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Superimposed dual-isotope SPECT using ^{99m}Tc-hydroxymethylene diphosphonate and ^{201}Tl-chloride to assess cartilage invasion in laryngohypopharyngeal cancer

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Objective: Cartilage invasion in laryngohypopharyngeal cancer has a significant impact on the choice of treatment modality and outcome of the disease. We examined invasion of cartilage in laryngohypopharyngeal cancer by simultaneous bone and tumor dual-isotope SPECT using ^{99m}Tc-hydroxymethylene diphosphonate and ^{201}Tl-chloride. ***Methods:*** Early and delayed simultaneous bone and tumor dual-isotope SPECT were performed on 19 patients with laryngohypopharyngeal cancer. Dual-isotope SPECT images were superimposed to project tumor location from tumor SPECT onto the osseous structures shown by bone SPECT. The presence or absence of cartilage invasion was evaluated histopathologically or by radiological studies such as CT and/or MRI. ***Results:*** Histopathological or radiological examination of the cartilage revealed invasion in 5 patients and no invasion in 14 patients. The results of both early and delayed dual-isotope SPECT were exactly the same. Using dual-isotope SPECT, the sensitivity, specificity, and accuracy in detecting cartilage invasion by laryngohypopharyngeal cancer were: 80% (4/5), 92.9% (13/14), and 89.5% (17/19), respectively. ***Conclusions:*** Results of the present study suggest that superimposed early bone and tumor dual-isotope SPECT images may be sufficient for the diagnostic evaluation of cartilage invasion by laryngohypopharyngeal cancer. Superimposed dual-isotope SPECT imaging is a useful technique in the evaluation of cartilage invasion in laryngohypopharyngeal cancer.

Key words: superimposed dual-isotope SPECT, ^{99m}Tc-hydroxymethylene diphosphonate, ^{201}Tl-chloride, laryngohypopharyngeal cancer, cartilage invasion

INTRODUCTION

CARTILAGE INVASION in laryngohypopharyngeal cancer is generally associated with a lower response rate to radiation therapy and a higher risk of tumor recurrence than involvement of soft tissue, and may also result in radiation-induced necrosis.[1–6] Most investigators, therefore, believe that extensive surgery is the only way to offer curative treatment if the cartilaginous framework of the larynx has become invaded by tumor tissue.[4–6] The grave prognostic implication of invasion of cartilage by laryngeal and hypopharyngeal tumors is reflected in the TNM classification, where it falls automatically into a T4 class.[7]

Correct diagnosis of cartilage invasion is important because a false positive interpretation of tumor involvement may lead to over-treatment, or in the worst case, to a needless total laryngectomy. Both computed tomography (CT) and magnetic resonance imaging (MRI) are widely used in the staging of laryngohypopharyngeal cancer. CT is considered to be a rather specific method for detecting intracartilaginous tumor spread, but it may lead to an underestimation of the extent of cartilage invasion.[2,8] A few studies have shown that MRI is more sensitive than CT in the evaluation of tumor spread into the cartilage, but it may lead to an overestimation of the spread.[8,9]

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There is at least one case report suggesting that planar bone scintigraphy may be a useful technique for demonstrating thyroid cartilage invasion of laryngeal carcinoma.[10] Chan et al.[11] reported that the normal and abnormal transaxial anatomy of the face and skull could be defined clearly by single photon emission computed tomography (SPECT). For tumor imaging, SPECT with ^{201}Tl-chloride (^{201}Tl), a radiopharmaceutical that displays preferential accumulation in a variety of tumor types, is commonly used. Several reports have demonstrated the efficacy of ^{201}Tl SPECT in evaluating and localizing malignant tissue, especially in the lung,[12,13] thyroid[14] and head and neck.[15,16]

The purpose of the present study was to examine simultaneous bone and tumor dual-isotope SPECT for localization of two bone and tumor-specific radiopharmaceuticals, namely ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP) and ^{201}Tl, in patients with suspected cartilage invasion by laryngohypopharyngeal cancer.

