Journal of Clinical and Translational Pathology **2026** | Epub
DOI: 10.14218/JCTP.2026.00013

Original Article

CXCR2 and SSTR2 Expression in Pancreatic and Small Intestinal Neuroendocrine Tumors: A Cross-Sectional Study

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Received: March 29, 2026 | **Revised:** July 09, 2026 | **Accepted:** September 01, 2026 | **Published online:** September 24, 2026

Abstract

Background and objectives: CXC chemokine receptor 2 (CXCR2) expression has been observed in normal neuroendocrine cells, but its role in neuroendocrine neoplasms is less well established. We aimed to evaluate CXCR2 expression with somatostatin receptor type 2 (SSTR2) expression in pancreatic neuroendocrine tumors (PanNETs) and small intestinal neuroendocrine tumors (SI-NETs).

Methods: This was a cross-sectional study. Pathology archives were searched for PanNETs with ≥2 resected liver metastases and SI-NETs with resected liver metastases, mesenteric tumor deposits (MTDs), and/or peritoneal metastases. Immunohistochemistry for CXCR2 was performed on de-identified tissue microarrays containing PanNETs and SI-NETs. SSTR2 and CXCR2 immunohistochemistry was also performed on tumor blocks from primary and metastatic PanNETs and SI-NETs. Based on H-scores, expression was scored as negative (<50), weak (50–100), moderate (>100–200), or strong (>200). Marker expression was descriptively reported among primary tumors, liver metastases, MTDs, and peritoneal metastases.

Results: Among 12 primary PanNETs and 38 liver metastases, mean CXCR2 H-scores were 269.6 ± 36.7 and 254.6 ± 75.5, respectively, and mean SSTR2 H-scores were 261.5 ± 61.9 and 259.3 ± 70.9, respectively. All 84 SI-NET lesions showed moderate/strong CXCR2 expression, whereas 12 showed negative/weak SSTR2 expression. CXCR2 H-scores were 284.0 ± 26.5 in primary tumors, 272.5 ± 28.7 in MTDs, 269.6 ± 42.8 in liver metastases, and 265.0 ± 51.5 in peritoneal metastases. SSTR2 expression appears to be lower in MTDs than in primary tumors (182.2 ± 76.5 vs 235.9 ± 55.9).

Conclusions: CXCR2 is moderately/strongly expressed in most sampled PanNETs and all sampled SI-NETs. In SI-NETs, moderate/strong CXCR2 expression is less heterogeneous than SSTR2 expression.

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), well-differentiated tumors originating from neuroendocrine cells, can occur anywhere along the gut or pancreas and have shown a significantly increasing incidence over the past few decades.[1] Although most GEP-NETs are diagnosed at an early stage, pancreatic and jejunal/ileal primary tumors are often diagnosed at an advanced stage with distant metastases, especially to the liver. Despite recent advances in diagnostic and therapeutic technologies for GEP-NETs, further improvements in patient management and treatment are still needed.

High expression of somatostatin receptor type 2 (SSTR2) is frequently seen in GEP-NETs, especially in pancreatic (PanNETs) and small intestinal (jejunal/ileal) NETs (SI-NETs).[2] Currently, SSTR2 is the main target for treatment and molecular imaging in somatostatin receptor-expressing NETs.[3,4] Heterogeneous expression of SSTR2 has been reported and can be present within a single tumor or among different metastatic lesions from the same tumor.[5] Peptide receptor radionuclide therapy (PRRT), a treatment that targets SSTR2, is currently used to treat patients with metastatic NETs. However, its treatment effect varies among patients, which has been partially attributed to heterogeneous somatostatin receptor expression in some studies.[6-9]

Keywords: Pancreatic neuroendocrine tumor; Small intestinal neuroendocrine tumor; CXCR2; SSTR2; Immunohistochemistry; Liver metastasis; Mesenteric tumor deposits; Peritoneal metastasis.
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How to cite this article: Fan X, Logan K, Li H, Chen W, Huang J, Morse MA, *et al*. CXCR2 and SSTR2 Expression in Pancreatic and Small Intestinal Neuroendocrine Tumors: A Cross-Sectional Study. *J Clin Transl Pathol*. Published online: Sep 24, 2026. DOI: https://doi.org/10.14218/JCTP.2026.00013.

Similar to SSTR2, CXC chemokine receptor 2 (CXCR2) is also a G protein-coupled receptor that is expressed on the surface of myeloid cells, neuroendocrine cells, and some malignant tumor cells.[10,11] In many cancers, increased CXCR2 expression is associated with poor prognosis; therefore, CXCR2 is thought to have protumor functions.[10,11] In addition, CXCR2 is a potential therapeutic target for some cancers, including hormone-resistant prostate cancer.[12,13] CXCR2 antagonists have been investigated in clinical trials to treat several malignancies.[12] Only one previous study investigated CXCR2 expression in GEP-NETs and reported high-level CXCR2 expression; however, only a few cases were evaluated in that study.[14] In this study, we aimed to investigate CXCR2 as a potential molecular target in patients with metastatic PanNETs and SI-NETs in comparison with SSTR2.

