hughes et al.[32] corroborated this finding in their study of first-degree relatives of SI-NET patients where they found that nearly a quarter of them had occult SI-NETs themselves. Similarly, various hereditary syndromes have been found to be associated with an increased risk of tumor developement.[24] Multiple endocrine neoplasia type 1 (MEN-1), an autosomal-dominant syndrome caused by mutations of the *MEN-1* gene, is characterized by tumors in multiple locations, including the pancreas.[33] The majority of pNETs arising in the context of this syndrome, however, are relatively indolent and non-functional.[34] Other hereditary syndromes associated with the development of pNETs include von-Hippel-Lindau (VHL) syndrome and tuberous sclerosis. VHL syndrome is an autosomal dominant syndrome caused by mutations of the *VHL* tumor suppressor gene,[35] while tuberous sclerosis is an autosomal dominant syndrome caused by the simultaneous inactivation of two tumor suppressor genes, *TSC1* and *TSC2*.[36]

Clinical Presentation of GEP-NETs

The clinical presentation of GEP-NETs is diverse and depends primarily on tumor location, functionality, and malignant potential. The majority of pNETs, for example, are hormonally-silent (90%)[37] and many are diagnosed incidentally.[23] Unfortunately, these tumors are not symptomatic until more advanced stages, which tends to delay diagnosis.[23] When they do become symptomatic, patients often present with symptoms related to mass effect or metastasis, such as abdominal pain.[38] Conversely, functional pancreatic NETs, tumors that secrete pancreatic hormones, present earlier and their symptoms are a function of the hormones they secrete in excess. Tumors of this subset include insulinomas, gastrinomas, VIPomas, glucagonomas, and somatostatinomas. Insulinomas are tumors that oversecrete insulin, a hormone secreted in response to increasing blood glucose levels. These tumors tend to be small, solitary, hypervascular lesions and often exhibit a low malignant potential.[23] Classically, they present as the “Whipple triad” – symptomatic hypoglycemia, low serum glucose, and relief of symptoms after glucose administration.[39] Gastrinomas are tumors that oversecrete gastrin, a hormone secreted in response to decreased gastric acid production. These tumors are more likely to be malignant and present as Zollinger-Ellison syndrome, which is characterized by peptic ulceration, acid reflux, and diarrhea.[23] Fortunately, these symptoms can be effectively managed with proton pump inhibitors[40], which suppress acid production. VIPomas are tumors that oversecrete vasoactive intestinal peptide (VIP), a hormone that stimulates large intestinal secretion and inhibits water and electrolyte absorption. These tumors cause Verner-Morrison syndrome, which is characterized by profuse, watery diarrhea and electrolyte abnormalities, including hypokalemia.[41] Glucagonomas are tumors that oversecrete glucagon, a hormone secreted in response to decreasing blood glucose levels. These tumors can cause hyperglycemia, weight loss, venous thrombosis, glossitis, and necrolytic migratory erythema.[42] Somatostatinomas are tumors that oversecrete somatostatin, a hormone that plays a major role in the digestive tract, including inhibition of bowel motility, gall bladder contraction, and intestinal absorption, as well reduction of mesenteric blood flow and suppression of the secretion of various hormones, such as serotonin, gastrin, and cholecystokinin.[23] These tumors usually present with steatorrhea, achlorhydria, diabetes mellitus, and cholelithiasis.[31] Overall, functional pancreatic tumors are rare but present with symptomology arising from their respective hormonal secretions.

SI-NETs are one of the most common types of GEP-NETs in the United States.[4] Within the small intestine, the ileum is the most common site of tumor development, followed by the jejunum, and then the duodenum.[23] Additionally, NETs of the ileum and jejunum are more likely to metastasize than the duodenum and the most common sites of metastasis are the liver, mesentery, and peritoneum.[23] Unfortunately, symptoms often do not present until the tumor has metastasized and, therefore, these tumors are rarely diagnosed early.[43] They often produce serotonin, which, in large enough amounts, causes vasodilation, bronchoconstriction, and smooth muscle contraction. After metastasis to the liver, the tumor secretes serotonin directly into systemic circulation, as opposed to portal circulation, which can cause carcinoid syndrome.[23] This classic symptomology is characterized by watery diarrhea, abdominal pain, flushing, bronchospasm, hypotension, and right-sided heart disease. Additionally, serotonin receptors exist on the subendocardial cells of heart valves and, thus, persistently elevated levels of serotonin can cause valvular heart disease, which can impair cardiac function.[44] The advent of serotonin-inhibiting therapies, however, has sharply reduced the incidence of carcinoid heart disease.[45] Compared to ileal and jejunal tumors, duodenal tumors are rarely functional and may present instead with duodenal and/or biliary obstruction.[46] They are usually detected incidentally on upper endoscopy.[46] Overall, SI-NETs are one of the most common types of GEP-NETs with carcinoid syndrome representing a major clinical outcome in patients with these tumors.

Gastric NETs are classified into three types based on etiology and presentation. Type I gastric NETs, the most common (80%), occur in patients with chronic atrophic gastritis.[47] In this type, the absence of gastric acid production causes neuroendocrine cells in the stomach to undergo hyperplasia in response to increased gastrin secretion. This tumor type is usually benign and aggressive treatment is rarely indicated.[23] Type II gastric NETs, similarly, are caused by hypergastrinemia but in patients with an underlying gastrinoma in the setting of MEN-1 syndrome.[23] This type of NET usually presents with symptoms of Zollinger-Ellison syndrome and tend to be small, multifocal, and unaggressive.[23] Conversely, the etiology of type III gastric NETs is unknown. This class of gastric NETs is characterized by large, solitary tumors that have a considerably higher malignant potential than types I or II.[23]

Appendiceal NETs are often small, asymptomatic tumors confined to the appendix. The diagnosis of these tumors is typically established postoperatively from the pathology of appendectomy specimens. Most of these tumors are benign but their malignant potential appears to be proportional to tumor size.[48] Similarly, colorectal NETs are often discovered incidentally on colonoscopy, however, they may also present with rectal bleeding, pain, or a change in bowel habits.[49] Often, these tumors are small, submucosal, and well-differentiated and can be resected endoscopically or transanally. Larger rectal tumors, however, tend to be fairly aggressive, and often present metastatically on initial diagnosis.[49] Furthermore, large, colonic NETs distal to the cecum are more aggressive than rectal NETs and tend to have a worse prognosis.[50]

