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UTILITY OF SOMATOSTATIN RECEPTORS IN GASTROINTESTINAL TRACT AND PANCREAS NEUROENDOCRINE TUMORS

GASTROİNTESTİNAL VE PANKREATİK NÖROENDOKRİN TÜMÖRLERDE SOMATOSTATİN RESEPTÖRLERİNİN ÖNEMİ

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The study protocol conforms the ethical guidelines of the 1975 Declaration of Helsinki and the study was approved by the local Ethics Committee and Institutional Review Board as meeting number 57, in 2016.

Abstract

Aim: Neuroendocrine tumors (NETs) are heterogenous group of tumors. Most of gastroenteropancreatic NETs (GEPNETs) are well-differentiated low-grade tumors but a subset of them displays aggressive behavior. Somatostatin receptors (SSTR) play an im-portant role in the pathogenesis of GEPNETs, and they display targets for therapy. We aimed to evaluate SSTR2, SSTR3, SSTR5 by immunohistochemistry in GEPNETs and correlate with clinicopathological findings.

Materials and Methods: Totally 61 cases were enrolled into this study and evaluated for SSTR2, 3, and 5 by im-munohistochemically.

Results: Mostly the patients had low-grade neoplasms and 23% of them had metastatic disease. Total-ly, 73%, 47%, and 26% positivity were found by SSTR2, SSTR3, and SSTR5, respectively. The histopathological grade was increased relative to decreasing expression levels of SSTRs. Among metastatic neoplasms, SSTR2 positivity was found to be greater than a non-metastatic disease.

Conclusion: In conclusion, SSTRs are useful to predict the clinical outcomes as well as target of therapy.

Keywords: Neuroendocrine, somatostatin, gastrointestinal, pancreas.

Öz

Amaç: Nöroendokrin tümörler heterojen bir grup tümördür. Çoğu gastrointestinal ve pankreatik nöroendokrin tümör (GEPNET) düşük dereceli olmasına rağmen agresif davranış gösterir. Somatostatin reseptörleri GEPNET'de patogenezde yer alan ve tedavide hedef teşkil eden moleküllerdir. Çalışmamızda GEPNET vakalarında somatostatin reseptörü (SSTR) 2, 3 ve 5'in tümörlerin klinikopatolojik verileri eşliğinde korelasyonunu araştırmak amaçlanmıştır.

Materyal ve Metot: Çalışmada 61 vakanın patolojik spesmenlerine somatostatin reseptörleri immüno-histokimyasal olarak uygulanmıştır.

Bulgular: Olguların çoğu düşük dereceli olup, %23 olguda metastaz mevcuttur. SSTR2 %73 oranında pozitif boyanırken, SSTR3'te %47, SSTR5'te % 26 pozitif boyanma saptanmıştır. Olguların histolojik dereceleri arttıkça boyanma yüzdelerinde düşüş mevcuttur. Metastatik tümörlerde ise SSTR2'de pozitif boyanma oranı, metastatik olmayan olgulara göre daha düşüktür.

Sonuç: Sonuçta somatostatin reseptörleri, olguların klinik gidişini tahmin etmede faydalı olabileceği gibi hedef tedavide de yer almaktadır.

Anahtar Kelimeler: Nöroendokrin, somatostatin, gastrointestinal, pankreas.

INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogenous group of tumors derived from enterochromaffin cells of the neuroendocrine system that gastrointestinal (GI) tract and pancreas (GEP) represent about 65% of all NETs[1,2]. There are three main groups; Grade 1, Grade 2, and Grade 3 according to mitotic count (<2, 2-20, >20) and Ki 67 proliferation index (≤2%, 3-20%, >20%), respectively[3].

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Most of the GEPNETs are well-differentiated low-grade tumors but a subset of them displays aggressive behavior. Also, the Grade 3 NETs that have a 20-50% Ki 67 proliferation index displays a better prognosis[4].

Localization has an importance on prognosis and pathogenesis. For instance, gastric well-differentiated NETs are commonly seen especially in the background of atrophic mucosa and small bowel NETs (SBNETs) tend to be multifocal which has no influence on behavior but they are slow-growing lesions, the diagnosis is usually delayed until advanced stages[5,6]. The majority of pancreatic NETs are considered indolent relative to other gastrointestinal malignancies but, 10% of them exhibit aggressive behavior[7].

Tumor size is another prognostic factor. Regardless of the depth of invasion, localization, perineural invasion, serosal involvement appendiceal NETs smaller than one cm is always behave as benign fashion[8].

