

A NOVEL TECHNETIUM-99m LABELED MONOCLONAL ANTIBODY (174H.64) FOR STAGING HEAD AND NECK CANCER BY IMMUNO-SPECT

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A novel murine monoclonal antibody (Mab 174H.64) was labeled with ^{99m}Tc by a direct method. Mab 174H.64 detects a cytokeratin-associated antigen which is expressed by over 90% of all squamous cell carcinomas. Panendoscopy, sonography and computerized tomography scan were performed in all cases as well as magnetic resonance imaging (in selected patients). Pre-operative immunoscintigraphy was performed in 21 patients with histologically proven primary carcinomas (18 with remaining primary tumors and 3 with lymph node recurrences). Scintigraphic images were obtained 4–6 h after injection of 1.1 GBq of the ^{99m}Tc -labeled antibody (2 mg). Late images were acquired 18 to 24 h after injection. Single-Photon-Emission-Computed Tomography (SPECT) of the head and thorax was performed in all patients. The primary tumors were immunoscintigraphically visualized in all 18 patients with remaining primary tumor. Fifteen of 18 loco-regional lymph node metastases were visualized by immunoscintigraphy (the smallest lesions had a diameter of < 1 cm), in one patient lymph node metastases were detected by immunoscan only. Two metastatically involved lymph nodes were identified by histology only (micrometastases). Distant metastases were present in 3 patients, of which two were identified by immunoscintigraphy. Immuno-SPECT according to this method was a sensitive and specific imaging modality for preoperative staging of patients with squamous cell carcinoma of the head and neck and detected lymph node metastases with higher accuracy than conventional clinical and imaging modalities.

The 1990 incidence of head and neck tumors in the USA was 43 000 cases, of which 39 000 were classified as squamous cell carcinomas (SCC) (1). About 40% of the newly discovered cases were early-stage lesions while the remaining 60% of the patients had advanced-stage disease.

About 30% from the latter group could be cured with single and/or combined modality approaches (2, 3). Normally, treatment of head and neck cancer is dependent on the size and localization of the tumor and the extent of tumor infiltration and metastases to the cervical lymph nodes. Metastatic disease is found in less than 10% of patients with glottic carcinoma (4) whereas 50% or more of the cases with supraglottic laryngeal carcinoma exhibit metastatic lesions (5). Withehurst & Droulias (6) showed the prognostic importance of lymph node metastasis in a study involving 150 patients who were only surgically treated for a squamous cell carcinoma of the oral tongue. The same authors reported an overall survival rate of approximately 68% while the survival was only 31% in patients with cervical lymph node metastasis. In addition, an inverse correlation between the rate of response to

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radiotherapy and/or chemotherapy and the stage of the primary tumor was reported (7). Dreyfuss & Clarck (8) reported that chemotherapy achieved a complete regional remission in 25% of the patients who exhibited metastases of the regional lymph nodes (N1-classification), whereas only 14% of the N2-classified patients had a complete regional response (CR). In only 4% of the patients with tumors belonging to the N3-classification did CR occur. All the above mentioned reports show the need for as exact a tumor staging as possible for adequate therapy planning.

The aim of our prospective study was the detection of loco-regional lymph node metastases which are difficult to find by conventional clinical and imaging modalities.

Material and Methods

The utility of immunoscintigraphy was studied in 21 patients with histologically proven squamous cell carcinoma (SCC) of the head and neck, using a murine monoclonal antibody (MAb 174H.64, Tru-Scint^R SQTM) obtained from BIOMIRA Inc., Edmonton, Canada. Eighteen of these patients presented with a primary tumor while the remaining 3 had lymph nodes recurrences.

The injected antibody has been previously described (9) as an immunoglobulin of the IgG₁ subclass with specificity for a cell surface marker which is expressed by more than 90% of squamous cell carcinomas. The marker belongs to the class of cytokeratins. It is expressed by well-differentiated cells of the stem cell population of normal stratified epithelium and all squamous cell carcinomas (9). The intact murine antibody (2 mg) was provided as single vial kit to be directly labeled with 1.1 GBq of technetium-99m as TcO₄⁻. Our labeling procedure was almost complete in 5–10 min with a labeling efficiency greater than 98%, as measured by Thin Layer Chromatography. The material was administered intravenously, as a bolus injection over 1 min, after obtaining the written informed consent. A series of diagnostic tests (sonography, CT scan, magnetic resonance imaging (MRI), and panendoscopy as well as the clinical examination) was performed prior to immunoscintigraphy. Immunohistochemical staining of the surgically resected tumors or recurrences was also used to confirm our imaging results.