Diagnosis of GEP-NETs

The diagnosis of GEP-NETs is based on clinical presentation, biochemical and tissue markers, endoscopy, and conventional or functional radiology. Chromogranin A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA) are commonly measured serum and urinary markers, respectively, in patients with GEP-NETs. CgA, a secretory glycoprotein contained in vesicles of neuroendocrine cells, is a biomarker found in many types of GEP-NETs.[27] The majority of these tumors, especially non-functional tumors, exhibit increased levels of circulating CgA.[27] The concentration of this biomarker can also be representative of tumor bulk, differentiation, and functionality, which is helpful when deciding between various treatment regimens.[44] CgA, however, can be elevated in other situations, such as renal failure.[27] 5-HIAA, a breakdown product of serotonin, is often ordered as a lab assay in patients presenting with symptoms of carcinoid syndrome.[23]

This biomarker is measured in the urine over a period of 24-hours, however, a recent study found that a plasma 5-HIAA assay has similar accuracy to a 24-hour urinary 5-HIAA measurement.[51] This marker, however, is not useful in detecting tumors that do not secrete serotonin, such as rectal NETs.[44] Furthermore, patients with suspected pNETs who present with hormonal syndromes should undergo testing for the corresponding hormone, such as insulin, gastrin, glucagon, somatostatin, and VIP. If elevated, this level can then be tracked to monitor progression or response to treatment.[23] Lastly, tissue markers, such as CgA, synaptophysin, and neuron-specific enolase (NSE), are useful in distinguishing tumors as neuroendocrine, while markers for proliferation, such as Ki-67 and MIB-1, are useful in determining tumor grade and prognosis.[27]

Besides biochemical and tissue markers, endoscopy, as well as conventional and functional radiology, are important in the diagnosis of GEP-NETs. Upper endoscopy is the primary diagnostic modality for gastric and duodenal NETs, while lower endoscopy is the standard for diagnosing colorectal NETs. Barium studies, as well as computed tomography (CT) imaging, are useful in the diagnosis of jejunal and ileal tumors though tumors in early stages can be ill-defined and, therefore, challenging to image.[44] In these situations, angiography is useful as GEP-NETs tend to be hypervascular even in earlier stages.[44] CT imaging of the abdomen can also be utilized in the diagnosis of pNETs. Other imaging modalities, such as magnetic resonance imaging (MRI) and ultrasonography (US), are highly sensitive for the detection of liver metastases.[52] Functional radiology has recently become more utilized than other imaging modalities in the diagnosis of GEP-NETs as it is based on the principle that these tumors tend to express high levels of somatostatin receptors.[53] Octreotide, a somatostatin analog, has a high affinity for somatostatin receptors and can be labeled with radioactive tracers, such as indium-111 (^{111}In). This radiolabeled somatostatin analog (SSA), in conjunction with PET/CT, has been used in the past to identify neuroendocrine tumors and their metastases throughout the body.[23] Gallium-68 (^{68}Ga)-DOTATATE, an improved version of radiolabeled SSAs, has become the preferred modality for functional radiology with a sensitivity of 94% and a specificity of 92% for the diagnosis of GEP-NETs.[23]

Treatment of GEP-NETs

The treatment options for GEP-NETs have increased considerably in recent years. For localized tumors, surgery continues to be the gold standard.[23] Localized pNETs, for example, require surgery for tumors that are functional, high grade, or >2cm in greatest dimension.[23] In these situations, surgery includes either a pancreaticoduodenectomy (Whipple procedure) or a distal pancreatectomy, depending on tumor location within the pancreas.[23] Enucleation, a less invasive surgical intervention for small, localized pNETs without perineural or vascular invasion, remains a viable option for the appropriate candidate, however, this technique may not guarantee tumor-free resection margins.[54] The management of localized pNETs <2cm in greatest dimension is controversial but guidelines suggest continued surveillance, except for patients with MEN-1 syndrome for whom surgical intervention is appropriate.[55] Treatment of midgut NETs primarily depends on tumor location. Localized jejunal and ileal NETs are often removed surgically via partial small bowel resection, whereas tumors near the ileocecal junction are removed via right hemicolectomy.[23] For metastatic SI-NETs, surgery is usually palliative and is performed when the patient becomes symptomatic. Furthermore, for localized appendiceal tumors, appendectomy is usually sufficient for complete tumor removal, however, tumors >2cm in greatest dimension require additional surgical intervention via right hemicolectomy.[23] Localized, rectal tumors <2cm in greatest dimension can be managed with simple, endoscopic resection or transanal excision, whereas larger tumors require either a low anterior resection or abdominoperineal resection with sampling of adjacent lymph nodes for possible metastatic spread.[23] Similarly, localized colonic tumors can be managed endoscopically or with partial colectomy for larger tumors.[23] Type I and II gastric NETs rarely need surgical intervention but type III gastric NETs, which have more malignant potential, may be managed with surgical wedge or endoscopic resection.[56]

For metastatic tumors not amenable to surgery, other therapeutic options exist, such as systemic or liver-directed therapy. Carcinoid syndrome, which often presents in SI-NETs metastatic to the liver, can be treated with SSAs, such as octreotide or lanreotide.[23] These medications are agonists of the somatostatin receptor, which have been found to reduce diarrhea, flushing, and bronchospasm, as well as reduce levels of 5-HIAA in patients with carcinoid syndrome.[57] Interestingly, they have also been shown to inhibit tumor growth.[58] Peptide receptor radionuclide therapy (PRRT), which utilizes radiolabeled SSAs, is a form of systemic radiotherapy that delivers targeted radiation to tumor cells expressing somatostatin receptors. Recent studies have shown that PRRT has significant anti-tumor activity when the SSA is labeled with yttrium-90 (^{90}Y) or lutetium-177 (^{177}Lu).[59] Adverse side effects reported with PRRT include renal insufficiency and bone marrow toxicity.[23] Everolimus, an mTOR inhibitor, represents another viable treatment option. In the RADIANT-3 trial, everolimus was shown to have significantly greater progression-free survival in patients with pNETs compared to placebo.[60] Other therapeutic agents, such as sunitinib, have also been shown to increase progression-free survival in patients with pNETs.[61] Sunitinib targets the proangiogenic factors PDGF and VEGF, which contribute to the vascularization of pNETs. For patients with advanced, poorly-differentiated GEP-NETs, chemotherapy is a modestly successful treatment option. Platinum-based combination therapy with cisplatin and etoposide has been shown to have response rates ranging from 42%-67%, however, these remissions are usually short-lived.[62] Limited second-line therapies exist for patients who have progressed through platinum-based therapy, though there has been some response with combinatory agents, such as FOLFIRI (folinic acid, 5-fluorouracil, and irinotecan) and FOLFIRINOX (FOLFIRI plus oxaliplatin).[63,64] Finally, liver-directed therapies are a treatment option for patients with symptomatic liver metastases. Various ablative procedures, such as cryoablation and radiofrequency ablation, are commonly performed.[23] Other procedures, such as hepatic transarterial embolization and radioembolization, have also been shown to have a modest response rate in institutional series reports.[23] Overall, options for the treatment of localized and metastatic GEP-NETs are myriad and continue to advance as these tumors become increasingly studied.

