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Initial Staging of Lymphoma With Octreotide and Other Receptor Imaging Agents

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Somatostatin receptor scintigraphy is useful in diagnosing tumors with increased expression of somatostatin receptors. The correct use of this technique reveals the localization of neuroendocrine primary tumors and unknown metastases in approximately 90% of patients. However, somatostatin receptor scintigraphy also can image many other human tumors expressing somatostatin receptors, including malignant lymphomas and thymomas. The sensitivity of somatostatin receptor scintigraphy to image somatostatin receptor-positive tumors is very high, but due to the variable expression of specific receptor subtypes, the specificity can be relatively low. This drawback is crucial in evaluating lymphoproliferative diseases, or, in general, when immune cells are involved. The sensitivity of somatostatin receptor scintigraphy for Hodgkin's lymphoma is 95%-100%, whereas for non-Hodgkin's lymphoma it is around 80%. It has been shown that the uptake of [^{111}In-DTPA^0]octreotide in lymphomas is lower compared to the uptake in neuroendocrine tumors. This is mainly attributed to the low number of receptors on immune cells compared to neuroendocrine cells; however, ligand-induced internalization and differential receptor regulation may also participate in determining this phenomenon. Therefore, caution should be taken when interpreting data from some studies. Several new ligands are currently under study to improve these limits and the expression of other neuropetide receptors is being investigated to provide a molecular basis for in vivo multireceptor targeting of tumors. With the use of currently available somatostatin analogs, somatostatin receptor scintigraphy does not seem to have a significant impact in patients with lymphomas for diagnostic purposes. There are a few exceptions, however. Among these, the staging and restaging of extragastric lymphoma MALT-type may present some advantages. Conversely, somatostatin receptor scintigraphy in the imaging of thymic malignancies could enhance both our diagnostic and therapeutic capabilities. Somatostatin receptor scintigraphy is diagnostically relevant in differentiating malignant from benign lesions, especially in those patients with associated paraneoplastic syndromes, and is the main criterion to select patients suitable for therapy with somatostatin analogs. Recent findings emerging from in vitro studies on somatostatin receptor physiology in immune cells will certainly reopen and expand the potential applications of somatostatin analogs for in vivo diagnostic and therapeutic options.
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Somatostatin (SS) receptor (SSR) scintigraphy (SRS) is useful in diagnosing tumors with increased expression of SSR.[1] SSRs are expressed in selected human malignancies and, among these, they are frequently expressed in both primary and metastastic neuroendocrine tumors (NET). The intense and homogeneous distribution of a specific SSR subtype, namely sst_2, on tumor cells forms the basis of the development of SRS, in which sst_2-positive tumors can be imaged in vivo. [^{111}In-DTPA^0]octreotide, injected into patients who are suspected of having sst_2-positive tumors, allows planar and emission computed tomography (CT) images by γ-camera.[2] This technique may reveal the localization of the primary tumor and, in most instances, its previously unknown metastases in nearly 90% of patients with NET. A close relationship exists between the in vitro detection of SSR in tumors with autoradiography and the positive scans obtained in vivo after the injection of radionuclide-coupled octreotide.[1] The use of SRS in the initial analysis of patients with

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NET is mainly to image multiple or metastatic tumors, which is important to stage the patient and also to determine the optimal treatment strategy.[1,2] SRS allows imaging not only of NET, but most well-differentiated brain tumors, such as meningiomas, low-grade astrocytomas and neuroblastomas. Merkel cell tumors, thyroid cancers, prostate cancers, and primary breast cancers can be imaged as well.[1,2] After successful imaging of NET and other solid human tumors, it was also demonstrated that malignant lymphomas and sites of other diseases involving immune cells could be visualized in vivo by SRS.[3,4] However, sensitivity of imaging was found to differ in several studies, although all these tumor types variably express sst_2.[5,6] Indeed, the sensitivity of SRS to image sst_2-positive processes is very high, but because of the variable expression of this receptor subtype both in NET and non-NET as well as in most immune diseases, its specificity is relatively low.[7] As mentioned previously, the density of SSR on neoplastic cells is often high and the distribution is usually homogeneous. Although sst_2 is clearly the predominant SSR subtype expressed, other subtypes can be expressed as well. In fact, apart from [^{111}In-DTPA^0]octreotide, other ligands for SRS are currently under study.[8] It is expected that ligands that specifically bind to sst rather than sst_2 will be developed for SRS shortly.[9] Moreover, several human tumors can express peptide receptors other than SSR: insulinomas have more glucagon-like peptide 1 receptors than SSR, but NET may also express cholecystokinin 2, bombesin or vasoactive intestinal peptide (VIP) receptors; normal and altered lymphoid cells densely express VIP and substance P receptors. Often, several of these peptide receptors are expressed simultaneously in tumor cells, providing a molecular basis for in vivo multireceptor targeting of such tumors.[9,10]

