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The Current Status of Somatostatin Receptors in Malignant Melanoma

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On the basis that melanomas are of neural crest origin and might contain somatostatin receptors, the authors utilized ^{111}In Pentetreotide (OctreoScan) to image 16 melanoma patients with known sites of disease. Twelve of 16 patients were positive with 38 percent imaging all sites. No lesion less than 1.5 cm imaged nor did one ocular and one amelanotic melanoma. Of the five described somatostatin receptors, OctreoScan binds only 2 and 5 suggesting that not all melanomas contain those receptors. It is concluded that melanomas contain somatostatin receptors and that this property might be used for imaging, tumor suppression with Octreotide, and/or as a target for Octreotide labelled with therapeutic agents such as immune complexes, chemotherapeutic agents or high energy radioisotopes.

INTRODUCTION

Early in 1995, we hypothesized that malignant melanoma, being of neural crest origin, might contain somatostatin receptors. If melanomas did contain somatostatin receptors, it should be possible to image them with ^{111}In Pentetreotide (OctreoScan) as is the case with other neuroendocrine tumors such as carcinoids, small-cell carcinoma of the lung and islet cell tumors of the pancreas. A search of the literature provided one reference by Hoefhagel et al. [1] that described one melanoma patient with a positive OctreoScan. A note added in proof stated that six of eight total melanoma patients had been imaged by OctreoScan.

MATERIALS AND METHODS:

A supply of OctreScan was obtained courtesy of Dr. L.K. Kvols, Mallinckrodt, Inc., and 16 successive patients with known metastatic malignant melanoma were imaged. Patients were seen and selected from the senior author's patients. If malignant melanoma patients had measurable disease, they were considered for study with OctreoScan. Measurable disease included shallow, small skin lesions, palpable nodes, or masses found by other radiologic tests.

Gamma cameras used were Prism 2000XP and Prism 300 (Picker International, two- and three-headed cameras) and Genesys (ADAC). Planar acquisitions were 10 minutes/image, except some of the 48 or 72 hour images were 20 minutes. Single photon emission computed tomography (SPECT)[b] imaging was carried out on the Prism cameras,

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[b] *Abbreviations:* SPECT, single photon emission computed tomography.

using 40 second stops at 6-degree intervals; on some 48 or 72 hour images, the time was increased to 60 seconds.

Patients were interviewed and given six mCi (222 megaBecquerels) of ^{111}In pentetreotide intravenously. Most had planar imaging at four hours at the site of known disease, and all had planar imaging at 24 and 48 hours. A few had additional imaging at 72 hours. SPECT imaging was carried out of chest (usually at 24 hours), abdomen (usually at 48 hours) or pelvis (usually at 48 hours), or two or three of these areas, depending on known/suspected site(s) of disease. One patient did not fit within the SPECT gantry, and only planar imaging was performed.

SPECT images were reconstructed on an Odyssey VP workstation (Picker) using a ramp pre-filter and a low-pass Butterworth filter of order and cut-off determined by the appearance of the images. They were re-sliced in orthogonal planes and viewed on a workstation and printed. They were also used to construct a Max Pixel Raytrace image viewed on the workstation.

Images were examined by several Nuclear Medicine/Radiology staff. Any other imaging modalities available were also examined at the time of initial interpretation, and a clinical report was generated.

Seventeen scans were performed in 16 patients. Ages ranged from 29 to 82 with a mean of 58 years. There were eight men and eight women. There was one ocular melanoma, and 15 cutaneous melanoma, of which 14 were melanotic and one was amelanotic.

RESULTS

In four patients, or 25 percent, Octreoscan was completely negative, despite known disease. In six patients, or 38 percent, some lesions were imaged and some were not. In the remaining six patients, or 38 percent, all known disease was identified by Octreoscan. Seventy-five percent of patients had at least some lesions identified.

The smallest lesions detected by Octreoscan was a 1.5 cm lung metastasis noted on computed tomography. Of note in the six patients with known disease partially imaged, a total of eight lesions were missed. Four of these eight lesions were smaller than 1.5 cm.

In the patient in which a follow-up Octreoscan was obtained one year later, the second scan depicted progression of cutaneous lesions with regression of lung disease.

Ten of the imaged patients underwent excision of some or all of their tumor, which is being analyzed for somatostatin receptors by Dr. Sue O'Dorisio at Ohio State University in Columbus, Ohio. Correlation of results is pending, and it is anticipated we may determine the receptor makeup of patients whose tumors are imaged by OctreoScan [2]. Several patients with large lesions in the liver or spleen that did not take up OctreoScan provided definite negative images, which afforded a useful diagnostic image.

DISCUSSION

These data confirm Hoefhagel's observation that some melanomas can be imaged by OctreoScan, indicating the presence of functional somatostatin receptors. While the percentage of positive scans limits the diagnostic utility of Octreoscan in melanoma at present, this is a very preliminary report, and further experience will be required to determine the true sensitivity and specificity of the test when compared to histologic verification of melanoma.

The finding that some melanomas contain somatostatin receptors confirm that melanoma is a neuroendocrine tumor and implies some host control of melanoma growth.

Given the paucity of effective therapies for melanoma, this is a very exciting observation. It suggests the possibility of suppressing melanoma growth with somatostatin analogs such as long-acting Octreotide. Perhaps more importantly, somatostatin receptors provide a potential target for somatostatin analogs labeled with tumor specific immune complexes, chemotherapeutic agents or high-energy radiotherapeutic sources.

The first long-acting somatostatin analog to be developed for clinical use was octreotide, with a half-life of two hours, yet retaining similar physiologic actions. Unlike somatostatin-14 and -28, which bind to all five somatostatin receptor subtypes with high affinity, octreotide binds to somatostatin receptor subtypes 2 and 5 with similar affinity as native somatostatin-14 and -28, but with much lower affinity for somatostatin receptor subtypes 1, 3 and 4.

Since some melanomas did not image at all with OctreoScan, we can assume that not all melanomas contain somatostatin receptors 2 or 5. It is of note that neither the ocular or the amelanotic melanoma in this series were imaged by OctreoScan. Both of these tumors are aggressive and particularly resistant to host control or treatment once they have metastasized. Very possibly their receptor content is related to this resistance.

In summary, current potential clinical application of OctreoScan in melanoma patients appears limited to that subset of patients who have disease expressing somatostatin receptor 2 or 5. For this group, OctreoScan may be useful in 1) diagnosing disease, as a potential adjunct to scintigraphy and identification of sentinel lymph nodes in selective lymph node dissection or as a means to localize early metastatic disease; 2) therapy, by selectively targeting tumors with high somatostatin receptor subtype 2 or 5 expression with radionuclide therapy or perhaps in trials of systemic octreotide administration; and 3) follow-up of patients with known somatostatin receptor subtype 2 or 5 disease. Limitations of practical use for OctreScan may be overcome in the future with the development of somatostatin analogs that selectively bind the other somatostatin receptor subtypes 1, 3 and 4.

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