Metastatic well-defined NETs exhibit a five year survival rate of 50-70%. The prognostic indicators of metastatic NETs include tumor grade, stage, and site[9].

Somatostatin receptors (SSTR) are G-protein coupled receptors and there have been five subtypes[10-12]. Among them, SSTR2 is most widely used in GEPNETs because of high expression rates such as 90% of GI and 80% of pancreatic NETs.

Recently NETs have targeted therapy by somatostatin analogs (SSAs) which show an antitumor effect through growth arresting and pro-apoptotic effect[13,14].

Hence, we aimed to evaluate SSTR2, SSTR3, SSTR5 by immunohistochemistry in GEPNETs and correlate with clinicopathological findings with PET-CT imaging.

MATERIAL-METHODS

The study protocol conforms the ethical guidelines of the 1975 Declaration of Helsinki and the study was approved by the local Ethics Committee and Institutional Review Board as meeting number 57, in 2016.

Case selection and definition

This retrospective study included 86 cases of GEPNETs which were diagnosed at a single center from 2011 to 2017. Inclusion criteria were as follows; having a diagnosis of NETs, localization at GI tract or pancreas, adequate tumor tissue for immunohistochemistry, and clinical follow-up. Exclusion criteria were as follows; inadequate tumor tissue, metastatic liver NETs without primary origins, inadequate clinical data.

Technical issues

Excision or biopsy materials were sampled, paraffin-embedded tissues were sectioned four µm thickness and stained with hematoxylin & eosin, routinely. The slides were examined for tumor grading, tumor size, depth of invasion, excision margins, mitotic count, necrosis, anaplasia, lymphovascular invasion, perineural invasion.

GEPNETs were classified according to WHO classification as Grade 1, Grade 2 and Grade 3 according to mitotic count and Ki 67 proliferation index.

Per slide of each sample was manually stained with SSTR2 (1:100, Abcam), SSTR3 (1:2500, Abcam) and SSTR5 (1:2500, Abcam) and automatically stained with Ki 67 by immunohistochemically.

Ki 67 was scored as nuclear staining percentage of tumor cells.

SSTR2 was scored in a semiquantitative method according to a scoring system explained before[15]. SSTR3 and SSTR5 were scored as positive or negative staining by using the cut off value for staining of 10% tumor cells.

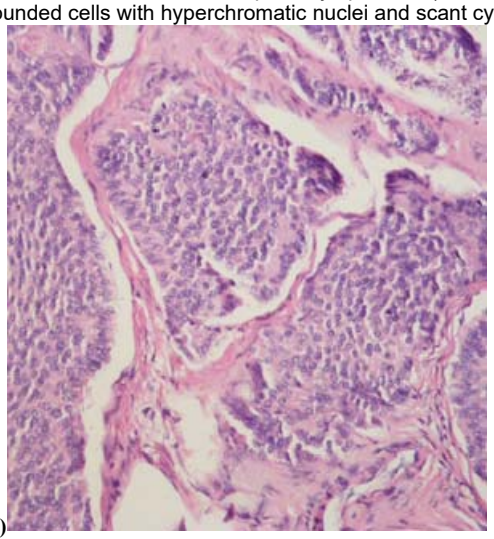
RESULTS

A total of 86 patients with GEPNETs were enrolled in the study. Eighteen patients' pathological materials were inadequate for immunohistochemical examination.

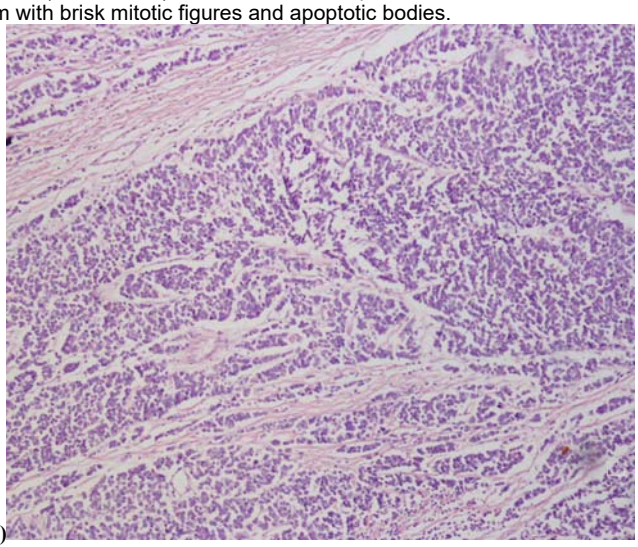
The female/male ratio was 0,9 and the mean age was 47,9 years old (min:8-max:86). Localization of tumors were as follows; stomach (n:33-36,5%), small bowel (n:8-9,4%), large bowel (n:11-12,9%), appendix (n:14-16,5%), pancreas (n:18-21,2%) and gallbladder (n:2-2,4%).