Existing research

Multiple studies examining the epidemiology of GEP-NETs in the United States and Canada report that the small intestine is one of the most common sites of GEP-NET development in Caucasians (Table 1).[2,4,9,10] This pattern is further corroborated by multiple European studies with predominantly Caucasian cohorts (Table 2).[5–8] Smaller studies from Asian countries, however, report a considerably lower proportion of SI-NETs in their countries' populations as compared to Caucasians (Table 3).[11–19] This difference is further supported by a study that explores the anatomic distribution of GEP-NETs by race in the United States (Table 4).[4] Overall, the consistency of this pattern across multiple studies in various countries suggests that the difference in proportions of SI-NETs between the two races represents a true difference in distribution by race and, therefore, warrants further exploration.

Table 1. Anatomic distribution of GEP-NETs in North America demonstrates a SI-NET preponderance in predominantly Caucasian cohorts (see Appendix for study details).

Yao et al. 2008 (United States)		Sackstein et al. 2018 (United States)		Lawrence et al. 2011 (United States)		Hallet et al. 2015 (Canada)	
Site	% of all NETs	Site	% of all NETs	Site	% of GEP-NETs	Site	% of all NETs
SI	**19%**	Rectum	18%	**SI**	**30%**	**SI**	**18%**
Rectum	17%	**SI**	**12%**	Rectum	25%	Colon	13%
Colon	8%	Pancreas	9%	Pancreas	11%	Rectum	12%
Pancreas	7%	Colon	6%	Appendix	9%	Pancreas	9%
Stomach	5%	Stomach	5%	Stomach	9%	Stomach	5%
Appendix	4%	Appendix	4%	Colon	8%	---	---

Table 2. Anatomic distribution of GEP-NETs in Europe demonstrates a SI-NET preponderance in predominantly Caucasian cohorts (see Appendix for study details).

Ellis et al. 2010 (England)		Hauso et al. 2008 (Norway)		Korse et al. 2013 (Netherlands)		Hemminki & Li 2001 (Sweden)	
Site	% of all NETs	Site	% of all NETs	Site	% of GEP-NETs	Site	% of all NETs
SI	**34%**	**SI**	**26%**	Appendix	31%	**SI**	**35%**
Appendix	30%	Colon	8%	**SI**	**23%**	Appendix	23%
Colon	20%	Rectum	7%	Pancreas	14%	Colon	12%
Stomach	9%	Pancreas	7%	Rectum	11%	Rectum	8%
Rectum	7%	Stomach	6%	Colon	11%	Stomach	5%
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Table 3. Anatomic distribution of GEP-NETs in Asia demonstrates a considerably lower proportion of SI-NETs in Asian populations compared to Caucasian populations from previous studies (see Appendix for study details).

Tsai et al. 2013 (Taiwan)		Cho et al. 2012 (South Korea)		Lim et al. 2011 (South Korea)	
Site	% of all NETs	Site	% of all NETs	Site	% of GEP-NETs
Rectum	25%	Rectum	48%	Rectum	56%
Stomach	7%	Stomach	15%	Pancreas	17%
Pancreas	6%	Pancreas	9%	Stomach	10%
Colon	5%	Colon	8%	**SI**	**7%**
SI	**5%**	**SI**	**8%**	Colon	5%
Appendix	4%	Appendix	3%	Gallbladder	1%

Fan et al. 2017 (China)		Zhang et al. 2017 (China)		Wang et al. 2012 (China)	
Site	% of all NETs	Site	% of all NETs	Site	% of GEP-NETs
Pancreas	32%	Stomach	26%	Pancreas	35%
Rectum	30%	Rectum	8%	Rectum	20%
Stomach	27%	Pancreas	7%	Stomach	14%
SI	**6%**	Esophagus	7%	**SI**	**10%**
Colon	3%	**SI**	**6%**	Esophagus	4%
Appendix	2%	---	---	Appendix	3%

Jiao et al. 2015 (China)		Zeng et al. 2013 (China)		Ito et al. 2010 (Japan)	
Site	% of all NETs	Site	% of all NETs	Site	% of GEP-NETs
Pancreas	41%	Pancreas	53%	Hindgut	60%
Rectum	23%	Rectum	23%	Foregut	30%
Stomach	22%	Stomach	14%	**Midgut**	**10%**
Colon	5%	**SI**	**5%**	---	---
SI	**5%**	Appendix	4%	---	---
Biliary Tract	3%	Colon	2%	---	---

Table 4. Anatomic distribution of GEP-NETs in the United States stratified by race demonstrates a considerably lower proportion of SI-NETs in Asian populations compared to Caucasian populations from previous studies.

Yao et al. 2008							
Caucasian		Asian/PI*		African-American		AI/AN**	
Site	% of all NETs	Site	% of all NETs	Site	% of all NETs	Site	% of all NETs
SI	**19%**	Rectum	41%	Rectum	26%	Rectum	32%
Rectum	17%	Pancreas	8%	**SI**	**22%**	Pancreas	10%
Colon	8%	**SI**	**8%**	Colon	8%	Stomach	9%
Pancreas	7%	Stomach	6%	Pancreas	6%	**SI**	**7%**
Stomach	5%	Colon	5%	Stomach	5%	Colon	7%
Appendix	4%	Appendix	2%	Appendix	3%	Appendix	1%

