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Original Contribution

Somatostatin receptor SSTR2A and SSTR5 expression in neuroendocrine breast cancer☆,☆☆,☆☆☆

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ABSTRACT

Neuroendocrine breast cancer (NEBC) is a group of rare tumors, which could benefit from therapy targeting the somatostatin receptors (SSTRs). In particular, SSTR2A and SSTR5 are potential targets given their consistent expression in gastrointestinal and pancreatic primary and metastatic neuroendocrine cancers. Currently, there are no studies describing the expression of SSTRs in NEBC. The purpose of our study was to characterize the immunohistochemical expression of SSTR2A and SSTR5 in a cohort of NEBC.

Thirty-one primary NEBC cases were analyzed, and SSTR2A and SSTR5 immunohistochemistry performed and scored using the modified immunoreactive score proposed by Remmele and Stanger.

All patients were females with a mean age of 66.6 years (SD = 14). 77% of cases were histological grade 2. SSTR2A showed a weak positivity in 11 cases (35.5%), moderate positivity in 6 cases (19.4%) and strong positivity in 5 cases (16.1%). Nine cases were negative for SSTR2A (29%). SSTR5 showed a weak positivity in 16 cases (51.6%), moderate positivity in 6 cases (19.4%), while no cases showed strong positivity. Nine cases were negative for SSTR5 (29%). Five cases were negative for both SSTR2A and SSTR5.

A weak to moderate SSTR2A and SSTR5 expression was observed in 50–70% of the cases. A subset of NEBCs with strong SSR2A expression may benefit from SSTRs targeted therapy. These results need further validation in a larger series including metastatic NEBC, to provide potential therapeutic targets for patients with advanced disease.

1. Introduction

Neuroendocrine breast cancer (NEBC) is a group of rare tumors. Their reported incidence among breast cancers as a whole varies between 0.1% and 18%, [1-5] depending on specific diagnostic criteria used in the respective series. This variation is mostly dependent on a lack of well-established diagnostic criteria. According to the current (2012) World Health Organization (WHO) classification of tumors [6], NEBC includes 3 subtypes, namely poorly differentiated small cell carcinoma, well differentiated carcinoma and invasive breast carcinoma with immunohistochemical (IHC) evidence of neuroendocrine differentiation, as measured by neuroendocrine (NE) markers, such as synaptophysin and chromogranin A. Among the latter group, no special type (NST) invasive breast cancer is most common. However, among special types of breast cancer, NE differentiation is most often associated with the solid papillary and cellular mucinous subtypes [6]. The previous, 2003, WHO classification required that at least 50% of tumor cells show IHC positivity to NE markers [7]. This difference partly explains the variability in incidence among different series. Additionally, previous studies have shown that NEBC could be underdiagnosed, if one is to employ routine H&E (hematoxylin and eosin) stained slides as the primary diagnostic tool, with NE markers used only to confirm the

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diagnosis [4,8].

There is some controversy regarding the prognosis of NEBC, with some studies showing overall survival comparable to matched no-special-type cases, but reduced disease-free survival [4,9], while others showed worse overall survival [1,10].

Somatostatin receptors (SSTRs) are G-protein coupled receptors. When activated by the peptide somatostatin (SST) they function as potent inhibitors of hormonal secretion and demonstrate an antiproliferative effect. Cells of NE tumors (NETs) of lung, prostate and gastrointestinal system, as well as NST breast cancer express somatostatin receptors (SSTR) [11-16]. There are five known subtypes of SSTRs (numbered 1–5), with SSTR2A being associated with the strongest antiproliferative effect in vitro [17], as well as being the subtype most commonly expressed in NST breast cancer [18]. The luminal, estrogen receptor positive, subtype of breast cancer seems to be most closely associated with expression of SSTRs [19].

No official guidelines exist for the treatment of NEBC [6,20]. Conventional breast cancer therapy is the mainstay of treatment, although one recent study provides some evidence for targeted treatment options [21]. In the past, clinical trials of combination therapy including SST analogues in metastatic NST breast cancer have demonstrated some benefit, with studies using higher doses yielding better results [22]. However, no recent trials are available.

The aim of this study was to investigate the SSTR2 and SSTR5 expression in a retrospective multicenter series of NEBC.