Materials and methods

Patient selection

This cross-sectional descriptive study included archival cases collected between January 1, 2003 and October 1, 2020 and was approved by the Duke Health Institutional Review Board. The Pathology Archives were searched for: 1) PanNET cases with ≥2 resected liver metastases, and 2) SI-NET cases with liver metastases (multiple liver metastases resected if liver metastases were the only metastatic sites), mesenteric tumor deposits (MTDs), and/or peritoneal metastases that were resected. MTDs were defined as irregular mesenteric masses with entrapped nerves and large vessels that are likely caused by tumor venous invasion with extravenous growth.[15,16] All cases meeting the above criteria and with blocks available for immunohistochemistry (IHC) were included in the study. Specifically, the exclusion criteria for all cases were: 1) slides were not available for review, and 2) blocks of metastatic lesions were not available for IHC. Additional exclusion criteria for SI-NETs were: 1) cases in which only one liver metastasis was resected in addition to the primary tumor, and 2) cases in which only an MTD was resected in addition to the primary tumor. Two PanNET cases with multiple liver metastases resected but lacking primary tumor blocks were included to capture the highest number of liver lesions. In addition, one SI-NET case with resected peritoneal disease but lacking primary tumor blocks was included to maximize the peritoneal sample size. A case selection flowchart is included in Figure 1. Medical charts were reviewed to collect clinicopathological information. Specifically, tumor grade and TNM stage were determined based on the primary tumor resection specimen. Tumor grade was re-assigned according to the 5th World Health Organization classification, and TNM stage was retrospectively re-staged according to the American Joint Committee on Cancer 8th edition criteria.

SSTR2 and CXCR2 IHC

Immunohistochemical staining for CXCR2 was first performed on de-identified tissue microarrays (TMAs) containing 68 PanNETs and 15 SI-NETs. The TMAs were constructed using primary tumor resection specimens from patients with PanNETs or SI-NETs. TMA cases were excluded if hematoxylin and eosin (H&E)-stained slides were unavailable for review, tumors were enucleated, blocks were not available, or insufficient tumor tissue was available for TMA construction. To ensure representation of all morphologic variants within the tumor, at least 3 tissue cores were sampled. IHC for both CXCR2 and SSTR2 was also performed on formalin-fixed, paraffin-embedded tumor blocks from pathologically confirmed primary and metastatic tumors from 32 patients, including 14 with PanNETs and 18 with SI-NETs. Those cases did not overlap with the TMA cases.

Five-µm unstained sections cut from TMA blocks and formalin-fixed, paraffin-embedded tumor blocks were used for IHC labeling for CXCR2 (6C6, BD Biosciences, Franklin Lakes, NJ, USA, Cat No 555932) and SSTR2 (EP149, BioSB, Santa Barbara, CA, USA, Cat No BSB-3748-7). The CXCR2 antibody was used at a 1:100 dilution with Discovery Antibody Diluent (Roche Diagnostics, Indianapolis, IN, USA). CXCR2 IHC was performed using the Discovery Ultra automated staining platform (Roche Diagnostics). The tissue sections were pretreated for epitope retrieval with Roche Cell Conditioning Solution CC1 (Roche Diagnostics) for 56 min and then incubated with mouse monoclonal anti-CXCR2 antibody for 60 min at 36 °C. Mouse immunoglobulin G, substituted for the primary antibody, was used as the negative control. After binding of the primary antibody, anti-mouse HQ (Roche Diagnostics) was applied and incubated for 12 min, followed by a 12-min incubation with anti-HQ horseradish peroxidase (Roche Diagnostics) for antigen detection. The IHC reaction was visualized with 3,3′-diaminobenzidine chromogen and counterstained with hematoxylin. The SSTR2 antibody was prediluted, and antigen retrieval was performed with Bond ER2 antigen retrieval buffer (BioSB) for 20 min. SSTR2 IHC was performed according to the manufacturer's instructions using the Leica Bond III platform (Leica Biosystems, Nussloch, Germany).

IHC analysis

The H-score was calculated for all cases based on the proportion and intensity of positive cells (H-score = 1 × percentage of cells with weak staining + 2 × percentage of cells with moderate staining + 3 × percentage of cells with strong staining). Examples of strong, moderate, and weak staining are shown in Figure 2. Both cytoplasmic and membranous staining were considered positive, although membranous staining was predominant in the vast majority of PanNETs and SI-NETs. Based on H-scores, SSTR2 and CXCR2 expression was further categorized as negative (H-score < 50), weak (H-score 50–100), moderate (H-score > 100–200), or strong (H-score > 200). SSTR2 and CXCR2 IHC staining was independently assessed by CS and by a consensus evaluation of XF and HL. CS independently reviewed and scored all cases, while XF and HL jointly reviewed the same cases and reached a consensus score, which was treated as a single observer for the analysis. The final H-scores were determined by averaging the score from CS and the consensus score from XF and HL.

