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Somatostatin Receptor Type 2 (SSTR2) and Thyroid Stimulating Hormone Receptor (TSHR) Expression in Oncocytic Thyroid Neoplasms: Implications for Prognosis and Treatment

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Abstract

Somatostatin receptor type 2 (SSTR2) and thyroid stimulating hormone receptor (TSHR) display variable expression in primary thyroid tumors and have been implicated as theranostic targets. This study was designed to explore differential expression of SSTR2 and TSHR in oncocytic (Hurthle cell) carcinoma (OC) versus oncocytic adenoma (OA). We performed a retrospective review for oncocytic neoplasms treated at our institution from 2012 to 2019. Formalin-fixed paraffin embedded (FFPE) tissue blocks were utilized for tissue microarray (TMA) construction. TMA blocks were cut at 5 micron sections and stained with anti-SSTR2 and anti-TSHR antibody. Immunostains were analyzed by 3 independent pathologists. Chi-squared and logistic regression analysis were used to analyze clinical and pathologic variables. 67 specimens were analyzed with 15 OA and 52 OC. The mean age was 57 years, 61.2% were female, and 70% were white. SSTR2 positivity was noted in 2 OA (13%) and 15 OC (28%, 10 primary, 4 recurrent, 1 metastatic) (p=0.22). TSHR positivity was noted in 11 OA (73%) and 32 OC (62%, 31 primary, 1 metastatic) (p=0.40). Those who presented with or developed clinical recurrence/metastasis were more likely to be SSTR2 positive (50% vs 21%, p=0.04) and TSHR negative (64.3% vs 28.9%, p=0.02) than primary OC patients. Widely invasive OC was more likely to be SSTR2 positive compared to

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Author Contributions:

R.J-S., R.Z.P., D.L., T.P., and H.C. performed development of methodology. D.W., J.N. performed the imaging, R.L., M.L.G. and D.L. performed the image classification, R.G., A.C., and J.N. prepared the samples. A.G. and C.M. performed the statistical analysis of the data. A.G., R.Z.P, D.L., and R.J-S. wrote the manuscript. All the authors reviewed and revised the manuscript. All authors read and approved the final paper.

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all other OC subtypes (minimally invasive, angioinvasive) (p=0.003). For all OC patients, TSHR positivity was inversely correlated with SSTR2 positivity (OR: 0.12, CI[0.03–0.43], p=0.006). This relationship was not seen in the OA patients (OR: 0.30, CI[0.01–9.14, p=0.440). Our results show that recurrent/metastatic OC was more likely to be SSTR2 positive and TSHR negative than primary OC. OC patients displayed a significant inverse relationship between SSTR2 and TSHR expression that was not seen in OA patients. This may be a key relationship that can be utilized to prognosticate and treat OCs.

Introduction

Oncocytic (formerly Hurthle cell) thyroid malignancies comprise 3% to 5% of all thyroid cancers. [12,3] Oncocytic carcinoma (OC) can have a variety of presentations and unpredictable course from relatively indolent to rapidly progressive and metastatic. OC can be particularly difficult to diagnose and prognosticate before or during surgery from its benign counterpart oncocytic adenoma (OA). Overall, OC has more aggressive biologic features and worse overall prognosis than other differentiated thyroid cancers (DTC), including papillary and follicular subtypes.[4]

OC is treated with surgical resection of the thyroid.[5,6] Post-operative therapy usually consists of thyroid hormone suppression and radioactive iodine (RAI) ablation for microscopic adjuvant or recurrent disease. Unfortunately, OC has a significant risk of RAI insensitivity making continued surveillance and nonsurgical treatment particularly difficult in some cases.[7–10] In addition, even when OC appears RAI sensitive, there have recently been concerns raised over its effectiveness in improving cancer-specific survival.[11] These observations draw attention to the need for novel diagnostic and therapeutic approaches.