New knowledge and the findings from these studies are providing new perspectives for the staging and treatment of several neoplasms, including lymphomas. Before entering the discussion on the role of SRS in lymphomas, some retrospective information on SSR and on the significance of their expression in immune cells should be reviewed, and new insights on SSR physiopathology should be taken into account. First, lymphoma cells do express SSR; however, subtype receptor expression seems qualitatively limited to 2 SSR subtypes (sst_2 and sst_3) and the number of receptors is also very low.[11] Second, other neuroendocrine products, as well as their respective receptors, have been detected in cells of the immune system.[12] More recently, it has been shown that human lymphoid tissues and immune cells express different levels of cortistatin (CST), suggesting its potential importance as an endogenous ligand for SSR in the human immune system, rather than SS itself.[13] In fact, the selective expression of CST mRNA and not SS mRNA was only found in isolated cells of the human immune system, whereas other SS-target tissues expressed both SS and CST mRNA.[14] It is intriguing that among the hormone and neuropeptides influencing the immune system, SS mainly seems to inhibit cell activities. Indeed, SS inhibits hormone secretion and cell proliferation in neuroendocrine and non-neuroendocrine tissues and may modulate the response of various cells to endocrine stimulation.[12] Controversial effects have been obtained in several experimental conditions where SS may stimulate certain immune cell functions, such as secretion of specific products (immunoglobulin, cytokines), cell migration, and cell adhesion to extracellular matrix components.[15-19] SS and synthetic SS analogs exert their effects via the 5 specific SSR subtypes. SSRs display a tissue specific distribution, but the majority of SS-target tissues may coexpress multiple subtypes.[20,21] Recently, SSR subtype expression in human tissues and cells has been better defined and characterized by immunohistochemistry and immunofluorescence, as well as by RT-PCR and in situ hybridization.[22,23]

Significance of Somatostatin, Cortistatin, and Somatostatin Receptor Expression in Lymphoid Cells

SS-like peptides have been found endogenously synthesized in rat basophilic leukemia cells, demonstrating the presence of neuropeptides in immune cells and suggesting their potential involvement in the transition of immune cells from normal to a pathological state.[24] SS-14 and SS-28 have been identified in rat lymphoid organs (spleen and thymus) using anti-SS antibodies,[25] and activated macrophages isolated from granulomas of *Schistosoma mansoni*-infected mice may produce the peptide locally.[26] More recently, SS has been found highly expressed in both cortical and medullary epithelial cells in murine thymus[27]; whereas, in human thymus, SS has been localized in nerve endings and is also endogenously produced in a subset of thymic epithelial cells.[28] Recently, increased attention has been shown to CST, an endogenous ligand for SSR so termed because of its predominant cortical expression.[29] Actually, among human lymphoid tissues, SS mRNA has been detected only in thymic epithelial cells, while not in thymocytes or in other isolated immune cells.[14,28,30] Conversely, CST mRNA has been observed in diverse immune cells, including thymocytes and peripheral lymphocytes, as well as in other lymphoid tissues investigated using quantitative RT-PCR.[13,14] Interestingly, the expression of CST mRNA appeared to be up-regulated during differentiation of monocytes into macrophages and dendritic cells, pointing to a regulatory role of CST in the human immune system.[31]

Generally, the existence of a ligand suggests the expression of its own receptor(s) on that cell. First observations showed a variable presence of SSR in different animal and human lymphoid cell lines. Caution should be taken when extrapolating data derived from immortalized cell lines, since these cells may have characteristics different from primary lymphoid cells. Moreover, the existence of species variability in the distribution of neuropeptide receptors in immune cells has been demonstrated as well, suggesting that an animal model might display a different receptor subtype pattern compared with the human cells.[32-34] In general, SSR expression on endocrine cells is actively regulated (up- or down-regulated) by endogenous and exogenous factors, as well as by changes in microenvironmental conditions. This observa-

tion is even more important for immune cells, where the expression of a given receptor is strongly related to the activation and/or proliferation state of the cells, or may greatly change when cells circulate in peripheral blood or migrate and differentiate in specific tissues (reviewed in refs. 34-36).