Most tumors were well-differentiated Grade 1 NETs (56,9%), followed by Grade 3 (33,7%). (Figure 1 a, b) Former NETs were commonly at stomach (34%), appendix (22,4%) and pancreas (22,4%). Grade 3 NETs were particularly seen at stomach (44,8%), large bowel (27,5%) and pancreas (13,7%).

Figure 1. a) Grade I NET (H&E, X200) the tumor is composed of monomorphic small rounded cells with salt and pepper chromatin and scant eosinophilic cytoplasm. b) Grade III NET (H&E, X100) the tumor is com-posed of monotonous small rounded cells with hyperchromatic nuclei and scant cytoplasm with brisk mitotic figures and apoptotic bodies.



A)



B)

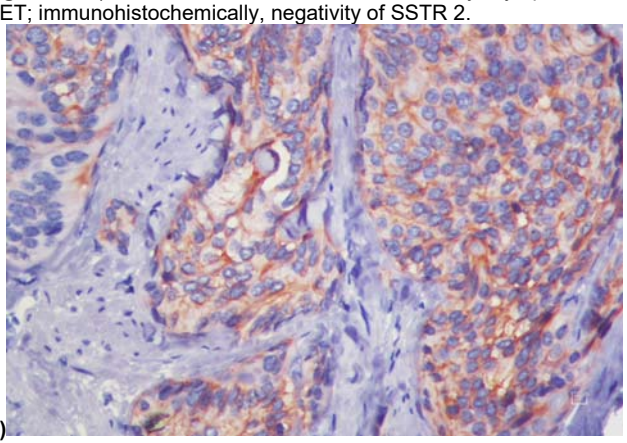
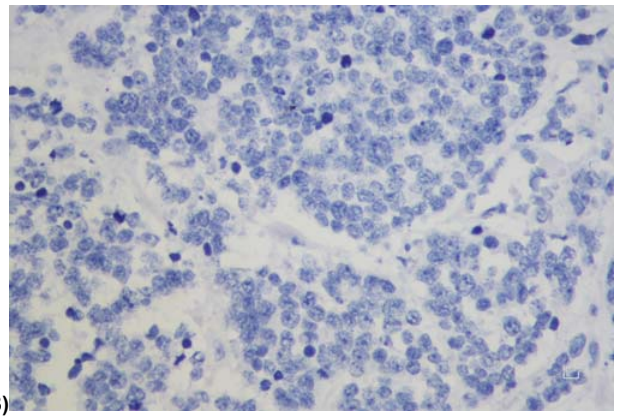
Totally 23% of cases had metastatic diseases; two cases (4%) of Grade 1 NETs had liver and peritoneal spread while 17 cases (58,6%) of Grade 3 NETs had metastatic NETs. In Grade 3 NETs, peritoneal spread (n:7) is followed by regional lymph node metastasis (n:5).

Totally seven (8,7%) cases that had grade NETs have died of the disease. Two of them were metastatic to the liver.

SSTR2 immunostaining was performed in 61 cases. Positive staining was determined in 45 cases (73,7%) regardless of grade. While 88% of Grade 1 cases were positively stained with SSTR2, the

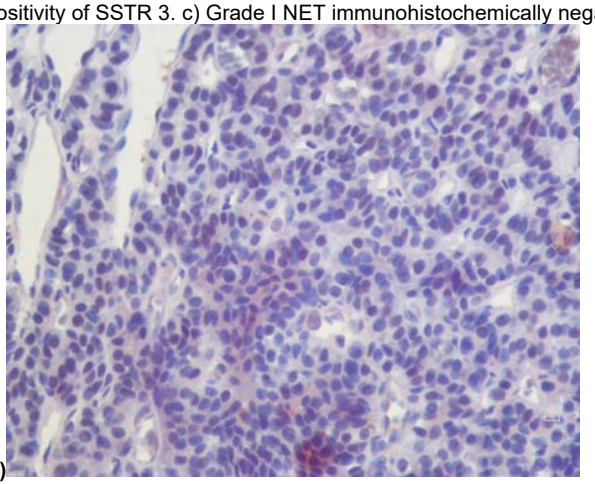
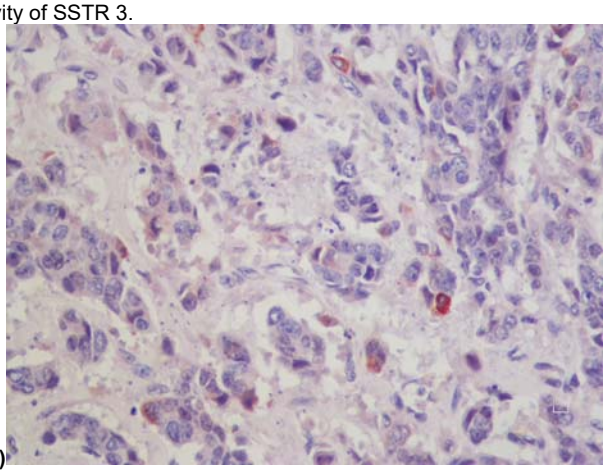
ratio decreased to 50% in Grade 3 NETs. (Figure 2 a, b) The localization of positively stained tumors were stomach (37,7%), small bowel (11,1%), appendix (17,7%) and pancreas (15,5%).