Of particular interest is the potential to leverage membrane bound G-protein-receptors found on thyroid cells: SSTR2 and TSHR. Somatostatin receptors comprise a large family with differential expression in normal tissues as well as solid malignancies.[12] Our group and others have noted the incidental increased expression of SSTR2 in oncocytic neoplasms.[13] Peptide receptor radionuclide therapy (PRRT), Lutathera ([177Lu]DOTATATE) has been approved by FDA for the treatment of SSTR2 positive gastroenteropancreatic neuroendocrine tumors.[14,15] However, there is only a single clinical trial evaluating SSTR2 as a potential target for imaging of metastatic thyroid cancer (OC, DTC, and medullary thyroid cancer).[16,17] Therefore, there is a need to stratify patients with oncocytic thyroid malignancies by those who may be eligible for SSTR2 targeted imaging and potential therapy.

TSHR displays variable expression in primary thyroid tumors as well as other tissues.[18] Some data support a positive correlation between degree of differentiation and TSHR expression, but this is not universally seen.[19] Traditionally, the TSHR is targeted in the adjuvant setting by treating patients with suppressive doses of levothyroxine in order to lower TSH levels and minimize thyroid cancer regrowth. Novel therapeutics are being investigated using TSHR as a target for drug delivery with small molecule antagonists or chimeric antigen receptor T cells (CAR-Ts).[20–23]

Both TSHR and SSTR have been implicated as theranostic (both therapeutic and diagnostic) targets in other tumors, and could potentially play a role in oncocytic neoplasms. However the frequency of both SSTR2 and TSHR expression must be defined in oncocytic thyroid neoplasms in order to determine their utility. Therefore, this study was designed to explore differential expression of SSTR2 and TSHR in thyroid OC versus OA.

Materials and Methods

Sample preparation and imaging

With Institutional Review Board approval, we performed a retrospective review for oncocytic neoplasms diagnosed at a single tertiary referral center from 2012 to 2019 using a digitized information system (Cerner Millennium, Kansas, MO). Cytology specimens were excluded. Per WHO 2022 guidelines, oncocytic neoplasms contained at least 75% oncocytic cells with carcinomas identified by vascular or full thickness capsular invasion.[1]

Formalin-fixed paraffin embedded (FFPE) tissue blocks were utilized for tissue microarray (TMA) construction. An expert head and neck pathologist (DL) reviewed resection hematoxylin and eosin slides and marked tumor areas for harvesting cores. An average of three 2mm cores per tumor were used for TMA assembly. Normal thyroid tissue cores were used as SSTR2 negative controls and TSHR positive controls. SSTR2 positive control cores were from a pancreatic neuroendocrine tumor. Slide marking and digital analysis (Galileo TMA CK3600 Tissue Arrayer, Integrated Systems Engineering S.r.l., Milan, Italy) were used to punch 2 mm cores from FFPE blocks and assemble TMAs. TMA paraffin blocks were cut at 5 micron sections and were baked overnight at 60° C, then de-paraffinized in 3 changes of xylene and hydrated using graded concentrations of ethanol to deionized water. The tissue sections where subjected to antigen retrieval by 0.01 M Tris-1mM EDTA buffer (pH 9) in pressure cooker for 5 min (buffer preheated). Following antigen retrieval, all sections were washed in deionized water, then transferred in to 0.05 M Tris-based solution in 0.15M NaCl with 0.1% v/v Triton-X-100, pH 7.6 (TBST). Endogenous peroxidase was blocked with 5% hydrogen peroxide for 15 min.

To reduce further nonspecific background staining, slides where incubated with 5% normal goat serum (Sigma, G9023) for 60 min at RT. All slides then where incubated at 4° C overnight with anti-TSHR (Abcam (Cambridge, United Kingdom), ab218108, rabbit monoclonal (EPR19751)) or anti-SSTR2 (Abcam, ab134152, rabbit monoclonal (UMB1)). After washing with TBST, sections then incubated with the Goat Anti-Rabbit IgG H&L secondary antibody conjugated with HRP (Abcam ab6721, 1:1000.) Vector Laboratories - ImmPACT DAB Peroxidase (HRP) Substrate Kit (SK4105) was used as the chromogen and hematoxylin (no. 7221, Richard-Allen Scientific, Kalamazoo, MI) as the counterstain.