***PI: Pacific Islander; **AI/AN: American Indian/Alaskan Native**

Anatomic distribution of GEP-NETs among Caucasians in North America

The SEER Program has been pivotal for cancer epidemiology research in the United States. The database, which was formed in 1973, collects data on cancer cases from various locations and sources throughout the country. It has allowed extensive epidemiological research to be carried out on all types of NETs. From the perspective of this review, the SEER database has provided valuable data on the anatomic distribution of GEP-NETs across various races in the United States. Yao et al. 2008[4] is one of the hallmark studies to use the SEER database in the analysis of GEP-NET epidemiology in the United States. In this study, the authors included 35,618 patients with a diagnosis of any type of NET in the SEER database between 1973 and 2004. Their patient population was 81% Caucasian, 12% African-American, 5% Asian/Pacific Islander, 1% American Indian/Alaskan Native, and the remaining 1% were unknown. The cohort was stratified first by location of the primary tumor and then by race. The authors found that the most common primary site for GEP-NETs in Caucasians was the small intestine, followed closely by the rectum (Table 1).[4] Despite being a large, population-based cohort, the SEER database likely underestimates the total number of patients in the United States with NETs. This database only includes malignant NETs and, therefore, likely excludes many small, benign-appearing tumors (e.g. appendiceal NETs), which may influence the overall distribution of NETs by primary site. This limitation, unfortunately, is seen in all studies that utilize the SEER database. Overall, this study identifies the small intestine as the most common site of GEP-NET development in Caucasians.

The data from Yao et al. 2008[4] is further corroborated by data from Sackstein et al. 2018[2], which also used the SEER database to examine epidemiological trends of NETs in the United States. In this study, the authors included 85,133 patients from the SEER database with a diagnosis of any type of NET between 1995 and 2014. Of these patients, the most common primary site for GEP-NETs was the rectum, followed closely by the small intestine (Table 1).[2] The majority of the patients in this study were Caucasian (78%), however, as the authors did not stratify the primary site by race, these results are less generalizable to Caucasians as a whole. Additionally, this study period includes an additional decade (2005-2014) of patients not included in the previous study and excludes two other decades (1973-1994) that were previously included in Yao et al. 2008.[4] These results, therefore, more accurately reflect the current anatomic distribution of GEP-NETs in Caucasians in the United States, which would indicate that the rectum surpassed the small intestine as the most common GEP-NET primary site. Overall, though, the study suggests that the rectum, small intestine, and pancreas are the most common primary sites of GEP-NET development in Caucasians in the United States, similar to the data presented by Yao et al. 2008[4]

Lawrence et al. 2011[9] was another study to use the SEER database in their epidemiologic review of GEP-NETs in the United States, however, unlike Yao et al. 2008[4] and Sackstein et al. 2018[2], this study also included data from the End Results Group (ERG) and the Third National Cancer Survey (TNCS). These additional databases provide data on GEP-NETs prior to the inception of the SEER database. Overall, this study examined the incidence of GEP-NETs in the United States between 1950 and 2007 in 31,644 patients and concluded that the most common primary site for GEP-NET development was the small intestine, followed closely by the rectum (Table 1).[9] The study, however, did not describe the demographics of the patient population and, thus, the percentage of Caucasians in this study is unknown. However, based on the distribution of race in prior SEER studies, the majority of patients are likely to be Caucasian, which again, suggests that the small intestine and rectum are the most common primary sites of GEP-NET development in Caucasians in the United States. This dataset, unlike those in the two previously described studies, has the advantage of covering a larger study period and, therefore, reflects more accurately the anatomic distribution of GEP-NETs in the United States over time. Overall, this data further corroborates the findings of Yao et al. 2008[4] and Sackstein et al. 2018[2].

Outside of the United States, Hallet et al. 2015[10] provided data on a population-based, retrospective cohort of Canadian patients documented in the Ontario Cancer Registry. Patients with a diagnosis of any type of NET between 1994 and 2009 were included. In total, there were 5,619 patients included in this study. The most common primary site for GEP-NET development was the small intestine (Table 1).[10] Demographics were again not included, which limits the generalizability of this data to Caucasians. However, according to a Canadian census in 2001, 83% of the population was Caucasian[65], which again suggests that the majority of patients in this cohort were Caucasian as well. Overall, the results presented by Hallet et al. 2015, which suggest that the small intestine and rectum are the most common sites of GEP-NET development in Caucasians, further corroborate those from the United States.

Anatomic distribution of GEP-NETs among Caucasians in Europe

Outside of North America, European countries provide a wealth of data in the epidemiology of GEP-NETs. The English Cancer Registry, one of the most extensive European cancer databases, covers a population in excess of 50 million people and is known to demonstrate a high degree of accuracy and completeness.[66] Ellis et al. 2010[5] is one of the larger studies to utilize this database in the setting of GEP-NET epidemiology. In this study, the authors examined 10,324 English patients with a diagnosis of a gastrointestinal NET (GI-NET) between 1971 and 2006. The most common primary site of GI-NETs was the small intestine, followed closely by the appendix (Table 2).[5] Of note, their study did not include the pancreas as a primary site for gastrointestinal NETs, which leads to an overestimation of the proportion of GI-NETs by primary site. Furthermore, racial status is not available for subjects in this study. However, according to an English demographics study, the English population was predominantly Caucasian during this study period[67], which makes this data generalizable to Caucasians. Overall, these results further corroborate those from North America, which describe the small intestine as one of the most common sites of GEP-NETs in Caucasians. Interestingly, this population had a lower proportion of rectal tumors as compared to their North American counterparts. This difference may be due to the fact that the English population has a lower percentage of non-Caucasians than the United States and non-Caucasians have been found to have a higher proportion of rectal GEP-NETs than their Caucasian counterparts.[4]

Norway is another European country with a population-based cancer registry that provides robust data on cancer epidemiology. Hauso et al. 2008[6] utilized the Norwegian Cancer Registry to examine patterns of NET epidemiology. In this study, the authors identified 2,030 patients with a diagnosis of any type of NET between 1993-2004. Overall, the most common primary site for GEP-NETs in this population was the small intestine (Table 2).[6] Again, racial status was not described but, according to the Norwegian Cancer Registry, the Norwegian population is primarily Caucasian with an immigrant population of only 8%. Given the Caucasian majority, this study provides more strong data in support of the small intestine being the most common primary site of

GEP-NETs in Caucasians and further corroborating the trend of anatomic distribution seen in Caucasians in North America and England. This study, however, examines patients in a relatively recent study period and, thus, may exhibit a degree of sample bias given the rapidly advancing diagnostic techniques not seen in earlier decades. This limitation remains true for other studies in this review as well.