Planar multiple overlapping anterior and posterior images of the whole body were obtained at 4 to 6 h and 18 to 24 h after injection (1 000 kcts per image, 256 × 256 matrix, Sopha Medical Gamma Camera). SPECT of head, neck and thorax was performed at 6 and 18 h (optimally) after injection, using a high-resolution collimator (360° rotation, 26 min rotation time, frame reconstruction with a modified Shepp-Logan or Wiener-Filter; slice thickness 6 mm).

Results

We studied prospectively a group of 21 patients with squamous cell carcinomas of the head and neck region (Table 1); 18 of these patients presented with primary tumor while 3 had lymph node recurrences (Table 2). The primary tumor was successfully detected by immuno-SPECT in all cases. In addition, 15 out of 18 metastases in the regional cervical lymph nodes (histologically confirmed) were localized as scintigraphic hot spots. In addition, histopathology showed micrometastases in three lymph nodes (removed surgically); these lesions were not detected by any imaging modality. A true positive immunoscintigraphic result was observed in one patient, not found by the other imaging methods but later confirmed by histology. Taking into account tumor involvement of the lymph nodes only, the accuracy of palpation was 67%, and the detection rate 61%; CT scan had a detection rate of 78% and an accuracy of 76%; sonography a detection rate of 78% and a diagnostic accuracy of 81%; whereas immunoscintigraphy had a detection rate of 83% and was the most accurate procedure (81%, Table 3). Distant metastases were first detected by immuno-SPECT in two patients (paraortic lymph node metastases, and a lesion localized at the clavicular level) and histologically confirmed. One lung metastasis (confirmed by radiological follow-up) had been missed by immunoscintigraphy. Another lung lesion, seen on the chest roentgenogram, did not show antibody uptake and turned out to be a tuberculoma.

Table 1

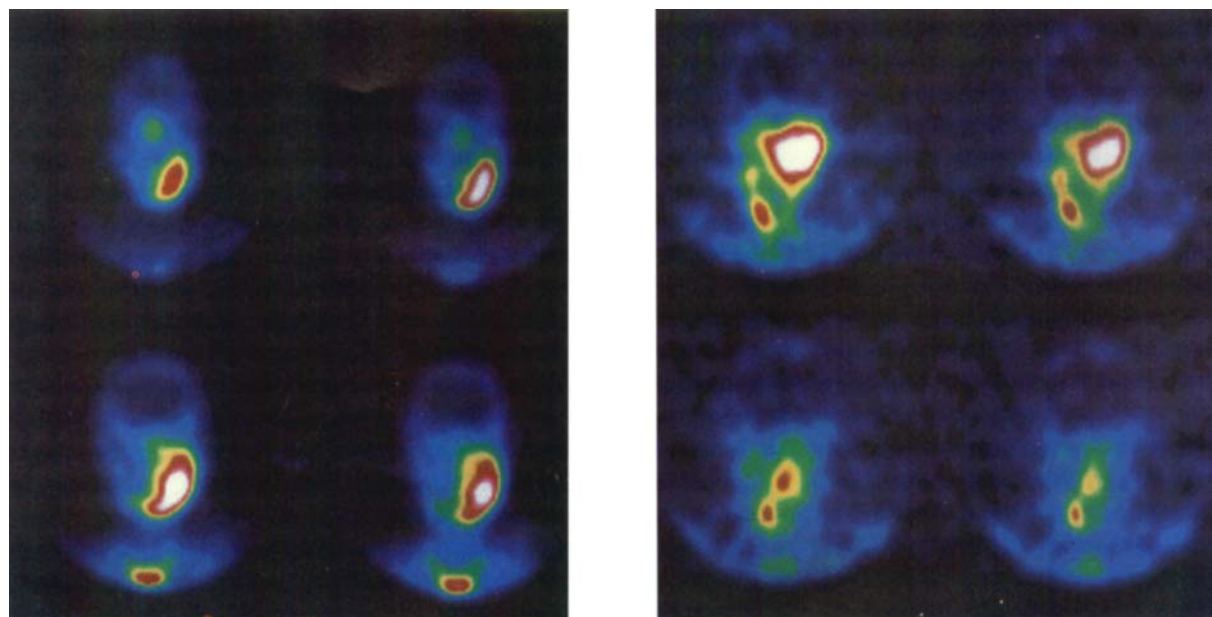
Site of tumors in 21 patients with head and neck squamous cell carcinomas