Immunohistochemistry stains were analyzed and scored by 3 independent pathologists with expertise in thyroid and head and neck pathology (DL, MLG, RVL). Since both receptors are membrane bound, complete circumferential membranous staining in at least 10% of tumor cells was considered positive as previously described.[24] Disagreements were resolved by the most senior pathologist (RVL).

Statistical analysis

Patient demographics, biochemical data, pathology, recurrence rates, and stain positivity on FFPE tissue blocks were recorded. OCs were divided by invasiveness (minimally, widely) and degree of angioinvasion according to the number of foci of vascular invasion (less than or greater than 4 foci). Advanced disease was described as OC that clinically developed recurrence and/or locally or distantly metastatic disease.

Inter-observer agreement was determined utilizing the kappa statistic (*K*) across both receptors. Chi-squared statistic was utilized to analyze receptor positivity and logistic regression analyses were used to analyze correlation between receptors in each population. Statistics were completed using R[25]. Alpha level was set at $p<0.05$ to establish statistical significance.

Results

67 specimens were identified with a diagnosis of oncocytic neoplasm including OA (n=15) and OC (n=52) (Table 1). The mean patient age was 57 (+/−14) years, 61.2% were female, and 70% were white race. The OC group of specimens consisted of 45 primary tumors, 5 localized recurrences, and 2 metastases (1 to lung and 1 to distant lymph nodes). Of the OC primary tumors, the mean tumor size was 3.6cm (SD: 2.5cm). We cannot comment on rates of RAI sensitivity since many patients were lost to follow up after surgical resection or refused n=19/52 (37%). Of those OC with follow up imaging, 31/33(94%) were RAI sensitive and 2 (6%) were RAI resistant (both SSTR2+/TSHR−).

When examining the pathologic subtypes of OC, n=18 (35%) were described as minimally invasive, n=11 (21%) were widely invasive, and n=16 (31%) were angioinvasive. Of the 16 angioinvasive, n=9 (56%) had >4 foci of vascular invasion identified and n=7 (44%) had ≤4 foci. Mean patient follow up was 3.25 years with 7 patients who had their primary tumor resected developing clinical recurrence or metastasis and 7 additional patients presenting with recurrence or metastasis that were resected or biopsied (with no primary tissue obtained at treating institution). Combined these were categorized as “advanced disease” (n=14) in comparison to those who did not develop metastases or recurrence.

Interobserver agreement was substantial for both receptors with a Kappa statistic of 0.80 for SSTR2 and 0.82 for TSHR. SSTR2 positivity was noted in 2 OA (13%) and 15 OC (28%) (p=0.224) (Table 2). Among those OC samples with SSTR2 positivity, 10 were primary tumors, 4 were recurrent tumors and 1 was a metastatic tumor sample (distant lymph node).There was no difference in SSTR2 positivity (versus no expression) by age (mean 58 years (SD: 10) vs 56 years (SD:15), p=0.68), sex (53% vs 64% female, p=0.42), race (65% versus 74% white, p=0.492), tumor size >2cm (52% vs 76%, p=0.073), or lymph node positivity (18% vs 2%, p=0.056). SSTR2 positive specimens were more likely to exhibit extrathyroidal extension 23.5% vs 4% in SSTR2 negative specimens (p=0.045). One primary OC specimen was high grade due to elevated proliferative index (MIB-1 30%) with necrosis, and was SSTR2 positive. The tumor was widely invasive with a mitotic count was $<1/5mm^2$. However, it did not meet growth pattern criteria for PDTC.

TSHR positivity was noted in 11 OA (73%) and 32 OC (62%) (p=0.401). There was no difference in TSHR positivity (versus no expression) by age (mean age 55 years (SD: 15) versus 60 years (SD:11), p= 0.21), sex (67% versus 50% female, p=0.16), race (69% vs 75% white, p=.607), tumor size >2cm (72% vs 67%, p=0.642), extrathyroidal extension (61% vs 46%, p=0.477), or lymph node positivity (5% vs 8%, p=0.824). Of those OC with TSHR positivity, 31 were primary tumors and 1 was a metastatic tumor (distant lymph node).

