Indium-111 pentetreotide scintigraphy and CT scans after 3 years in the follow-up of patients with malignant melanoma

Abstract

Somatostatin receptor scintigraphy (SRS) has been used for the detection of neuroendocrine tumors. Melanoma is a malignant tumor of melanocytes, considered to derive from the neural crest. As the prognosis of melanoma is very poor, early detection of the disease, of recurrences and of distal metastases, is important. *The aim* of our study was to evaluate the clinical impact of indium-111-diaethyleno triamino pentaacetic acid-d-phe1-octreotide (^{111}In-DTPA-octreotide or octreoscan or ^{111}In-O) in the management of melanoma patients after first diagnosis and first surgery and during three years of follow-up. *We have studied* 35 patients 20 female and 15 male, with histological proven melanoma. Scintigraphic images with single photon emission tomography γ-camera (Millenium GE-USA) were performed after the administration of 220MBq ^{111}In-O. The scintigraphic data were compared to axial computerized tomography (CT). Patients were followed for 3 years after the initial diagnosis and surgery. *Our results* showed that during the 3 years follow-up period, 26/35 patients had a clinical recurrence. Twenty of them had positive ^{111}In-O scans with 56 lesions mainly metastatic, while 6 had negative scans. The CT scans showed only 31/56 lesions. In *conclusion,* SRS with ^{111}In-O, for diagnosing metastases from malignant melanoma, showed a sensitivity and specificity of 87% and 94% respectively and within the 3 years of follow-up, the stage of melanoma and surgical strategies were modified by 48% and 32%, respectively. Twenty five tumor sites, unsuspected by CT were visualized by ^{111}In-O.

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Introduction

Malignant melanoma is an aggressive often metastatic tumour. The incidence of melanoma in the USA, northern Europe, Australia, and Canada is rising faster than for any other cancer and doubling every 10 years. In Australia melanoma is now the third most common cancer both in males and females. Regional metastases are seen in two thirds of the patients at first diagnosis [1-3]. Patients may initially present with cutaneous or subcutaneous nodules indicating distant metastases. The ability to metastasize and the resulting high mortality rates for melanoma, underline the importance of early detection of both primary and metastatic disease. Early detection decreases mortality and morbidity and provides the best chance for optimal clinical management [4]. Tumor markers such as neuro specific enolase (NSE) and S-100b are used in the follow up of these patients [5]. Anatomical noninvasive imaging modalities such as ultrasonography (US), axial computerized tomography (CT) and magnetic resonance imaging (MRI), may depict lesions of metastatic melanoma [6].

Melanocytes, are considered to be derived from the neural crest and as other neuroendocrine tumours, contain somatostatin receptors (SRS). Indium-111-diaethyleno triamino pentaacetic acid-d-phe1-octreotide (^{111}In-DTPA-octreotide or octreoscan or ^{111}In-O) has already been used for scintigraphic localization of neuroendocrine tumors.

Our aim was to evaluate ^{111}In-O scintiscan in malignant melanoma for the detection of recurrence and metastatic disease, after clinical and histological diagnosis and initial surgery treatment and during 3 years of follow up.

Patients and methods

We have studied 35 patients, 20 female and 15 male, mean age 46±7, range 32-51 years, with malignant melanoma, during a three years follow-up period after the first diagnosis in the Nuclear Medicine Departments of the Greek Anticancer Institute "Agios Savas" and the University Hospital of Alexandroupolis. In 5 patients the melanoma was sited at the skull, in 15 at the back of the torso, in 9 at the arms and in 6 at the feet.

The diagnosis was based on biopsy of the primary lesion. Tumor-node-metastases (TNM) classification was performed according to the American Joint Committee on Cancer/Union International Contre Cancer (AJCC/UICC) staging system [7].

Every patient gave his/her informed consent to participate in the study. The study was approved by the Ethics Committee of our hospitals. All patients had a SRS with ^{111}In-O immediately after the histological diagnosis of malignant melanoma and repeated every six months during the follow-up period. Conventional imaging techniques included chest radiography (X-rays), high-resolution CT, US, bone scintigraphy and magnetic resonance imaging (MRI). The patients' treatment after surgery included interferon alpha 2b and in 4, recurrent immunotherapy with high doses of interleukin 2.