Statistical analysis

Clinicopathologic characteristics were compared using a two-sample Student's t-test for age and Fisher's exact test for categorical variables. $P < 0.05$ was considered statistically significant. Marker expression was descriptively reported for the primary tumor and metastatic sites (liver metastasis, MTD, or peritoneal metastasis). No further adjustment for potential

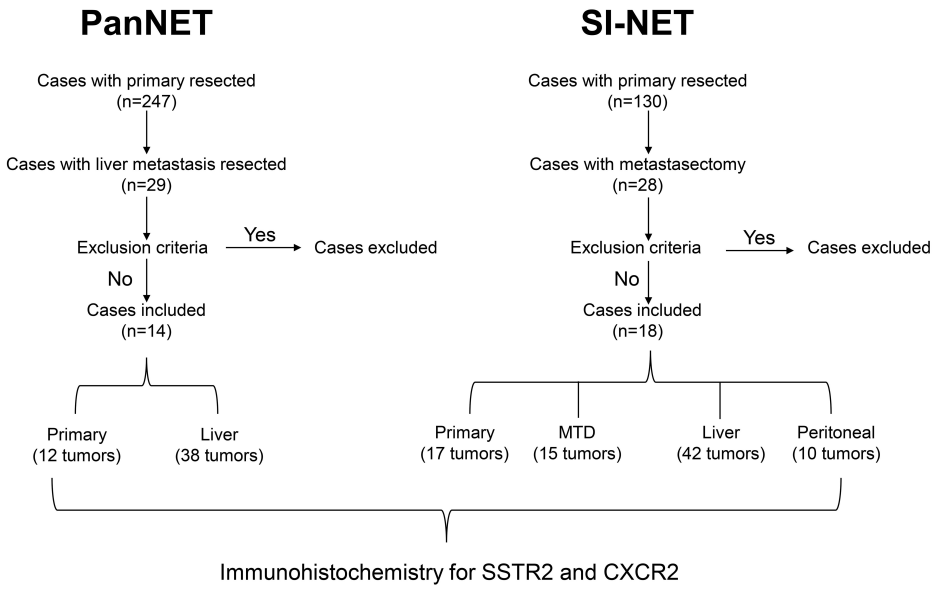

Fig. 1. Study cohort selection and analysis flowchart. The numbers of cases available for evaluation of CXCR2 and SSTR2 expression at each anatomic site are shown. CXCR2, CXC chemokine receptor 2; MTD, mesenteric tumor deposit; PanNET, pancreatic neuroendocrine tumor; SI-NET, small intestinal neuroendocrine tumor; SSTR2, somatostatin receptor type 2.

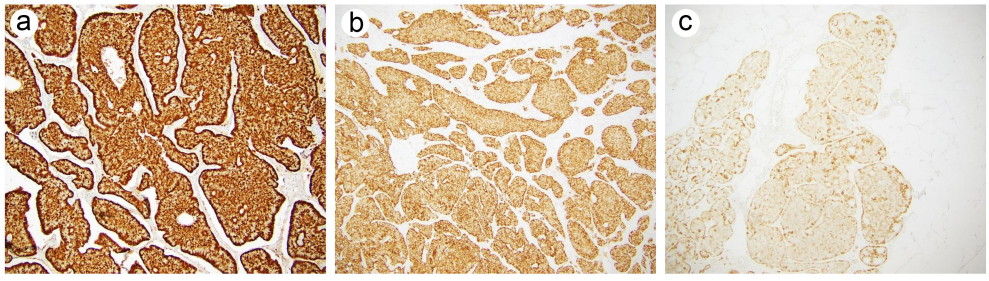

Fig. 2. Examples of CXCR2 expression (original magnification ×100). (a) Strong expression. (b) Moderate expression. (c) Weak expression. CXCR2, CXC chemokine receptor 2.

confounders was performed. To evaluate the reproducibility of H-score assessment, interobserver agreement between pathologists CS and XF/HL was analyzed across all cases using a two-way mixed-effects, absolute-agreement, single-measure intraclass correlation coefficient model (ICC).

Although clinical follow-up data were collected to provide the clinicopathologic characteristics of the cohort, they were not analyzed in relation to CXCR2 and SSTR2 expression in this study because of the cross-sectional study design.

Results

Clinicopathologic characteristics

Patients' clinicopathologic characteristics are listed in Table 1 and Supplementary Table. 1. The cohort included 14 PanNET and 18 SI-NET cases. Patients with SI-NETs were significantly older than those with PanNETs (mean age, 61 vs. 54 years; $P = 0.019$). There was no significant difference in sex distribution or tumor grade between the two groups. SI-NETs were more frequently associated with advanced disease, including higher T, N, and M categories, compared with PanNETs. The use of somatostatin analog therapy and final follow-up status did not differ significantly between the two groups. One patient with an SI-NET had no follow-up data.