When examining primary OC patients by the 3 histologic subtypes, SSTR2 expression significantly differed (p=0.014). This difference was specifically driven by those with widely invasive disease with 55% staining positive for SSTR2 compared to 12% of all other subtypes (minimally invasive and angioinvasive) (p=0.007). There were no differences in TSHR positivity by histologic subtypes (p=0.468).

Clinically, those OC patients who presented with recurrence or metastatic disease (n=7) only 2 had their concurrent primary tumor available in our archives for analysis. For one patients, SSTR2 was negative in both the primary and metastatic sample. The remaining 5 patients had their thyroid surgery performed elsewhere and their specimens were not available for analysis. Among the advanced disease cohort, they were more likely to be SSTR2 positive compared to primary OC patients that did not develop advanced disease (50.0% vs 21.1%, p=0.04) (Table 3). Those with advanced disease were also more likely to be TSHR negative when compared to primary OC patients (64.3% vs 28.9%, p=0.02). Immunostaining results for SSTR2 positive and TSHR negative OC are shown in Figure 1 and TSHR positive and SSTR2 negative OC are shown in Figure 2.

In logistic regression, for all OC patients, TSHR positivity was inversely correlated with SSTR2 positivity (OR: 0.12, 95% CI [0.03–0.43], p=0.006). This relationship was not seen in the OA patients (OR: 0.30, 95% CI [0.01–9.14], p=0.440).

Discussion

We completed an immunohistochemistry analysis of the expression of two membrane bound receptors in oncocytic thyroid neoplasms among 67 specimens. There were no overall significant differences in expression of TSHR or SSTR2 when all OC cases were compared to OA. However, when examining recurrent/metastatic OC separately, advanced OC cases were more likely to be SSTR2 positive and TSHR negative when compared to primary OC cases (Figure 3). This could indicate that SSTR2 only becomes significantly expressed in the advanced OC group. Most clinical and pathologic factors examined in this study (age, sex, race, lymph node positivity) were unable to predict SSTR2 or TSHR expression, reinforcing the complex clinical situation in this patient population, making prognostication difficult.

When examining all OC patients, there was a significant inverse relationship between SSTR2 and TSHR expression that was not seen in OA patients. If OC patients displayed SSTR2 expression, they were less likely to express TSHR. This could be an indication of dedifferentiation within the thyroid neoplasm. It is unclear what biological mechanism causes this transition of increasing SSTR2 with decreasing TSHR expression in OC. Of note, there were a few OA samples which were both SSTR2 positive and/or TSHR negative.

However, the significant inverse relationship between SSTR2 and TSHR was not seen in OA.

Others have linked increased angioinvasion and widely invasive disease to increased aggressiveness of disease and recurrence.[26] Interestingly, when examining the aggressive histologic subtypes of our primary OC, angioinvasion did not predict SSTR2 positivity and TSHR negativity. However, in our cohort, widely invasive histology and clinical extrathyroidal extension were more common in those with SSTR2 positivity. These findings also suggest that SSTR2 expression may be associated with a more aggressive OC phenotype.

Our data are unable to comment on recurrence or RAI sensitivity given our lack of sufficient patient population with standardized follow-up data. However, we feel that the finding of increased SSTR2 positivity in those with advanced OC may support this.

OC can have an unpredictable clinical course and can be a potentially aggressive and rapidly metastatic thyroid tumor.[27] Improving diagnosis and treatment options may dramatically change the landscape of caring for patients with this malignancy. Novel molecular biology and genetic targets are being explored to improve treatment of the clinical challenge that is OC.[28] Of particular usefulness would be to discover markers that help to predict which patients are likely to display aggressive disease following thyroidectomy. This newly investigated relationship between the membrane bound receptors TSHR and SSTR2 may be a key discovery that can be utilized to diagnose and prognosticate OC.