Patients were infused intravenously with 220MBq of ^{111}In-O. Scintigraphic images were acquired using a single-head circular "large field of view" rotating gamma camera (Millenium GE, U.S.A.), with a medium resolution parallel-hole collimator, and a 256x256 word matrix with a preset time of at least 10min. Acquisition was adjusted to both ^{111}In photopeaks of 171 and 245keV to 64 projections over 360 rotations, and to 60sec per image, with 64x64 matrix. Slices were reconstructed after back projection using a Wiener filter. Planar images were obtained at 4h after injection of the radiopharmaceutical, in the anterior and posterior views of the head, neck, thorax, abdomen and the pelvis. At 24h, the acquisition included whole body anterior and posterior views and planar images in the same areas as above. Single photon emission tomography (SPET) scans were performed, to comparatively evaluate planar images at 24h. Delayed images were performed when necessary in the anterior and posterior views at 48h after injection [8].

Results

During 3 years of the follow-up period, 26/35 of the patients had clinical recurrence. Seventeen patients showed regional lymph node metastases, while nine distal metastases. From the whole body ^{111} In-O study, 20/26 patients had positive scans with 56 lesions, 1-3 lesions each, while 6 had negative scans indicating absence of receptors or small size tumours of less than 1cm. In comparison, CT images showed only 31 lesions.

The best scanning time for tumor detection was 24h. Earlier images were also helpful in the abdomen for the detection of lesions because at that time radioactivity in the liver and kidneys is low and is absent in the bowel. SPET scans provide additional information regarding tumor localization.

Patients' characteristics and the site of all lesions are shown in Table 1. Figures 1-6 demonstrate the sites of lesions in some of the patients.

Discussion

As functional modality, nuclear medicine offers a variety of possibilities to assist clinical management of melanoma, such as gallium-68 scan, immunoscintigraphy, radiolabeled a-

Table 1. *Patients' data*

Patients	Mean age	Range
N = 35 Male 15 Female 20	46 ± 7	32 - 51
Tumor site		
Skull	5	male 2 female 3
Back	15	male 5 female 10
Hands	9	male 5 female 4
Feet	6	male 2 female 4
Site of lesions- detected by		
Site of lymph	^{111}In-O scan	CT
Nodes		
Neck	12	8
Axillaries	16	9
Inguinal	13	8
Liver metastases	6	3
Bone metastases	5	1
Lung metastases	4	2
Total	56	31

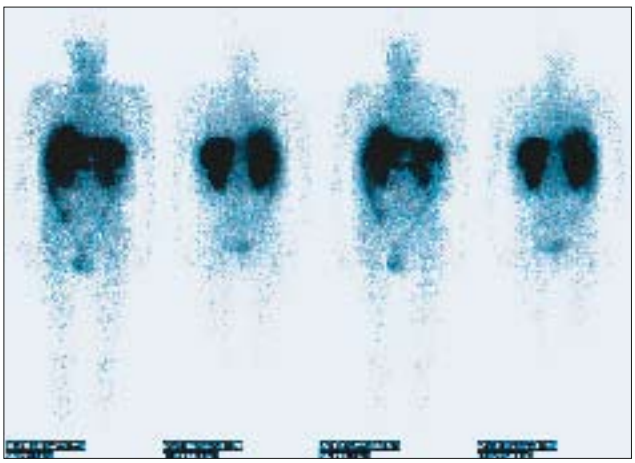

Figure1. Normal ^{111}In-O whole body imaging.