Frequent CXCR2 expression in primary PanNETs and SI-NETs

To explore the frequency of CXCR2 expression in PanNETs and SI-NETs, we first performed IHC for CXCR2 using de-identified TMAs. CXCR2 expression was consistently moderately to strongly positive in 15 primary SI-NETs (100%) and 68 PanNETs (100%) on TMAs. Sixty-six of 68 (97.1%) PanNETs and 15 of 15 (100%) SI-NETs demonstrated a predominantly membranous pattern of expression. Only two PanNETs and no SI-NETs showed

Table 1. Clinicopathologic characteristics of 32 patients with PanNETs or SI-NETs

		PanNET		SI-NET		Total		*P*-value
		Mean or n	Range or %	Mean or n	Range or %	Mean or n	Range or %	
Age, years (mean, range)		54	(43–80)	61	(51–74)	58	(43–80)	0.019*
Sex	Female	7	(50.0)	12	(66.7)	19	(59.4)	0.473
	Male	7	(50.0)	6	(33.3)	13	(40.6)	
Tumor grade	1	6	(42.9)	10	(62.5)	16	(53.3)	0.363
	2	7	(50.0)	6	(37.5)	13	(43.3)	
	3	1	(7.1)	0	(0.0)	1	(3.3)	
T	2	6	(42.9)	1	(5.6)	7	(21.9)	0.028*
	3	8	(57.1)	13	(72.2)	21	(65.6)	
	4	0	(0.0)	3	(16.7)	3	(9.4)	
	X	0	(0.0)	1	(5.6)	1	(3.1)	
N	0	4	(28.6)	1	(5.6)	5	(15.6)	0.032*
	1	5	(35.7)	11	(61.1)	16	(50.0)	
	2	0	(0.0)	4	(22.2)	4	(12.5)	
	X	5	(35.7)	2	(11.1)	7	(21.9)	
M	0	6	(42.9)	1	(5.6)	7	(21.9)	0.027*
	1	8	(57.1)	17	(94.4)	25	(78.1)	
SSA therapy	no	13	(92.9)	16	(88.9)	29	(90.6)	1.00
	yes	1	(7.1)	2	(11.1)	3	(9.4)	
Status (last follow-up)**	Alive with disease	9	(64.3)	8	(47.1)	17	(54.8)	0.820
	Alive without disease	2	(14.3)	2	(11.8)	4	(12.9)	
	Died of disease	3	(21.4)	6	(35.3)	9	(29.0)	
	Died of other causes	0	(0.0)	1	(5.9)	1	(3.2)	

*$P < 0.05$. Tumor grade was unavailable for two patients with SI-NETs; percentages exclude missing data. **One patient with an SI-NET did not have follow-up information available and was not included in the status row. M, distant metastasis; N, regional lymph node; PanNET, pancreatic neuroendocrine tumor; SI-NET, small intestinal neuroendocrine tumor; SSA, somatostatin analog; T, primary tumor; X, cannot be assessed.

predominant cytoplasmic expression.

Comparison of CXCR2 and SSTR2 expression in primary and metastatic PanNETs

Fourteen PanNET cases with two or more resected liver metastases were identified. Overall, 12 primary PanNETs and 38 liver metastases were subjected to SSTR2 and CXCR2 IHC. All primary tumors had moderate to strong CXCR2 expression (100%), and all but one primary tumor had moderate to strong SSTR2 expression (91.7%). Expression of both CXCR2 and SSTR2 was membranous in all primary tumors. Thirty-three of 38 liver metastases (86.8%) had moderate to strong CXCR2 and SSTR2 expression; 2 had moderate to strong SSTR2 expression but negative to weak CXCR2 expression; 2 had moderate to strong CXCR2 expression but negative to weak SSTR2 expression; and 1 had negative to weak expression of both CXCR2 and SSTR2. One liver metastasis with moderate to strong CXCR2 expression showed predominantly cytoplasmic CXCR2 expression. For H-scores, CXCR2 expression was 269.6 ± 36.7 in primary tumors and 254.6 ± 75.5 in liver metastases, while SSTR2 expression was 261.5 ± 61.9 in primary tumors and 259.3 ± 70.9 in liver metastases (Fig. 3).

Comparison of CXCR2 and SSTR2 expression in primary tumors, MTDs, and metastatic SI-NETs

Eighty-four specimens from 18 patients with SI-NETs were subjected to SSTR2 and CXCR2 labeling, including 17 primary tumors, 15 MTDs, 42 liver metastases, and 10 peritoneal metastases. Overall, moderate to strong CXCR2 expression was observed in all lesions (100%), whereas moderate to strong SSTR2 expression was observed in 72 of 84 lesions (85.7%; Fig. 4a). Specifically, among the 42 liver metastases, 7 (16.7%) showed negative to weak SSTR2 expression, whereas all lesions had moderate to strong CXCR2 expression. One of 17 (5.9%) primary tumors, 2 of 15 (13.3%) MTDs, and 2 of 10 (20%) peritoneal metastases also showed negative to weak SSTR2 expression. CXCR2 expression was predominantly membranous. Four of 12 lesions with negative or weak SSTR2 expression demonstrated predominantly cytoplasmic labeling, whereas all lesions with moderate to strong SSTR2 expression had