Given the difficulty in diagnosing OC versus OA on fine needle aspiration, and occasionally at the time of final pathology, innovative ways to approach these patients are needed. [29,30] For example, patients with OA may be treated with a unilateral thyroid lobectomy while those patients with OC, especially those with large size tumors, likely benefit from total thyroidectomy.[7,31] But this distinction is rarely known preoperatively. In addition, those with OC need close post-operative monitoring and possibly RAI ablation if the tumor is RAI-sensitive. Thus, knowledge of SSTR2/TSHR status may help in guiding the surgical approach and perioperative management. If SSTR2 is positive and TSHR is negative, this may be a prognostic indicator for aggressive malignancy. Further prospective investigation needs to be completed to substantiate this hypothesis.

Previous studies have supported loss of SSTR2 expression with increasing tumor aggressiveness in neuroendocrine tumors.[24,32,33] Surprisingly, we report the opposite relationship in OCs, since SSTR2 positive tumors are associated with more aggressive behavior. It is possible that the reduced expression of TSHR in OC cells that express SSTR2 explains this observation, given that these tumors are unlikely to respond to TSH suppressive therapy. Indeed, reduced expression of TSHR has been shown to correlate with increased distant metastasis in DTC.[34] Guidelines for the management of thyroid cancer recommend to maintain suppressed TSH levels with exogenous levothyroxine. However, this strategy may not be effective if tumors do not express TSHR, but this is not currently tested in standard clinical practice. Prolonged levothyroxine therapy may cause several side

effects such as atrial fibrillation.[35] Testing for TSHR may facilitate personalized medical decision-making in OC regarding the utility of levothyroxine suppressive dosing.

Unfortunately, some OC are not RAI-sensitive and even those that are, may not benefit from radioactive iodine.[11] Lack of differentiation in OCs also portends a poor prognosis with many of these tumors frequently being RAI- refractory when compared to non-oncocytic poorly differentiated thyroid carcinomas.[36] This makes it imperative to discover alternative methods of treating recurrent and metastatic OC. This may include tyrosine kinase inhibitors (TKIs), but data on efficacy and improvement in outcomes for those specifically with OC are limited.[37] Additionally, TSHR, has been evaluated as a theranostic target in several preclinical models. Szkudlinski et al.[38] described development of the first recombinant human TSH (rhTSH) analog with high receptor binding affinity and enhanced *in vitro* and *in vivo* bioactivity.[39] Later studies examined this analog labeled with 99mTc (99mTc-TR1401 and 99mTc-TR1402) in nude CD-1 mice bearing differentiated thyroid cancer (DTC) xenografts and dogs with spontaneous follicular thyroid carcinoma. In both tumor-targeting experiments, a focal uptake was observed and TSHR expression was confirmed by immunostaining. There are also reports investigating the TSHR as a target for immunotherapy. It has been shown that CAR-T directed at TSHR had strong anti-tumor efficacy against DTC subcutaneous xenograft mouse model when no prominent toxicity was observed.[40,41]

SSTR2 expression has been explored in pancreatic neuroendocrine tumors for imaging and therapeutic indications.[14,15,32,42,43] Tumors that overexpress SSTR2 can be treated with receptor targeted therapies including somatostatin analogs with a proven progression free survival benefit.[44] A few studies have reported on the theranostic use of SSTR directed peptide receptor radionuclide therapy (PRRT) in metastatic thyroid cancer, including OC.[16,45] Budiawan et al, reported results in three OC patients following PRRT and ^{90}Y-or ^{177}Lu-DOTA-TATE.[46] One patient showed a partial response, one patient showed disease stabilization, and one patient did not respond to therapy. This and other studies report mixed results in OC with PRRT targeting SST receptors, a finding that may be due to the variable expression of SSTR2 in OC as reported here. There are also emerging therapies to epigenetically upregulate SSTR2 in cancers hopes of making them candidates for treatment as well as new clinical trials soon to be recruiting.[47] Similar strategies are being investigated to upregulate TSHR in thyroid tumors to enhance treatment options.[18,48,49]

There are some limitations to this study. This is a single institution study and the number of OAs analyzed is low, limiting generalizability of the data to all patients with oncocytic neoplasms. This could also explain a lack of statistically significant difference between all-comer OC and OA patients (chance of a type 2 error). Additionally, the lack of SSTR2 information for the primary tumor for the majority of the advanced disease specimens limits the ability to compare SSTR2 expression between primary and metastatic/recurrent tissue.