SSRs have been found in different organs of the human immune system, such as the lymph nodes, tonsils, Peyer's patches, spleen and thymus.[28,37,38] Using ligand-binding techniques, SSRs have been detected in animal and human circulating B and T-cells, as well as in spleen-, lymph node-, and thymus-derived cells.[39-41] On peripheral human lymphocytes, sst_3 mRNA has been found constitutively expressed, whereas sst_5 mRNA seemed up-regulated after the activation of these cells.[42,43] Conversely, inactivated monocytes do not express SSR, however, the activation of these cells seems to induce the expression of sst_{2A}.[43,44] The differential expression of SSR in lymphocytes and monocytes suggests a functional significance for the CST-SSR, rather than SS-SSR, interplay in immune cells. Additional evidence of the plasticity of this pathway in the immune system is provided by the finding that the SSR number decreases with the increasing age of the thymus, while the expression of distinct subtypes of SSR seems developmentally regulated in different subsets of thymocytes.[45,46]

Significance of Somatostatin Receptor Expression in Lymphoproliferative Diseases: Evidence from Basic Studies

Several neuropeptide receptors have been detected in cells from patients with lymphoproliferative diseases and hematological malignancies. A typical example is the expression of SSR in these cells. Again the first observations derived from cell lines, such as the Jurkat line of human leukemic T-cells and U-266 IgE-producing myeloma cells, which displayed high- and low-affinity binding sites for fluorescent and radiolabeled SS, whereas low and high affinity classes of SS-binding sites were detected on lymphoblastic leukemia cells.[47,48] Moreover, a large number of SSRs were found on the human adult T leukemic cell line MT-2 and on the human T-cell line Molt-4F, while a lower number was expressed on the Epstein-Barr virus transformed B-cell line Isk.[49] By RT-PCR, which allows receptor subtype characterization, a number of lymphoid cell lines of different origins (T- and B-cell, myeloma, as well as leukemic clones) were shown to express a variable amount of sst_2, sst_3, sst_4, and sst_5 mRNAs, while sst_1 was consistently absent.[50,51] Interestingly, sst_2 mRNA expression in normal human peripheral blood mononuclear cells (PBMC) has been found to be very low compared to the expression of this SSR subtype in cell lines and in PBMC from leukemic patients. In addition, sst_2 mRNA expression in normal PBMC increased after activation, again supporting the concept that the SSR expression pattern in lymphoid cells depends on their state of activation.[50] Furthermore, it has been demonstrated that the Jurkat T-cell line selectively expresses sst_3 mRNA, suggesting the involvement of this subtype in the regulation of T-cell function.[51] An important study showed that the SS analog octreotide inhibited growth of different interleukin-6 (IL6)-dependent and IL6-independent human multiple myeloma cell lines.[52] The effect of octreotide on these cell lines, expressing sst_2, sst_3, and sst_5 receptors, was mainly cytostatic; however, in 3 of 8 lines a weak octreotide-induced apoptosis was detected similar to the apoptosis observed in B-B4$^+$ plasma cells isolated from the bone marrow of patients with multiple myeloma and treated with octreotide.[52] This supports the possibility that octreotide-induced apoptosis may occur in cells that express sst_3, as it is involved in this pathway.[53]

SSRs have been found by autoradiography in biopsies from patients with both T and B non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) and their metastases.[5,54,55] While the in vivo imaging technique using [^{111}In-DTPA^0]octreotide has contributed to optimized staging procedures in patients with malignant lymphomas (see below), in vitro autoradiography after ligand-binding studies demonstrated the presence of a low number of SSRs, although localized predominantly in the lymphoblastic areas of the lymphomatous tissues, which represents the active part of these tumors.[54] The number of SS-binding sites in these neoplastic tissues is significantly lower compared to classical neuroendocrine SSR-expressing tumors displaying a similar amount of in vivo radioactivity uptake at SRS.

Somatostatin Receptor Scintigraphy in Lymphoproliferative Diseases

Additional important information on SSR expression in human immune cells in pathological conditions derives from in vivo SRS studies. As previously mentioned, this technique has been employed to visualize other non-NET expressing SSRs.[1,56-58] SRS by means of [^{111}In-DTPA^0]octreotide has been noted, after successful imaging of NET, to detect and stage solid, hematological, malignancies.[4,59,60] The sensitivity of SRS was found to be different in the detection of lymphoma in a published series.[4-6] Tumor size and location were considered to play a pivotal role in lymphoma detection.[5] Furthermore, histological lymphoma type was demonstrated to significantly affect the sensitivity of SRS, being higher in depicting HL deposits than NHL ones.[2,5]

Hodgkin's Lymphoma

Preliminary reports showed an elevated accuracy of SRS in detecting HL at initial staging. In fact, SRS was positive in 55 of 56 untreated patients with HL (98%) at sites of documented disease.[61] The added values of SRS were: (1) the detection, in 20 patients, of HL deposits missed by other conventional modalities of staging; (2) the change of stage in 12 cases (21%); and (3) the change in treatment in 7 cases (13%).[55,61] In a larger series of 126 newly diagnosed HL patients, the results of SRS were compared with those of conventional staging procedures, such as CT and ultrasound.[62] The overall lesion-related sensitivity was 94%, rang-

ing from 98% for suphradiaphragmatic to 67% for infradiaphragmatic lesions. SRS was largely superior to CT and ultrasound for disease identification in stages I and II supradiaphragmatic HL patients, detecting more advanced disease in 18% of cases who were upstaged to stage III or IV and affecting the patients' management.[62] Conversely, below the diaphragm the CT was more sensitive than SRS.