MATERIALS AND METHODS

Patients

The study was conducted on 19 consecutive patients (all men; mean age 64.7 y; age range, 50–79 y) who were referred to our institution during the past 3 years on suspicion of having cartilage invasion by laryngohypopharyngeal cancer. All patients underwent simultaneous bone and tumor dual-isotope SPECT for routine assessment of cartilage invasion. The presence or absence of cartilage invasion was evaluated histopathologically or by radiological findings (CT and/or MRI). The study was approved by the local ethics committee, and all patients provided written or oral informed consent.

Simultaneous Bone and Tumor Dual-Isotope SPECT

Dual-isotope SPECT imaging was performed with triple-head gamma cameras (Picker Prism 3000; Picker International, Cleveland, OH) fitted with high-resolution, parallel-hole collimators. This camera was interfaced to a dedicated computer (ODYSSEY, Picker International, Cleveland, OH). The imaging protocol included: a) intravenous injection of 740 MBq ^{99m}Tc-HMDP with a 3 h waiting period; b) 20 min whole body planar bone scintigraphy; c) intravenous injection of 111 MBq ^{201}Tl-chloride; d) early dual-isotope SPECT of the neck 10 min after injection of ^{201}Tl-chloride (3.5 h after injection of ^{99m}Tc-HMDP); and e) delayed dual-isotope SPECT of the neck 2 h after injection of ^{201}Tl-chloride (5.5 h after injection of ^{99m}Tc-HMDP).

For SPECT images of the neck, 72 projections were obtained using a 128 × 128 matrix for 60s per view in a step-and-shoot mode. Using a triple head camera, the total actual acquisition time was 24 min. Three energy analyzers were used for acquisition. These were set at 71 keV with a 15% window for ^{201}Tl images, 90 keV with a 10% window for scatter images, and 140 keV with a 15% window for ^{99m}Tc images. The projection data were processed with a 2-dimensional low-pass filter and then corrected for contamination scatter. Image reconstruction

Table 1 Clinical data, results and evaluation on early and delayed SPECT and radiological and histopathological examinations and final evaluation in patients with laryngohypopharyngeal cancer

Patients no.	Age	Sex	Early SPECT			Delayed SPECT			Radiological examination	Histopathological examination	Final evaluation
			bone	tumor	evaluation	bone	tumor	evaluation			
1	54	M	+	+	Invasion	+	+	Invasion	Invasion	Invasion	Invasion
2	72	M	+	+	Invasion	+	+	Invasion	Invasion	Invasion	Invasion
3	64	M	+	+	Invasion	+	+	Invasion	Invasion	Invasion	Invasion
4	53	M	+	+	Invasion	+	+	Invasion	Invasion	Invasion	Invasion
5	62	M	–	–	No invasion	–	–	No invasion	Invasion	Invasion	Invasion
6	54	M	+	+	Invasion	+	+	Invasion	Invasion	No invasion	No invasion
7	70	M	–	–	No invasion	–	–	No invasion	Invasion	No invasion	No invasion
8	66	M	–	–	No invasion	–	–	No invasion	No invasion	No invasion	No invasion
9	74	M	–	–	No invasion	–	–	No invasion	No invasion	No invasion	No invasion
10	65	M	–	–	No invasion	–	–	No invasion	No invasion	No invasion	No invasion
11	61	M	–	–	No invasion	–	–	No invasion	No invasion	No invasion	No invasion
12	75	M	–	–	No invasion	–	–	No invasion	No invasion	n.d.	No invasion
13	57	M	–	–	No invasion	–	–	No invasion	No invasion	n.d.	No invasion
14	50	M	–	–	No invasion	–	–	No invasion	No invasion	n.d.	No invasion
15	76	M	–	–	No invasion	–	–	No invasion	No invasion	n.d.	No invasion
16	79	M	–	–	No invasion	–	–	No invasion	No invasion	n.d.	No invasion
17	73	M	–	–	No invasion	–	–	No invasion	No invasion	n.d.	No invasion
18	62	M	–	–	No invasion	–	–	No invasion	No invasion	n.d.	No invasion
19	64	M	–	–	No invasion	–	–	No invasion	No invasion	n.d.	No invasion

