Occult Primary Tumors of the Head and Neck

Accuracy of Thallium 201 Single-Photon Emission Computed Tomography and Computed Tomography and/or Magnetic Resonance Imaging

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Objective: To determine the accuracy of thallium 201 single-photon emission computed tomography (thallium SPECT) and computed tomography and/or magnetic resonance imaging (CT/MRI) in the detection of occult primary tumors of the head and neck.

Design: Study of diagnostic tests.

Setting: National Cancer Institute, Amsterdam, the Netherlands.

Patients and Methods: Thirty-two patients with a neck node metastasis of an epithelial tumor and negative findings by mirror examination at initial presentation were included in the study. Twenty-nine patients underwent thallium SPECT and CT/MRI before examination under general anesthesia (EUA). In 3 patients only thallium SPECT was performed before EUA. Histological confirmation of an occult primary tumor during EUA was used as the gold standard. Negative radiodiagnostic and nuclear findings in the upper aerodigestive tract in the presence of a primary carcinoma other than of the head and neck were interpreted as true-negative findings.

Results: For thallium SPECT the following results were recorded: sensitivity, 67%; specificity, 69%; accuracy, 69%; positive predictive value, 33%; and negative predictive value, 90%. In 1 patient, thallium whole body scan indicated a primary carcinoma beyond the mucosal lining of the upper aerodigestive tract. The CT/MRI results were as follows: sensitivity, 71%; specificity, 73%; accuracy, 72%; positive predictive value, 45%; and negative predictive value, 89%.

Conclusions: Thallium SPECT and CT/MRI showed comparable results for detection of occult primary tumors of the head and neck. A potential advantage of thallium SPECT is that it allows total body screening.


PATIENTS WITH squamous cell carcinoma of the head and neck frequently present with a neck node metastasis as the first symptom. Most primary tumors are diagnosed during the first routine head and neck evaluation. In a few cases (1% to 6%), the primary tumor, if present, remains occult after careful clinical examination, imaging (computed tomography and/or magnetic resonance imaging [CT/MRI]), and panendoscopy.1-10 Examination under general anesthesia (EUA) with biopsy specimens of various head and neck sites at risk and/or tonsillectomy have been recommended for the detection of the occult primary tumor.10-12 However, these diagnostic procedures remain relatively inaccurate and are directed to subsites where occult primary tumors may be expected. Based on epidemiological evidence, occult primary tumors most frequently occur, in decreasing order, in the tonsillar fossa, nasopharynx, base of tongue, and piriform sinus.2,5,6,9-11 Prebiopsy radiodiagnostic workup may increase the yield of the panendoscopy by identification of potential biopsy sites. The use of CT/MRI under these circumstances has increased the detection of occult head and neck primary tumors.4,11,13 On the other hand, normal radiodiagnostic findings are usually not followed by positive findings with EUA. In our earlier experience, thallium 201 single-photon emission CT (thallium SPECT) appeared to be a possible adjunct in detecting occult primary head and neck tumors.14-16 To investigate the role of these imaging modalities in the diagnostic workup, we set up a prospective study of patients presenting with a neck node metastasis of an unknown primary origin.

RESULTS

A primary site related to the neck node metastasis was identified in 11 patients (34%). Seven primary squamous cell carcino-
PATIENTS AND METHODS

Thirty-two patients with cytologically proven lymph node metastases from an epithelial tumor were included after negative mirror and/or endoscopic evaluation results by 2 independent head and neck surgeons (A.J.M.B. and I.B.T.) between 1995 and 1999. There were 25 men and 7 women, with a median age of 58.3 years (range, 40-87 years).

Cytological results were as follows: squamous cell carcinomas (n=20), undifferentiated carcinomas (n=9), and adenocarcinomas (n=3). The distribution of lymph node metastases among the different levels was as follows: level I (n=0), II (n=26), III (n=16), IV (n=6), and V (n=3).

The CT scan images were obtained with the patient in a supine position and with quiet respiration (Philips Tomoscan AV; Best, the Netherlands). Contiguous 3-to-5-mm sections were made through the skull base, nasopharynx, oropharynx, larynx, hypopharynx, and entire neck. The optimal field of view varied between 14 and 18 cm, depending on the size of the patient. Prescanning bolus administration followed by drip infusion of intravenous (nonionic) contrast material was used for all studies.