Korse et al. 2013[7] provides another epidemiological study of GEP-NETs in a European country utilizing a population-based cancer registry. This study used the Netherlands Cancer Registry and included 6,475 patients with a diagnosis of GEP-NET between 1990-2010. The most common primary site for GEP-NETs was the appendix, followed closely by the small intestine (Table 2).[7] Again, demographics of this patient population were not reported, however, according to a demographic study of the Netherlands in 2013, the Dutch population was 79% Caucasian[68], suggesting that this data may be applied to Caucasians as a whole. Interestingly, this study reports the appendix as being the most common primary site of GEP-NET distribution, however, the small intestine follows closely in proportion, which further corroborates the findings from the United States and other European countries.

Lastly, Hemminki and Li 2001[8] provide an epidemiological study of GI-NETs in Sweden. The authors identified 5,184 NETs of any type between 1958 and 1998 using the Swedish Cancer Registry. The most common primary site for GI-NETs in this population was the small intestine, followed closely by the appendix (Table 2).[8] Of note, this study did not include pNETs, which overestimates the proportion of GI-NETs by primary site described in this study. The study also did not describe the racial status of the patient population but, according to a demographic review of the country[69], the majority of the Swedish population is Caucasian. Thus, this data is most likely generalizable to Caucasians as a whole and, therefore, further supports the findings from prior studies in North America and Europe describing the small intestine as the most common primary site of GEP-NETs in Caucasians.

Anatomic distribution of GEP-NETs among Asians in Asia

Large, population-based studies on the epidemiology of GEP-NETs in Asian populations is lacking, however, Tsai et al. 2013[11] published a small, population-based study on this topic in Taiwan. In this study, the authors identified 2,187 NET cases in Taiwan between 1996 and 2008 using the Taiwan Cancer Registry, which according to the Taiwanese Department of Health, captures 97% of all cancer cases in Taiwan. The most common primary site of GEP-NETs in this study population was the rectum (Table 3).[11] Interestingly, the proportion of SI-NETs in this Asian population was markedly lower than that of Caucasians in North American and European populations. This difference may simply be due to sample bias given that the Taiwanese Cancer Registry has considerably fewer patients than many of the databases used in Caucasian studies. However, this database is a population-based registry that captures a high percentage of all cancer cases in Taiwan and, therefore, may truly reflect the anatomic distribution of NETs in their Asian population. The registry, though, was started much later than many of those in North America and Europe and, therefore, may be more reflective of a study period influenced by more advanced diagnostic modalities. Overall, this study represents the only known population-based study assessing NET epidemiology in the Far East, however, there are multiple, retrospective case series on this topic in other Asian countries that are worth exploring further.

Cho et al. 2012[12] provides a retrospective, cohort study examining the epidemiology of GEP-NETs in South Korea. In this study, the authors collected 4,951 pathology reports with a diagnosis of GEP-NET from university and general hospitals in South Korea between 2000 and 2009. Based on these reports, the most common primary site of GEP-NETs was the rectum (Table 3).[12] Interestingly, this data seems to suggest a low frequency of SI-NETs, in contrast to the findings from predominantly Caucasian populations. However, this study most certainly has a sample bias because patient data was collected from select hospitals in South Korea and, therefore, may not be representative of the South Korean population as a whole. Additionally, the study period is much more recent compared to many of the studies from North America and Europe, which makes the ability to draw comparisons between the two populations more complex when taking into the account the differing methodologies of diagnosing these tumors over time. Another study from South Korea, however, further supports a lower proportion of SI-NETs in an Asian population. Lim et al. 2011[13] conducted a single-center, retrospective cohort study of 470 patients with GEP-NETs in South Korea between 2001 and 2006. In this study, the authors found that the most common primary site of GEP-NETs was the rectum with the small intestine much lower in proportion (Table 3).[13] This study is limited, however, given that the patient cohort is from a single institution and, therefore, makes generalizability to Asians as a whole much more difficult. This limitation is also seen in the majority of the following studies from China.

In China, multiple, retrospective case series examining GEP-NET epidemiology support a difference in the anatomic distribution between Asian and Caucasian populations. First, Fan et al. 2017[14] conducted a multi-center, retrospective study that analyzed data on 2,010 patients with a diagnosis of GEP-NET from various tertiary referral hospitals in China between 2001 and 2010. Overall, the most common primary site for GEP-NETs was the pancreas, followed closely by the rectum (Table 3).[14] Second, Zhang et al. 2017[15] conducted a single-center, retrospective study that collected data on 440 patients with a confirmed diagnosis of NET at a single institution in China between 2011 and 2016. The most common primary site for GEP-NETs at this institution was the stomach (Table 3).[15] Third, Wang et al. 2012[16] conducted a retrospective cohort study analyzing data on 178 patients with a diagnosis of GEP-NET treated at a single institution in China between 1995 and 2012. In this study, the most common primary site of GEP-NET development was the pancreas (Table 3).[16] Fourth, Jiao et al. 2015[17] conducted another retrospective cohort study analyzing data on 154 patients with a diagnosis of GEP-NET treated at a single institution in China between 2001 and 2013. The authors found that the most common primary site of GEP-NETs was the pancreas (Table 3).[17] Lastly, Zeng et al. 2013[18] conducted a retrospective cohort study analyzing data on 122 patients with a diagnosis of GEP-NET treated at a single institution in China between 2000 and 2011. In this study, they found that the most common primary site of GEP-NETs was the pancreas (Table 3).[18] Overall, the results from these five studies in China most likely have sample bias because the data comes from either single-center or multicenter cohorts, as opposed to population-based cancer registries. Additionally, the sample sizes for each of these studies is relatively small compared to those of North America and Europe, which makes drawing comparisons between the two populations much more difficult. Nonetheless, each study further supports the finding that SI-NETs occur at a significantly lower proportion in Asian populations as compared to Caucasian populations, which, collectively, argues that this difference is real, regardless of sample bias.

Finally, Ito et al.[19] conducted a nationwide survey to examine the epidemiology of GI-NETs in Japan. In this study, the authors used a stratified random sampling method to identify medical facilities in which patients with GI-NETs were treated in 2005. Clinical data was then obtained from surveys sent to patients identified as being treated for those tumors. Overall, the total number of patients treated for GI-NETs was estimated to be 4,406 (95% CI 3,321-5,420). The authors then stratified the patients treated for GI-NETs based on primary tumor location using a classification system based on embryonic derivation (foregut, midgut, hindgut). The most common primary site of GI-NETs in this study population was the hindgut, followed by the foregut, and then the midgut (Table 3).[19] The small intestine, which would be classified as predominantly midgut (jejunum, ileum) with a portion in the foregut (duodenum), again was less common proportionally. However, this study has a survey bias, which limits the utility of these results. Overall, though, these results represent findings from yet another Asian country that support the finding that SI-NETs occur at a significantly lower proportion in Asian populations as compared to Caucasian populations.