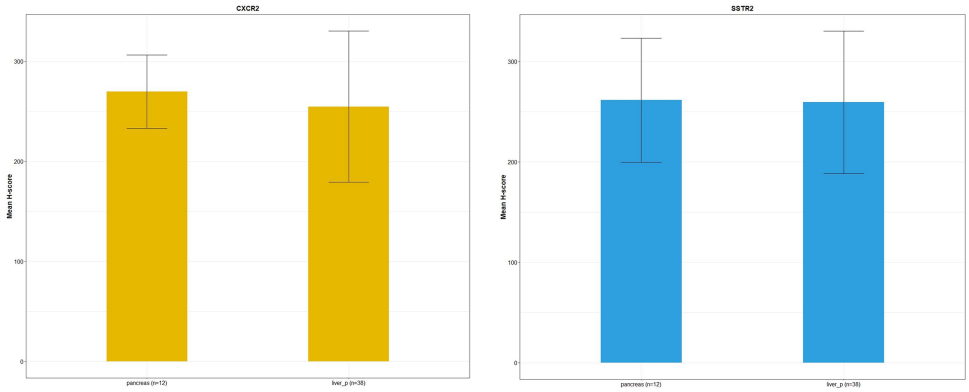

Fig. 3. CXCR2 and SSTR2 expression in primary pancreatic neuroendocrine tumors and their liver metastases. Error bars in (a) and (b) represent ±1 SD. CXCR2, CXC chemokine receptor 2; SD, standard deviation; SSTR2, somatostatin receptor type 2.

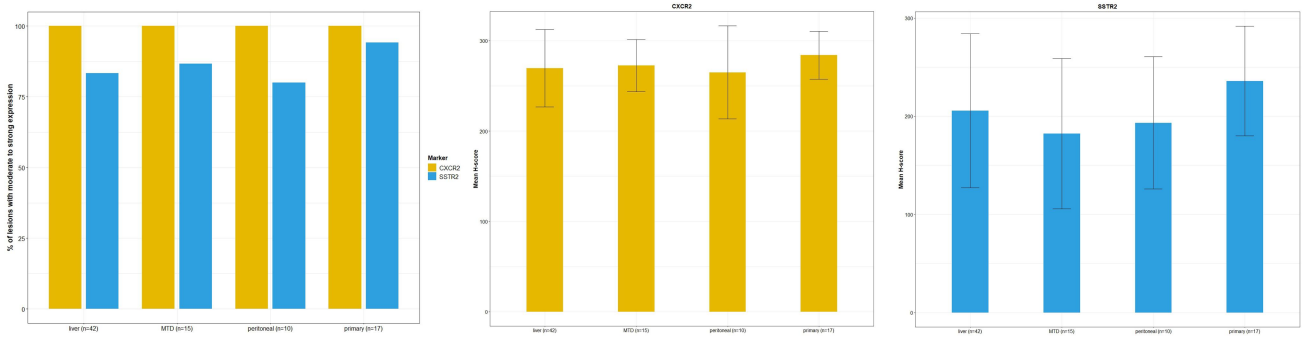

Fig. 4. CXCR2 and SSTR2 expression in primary small intestinal neuroendocrine tumors and their MTDs, liver metastases, and peritoneal metastases. (a) Frequency of moderate to strong expression in all lesions, primary tumors, MTDs, liver metastases, and peritoneal metastases. (b) CXCR2 H-scores in primary tumors, MTDs, liver metastases, and peritoneal metastases. (c) SSTR2 H-scores in primary tumors, MTDs, liver metastases, and peritoneal metastases. Error bars in (b) and (c) represent ±1 SD. CXCR2, CXC chemokine receptor 2; MTD, mesenteric tumor deposit; SD, standard deviation; SSTR2, somatostatin receptor type 2.

predominantly membranous labeling.

H-scores for both CXCR2 and SSTR2 IHC were summarized descriptively across primary tumors, MTDs, liver metastases, and peritoneal metastases. CXCR2 H-scores were 284.0 ± 26.5 in primary tumors, 272.5 ± 28.7 in MTDs, 269.6 ± 42.8 in liver metastases, and 265.0 ± 51.5 in peritoneal metastases (Fig. 4b). SSTR2 H-scores were 235.9 ± 55.9 in primary tumors, 182.2 ± 76.5 in MTDs, 205.5 ± 78.5 in liver metastases, and 193.3 ± 67.3 in peritoneal metastases (Fig. 4c). Overall, CXCR2 H-scores appears to be consistent across the lesions, while SSTR2 H-scores were numerically lower in MTDs than in primary tumors.

Figures 5 and 6 provide two examples showing heterogeneous or decreased SSTR2 expression but consistent CXCR2 expression in MTDs, liver metastases, and peritoneal metastases. As expected, inflammatory cells adjacent to the tumors expressed both SSTR2 and CXCR2. Figures 5g and 5h show strong SSTR2 labeling in inflammatory cells but decreased SSTR2 expression in tumor cells.

Inter-observer agreement assessment

To evaluate the reproducibility of the H-score assessment, inter-observer agreement between the evaluating pathologists (CS and XF/HL) was analyzed across all cases. Using an ICC model, the inter-observer agreement was determined to be excellent (CXCR2: ICC = 0.939; 95% confidence interval: 0.895-0.965; $P < 0.001$, and SSTR2: ICC = 0.930; 95% confidence interval: 0.880-0.960; $P < 0.001$). This demonstrates highly consistent and reproducible continuous H-score quantification between the reviewers.