2. Materials and methods

2.1. Subjects

Thirty-one primary neuroendocrine breast cancer cases were selected from the archives of the Institute of Pathology of the “Sestre milosrdnice” University Hospital Centre, in Zagreb, Croatia and from the Department of Pathology of the Sarajevo University Hospital Centre, in Sarajevo, Bosnia and Herzegovina, for the period between 2006 and 2017. The study was in accordance with the Ethics Committee recommendations of “Sestre milosrdnice” University Hospital Centre (Croatia) and Sarajevo University Hospital Centre (Bosnia and Herzegovina).

Patient and case information was retrieved from electronic medical records. All cases were diagnosed on formalin fixed, paraffin embedded, glass mounted, and H&E stained slides, based on histological criteria of NE differentiation. The diagnosis was confirmed with synaptophysin and/or chromogranin immunohistochemistry in all cases. Subtyping was performed using human epidermal growth factor receptor 2 (Her2/neu), progesterone receptor (PR), estrogen receptor (ER), and Ki-67 IHC. According to the St Gallen consensus criteria [23] Ki-67 cutoff was set to 20%. Pre-2012 cases were diagnosed using the 50% positivity cut-off for NE markers [24], while for post-2012 cases no cut-off was used. Histologic grade was assessed using the Nottingham histologic grading [25].

2.2. Immunohistochemical analysis

All cases were reviewed by an expert pathologist (A.D.) to confirm the diagnosis and select the appropriate slides for analysis. From each case, one representative block was selected for SSTR IHC. Immunohistochemistry for SSTR2A and SSTR5 was performed on Autostainer link 48 machines (Dako, Denmark) with antibodies by Abcam (USA), using the indirect EnVision polymer-based method. Antibody characteristics are given in Table 1. Neuroendocrine pancreatic carcinoma served as a positive control and replacement of the primary antibody with isotype-matched immunoglobulin was used as a negative control. The whole mounts of the chosen slides were examined under low (×40) and medium magnification (×200) by three independent pathologists (A.D., D.T. and M.P.B.), who were blinded to the clinical course of the patients, and any difference was resolved by a joint review at a multi-headed microscope.

Table 1
Summary of antibodies, clones, dilutions.

Antibody	Company	Reference	Clone	Origin	Isotype	Dilution
SSTR2A	Abcam	ab134152	UMB1	Rabbit monoclonal	IgG	1:200
SSTR5	Abcam	ab109495	UMB4	Rabbit monoclonal	IgG	1:200

Only membranous staining was considered as a positive reaction. The modified immunoreactive score of Remmele and Stanger (IRS) method described by Kaemmerer et al. [26], was used as follows. A score between 0 and 4 was assigned according to the percentage of positive cells (0 = no positive cells, 1 ≤ 10% positive cells, 2 = 10–50% positive cells, 3 = 51–80% positive cells, 4 ≥ 80% positive cells). This score was then multiplied by a number between 0 and 3, representing the intensity of staining (0 = no color reaction, 1 = mild reaction, 2 = moderate reaction, 3 = intense reaction). The product of the two numbers was classified as follows: 0–1 = negative reaction; 2–3 = positive, weak reaction; 4–8 = positive, moderate reaction; 9–12 = positive, strong reaction.

2.3. Statistical analysis

The Shapiro-Wilk test was used to check for normalcy of data. Correlations between both SSTR2A and SSTR5 expression and patient age, tumor size, tumor grade, Her2, ER and PR respectively were calculated using the Spearman method. Bonferroni correction was applied, and a $p < 0.05$ was considered statistically significant. All statistical calculations were performed using the R environment [27].

3. Results

Data collected for each patient are shown in Table 2. The mean patient age was 66.6 ± 14 years (range: 28–86 years), and all were female. Mean tumor diameter was 26.5 ± 16.3 mm (range: 7–87 mm). Twenty-four cases (77%) were grade 2, three cases (10%) were grade 1 and 4 cases (13%) were grade 3 cancers. Luminal A tumors constituted 35% of cases, while 55% were luminal B. Among these, 3 cases (10%) were Her2/neu positive. Two cases (6%) were triple negative, and one case (3%) showed a non-Luminal Her2/neu negative phenotype.

SSTR2A and SSTR5 IHC results are summarized in Table 3. The total percentage of cases showing a positive membrane IHC reaction was 71% for both SSTR2A and SSTR5. Partial weak cytoplasmic staining was also observed, but not considered positive. No nuclear staining was observed in any case. Fig. 1 shows examples of positive reactions with different staining intensities.