Non-Hodgkin's Lymphoma

SRS was positive in 85% of 72 patients with NHL, showing additional sites of disease in 21% of cases, upstaging 13 patients.[55] However, the scintigraphic results did not correlate with the degree of malignancy.[55] SRS in the initial staging of patients of untreated, low-grade NHL was compared with the results of conventional imaging.[63] SRS was positive in 42 of 50 cases (84%), revealing in 10 cases (20%) more lesions than conventional imaging modalities. Their upstaging caused a change in the therapeutic plan in 5 cases. However, in a per site evaluation, SRS sensitivity was relatively low, ranging from 44% for infradiaphragmatic to 62% for supradiaphragmatic lesions. Thus, although SRS was positive in a large proportion of patients with low-grade NHL, only a part of the disease deposits were visualized. Such a limited sensitivity, in a per site analysis, does not support the use of SRS as a diagnostic tool for initial staging in low-grade NHL.[63]

SRS seems to have a valuable clinical role in the management of patients with cutaneous malignant lymphoma, being able to differentiate dermatopathic lymphadenopathy from malignant lymph node infiltration.[64] Confirmation of preliminary results in a larger series of cases is strongly required to move from an investigational to a clinical phase.

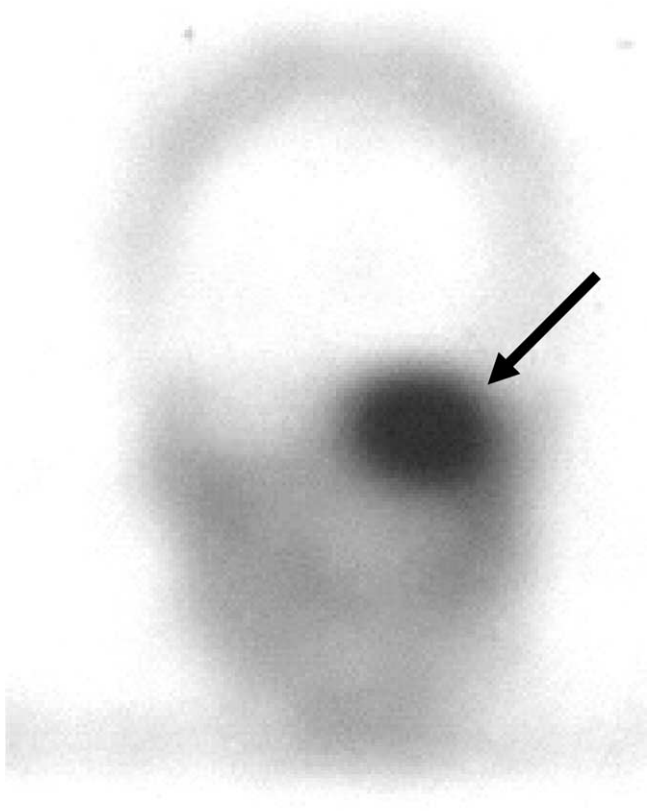

Figure 1 Somatostatin receptor scintigraphy in lymphoma. MALT-type lymphoma of the orbital tissue showing detectable expression of somatostatin receptor positive cells. Head SPECT acquired 24 hours after radoligand injection. In the coronal view, [^{111}In-DTPA^{0}]octreotide uptake is evident in the left orbit (arrow).

MALT Lymphoma

Mucosa-associated lymphoid tissue (MALT)-type lymphomas are a distinct clinical entity among NHL. Although frequently of a gastric origin, they may also have an extragastric origin.[65,66] The staging of MALT-type lymphoma by SRS has been extensively investigated. In 29 consecutive patients, Raderer and colleagues found that SRS had extremely poor results in detecting primary gastric MALT-type lymphoma (1/15 endosonographically-documented lesions), as well as in detecting lymph node involvement in patients at stage II.[67]

Conversely, in patients with primary, extragastric, MALT-type lymphoma, the large majority of neoplastic deposits showed a significant uptake of [^{111}In-DTPA^{0}]octreotide. In vitro evaluation of SSR expression by Northern blotting demonstrated large amounts of mRNA for sst_2 in extra-gastric MALT-type, while gastric MALT lymphomas showed a faint expression of mRNA for sst_3 and sst_4, but not for sst_2.[67] Recently, Dalm and coworkers, using several in vitro methods, confirmed the lack or relatively low expression of SSR subtypes in a series of different lymphoma histotypes.[11] This in vitro evidence may be the most reliable explanation for the controversial results of SRS in patients with lymphoma and the main drawback for radiotherapeutic approaches.[11] The ability of SRS to accurately stage extragastric MALT-type lymphomas has been confirmed in a subsequent study by Raderer and coworkers, who also highlighted the early detection of relapses, documented later only by other imaging modalities.[68] Furthermore, SRS has been proposed for monitoring the response to treatment, as recently reported in an unique case of extragastric, stage I, MALT-type lymphoma of the lachrymal gland treated with rituximab.[69] An example of lacrimal MALT-type lymphoma, with elevated [^{111}In-DTPA^{0}]octreotide uptake is shown in Figure 1.