+ = Positive; – = negative; n.d. = not done

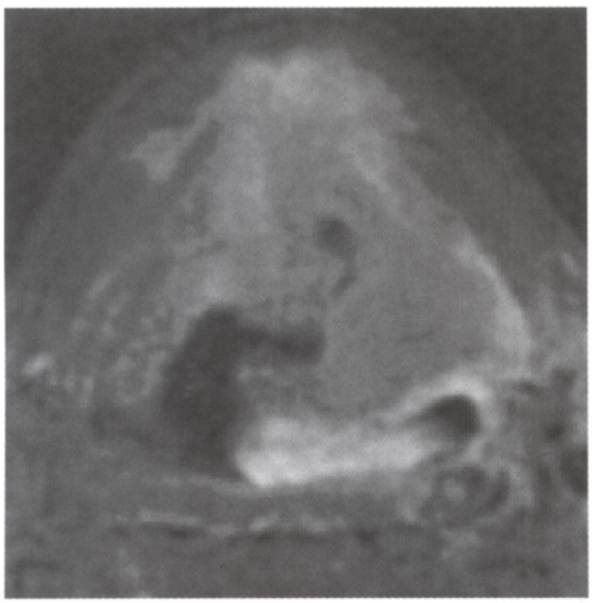
was performed using filtered backprojection with a ramp filter. Transverse, coronal, and sagittal sections were reconstructed. The system was 7.2 mm full width at half maximum, and the slice thickness was 6.88 mm.

Contamination Scatter Correction for Each Radionuclide

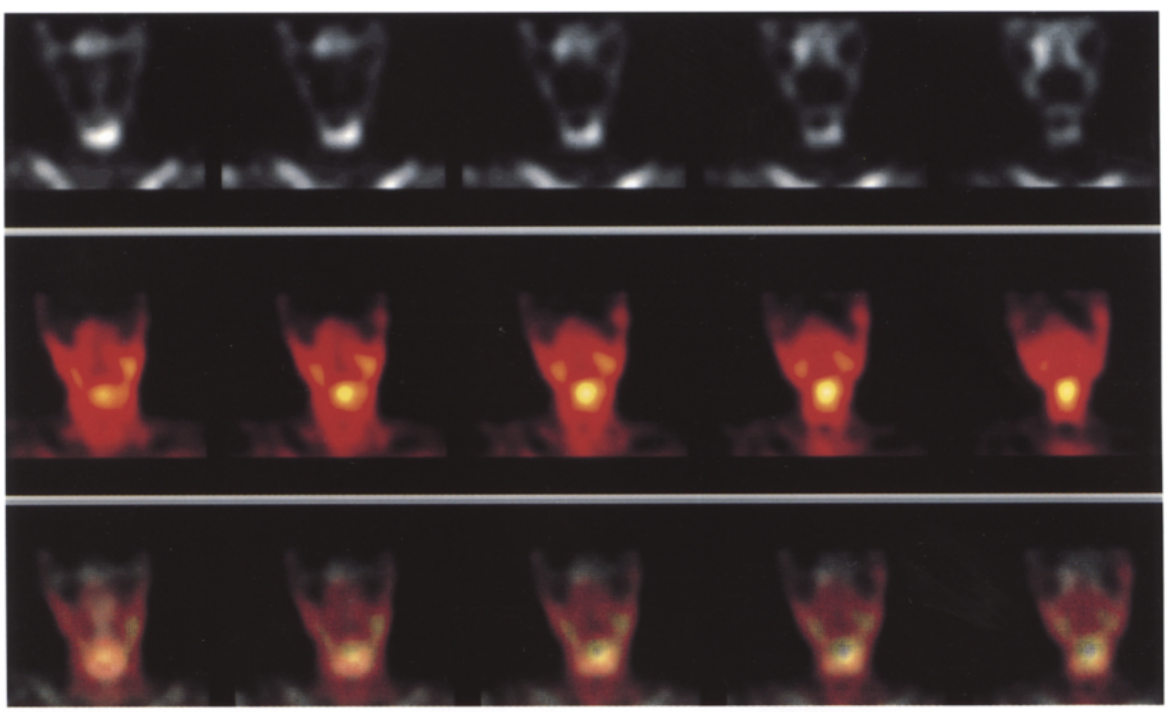
Because the study involved simultaneous dual-isotope imaging, the raw data at the 71 keV window were contaminated by ^{99m}Tc Compton scatter, and that at the 140 keV window included the 167 keV γ-ray count for ^{201}Tl. To eliminate such contamination scatter, the raw ^{99m}Tc and ^{201}Tl data were corrected according to the equations in each pixel. Measurements of scatter and cross-talk coefficients were performed according to our previously reported method.[17] Briefly, the scatter correction coefficient, α, was measured to be 1.07, whereas the cross-talk correction coefficient, β, was measured to be 0.14. The corrected counts in the 71 keV window for ^{201}Tl, a, and in the 140 keV window for ^{99m}Tc images, b, were calculated as follows: $a = A - \alpha C$; $b = B - \beta a$, where A, B and C stand for the raw counts in the 71, 140 and 90 keV windows, respectively.