Five cases (16.1%) were negative for both SSTR2A and SSTR5, among which three cases were Luminal A, one case was Luminal B Her2 negative and one case was negative for both ER and Her2 (triple negative).

After application of the Bonferroni correction, no statistically significant correlations were observed between SSTR receptor expression, patient age and tumor characteristics (tumor grade, size, ER expression, PR expression, Her2 expression, and Ki-67 proliferation index).

4. Discussion

The present study is the first to investigate the expression of SSTR2A and SSTR5 in primary NEBC. Our data show that SSTR2A and SSTR5 are expressed in the majority (71%) of NEBC in our series. These results are in line with previously published studies of SSTR expression in breast carcinomas of NST [18,19] and NETs of other primary sites

Table 2
Patient characteristics and results.

Case	Age	Tumor grade	Tumor size (mm)	ER	PR	Ki67	Her2/neu	St. Gallen subtype	SSTR-2 IRS	SSTR-2 class	SSTR-5 IRS	SSTR-5 class
1	51	1	12	100	90	7	0	Luminal A	9	Strong	0	Negative
2	30	2	30	0	0	30	0	Her2+ non luminal	1	Weak	3	Weak
3	86	2	10	100	90	35	0	Luminal B Her2−	2	Weak	2	Weak
4	63	2	22	100	100	27	0	Luminal B Her2−	6	Moderate	3	Weak
5	60	3	48	80	0	20	0	Luminal B Her2−	0	Negative	2	Weak
6	62	2	16	100	0	7	1+	Luminal A	0	Negative	2	Weak
7	57	2	15	100	0	12	0	Luminal A	2	Weak	4	Moderate
8	59	2	23	0	0	80	0	Triple negative	0	Negative	0	Negative
9	68	2	23	100	70	20	1+	Luminal B Her2−	0	Negative	1	Weak
10	75	2	33	100	100	14	0	Luminal A	4	Moderate	4	Moderate
11	28	2	20	100	100	28	1+	Luminal B Her2−	1	Weak	2	Weak
12	80	2	21	100	40	21	0	Luminal B Her2−	2	Weak	4	Moderate
13	79	2	25	80	70	9	0	Luminal A	0	Negative	0	Negative
14	61	3	87	0	0	80	0	Triple negative	6	Moderate	0	Weak
15	76	2	25	100	100	30	0	Luminal A	9	Strong	2	Weak
16	79	3	11	100	0	18	0	Luminal B Her2−	9	Strong	2	Weak
17	80	2	33	100	0	17	1+	Luminal A	2	Weak	2	Weak
18	80	2	16	100	0	36	3+	Luminal B Her2+	1	Weak	6	Moderate
19	62	2	22	100	100	23	1+	Luminal B Her2−	6	Moderate	1	Weak
20	67	2	9	100	0	9	1+	Luminal A	1	Weak	1	Weak
21	67	1	14	100	100	18	0	Luminal A	6	Moderate	6	Moderate
22	54	3	18	100	100	68	1+	Luminal B Her2−	9	Strong	4	Weak
23	75	2	55	100	100	22	2+	Luminal B Her2+	2	Weak	2	Weak
24	75	1	7	100	15	21	0	Luminal B Her2−	0	Negative	4	Moderate
25	78	2	45	40	40	25	0	Luminal B Her2−	1	Weak	1	Weak
26	84	2	18	95	100	20	0	Luminal B Her2−	0	Negative	0	Negative
27	70	2	40	50	50	25	0	Luminal B Her2−	3	Weak	0	Negative
28	51	2	30	80	0	25	0	Luminal B Her2−	9	Strong	0	Negative
29	78	2	25	50	20	2	0	Luminal A	0	Negative	0	Negative
30	66	2	27	100	100	16	0	Luminal A	0	Negative	0	Negative
31	65	2	40	90	60	14	0	Luminal B Her2+	6	Moderate	0	Negative

ER: estrogen receptors; PR: progesterone receptors; HER2/neu: human epidermal growth factor receptor 2; SSTR: somatostatin receptor; IRS: immunoreactivity score of Remmele and Stanger.

Table 3
Results of SSTR2A and SSTR5 immunohistochemistry.