In a small series of patients, we have found a relatively more elevated uptake of [^{111}In-DTPA^{0}]octreotide in primary or metastatic deposits of extragastric MALT-type lymphoma than in other positive NHL histotypes (S. Lastoria, F. Frigeri, A Pinto, personal experience). Tumor-to-background (T/B) ratios were extremely lower when compared with those measurable in NET. The T/B ratios ranged, for visualized lesions, from 1.4 to 3.8-fold. A significant difference was also found in the magnitude of T/B ratios measured in extragastric MALT-type lymphoma patients (7; 2.7 $\pm$ 1.3) versus those measurable in patients

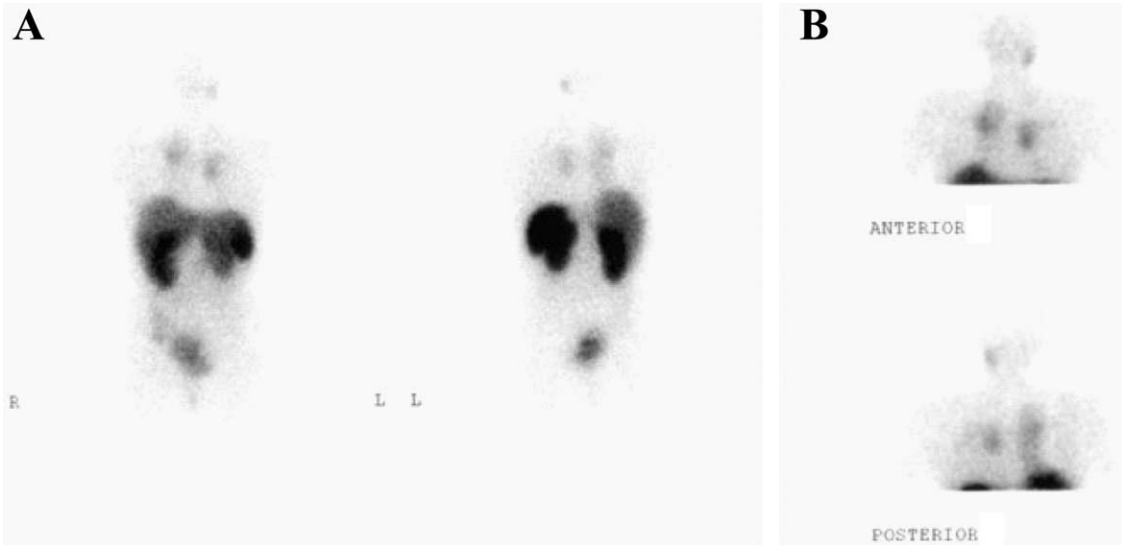

Figure 2 Somatostatin receptor scintigraphy in lymphoma. (A) Anterior and posterior views of a patient during a whole body scan 24 hours after the injection showing the uptake of [^{111}In-DTPA^{0}]octreotide in NHL deposits. (B) Detail of the anterior and posterior view of the chest and head in the same patient.

with other extranodal NHL types (9; previously untreated and treated). The magnitude of T/B ratios for the detected lesions in the first group of 6 untreated patients lowered to 1.8 ± 1.2 in the second, larger group of patients.

The difference in the magnitude of radioligand uptake is clearly evident in our experience. In 2 cases with a primary extranodal NHL, the untreated NHL showed an intense, but heterogeneous, accumulation of [^{111}In-DTPA^{0}]octreotide, with a T/B ratio of 3.6-fold; the relapsing NHL had a lower T/B ratio of 2.1-fold (Fig. 2). The different T/B ratios did not affected the tumor detection.

In 2 cases, the use of SRS was inadequate to follow the behavior of the disease, missing extranodal lung metastases, as well as other metastatic localizations (spleen, bone, and bone marrow). In 5 patients, SRS, at each specific step, consistently confirmed or ruled out the presence of disease, being perfectly concordant with the clinical and diagnostic findings. In these 5 patients, SRS did not add further, valuable data of clinical utility for the patients' management. The different magnitude of [^{111}In-DTPA^{0}]octreotide uptake in NHL and the in vitro results evaluating the SSR expression may indicate that autoradiography or other binding assays often may underestimate the density of receptors.