For MRI studies, a 1.5-T scanner (Siemens Magnetom 63 SP4000; Siemens, Erlangen, Germany) was used. Section thickness was 4 mm or less, with interslice gap of 1 mm or less. The optimal field of view for the axial views was 16 to 18 cm for T1-weighted sequences and 18 to 20 cm for T2-weighted sequences. Intra- and postcontrast magnetic contrast material was injected routinely. T1-weighted images were obtained before and after injection of intravenous (nonionic) contrast material. Fourteen patients were studied using MRI, 5 patients with CT, and 10 patients with both modalities.

A thallium SPECT scan was performed in all patients with the use of a Vertex dual-head gamma camera (ADAC Laboratories, Milpitas, Calif) equipped with low-energy, high-resolution collimators 60 minutes after intravenous injection of 150 MBq of thallous chloride Tl 201. Acquisition was based on 360° noncircular rotation with 6° step angles, 60 seconds per frame, 64 × 64 × 16 matrix, and zoom factor of 1.83 (pixel size, 5 mm). The images were reconstructed with a Butterworth filter (order 3, cutoff 0.35, 1-pixel images) obtained in the sagittal, coronal, and transverse planes. Additional 3-dimensional volume reconstructions were used to identify tumor sites. In addition, simultaneous anterior and posterior planar, 30-minute, whole body studies (512 × 1024 matrix) were performed just before the SPECT studies.16

After the imaging procedures, panendoscopy under general anesthesia was performed with special attention to sites suggestive of carcinoma by CT/MRI and thallium SPECT. Biopsy specimens were taken from sites suggestive of carcinoma, and histological proof of the occult primary tumor of the upper aerodigestive tract was used as the gold standard, meaning that a true-positive finding represents the histological confirmation of a imaging finding suggestive of carcinoma. In case of negative imaging findings, nondirected biopsy specimens were taken from the nasopharynx, tonsil, and base of tongue. Negative radio-diagnostic and isotope imaging of the upper aerodigestive tract in the presence of a histologically confirmed primary tumor beyond this area was interpreted as a true-negative finding. Based on this protocol, sensitivity, specificity, and accuracy rates were calculated according to the following definitions: true positive, a; false positive, b; false negative, c; true negative, d; where sensitivity = a/(a+c); specificity = d/(b+d); accuracy = (a+d)/(a+b+c+d); positive predictive value = a/(a+b); and negative predictive value = d/(c+d).

Rereading of the initial CT/MRI studies and thallium SPECT examinations by 4 of the authors (S.A.J.M.V.V., A.J.M.B., R.A.V.O., and F.A.P.) was done for all primary tumors that originated in the mucosal lining of the upper aerodigestive tract (n=7) with knowledge of the biopsy-proven primary tumor site.

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In patient 11 (Table 1), a carcinoma of the sub-mandibular gland was found after neck dissection. Both metabolic and radiodiagnostic study results were negative for a primary tumor. Rereading with the knowledge of the biopsy-proven primary tumor site changed the initial reading of thallium SPECT in 1 case. This patient had a primary tumor in the base of tongue visible on CT and MRI (patient 28, Table 1). The initial reading of the thallium SPECT study located this lesion in the hypopharynx. In 3 MRI studies, false-positive (n=1) and false-negative (n=2) results changed to true-positive results, retrospectively (Table 4). In 2 cases (patients 8 and 26, Table 1), the primary site could only be appreciated retrospectively. In patient 8, there was minimal asymmetry of the epiglottis ipsilateral to the nodal disease visible on 1 MRI section. In patient 26, the MRI showed complete symmetry of the tonsils, but (retrospectively) the side ipsilateral to nodal disease showed minimal increase in signal intensity. In the third case (patient 1, Table 1), there was a focal mass in the nasopharynx that was missed at initial reading (ie, reading error).
radiation. Panendoscopy has its limitations in detecting small, superficially growing lesions or submucosal tumors. In current clinical practice, biopsy specimens are taken from subsites known for harboring primary lesions, such as the nasopharynx, tonsil, base of tongue, and piriform sinus. To reduce the chance of missing a primary lesion by this approach, imaging techniques may be of value to indicate areas suggestive of carcinoma. The use of CT/MRI has been advocated for this purpose. In a prospective study of 12 patients with a neck node from unknown primary squamous cell carcinoma, CT identified a primary occult lesion in 33% of patients. In a more recent series, CT/MRI correctly identified the primary site in 28 (50%) of 56 patients. In the present study, the primary tumor (n=7) or metastatic disease (n=1) at the mucosal lining of the upper aerodigestive tract was correctly identified by CT/MRI in 5 of 8 patients. Most of these occult tumors consisted of T1 and T2 lesions (Table 1). One T4 hypopharynx carcinoma, with a nonbulky submucosal growth pattern, remained undetected during routine ear, nose, and throat mirror examination. This again emphasizes the need for careful radiologic and endoscopic evaluation of these patients, since submucosally growing carcinomas often stay clinically occult.