Anatomic distribution of GEP-NETs among Asians in the United States

Returning to Yao et al. 2008[4], this large, population-based study examining the epidemiology of GEP-NETs in the United States offers another interesting perspective on the anatomic distribution of these tumors. This study, which utilizes the SEER database, presents data on the stratification of primary site of GEP-NETs by race. Here, the authors included 35,618 patients with a known diagnosis of any type of NET recorded in the SEER database between 1973 and 2004. Of these patients, 81% were Caucasian, 12% were African-American, 5% were Asian/Pacific Islander, 1% were American Indian/Alaskan Native, and the remaining 1% were unknown.[4] After stratifying the patients by location of primary tumors, the authors then stratified each anatomic grouping by race and found that primary tumor site varied significantly by race ($p < 0.001$).[4] Specifically, the authors demonstrated that jejunal/ileal NETs occurred at a significantly higher ratio in Caucasian and African-American patients than in Asian/PI and AI/AN patients (Table 4).[4] In contrast, rectal NETs occurred at a significantly higher ratio in Asian/PI, AI/AN, and African-American patients than among Caucasian patients (Table 4).[4] The major strength of this study compared to others presented in this review is its ability to directly compare the anatomic distribution of GEP-NETs by race, as opposed to having to make qualitative comparisons across multiple studies. This study could, therefore, be used to help control for environment when comparing the ratio of SI-NETs in Caucasian versus Asian populations. Overall, this study helps to corroborate the finding that SI-NETs occur at a significantly lower proportion in Asian populations as compared to Caucasian populations and seems to suggest that genetics, rather than environment, may explain this difference.

The role of genetics in SI-NET tumorigenesis

Epidemiological data from North America, Europe, and Asia regarding the anatomic distribution of GEP-NETs suggests that the proportion of SI-NETs in Asian populations is significantly lower than that in Caucasian populations.[2,4–19] Yao et al. 2008[4] demonstrated that this pattern persists even in Asian populations living in the United States, which suggests that genetics may play a predominant role in driving this difference. Genetic studies have been performed on SI-NETs but only in predominantly Caucasian cohorts.[20–22] Overall, these studies detected multiple genetic alterations, including recurrent chromosomal gains and losses, gene mutations, and epigenetic dysregulation.

First, Kulke et al 2008[20] performed a high-resolution, single nucleotide polymorphism (SNP) array analysis of 24 SI-NET samples (14 primary tumors, 10 metastases) from 18 patients. Their results demonstrated several regions of recurrent chromosomal gains (4, 7, 14q) and losses (9p, 16q, 18). Most notably, they found complete loss of heterozygosity of chromosome 18 (chr18 LOH) in 11/18 patients (61%). This finding has been recapitulated in other studies as well. Francis et al. 2013[21] performed whole-exome sequencing on 55 SI-NETs from 50 patients and found that 43/55 samples (78%) exhibited this same chr18 LOH. This study also noted frameshift mutations in the *CDKN1B* gene but only in 5/50 samples (10%). This gene, the only known, recurrent mutation in SI-NETs, encodes for p27, a cell cycle inhibitor. Lastly, Karpathakis et al. 2016[22] performed multiple genetic analyses on 97 SI-NET samples (72 primary tumors, 25 liver metastases). Their copy-number variance (CNV) analysis, again, found chr18 LOH in 30/47 SI-NET primary tumors (64%). Another analysis in this study found extensive epigenetic dysregulation in the majority of samples. Overall, the most common genetic alteration in studies to-date on SI-NETs has been chr18 LOH. This study proposal, therefore, will look to explore the genetics of SI-NETs, specifically, the proportion of SI-NETs with chr18 LOH in Asian versus Caucasian populations to potentially help explain the difference in the ratio of these tumors between the two races.

METHODS

Study Design

A multicenter, cross-sectional study will be conducted to compare the proportion of SI-NETs with chr18 LOH in Asian versus Caucasian populations by performing a fluorescence in-situ hybridization (FISH) analysis of SI-NET tissue from both Asian and Caucasian samples.

Study Population and Sampling

The study population will include tissue samples from adult (≥ 18 years) Asian and Caucasian patients with a histopathological diagnosis of SI-NET from three institutions: Dana-Farber Cancer Institute (DFCI), MD Anderson Cancer Center, and University of California San Francisco (UCSF) Cancer Center. In this study, Asian will be defined as Chinese, Japanese, South Korean, or Taiwanese based on the availability of preexisting epidemiological data on GEP-NETs in these countries. Patients will have previously provided informed written consent for tissue collection and analysis, and these samples will have originated from surgical resection of either the primary tumor or its liver metastasis. Biopsy samples will be excluded due to inadequate amounts of DNA.

According to Francis et al. 2013[21], the rate of chr18 LOH in SI-NETs was 78% (43/55), which, given the presumed Caucasian predominance of this cohort, will be used as the baseline risk in Caucasian SI-NETs when calculating the sample size of this study. Therefore, based on calculations assuming an α-level of 0.05, a β-level of 0.80, and an odds ratio of 0.50, the estimated sample size will be 354 (177 Asian samples, 177

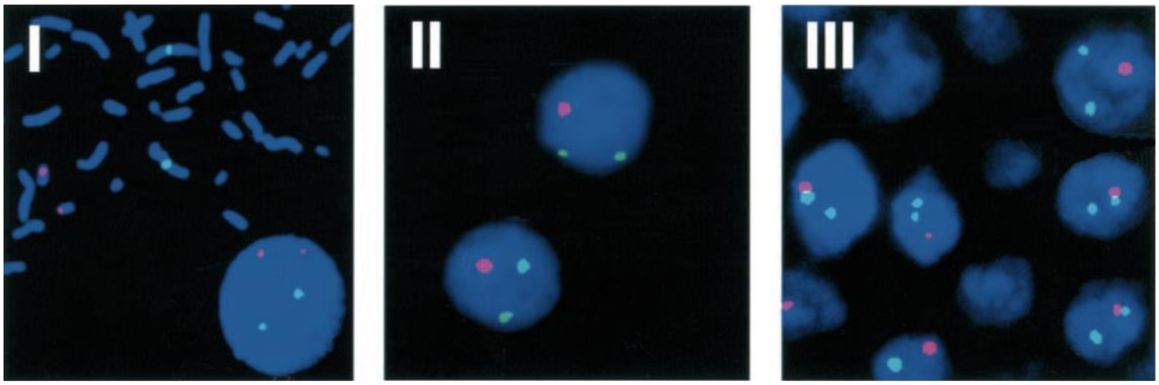
Caucasian samples). According to Rosenthal 1996[70], an odds ratio of 0.50 represents a moderate strength of association and, thus, will be used as the odds ratio this study will be powered to detect.