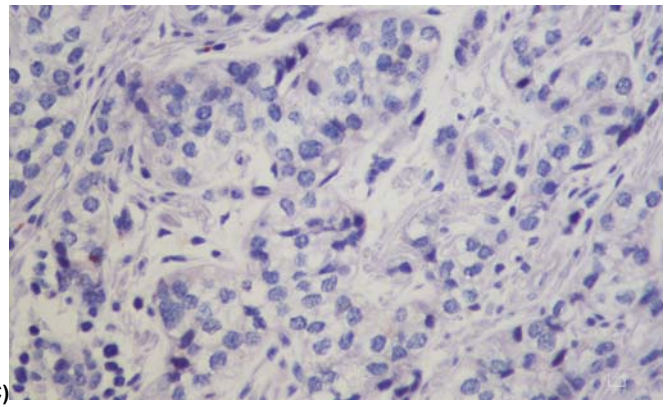
Figure 2. a) Grade I NET; immunohistochemically, cytoplasmic and membranous strong positivity of SSTR 2. b) Grade III NET; immunohistochemically, negativity of SSTR 2.

A)  B) 

SSTR3 immunostaining was performed in 61 cases. Positive staining was determined in 29 cases (47,5%) regardless of grade. While 51% of Grade 1 cases were stained with SSTR3, the ratio decreases to 40% in Grade 3 NETs. (Figure 3 a, b, c) The localization of positively stained tumors were stomach (27,5%), small bowel (6,8%), large bowel (27,5%), appendix (13,7%) and pancreas (24,1%).

Figure 3: a) Grade I NET; immunohistochemically, cytoplasmic positivity of SSTR 3. b) Grade III NET; immunohistochemically, positivity of SSTR 3. c) Grade I NET immunohistochemically negativity of SSTR 3.

A)  B) 

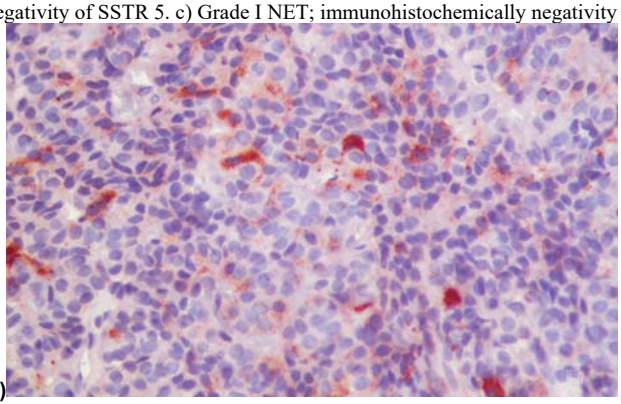
C) 

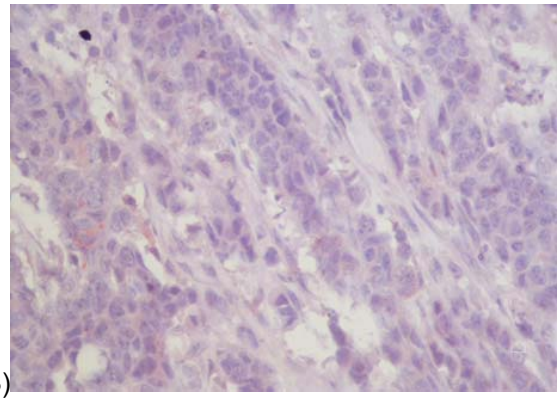
SSTR5 immunostaining was performed in 61 cases. Positive staining was determined in 16 cases (26,2%) regardless of grade. While 30% of Grade 1 cases were stained with SSTR5, the ratio