The in vivo and in vitro results in patients with primary, extragastric, MALT-type lymphomas made this subset of patients eligible for SRS and potentially for therapies based on the use of SS analogs because of the sst_2 density. A larger evaluation of SRS is needed in patients with extragastric NHL MALT-type lymphoma for staging purposes. The limited/absent value of positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in this histotype has been shown negative.[70,71]

Somatostatin Receptor Scintigraphy in Particular Clinical Circumstances

Evaluation of Bone Marrow Infiltration

A very detailed analysis of this clinical aspect is not commonly present in the literature. Sometimes the ability of SRS to detect or not detect bone marrow infiltration is described. Generally, these sites of disease are missed by SRS, as reported for the 2 patients with cutaneous malignant lymphoma.[64] This problem occurred in 11 of 12 patients, either at diagnosis or during restaging.[6] In a series of 10 patients with proven NHL having from 50% to 100% bone marrow involvement, a double dose of radiolabeled peptide was given to enhance the detection of bone marrow infiltration.[72] The sensitivity for bone marrow involvement was 10%, clearly under reliable values for clinical implications. This area of diagnosis is not covered better by PET-FDG.[71]

Evaluation of the Central Nervous System

No adequate data exist to evaluate the potential role of SRS in this subset of patients. Primary lymphoma of the central nervous system constitutes about 1% of all brain malignancies in the common population and it may rise to 6% in a population of AIDS patients. Primary cerebral lymphomas are usually detected by CT and magnetic resonance imaging (MRI). The lack of specific characteristics in radiological images does not allow differentiation from gliomas, meningiomas, metastases, or cerebrovascular accidents. The SRS approach has been reported in one case to detect the primary lesion and, on follow-up, show persistence of lymphoma after radiotherapy, while CT showed a significant regression in the tumor lesion.[73]

Evaluation of Childrens' Lymphoma

The application of SRS with [^{111}In-DTPA^0]octreotide in children with lymphoma is extremely limited, while of some interest is the approach using ^{99m}Tc-depreotide.[74] This SS analog is a 10-amino acid synthetic peptide which binds with high affinity to sst_2, sst_3, and sst_5, and has been able to image in vivo and to bind in vitro to several solid human tumors.[75] A preliminary experience using this new analog in a low number of adult patients with NHL suggested the possibility of potential therapy with γ-emitter–labeled peptides.[76] However, depreotide did not appear to be a suitable candidate as a targeting agent due to the relatively high bone marrow concentration.[76] Cholewinski and coworkers have investigated SRS with ^{99m}Tc-depreotide in 15 children (8 with HL and 7 with NHL). In all cases, foci of increased radiopeptide uptake were seen.[74] Although the majority of the lesions was localized in the neck and in the chest, abdominal sites of disease were detected as well as bone/bone marrow infiltration.[74] In 11 of 15 children, the number of lesions detected by SRS with ^{99m}Tc-depreotide was greater than that detected by CT, allowing upstaging in 3 of them. This approach, because it is a one-day procedure and it seems to have promising insights, deserves to be investigated in a larger series, either in adult or children.

Another ^{99m}Tc-labeled synthetic peptide, ^{99m}Tc-EDDA/HYNIC-TOC, binds to SSR with higher affinity than [^{111}In-DTPA^0]octreotide and is highly promising for SRS.[77] The evaluation of the spleen infiltration and stem cell transplantation, as well as specific studies to image lymphoma of the bone or other extranodal entities by SRS, are not performed because of the excellent results with PET-FDG.

Somatostatin Receptor Scintigraphy in Thymic Tumors

During the last 10 years, interesting findings emerged from in vivo and in vitro studies on SSR expression and function in thymic tumors that has improved the knowledge of SSR physiopathology in immune system.

Thymic tumors are epithelial neoplasms frequently associated with an exuberant lymphoid component, which is usually composed primarily of immature cortical lymphoid cells. These thymocytes, growing at rates comparable to those observed in fetal thymuses, have phenotypic abnormalities, polyclonal rearrangements of T-cell receptor genes, and cytoplasmic expression of aspecific products.[78] Several authors have shown that SRS with [^{111}In-DTPA^0]octreotide enables the detection of primary and metastatic thymic tumors with elevated levels of uptake.[78-83] These results were unexpected because previous in vitro autoradiography experiences did not show SSR in bioptic thymic lesions, but in thymic carcinoids.[3] More accurate studies since then demonstrated that SSR expression was the reason for successful external γ-imaging by [^{111}In-DTPA^0]octreotide in human thymic tumors, as well as, in part, for the therapeutic results with SS analogs.[82,83] In fact, sst_1, sst_{2A}, and sst_3 have been demonstrated by immunohistochemistry and RT-PCR in thymic tumor tissues,[82,83] with a considerable heterogeneity of SSR immunoreactivity within and among the thymic tumors, which might play a crucial role in determining the in vivo uptake of radiolabeled SS analogs.[83] However, from the evidence in these tumors, the presence of sst_2 receptors does not seem a prerequisite for the visualization of SSR-positive tissues during [^{111}In-DTPA^0]octreotide scintigraphy. In fact, in 2 thymomas with similar clinical presentation, in vivo SSR scintigraphy detected a different degree of [^{111}In-DTPA^0]octreotide uptake, although the 2 thymic tumors had a similar volume.[83] SSR subtype patterns studied in vitro in the surgical specimens of the 2 thymomas revealed that the relative expression of sst_{2A} mRNA was similar, whereas the expression of sst_3 mRNA was significantly higher in the neoplasm with the highest accumulation of the radioligand in vivo.[83] In general, untreated thymic lesions had significantly more avid [^{111}In-DTPA^0]octreotide than those previously treated, as documented by measured T/B ratios (4.34 ± 1.57 versus 2.68 ± 1.18). An example of untreated thymic tumors is shown in Figure 3 with a relative CT scan of the chest.