Discussion

CXCR2, a seven-transmembrane Gαi protein–coupled receptor, plays important roles in inflammation, immunity, and cancer.[10,11] Depending on the cancer type, CXCR2 can be protumoral or anti-tumoral but is protumoral in most malignancies.[11] Despite SI-NETs and PanNETs being mostly indolent, they highly express CXCR2, suggesting that the role of CXCR2 in SI-NETs and

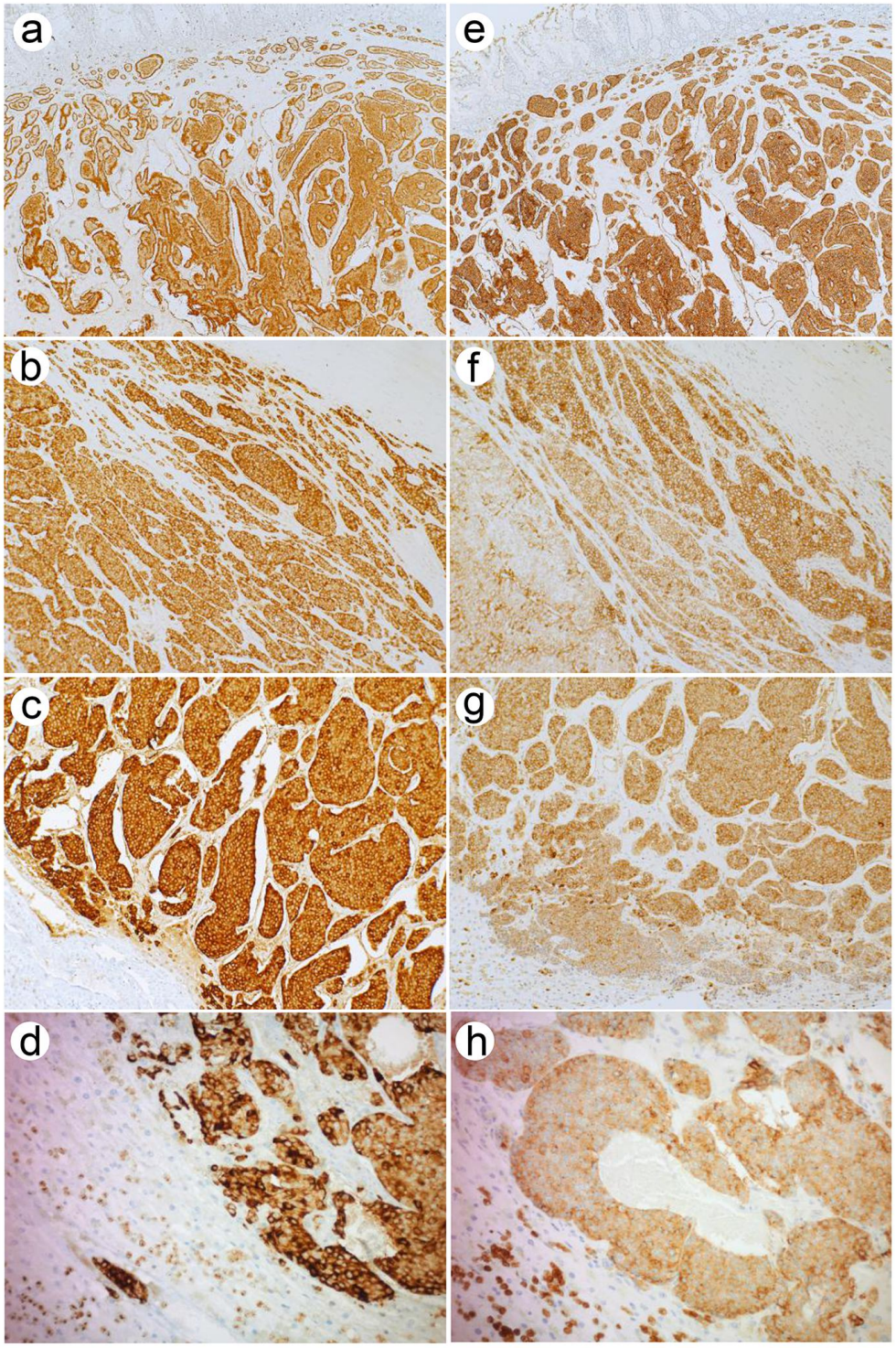

Fig. 5. An example of a small intestinal neuroendocrine tumor. (a–d) Homogeneous strong CXCR2 expression in the primary tumor (a), mesenteric tumor deposit (b), liver lesion #1 (c), and liver lesion #2 (d). (e) Diffuse strong SSTR2 expression in the primary tumor. (f) Heterogeneous weaker SSTR2 expression in the mesenteric tumor deposit. (g, h) Weaker SSTR2 expression in liver lesion #1 (g) and lesion #2 (h). (a, b) Original magnification ×40. (c–h) Original magnification ×100. Note: Background inflammatory cells show strong SSTR2 expression, whereas tumor cells show weak, predominantly cytoplasmic expression (g–h). CXCR2, CXC chemokine receptor 2; SSTR2, somatostatin receptor type 2.