Future directions include prospectively validating these data with a larger sample size and incorporating external datasets from collaborators. These data could be utilized to explore interventional pilot trials of anti-SSTR2 therapy in RAI-resistant OC.

In conclusion, our data demonstrate differential expression of SSTR2 and TSHR in OCs as compared to OAs. This finding has theranostic implications from ease of diagnosis to wider treatment options for this clinically difficult malignancy.

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Data Availability Statement:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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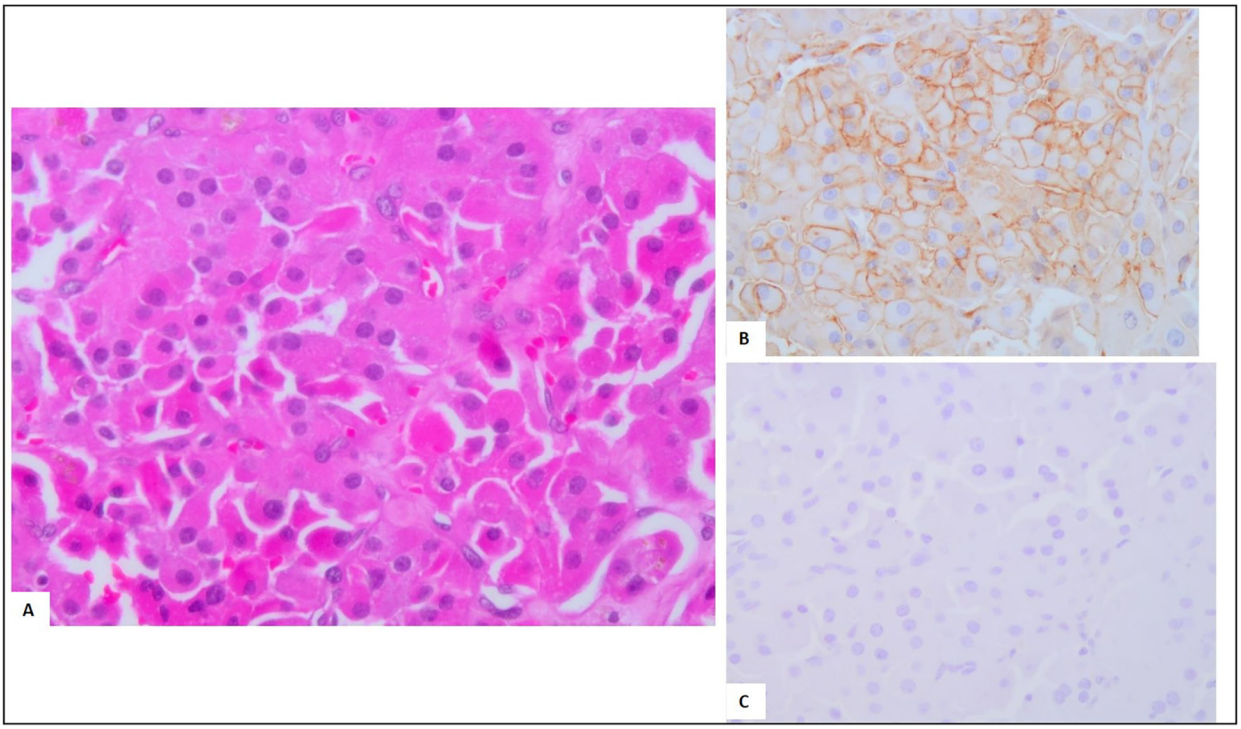

Figure 1:
A case of recurrent Oncocytic Carcinoma (OC) (A-left) shows membranous positivity for Somatostatin Receptor 2 (SSTR2) (B-top right) and is negative for Thyroid Stimulating Hormone Receptor (TSHR) (C-bottom right).