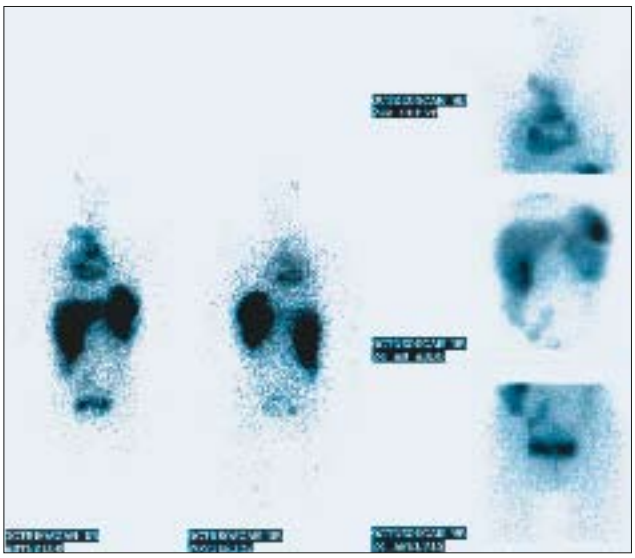

Figure 2. ^{111}In-O whole body imaging from left to right clockwise: anterior-posterior- left and right lateral thoracic obliques- and specific anterior abdomen scans: Notice the mediastinal lymph nodes.

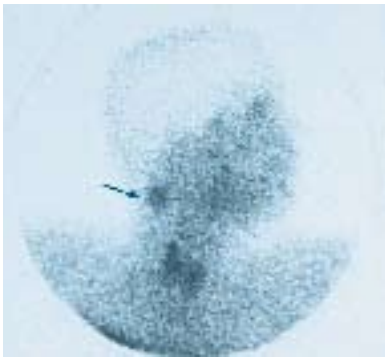

Figure 3. Right lateral oblique ^{111}In-O scan of the head and neck. Notice the lymph nodes (arrow).

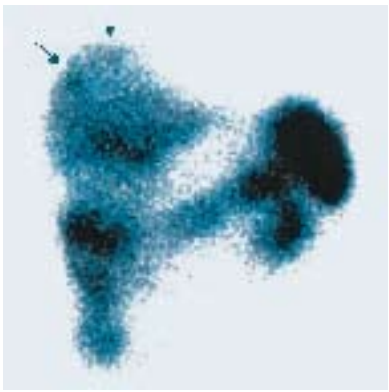

Figure 4. Anterior abdominal ^{111}In-O scan showing liver metastases (arrows).

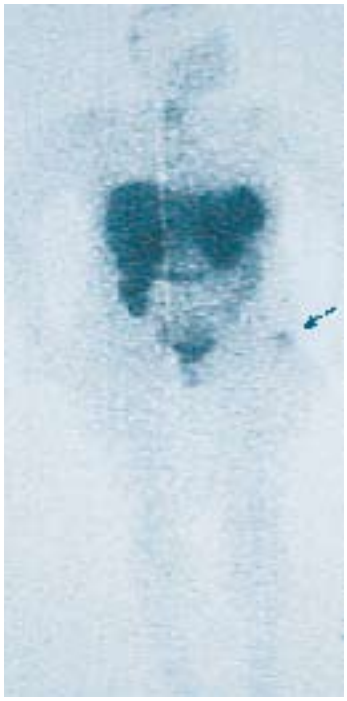

Figure 5. Anterior ^{111}In-O scan showing inguinal lymph nodes.

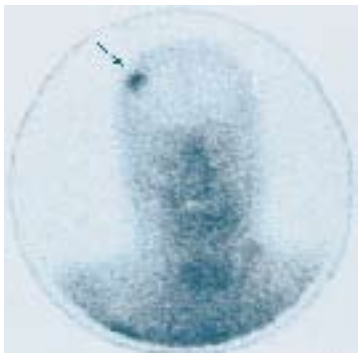

Figure 6. Increased accumulation of the radiotracer of the ^{111}In- O scan, in the scalp (arrow).

melanocyte stimulation hormone, thallium-201 chloride scan, technetium-99m sestamibi scan, ^{18}F-fluoro-2-deoxy-d-glucose positron-emission tomography and SRS [9, 10].