Dual-Isotope SPECT Interpretation

The study involved superimposing the bone and tumor SPECT images, which could be done easily using another dedicated computer (FX; Shimadzu, Kyoto, Japan). Because bone and tumor images were acquired simultaneously, the slice pitch and position were exactly the



A



B

Fig. 1 Carcinoma of the left piriform sinus in a 53-year-old male. A: Contrast enhanced axial MRI shows a large tumor mass that arises from the left piriform sinus and invades thyroid cartilage. B: Superimposed coronal bone and tumor SPECT images show abnormal ^{99m}Tc-HMDP accumulation corresponding to tumor positive site in the thyroid cartilage (*top*, bone SPECT; *middle*, tumor SPECT; *bottom*, superimposed SPECT). In this patient, dual-isotope SPECT evaluation indicated invasion, surgical results showed invasion, and MRI and dual-isotope SPECT were true positives.

same. Two independent and experienced nuclear medicine physicians, who were unaware of the histopathologic and radiological findings, visually evaluated the abnormal accumulation in superimposed dual-isotope SPECT on color films. A consensus was reached regarding all findings. Dual-isotope SPECT images were superimposed to project tumor location from tumor SPECT onto the osseous structures shown by bone SPECT. A positive accumulation in the same area of the cartilage on both bone and tumor SPECT was interpreted as invasion. A positive accumulation only on bone or tumor SPECT was interpreted as no invasion. A negative accumulation on both bone and tumor SPECT was also interpreted as no invasion.

MRI and CT Interpretation

CT studies were performed with a HiSpeed Advantage (model 9800; General Electric Medical System, Milwaukee, WI) or Aquilion (Toshiba, Tokyo, Japan) scanner. The imaging protocol involved taking of 5-mm contiguous axial images from the skull base to the thoracic inlet. Intravenous contrast material was administered in all patients.

Two 1.5 T superconducting units, Signa Advantage (General Electric, Milwaukee, WI) and Visart (Toshiba, Tokyo, Japan), were used for MRI. T1 weighted spin-echo images were obtained with sequences of 500/15/2 (TR/TE/excitations), and T2 weighted fast spin-echo images with sequences of 4000/120/2. In addition, 0.1 mmol/kg of Gd-DTPA was administered for a post-contrast study.