IRS class	SSTR2A (n)	%	SSTR5 (n)	%
Negative	9	29.0	9	29.0
Positive, weak	11	35.5	16	51.6
Positive, moderate	6	19.4	6	19.4
Positive, strong	5	16.1	0	0.0
Total n	31	100	31	100

SSTR: somatostatin receptor; IRS: immunoreactivity score of Remmele and Stanger.

[13,14,26,28]. The modified IRS score, used in the present study, was developed by Kaemmerer et al. [26]. It is based on the immunoreactive score of Remmele and Stanger, developed in 1987 for the quantification of estrogen receptor positivity in breast cancer [29]. We found it an easy to use method that could be a useful tool for quantifying SSTR IHC expression in a routine clinical setting.

Kumar et al. [18] correlated SSTR1–5 mRNA expression with immunocytochemical SSTR1–5 protein expression in NST breast carcinomas and found significant positive correlations. SSTR1–5 mRNAs were expressed in 91% (SSTR1), 98% (SSTR2), 96% (SSTR3), 76% (SSTR4), and 54% (SSTR5). Using IHC, they found cytoplasmic and membrane distribution of SSTR2 and SSTR5. A heterogeneous expression pattern of different SSTRs seems to be the case for NST breast carcinomas as a group, with SSTR2 being the most consistently expressed. The different staining intensity of SSTR2A and SSTR5 in our data supports the view that this is also the case in NEBC.

Frati and colleagues [19] performed tissue microarray analysis using SSTR2A and SSTR4 IHC in NST breast carcinomas. They also showed membranous distribution in cancer cells, with SSTR2A being expressed in 21% of cases. This lower positivity was explained by the authors as being due to the relatively young cohort and increased proportion of receptor negative and Her2 positive carcinomas.

Both the Kumar and Frati studies showed a positive correlation between SSTR2A expression and ER and PR levels. Whether a lack of such a correlation in our data is a matter of different cancer biology between breast carcinomas NST and NEBC or a lack of statistical power in our study remains to be further tested by a larger series.

By IHC characteristics, NEBC tend mostly to fall in the category of luminal breast cancers, with luminal A and B having more or less equal distribution [4,9]. We found 55% of cases to be of Luminal B subtype, of which most were Her2 negative and only 3 were Her2 positive. This is in line with previously published data. In one series of NEBC detected by IHC positivity to NE markers, Bogina et al. [4] found 65/128 cases to be ER+/Her2−/Ki67 > 14% while 9/128 as ER+/Her2+, giving a total of 74/128 (57%) as Luminal B subtype. In their series, Lavigne et al. [9] reported 51% of their cases as Luminal A, while the rest were Luminal B.

SSTRs are targets for biological therapy in NETs. Somatostatin analogues, such as octreotide and lanreotide, have an antiproliferative effect in systemic NETs, leading to mass shrinkage and an increase in progression-free survival [11]. Partly because of their disease stabilizing effect, somatostatin analogues are recommended by international guidelines for the therapy of well differentiated, grade 1 and 2 carcinoid tumors [30]. Another therapeutic approach in systemic NETs uses peptide receptor radionuclide therapy (PRRT), which consists of a radiolabeled somatostatin analogue. Using this technique radiotherapy can be administered selectively to cancer cells expressing SSTRs. Both systemic and local embolization methods are employed, with evidence of increased progression-free survival [31,32]. These studies however have not demonstrated an increase in overall survival.

Similarly to other NET sites, SSTRs in primary NEBC could be a potential therapeutic target, and antiproliferative therapies, such as somatostatin analogues similar to those employed in neuroendocrine