Neuroendocrine tumor cells frequently overexpress somatostatin receptors at their cell surfaces [11, 12]. Somatostatin a native peptide hormone expressed in two major 14- and 28-amino-acid forms [13, 14] was first isolated in 1968 from the rat hypo-thalamus and found to inhibit in humans the release of growth hormone, insulin, glucagon, thyrotropin, and other biological substances [15, 16]. Its action is mediated by binding to 5 receptors subtypes (1-5) distributed in a tissue-specific manner [17] and having specific biochemical characteristics [18-21].

The first long-acting somatostatin analog developed for clinical use was octreotide, with a biological half-life of 2h. Octreotide binds to SR subtypes 2 and 5 with affinity similar to that of native somatostatins 14 and 28 and with much lower affinity to the other 3 receptor subtypes [22].

^{111} In-O has an improved ability to localize tumors with SR deriving embryologically from cells of neural crest origin like malignant melanomas [9]. Lam et al. (2001) found that all of the 23 resected melanoma specimens, expressed SSTR1 mRNA. More than 80% expressed SSTR2 mRNA, and slightly more than half of them expressed SSTR3 and SSTR4 mRNA. Although ^{111}In-O binds preferentially to SSTR2 and SSTR5, only two of the specimens expressed mRNA for SSTR5 [23, 24]. In the above study, no correlation between SSTR subtype distribution and success or failure of imaging with ^{111}In-O was found [23].

Similar to SSTR subtype analysis was found other neuroendocrine tumors, such as carcinoids [25], pancreatic islet cell tumors [22], central primitive neural ectodermal tumors, and Ewing's sarcomas [26]. The density of somatostatin receptors and/or their affinity in malignant melanoma seems to be lower than in neuroendocrine tumours and intra-individual heterogeneity in somatostatin receptor expression is noticed [27].

Since ^{111}In-O binds preferentially to SSTR 2 and SSTR 5 [22] it may be that the 6 patients of our study with negative scans had no SSTR 2 or 5 receptors.

Positive findings in 67% of malignant melanomas with 83% sensitivity, have already been reported [28]. In another study ^{111}In-O scintigraphy in 24 patients with cutaneous or ocular melanomas found positive scintiscans in 87.5%, but in lesions basis the overall sensitivity was 59%. In that study, subcutaneous lesions and lymph node metastases were best detected, in contrast to bone metastases. In 7/24 patients, 11 clinically unsuspected lesions were found [9]. SRS is particularly efficient for tumors larger than 10mm with a detection rate 92%, in contrast to 48% for tumors smaller than 10mm. For smaller lesions SRS combined with US, CT or MRI detects 90% of all primary tumors [28].

Others, in 151 patients with melanoma who received a chest and abdomen CT scan for staging found that only 19% of the patients had a CT scan suspicious for metastases. The most common radiologic findings in this study were single hepatic and single multiple pulmonary nodules [30]. In another study, in 347 patients with stage III melanoma CT scan identified only 33/788 (4.2%) sites of metastatic melanoma with 8.4% false positive studies. Chest CT had the highest yield in patients with cervical lymphadenopathy and the low-

est yield in patients with groin lymphadenopathy. Pelvic CT diagnosed metastases in 7/94 (7.4%) of the patients with groin lymphadenopathy but no patient with palpable axillary or cervical nodes. Thus, routine CT in patients with clinical stage III melanoma infrequently identifies metastatic disease. Head CT in the asymptomatic patient, chest CT in patients with groin lymphadenopathy, and pelvic CT in the presence of axillary or cervical lymphadenopathy are not indicated. Selective use of chest CT in patients with cervical lymphadenopathy or pelvic CT in the presence of groin disease may be useful [31]. This study although with a small number of patients demonstrates that ^{111}InO is a selection criterion for melanoma patients.

*In conclusion, o*ur results showed that by SRS with ^{111}In-O, in melanoma patients unsuspected tumors were found in 64% of the cases. This finding modified therapeutic management of these patients. CT scans were much less effective because during the 3 years follow-up period, the CT scans showed only 31 of the 56 lesions shown by the ^{111}In-O scan. The best (92%) compromise for tumor detection concerns the 24h images.

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