 DOI: 10.14218/JCTP.2026.00013 | 2026

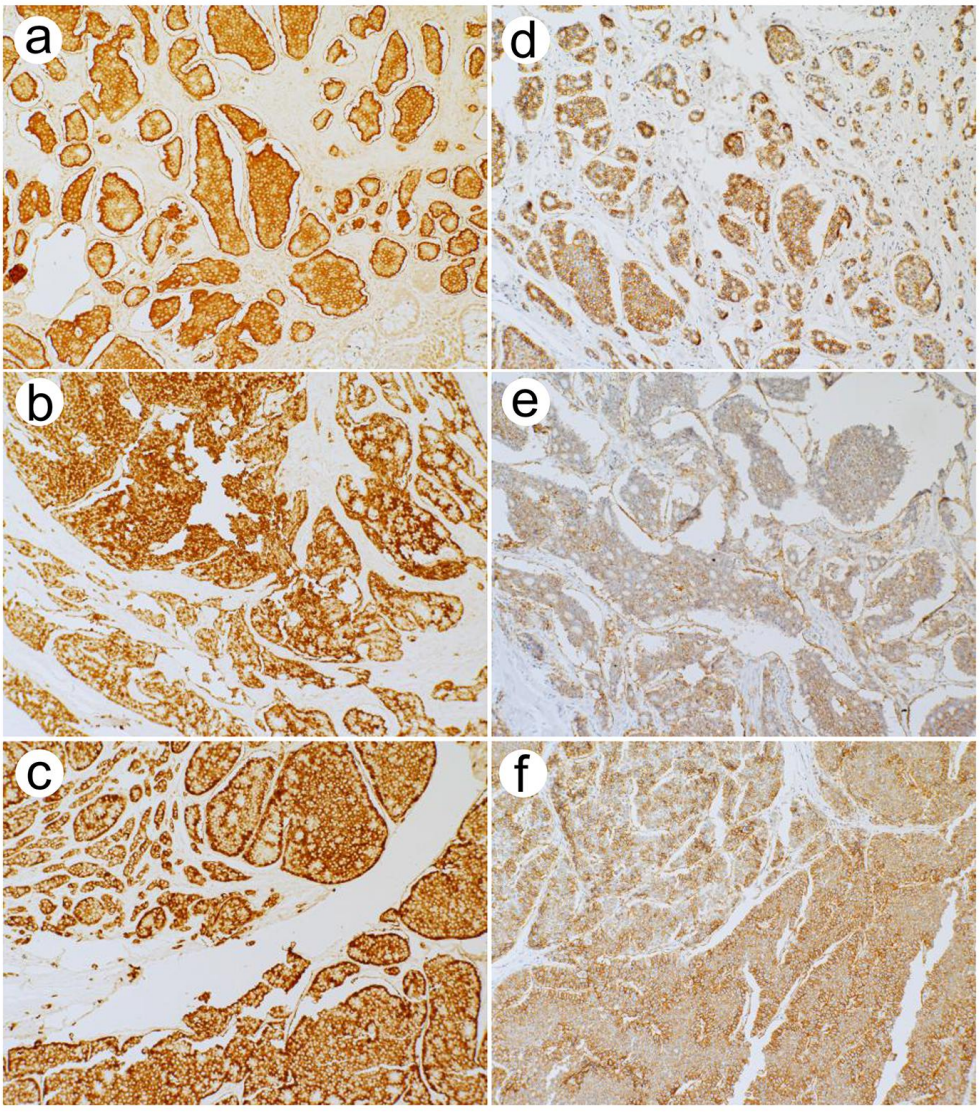

Fig. 6. Another example of a small intestinal neuroendocrine tumor (original magnification ×100). (a–c) Homogeneous strong CXCR2 expression in the primary tumor (a), mesenteric tumor deposit (b), and peritoneal metastasis (c). (d) Primary tumor section showing heterogeneous SSTR2 expression. (e) Weak SSTR2 expression in mesenteric tumor deposits. (f) Heterogeneous SSTR2 expression in the peritoneal metastasis. CXCR2, CXC chemokine receptor 2; SSTR2, somatostatin receptor type 2

PanNETs differs from its protumoral function in other cancers. The paradoxical behavior of CXCR2 may stem from the NET-specific microenvironment,[17-19] which likely alters receptor activation, internalization, or downstream signaling cascades.