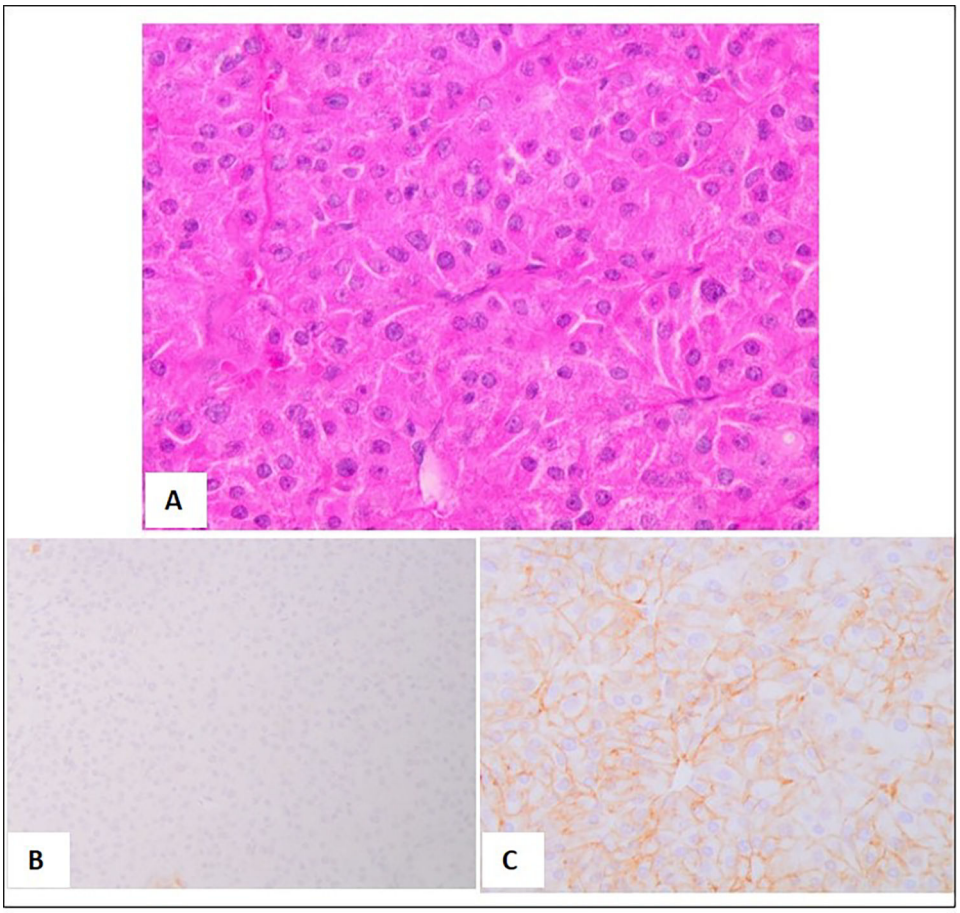

Figure 2:
A case of primary Oncocytic Carcinoma (OC) (A-top) shows membranous negativity for Somatostatin Receptor 2 (SSTR2) (B-bottom left) and positivity for Thyroid Stimulating Hormone Receptor (TSHR) (C-bottom right). The patient had no recurrences or metastases.

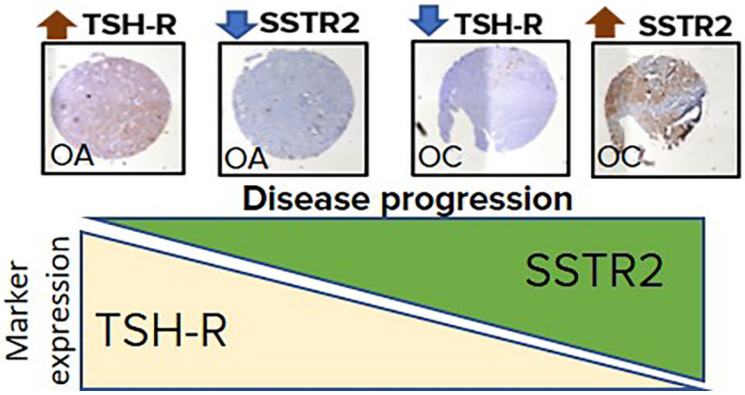

Figure 3:
Schematic of the proposed alteration of membrane receptor expression in benign oncocytic adenoma to aggressive oncocytic neoplasms.