The CT and MRI criteria used were: no invasion if the cartilage was intact; and invasion, in the case of destruction of the inner and/or outer aspects of the cartilage. At CT, asymmetric sclerosis of cartilage was considered a sign of cartilaginous invasion even if tumor was seen only on the inner aspect of the cartilage. At MRI, an area of enhancement within the cartilage adjacent to the tumor was considered a sign of cartilaginous invasion if the tumor was seen only on the inner aspect of the cartilage. Both the CT and MRI scans were evaluated by 2 independent and experienced radiologists, who were unaware of the results of other modalities. In case of disagreement, a consensus was reached.

Analysis

Positive dual-isotope SPECT findings without histopathological and/or radiological proof of cartilage involvement were defined as false positive, while negative dual-isotope SPECT results in the presence of proof of positive cartilage involvement were regarded as false negative. The diagnostic value of dual-isotope SPECT was compared to the final diagnostic assessment by calculating sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. Sensitivity was calculated as: (true positive)/(true positive + false negative); specificity as: (true negative)/(true negative + false positive); positive predictive value as: (true positive)/(true positive + false positive); negative predictive value as: (true negative)/(true negative + false negative); and accuracy as: (true positive + true negative)/total.

RESULTS

Clinical data and results of evaluation of cartilage invasion using dual-isotope SPECT and radiological and histopathological examination are given in Table 1. Of the 19 patients studied, histopathological and/or radiological examination revealed invasion of the cartilage in 5 and no tumor invasion in 14 patients. Results from both early and delayed dual-isotope SPECT were exactly the same. Of the 5 patients who revealed invasion of the cartilage, 4 showed abnormal accumulation in the cartilage on dual-isotope SPECT. Of the 14 patients without tumor invasion of the cartilage, 13 showed no abnormal accumulation on dual-isotope SPECT. On both early and delayed dual-isotope SPECT, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in detecting cartilage invasion by laryngohypopharyngeal cancer were 80%, 92.9%, 80%, 92.9%, and 89.5%, respectively. The corresponding values using radiological examination were 100%, 85.7%, 71.4%, 100%, and 89.5%, respectively.

Radiological findings in a representative case are shown in Figure 1.

DISCUSSION

In a previous study, we examined mandibular invasion of intraoral squamous cell carcinoma by dual-isotope SPECT using both bone (^{99m}Tc-HMDP) and tumor (^{201}Tl-chloride) tracers.[18] Results of that study showed that superimposed dual-isotope SPECT is useful in the diagnostic evaluation of mandibular invasion by intraoral carcinoma.[18] In the present study, using the dual-isotope SPECT we examined invasion of cartilage by laryngohypopharyngeal cancer. Results show a comparable sensitivity and specificity for the detection of intracartilaginous spread as reported recently for CT and/or MRI.[8,9]

Evaluation of tumor invasion using superimposed bone and ^{201}Tl SPECT was found to be superior to CT imaging in patients with intraoral carcinoma,[18] but the topographic orientation may be difficult for the surgeon in the absence of familiar anatomic landmarks. In the present study, the results of dual-isotope SPECT were the same as those of ^{201}Tl tumor SPECT alone. There was no difference in tumor size or location between the patients with and without cartilage invasion. Therefore, tumor progression into the cartilage structures may only be suspected on dual-isotope SPECT but not confirmed with ^{201}Tl SPECT alone. A combined assessment of bone and tumor tracer studies may be able to correctly differentiate osseous

tumor spread from nonmalignant cause of increased bone turnover in laryngohypopharyngeal cancer during the primary staging. As reported previously, an unspecific periostal reaction in mandible adjacent to a squamous cell carcinoma in the mouth floor may be visualized as a hot spot on bone SPECT.[19] If bone scintigraphy is assessed without image fusion with a tumor avid tracer, the tumor stage may be overestimated and the patient may be unnecessarily subjected to extensive and mutilating surgery.[19]

Almeida et al. reported one case with markedly and uniformly increased bone tracer accumulation in thyroid cartilage associated with laryngeal cancer.[10] Israel et al.[20] showed that SPECT could provide precise localization and define the extent of skull base bone involvement, especially for small, deep lesions of the skull base, which are difficult to detect with planar imaging. Tumor tracer (^{99m}Tc-MIBI) combined with bone SPECT has been used by Leitha et al.[21] in diagnosing tumor invasion in patients with primary and recurrent head and neck tumors. In their study,[21] bone SPECT had to be performed on separate days although the patient's head was placed into a shell to prevent head movement. Thus, superimposition of both SPECT images is difficult to align the images completely. In the present study, bone and tumor SPECT imaging was performed simultaneously and image fusion was easy.