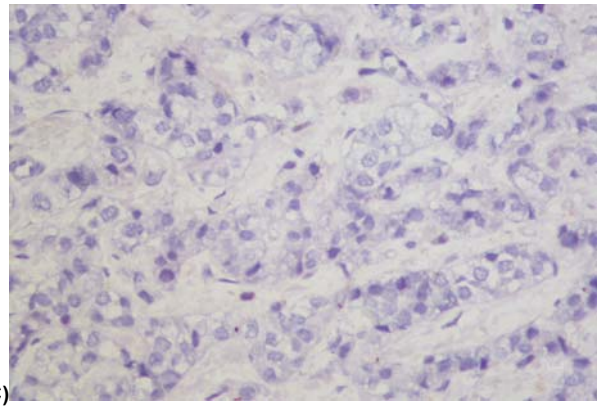
decreases to 24% in Grade 3 NETs. (Figure 4 a, b, c) The localization of positively stained tumors were stomach (31,2%), small bowel (18,7%), large bowel (6,2%), appendix (6,2%) and pancreas (31,2%).

Metastatic NETs showed 56% SSTR2 positivity, 43% SSTR3 positivity and 23% SSTR5 positivity.

Figure 4. a) Grade I NET; immunohistochemically, cytoplasmic moderate positivity of SSTR 5 b) Grade III NET; immunohistochemically, negativity of SSTR 5. c) Grade I NET; immunohistochemically negativity of SSTR 5.

A) 

B) 

C) 

DISCUSSION

In this retrospective study, we assessed the expression of SSRT2, 3 and, 5 in gastrointestinal and pancreatic NETs. Although some prognostic factors such as Ki 67 proliferation index or grade, NETs have an unpredictable outcome. Hence, additional techniques were applied to detect the additional value on prognosis. Among alternative methods, the SSTR profile is a reliable parameter to manage therapy and to show prognostic value[16].

Immunohistochemistry is a useful method to detect SSTR expression on NETs. SSTR expression levels are diminished along grade 1 to 3 NETs, 100%, and 14% respectively[17].

High levels of SSTR2 were reported in previous studies[18-20]. Similarly, SSTR2 was widely expressed among Grade 1 tumors (88%) among our patients.

Immunohistochemical expression of SSRT5 was evaluated in tumor tissue and the authors suggested that SSTR5 is also potentially a relevant marker for targeted therapy[18]. SSTR5 (26,2%) had low rates of expression than SSTR 2 (73,7%). Besides this, we detected 47,5% of SSTR3 expression which is another potential marker for targeted therapy.

Another study investigated the resistance to SSAs and they found that SSTR2 was decreased/ineffective by defects on presence, activation or downstream signaling in SSAs resistant NETs[21]. It is suggested that decreased SSTR2 expression might have a role in drug resistance and poor prognosis on Grade 3 NETs. We found decreased SSTR2 expression in Grade 3 NETs than Grade 1 NETs, 50%, 88% respectively.

There are contradictory studies about the influence of SSTR2 and SSTR5 expression on the prediction of survival in low-grade NETs[16,22,23]. We found lower expression rates of SSTR2 in metastatic NETs but there was no difference at SSTR5. Most of the metastatic NETs in our series were high-grade.

Localization of NETs might be valuable to predict prognosis. Pancreatic NETs have lower progression-free survival than small bowel NETs[24]. Carcinoid tumors comprise approximately 40% of all small intestinal primary tumors; although SBNETs have a high risk for delayed diagnosis and they are usually detected when they are metastatic to the liver[25]. Another interesting point of view is that lymph node metastasis of NETs has an influence on the overexpression of SSTRs while a lower SSTR expression is observed in NETs with liver metastasis[18].

Surgery is the first choice for resectable tumors. For instance, surgical excision of both primary and metastatic pancreatic NETs has been associated with improved survival[26]. SSAs are used for advanced stage diseases[27-29]. SSAs preferentially target SSTR2 and this study emphasizes the importance of detection of SSTR2. Besides this, SSTR3 and SSTR5 might be useful to detect the benefit from targeted therapy.

One study showed the correlation between SSTR2 expression and pentetreotide scintigraphy[15]. That study had limitations to detect grade of the tumor by only scintigraphy, they emphasized the correlation between immunohistochemical staining and tumor grading.

In conclusion, NETs are a heterogenous group of tumors and they should be evaluated by a multidisciplinary approach. One method is not enough to manage the patients' therapy. SSRT subtypes are satisfactory for choosing the right treatment protocol.

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