Study Variables, Outcomes, and Measurements

The single explanatory variable in this study will be race (Asian or Caucasian). Additional independent variables in this study will be age and gender, as well as tumor location (duodenum, jejunum, ileum, or liver), grade (low or high), and histology (well-differentiated or poorly-differentiated). This information will be obtained from deidentified clinical data associated with each tissue sample.

The primary outcome of this study will be detection of chr18 LOH in Asian and Caucasian SI-NET tissue. Chr18 LOH will be measured by FISH analysis of chromosome 18 in SI-NET tissue. The protocol to be used for FISH analysis in this study is based on that from Zhao et al. 2000[71], which utilized this protocol in their analysis of genomic alterations in various neuroendocrine tumors. In short, the centromere probe of chromosome 18 will be indirectly labeled using digoxigenin-11-dUTP.[71] Then, DNA from both the probe and SI-NET tissue will be denatured, and subsequently, combined to allow annealing of complementary DNA sequences.[71] Lastly, a fluorescent antibody derived from sheep will be applied to bind directly to the digoxigenin-11-dUTP-labeled centromere probe.[71] If chromosome 18 is present, then two signals will appear on each parental copy of the chromosome; if absent, then only one signal will appear on each copy (Figure 1). Overall, the presence of only one signal will confirm ch18 LOH.

Figure 1. Representative pictures of FISH analysis (from Zhao et al. 2000[71]). **I**: Signals of centromere probes specific for chromosomes 1 (green) and 18 (red) in metaphase from normal human lymphocytes. **II**: Deletions of chromosome 18 on paraffin-embedded tissue samples. **III**: Deletions of chromosome 18 on interphase touch preparations.



Recruitment

This study will collect deidentified clinical data and tissue samples from Asian and Caucasian patients at DFCI, MD Anderson Cancer Center, and UCSF Cancer Center who have already provided consent for participation in biobanking studies, and who also meet the inclusion criteria for this study.

Specimen and Data Collection

Deidentified tissue samples will be requested from the biobanks at DFCI, MD Anderson Cancer Center, and UCSF Cancer Center. Deidentified clinical data associated with each tissue sample, including patient age, gender, and race, as well as tumor location, grade, and histology, will also be requested in the form of a spreadsheet.

Data Analysis

Descriptive statistics, including the range, mean, and standard deviation of patient age, as well as the frequency and percentage of patient gender and tumor location, grade, and histology, will be calculated to describe the Asian and Caucasian cohorts. Then, the proportion of SI-NETs with chr18 LOH in Asian samples will be compared to that in Caucasian samples using an odds ratio. Next, the standard error will be calculated, which will be used to generate a 95% confidence interval to estimate the precision of this odds ratio. Finally, a chi-squared test will be performed to determine the p-value and overall statistical significance of the results. If $p \leq 0.05$, we will reject the null hypothesis and assume there is a difference in the proportion of SI-NETs with chr18 LOH in Asians as compared to Caucasians. If $p > 0.05$, then we will have failed to reject the null hypothesis and, therefore, have not demonstrated a difference between the proportions. This study will also stratify the proportion of SI-NETs with and without chr18 LOH by gender, tumor location, tumor grade, and tumor histology. Inferential statistics as outlined above will be performed on each of these sub-analyses.

Timeline and Resources

IRB approval for initiation of this multicenter study will take approximately one month. Then, requesting tissue samples and their associated clinical data from the biobanks at DFCI, MD Anderson Cancer Center, and UCSF Cancer Center will take approximately two months. FISH analysis for 354 samples (177 Asian, 177 Caucasian) will take approximately six months. Next, data analysis will take approximately three months and, finally, writing the manuscript will take an additional three months. Study personnel will include primary investigators, statisticians, research technicians, and clinical research coordinators. Laboratory space, reagents, and equipment will be required, as well as external funding from the American Cancer Society for the collection and transfer of deidentified tissue samples and their associated clinical data from multiple institutions.

Institutional Review Board

We intend to submit this study proposal for IRB exemption. This study only involves the use of previously collected and deidentified tissue samples and their associated clinical data and, therefore, meets the criteria as outlined by Category 5 of the Common Rule Expedited Categories section in the Policies and Procedures document provided by the Boston Medical Center and Boston University Medical Campus Human Research Protection Program.

CONCLUSION

Discussion

The results of this study may help to explain why the proportion of SI-NETs are considerably lower in Asian populations as compared to Caucasian populations, which may also provide valuable information regarding the genetic drivers of SI-NET tumorigenesis. However, this study has several limitations. First, the three institutions used for recruitment of tissue samples in this study are tertiary referral hospitals and, therefore, may not accurately reflect the types of SI-NETs seen in the general community with regards to tumor histology and grade. Second, chr18 LOH has been described as the most common chromosomal aberration in SI-NETs[20–22], but other genomic alterations have also been identified. Kulke et al. 2008[20] reported that gains were common on chromosomes 4, 7, and 14q, while losses were common on chromosomes 9, 12, and 16q. Francis et al. 2013[21] demonstrated that the *CDKN1B* gene was the most commonly identified genetic mutation, however, it was only found in 10% of their samples. Karpathakis et al. 2016[22] found considerable epigenetic dysfunction in their analysis of SI-NETs. Therefore, chr18 LOH may be the most common chromosomal aberration in SI-NETs but other previously described genomic alterations may account for some of the difference observed between Asian and Caucasian populations in regards to proportion of SI-NETs. Third, this study only examines the difference in proportion of SI-NETs between Asians and Caucasians, however, Yao et al. 2008[4] reported that the proportion of SI-NETs was also significantly higher in African-Americans as compared to Asians. Therefore, further exploration into the proportion of SI-NETs with chr18 LOH in

African-Americans may help to provide a more complete explanation as to why these differences exist between races, as well as to further elucidate genetic drivers of SI-NET tumorigenesis. Overall, despite these limitations, this study will provide a good starting point for further investigation into the genetic variation of SI-NETs by race.