Ossification of the laryngeal cartilage usually begins after the second or third decade of life. Ossification of the thyroid cartilage has been noted to follow a defined, symmetrical pattern which usually begins at the posterior border near the root of the inferior horn, spreading along the inferior border and reaching the midline where there is usually a separate center of ossification.[22,23] Bone tracer uptake noted in the lower neck on anterior view of bone scans is usually mild and diffusely irregular. This pattern of uptake is most commonly associated with osteoarthritis or cartilage invasion of the laryngeal cancer.[10] If bone scintigraphy is assessed without image fusion with a tumor-avid tracer, tumor stage is overestimated.

Many published reports have emphasized the usefulness of the delayed ^{201}Tl scan in differentiating malignant from benign tumors in various organs, because ^{201}Tl activity in malignant tumors shows a delayed washout compared with benign tumors.[12,13] From this point of view, delayed ^{201}Tl image may be more suitable for tumor evaluation. However, in the present study, on visual analysis, the results of early dual-isotope SPECT were exactly the same as those of delayed dual-isotope SPECT. This suggests that only early dual-isotope SPECT may be sufficient for the detection of cartilage invasion in laryngohypopharyngeal cancer. Furthermore, it can yield a quick result and save time in a busy clinical setting.

Nuclear medicine imaging provides excellent information concerning functional biology. However, the anatomic information available using this technique is quite limited. The findings of dual-isotope SPECT in the present study changed the therapeutic approach in 1 (no. 7 in Table 1) of 19 patients. In this patient MRI showed cartilage invasion. However, dual-isotope SPECT did not show the cartilage invasion. For this case, the surgery field was re-defined on the basis of dual-isotope SPECT. Becker et al.[9] reported MRI false positive findings caused by nonneoplastic peritumoral reactions and changes in the cartilage, namely extensive fibrosis, inflammation, and bone resorption adjacent to the tumor. One patient (no. 6 in Table 1) showed false-positive finding on both dual-isotope SPECT and radiological studies. The cause of the false-positive finding is thought to have been on inflammatory process around the cartilage. In another patient (no. 5 in Table 1) in the present study, dual-isotope SPECT did not show invasion of cartilage. However, histologic work-up of the tissue confirmed that malignant tissue had invaded the cartilage. In this case, both CT and MRI could accurately demonstrate cartilage invasion. False-negative finding of dual-isotope SPECT was thought to indicate minor cartilage invasion. Dual-isotope SPECT failed to depict minor cartilage invasion. In the present study, the accuracy on dual-isotope SPECT was the same as that on radiological examination. From this point of view, dual-isotope SPECT has a complementary role to radiological examinations such as CT and MRI for the detection of cartilage invasion in laryngohypopharyngeal cancer. In the presence of inconclusive lesions, early dual-isotope SPECT and CT and/or MRI may help in early functional and anatomic characterization, thus preventing any unnecessary delay in patient management caused by referral for repeat imaging and invasive diagnostic procedures. Further studies, however, are necessary to demonstrate the contribution of superimposed dual-isotope SPECT and CT and/or MRI in laryngohypopharyngeal cancer based on a larger number of patients.

CONCLUSION

Superimposed dual-isotope SPECT imaging is useful in the detection of intracartilaginous tumor spread by laryngohypopharyngeal cancer. The early dual-isotope SPECT images alone may be sufficient for the diagnostic evaluation of cartilage invasion by laryngohypopharyngeal cancer.

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