Site	Number
Oropharynx	7
Larynx	5
Hypopharynx	3
Oral cavity	3
Lymph nodes (recurrences)	3

Table 2

Tumor stages

Stage	Number
pT1	3
pT2	3
pT3	7
pT4	5
pN0	3
pN1	8
pN2	8
pN3	2
M0	18
M1	3



a)

b)

Fig. 1. Squamous cell carcinoma of the left alveolar process. Comparison of ^{99m}Tc -labeled antibody and ^{111}In -labeled somatostatin analogue uptake. a) Coronal SPECT slices obtained 7 h after injecting ^{99m}Tc -labeled Mab 174H.64 (Tru-Scint): High uptake in the large tumor. b) Coronal SPECT slices obtained 7 h after injection of ^{111}In -labeled pentatreotide (octreoscan): High uptake in the tumor as well as in the surrounding tissue (inflammatory reaction) and in lymph nodes (activated T-cells).

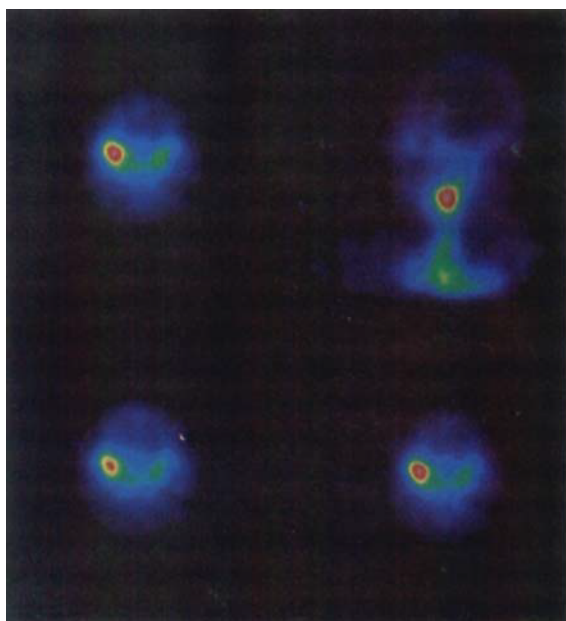


Fig. 2. Lymph node metastasis of squamous hypopharynx carcinoma. Transversal (upper left and lower panel) and sagittal (upper right panel) SPECT slices 18 h after injection of 1.1 GBq ^{99m}Tc -labeled Mab 174H.64: Obvious focal uptake in a para-jugular lymph node metastasis (confirmed by histology).

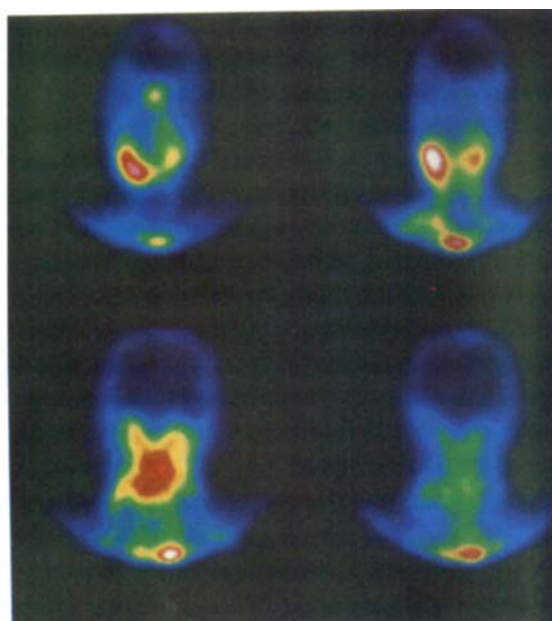


Fig. 3. Squamous cell carcinoma of the anterior floor of the mouth (pT4 N2). Coronal SPECT slices obtained 18 h after antibody injection: High focal uptake in the primary tumor on the right site and in bilateral cervical lymph node metastases (confirmed by histopathology).