SSTR2 is the main molecular and therapeutic target for GEP-NETs. Somatostatin analogs have been used as antiproliferative agents in patients with well-differentiated NETs.[3] Somatostatin receptor positron emission tomography has been widely used to detect metastatic disease in patients with NETs.[4] PRRT targeting SSTR2 is effective in controlling advanced, metastatic, inoperable, or progressive NETs; clinical trials have shown its cytoreductive potential and ability to prolong progression-free survival.[20] However, treatment response to PRRT is inconsistent, and heterogeneous SSTR2 expression might be one of the primary mechanisms.[9] Heterogeneity of SSTR2 expression in primary SI-NETs and their liver metastases has been reported previously,[6-9] and was also confirmed by this study. In contrast, our current study demonstrated that CXCR2 expression was rather homogeneous in the primary tumor, MTDs/mesenteric masses, liver metastases, and peritoneal metastases. CXCR2 may deserve further exploration as a potential target molecule in digestive NETs, especially SI-NETs, given that CXCR2 antagonists are commercially available and clinical trials investigating anti-CXCR2 treatment for several malignancies are underway.[12,21] For example, the CXCR2 antagonist AZD5069 has been evaluated as a potential anticancer agent in combination with an anti-PD-L1 antibody in metastatic carcinomas,

including metastatic pancreatic ductal adenocarcinoma. In addition, several dual CXCR1/CXCR2 antagonists have also been investigated as anticancer agents in clinical trials.[13] It has been hypothesized that these agents achieve their efficacy primarily by dismantling the immunosuppressive shield established within the tumor microenvironment.[13] Most NETs are characterized by an immunosuppressive tumor microenvironment,[17-19] which could be a potential target of these agents.

In addition, PRRT might not be an effective treatment for reducing the size of SI-NET-associated mesenteric masses.[22] Mesenteric masses are a common finding in patients with SI-NETs. Mesenteric masses are frequently associated with mesenteric fibrosis, leading to intestinal ischemia due to obstruction of mesenteric vessels and small bowel obstruction due to kinking of the adjacent small bowel.[23,24] However, in many patients, mesenteric masses are located close to the mesenteric root and may not be amenable to resection. Strosberg *et al*. reported a risk of bowel obstruction in patients with mesenteric disease receiving PRRT.[25] In this study, we observed lower SSTR2 expression in MTDs compared with the primary tumors. Conversely, MTDs retained CXCR2 expression similar to that of the primary tumors. In addition, the signaling pathways mediated by CXCR2 may be involved in fibrosis,[12,26,27] providing a potential rationale for targeting CXCR2 to address fibrosis associated with NETs.

The effect of PRRT on peritoneal metastases has not been reported. However, Strosberg *et al.* also reported a risk of bowel obstruction in patients with peritoneal disease receiving PRRT.[25] Peritoneal carcinomatosis is a serious metastatic complication associated with substantial morbidity and increased mortality. SSTR2 expression was numerically lower in peritoneal metastases than in primary tumors. CXCR2 expression was similar between peritoneal metastases and primary tumors.

Limitations

There are several limitations to this study. First, this is a descriptive cross-sectional study performed at the lesion level. No statistical analysis accounting for potential within-patient clustering was performed because specimens from different anatomic sites were not consistently available from the same patients. Therefore, the findings should be interpreted as descriptive comparisons of receptor expression across lesions rather than patient-level comparisons. Future studies with more comprehensive paired sampling are warranted to validate these findings. In addition, some subgroups, especially the peritoneal tumor group, had limited sample sizes for the immunohistochemical studies. Furthermore, the study was based solely on immunohistochemical expression without functional validation or clinical correlation. Therefore, the findings of this study are hypothesis-generating. Establishing CXCR2 as a therapeutic target in PanNETs and SI-NETs requires further prospective investigation.

Conclusions

While CXCR2 expression is similar to SSTR2 expression in PanNETs, moderate to strong CXCR2 expression is more consistently retained than SSTR2 expression across sampled SI-NET lesions. It might be worthwhile to further explore CXCR2 as a molecular target in digestive NETs, especially in SI-NETs with metastatic disease.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/JCTP.2026.00013.

Acknowledgments

We thank the Duke University BioRepository and Precision Pathology Center (supported by P30CA014236) and the National Cancer Institute's Cooperative Human Tissue Network (supported at Duke University by UM1CA239755) for performing immunohistochemistry.

Funding

None.

Conflict of interest

JH is a consultant for or owns shares in the following companies: Artera, Kingmed Diagnostics, MoreHealth, OptraScan, York Biotechnology, and Sisu Pharma. JH is an Advisory Board Member of the *Journal of Clinical and Translational Pathology.* Other authors have no conflicts of interest.

Author contributions

Data collection (XF, KL, HL), data analysis (XF, WC, CS), concept development (JH, MAM, CS), study design (JH, MAM, CS), writing of the manuscript (CS), and editing of the manuscript (XF, KL, HL, WC, JH, MAM, CS). All authors have approved the final version and publication of the manuscript.

Ethical statement

This research used archived tissues, with no samples collected and no procedures or interventions performed solely for research purposes. The research involved no more than minimal risk. Informed consent was waived. This study was approved by the Duke Health Institutional Review Board (approval nos. Pro00107127 and Pro00106109). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2024).

Data sharing statement

The de-identified data used to support the findings of this study are available from Dr. Chanjuan Shi (Chanjuan.Shi@Duke.Edu) upon request and institutional approval.

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