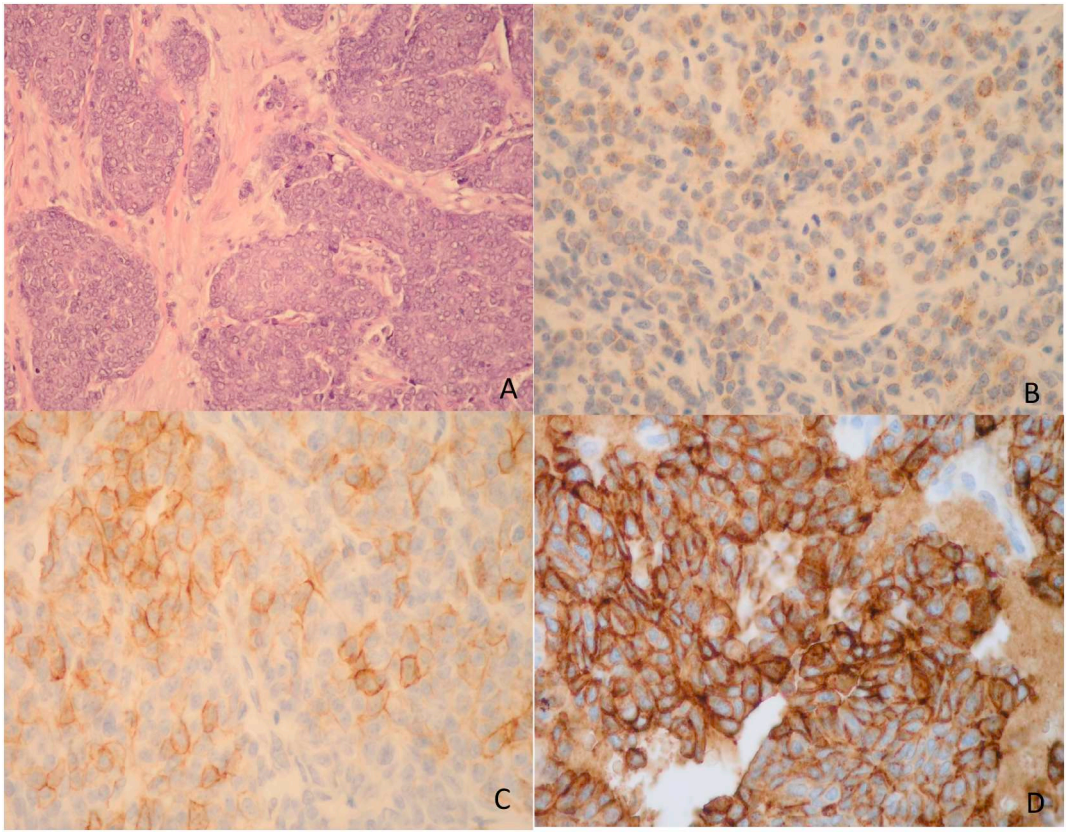

Fig. 1. Example of case of neuroendocrine breast carcinoma on hematoxylin and eosin staining (A, 200× magnification), positive, weak IHC reaction to SSTR2A (B, 400× magnification), positive, moderate reaction to SSTR2A (C, 400× magnification) and positive, strong reaction to SSTR2A (D, 400× magnification).

digestive tract tumors [11,30] could be added to existing regimens as first line treatment. Previous trials of somatostatin analogues in systemic NST breast cancer [22,33] have generally shown poor results. This failure could be partly attributed to a lack of SSTR status evaluation prior to beginning of therapy [34], as well as conservative dosage employed, and advanced disease [22]. In our study, 16% of cases were negative for SSTR2A and SSTR5 and studies of NET in other sites have shown similar results. Given the relatively high proportion of SSTR negative cancers, future studies should measure IHC SSTR status prior to commencing SSTR analogue therapy, in order to increase the likelihood of therapeutic success.

The PRRT approach could potentially be employed in SSTR positive advanced and/or metastatic NEBC. In a case report Savelli et al. used PRRT in a case of systemic NEBC as third line therapy, and showed a significant shrinkage of metastatic liver masses [35].

In conclusion, we have shown a consistent IHC expression of SSTR2A and SSTR5 in our cohort of primary NEBC. In the future, a broader diagnostic and clinical effort is necessary to scrutinize the potential diagnostic and therapeutic role of somatostatin receptors in the treatment of NEBC.

References

[1] Wang J, Wei B, Albarracin CT, Hu J, Abraham SC, Wu Y. Invasive neuroendocrine carcinoma of the breast: a population-based study from the surveillance, epidemiology and end results (SEER) database. BMC Cancer 2014;14:147. https://doi.org/10.1186/1471-2407-14-147.

[2] Kwon SY, Bae YK, Gu MJ, Choi JE, Kang SH, Lee SJ, et al. Neuroendocrine differentiation correlates with hormone receptor expression and decreased survival in patients with invasive breast carcinoma. Histopathology 2014;64:647–59. https://doi.org/10.1111/his.12306.