Summary

The incidence of NETs has been steadily rising over the past several decades. According to multiple studies, the proportion of SI-NETs in Asians appears to be considerably lower than that of Caucasians. This pattern persists even when examining the proportion of SI-NETs in Asians living in the United States, which seems to suggest that genetics, as opposed to environment, is more responsible for this difference. Several studies have examined the genetic profiles of SI-NETs but only in predominantly Caucasian cohorts. These studies have revealed that chr18 LOH is the most commonly identified chromosomal aberration in these tumors. Unfortunately, this data is lacking in Asian cohorts. Therefore, this study looks to explore the genetic profile of SI-NETs in a strictly Asian population. Specifically, this study will examine the proportion of SI-NETs with chr18 LOH in Asians compared to Caucasians. Overall, the results of this study may help to identify possible mechanisms driving the difference in proportion of SI-NETs between Asians and Caucasians, which may help to better characterize the genetic events leading into SI-NET tumorigenesis.

Clinical Significance

The pathophysiology of SI-NET tumorigenesis remains largely unknown. Previous studies in predominantly Caucasian cohorts have demonstrated the presence of chromosomal gains and losses as possibly being implicated in tumorigenesis.[20] Other studies have found recurrent *CDKN1B* mutations but only in a limited portion of these tumors.[21] More recently, epigenetic dysregulation has been shown to be widespread in SI-NETs.[22] The most commonly identified genetic alteration, however, has been chr18 LOH and, therefore, was selected as the focus for this study to help explain the differences in proportion of SI-NETs in Asian and Caucasian populations. In this study, if we fail to reject the null hypothesis and find that the proportion of SI-NETs with chr18 LOH between the two races is similar, then we can assume that this particular chromosomal aberration is not the principle cause of the perceived differences in SI-NET tumorigenesis by race. Conversely, if we reject the null hypothesis and find that the proportion of SI-NETs with chr18 LOH is significantly reduced in Asians compared to Caucasians, then we can assume that chr18 LOH is playing a role in driving these differences.

If the latter outcome is found, other drivers of tumorigenesis must be at play given that the proportion of SI-NETs in Asian populations is non-zero, despite having a significantly reduced proportion of tumors with chr18 LOH. Karpathakis et al. 2016[22] was one of the more recent studies to examine the genetic profile of SI-NETs. In their analysis of a predominantly Caucasian cohort, the authors replicated the results of prior studies in regards to chr18 LOH and *CDKN1B* mutations but also discovered that SI-NETs are highly epigenetically dysregulated. Upon further analysis, they were able to characterize a panel of twenty-one genes that are epigenetically altered in 70-80% of cases.[22] These findings suggest that epigenetic dysregulation may also be playing a role in driving SI-NET tumorigenesis. Therefore, further exploration into the epigenetic profile of these tumors in Asian populations as compared to Caucasian populations may help to further explain the difference in proportion of SI-NETs between the two races and, ultimately, further characterize the genetic drivers of SI-NET tumorigenesis.

APPENDIX

Table 1. Study details for articles regarding the anatomic distribution of GEP-NETs in North America, Europe, and Asia.

Article	Country	Database	Timeline	Tumor	N
Yao et al. 2008	United States	SEER	1973-2004	All NETs	35,618
Sackstein et al. 2018	United States	SEER	1995-2014	All NETs	85,133
Lawrence et al. 2011	United States	ERG, TNCS, SEER	1950-2007	GEP-NETs	31,644
Hallet et al. 2015	Canada	Ontario Cancer Registry	1994-2009	All NETs	5,619
Ellis et al. 2010	England	English Cancer Registry	1971-2006	GI-NETs	10,324
Hauso et al. 2008	Norway	Norwegian Registry of Cancer	1993-2004	All NETs	2,030
Korse et al. 2013	Netherlands	Netherlands Cancer Registry	1990-2010	GEP-NETs	6,475
Hemminki & Li 2001	Sweden	Swedish Cancer Registry	1958-1998	GI-NETs	5,184
Tsai et al. 2013	Taiwan	Taiwan Cancer Registry	1996-2008	All NETs	2,187
Cho et al. 2012	South Korea	Multicenter, retrospective cohort	2000-2009	GEP-NETs	4,951
Lim et al. 2011	South Korea	Single-center, retrospective cohort	2001-2006	GEP-NETs	470
Fan et al. 2017	China	Multicenter, retrospective cohort	2001-2010	GEP-NETs	2,010
Zhang et al. 2017	China	Single-center, retrospective cohort	2011-2016	All NETs	440

Wang et al. 2012	China	Single-center, retrospective cohort	1995-2012	GEP-NETs	178
Jiao et al. 2015	China	Single-center, retrospective cohort	2001-2013	GEP-NETs	154
Zeng et al. 2013	China	Single-center, retrospective cohort	2000-2011	GEP-NETs	122
Ito et al. 2010	Japan	Multicenter, retrospective cohort	2005	GI-NETs	4,406

LIST OF JOURNAL ABBREVIATIONS

Am J Med	The American Journal of Medicine
Ann Clin Biochem	Annals of Clinical Biochemistry
Arq Gastroenterol	Arquivos De Gastroenterologia
Best Pract Res Clin Gastroenterol	Best Practice and Research: Clinical Gastroenterology
BMC Endocr Disord	BMC Endocrine Disorders
BMJ	BMJ: British Medical Journal
Can Med Assoc J	Canadian Medical Association Journal
Cancer Res Treat	Cancer Research and Treatment
Chin J Cancer Res	Chinese Journal of Cancer Research
Clin Cancer Res	Clinical Cancer Research
Curr Opin Oncol	Current Opinion in Oncology
Dis Colon Rectum	Diseases of the Colon and Rectum
Endocr Relat Cancer	Endocrine-Related Cancer
Eur J Endocrinol	European Journal of Endocrinology
J Gastrointest Cancer	Journal of Gastrointestinal Cancer
J Gastrointest Surg	Journal of Gastrointestinal Surgery
JAMA Oncol	JAMA Oncology
N Engl J Med	New England Journal of Medicine
NEN	Neuroendocrinology
Physiol Rev	Physiological Reviews

PLoS One	Public Library of Science
Radiol Clin North Am	Radiologic Clinics of North America
Semin Oncol	Seminars in Oncology
Surg Clin North Am	The Surgical Clinics of North America

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