Radiodiagnostic and/or nuclear findings can be helpful in these cases. However, even when guided by imaging findings, it can still be difficult to locate the primary site. This was the case in patient 28 with a T1 carcinoma of the base of tongue undetected at initial routine ear, nose, and throat examination (Figure 2). Even when guided by CT/MRI findings, it was still difficult to locate the lesion under general anesthesia.

The efficacy of CT/MRI depends on the use of optimal radiographic techniques. If imaging is to help identify occult primary tumors, it has to be performed before endoscopy and biopsy. In prebiopsy imaging, any asymmetric mucosal thickening ipsilateral to the site of nodal involvement may be suspected of harboring a primary tumor. In our study, we have mainly used MRI (n=14) or the combination of CT and MRI (n=9, after exclusion of the MRI scan in patient 14, Table 1). In this era of cost concern, it seems to be a good principle to do a cross-sectional study that accurately answers the clinical question for the lowest price. For evaluation of the head and neck for “suspected unknown primary,” several authors use contrast-enhanced CT as a first choice. In this case, MRI is used as a supplement for focused evalu-

| Table 3. Calculated Values for Thallium SPECT and CT/MRI* |
|----------------|----------------|----------------|----------------|----------------|
| Imaging         | Sensitivity, % | Specificity, % | Accuracy, % | Positive Predictive Value, % | Negative Predictive Value, % |
| Thallium SPECT (n = 32) | 67              | 69              | 69          | 33            | 90          |
| CT/MRI (n = 29)  | 71              | 73              | 72          | 45            | 89          |

*Thallium SPECT indicates thallium 201 single-photon emission computed tomography; CT/MRI, computed tomography and/or magnetic resonance imaging.

| Table 4. Summary of Initial Imaging Results and After Rereading With Knowledge of the Biopsy-Proven Primary Tumor Site* |
|----------------|----------------|----------------|-----------------
| Patient No. | Imaging       | Initial Reading | Rereading (T+) |
| 1           | MRI           | F+, oropharynx  | Nasopharynx    |
| 8           | MRI           | F-, epiglottis  |                 |
| 26          | MRI           | F-, tonsil      |                 |
| 28          | Thallium SPECT| F+, hypopharynx | Oropharynx      |

* T+ indicates true positive; MRI, magnetic resonance imaging; thallium SPECT, thallium 201 single-photon emission computed tomography; F+, false positive; and F-, false negative.

Figure 1. Axial single-photon emission computed tomogram (SPECT) (A), coronal SPECT (B), axial magnetic resonance image (C), and coronal short TI inversion recovery (D) of patient 17 demonstrating a submucosally growing primary tumor in the base of tongue (solid arrows) and an enlarged lymph node in the left side of the neck (dotted arrows).

Figure 2. Axial single-photon emission computed tomogram (A); initial reading located this lesion in the hypopharynx (arrow). SM indicates submandibular gland. Axial computed tomographic scan (B) demonstrating a small focal mass in the base of tongue (arrows).
Figure 3. Algorithm for analysis of patients presenting with a neck node metastasis of a squamous cell carcinoma of unknown origin. ENT indicates ear, nose, and throat; CT, computed tomography; MRI, magnetic resonance imaging; thallium SPECT, thallium 201 single-photon emission computed tomography; minus sign, negative; and plus sign, positive.

Fluorine 18–labeled deoxyglucose (FDG) SPECT imaging seems to have modest value for the detection of occult primary lesions. In a series of 18 patients, Mukherji et al1 found a specificity of 38% for this technique and a sensitivity of 81%. The authors suggest a complementary role for FDG SPECT and CT in the detection of occult lesions, increasing the sensitivity to 91%. In a series of 17 patients, AAssar et al1 suggest a substantial contribution by FDG positron emission tomography for detection of occult primary tumors. With this technique, the number of patients with established primary sites increased to 47% (7/15) compared with 33% (5/15) identified with CT/MRI.1 Similar encouraging results were reported by Braams et al.17 The results of the aforementioned studies must be interpreted with caution, because relatively small numbers of patients were included. AAssar et al1 accept a small number of false-positive results given the accessibility and minimal risk of taking biopsy specimens in the head and neck and the importance of establishing a definitive diagnosis. Compared with other metabolic studies,1,3,11 we confirmed a higher specificity (69%) with an accuracy of 69%. However, the additional value of thallium SPECT was limited to 1 case in which the MRI result was false positive (patient 1, Table 1).