[3] Miremadi A, Pinder SE, Lee AHS, Bell JA, Paish EC, Wencyk P, et al. Neuroendocrine differentiation and prognosis in breast adenocarcinoma. Histopathology 2002;40:215–22.

[4] Bogina G, Munari E, Brunelli M, Bortesi L, Marconi M, Sommaggio M, et al. Neuroendocrine differentiation in breast carcinoma: clinicopathological features and outcome. Histopathology 2016;68:422–32. https://doi.org/10.1111/his.12766.

[5] Inno A, Bogina G, Turazza M, Bortesi L, Duranti S, Massocco A, et al. Neuroendocrine carcinoma of the breast: current evidence and future perspectives. Oncologist 2016;21:28–32.

[6] Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ. WHO classification of tumours of the breast. 4th ed. Lyon: International Agency for Research on Cancer; 2012.

[7] Tavassoli Fattaneh A, Devilee Peter. WHO classification of tumors. Tumors of the breast and female genital organs. International Agency for Research on Cancer: Lyon; 2003.

[8] Brask JB, Talman M-LM, Wielenga VT. Neuroendocrine carcinoma of the breast - a pilot study of a Danish population of 240 breast cancer patients. Acta Pathol Microbiol Immunol Scand 2014;122:585–92. https://doi.org/10.1111/apm.12197.

[9] Lavigne M, Menet E, Tille J-C, Lae M, Fuhrmann L, Bonneau C, et al. Comprehensive clinical and molecular analyses of neuroendocrine carcinomas of the breast. Mod Pathol 2018;31:68–82. https://doi.org/10.1038/modpathol.2017.107.

[10] Wei B, Ding T, Xing Y, Wei W, Tian Z, Tang F, et al. Invasive neuroendocrine carcinoma of the breast: a distinctive subtype of aggressive mammary carcinoma. Cancer 2010;116:4463–73. https://doi.org/10.1002/cncr.25352.

[11] Rinke A, Krug S. Neuroendocrine tumours - medical therapy: biological. Best Pract Res Clin Endocrinol Metab 2016;30:79–91. https://doi.org/10.1016/j.beem.2015.09.004.

[12] Watt HL, Kharmate G, Kumar U. Biology of somatostatin in breast cancer. Mol Cell Endocrinol 2008;286:251–61. https://doi.org/10.1016/j.mce.2008.01.006.

[13] Song KB, Kim SC, Kim JH, Seo D-W, Hong S-M, Park K-M, et al. Prognostic value of somatostatin receptor subtypes in pancreatic neuroendocrine tumors. Pancreas 2016;45:187–92.

[14] Diakatou E, Kaltsas G, Tzivras M, Kanakis G, Papaliodi E, Kontogeorgos G. Somatostatin and dopamine receptor profile of gastroenteropancreatic neuroendocrine tumors: an immunohistochemical study. Endocr Pathol 2011;22:24–30. https://doi.org/10.1007/s12022-011-9149-8.

[15] Kaemmerer D, Specht E, Sänger J, Wirtz RM, Sayeg M, Schulz S, et al. Somatostatin receptors in bronchopulmonary neuroendocrine neoplasms: new diagnostic, prognostic, and therapeutic markers. J Clin Endocrinol Metab 2015;100:831–40. https://doi.org/10.1210/jc.2014-2699.

[16] Papotti M, Bongiovanni M, Volante M, Allìa E, Landolfi S, Helboe L, et al. Expression of somatostatin receptor types 1–5 in 81 cases of gastrointestinal and pancreatic endocrine tumors. A correlative immunohistochemical and reverse-transcriptase polymerase chain reaction analysis. Virchows Arch 2002;440:461–75. https://doi.org/10.1007/s00428-002-0609-x.

[17] Buscail L, Estève JP, Saint-Laurent N, Bertrand V, Reisine T, O'Carroll AM, et al.