SRS has been extensively investigated in those patients with advanced and/or metastatic thymic tumors in whom surgery alone, or associated with other conventional therapies, has not been sufficient. In vivo demonstration of SSR expression by SRS in these thymic deposits has been shown to be pivotal and reliable evidence to select those patients who will potentially respond to therapies based on the use of cold SS analogs.[84-86] Besides therapeutic implications, SRS has several more important diagnostic and clinical relevancies, making possible: (1) the differential diagnosis between thymic malignancy versus benign hyperplasia, being groundbreaking in patients with early-stage disease and myasthenia gravis, where CT and MRI often fail[78,79]; and (2) the identification of patients with multi-endocrine neoplasia (MEN) type 1 or 2, because SSRs are highly expressed in the associated NET.

SRS is not a substitute for other imaging modalities (CT and MRI) in the evaluation of recurrent and/or metastatic thymic tumors that add functional information, such as the receptor profile of thymic malignant lesions. The use of a multimodal diagnostic approach allows one to better characterize thymic masses with less cost burden considering the relative low incidence of such diseases.

New Directions and Conclusions

In reviewing published research and in our own experience, SRS in general does not seem to have a ground breaking impact in patients with lymphomas for diagnostic purposes. Staging is largely affected by the anatomical location of lymphoma deposits, being missed in a large percentage of underdiaphragmatic lesions. Furthermore, the density of SSR subtypes does not seem to be sufficient to allow clinically reliable images useful for the patients' management. Therefore, in the era of PET and/or PET/CT with FDG, the staging and restaging analysis should be ensured by the evaluation of FDG

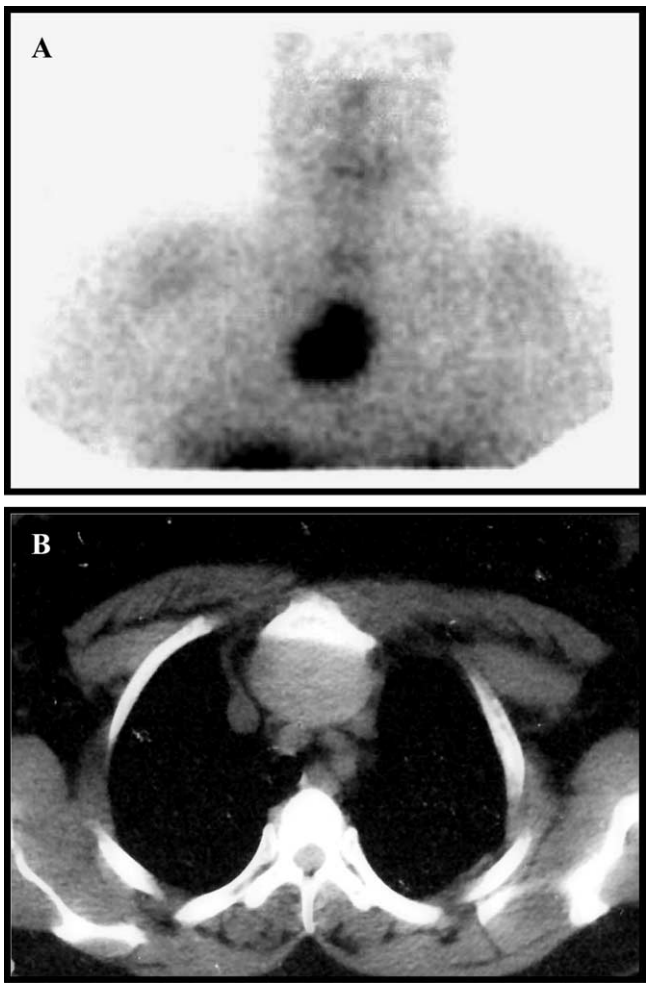

Figure 3 Somatostatin receptor scintigraphy in thymoma. (A) Large thymic mass showing intense and homogeneous [^{111}In-DTPA^{0}] octreotide uptake, which positively correlated with somatostatin receptor expression within malignant epithelial cells of this thymic mass. (B) CT slice of the same lesion allowing definition of the borders of the mass, which is not dissociable from the sternum anteriorly.