Discussion

Appropriate therapy of head and neck cancer patients is largely dependent on tumor stage, size and metastatic spread. Adequate localization and staging of these neo-

plasms and their metastases is therefore of great importance. Enlarged lymph nodes in the head and neck region can be detected by physical examination in up to 85% of examined patients (10). However, a palpable lymph node

Table 3
Comparison between conventional diagnostic methods and immunoscintigraphy

Methods	True pros.	True neg.	False pos.	False neg.	Accuracy	Detection rate
Palpation	11	3	0	7	67%	61%
CT	14	2	1	4	76%	78%
Sonography	14	3	0	4	81%	78%
Immunoscintigraphy	15	2	1	3	81%	83%

with slightly increased volume does not always indicate a metastasis since hyperplasia may also be a consequence of other non-related pathological conditions, such as inflammation associated with oral or dental infections, which are common in head and neck cancer patients (11). Ultrasound offers a good means for examining enlarged, palpable cervical lymph nodes, yielding important information as to whether such a node is cystic or solid in nature in addition to its relationship to surrounding anatomical structures. The main limitation of this diagnostic modality is that tissue can only be visualized to a depth of 4–6 cm and that the results are much dependent on the experience of the investigator (12). CT scan and MRI provide helpful means in localizing primary head and neck tumors and their relationship to adjoining anatomical structures (13). Compared with clinical examination CT increases the detection rate of neck node metastases from 47 to 90% in late tumor stages (T3 and T4). However, in earlier stages of the disease (T1 and T2), palpation of the lymph nodes provides a greater detection rate of metastases than CT (14). MRI can show increased values within a malignant lesion in the T₂-derived images. Various T₂-values have also been found in a number of inflammatory processes of the head and neck region. Thus, an elevated T₂-value does not always indicate the presence of tumor (14, 15). Tumor-avid substances such as gallium-67-citrate have also been used for the localization of head and neck carcinomas. In addition to the uptake in tumors, gallium-67 also accumulates in inflammatory tissues. Since some patients examined in our study had undergone radiation therapy, this precluded the use of gallium-67-citrate for imaging purposes due to the possible bilateral accumulation in the salivary gland as a result of local inflammatory processes (16). Furthermore, gallium-67-citrate fails to visualize lymph node metastases smaller than 2 cm and those larger in size can easily be palpated (10, 17).

Immunoscintigraphy provides a useful tool for the identification of a number of tumor-associated antigens and the study of tumor-specific metabolism. Indium-111 labeled anti-CEA (18), indium-111 labeled anti-epidermal growth factor receptor (EGF-R) antibody and ^{99m}Tc labeled antibody fragments (19, 20) have been proposed for the diagnosis of head and neck tumors. However, ¹¹¹In-EGF-R Mab 425 has failed to demonstrate tumors smaller

than 3 cm. The smallest tumor detected in our study with MAb 174H.64 was <1 cm in diameter (histologically proven). With the application of SPECT we were able to detect additional metastases in the lymph nodes in about 10% of the patients where conventional diagnostic methods had failed to indicate metastases. The possibility that the antibody uptake was due to inflammatory processes was excluded by immunohistochemical examination of the surgically resected material. A great advantage of radioimmunoscintigraphy over other diagnostic methods (especially CT-scan or MRI) is the ability to confirm the tumor nature of a lesion. The antigen detected by MAb 174H.64 is expressed by more than 90% of squamous cell carcinomas (9), which is in accordance with the results obtained in vivo in the present study.

In summary, immunoscintigraphy with MAb 174H.64 was found to be a good means for the pretherapeutical staging of patients with head and neck cancer and allowed in combination with other diagnostic procedures a more precise staging.

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