Inhibition of cell proliferation by the somatostatin analogue RC-160 is mediated by somatostatin receptor subtypes SSTR2 and SSTR5 through different mechanisms. Proc Natl Acad Sci U S A 1995;92:1580–4.
[18] Kumar U, Grigorakis SI, Watt HL, Sasi R, Snell L, Watson P, et al. Somatostatin receptors in primary human breast cancer: quantitative analysis of mRNA for subtypes 1–5 and correlation with receptor protein expression and tumor pathology. Breast Cancer Res Treat 2005;92:175–86. https://doi.org/10.1007/s10549-005-2414-0.
[19] Frati A, Rouzier R, Lesieur B, Werkoff G, Antoine M, Rodenas A, et al. Expression of somatostatin type-2 and -4 receptor and correlation with histological type in breast cancer. Anticancer Res 2014;34:3997–4003.
[20] Jurčić P, Krušlin B, Gatalica Z, Sanati S, Vranić S. Breast carcinoma with neuroendocrine features: a brief review. Endocr Oncol Metab 2016;2:9. https://doi.org/10.21040/eom/2016.2.2.6.
[21] Vranic S, Palazzo J, Sanati S, Florento E, Contreras E, Xiu J, et al. Potential novel therapy targets in neuroendocrine carcinomas of the breast. Clin Breast Cancer 2018. https://doi.org/10.1016/j.clbc.2018.09.001.
[22] Dolan JT, Miltenburg DM, Granchi TS, Miller CC, Brunicardi FC. Treatment of metastatic breast cancer with somatostatin analogues–a meta-analysis. Ann Surg Oncol 2001;8:227–33.
[23] Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies–improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol 2015;26:1533–46. https://doi.org/10.1093/annonc/mdv221.
[24] Sapino A, Papotti M, Righi L, Cassoni P, Chiusa L, Bussolati G. Clinical significance of neuroendocrine carcinoma of the breast. Ann Oncol 2001;12(Suppl. 2):S115–7.
[25] Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 1991;19:403–10.
[26] Kaemmerer D, Peter L, Lupp A, Schulz S, Sanger J, Baum RP, et al. Comparing of IRS and Her2 as immunohistochemical scoring schemes in gastroenteropancreatic neuroendocrine tumors. Int J Clin Exp Pathol 2012;5:187–94.
[27] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2017.
[28] Pisarek H, Pawlikowski M, Kunert-Radek J, Kubiak R, Winczyk K. SSTR1 and SSTR5 subtypes are the dominant forms of somatostatin receptor in neuroendocrine tumors. Folia Histochem Cytobiol 2010;48:142–7. https://doi.org/10.2478/v10042-008-0103-7.
[29] Remmele W, Stegner HE. Recommendation for uniform definition of an immunoreactive score (IRS) for immunohistochemical estrogen receptor detection (ER-ICA) in breast cancer tissue. Der Pathologe 1987;8:138–40.
[30] Oberg K, Knigge U, Kwekkeboom D, Perren A, on behalf of the ESMO Guidelines Working Group. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23:vii124–30. https://doi.org/10.1093/annonc/mds295.
[31] Hamiditabar M, Ali M, Roys J, Wolin EM, O'Dorisio TM, Ranganathan D, et al. Peptide receptor radionuclide therapy with 177Lu-octreotate in patients with somatostatin receptor expressing neuroendocrine tumors: six years' assessment. Clin Nucl Med 2017;42:436–43. https://doi.org/10.1097/RLU.0000000000001629.
[32] Strosberg JR, Halfdanarson TR, Bellizzi AM, Chan JA, Dillon JS, Heaney AP, et al. The North American Neuroendocrine Tumor Society consensus guidelines for surveillance and medical management of midgut neuroendocrine tumors. Pancreas 2017;46:707–14. https://doi.org/10.1097/MPA.0000000000000850.
[33] Bajetta E, Procopio G, Ferrari L, Martinetti A, Zilembo N, Catena L, et al. A randomized, multicenter prospective trial assessing long-acting release octreotide pamoate plus tamoxifen as a first line therapy for advanced breast carcinoma. Cancer 2002;94:299–304. https://doi.org/10.1002/cncr.10239.
[34] Hejna M, Schmidinger M, Raderer M. The clinical role of somatostatin analogues as antineoplastic agents: much ado about nothing? Ann Oncol 2002;13:653–68.
[35] Savelli G, Zaniboni A, Bertagna F, Bosio G, Nisa L, Rodella C, et al. Peptide receptor radionuclide therapy (PRRT) in a patient affected by metastatic breast cancer with neuroendocrine differentiation. Breast Care 2012;7:408–10. https://doi.org/10.1159/000343612.