consumption within lesions with few exceptions.[71] A diagnostic niche, where SRS seems to have a role, is in the staging and restaging of extragastric MALT-type lymphoma, also because of the relatively poor sensitivity of PET-FDG. Opposite conclusions may be drawn for the role of SRS in the imaging of thymic malignancies. SRS is diagnostically relevant in differentiating malignant from benign lesions, especially in those patients with myasthenia gravis. Moreover, SRS is the main criterion to select those patients eligible for SS analog-based therapies.[78,79,84-86]

Since the expression of SSRs in some NET seems to have a prognostic value,[87] it would be interesting to investigate this possibility in lymphoproliferative diseases as well. In fact, specific SSRs expressed in progenitors of immune cells are not present in the mature phenotype, while their expression can be detected in transformed cell lines. The possibility that such a marker expression is caused by oncogene can not be ruled out. Indeed, preliminary data in human lymphoid cells showed a developmental expression of SSR, which suggests evaluation of their potential role as a differentiation marker.[88]

Furthermore, the development of receptor-based localization and antitumor strategies may be extended to other G protein-coupled receptors. This could be valid for many different reasons: neuropeptide receptor homo- and heterodimerization has recently been shown to occur in transfected cell lines and involves different subtypes of SSR, as well as SSR and receptors for dopamine.[89-91] Dimer formation seems to enhance or modify the transduction pathway activated by the monomeric receptor.

In vivo imaging techniques of tumor *via* receptors for other well known neuroeptides, such as bombesin, VIP, substance P, and gastrin, have already been employed to visualize many neoplasms,[92] and ligand-binding studies clearly demonstrated neuroreceptor binding sites in human tumors.[10] Moreover, several new radioligands have been developed in many laboratories and are currently under investigation (Fig. 4). New applications will certainly become available in the future for lymphoproliferative diseases as well. The simultaneous expression of several peptide receptors in a given tumor type may lead to novel diagnostic and therapeutic strategies in the near future.[9] The use of a cocktail of peptide radioligands recog-

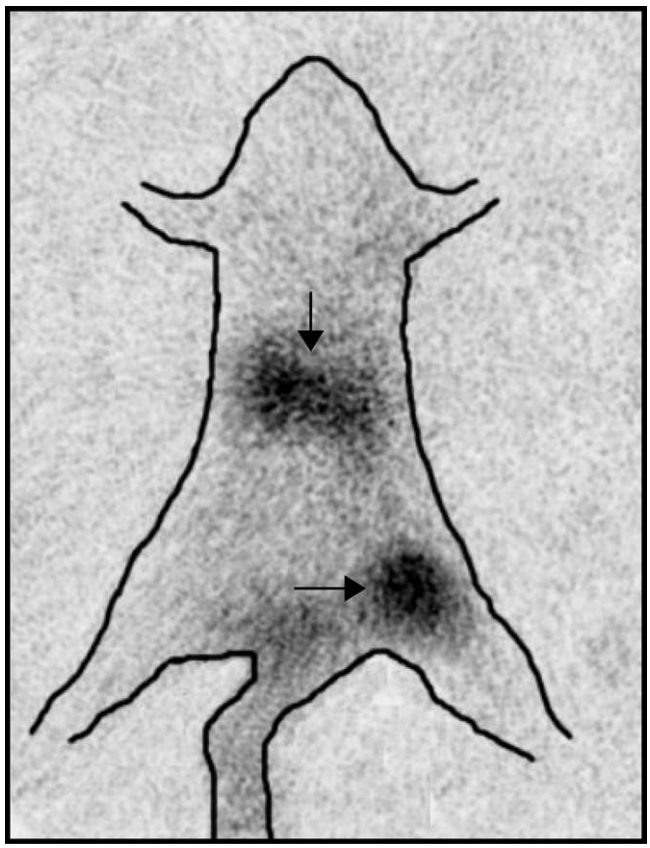

Figure 4 Nude mouse bearing human lymphoma cell line Raji5 imaged with a new experimental ^{111}In-DTPA coupled ligand direct to CXCR4 receptor. Whole body image of the mouse depicting two major localizations of tumor cells (arrows).

nizing their respective receptors may not only increase the scintigraphic signal of the scanned tumors, but also increase the dose of radioactivity, reaching therapeutic levels by binding to various tumor cell populations in polyclonal tumors. Whether the new agents or the new multireceptor strategies can be of value for both diagnostic and therapeutic purposes in lymphoproliferative diseases is still unknown, however, their development represents an innovative and promising perspective.

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