In a comparative study on thallium and FDG SPECT in 5 patients with biopsy-proven squamous cell carcinoma of the head and neck, Mukherji et al18 showed that FDG SPECT had advantages over thallium SPECT in detecting the primary tumors (5/5 vs 3/5), mainly because of its reduced salivary gland activity.16 In the present study, we have not found false-negative results of thallium SPECT due to “masking” of salivary gland uptake.

A thallium whole body scan has potential value in the detection of occult primary tumors other than in the head and neck area. In 1 patient, the thallium whole body scan showed a primary thyroid carcinoma outside the mucosal lining of the upper aerodigestive tract. In 1 patient, a gastric carcinoma was not visible on the whole body scan.

Earlier, we stated that normal radiodiagnostic imaging is usually followed by negative findings with EUA. The high negative predictive value of CT/MRI (89%) supports this statement. The negative predictive value of thallium SPECT was 90%, indicating that negative findings with EUA are also very likely after normal nuclear imaging findings.

Low positive predictive values for both thallium SPECT (33%) and CT/MRI (45%) were found. This indicates that when panendoscopy shows no macroscopic abnormality at the site that was indicated by imaging as a possible primary site, biopsies should always be performed on other sites that are known for harboring occult primary tumors, ie, nasopharynx, tonsil, base of tongue, and hypopharynx. Some authors argue in favor of routine ipsilateral (to nodal disease) or bilateral tonsillectomy in these circumstances.10-12 On the other hand, the high negative predictive values for both cross-sectional and nuclear imaging suggest that it is not necessary to repeat a subsequent negative panendoscopy in this setting.

In this study, thallium SPECT showed comparable results to CT/MRI in the detection of occult primary lesions. Although thallium SPECT scanning did not provide better detection of occult head and neck primary tumors in this study, its role may increase in the future. Potentially, metabolic techniques can detect subtle mucosal abnormalities not seen on cross-sectional imaging. In addition, thallium SPECT may reveal the site of the occult primary lesion in case of false-positive cross-sectional findings (patient 1, Table 1). Future developments in computerized fusion of radiodiagnostic and metabolic images may help improve localization of radioisotope uptake,19 reducing difficulties in interpreting anatomical sites (Figure 2). This needs to be investigated in future prospective correlative studies. For such studies, we would recommend the algorithm currently used in our institution, based on the results of the present study (Figure 3). If thallium SPECT is not available, this algorithm (excluding the metabolic study) can be used in daily practice for imaging analysis of patients...
presenting with a neck node metastasis of a squamous cell carcinoma of unknown origin (Figure 3).

Rereading of the initial radiodiagnostic studies with knowledge of the biopsy-proven primary tumor site changed false-negative (n = 2) and false-positive (n = 1) results to true-positive results in 3 patients. This underscores the importance of the use of optimal scanning protocols for both CT and MRI. The reading error in 1 case might have been prevented by double reading. Rereading of the metabolic studies in these cases changed a false-positive result to a true-positive result in 1 case (patient 28, Table 1). The hypopharynx, anatomically, is in close proximity to the base of tongue. It may be difficult to separate these subsites on a thallium SPECT study. When the cross-sectional studies and the thallium SPECT study were read together, it became clear that the location of the increased uptake on the SPECT study matched the abnormality in the base of tongue seen on CT and MRI (Figure 2).

In summary, the results of the present study suggest that in the search for the unknown primary tumor in patients with a cervical metastasis and negative findings with mirror and/or endoscopic examination at initial presentation, CT/MRI and thallium SPECT scanning are comparable.

Considering the choice between CT and MRI, the results of the present study support the approach advocated by several authors, with contrast-enhanced CT as a first choice. In this case, MRI is used as a supplement for focused evaluation of areas suggestive but not definitively positive on CT or when CT results are normal (Figure 3).

When, in addition, a thallium SPECT study is performed, we recommend simultaneous interpretation of both radiodiagnostic and metabolic studies. Whole body thallium scan has potential value in the detection of occult primary tumors beyond the mucosal lining of the upper aerodigestive tract.

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