Table 1:

Specimen characteristics, n=67

Characteristics	n (%)
Age, years (mean, SD)	57 (14)
Female	41 (61%)
White Race	47 (70%)
SSTR2 positivity	17 (25%)
TSHR positivity	43 (63%)
Tumor Size (cm), Mean (SD)	3.8 (2.4)
Oncocytic Adenomas	15 (22%)
Oncocytic Carcinomas (OC)	52 (78%)
Primary	45 (85%)
Recurrent	5 (19%)
Metastasis	2 (6%)
OC Level of Invasion	
Minimally Invasive	18 (35%)
Widely Invasive	10 (21%)
Angioinvasive	16 (31%)
<4 foci	7 (43%)
≥4 foci	9 (56%)
Primary OC Extrathyroidal Extension	6 (16%)
Primary OC Lymph Node Positivity	4 (11%)

Table 2:

IHC Staining Results (n=67)

	+ SSTR2		+ TSHR	
	n (%)	**p-value**	**n (%)**	**p-value**
Neoplasm type				
Adenoma (n=15)	2 (13%)	0.224	11 (73%)	0.401
Carcinoma (n=52)	15 (28%)		32 (62%)	
OC Clinical Subtype				
Primary OC without recurrence (n=38)	8 (21%)	**0.041**	27 (71%)	**0.020**
OC w/clinical recurrence or metastases (n=14)	7 (50%)		5 (36%)	
Pathologic OC Subtype				
Minimally Invasive (n=18)	2 (11%)	**0.014**	14 (78%)	**0.468**
Widely Invasive (n=11)	6 (54%)		6 (55%)	
Angioinvasive (n=16)				
<4 foci (n=7)	2 (29%)		4 (57%)	
≥4 foci (n=9)	0 (0%)		7 (78%)	

Membranous immunostain positivity rates by tumor type, clinical, and pathologic subtype **bold=p<0.05**

Table 3.

Primary Thyroid OC Clinicopathologic Details (n=7)

ID	Demographics	Tumor Size (cm)	pT stage	Presence of ETE	Margin status	Pathologic Subtype	Lymph node Involvement	Time to Recurrence (months)	Duration of Follow Up (months)	SSTR2 status	TSHR status	Primary tumor SSTR2 status	Primary tumor TSHR status
1	55 yo, White Male	12	3	extensive	+, tracheal	angioinvasive >4 foci	0/1	8, trachea	136	-	-	-	-
2	62 yo, White Male	7.2	4a	gross, soft tissue	+, multiple areas	widely invasive	6/6	2, locoregional disease	47	+	+	+	+
3	70 yo, White Male	3	2	none	-	angioinvasive, >4 foci	*x*	7, bone	85	-	-	NA	NA
4	51 yo, White Male	5.5	3	gross, strap muscle	+, peripheral	Widely invasive	*x*	9, locoregional in neck then bone	1410^	+	-	NA	NA
5	52 yo, Asian Female	Multifocal: 1.2, 0.7	3	present	+	Minimally invasive	*x*	4, mediastinum	1498	-	+	NA	NA
6	59 yo, African American Female	7.9	3	yes	+, unable to be fully resected	Widely invasive	*x*	0, at diagnosis, bone, mediastinum	12	+	-	NA	NA
7	61 yo, White Male	4.1	3	none	-	Widely invasive	*x*	0, at diagnosis metastatic, lungs	19	-	+	NA	NA

Clinical and Pathologic Details of Patients who presented with Primary Thyroid OC and Developed Recurrence or Metastasizes

x= no lymph nodes examined, ETE= extrathyroidal extension,

^=deceased, NA= no primary tumor tissue available